DeSIPhER: Developing Schizophrenia Identification using Physiological EEG Responses

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“**कर्मणये वाधिकारस्ते मां फलेषु कदाचन ।**
मां कर्मफलहेतुर्भूः मांते संङगोस्त्वकर्मणि।।”

Meaning: “Your right is to the duty only, not to the fruits thereof. Never consider yourself the cause of the results of your activities, and never be attached to not doing your duty.”

-Bhagvat Gita (Chapter 2, Verse 47)

Declaration of Author's Rights

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: Sibani P Mohanty

Date: 29.09.2022

This work is dedicated to my late father who inspired me to follow my heart and instilled my faith in goodwill and devotion to ones' work, always.

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Abstract

Schizophrenia is a serious mental illness that manifests itself with inconsistent, complex, and challenging to diagnose clinical symptoms. This study aimed to combine neurophysiological (electroencephalography or EEG), behavioural, and cognitive tests in one diagnostic protocol to probe the heterogeneous aspects of schizophrenia.

Four experiments were conducted with 19 healthy control subjects and 6 schizophrenia spectrum disorder patients (3 schizophrenia, 3 schizoaffective disorder). In the **auditory odd-ball task,** patients showed diminished mismatch negativity (MMN) to all the 5 deviant types. Schizophrenia patients had a longer location MMN peak latency compared to both control subjects and schizoaffective disorder patients. The computerized **Stroop task** did not elicit traditional Stroop effect. However, this task in patients showed high error rates and response latencies. The significant difference in the EEG response to the congruent and incongruent stimuli was absent in patients. The schizophrenia and schizoaffective disorder patients also showed a difference in task-specific neural mechanisms. Cambridge Neurophysiological Test Automated Battery (**CANTAB**) tests revealed significant deficits in motor response, visuo-spatial association, spatial working memory, and verbal recognition memory in patients. In the **facial emotion recognition task**, patients had significantly higher error rates and response latencies. Schizophrenia patients showed the highest error rate for angry and sad stimuli. The patients showed a deficit in the early face processing EEG response at the occipito-temporal electrode, and an elevated frontal EEG response relative to the healthy subjects.

This was an explorative study that conducted a diverse set of experiments with same group of healthy subjects and patients. It uncovered significant differences between the control and patient groups, and between the schizophrenia and schizoaffective disorder patients. These results exhibited a proof-of-concept for the importance of a combined protocol which could potentially lead to a discovery of biomarkers for diagnosis using a larger, diverse group of schizophrenia spectrum disorder patients.

Contents

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

%	Percent
<	Less than
<<	Much Less Than
=	Equal to
>	Greater than
µ	Micro
µV	Micro-Volts
kΩ	Kilo Ohm
ACC	Anterior Cingulate Cortex
AD	Alzheimer's Disease
ADJUST	Automatic EEG artifact Detection based on the Joint Use of Spatial and Temporal features
AERP	Auditory Event Related Potentials
Ag	Silver
AgCl	Silver Chloride
AH	Auditory Hallucinations
ANOVA	Analysis of Variance
BSD	Bipolar Spectrum Disorder
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAR	Common Average Reference
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
Cong	Congruent Trial
COVID-19	Corona Virus Disease of 2019
dACC	Dorsal Anterior Cingulate Cortex
dB	Decibel
Diff	Difference
DP	Difference Peak
DPL	Difference Peak Latency
DSM	Diagnostic and Statistical Manual of Mental Disorders
Dur	Duration Deviant
EEG	Electroencephalography
EEGLAB	Interactive MATLAB toolbox for EEG analysis
EOG	Electro-Occulogram
EPSRC	Engineering and Physical Sciences Research Council
ERP	Event Related Potentials
ERSP	Event Related Spectral Perturbation
FASTER	Fully Automated Statistical Thresholding for EEG artifact Rejection
FDR	False Discovery Rate
FFT	Fast Fourier Transform
fMRI	Functional Magnetic Resonance Imaging

FN	Frontal Negativity
Freq	Frequency Deviant
GABA	Gamma Aminobutyric Acid
GAF	Global Assessment of Functioning
Gap	Gap Deviant
GNT	Graded Naming Test
GP	General Practitioner
GWAS	Genome-Wide Association Study
HEOG	Horizontal Electro-Occulogram
Hz	Hertz
ICA	Independent Component Analysis
ICD	International Classification of Disease Criteria
Incong	Incongruent Trial
Int	Intensity Deviant
ISI	Inter-Stimulus Interval
Loc	Location Deviant
LORETA	Low Resolution Electromagnetic Tomography
LSD	Lysergic Acid Diethylamide
MADRS	Montgomery–Åsberg Depression Rating Scale
MATLAB	Analysis software by MathWorks
MEG	Magnetoencephalography
MHFA	Mental Health First Aid
mins	Minutes
MMN	Mismatch Negativity
MN	Minimum Norm
MOT	Motor Screening Task
MRI	Magnetic Resonance Imaging
ms	Millisecond
N1	Negative peak in ERP occurring at approximately 100ms
N100	Negative peak in ERP occurring at approximately 100ms
N170	Negative peak in ERP occurring at approximately 170ms
N250	Negative peak in ERP occurring at approximately 250ms
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMDA	N-Methyl-D-Aspartate
p	p-value
P100	Positive peak in ERP occurring at approximately 100ms
P300	Positive peak in ERP occurring at approximately 300ms
PAL	Paired Associate Learning Task
PANSS	Positive and Negative Symptoms Scale
PANSSG	Positive and Negative Symptoms Scale, General subscale
PANSSN	Positive and Negative Symptoms Scale, Negative subscale
PANSSP	Positive and Negative Symptoms Scale, Positive subscale

PC	Percent Correct
PCA	Principal Component Analysis
PCL	Percent Change in Latency
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Pre-Frontal Cortex
RL	Average Trial Response Latency
RN	Research Nurse
RS	Research Student
RT	Response Time
RTI	Reaction Time Task
RW	Response Window
S	Schizophrenia
SA	Schizoaffective Disorder
SANS	Scale of Assessment of Negative Symptoms
SAPS	Scale of Assessment of Positive Symptoms
SASICA	Semi-Automatic Selection of Independent Components for Artifact correction in the EEG
SD	Stimulus Duration
secs	Seconds
Stand	Standard Tone
Stats	Statistics
std	Standard Deviation
SWM	Spatial Working Memory Task
t-stat	t-statistic
t-test	Student's t-test
UK	United Kingdom
VEOG	Vertical Electro-Occulogram
VRM	Verbal Recognition Memory Task
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1.1 Mental Health

We, as human beings, are a species set apart from the rest of the animal kingdom for our unique abilities to think, reason, understand, create, plan, execute, emote, and express ourselves. Mental health and well-being are essential to develop these unique abilities to interact with each other and live a productive life.

Mental health problems cause loss of healthy years of life due to illness; striking as one of the major causes of the burden of disease worldwide. In the UK, 1 in 4 adults experience mental health issues every year, while 1 in 6 adults are suffering at any one point (Baker, 2021; MHFA England, 2019; Public Health Scotland, 2021). Based on a 2011 estimate, mental health issues in the UK were estimated to contribute to almost double (28%) the burden of disease, compared to approximately 16% each for cardiovascular diseases and cancer (Department of Health and Social Care, UK, 2011). The total expenditure, in terms of both social and economic costs of mental health in Scotland was found to be £10.7 billion for the year 2009/10 (*Fundamental Facts About Mental Health 2015*, 2015). More recent statistics from England show that these costs have risen from £105.2 billion in 2010 to £119 billion in 2019 (O'Shea & Bell, 2020). From a worldwide perspective, in the years between 2011 and 2030, mental disorders are estimated to result in a $16.3 trillion total loss of economic output. This economic output loss is close to the estimated loss due to cardiovascular diseases ($15.6 trillion), and far exceeds that of respiratory diseases, diabetes, and cancer ($14.8 trillion, combined) (Trautmann et al., 2016).

The estimation of numbers presented above precedes the ongoing COVID-19 pandemic, which has also resulted in adverse effects on the mental health of the general population. Recent reports have shown that in June 2020, 19% of surveyed adults in the UK experienced symptoms of depression, up from 10% before March 2020 (A. Abbott, 2021). However, due to the lockdown and the increased burden on healthcare services, fewer than expected mental illness and self-harm cases were recorded by primary care after March 2020 (Carr et al., 2021). This could soon lead to more severe cases and result in a larger burden of disease, than what was previously projected.

1.2 Schizophrenia- Prevalence and Causes

Schizophrenia is one of the most significant public health problems across the globe. It is a debilitating mental illness that affects 0.5% to 1% of the general population across the world (Weinberger & Harrison, 2010). According to the World Health Organisation (WHO), schizophrenia is considered as one of the important contributors to the burden of disease worldwide. It is a serious and chronic mental illness that affects a person's thoughts, feelings, and behaviour. It is not, as it is often wrongly perceived, a "split personality" disorder ("Schizophrenia" Schiz: split, Phren: mind). The media usually uses the word - unfairly - to describe violence and disturbance. Due to this and like most mental illnesses, it is often accompanied with social and self-stigmatization.

The textbook definition of the disease might sound simple and straightforward however, the manifestation of schizophrenia in individuals is highly complex. Epidemiological accounts have previously shown similar prevalence of schizophrenia across cultures and races across the world, however more recent evidence points to Black and Hispanic ethnicities diagnosed at a higher rate (C. I. Cohen & Marino, 2013; Halvorsrud et al., 2019; Olbert et al., 2018; Schwartz & Blankenship, 2014). According to two meta-analyses, men have 1.4 times higher risk of developing schizophrenia over their lifetime than women citing a higher incidence ratio in men than women (Aleman et al., 2003; J. E. McGrath & Tschan, 2004; Tandon et al., 2008).. This serious illness leads approximately 10% of its patients to suicide, which is also the largest contributor to reduced life expectancy in the patients of schizophrenia (Sher & Kahn, 2019). As this disease causes a lifelong disability in its patients, a significant cost is incurred by the NHS for their treatment plans and loss in working days.

Individuals often experience positive symptoms like auditory and visual hallucinations that threaten them or criticise their actions. This leads to patients developing strange beliefs and delusions. The disease also causes negative symptoms (affective flattening, asociality, etc.) and cognitive deficits that can be distressing to relatives or caregivers. A more comprehensive list of symptoms along with the pathophysiology has been explained in the **Chapter 2**.

The combination of stigma and the complexity of the disease makes it difficult to diagnose in the early stages. This further leads to the patients leading a degraded quality of life for a prolonged period. It has been systematically shown (Picchioni & Murray, 2007) that an early diagnosis and treatment can alleviate the outcomes of the disease.

Similar to the complexity of how the disease manifests, the causes of schizophrenia are also not well understood; they are varied and complex. The disease certainly has underlying genetic causes as the risk goes up from 1 in a 100 to 1 in 10 if a person has a parent with schizophrenia. This number goes up to 1 in 8 if a non-identical twin has the disease and 1 in 2 if the twin is identical (Timms, 2015). Several environmental factors at different stages of life also increase the risk. Patients are more likely have experienced complications during pregnancy, premature birth, low birth weight etc. (Picchioni & Murray, 2007). In their book Schizophrenia, Weinberger and Harrison highlight that in an adult, stressors like social isolation, urban environment or significant incidents like car accidents have been shown to precede worsening of symptoms. Also, drug and alcohol abuse are also theorized as a possible cause of schizophrenia in some patients (J. J. McGrath & Murray, 2010). Early and prolonged use of cannabis has also been proven to significantly increase the risk (Marder & Cannon, 2019; Nasrallah et al., 2011; Timms, 2015).

1.3 Current Diagnosis

The current classification of the neuropsychiatric disorder schizophrenia is not based on a single symptom alone but a cluster of symptoms that include positive symptoms, negative symptoms, and cognitive impairment. The inconsistency of such complex clinical features between patients of schizophrenia makes a diagnosis based upon clinical symptoms extremely challenging. The tools which are currently used to help aid diagnosis in schizophrenia are usually based on series of interviews to assess different criteria in the patients. Positive and Negative Symptoms Scale (PANSS) is one of such tools that assigns a severity rating for various positive (PANSSP), negative (PANSSN), and general (PANSSG) symptoms like motor retardation, postural impairment, poor attention, lack of judgment, anxiety, disorientation, etc (Kay et al., 1987). However, such tools have been shown to have several drawbacks. Specifically, the negative subscale PANSSN has been shown to have test-retest reliability ((Kring

et al., 2013). The scale has also been criticised as being too complex and leading to biased results when reporting the effectiveness of medications (Kumari et al., 2017). PANSS scale has also been shown to have hidden internal structure (Lefort-Besnard et al., 2018) and better represented by 4 to 7 factors (Lim et al., 2021) compared to the proposed three (PANNSP, PANSSN, PANSSG). The 5-factor representation with positive, negative, disorganized, excited, and depressed factors has had the most consensus across studies (Lim et al., 2021; Wallwork et al., 2012) but also further increases the complexity of the scale. Newer assessment scales like Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) which are concise and reliable have been proposed. However, they only assess the negative symptoms and still rely on subjective assessment by a clinician. They do not objectively measure the changes in brain function. This inadequacy of the present assessment tools in mental health diagnostics to objectively quantify various criteria during the disease diagnosis has led us to design a diagnostic protocol. A first of its kind, this diagnostic protocol uses a range of neurophysiological and behavioural measures that combine perceptual and cognitive testing that can serve as an early signature or biomarker for schizophrenia. Electroencephalography (EEG) is a non-invasive and radiation free method of recording brain activity from the scalp. Literature suggests that using EEG as a neuroimaging modality provides the basis from which sensitive biomarkers can be developed (Light et al., 2012). As a functional brain imaging technology, EEG is well tolerated and can be deployed in standard clinical or community settings (Barros et al., 2021; M. X. Cohen, 2014; Farnsworth, 2019; Ledwidge et al., 2018; H. S. Lee & Kim, 2022). EEG measurements do not require patients to be isolated for prolonged periods in a challenging environment like that of a Magnetic Resonance Imaging (MRI) scanner, thus, reducing the amount of paranoia and anxiety faced by them in an enclosed space.

In the process of developing this experimental protocol for diagnosing schizophrenia, a variety of task conditions that uniquely probe perceptual, cognitive, and emotional deficits were employed. **Chapter 3** gives insight into the study design and general methodology applied across all the experiments. The details about the specific tasks and the analyses related to them are outlined in their respective chapters.

The series of tests carried out within the protocol has generated a rich set of data that allows us to define a subject's overall state. These set of measurements establish an unbiased and objective link between the neurophysiology, behaviour, and disease state of the patients and differentiates them from healthy individuals and could be used as potential biomarkers.

1.4 Rationale and Aims of Study

Early diagnosis of schizophrenia and early intervention in high-risk or first-episode populations is crucial for improving the clinical outcome by mitigating the cognitive deficits and thus improving the quality of life of patients (Insel, 2010; D. Lee et al., 2021; Lin & Lane, 2019; Linszen et al., 1998). However, early diagnosis of schizophrenia has been a challenge and there is lack of appropriate biomarkers to study associated brain abnormalities (Nasrallah et al., 2011; M. J. Owen et al., 2016).

Starting from the underlying cause of the disease to the different ways it affects the patients, schizophrenia is almost like a different disease in each of its victims. The literature to date suggests that biomarkers based on single neurophysiological test may be inadequate to fully capture and categorize the onset and progression of schizophrenia due to the heterogeneous nature of the disease (Rodrigues-Amorim et al., 2017; Weickert et al., 2013). The overall aim of this explorative study was to combine neurophysiological, behavioural, and cognitive aspects into one diagnostic protocol. The diverse observations generated from our protocol encompass the heterogeneity of the disease which is not available through a single test.

For decades now, neurophysiological methods have been widely studied and used in the research of schizophrenia. These methods have many advantages that have led to them being researched for potentially useful biomarkers in developing new drug therapies and improving the overall functional outcome in patients. Some of them can be adapted into passive paradigms where a subject does not have to engage him/herself in a task or pay any attention.

According to various studies, the higher-order cognitive deficits and psychosocial behaviour in patients of schizophrenia have shown a correlation to the dysfunction in the neural activity at the pre-attentive and early attentive levels of information processing (Braff & Light, 2004). 70% of the patients with schizophrenia have reported auditory hallucinations (AH). It is believed that in patients of

schizophrenia, abnormalities in brain regions associated with memory integration could possibly generate hallucinations (Waters et al., 2012). **Chapter 4** explores this area by using an auditory oddball paradigm. This paradigm involved the subjects passively listening to a series of tones as they watched a pre-selected silent movie. This is advantageous in testing on younger patients and in the patients, who are difficult to engage in behavioural studies.

Event-Related Potentials (ERPs) are the various positive or negative potentials that are related to specific events or stimuli obtained from the time-locked activity of the brain after the raw EEG data is processed (Roach & Mathalon, 2008). Mismatch negativity (MMN), is an early auditory ERP (AERP) that has been determined as an index of an automatic, pre-attentive alerting mechanism, which stimulates an individual to respond to unexpected environmental events (Gené-Cos et al., 1999). MMN abnormalities are specific to schizophrenia, as no reliable MMN findings have been observed in other major psychiatric disorders (Fisher et al., 2011). The high temporal resolution of the data thus obtained is useful in tracing the flow of information from the regions of auditory cortex to the association areas where the auditory data is interpreted and processed. This helps in determining any impairment in auditory information processing at an earlier stage of the disease (Javitt et al., 2008).

The treatment regimes in schizophrenia mostly targets the improvement of positive symptoms in patients as these symptoms tend to relapse and remit. In a few cases patients tend to have some long-term residual psychotic symptoms (M. J. Owen et al., 2016). However, the medication is believed to have limited efficacy on the negative symptoms which are currently believed to be fundamental to the pathology of schizophrenia (Tandon et al., 2008). These negative symptoms are associated with deficits in motivation, affect, cognitive functioning, verbal and non-verbal communication and social behaviour; having a direct impact on the functional outcome of a patient (Bobes et al., 2010). As cognitive deficits are now considered as a core feature of schizophrenia, experiments that investigate them were included in the protocol. These cognitive deficits are not only present during the first episode of psychosis but are also found to be persistent over the period of illness regardless of the changes in symptomatic states. The emphasis has now been shifted from just treating

the positive symptoms to an overall approach where full range of symptoms including the cognitive deficits are being treated to improve the patient's quality of life.

Chapter 5 outlines the second task, a computerized Stroop task, which is a traditional neuropsychological test to assess cognitive deficits usually indicating the abnormality relating to the deficits in the working memory (Ghose & Tamminga, 2008), which is the small amount of information that is retained in the brain and quickly available while performing cognitive tasks (Cowan, 2014). Stroop task reflects selective attention, functioning of an executive system, and the ability to inhibit habitual response and to maintain the instruction set. The task required the subject to quickly change perceptual set when viewing matching and non- matching names of colours (Nehemkis & Lewinsohn, 1972). For example, the names of colours written either in the same colour or in a different colour (RED/RED or BLUE/BLUE).

Chapter 6 gives a detailed description of the third task which uses CANTAB (Cambridge Neuropsychological Test Automated Battery), a touch screen tablet with standardized cognitive tests which provides an effective measure of cognitive assessment. The CANTAB tests battery was used to assess executive functioning (mental processes that are required to perform a task with concentration (Diamond, 2013)), working memory, spatial recognition memory (mental process that helps one remember locations and relative positions of objects (Jacobs, 2003)), episodic memory (memory that helps one recall and mentally reexperience events from their past (Pause et al., 2013)), verbal memory (memory of information presented verbally, like word lists (Tatsumi & Watanabe, 2009)), and reaction time (time taken to process and react to a stimuli).

Patients of schizophrenia show impairments in recognition and discrimination of different facial emotions (Turetsky et al., 2007). Expressing emotions through ones' face is a widely studied component of non-verbal communication of emotions (Kring & Moran, 2008). A meta-analysis of 26 studies also revealed that emotional deficits also form an integral feature of the illness. According to some theorists, patients have an innate and reduced capacity to experience hedonic emotion while their responses to adverse emotions are intensified (A. S. Cohen & Minor, 2010).

Chapter 7 focuses on fourth and the final task which engaged the participants to recognize and categorize between basic emotions such as happiness, sadness, anger,

and neutral emotion from a series of schematic faces. The aim through this task was to probe into underlying inability in patients to recognize and categorize facial emotions that could be measured using EEG. The experimental design incorporated schematic faces instead of real human faces to avoid any adverse reactions from the patients.

By combining neurophysiological tasks, cognitive tasks, CANTAB standardized cognitive tests, and emotion recognition tasks with EEG, this study enabled us to quantify a wide range of deficits that are observed in schizophrenia. We anticipate that this study protocol is a step forward towards providing a basis to a full trial, which will further provide specificity and sensitivity that has been missing from schizophrenia biomarkers to date.

CHAPTER 2. LITERATURE REVIEW

2.1 Symptomology

The definition and concept of schizophrenia has changed over the past century making it a far more complex disease to define. "Dementia Praecox" was an early 19th century Kraepelinian concept (1856-1926) that described schizophrenia as an illness of early onset and progressive deterioration focusing mainly on abnormalities in cognition and emotion (Kraepelin, 1919). Around the same time, Eugene Bleuler (1857-1939) theorised that fragmented thinking was a core feature of this disease and coined the term schizophrenia meaning 'splitting or fragmented mind' (Bleuler, 1911). He conceptualised the division of the symptoms in two major categories: fundamental symptoms (occurring only in the patients of schizophrenia) and accessory symptoms (seen across in other mental disorders too). However, he focused on 'negative symptoms' as its core feature highlighting its chronic disability and deteriorating effect on the patient. It was not until many years later that psychiatrist Kurt Schneider focused on including the psychotic symptoms such as delusions and hallucinations as core features of the disease referring to them as Schneiderian first rank symptoms, almost ignoring the negative symptoms and cognitive features of the disease (Nasrallah et al., 2011; Weinberger & Harrison, 2010).

World Health Organisation's International Classification of Disease Criteria 11th revision (ICD-11) and American Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) are extensively used to understand and diagnose mental disorders (Padmanabhan & Keshavan, 2014). In the past 50 years, DSM-I to DSM-IV and ICD-6 to ICD-10 have included Bleuler's negative symptoms, the concept of chronicity from Kraepelin and Schneiderian first rank symptoms to define schizophrenia giving emphasis to one or all three concepts in varying degrees from time to time. Since 1980's, the introduction of DSM-III greatly enhanced the reliability of diagnosis in schizophrenia by broadly classifying the symptoms into "Positive" and "Negative" symptoms. However, the current DSM-5 and ICD-11 incorporates the distinct stages of the illness eliminating many discrepancies that existed in its previous versions, and thus marking a substantial evolution in the conceptualisation of schizophrenia (Padmanabhan & Keshavan, 2014).

The first signs of schizophrenia can seem confusing or even shocking. Drastic changes in one's behaviour can be very difficult to cope for the family members who

often remember how involved and vivacious the person was before the illness began. Other subtle changes like isolation, withdrawal, unusual thoughts, speech, or behaviour tend to occur before or while other psychotic changes are being exhibited. Most patients display delusions and hallucinations. However, the degree of impairment in thought processing varies from patient to patient. Deviating from the traditional definitions of the words, "positive" symptoms are the ones that the disorder adds, and "negative" symptoms are what the disorder takes away. According to DSM-5, there is a spectrum of schizophrenia and psychotic disorders which are all specified by varying degrees of presentation of the symptoms below (American Psychiatric Association, 2013b).

2.1.1 POSITIVE SYMPTOMS

Positive symptoms are unusual experiences which are more easily identifiable. In patients with schizophrenia, they can be very intense and distressing. It is also worth noting that positive symptoms are often the ones that are diminished well with treatment (Lieber, 2018). Following is a comprehensive list of such symptoms (American Psychiatric Association, 2013b).

2.1.1.1 DELUSIONS

A fixed set of personal beliefs that is not subject to reason or cannot be altered with presentation of contradictory evidence. Delusions can take up different themes such as:

a. *Persecution*: A person with persecutory delusions may believe they are being harmed, harassed, or conspired against by an individual or an organization (Spearing, 2002).
b. *Referential*: This is where the person thinks that certain gestures or comments even environmental cues are directed towards them. A bizarre example of this could be that the person is being controlled by a neighbour with magnetic waves (Spearing, 2002).
c. *Grandiose*: This would include a feeling that one has exceptional abilities, wealth or is an important figure or a celebrity.

2.1.1.2 HALLUCINATIONS

An experience of perception without the presence of an external stimuli. These perceptions are vivid and not under voluntary control. Though in patients with schizophrenia they can occur in any sensory form, auditory hallucinations are the most common. These "voices" can either be familiar or unfamiliar and are perceived as different from one's thoughts. They can describe what the person is doing, warn them of an impending disaster, or pass derogatory comments. A patient is most likely to experience hallucination of certain kind during their first psychotic episode during which it is estimated that 50% of the patient population might experience an auditory hallucination, while a very low percentage of patients may have a visual (15%) and tactile hallucinations (5%) (Arango & Carpenter, 2010).

2.1.1.3 DISORGANIZED THINKING OR SPEECH

An effect on the person's ability to "think straight". Individuals might have unrelated thoughts coming to them in rapid successions, making them jump from one topic to another. They might answer questions with completely unrelated/tangential answers. The patient is therefore ineffective in communicating. In some cases, the disorder is so severe that speech becomes incomprehensible. This symptom, also known as, *formal thought disorder* is often inferred from the person's speech. It is especially difficult to diagnose when the person is from a different linguistic background.

2.1.1.4 GROSSLY DISORGANIZED OR CATATONIC BEHAVIOUR

Agitated body movements or childlike "silliness". Patients may have difficulty performing goal directed motor behaviour thus making it challenging to perform daily living activity. Catatonic behaviour is a severe decrease in reacting to the environment. Patients may sit still for hours or assume a rigid posture with a complete absence of response to verbal or motor responses. It can also include the opposite where the person displays excessive movements for no apparent reason.

2.1.2 NEGATIVE SYMPTOMS

Negative symptoms account for a considerable portion of morbidity associated with schizophrenia than in any other psychotic disorders. Several of these can be

interpreted as person's laziness (Timms, 2015). This can especially make the patients and their family's lives even more difficult. These symptoms also respond poorly to medication and therefore, even though they are less dramatic, they can be more disabling (American Psychiatric Association, 2013b). These symptoms are present much before the onset of positive symptoms and exist through the outbreak of the psychotic episodes but are masked by the positive symptoms. These negative symptoms continue to persist in varying degrees despite the reduction in positive symptoms (Arango & Carpenter, 2010).

a. *Diminished Emotional Expression:* A demonstration of "blunt" or "flat" affect. This includes a reduction in expressiveness of the face, lack of eye contact and reduces hand and head movement. Patients may also speak in a monotonous voice.
b. *Avolition:* Lack of motivation to start a purposeful activity manifesting as person sitting for long periods of time and being disinterested in work or social activity.
c. *Alogia:* A diminished speech output
d. *Anhedonia:* Curbed ability to experience enjoyment in life or remember experiencing pleasure previously.
e. *Asociality:* Lack of interest in social interaction.

2.1.3 COGNITIVE DEFICITS

Patients with schizophrenia tend to experience several cognitive deficits much before the onset of any kind of symptomology. These deficits further diminish their quality of life. In some patients they can be subtle while being severe in others. These can include:

a. Poor "executive function", that is the ability to understand and use information in decision-making process.
b. Trouble focusing or paying attention
c. Problems with working memory and remembering things
d. *Anosognosia* or "lack of insight". This is the unawareness of the patient that he or she has schizophrenia.

2.2 Schizophrenia Spectrum and Other Psychotic Disorders

Prior to DSM-5, schizophrenia was categorised into distinct subtypes namely paranoid, disorganised, catatonic, simple, and undifferentiated. However, this categorisation was not reliable to cover the vast heterogeneity of the disease and has been found to have low validity (Mattila et al., 2015). Hence, the current DSM-5 and ICD-11 have eliminated these subtypes to improve the clinical definition of schizophrenia (Padmanabhan & Keshavan, 2014). Even in a number of Asian countries, many patients feel stigmatised being referred to as a patient of "schizophrenia" as the term does not describe what their disease accurately represents. This has led to elimination of the classification of the disease schizophrenia in these countries. For instance, in Japan the disease has been reclassified as "integration disorder" and similarly in Korea, the term "attunement disorder" is used (Balter, 2017; J. W. Cho et al., 2018; Lasalvia et al., 2015; Y. S. Lee et al., 2014; Sartorius et al., 2014; Yamaguchi et al., 2017).

Under the schizophrenia spectrum of disorders, the DSM-5 and ICD-11 list few specific clinical diagnoses based on how the previously described symptoms manifest in its patients. DSM-5 and ICD-11 in their current status share significant similarity between the names and diagnostic criteria of various clinical diagnoses than what was found between previous versions. However, there are still some differences between the two (First et al., 2021). Table 2.1 provides a high-level outline and comparison of diagnostic criteria between DSM-5 and ICD-11 mainly for the schizophrenia spectrum of disorders. The patients recruited in this study were previously diagnosed with either schizophrenia or schizoaffective disorders. The table also includes two bipolar disorders as one of the schizoaffective disorder patients was also categorised to likely have bipolar spectrum disorder (BSD). The first column of the table has the closest matching diagnoses between DSM-5 and ICD-11 followed by the diagnostic criteria for each. All the details in table were taken directly from the DSM-5 manual (American Psychiatric Association, 2013a), ICD-11 website (World Health Organization (WHO), 2022), and two other articles related to them (First et al., 2021; Substance Abuse and Mental Health Services Administration, 2016).

Table 2.1 Comparison of diagnostic criteria of mental disorders between DSM-5 and ICD-11

Closest Matching Clinical Diagnoses	DSM-5 Criteria	ICD-11 Criteria
DSM-5: *Schizophrenia* ICD-11: *Schizophrenia*	Continuous signs of at least one of the following present for at least 6 months: - delusions - hallucinations - disorganized speech with following present for significant portion of 1 month period: - catatonic behaviour and/or - negative symptoms	At least two of following symptoms present most of the time for 1 month or more: - persistent delusions - persistent hallucinations - disorganized thinking - experiences of influence - negative symptoms - grossly disorganized behaviour - psychomotor disturbances
DSM-5: *Schizophreniform disorder* ICD-11: *Not included*	Same as schizophrenia but lasting 1-6 months	Not Applicable
DSM-5: *Schizoaffective disorder* ICD-11: *Schizoaffective disorder*	Same as schizophrenia along with a major depressive or manic mood episode	Meeting diagnostic requirements of schizophrenia with moderate or severe depressive and/or manic episode
DSM-5: *Delusional disorder* ICD-11: *Delusional disorder*	Presence of delusions for at least 1 month but never meeting the other necessary criteria for schizophrenia.	Presence of delusions for at least 3 months and often longer with absence of other symptoms of schizophrenia
DSM-5: *Brief psychotic disorder* ICD-11: *Acute and Transient Psychotic Disorder*	Sudden (within 2 weeks) onset of at least one of: - delusions, - hallucinations, - disorganized speech and a return to previous level of functioning in less than 1 month.	Acute onset of psychotic symptoms including: - delusions, - hallucinations, disorganized thinking, - experiences of influence within 2 weeks with rapid change in nature and intensity and lasting up to 3 months

DSM-5: *Schizotypal disorder* ICD-11: *Schizotypal disorder*	Pattern of social and interpersonal deficits that do not occur during course of schizophrenia. Symptoms include: - odd beliefs - unusual perceptual experiences - eccentric behaviour - suspicious or paranoid ideation	Pattern of unusual speech, perceptions, beliefs that do not meet intensity or duration of schizophrenia, schizoaffective disorder, or delusional disorder. Symptoms include: - unusual beliefs - unusual perceptual distortions - eccentric behaviour - suspicious or paranoid ideation
DSM-5: *Psychotic Disorder due to another medical condition* ICD-11: *Secondary Psychotic Syndrome*	- prominent hallucinations or delusions - direct consequence of another medical condition - not better explained by another mental disorder	- prominent hallucinations and/or delusions - direct consequence of another medical condition - not better accounted by another mental disorder
DSM-5: *Bipolar I Disorder* ICD-11: *Bipolar Type I Disorder*	- at least one manic episode which may be preceded or followed by hypomanic or major depressive episodes - manic or major depressive episodes not better explained by schizophrenia spectrum of disorders	- at least one manic or mixed episode - typically recurrent depressive and manic or mixed episodes - some episodes may be hypomanic but at least one manic or mixed episode is must
DSM-5: *Bipolar II Disorder* ICD-11: *Bipolar Type II Disorder*	- at least one hypomanic episode and at least one major depressive episodes - manic episode has never occurred - episodes not better explained by schizophrenia spectrum of disorders	- at least one hypomanic episode and at least one depressive episode - typically recurrent depressive and hypomanic episodes - no history of manic or mixed episodes

A simplified schematic representation of schizophrenia progression is shown in figure 2.1 reproduced from (Yasui-Furukori, 2012). It is now recognized that schizophrenia is a disease that slowly manifests itself from infancy and continues through the lifetime of an individual (Nasrallah et al., 2011). The premorbid phase, where in one begins to experience a generic dysfunction in cognition, motor function and social interactions is observed in early childhood. This is followed by a 'prodromal' phase in the young adults (early to mid-teen years) where they begin to isolate themselves from others with a rise in certain positive and negative symptoms (Marder & Cannon, 2019; Nasrallah et al., 2011; Padmanabhan & Keshavan, 2014). A decline in their cognitive ability and functionality can also be observed during this phase. The first episode of psychosis (e.g. auditory hallucinations, delusions etc.) marks the onset of the disease. A patient may experience varying periods and instances of psychosis in their early course of illness. However, most of the patients tend to have a more stable 'plateau phase' usually represented by less pronounced psychotic symptoms. A varying degree of severity of the negative and cognitive deficits can also be observed in their lifetime depending upon how the symptom severity were managed and treated. All these symptoms significantly attenuate the quality of life by diminishing social functioning in the patients (Padmanabhan & Keshavan, 2014).

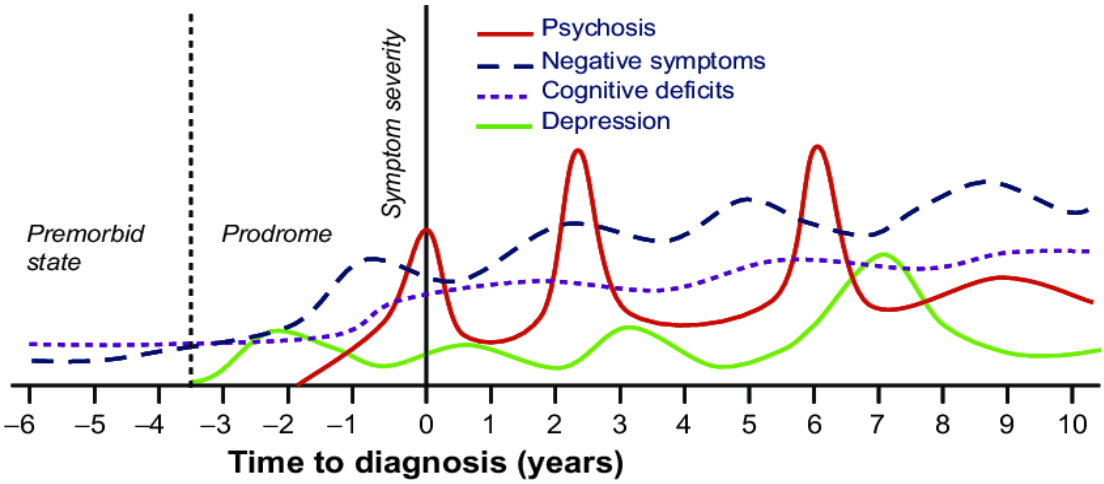


Figure 2.1 A schematic representation of schizophrenia progression. Reproduced from Yasui-Furukori, 2012.

2.3 Etiology

With a steady prevalence of 1% worldwide, schizophrenia is now ranked among the world's top ten causes of long-term disability. In recent years, schizophrenia has been shown to be highly heritable disease with genetic factors contributing 80-85% (Birnbaum & Weinberger, 2017; Janoutová et al., 2016; Marder & Cannon, 2019; M. J. Owen et al., 2016; Tandon et al., 2008). Earlier it was believed that the disease affected both males and females equally across the globe however, more recent meta-analysis show that males are at 1.4 times the risk of developing schizophrenia compared to females (Aleman et al., 2003; J. E. McGrath & Tschan, 2004; Tandon et al., 2008). Also, in males, the onset is generally early (between 17-25 years) and later in the female populations (20-30 years) (Nasrallah et al., 2011).

In a recent genome-wide association study (GWAS) on schizophrenia recruiting 37,000 schizophrenia patients in comparison to 113,000 healthy controls found 108 genes that were linked to the disease making it a polygenic disorder. Some variants of these genes were found to be correlated to signalling pathways of neurotransmitters and a few others were involved with the immune system (Birnbaum & Weinberger, 2017; Ripke et al., 2014; Stilo & Murray, 2019). Although, genetic predisposition may increase the risk of an individual developing schizophrenia, interaction with adverse environmental and social factors makes them more susceptible to it (Balter, 2017; Löhrs & Hasan, 2019; Misiak et al., 2018; Nimgaonkar et al., 2017; Stilo & Murray, 2019). These environmental factors may include childhood trauma, social adversity, cannabis use during adolescence, discrimination, etc (Löhrs & Hasan, 2019; Marder & Cannon, 2019; Nasrallah et al., 2011; Nimgaonkar et al., 2017; M. J. Owen et al., 2016; Patel et al., 2014; Stilo & Murray, 2019; Tsuang, 2000).

2.4 Pathophysiology

The pathophysiology of schizophrenia, like the manifestation of disease itself, is complex and not very well understood. There have been several theories relating to abnormalities within various neurotransmitter systems including dopamine (Howes et al., 2017; Howes & Kapur, 2009; Maia & Frank, 2017; McCutcheon et al., 2019), glutamate (Egerton et al., 2020; Goff & Coyle, 2001; Olney & Farber, 1995; Uno & Coyle, 2019), and serotonin (Aghajanian & Marek, 2000; Eggers, 2013; Patel et al.,

2014; Stahl, 2018). These are a result of genetic factors and their interplay with environmental conditions as mentioned above.

The most popular theory is related to a dysfunction in dopamine receptors and dopaminergic pathways. Though this largely explains the positive symptoms like hallucinations and delusion, it does not account for the myriad of deficits observed in schizophrenia (Egerton et al., 2020; M. J. Owen et al., 2016; Uno & Coyle, 2019). The negative and cognitive symptoms of schizophrenia are likely a result of abnormality in glutamate, the primary excitatory neurotransmitter, and its binding with the N-methyl-D-aspartate (NMDA) (Egerton et al., 2020; Uno & Coyle, 2019). The inter-neurons in the cerebral cortex and hippocampus which are sensitive to NMDA receptors produce gamma oscillations necessary for cognitive functioning (M. J. Owen et al., 2016; Uno & Coyle, 2019). Also, presence of NMDA antagonists has been shown to produce schizophrenia like negative and cognitive symptoms (Uno & Coyle, 2019). The finding that hallucinogens like Lysergic acid diethylamide (LSD) heightened the effect of serotonin led researchers to hypothesize the involvement of serotonin in schizophrenia (Aghajanian & Marek, 2000). Further evidence of medications that block both dopamine and serotonin receptors, improved both positive and negative symptoms in the patients, thus strengthening the serotonin hypothesis (Kantrowitz, 2020; Meltzer et al., 2003; Patel et al., 2014).

Physical changes in the brain have also been observed in schizophrenia. A decreased neuronal size (Arnold et al., 1995; Chana et al., 2003; Harrison, 2000; Roeske et al., 2021) along with some evidence of increased neuronal density has been observed (Chana et al., 2003; Harrison, 2000). The GABAergic inter-neurons also exhibit decreased functionality (Nakazawa et al., 2012; Nasrallah et al., 2011). An abnormality in the functioning of glial cells (responsible for neuronal maintenance and myelin sheath creation) is also observed in schizophrenia (Bernstein et al., 2015; Dietz et al., 2020; L. E. Duncan et al., 2014; Laskaris et al., 2016; M. J. Owen et al., 2016). Along with these, imaging modalities have reported reduced grey matter volumes notably in prefrontal and temporal cortices (DeLisi et al., 2006; Dietsche et al., 2017; Olabi et al., 2011) and decrease in frontal, parietal, and temporal white matter (DeLisi et al., 2006; Olabi et al., 2011). There has also been compelling evidence of

enlargement of lateral ventricles and frontal, parietal, and temporal white matter (DeLisi et al., 2006; Olabi et al., 2011; Svancer & Spaniel, 2021).

2.5 Diagnosis and Treatment in Schizophrenia

Despite decades of extensive research, the pathophysiology and etiology of the disease remain obscure. The absence of a single diagnostic feature for this disease and its highly heterogeneous nature, makes early recognition and intervention one of the biggest challenges in the field (Harris et al., 2013). Currently, the clinical diagnosis is made based on patient's history and their state of mental well-being. The 'prodromal' phase, also known as an ultra-high-risk phase, of schizophrenia can last for several years before the first psychotic episode. This commonly occurs in young adults who can experience negative symptoms and declined cognitive ability. In some cases, however, sudden onset has also been observed in previously healthy individuals (Nasrallah et al., 2011; M. J. Owen et al., 2016).

As has been mentioned earlier, the DSM-5 and ICD-11 have outlined complex diagnostic criteria to be used by physicians. However, it can be observed that even within the schizophrenia spectrum of diseases there are several possible diagnoses with subtle differences between them. There are several scales of assessment which use structured clinical interviews to evaluate disturbances in their thought processing, language, attention, and perception. These include Global assessment of Functioning Scale (GAF), Scale of Assessment of Negative (SANS) (Andreasen, 1989) or Positive (SAPS) symptoms (Andreasen, 1984), Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), etc. Each scale assigns a point rating to the individual to determine the severity of a subset of symptoms or the overall disease state. Each of these scales have their drawbacks. The GAF scale was included in the DSM-III and DSM-IV but dropped from DSM-5 due to lack of clarity and inter-rater reliability, which focuses on variability among raters on the same target (Grootenboer et al., 2012; Substance Abuse and Mental Health Services Administration, 2016). The SAPS and SANS scale has been shown to have poor inter-rater reliability (Norman et al., 1996) and have been criticized for dividing the symptoms of schizophrenia as only positive and negative (Kumari et al., 2017). The SANS scale has also been shown to have low test-retest reliability (Kring et al., 2013). The PANNS scale has been shown to have hidden internal structures (Lefort-Besnard et al., 2018) that could be better represented

as a five-factor model (Lim et al., 2021; Wallwork et al., 2012) instead to the three subscales proposed by Kay et al. Also like the SANS scale, the negative subscale of PANSS has shown low test-retest reliability (Kring et al., 2013). Despite these shortcomings, physicians heavily rely upon the results of these interviews to diagnose an individual instead of objective measurements of neural activity (H. S. Lee & Kim, 2022). It should be noted however, that the presence of several pathophysiological abnormalities outlined in previous section do not qualify as a definitive diagnostic marker (Nasrallah et al., 2011). Currently, there are no objective clinical tests or biomarkers used for diagnosis (M. J. Owen et al., 2016) in a clinical setting.

The first ever pharmacological treatment for psychotic symptoms, chlorpromazine, was serendipitously discovered in 1952. It marked the beginning of first generation or typical antipsychotic medications. These medications are effective in mitigating positive symptoms like hallucinations and delusions but are usually ineffective in treating the more chronic symptoms such as cognitive deficits and social withdrawal. They are also accompanied with a deluge of side effects like exacerbated negative symptoms, movement disorders, weight gain, restlessness etc (Marder & Cannon, 2019; Nasrallah et al., 2011; M. J. Owen et al., 2016; Patel et al., 2014). Several of these side effects are a consequence of excessive dopamine blockade (Marder & Cannon, 2019). The second generation or atypical medications work by blocking both dopamine and serotonin receptors (M. J. Owen et al., 2016) and were first discovered in 1990s. These medications have been observed to have fewer Parkinsonian type movement related side effects, however, carry a higher risk of cardiometabolic side effects. The strongest of this atypical medication is clozapine. However, it is prescribed only in the cases when other atypical antipsychotics prove ineffective. This is due to the additional risk of agranulocytosis and neutropenia (white blood cell disorders) observed with the administration of clozapine (M. J. Owen et al., 2016). There has been an effort to shift towards glutamate modulating antipsychotic treatments as this might be helpful is mitigating a broader range of deficits including negative and cognitive. These treatments would work by enhancing the activity of NMDA by increasing glycine levels near glutamate receptor site. However, these strategies have not been approved anywhere yet (Nasrallah et al., 2011).

The use of antipsychotics is crucial and primary approach of treatment for schizophrenia. However, in many developed countries it is also accompanied with psychotherapeutic treatments at individual and family or group level. Due to the side effects, paranoia, grandiosity, etc. patients are less likely to stay adherent to the medication. This increases the risk of relapse and psychotic episodes. Access to psychotherapy can greatly reduce the chance of non-adherence by keeping patients informed on their illness and importance of taking medication (Patel et al., 2014). In the UK, the National Institute of Health and Care Excellence (NICE) guidelines (NICE, 2016) require patients to be offered with cognitive behavioural therapy (CBT) to help them alter their behaviour that might be disease induced (M. J. Owen et al., 2016). In addition, psychotherapeutic approaches also encourage the patient's family to be involved. This has been seen to improve patient's social wellbeing and reduce the risk of rehospitalization (Marder & Cannon, 2019; M. J. Owen et al., 2016; Patel et al., 2014).

2.6 Electrophysiology

Electroencephalography (EEG) is the method of recording electrical activity of the brain using electrodes placed on the scalp. The signals recorded using such electrodes represent the synchronous activity from a large ensemble of neurons that are aligned in their spatial orientation. Being a non-invasive technique, EEG signals have been extensively used in studying the physiological response of the brain while performing a cognitive task. However, EEG signals show a high degree of variability between trials with same trial parameters. To mitigate this variability and study the EEG task response, researchers have used the Event-Related Potentials (ERPs) technique.

ERPs are the various positive or negative fluctuations that result from averaging large repeats of time-locked EEG activity. The EEG activity is obtained by exposing the subjects to the same stimulus for tens, or even hundreds of trials. This activity is then time-locked to either the stimulus or response to create short epochs that are averaged in time relative to the time of the event. The process of averaging reduces the signal variability across trials that might arise from surrounding noise or normal functioning of the brain and by doing so, it reveals the components of brain activity that correspond to the sensory and cognitive processes representative of the event or

task. These components are otherwise embedded in inherently noisy EEG signals from single trials (Roach & Mathalon, 2008). It is to be noted that ERP response still shows intra-subject variability when multiple repeated experiments are performed. This variability has been speculated to be caused due to state of the subject, for instance the hours of sleep, caffeine intake etc. As can be expected, ERP signals also show inter-subject variability (higher than intra-subject) which could result from differences in individual brain structure and processes (Luck, 2014c). For these reasons, researchers present grand averaged ERP results from a group of subjects as opposed to results from individual subjects in most cases. These averages provide an insight into the population response which can then be compared between different groups.

Patients diagnosed within the schizophrenia spectrum of disorders have shown deficits in their EEG response under different types of experimental conditions. In an auditory oddball task, a pre-attentive, involuntary, auditory mismatch negativity (MMN) response is observed on fronto-central electrodes in healthy subjects. The MMN response in schizophrenia spectrum patients is diminished (Light & Braff, 2005). If the subjects are instructed to attend to the stimuli, a deficit in P300 responses is also observed in schizophrenia patients when compared to healthy subjects (Light et al., 2015). In a Stroop task, which is used to test the cognitive and working memory deficits, schizophrenia patients have been previously shown to have comparable response of the congruent and incongruent trials, which is not the case with healthy subjects (Kim et al., 2012; Markela-Lerenc et al., 2009). In schizophrenia patients, difficulties in recognizing and categorizing facial emotions are also observed. This deficit is reflected in the early face-processing component (Earls et al., 2016) as well as later cognitive processing components of EEG response (McCleery et al., 2015). While each of these deficits have been observed in schizophrenia patients in separate studies, there is a lack of published research there has attempted to study all these electrophysiological deficits in the same patient group. This is one of the primary research goals of this thesis. The associated literature on each type of deficit in reviewed in detail in the respective chapters of the thesis.

2.7 Biomarker

In clinical research, a “biological marker” or a biomarker is a term designated to an objective measure of medical state observed from outside. This measure should also

be reliably reproducible to be categorised as a biomarker. There is a distinction between an objective measure of state and the symptom as later is subjective experience of an individual. A biomarker may either be a functional or physiological measure that is a predictor of the disease state (Strimbu & Tavel, 2010).

In the context of schizophrenia spectrum of disorders, this chapter has described several functional and physiological measurements that can be objectively recorded from patients. This includes the various neurotransmitter and pathway abnormalities, grey and white matter volume reductions, etc. However, as has been mentioned earlier, none of these measurements are reliable predictors of the disease states. Also, changes in pathways or brain volume are single snapshot of the state that cannot be easily obtained from the patients. For example, measurement of grey matter volume can be determined using an MRI which would require patients suffering from paranoia and anxiety issues to be isolated for prolonged periods in the challenging environment of a scanner. Using EEG as the neuroimaging modality, on other hand, is relatively affordable (both in deployment and maintenance) , portable, and requires less expertise to operate (Barros et al., 2021; M. X. Cohen, 2014; Farnsworth, 2019; Ledwidge et al., 2018; H. S. Lee & Kim, 2022) in a research laboratory or clinical setting. It also has an added advantage of high time resolution in measuring a response to stimuli.

In this thesis, multiple experiments were conducted with the same set of patients spanning neurophysiological, cognitive, and social aspects of the deficits observed in the schizophrenia spectrum. EEG recordings from these experiments to extract several neurophysiological measurements that define the state of each subject. These along with a set of behavioural response measures can be used to create an objective representation of an individual's disease state and could be potential new candidates for diagnostic biomarkers. These biomarkers can further be prospectively used to distinguish each subject from one another during diagnosis.

CHAPTER 3. METHODOLOGY

3.1 Study design

This was a pilot pathway study approved by the West of Scotland Research Ethics Service (REC reference: 15/WS/0083, REC approval date: 01 June 2015, IRAS project ID: 103549, see Appendix A). The research team consisted of the Chief Investigator (CI) for the study - Professor Robert Hunter, Consultant Psychiatrist Clinical Director PsyRING at University of Glasgow/Associate Director R&D NHS Greater Glasgow and Clyde, the Research Student (RS) Sibani Priyadarshini Mohanty from the Neurophysiology lab of Biomedical Engineering Department, University of Strathclyde, and two senior Research Nurses (RN) Catherine Deith and Paul Scouller from Glasgow Clinical Research Facility. This research was jointly funded by EPSRC and NHS Endowments Department and Patient Affairs Department, Gartnavel Royal Hospital, Glasgow.

3.1.1 STUDY POPULATION

In this study two groups of individuals were recruited, one that consisted of a healthy control group (n=19 healthy subjects) and the other that comprised of schizophrenia spectrum patients (n=6). All the patients who were recruited in the study satisfied the DSM-5 (American Psychiatric Association, 2013a) criteria for schizophrenia spectrum disorders and were on stable medication for a period of a month before they participated in the study.

3.1.2 INCLUSION AND EXCLUSION CRITERIA

The control group consisted of healthy volunteers with the below listed inclusion and exclusion criteria:

Control group inclusion criteria:

- Both male and female (non-pregnant), age group 18-55 years
- Normal hearing
- Normal or corrected vision
- Normal Upper limb function
- English as their first language

Control group exclusion criteria:

- Any evidence of existing mental, psychiatric or neurological conditions either in the subject or their first degree relatives
- Any evidence of neurophysiological damage
- Any implantable devices that might interfere with the EEG equipment colour blindness
- Any history of drug/alcohol abuse
- Use of medication that might interfere with normal neurophysiological processes

All participants in the control group were asked to fill out a screening questionnaire to determine if they met the inclusion criteria as mentioned above, and care was taken to exclude anyone who did not satisfy them or fell under any of the above-mentioned exclusion criteria.

The patient group consisted of participants that satisfied the DSM-5 criteria for schizophrenia spectrum of disorders. Further inclusion and exclusion criteria listed below were used.

Patient group inclusion criteria:

- DSM-5 criteria for schizophrenia
- Written informed consent
- Male or female (non-pregnant) age group 18-65 years
- Patients on atypical antipsychotic medication without any change in medication over a period of one month before the test sessions
- Normal hearing
- Normal or corrected vision
- Normal upper limb function
- English as their first language

Patient group exclusion criteria:

- Any other neurological disorder or significant medical condition, apart from schizophrenia
- Any implantable device

- Hearing deficits
- Vision deficits such as colour blindness
- Motor deficits
- Pregnant woman
- Patients who cannot communicate in English

We were able to recruit 6 male patients within the study time frame.

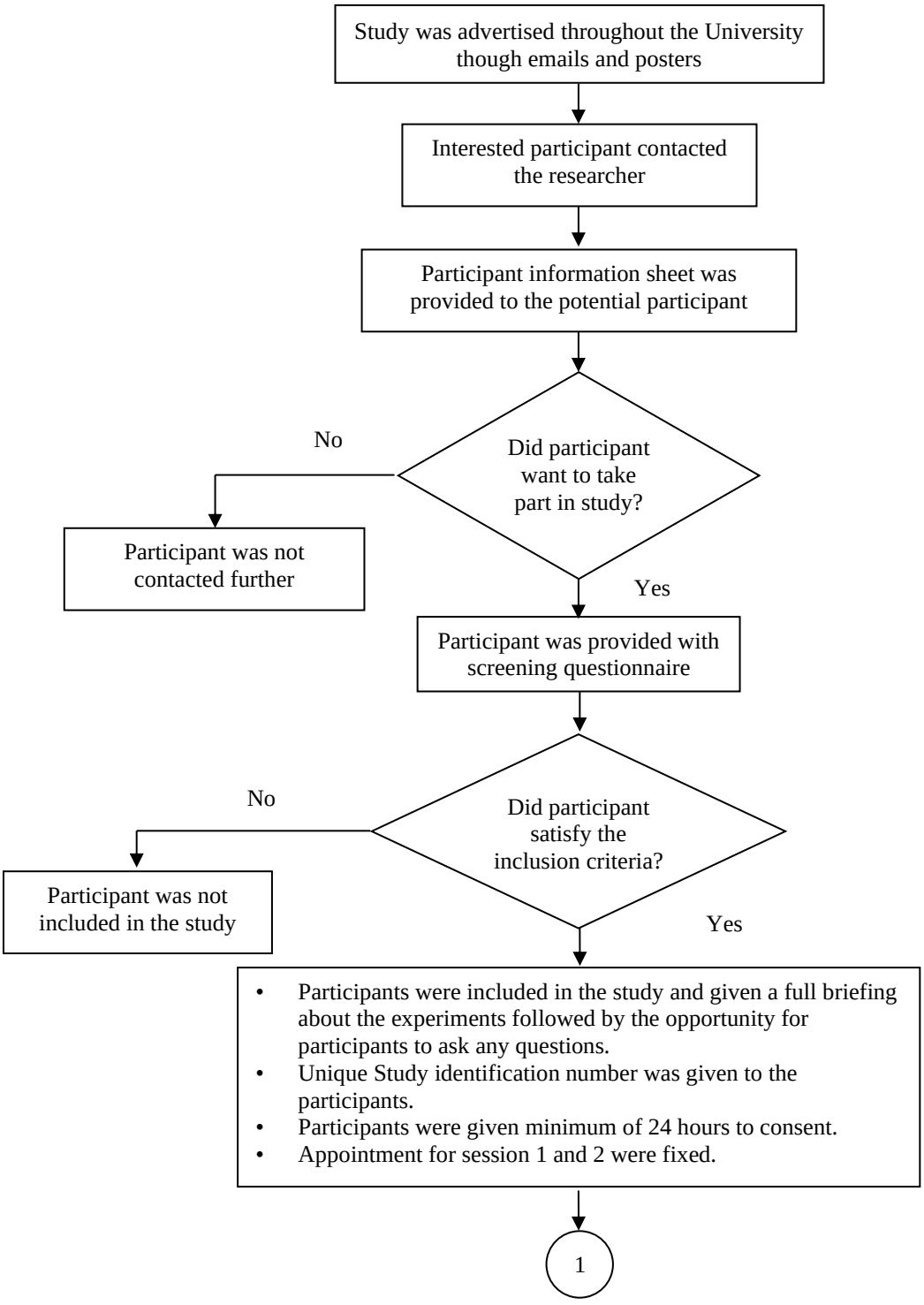
3.1.3 IDENTIFICATION OF PARTICIPANTS AND CONSENT

The RS recruited the control group participants by advertising the study among the staff and students of the University of Strathclyde. Before the study began, each control group participant was provided with a brief information regarding the study along with a screening questionnaire. This questionnaire was based on the inclusion/exclusion criteria of the study listed in section 3.1.2. If they met all the criteria, the participants were recruited to the study and given their study identification number. Participants were then provided with the information sheet 24 hours before the study. These participants are referred to as healthy control group/subjects or simply, control group/subjects in the rest of the thesis. Both, the screening and medical questionnaire are added in Appendix B.

The study was conducted over two sessions of testing for both control subjects and patients. Control participants were asked to fill out a short medical questionnaire on the day of their first session. The sessions for control participants were scheduled for 2 hours per session and they were assured that no clinical judgement was to be made based on any results obtained from the study. Participants were encouraged to ask any additional questions regarding any of the experiments during both the sessions. A few curious participants were also provided with the results of their CANTAB test, which gave them a normalized rating of their performance for certain tests relative to the general population. A study flow chart summarising the process of identification and recruitment of control subjects is shown in figure 3.1.

For the patient group, potential participants were identified by CI or RN in consultation with clinicians within the network of Community Mental Health Team (CMHT), Riverside, Riverview, Partick and Dumbarton areas of Glasgow and from Kelvin House, Gartnavel Royal Hospital, Glasgow. Once the patients were identified,

the study was briefly explained to each patient and a minimum of 24 hours was provided to consider the study and give their consent. The patients who satisfied the inclusion criteria were then approached by the research nurse in the presence of the clinician to discuss the study. Further, based on their interest in the study, written consent was obtained after all their queries and concerns with respect to the study had



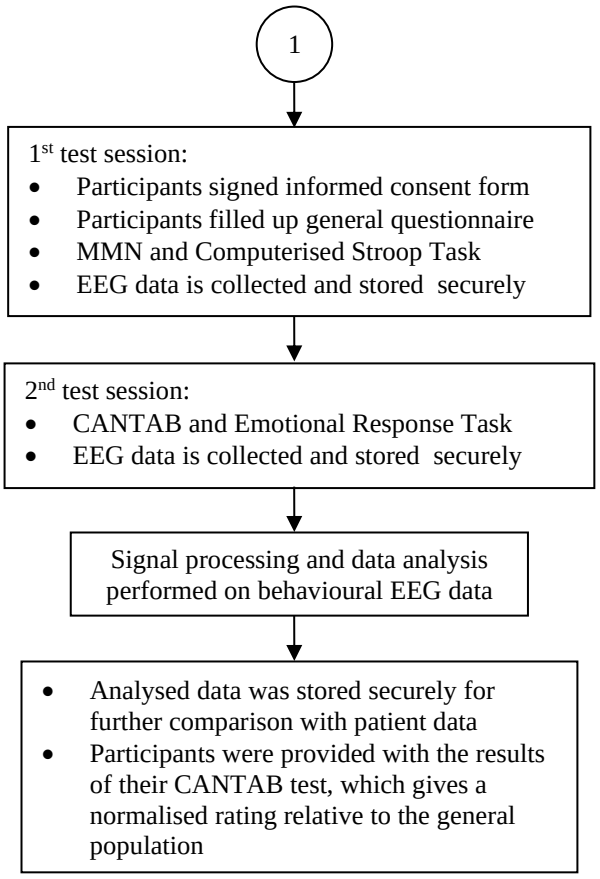
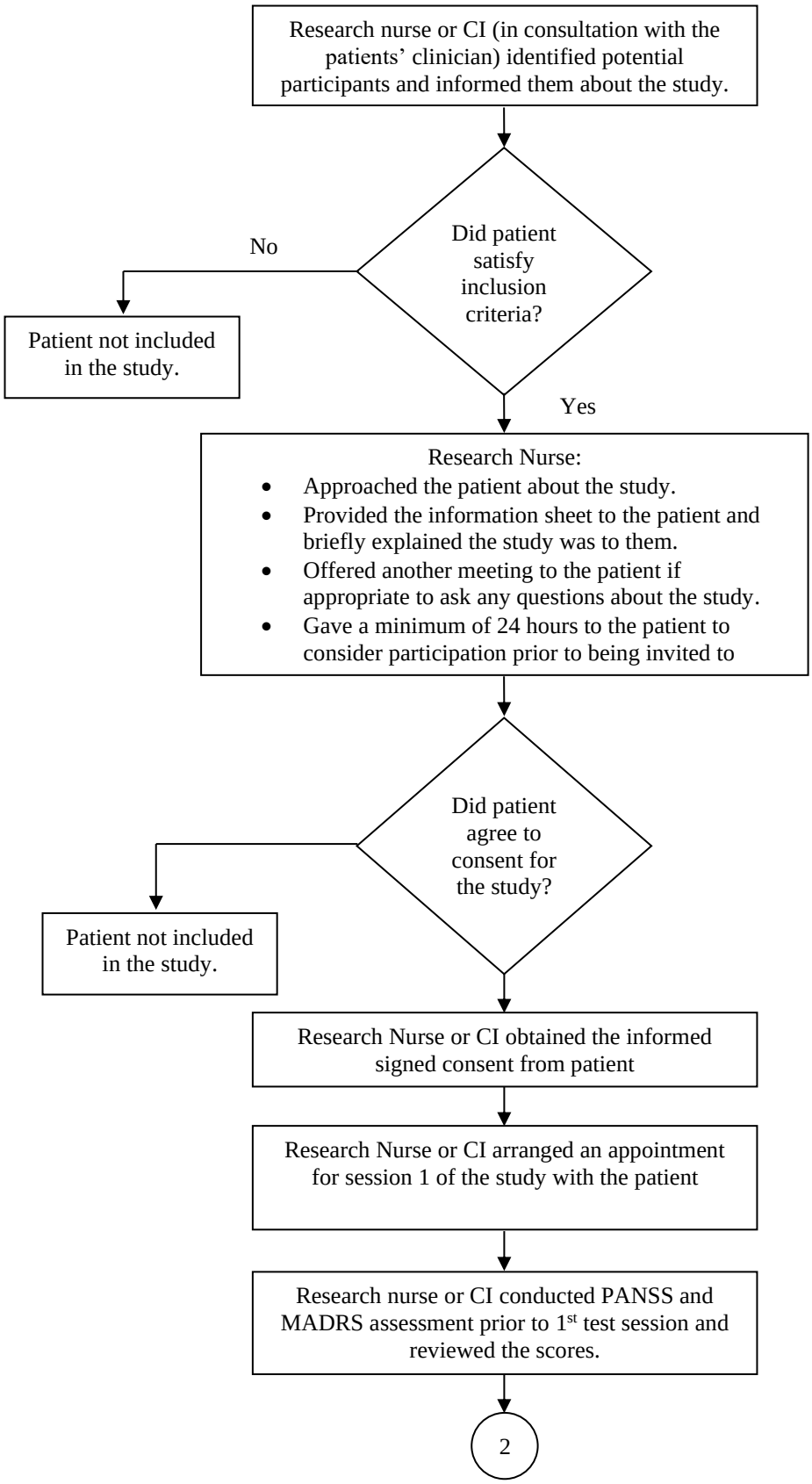


Figure 3.1 Study flow chart for healthy control group.

been appropriately answered. A study flow chart summarising the process of identification and recruitment of patients is shown in figure 3.2.


Research nurse or CI (in consultation with the patients' clinician) identified potential participants and informed them about the study.
Did patient satisfy inclusion criteria?
No
Patient not included in the study.
Yes
Research Nurse:
Approached the patient about the study.
Provided the information sheet to the patient and briefly explained the study was to them.
Offered another meeting to the patient if appropriate to ask any questions about the study.
Gave a minimum of 24 hours to the patient to consider participation prior to being invited to
Did patient agree to consent for the study?
Patient not included in the study.
Research Nurse or CI obtained the informed signed consent from patient
Research Nurse or CI arranged an appointment for session 1 of the study with the patient
Research nurse or CI conducted PANSS and MADRS assessment prior to 1st test session and reviewed the scores.
2

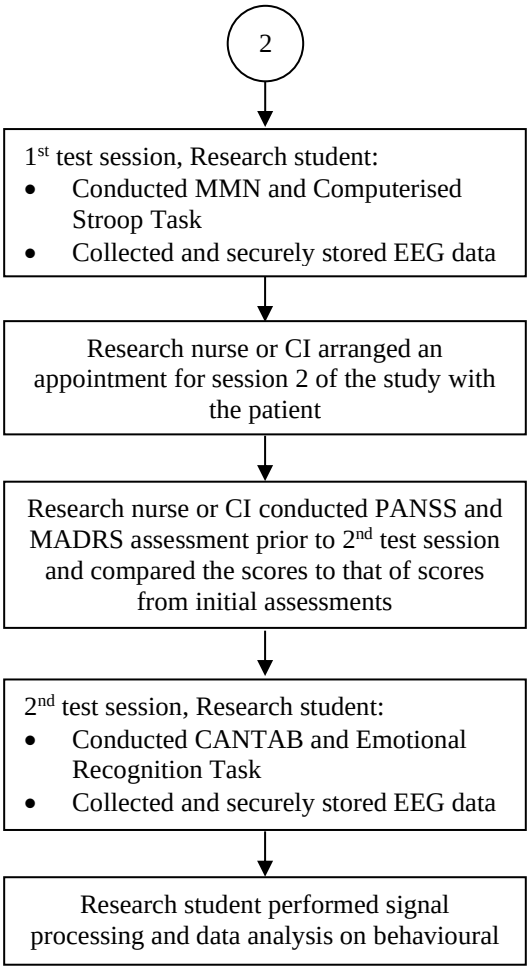


Figure 3.2 Study flow chart for patient group.

3.1.4 STUDY SCHEDULE

The study was divided in two sessions of experiments for both the healthy control and the patient groups. The experiments for the healthy controls were conducted RS at the Neurophysiology lab of Biomedical Engineering Department, University of Strathclyde. The data from patients was collected at Kelvin House, Gartnavel Royal Hospital, Glasgow. While conducting experiments with patients, the RS worked with CI and RN. The various procedures administered to the patients, the average time taken, and the personnel administering them are shown the table 3.1. The experimental sessions were scheduled after a consent was obtained from the participants. The sessions were designed to carry out a specific set of experiments and were kept consistent across subjects from both the groups. The study data collected from both the healthy controls and patients were analysed by the RS.

Table 3.1 Procedures administered to patients

Procedure	Number of Times Administered	Average Time per Administration	Administered by*
Interview with potential participants to provide information and request their consent to participate	1	30 mins	CI or RN
Psychiatric Interview: Positive and Negative Symptom Scale (PANSS) for Schizophrenia	2	30 mins	CI or RN
Psychiatric Interview: Montgomery Åsberg Depression Rating Scale (MADRS) for depression	2	30 mins	CI or RN
Session 1 experiments: MMN and Stroop task	1	60 mins	CI or RN with RS
Session 2 experiments: CANTAB, Emotion Recognition task	1	60 mins	CI or RN with RS

*CI: Chief Investigator, RN: Research Nurse, RS: Research Student

Session 1 consisted of two experiments, the Mismatch Negativity (MMN) experiment with the auditory oddball task, and the computerized Stroop task. Both these experiments required the use of EEG recordings. Session 2 also consisted of 2 experiments, the CANTAB test, and the Emotion Recognition (ER) task. As previously mentioned, for control subjects, session 1 began with a medical questionnaire before the experiments were carried out. For patients, both the sessions began with the assessments of their symptom severity using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and level of depression using the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) by the clinical research nurse. PANSS consisted of three sub-scales namely, Positive (PANSSP), Negative (PANSSN), and General Psychopathology (PANSSG). The PANSSP subscale assigns a total score between 7 and 49 and scores the severity of the patient's positive symptoms such as, hallucinations, delusion, etc. The PANSSN scale scores the patient's negative symptoms like social/emotional withdrawal, blunted affect, etc. This scale ranges from 7 to 49 as well. The PANSSG scale rates the patient based on measures like depression, anxiety, tension, etc and has a minimum and maximum score of 16 and 112, respectively. MADRS has a minimum score of 0 and maximum score of 60 depending on the severity of depression in the patient. Higher scores in both PANSS and MADRS imply increased psychopathology. All the questionnaires related to the healthy controls and patients are provided in Appendix B, along with the scoring criteria for PANSS and MADRS are provided in Appendix C.

Subjects were given appropriate breaks during the sessions that were accounted into the schedule beforehand. Special care was taken with patients by the clinical staff accessible during the sessions when needed.

3.1.5 PARTICIPANT DEMOGRAPHIC DATA

Demographic details of all the control subjects and patients are provided in tables 3.2 and 3.3, respectively. Table 3.2 shows the data collected from the healthy control subjects along with the experiments and analysis each subject was included in. Subjects were excluded from a certain experiment if the data was found to be corrupted due to any unforeseen technical problems with recording of the data and/or its storage. Those control subjects included in any experiment are represented with a 'Y' and those excluded with a 'N'. The specific details are provided in appropriate chapters for each

experiment. The last row in the table 3.2 shows the statistics from each column. These are the mean and standard deviations for age, gender distribution of participants (M for male, F for Female), and the total number of control subjects included in each experiment or type of data. In table 3.3 the patient codes (P1 to P6) were assigned by the date of their first session. The table shows the age, clinical diagnosis, and the PANSS and MADRS scores recorded during each of the two sessions from the patients.

Table 3.2 Healthy control demographic data and experiment inclusion

Subject Codes	Age	Gender	Experiments			
			MMN	Stroop	CANTAB	ER
C1	24	M	N	Y	N	Y
C2	24	F	Y	Y	Y	Y
C3	25	F	Y	Y	Y	Y
C4	30	M	Y	Y	Y	Y
C5	23	F	Y	Y	Y	Y
C6	31	F	Y	Y	Y	Y
C7	31	M	Y	N	Y	Y
C8	24	F	Y	Y	N	Y
C9	26	M	Y	Y	Y	N
C10	28	F	Y	Y	Y	Y
C11	55	M	Y	Y	Y	Y
C12	26	F	Y	Y	Y	Y
C13	24	F	Y	Y	Y	Y
C14	48	M	N	Y	Y	Y
C15	37	M	Y	Y	Y	Y
C16	39	M	Y	Y	Y	Y
C17	32	M	Y	Y	Y	Y
C18	26	M	Y	Y	Y	Y
C19	25	F	Y	Y	Y	Y
Stats	**Mean ± Std: 30.4 ± 8.5**	**Count: 10Male, 9Female**	**Count: 17**	**Count: 18**	**Count: 17**	**Count: 18**

Table 3.3 Patient demographic data

Patient	P1	P2	P3	P4	P5	P6
Gender	M	M	M	M	M	M
Age	35	26	57	64	59	47
Clinical Diagnosis*	SA	SA	SA/BSD	S	S	S
Session 1						
PANSS						
Positive	27	8	7	7	16	9
Negative	10	14	7	23	21	7
General	34	21	16	19	50	18
MADRS	9	7	4	2	18	5
Session 2						
PANSS						
Positive	28	8	7	7	18	26
Negative	27	9	10	12	20	23
General	38	19	17	17	49	59
MADRS	3	4	2	0	22	26

*** S: Schizophrenia, SA: Schizoaffective Disorder, BSD: Bipolar Spectrum Disorder**

3.2 Methods

3.2.1 EEG RECORDING

EEG recordings were acquired continuously using Neuroscan 4.5 Acquire software (Compumedics) and SynAmps^2 amplifiers from specific scalp locations according to the international 10/20 system. A 64-channel electrode array EA64 cap (Advanced Medical Equipment Ltd) was used comprising sintered Ag/AgCl metal electrodes with soft neoprene electrode gel reservoir, snapped onto an expandable and breathable Lycra material with shielded cables (fig 3.3). This cap was chosen because

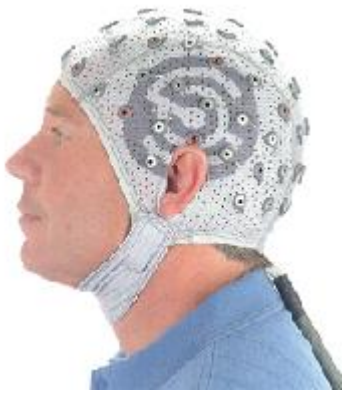


Figure 3.3 A model wearing Electrode Arrays EA-64 cap (Advanced Medical Equipment Ltd, 2019)

it reduced the setup time for recording in the clinical setting and eliminated the chances of individual electrodes detaching off during an experiment. Another reason to use this cap was to avoid any delusional ideas that could arise in our group of schizophrenia patients, possibly causing additional distress to their state of being.

In healthy control subjects all 64 electrodes were used for recording. In patients, the number of electrodes was reduced to 37 (FP1, FP2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, PO5, PO3, POz, PO4, PO6, O1, Oz, O2, M1, M2) to decrease the time taken for the setup. In both cases, two bipolar channel electrodes were used to monitor eye movements and blink artefacts: left vertical electro-oculogram (VEOG) and horizontal electro-oculogram (HEOG). The skin under these electrodes was cleaned using

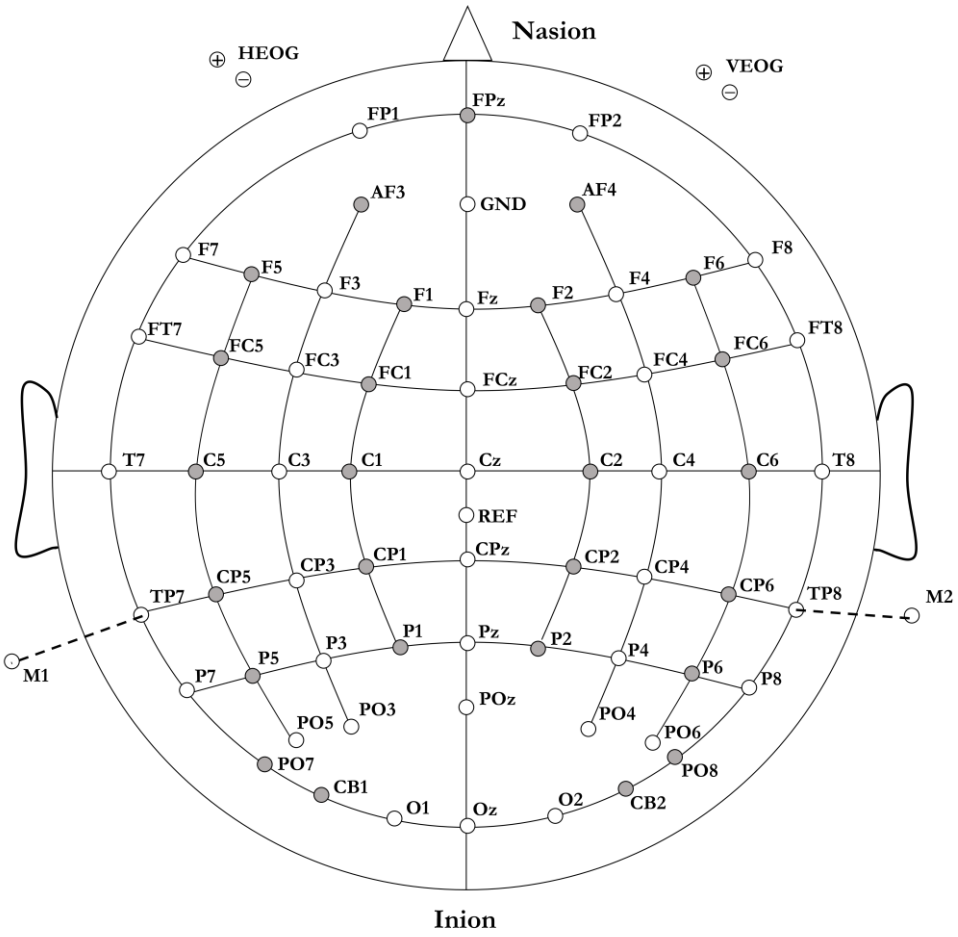


Figure 3.4 EEG electrode configuration on a head schematic. Electrodes are shown as circles and their labels are on to their right. All electrodes (64) were used in recording for the healthy control subjects and the white electrodes (37) were used for the patient group. The bipolar channels HEOG and VEOG were used across both the groups for recording the eye movements.

abrasive gel (Nuprep ECG and EEG abrasive and prepping gel). The EOG electrodes were then attached to the skin using double sided adhesive O-rings (manufactured by EasyCap). To maintain the impedance below 5 kΩ in the scalp electrodes, the above-mentioned abrasive gel was first inserted into each electrode followed with a conductive gel (Electro-Gel, Brain Vision UK), using a syringe (BD 10 ml Syringe, Luer-Lok^{TM} Tip) with a blunt nosed needle (SRS needles). The cap also had a vertex reference electrode at the top of the head and a ground electrode at the top of forehead. All the recorded EEG data was referenced to vertex electrode and stored for post-hoc processing at a sampling rate of 2000Hz on hard drive in Neuroscan's *cnt* file format. The configuration of EEG electrodes is shown on a head schematic (viewed from the top) in figure 3.4. The mastoid electrodes (M1 and M2) were placed behind the ear.

The processing and analysis of EEG data involved a series of steps that was generally followed for each EEG experiment in this thesis. An overview of these steps in shown as a flow chart in figure 3.5. The pre-processing steps applied to the raw continuous EEG data are shown in green. These steps are explained in detail in section 3.2.2. Following the pre-processing steps, the continuous data was converted into stimulus locked epochs. The steps involved in this process are shown in green in the figure and explained in section 3.2.3. The epoched data was then cleaned by removing artefacts and rejecting some of the epochs with residual artefacts. The steps followed

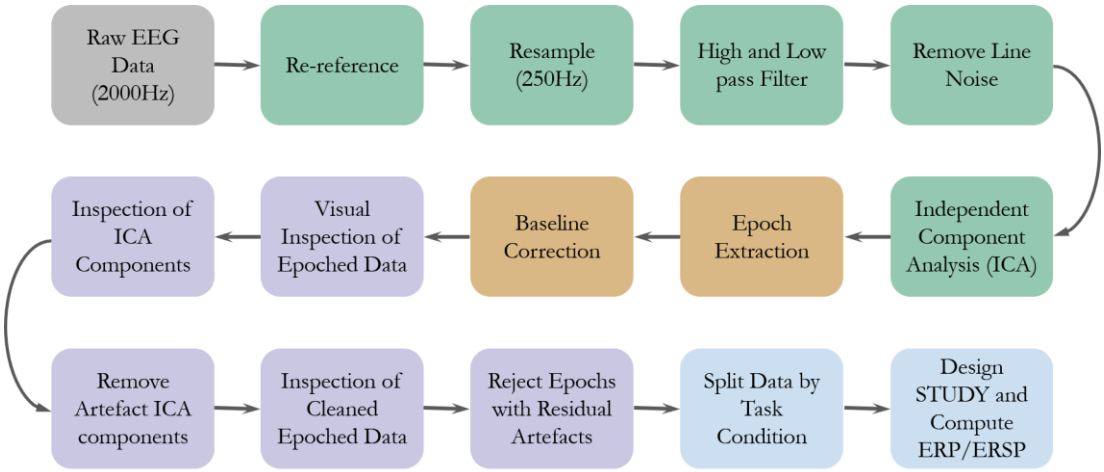


Figure 3.5 Flowchart depicting general steps in EEG processing and analysis. Raw EEG data recorded during experiments is shown in the top-left box in grey. Following steps are shown in green for pre-processing, orange for converting continuous data to stimulus locked epochs, purple for cleaning the data by suppressing artefacts and rejecting epochs, and blue for analysis by task condition and subject group.

for this are shown in purple in the figure, with the techniques described in section 3.2.4. After this step, the data was analysed based on its task conditions and/or group of subjects in each experiment. The general steps in this process are shown in blue in the figure and the details of analysis common across each experiment are presented in sections 3.2.5 to 3.2.8.

3.2.2 EEG PRE-PROCESSING

The stored EEG signals were subjected to a several steps of pre-processing and cleaning before any analysis could be performed on them. Most of the pre-processing steps were common across the different experiments and have been outlined in this section. The widely used MATLAB toolbox EEGLAB (Delorme & Makeig, 2004) was chosen for carrying out pre-processing, cleaning, and analysis of the collected EEG data. The toolbox provided a flexible graphical user interface to easily visualize the processing or analysis that was being carried out. This was helpful in determining the best set of methods that could be used on the data. Once the steps were decided, scripting functionality in MATLAB using the toolbox was then used for carrying out pre-processing and analysis in batches efficiently. The EEGLAB version 14.1.2 was used for all the analyses.

The effects of first few steps of processing the EEG data, from three midline electrodes, namely Fz, Cz and Pz, are shown in figure 3.6. The figure 3.6a shows the raw EEG signal. This signal, as mentioned earlier, was sampled at 2000Hz, and was recorded relative to the vertex reference electrode on the EEG cap. As only two seconds of the EEG data is shown in the figure, the plot does not show the drift in the EEG signal that usually occurs over the entire length of the recording. In the top row plot, a relative difference in the signal amplitude between the three electrodes is observed. This occurred due to the close proximity of the reference electrode to Cz and Pz electrodes when compared to the electrode Fz.

The first pre-processing step was re-referencing the raw EEG data. This is the process of changing the reference from what it originally was, to using either one or more recording electrodes as the new reference to the raw EEG data. For example, in the auditory oddball experiment (Chapter 4), following the widely used convention in the literature, the EEG signals were re-referenced to the average of the left and right mastoid electrodes. In other experiments, a common average reference (CAR) was used which, as the name suggests, is the average of the activity across all the EEG electrodes used during the recording. Different types of referencing methods can lead to significant differences in the resulting signal. The reason for using CAR with the EEG data (except auditory oddball experiment) was, that it does not bias the resulting signal in anyway. It was also the most common referencing method used in the EEG studies that were reviewed. The other advantage of re-referencing the signal was that by using either the linked mastoid reference or CAR, the signal power on the Cz and Pz electrodes was improved. This can be seen in figure 3.6b. This plot was made following the re-referencing and resampling of the EEG data. The resampling step is

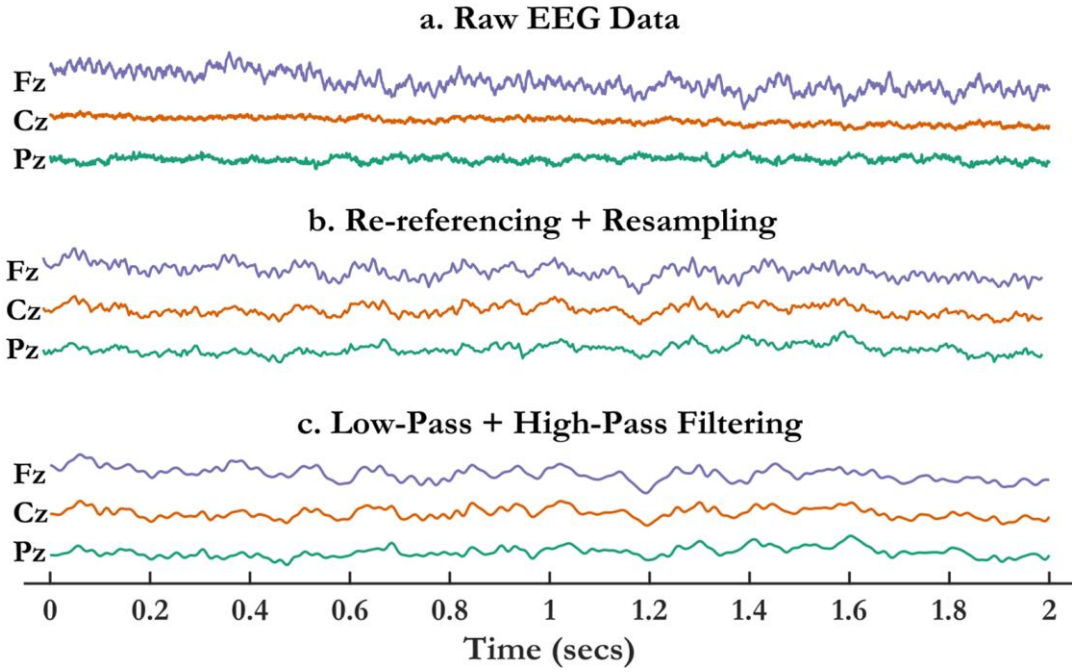


Figure 3.6 EEG initial pre-processing steps. a. Raw EEG data recorded during the experiment, b. EEG signal after re-referencing to average of left and right mastoid, followed by resampling to 250Hz, c. EEG signal after applying low-pass filter at 45Hz cut-off and high-pass filter at 0.05Hz cut-off. All plots show 2 seconds of signals from three midline electrodes Fz, Cz, and Pz.

the process of reducing the sample rate of the data to reduce its overall size, making it feasible for further analysis. A sampling rate of 250 Hz was used as frequency range above 50 Hz was not studied in this thesis. This comfortably satisfied the Nyquist theorem which states that in order to adequately reproduce a signal it should be periodically sampled at least at a rate that is 2 times the highest frequency we wish to record. This also resulted in comparatively smaller size of EEG data that was used for further pre-processing steps.

After re-referencing and resampling the raw EEG data, a high-pass and a low-pass filters were applied to it. As mentioned earlier, the recorded EEG data often has very low frequency (<0.01Hz), but also high amplitude drifts. These are usually caused by the changes the in the skin potentials or sweating resulting in changes in electrode recordings over the time course of the experiment (Luck, 2014b). The high-pass filter was used with the 6dB cut-off frequency equal to 0.05 Hz to attenuate these low frequency changes in the EEG signal, which are not a representation of the neural activity. Using the high-pass filter also helps in mitigating the distortions that could be caused while computing the average trial responses. The low-pass filter cut-off was set at 45Hz. The 45Hz cut-off provided a good balance between the range of EEG frequencies to be investigated in the experiments and the line noise at 50 Hz and its subsequent harmonics. The electromyographic (EMG) activity that occurs at higher frequencies (>100 Hz) was also suppressed to a large extent using the low-pass filter. EEG data was filtered using the Hamming windowed sinc FIR filter. The filtered EEG signal is shown in figure 3.6c. Comparing with the figure 3.6b, a clear decrease in the high-frequency noise components in each of the electrodes is seen. The low frequency suppression is not visible in this plot as it shows only two seconds of EEG activity. In addition to using the high and low-pass filters, an EEGLAB plugin CleanLine was also used to further reduce the sinusoidal noise caused by the line frequency harmonics (Mullen, 2012). This plugin uses an adaptive approximation and removal of the line noise. Though it was a part of the pre-processing pipeline, no changes were observed while visually comparing the data from before and after the application of the function. This was likely because most of the line noise was already suppressed from the data due to the application of the low-pass filter.

Following these pre-processing steps, independent component analysis (ICA) was performed on the EEG data. The EEG activity recorded from the channel array placed on the scalp results from mixture of several sources in the brain. At each electrode, a weighted sum of these sources is observed, with the weights defined by the relative location and strength of the individual neural generators. ICA is a technique that can be used to unmix the observable EEG activity into the underlying sources (Hyvärinen & Oja, 2000). The ICA decomposition of the recorded EEG data was computed mainly to suppress the components contributing to the noise in the recordings. This technique proved helpful in removing noise from the data that could not be effectively eliminated by using the previously discussed pre-processing steps alone. The details of identifying and suppressing these noise components are provided in the section 3.2.4.

3.2.3 EPOCH EXTRACTION

The pre-processing steps in the previous subsection were carried out on the continuous EEG data. Each experiment in this thesis is comprised of hundreds of trials for varying stimulus condition. To study the dynamics of EEG activity as a response to the different task conditions, in any experiment the continuous data was first transformed into individual *epochs* of data associated with each trial. An epoch is a short time-chunk of EEG data locked to the event of interest. For example, in the auditory oddball experiment, subjects were presented with an auditory tone stimulus once every second. The epoch in this case was defined as the segment of EEG data that began 200ms before the stimulus and ended 800ms after the stimulus.

Though the post-stimulus EEG activity is of prime interest, each epoch started before the stimulus onset event to establish a baseline period. It was assumed that the activity in the baseline period was unaffected by the current or the previous stimulus. The EEG activity in each epoch was “corrected” using the average activity in the baseline period. This involved subtracting the baseline average from the whole trial activity, with the rationale that it transforms all the trials to the same average relative voltage level. It can be deduced that longer baseline period would lead to a better estimation of the baseline average. However, this period was restricted by the inter-stimulus interval and assuming that the activity was not affected by the previous stimulus. A high-pass filter in the pre-processing pipeline was used to mitigate the

drifts in the EEG signal over time. Baseline correction was another step that helped in doing the same. By eliminating the absolute differences between same task conditions separated by long durations within the experiment, it was ensured that the average trial response was a representation of only the evoked activity and did not include fluctuations caused by the changes in skin hydration, static charges, etc (Luck, 2014b).

A justification for the baseline correction is best illustrated in figure 3.7 which was adapted from Steven Luck's book (Luck, 2014b). The figure shows how the EEG activity on a single electrode can drastically vary between trials of same condition (marked by 'X's and 'O's). The rectangular boxes represent the epoch boundaries with the dotted line representing the stimulus onset time. It is clear from the figure that averaging EEG activity from all the 'X' trials and all the 'O' trials would result in highly variable and inaccurate representations of average EEG dynamics if the baseline correction is not applied. The drift in the EEG data in this figure is further exaggerated by not incorporating the high-pass filter.

Following the epoch extraction, data for individual subjects was stored for further processing. This was a necessary intermediate step to enable artefact rejection and deletion of noisy epochs through visual inspection of EEG data and/or ICA component suppression. These steps are outlined in the following sub-section.

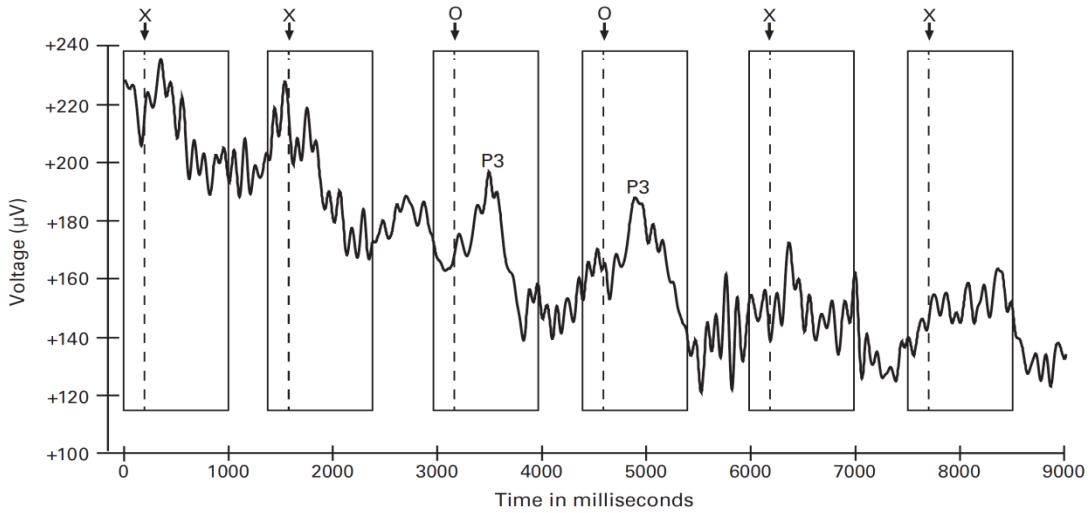


Figure 3.7 Epoch extraction and the need for baseline correction. Boxes in the plot represent the epoch boundaries with dotted lines separating pre and post stimulus periods. X's and O's mark the same trial conditions. The EEG signal is seen to have a significant voltage offset and downward drift. Reproduced from (Luck, 2014b)

3.2.4 ARTEFACT REJECTION

After the pre-processing pipeline and the extraction of epochs from the continuous data, it was necessary to reject the trials that had noise associated with them. This was an important step in EEG analysis to ensure that average evoked response was minimally affected by the various artefacts that might occur during the experiment. In the experiments described in this thesis, the EEG activity for the tasks were recorded continuously for intervals ranging between 10 and 25mins. During this time, the subjects blinked, adjusted themselves to get comfortable, moved their head, had random micro-twitches in their scalp muscles, etc. All these caused different types of artefacts that were picked up by the electrodes. Artefact rejection is a set of steps that were followed to minimize the effect of these unwanted signals on the analysis.

The EEGLAB toolbox contains a graphical user interface (GUI), that can be used for both analysis and visualization of the data. In the first pass of artefact rejection the interface provided by the toolbox was used to visually inspect and mark the noisy epochs for rejection. This involved manually scrolling through several minutes of EEG epoch data to look for signs of eye blinks, movement artefacts, swallows and tongue movements, signal discontinuities etc. As humans blink on an average 15 blinks per minute while looking at a computer screen (Chu et al., 2014), blink and other eye movement artefacts were present in every subject, through the duration of the experiment. In some cases, these signals were only observed on the EOG electrodes, however, on several occasions they were also picked up on other scalp electrodes. There were also instances of large EMG activity, signal discontinuities, etc. but these were rare and lasted only for a few epochs randomly occurring during the experiment. In this first pass of artefact rejection through visual inspection, all such noisy epochs were marked for rejection.

After visually inspecting the epochs for above listed noises, the numbers of epochs that were to be rejected and retained were analysed. On average, across multiple experiments, more than 50% percent of the epochs were clean and retained (mean 56.27%). However, in approximately 15% of the cases, less than 20% of the trials were retained. On further inspection, it was found that the low retention rate occurred in cases where the eye related artefacts were large, more frequent, and

occurred through the experiment period. To reduce the number of rejected epochs, ICA artefact suppression was also used.

Independent component analysis or ICA, unmixes the recorded multi-channel EEG activity and outputs the same number of independent components. These components are, theoretically, a representation of the various sources generating the activity recorded on the scalp electrodes. As the ICA components are a linear combination of the electrode activity, the decomposition of the EEG signals gives a matrix transformation that can be used to transform one activity into the other. Similarly, once the noisy components are identified, their weights in the transformation matrix can be set to zero to suppress the noise from the EEG data.

The identification of the noisy ICA components is not a trivial task and needs careful inspection of each component to determine its likely origins. The EEGLAB GUI has tools to visualize component scalp maps, frequency spectrums, event related activation, etc. To keep the artefactual component identification as objective as possible, an additional EEGLAB plugin called SASICA (version 1.3.4) was used (Chaumon et al., 2015). This plugin computes several measures to define the components. Some of these measures were designed by the creators of the plugin, while others were adapted from previously used automatic ICA rejection algorithms, ADJUST (Mognon et al., 2011) and FASTER (Nolan et al., 2010).

The GUI interface of the SASICA plugin allowed to select several options to compute specific measures defined within the plugin. Apart from specifying the EOG electrodes in our recordings, the default parameters were used. A typical output of the computed measures from plugin, for a single ICA component, is shown in the figure 3.8a. On the top-left we see the scalp activation map of this component. This component has a high concentrated activity close to the right eye of the subject. The image plot on the top right of figure 3.8a shows the activity of the component during the epoch-trial period. We see that this component was active randomly within the trial period. This is an indication that this component does not show an event related activation. The following row in this plot shows the frequency spectrum of the component. This is followed by rows of different parameters computed; for example, the correlation with the vertical (CorrV) and horizontal (CorrH) EOG activity computed by SASICA, correlation with the EOG electrodes computed by the FASTER

algorithms (EOGCorr), etc. These measures are also associated with the adaptive thresholds shown on the y-axis of each plot. Based on all the computed measures and the various plots shown by SASICA plugin, this component can be confidently marked as a blink artefact. The specific details of each measure and method of computation have been defined in the paper by Chaumon *et. al.* (Chaumon et al., 2015).

The guidelines provided by the Chaumon *et. al.* paper were used to inspect each component and determine if it should be marked for rejection. It should be noted that ICA decomposition of EEG signals is not perfect, and components that are a mixture of noise and neural activity are also seen. The goal of ICA artefact rejection was to eliminate a minimum number of components that were clearly capturing only the noise in the signal. Typically, only 2-3 components from each subject were rejected. In almost all subjects, across all the EEG experiments, the eye blink artefact was present. This artefact was strong enough to be completely picked up by one or two ICA components. Apart from these, depending on the subject, components that were representative of artefacts like muscle activity, heartbeat, or just random noise, were also rejected.

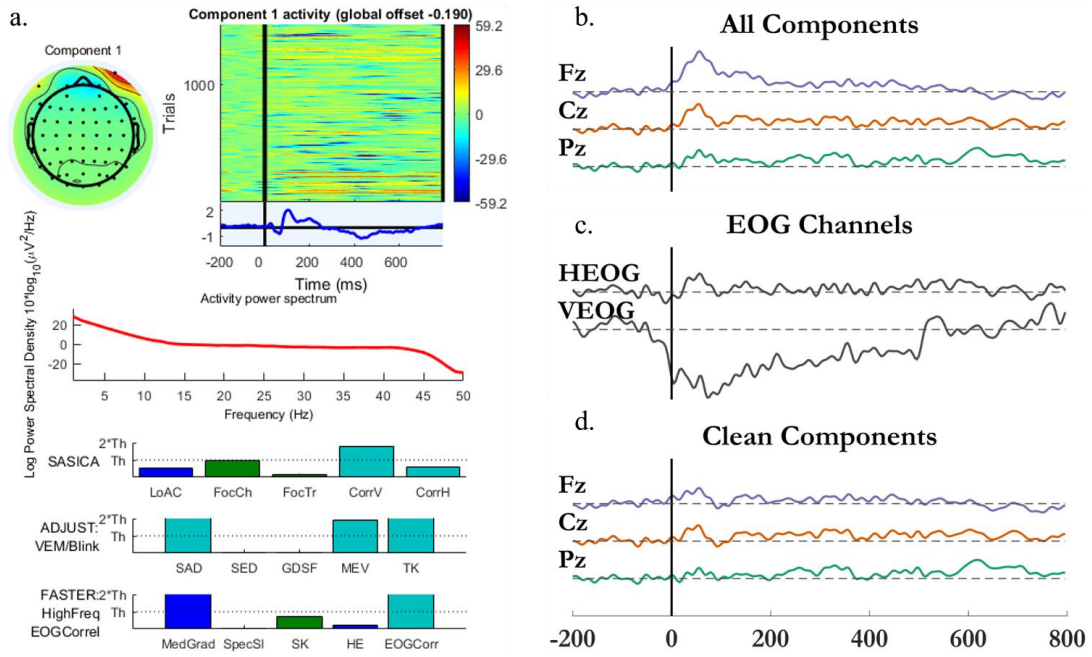


Figure 3.8 Artefact rejection by suppression of noisy ICA components. a. Output of SASICA EEGLAB plugin for a single ICA component, b. An epoch of EEG activity at midline electrodes with all ICA components, c. Recorded EOG activity during the same epoch, d. The epoch activity after ICA component (shown in a) capturing the blink artefact was removed.

An example of artefact rejection on the EEG activity is shown in figure 3.8b-3.6d. This shows the activity at three midline electrodes from a single epoch. The plot in figure 3.8b shows the activity before artefact removal. The plot in figure 3.8c shows the EOG electrode activity in the same epoch. The plot in figure 3.8d shows the activity from the same epoch as 3.8b, but after removal of the blink artefact ICA component shown in figure 3.8a. In this case, it is observed that Fz and Cz electrodes were extremely sensitive to the eye blinks, leading to high magnitudes of activity on these electrodes. This artefact was greatly suppressed after the blink related component was removed.

The ICA based artefact rejection was able to eliminate several different types of artefacts by suppressing the noisy ICA components. However, there were components that were likely a mixture of noise and neural signal. These components were retained to preserve the neural activity present in them. Due to the presence of such components, some artefacts could not be eliminated by using ICA artefact rejection alone. This was particularly true in cases where there were large movement artefacts or discontinuities during the recording that exist for a few epochs or seconds. It was noticed in the ICA space that, these were present on one or several, otherwise "clean" components. For this reason, after completing ICA based artefact rejection from all the subjects and experiments, the cleaned epoched EEG data was again visually inspected. All the epochs that still had artefacts in them were rejected in this step. As before, the numbers of rejected and retained trials were analysed. The percentage of accepted trials retained was computed in all subjects across different experiments. Figure 3.9 shows the kernel density estimation of these retained trial percentages with and without using ICA based artefact rejection. The vertical lines represent the means of the distribution without using ICA rejection (56.27%) and with using ICA rejection (82.58%). The figure shows that percentage of retained trials was higher when ICA based artefact rejection was used. The mean percentage of trials increased almost by 30% and in most cases more than 80% of the trials were preserved.

After the artefact rejection was completed, the data for each subject in each experiment was split by the task condition. The trials marked for rejection (based on visual inspection after ICA artefact rejection), and any incorrect trials during the experiment were then dropped. This data was again stored as clean dataset files for group level analysis. This analysis was done using the EEGLAB structure called STUDY. This is elaborated in the following section.

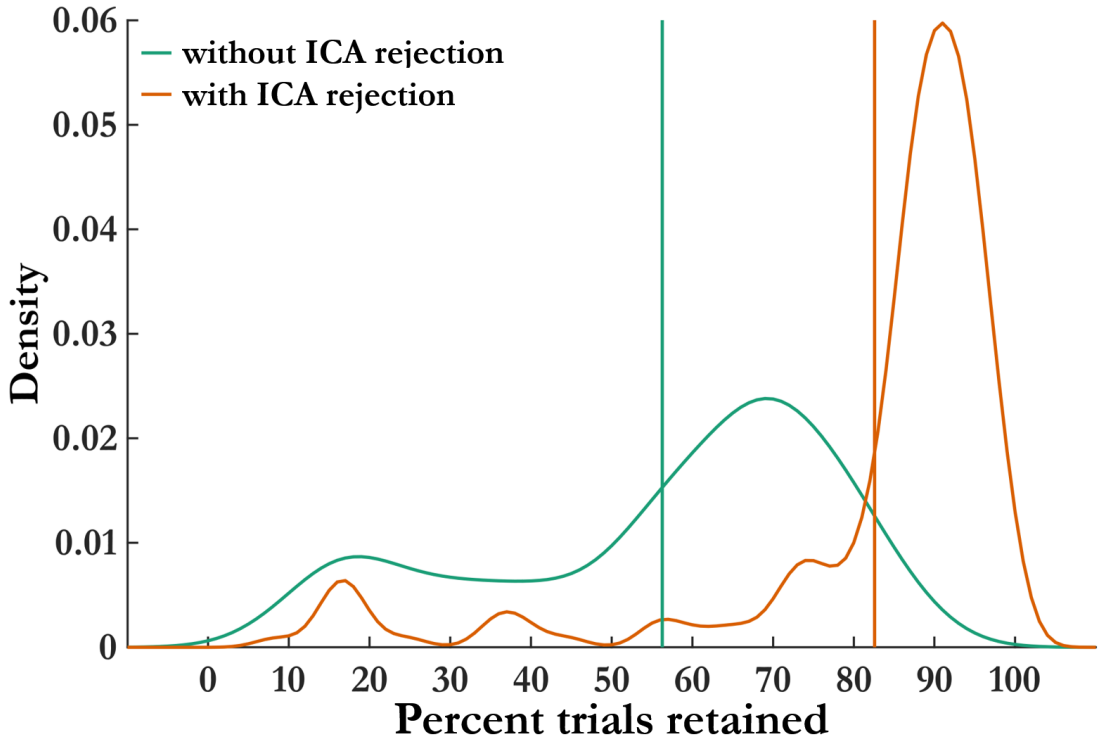


Figure 3.9 Distribution of percentage of trials retained with and without ICA artefact rejection. The vertical lines represent the mean of each distribution.

3.2.5 MULTI-SUBJECT ANALYSIS

All the previously described steps, from the recording of EEG data to the artefact rejection were applied to data from individual subjects. To make comparisons between the group of healthy controls and the patients recruited for the experiments, analysis and inference needed to be carried out on collective response of a group. Even if a single subject's response within the group was to be observed, it was important to setup an environment that could apply the same set of steps to each dataset. EEGLAB provides with a data structure called STUDY which was used in conducting such type of analysis.

For each experiment, a STUDY structure was created for each group of subjects, the healthy controls, the patients, and the two groups of patients segregated by clinical diagnosis (schizophrenia and schizoaffective disorder). To create the structure, the clean dataset files were used by specifying the subject and the task condition data stored in the file. Once all the clean datasets were added to the data structure, several EEGLAB STUDY designs were used to compare between different combinations of task conditions. For example, in the auditory oddball experimental paradigm, the standard tone stimulus trials were compared with the five types of deviant stimuli using five STUDY designs. For each design, the event related potential (ERP) and the event related spectral perturbation (ERSP) measures (described in the following sections), were also precomputed. By precomputing and storing these measures at this stage, different plots of interest and statistics could easily be computed later. In the STUDY data structure, these measures for every subject can either be stored as an average, or as individual trials. The individual trial data was stored only in the patient group STUDY designs. This was done to allow statistical analysis on individual patients as well as the patient group. In all the other cases only the average measures for each subject were stored.

The EEGLAB toolbox provides with different types of statistical tests that can be carried out on the STUDY data structure and design. The tests used in the analysis for this thesis are described in section 3.2.8 below. The toolbox also provides with some visualization and plotting functionality. Few elements of these functionality were adapted, and changes were made to generate more informative figures.

3.2.6 EVEN RELATED POTENTIAL ANALYSIS

The event related potential or ERP is defined as the average or stereotypical EEG response to the occurrence of an event (Luck, 2014a). In the experiments described in this thesis, ERP was calculated with respect to the onset time of each stimulus condition. In the precomputation step of STUDY structure and design creation, the ERP response for each task condition was calculated and stored for each subject. The grand averaged ERP were also computed for different groups of subjects while studying an average group response or making comparisons between different groups. These responses were computed by the taking the mean of the average responses of subjects within the group.

3.2.7 TIME-FREQUENCY ANALYSIS OR ERSP

The ERP response provides the time domain response of the EEG activity to a given stimulus. However, the EEG signal is comprised of a wide frequency band of neural activity which is averaged out in the ERP response. The event related spectral perturbation or ERSP is the average change of the frequency spectrum of the EEG signal as a function of time (Makeig, 1993). Like the ERP, the ERSP is calculated relative to the stimulus onset event. Thus, the ERSP provides a more granular, time and frequency domain view of the dynamics of the neural response. The mathematical definition of ERSP, as stated by Delorme and Makeig (Delorme & Makeig, 2004), is:

$$ERSP(f,t) = \frac{1}{n}\sum_{k=1}^{n}|F_k(f,t)|^2$$

In the above equation f is the frequency, t the time relative to the stimulus onset, n the number of trials and $F_k(f,t)$ is the spectral estimate of the power at the given time-frequency point. The ERSP values were computed for 100 frequencies logarithmically distributed between 2Hz and 50Hz keeping with the limitation associated with the sampling rate for EEG acquisition and filter settings (see section 3.2.2). EEGLAB provides with several options for estimating the frequency spectrum ($F_k(f,t)$), but the best compromise between time and frequency resolution was obtained using a standard FFT estimation with a 250ms time window.

Similar to the ERP response precomputation, a precomputed ERSP response for each subject was stored for each task condition. The grand averaged ERSP response of a group, for a given stimulus condition, was calculated by taking the mean of the stored precomputed values of subjects within that group.

3.2.8 STATISTICAL TESTING

Suitable statistical tests were used to determine the significance of the various results obtained from analysis of collected data from the various experiments. All the tests were performed using the standardized functions present in MATLAB or specifically defined in the EEGLAB toolbox. The behavioural measures computed from the various tasks performed by subjects were tested for statistical significance using t-tests. Paired statistics were used in the cases where comparison was made

within the group between responses to two different stimuli. Unpaired t-test was used to make between group comparisons.

The ERP and ERSP responses to various stimuli were compared for statistical differences with each other. Unlike the scalar values of behavioural responses, the EEG measures are one- or two-dimensional vectors. For this reason, univariate comparisons were made at every point in either the time (ERP) or time-frequency (ERSP) space. As this was a multiple comparisons problem, a p-value for statistical significance could not be used without applying a correction method. EEGLAB has implementations of several parametric and non-parametric tests and provides standard options for multiple comparisons analysis like the Bonferroni correction or false discovery rate (FDR).

Bonferroni correction method is widely used in statistics however, it is not suitable for comparing time domain or time-frequency domain data. To account for multiple comparisons, Bonferroni correction scales the p-value threshold (typically 0.05) by the number of univariate tests carried out. This number ranges from a few hundred in the case of ERP analysis, to a few 10s of thousands for ERSP analysis. This would result in an extremely strict significance criteria which is very unlikely to be met by any statistical effects present in the data. Another problem with using Bonferroni correction with EEG data is that it treats each point in the data independently. As ERP is a temporal signal, it is highly dependent on preceding time points. This also applies to the time-frequency space of ERSP data in both the dimensions, with an additional dependence introduced in time by the moving window estimation of the spectrum. Lastly, the Bonferroni correction factor is directly controlled by the number of tests and not the information content. Thus, the number of tests can be easily reduced by changing the sampling rate or the frequency bins, resulting in higher corrected p-value without any change in the actual effects observed in the data.

Cluster-based permutation tests, implemented in the Fieldtrip plugin (Oostenveld et al., 2010) of EEGLAB, were used to solve the multiple comparisons problem, and to determine statistically significant regions in the ERP and ERSP responses. The cluster-based permutation tests were first proposed by Maris and Oostenveld in 2007 (Maris & Oostenveld, 2007). The test worked by first computing

a univariate t-statistic between the responses of the two stimuli being compared (say, Stimulus1 and Stimulus2) and thresholding it to a desired significance value (*e*.g., p=0.05). All the values that satisfied this threshold were combined into clusters based on their connectivity, either in the time domain (ERP) or time-frequency space (ERSP). The cluster-level statistic was calculated by taking the sum of the t-statistics in each cluster. To determine the significance of each of the clusters thus obtained, the Fieldtrip plugin employed a *Monte Carlo* sampling method. At every iteration, a set number of samples were drawn from the whole dataset and randomly assigned to either of the two groups (Stimulus1 or Stimulus2). On this newly created sample distribution, the t-statistics and the corresponding cluster-level statistics were computed. These iterations were carried out many times to determine the distribution of cluster statistics from a randomly generated dataset (more iterations resulted in higher accuracy). The originally obtained clusters, from the real distribution of responses, were then said to be significant at p=0.05 if they lied outside the 95^{th} percentile range of the random cluster-level statistic distribution (Maris & Oostenveld, 2007).

The significant clusters obtained from such an analysis can be used to identify the regions in the data where the effect was most prominent. It should be noted that though the cluster of data denoted significantly different activity within its boundaries, it did not imply that each point within the cluster individually met the significance criteria. For this reason, making any claims about individual time points or time-frequency point, except that they lie within a significant cluster, would be inaccurate (Sassenhagen & Draschkow, 2019). In figures in the following chapters of this thesis, the significant clusters are represented either by marking the time-region in ERP analysis or by drawing contours representing cluster boundaries in the difference ERSP plots.

Measures like peak and latency from the ERP data of individual subjects were also computed. These measures were governed by multiple factors like the stimulus condition, group the subject belonged to, and the location of the electrode. Mixed factor analysis of variance (ANOVA) was used for statistical comparisons of these measures. The standard functions available in MATLAB's Statistics and Machine Learning Toolbox were used for this purpose.

CHAPTER 4. MISMATCH NEGATIVITY

4.1 Event Related Potentials

An event related potential (ERP) is the EEG activity time-locked to a certain event like the onset of a stimulus and averaged over multiple trials. This chapter studies the ERP signals in response to an auditory oddball task. The auditory ERP (AERP) has several positive and negative components that are observable starting from a few milliseconds after the stimulus (fig 4.1a). The early AERP (<10ms) is composed of positive deflections called Wave I-VI (in roman numerals) which represent the response dynamics of the auditory brainstem (Hillyard & Kutas, 1983). Wave V can be recorded to show that the brain is receiving auditory input and can be used to test hearing without the need of a subjective response (Picton, 2006). Following the brainstem response, the AERP components are named based on their polarity (P for positive, N for negative), in an alphabetical sequence. The Pa, Na, Nb, etc, deflections occur within the 100ms of stimulus presentation. These components encode the parameters of the stimulus and are therefore called exogenous or stimulus driven components (Hillyard & Kutas, 1983).

The later components of the AERP are again named after their polarity but now followed by a number representing the approximate time of their occurrence. These longer latency components are modulated by the cognitive requirements of the task performed and are therefore called endogenous or context-driven components (Hillyard & Kutas, 1983). The most studied of these are the N1 or N100 and the P3 or P300. The N1 component peaks at a latency of 100ms and is observed every time an auditory stimulus is presented. The P3 component is elicited when the subjects attend to the changes in the auditory stimulus and peaks around 300ms. However, the experiments presented in this chapter study a different component of AERP called the Mismatch Negativity or MMN. This is a component of ERP that has been shown to occur when a series of repetitive standard tones is interrupted by an infrequent deviant tone, an “oddball”, differing in a parameter from the standard, like its frequency, intensity, etc. An ideal MMN response to a deviant tone is shown in figure 4.1b, using a figure adapted from (Brattico, 2006). It is observed to be elicited as a large negativity in the difference waveform calculated by subtracting the standard AERP from the deviant AERP. MMN is elicited automatically without the need of subject to pay

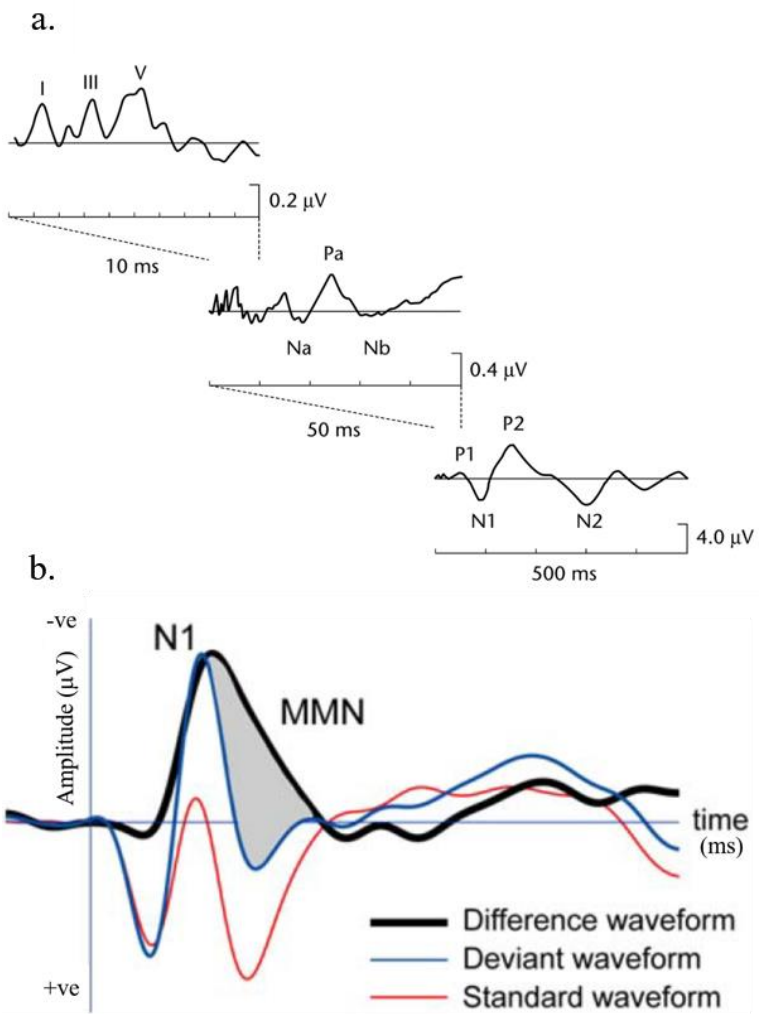


Figure 4.1 Auditory ERP signal and schematic of MMN. a. AERP recorded at the vertex electrode is shown at three levels of zoom from shorter (upper left) to longer (lower right) time window. Adapted from Picton, 2006. b. AERP evoked at a frontal electrode as a response to a standard tone (blue) and deviant (red). The difference waveform (black) was generated by subtracting the standard AERP from the deviant AERP. MMN is seen as a large negativity to the deviant tone. Adapted from Brattico, 2006.

attention, unlike P3. Also, unlike N1, the MMN component has a longer latency and is observed only when there is a change in the stimulus parameter (Picton, 2006). To prevent other attention-dependant ERP components that might overlap or elicit with the MMN, experimenters usually have the participants attend to another stimulus. This involves either watching a familiar (muted) video or reading a book through the duration of the experiment (Michie et al., 2000; Michie, 2001).

4.2 Mismatch Negativity

Mismatch negativity was documented by Risto Näätänen and his colleagues and presented in an article in 1978 (Näätänen et al., 1978). In a set of experiments carried out in 1975, Näätänen *et. al.* presented subjects with standard auditory tones of 1000Hz frequency and 70dB intensity in a single, randomly selected, ear at each trial. Subjects were also presented with a rare target tone which differed either in intensity in one experiment or in frequency in another experiment. The subjects were instructed to attend (count) to these target tones in only one of the ears.

The experimenters observed that the target tones resulted in a negative deviation in the ERP signals recorded from the top of the head (Cz) and from the temporal electrodes (T3 and T4). More specifically, the negative deviation was present at a latency of approximately 100-300ms after stimulus for both attended and unattended trials. They also noticed a positive deviation around 300ms, but only for the attended trials. Näätänen *et. al.* concluded that the negative deviation was an automatic response to the change in the stimulus and coined the term *Mismatch Negativity* (Näätänen et al., 1978). MMN is typically seen as a negative displacement at the fronto-central and the central electrodes with respect to a mastoid or a nose reference electrode. However, a reversed polarity (positive deviation) MMN is generally observed at the mastoids when a nose reference is used (Näätänen et al., 2007)

Since its first discovery in 1978, MMN has been extensively studied in both healthy control and patient populations with varying pathologies. The following sub-sections summarize different aspects of research on MMN. Section 4.2.1 describes the types of auditory deviant stimuli that have been observed to generate an MMN response. It also discusses how this response varies with changing deviant parameters. Sections 4.2.2 and 4.2.3 describe the current understanding of the neural basis of MMN and the mechanisms that have been proposed to explain it. Section 4.2.4 discusses how MMN is affected in different neuropathologies, with an emphasis on schizophrenia.

4.2.1 CHARACTERISTICS OF MMN

MMN can be reliably recorded when a stimulus parameter is varied in an auditory oddball task. Various types of changes to the stimuli like, frequency, intensity,

duration, location, phonetic structure, partial omission, etc have been reported to elicit this negative deviation.

MMN response to frequency change was first reported with the discovery of MMN in the 1978 paper by Näätänen *et. al.* (Näätänen et al., 1978). Sams *et. al.* further studied the frequency MMN by varying the deviant frequency in each block relative to the standard tone (Sams et al., 1985). They used a 1000Hz standard tone and used deviants of 1002, 1004, 1008, 1016, and 1032 Hz. Their observations showed that MMN was elicited at deviant frequencies of 1008Hz and above. The MMN amplitude was small at 1008 Hz and nearly the same at higher frequencies. Other studies have shown that the latency of frequency MMN decreased as the deviant frequency is further increased. Researchers have since concluded that because the MMN amplitude is saturated at lower frequency deviations, latency is a more reliable measure of frequency deviation (Näätänen, 1992).

Changes to standard stimulus intensities leading to an MMN response were meticulously studied in the early 1990s. Näätänen *et. al.* varied the stimulus intensity above and below the standard tone, and MMN was calculated at the central (Cz), frontal (Fz, FPz), and parietal (Pz) electrodes (Näätänen, 1992). Deviant intensities both below and above the standard were observed to produce an MMN response. Like the frequency MMN, the amplitude and latency of MMN were modulated by the difference in the intensities. A larger difference in intensities of the deviant and standard tones led to a larger amplitude and a shorter latency. The amplitude, however, did not show an early saturation that was observed with frequency MMN. The latency of MMN at larger differences (intensities both above and below standard tone) was closer to 100ms and led to an overlap between the MMN and N1 response. An interesting difference between the deviants was that higher intensity (compared to standard tone) deviants also elicited a P3a wave, while the lower intensity deviants did not (Näätänen, 1992; Näätänen et al., 2007).

An infrequent presentation of deviant, longer or shorter in duration, compared to the standard stimuli, also elicits an MMN response (Kaukoranta et al., 1989; Näätänen et al., 1989). Studies from 1989 showed that decrement deviants that were half the duration of the standards, between 25ms to 200ms, showed a clear MMN response. Similarly, blocks with duration increment deviants of 100ms and 200ms, with standard

tones of half their corresponding durations, also elicited an MMN response. More complex temporal changes in the stimulus, like, changes in inter-stimulus interval (ISI) (Näätänen, 1992), rise time, an omission of second tone in a paired stimulus (Näätänen et al., 2007), and a silent gap in the middle of a stimulus have also shown MMN elicitation (Bertoli et al., 2001; Desjardins et al., 1999; Pihko, 1997).

Another study demonstrated that MMN was elicited when the location of the speakers producing the sound was changed from straight ahead to an angle of either 10, 45 or 90 degrees. MMN was also seen when the location change was only perceived (versus real) by varying the intra-aural phase or intensities using an earphone. This study showed a gradual increase in the MMN amplitude with the increase in perceived angle change. However, even a small (10 degrees) change in the physical location of the speakers elicited a large MMN response. The authors reasoned that this could be due to more discernible cues of change in location in the latter case (Näätänen, 1992).

The change in MMN amplitude and latency has been previously discussed to vary with the increase in magnitude of stimulus deviation. These amplitude and latency effects have been seen in various types of stimulus changes like intensity, frequency, location, etc. The MMN amplitude has been further shown to increase with a decrease in the probability of the deviant stimuli. Sequential analysis of the experimental data revealed that local stimulus probabilities, and the sequence of stimuli, also affect the MMN. For example, increase in the number of standards preceding a deviant increases the MMN amplitude. When two deviants occur one after the other, MMN generated by the second deviant is smaller in amplitude than the first. However, the MMN generated by the second deviant does not attenuate when the two consecutive deviants differ from each other in their attribute when compared to the standard. The standard signal has also been shown to elicit a small negativity when preceded by a deviant (Näätänen, 1992; Näätänen et al., 2007).

Researchers have also studied the effect of ISI on the MMN response. As mentioned briefly before, an infrequent reduction in the ISI leads to a small but significant MMN. Studies with varying ISI have revealed that MMN amplitude due to a deviant gradually decreases with increasing ISI. Though the results from different studies are conflicting, MMN was not elicited with longer ISI of 4 or 8 secs. On the

other end, MMN elicitation has been observed with ISI as low as 60ms (Näätänen, 1992).

The above-described studies have shown that the MMN response is dependent on the parameters of the deviant stimulus. The MMN amplitude and latency is seen to vary when the same type of deviant stimuli is modulated. This has led researchers to employ various methodologies in deciphering the areas of brain contributing to the generation of MMN. There have also been predominantly two theories to explain the mechanism of the MMN phenomenon and consequently several studies to test each one of them. The following sub-sections discuss the generation and the theories of mechanisms of MMN.

4.2.2 GENERATION AND ORIGINS OF MMN

Primarily, MMN has been shown to be a result of activity from two regions of the brain: a. bilateral process in the supratemporal regions which encompass the primary auditory cortex, and b. largely unilateral process from the right frontal cortex (Näätänen et al., 2007, 2012; Winterer & McCarley, 2010). One of the first evidence of multiple mechanisms adding to the generation of MMN was the polarity reversal at the mastoid electrodes referenced to the nose (Näätänen, 1992; Näätänen et al., 2007). There have also been some evidence of subcortical areas like hippocampus and thalamus responsible for contributing to certain subcomponents of the MMN response (Alho, 1995; Csépe, 1995; Näätänen et al., 2007; Winterer & McCarley, 2010).

Kimmo Alho (Alho, 1995) and Valeria Csépe (Csépe, 1995) in 1995 simultaneously reviewed several earlier studies of origin and generation of MMN. Alho's review focused on findings of different methodologies and modalities that researchers had used to determine brain regions contributing to MMN. Csépe, on the other hand was more interested in animal analogues, development, and clinical importance of MMN. Scalp EEG distributions along with current density analysis have shown that MMN responses to different stimulus parameters like frequency, intensity, and duration, fit different dipoles. Though all these are located in the auditory cortex, they differ in orientation and location within the region. These recordings have also located generators in the right frontal cortex, which has been theorized to cause involuntary switching of attention to the change in auditory stimulus (Alho, 1995; Näätänen et al., 2007). More recently, independent component analysis (ICA) of scalp

recordings has shown similar results with components clustered in auditory and right frontal cortices (Rissling et al., 2014). Source localization has also been performed on Magnetoencephalographic (MEG) recordings to provide a unique view of the MMN and its generators. MEG is blind to the radial sources in the frontal cortex and thus, it can be uniquely used to study the generation on MMN in auditory cortex and in detecting processing deficits in various pathologies (Näätänen et al., 2012).

Non-human primate studies to determine the origin of MMN, have been related to the activity of the glutamatergic N-methyl-D-aspartate (NMDA) receptor system (Alho, 1995; Javitt et al., 1996; Näätänen et al., 2007). Javitt *et. al.* showed that the presence of an NMDA antagonist MK-801 led to an elimination of MMN like response to frequency and intensity deviants, while keeping the initial obligatory responses to auditory stimuli intact (Javitt et al., 1996). However, some studies have also suggested that NMDA antagonist suppression is non-specific (Farley et al., 2010). Other animal studies have shown the involvement of hippocampus (cats) and thalamus (guinea pig) in MMN generation (Alho, 1995; Csépe, 1995). Human patients with lesions to thalamus have shown reduced MMN response. However, intercranial recording from human thalamus, hippocampus, basal ganglia, and amygdala do not show an MMN response. The reduced MMN due to lesions to thalamic nuclei, thus points to a necessity of sustained input from subcortical regions to the auditory cortex for processes responsible for MMN generation (Alho, 1995). Lastly, even minor ethanol intoxication leading to diminished attention, has been shown to diminish the MMN at the frontal electrodes that record contributions from both the primary generators. The polarity-reversed component recorded from mastoid, representing the auditory cortex generator, remains unaffected in this case (Näätänen et al., 2012).

4.2.3 MECHANISMS OF MMN

The research effort in studying mismatch negativity has been extensive over the past few decades. It has been, and is currently, being used in several areas of clinical research. However, the mechanisms and meaning of MMN are not well understood. Two prominent schools of thought have gained popularity and remain a point of debate in the MMN research community: a. *neural adaptation* hypothesis, and b. *sensory memory* hypothesis. These two theories of MMN generation have been hypothesised

since the discovery of MMN (Näätänen, 1992) and have, in a manner, divided the research community into two groups.

The neural adaptation hypothesis states that, MMN is a lower level phenomenon which represents the activities of different groups of neurons that encode the properties of the stimulus (Fishman, 2014; May & Tiitinen, 2010). As has been stated before, MMN is a difference signal between the average response to an intermittent deviant stimulus and the average response to a standard, more probable, stimulus. According to the neural adaptation hypothesis, the repeated presentation of standard stimulus leads to an adaptation, or attenuation of response, of the neural afferents encoding its properties. It states that the population encoding the parameters of the standard stimulus suffers from refractoriness as it is presented continuously (May & Tiitinen, 2010). At this point, when a deviant stimulus with a distinct parameter like change in frequency is presented, the "new" population encoding these parameters is activated, resulting in a production of a large response. This leads to the difference observed in the average responses quantified as mismatch negativity or MMN. It is to be noted that, according to this hypothesis, MMN is not a distinct phenomenon but rather, a latency and amplitude modulation of the "obligatory" auditory N1 response (May & Tiitinen, 2010).

The sensory memory hypothesis regards MMN as a higher-level response that represents the output of a comparison process. It states that, the series of standard stimuli form an echoic memory trace that encodes the regularity of features in them (Fishman, 2014; Näätänen et al., 2007). When a deviant stimulus is presented, its features are compared to this trace, and MMN is a result of a mismatch between the two. A similar interpretation of this hypothesis is termed as the predictive coding model (Garrido et al., 2009). From the perspective of predictive coding, brain creates a model of the environment by continuously integrating inputs received. The change in stimulus from a series of standards to a deviant, results in a prediction error in the model. This is the effect of the "encoded" environment of the standards being different from the "observed" environment of the deviant. The MMN is hypothesized as the representation of this error signal, that can further be used to update the model.

Extensive research has been performed in collecting evidence in favour of each of the two prominent theories of mechanism of MMN generation. Two prominent

review articles by Patrick May and Hannu Tiitinen (May & Tiitinen, 2010), and by Yonatan Fishman (Fishman, 2014) have summarised the findings of several of these studies. The article by May and Tiitinen is an attempt to bolster the lesser accepted, neural adaptation hypothesis. Fishman on the other hand, provides an unbiased and overall review of evidence both, in favour, and against the two hypotheses. He concludes that the neural adaptation hypothesis is, at least, in-part a result of latency and amplitude modulation of the obligatory response, and that it is still unclear if it also represents a higher-level process of memory trace mismatch or predictive coding error.

4.2.4 MMN IN SCHIZOPHRENIA AND OTHER CLINICAL CONDITIONS

Changes in MMN have been reported in several neurological, neuropsychiatric, and neurocognitive disorders. MMN can be used to index different kinds of information like auditory processing (discrimination, abnormal perception, etc.), attention switching, loss of grey matter, progression and prognosis of clinical condition, genetic inclination towards a disorder, etc. Due to this reason, MMN has been extensively used in clinical research; an extensive review can be found in (Näätänen et al., 2012). This section provides some details on MMN research and its importance, specifically in the field of schizophrenia.

Studies with schizophrenia patients have consistently replicated a reduction in MMN amplitude. Light and Braff compared 25 schizophrenia patients who met DSM-IV criteria with age, sex, and education matched controls showing a significantly reduced duration MMN amplitude in patients (Light & Braff, 2005). A meta-analysis of 32 studies involving schizophrenia patients found that the neuropathological changes underlying MMN caused a significant effect on temporal processing. The study reported that duration deviant MMN deficits were significantly larger than frequency deviant MMN deficits (C. C. Duncan et al., 2009). This finding provided further confirmation to similar observations by an earlier 2000 study (Michie et al., 2000). This study found that the duration MMN amplitude was significant smaller than that of the frequency MMN for schizophrenia patients, but not for control subjects. Duration MMN deficits have also been observed in first degree biological relatives of schizophrenia patients (Michie et al., 2002). As has been described previously, in healthy subjects, larger differences in deviant and standard magnitudes, and lower

probabilities of deviants yield MMN with larger amplitudes and shorter latencies. However, according to a recent meta-analysis by Erickson *et. al.*, MMN does not seem to be related to deviant characteristics in patients with schizophrenia (Erickson et al., 2016).

Length of illness has also been shown to alter the deficit in MMN response. A study by Todd *et. al.* showed that, early-stage schizophrenia patients (mean illness 2.6 years) exhibit MMN deficit to duration deviants but not to frequency deviants. Late stage patients (mean illness 18.9 years) however showed MMN deficits in both duration and frequency deviants (Todd et al., 2008). This study could have had a secondary effect of severity of illness between the patients along with the length of illness (Winterer & McCarley, 2010). The secondary effect issue was addressed by Salisbury *et. al.* by studying 3 groups of subjects (healthy controls, schizophrenia, and bipolar disorder) from their first hospitalization for psychosis to an average of 1.5 years into illness. Their results clearly show that only the frequency MMN in schizophrenia patients showed a significant decrease from initial hospitalization to 1.5 years of illness (Salisbury et al., 2007). The previously mentioned meta-analysis by Erickson *et. al.* (Erickson et al., 2016) also studied the effect of length of illness on 47 schizophrenia patients from several different studies and found a small positive relationship which was not significant. This meta-analysis included patient categories of first episode, chronic, and a broader category *all* of patients not separated by the included studies. Based on this patient distribution, and findings of previous studies (Salisbury et al., 2007; D. Umbricht & Krljes, 2005), it was speculated that MMN deficits in schizophrenia patients do worsen over the first few years of illness, but remain stable thereafter (Erickson et al., 2016).

The study by Salisbury *et. al.* also performed Magnetic Resonance Imaging (MRI) of the three groups of subjects. The volumetric measurements from the imaging data revealed a negative correlation between MMN amplitude and left hemisphere Heschl's gyrus grey matter volume in schizophrenia patients, even at first hospitalization. Heschl's gyrus contains the primary auditory cortex and some of the secondary auditory cortex. The longitudinal measures of MMN amplitude and Heschl's gyrus volume also showed a positive correlation in schizophrenia patients alone (Salisbury et al., 2007). The finding suggests the possibility of a pathological

process causing a reduction in grey matter volume of Heschl's gyrus which is sufficiently advanced to produce MMN deficits only at a later stage (Winterer & McCarley, 2010).

Studies have also reported reduction in pre-frontal and frontal cortex in schizophrenia patients (Benoit et al., 2012; Harms et al., 2010; Rasser et al., 2011). The pre-frontal cortex (PFC) co-ordinates information relayed from the association areas over the entire cortex. Association areas are the regions in the cortex which interpret information or coordinate a motor response. PFC performs abstract intellectual functions, interprets ongoing circumstances, and predicts future consequences. Feelings such as anxiety, tension, and frustration are evoked in the PFC. In an MMN source analysis study, altered electromagnetic activity in the PFC of schizophrenia patients was found. Reductions in the amplitude of MMN could be linked to mechanisms in the PFC, like its contribution to switching involuntary attention (Baldeweg et al., 2002) and in controlling the direction of attention (Näätänen et al., 2007). Moreover, deficits in verbal memory and attentional switching are correlated to reduction in temporal and frontal MMN (Hermens et al., 2010). Schizophrenia patients do not have an effective attention switching ability. As social interactions require dynamically switching attention, the lack of this ability in schizophrenia patients may be a contributing to their social withdrawal (C. C. Duncan et al., 2009). In schizophrenia patients, there is also a reduction in MMN amplitude due to frequency deviant which is related to the grey matter reduction in the bilateral Heschl's gyrus, as well as, motor and executive regions of the frontal cortex (Rasser et al., 2011). Thus, from the above findings, the temporal lobe changes are likely associated with pre-perceptual change detection, while the PFC and frontal lobe changes are responsible for deficiency in involuntary attention switching and higher-order cognitive processes.

4.3 Aims of Study

To establish a significant contribution of MMN to the research and treatment of schizophrenia, it is essential to be able to predict the functional outcome of patients, and provide an endophenotype for genetic studies (C. C. Duncan et al., 2009). MMN has been shown to predict the likelihood of conversion to psychosis in clinically high-

risk individuals. Individuals that did convert to first-episode psychosis, had significantly smaller MMN amplitude at baseline, compared to the ones that did not (Bodatsch et al., 2011). MMN has been shown to have a stable relationship with psychosocial and cognitive assessment of both patients and healthy controls (Light & Braff, 2005; Light & Näätänen, 2013). MMN has also been demonstrated as one of the most reliable neural endophenotype (Light et al., 2012), as well as, a feasible biomarker for multi-site clinical studies (Light et al., 2015) of schizophrenia amongst other measures like P3a, N100, etc. For these reasons, it is one of the most useful targets for developing drugs and possibly even *precision medicine* to improve the cognitive and functional deficits in schizophrenia (Light & Näätänen, 2013).

Following were the aims of this study:

1. To use an auditory oddball task with multiple deviant tone types that elicited a MMN response in both healthy control subjects and patients diagnosed with the schizophrenia spectrum of disorders.
2. To compute the ERP, MMN, and ERSP responses to each deviant tone and study the similarities and differences across each deviant tone. Previous research discussed in section 4.2.1 has shown that MMN response exhibits different characteristics depending on the type of deviant tone. We hypothesized that this experiment would let us explicitly visualize these differences in both the time and frequency domain of EEG data, and in the EEG measures such as MMN peak amplitude and peak latency.
3. To visualize and calculate statistical differences between the response from healthy control group and patient groups. We hypothesized that MMN elicited by patient group would be significantly diminished when compared to the healthy control group.
4. To compute the correlations between the EEG measures and patient symptom severity. We hypothesized to see a positive correlation between the MMN deficit, and the severity of patient symptoms as recorded by the PANNS and MADRS scales.

4.4 Experimental Methods

4.4.1 ODDBALL TASK DESCRIPTION

The task used to elicit and study MMN in subjects is called an auditory oddball task. This task involved subjects listening to a series of tones using foam ear inserts (Advanced Medical Equipment Ltd.), while they watched a pre-selected muted video clip. The tones played comprised a standard tone which occurred with a probability of 50% and 5 different deviant tones at 10% probability each. The subjects were also instructed to not pay attention to the tones, to produce a cleaner MMN response, free from ERP response patterns resulting from attention related processing in the brain. This was a passive task without any response from the participants.

In the experimental setup for this chapter, the Stim^2 Gentask software (Neuroscan Inc.) was used to generate the stimuli and the triggers were interfaced with NeuroScan 4.5 Acquire software using the Stim^2 hardware. The sequence of tones was closely based on an optimal paradigm proposed by Näätänen and colleagues in their 2004 paper (Näätänen et al., 2004). This paradigm was designed to shorten the time of the auditory oddball task while eliciting similar MMN amplitude response. Instead of presenting multiple time sequences for each type of deviant tone, like it was done in standard auditory oddball tasks, the method proposed in the 2004 paper used only one time-sequence with multiple types of deviants. Each tone was presented with an inter-stimulus interval (ISI) of 1000ms. The experiment started with a series of 10 standard tones followed by an alternating pattern of one standard and one of the deviant tones. The five different deviant tones presented were duration, frequency, intensity,

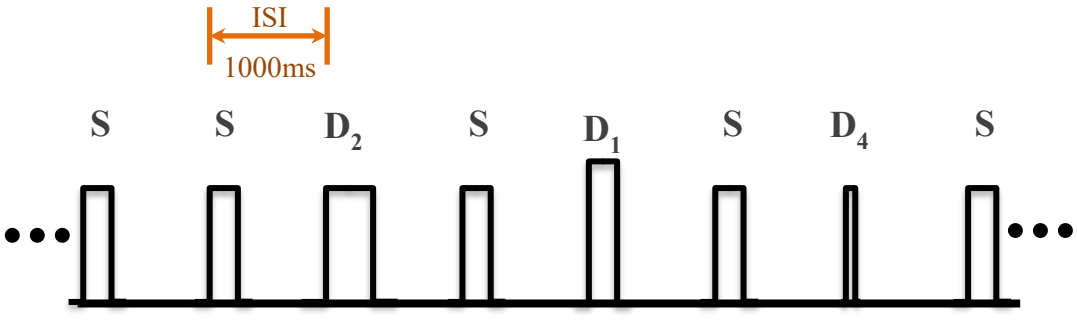


Figure 4.2 Timing diagram schematic of the auditory oddball task. S: Standard tones, D_n: Deviant tones. The experiment begins with 10 standard tones after which one of the deviants (randomly chosen) and standard tones are presented in an alternating pattern. Same deviant does not occur consequently.

location, and gap. These deviant tones followed a pseudo-random sequence with no two consecutive deviant tones of the same type. In all, 1510 stimuli were presented with 760 standard tones and approximately 150 of each deviant tone. The experiment took approximately 25 minutes to complete. The timing diagram of the task is presented in figure 4.2 and the details of the optimal paradigm used are outline in table 4.1.

Table 4.1 Optimal MMN experimental paradigm (adapted Näätänen et. al. 2004).

Parameter	Comment
Optimal Paradigm	One frequent standard, five rare deviant tones
Standard	Harmonic stimulus comprising 3 sinusoidal partials of 500, 1000, and 1500Hz, with intensity of second and third partials 3dB and 6dB lower than the first partial.
Duration	75ms, 5ms rise/fall
Intensity	80dB SPL
Interstimulus interval	1000ms (fixed)
Location	Midline (binaural)
Deviants	
Duration	25ms, 5ms rise/fall
Frequency	Half of frequency deviants are 10% higher partials; half are 10% lower partials.
Intensity	Half of intensity deviants are 10dB higher, half are 10dB lower.
Location	Half of location deviants are perceived as having a spatial location 90° to the right and half 90° to the left of the midline by introducing an interaural time difference of 800μs.
Gap	Silent gap of 7ms (including 1ms rise/fall) in the middle of a 75ms stimulus.
Probabilities	.50 (standard), .10 (each of the deviants), one standard between each deviant

4.4.2 SUBJECTS

All the recruited healthy control subjects (n = 19) performed the auditory oddball task. However, 2 subjects were excluded from the analysis due to noise and corrupted data. Therefore, data from 17 healthy control subjects was analysed and is presented for this experiment. All the recruited patients performed the auditory oddball task. Each patient was included in the analysis for this experiment and results are presented for individual patients as well as three groups of patients. The groups of patients include schizophrenia patients (P4, P5, P6), schizoaffective disorder patients (P1, P2, P3), and all patients grouped together.

4.4.3 EEG MEASUREMENT

The standard EEG recording, and processing steps described in Section 3.2 of Chapter 3 were used in this experiment. The epoch for individual trials in the oddball task was defined as -200ms to +800ms relative to stimulus onset with the average amplitude of the 200ms pre-stimulus used for baseline correction. A mean of 86% of trials were retained in the healthy control group after artefact rejection and cleaning of the EEG data. In the patient group, more than 85% of the trials were retained from each patient except patient P1. Patient P1's signals were very noisy even after artefact rejection and approximately only 36% of trials were preserved in this case.

After each subject's EEG data was pre-processed and cleaned, it was used for ERP and ERSP analysis. ERP and ERSP responses were computed for the standard tone and each of the 5 deviant tones. MMN for each deviant tone was computed as the difference between the deviant tone ERP and the standard tone ERP. Similarly, a difference ERSP was computed as the difference between the deviant tone ERSP and the standard tone ERSP. Based on the literature review, maximum MMN effect is observed on the fronto-central EEG electrodes. Hence, the ERP and ERSP responses at electrodes Fz and Cz are reported in this chapter.

Three EEG measures, namely MMN peak amplitude, MMN peak latency, and average MMN amplitude, were computed for each individual subject, and all the subject groups (healthy controls, schizophrenia patients, schizoaffective disorder patients, all patients). These measures were calculated using their definition in the 2004 paper by Näätänen and colleagues (Näätänen et al., 2004). The MMN peak

amplitude was defined as the largest negative peak in the 90-250ms post-stimulus period and the MMN peak latency was defined as the latency measured for this peak. The average MMN amplitude was defined as the mean voltage of the 40ms period centered at the MMN peak latency. Other researchers have used shorter periods (135-205ms) for MMN peak and latency computation (Hermens et al., 2010; Light et al., 2007). However, these studies used only a single deviant type and therefore had smaller variability in the MMN response. The 90-250ms duration considers all the 5 deviant types used in the experiment described in this chapter, similar to (Näätänen et al., 2004). The computation of EEG measures was expanded to 5 midline electrodes including the two electrodes Fz and Cz at which ERP and ERSP responses were visualised, and electrodes FCz, CPz, and Pz. These measures were used to visualize the variation across midline electrodes and subject groups and for statistical analysis.

4.4.4 SATISTICAL ANALYSIS

Non-parametric permutation tests and cluster-based multiple comparisons correction were used to analyse the statistical significance of the differences between the responses to standard and deviant tones, in both ERP and ERSP analysis. When presenting the group results, these tests were paired statistical tests as the same subjects within each group were presented with both standard and deviant tones. However, when presenting the results for individual patients, unpaired statistical measures were used as the standard and deviant tone trials presented to each patient were not paired with one another.

A mixed factor 3x5x5 ANOVA was carried out for the MMN peak amplitude, MMN peak latency, and average MMN amplitude measures. Group of the subject (healthy control, schizophrenia, and schizoaffective) was used as the between-subject factor and electrode locations (Fz, FCz, Cz, CPz, and Pz) and deviant type (duration, Frequency, Intensity, Location, and Gap) were used as the within-subject factors. With a total of 23 subjects (17 healthy controls, 3 schizophrenia, and 3 schizoaffective) the analysis was performed on 575 (23*5*5) data points in each case.

4.5 Results and Comparisons

The results from the oddball task are presented in seven subsections. The first five subsections present the results for the five individual deviant tones. The sixth subsection presents the results from the three measures computed from the five deviant tones including their visualization and statistical analysis. The final subsection presents the correlations between the computed measures and patient demographic data.

Each of the first five subsections is divided further in three sub-subsections one each for ERP analysis, ERSP analysis, and summarized key findings. Both the ERP and ERSP sub-subsections follow the same specific order of results. First, results from the group of healthy control subjects are presented. This is followed by individual patient results. After this, results from the two groups of patients (schizophrenia, schizoaffective disorder) along with a grand average of all patients are shown. In all the ERP analysis figures, standard tone ERP is shown in black, deviant tone response is shown in grey, and MMN response is shown in yellow. The black bars at the bottom of each plot represent the clusters of period that showed significant difference ($p<0.05$) between the standard and the deviant ERP. For the group ERSP analysis figures, response to the standard tone is plotted in the right column, response to the deviant tone is plotted in the middle column, and difference ERSP is plotted in the left column. The clusters of significant differences between responses to the standard and deviant tones are shown using black contours overlaid on the difference ERSP plots. ERSP results are presented in the same sequence as the ERP results. For the ERSP analysis figures of individual patients only the difference ERSP plots are shown.

4.5.1 DURATION DEVIANT MMN

4.5.1.1 EVENT RELATED POTENTIAL ANALYSIS – DURATION DEVIANT

The duration deviant tone was shorter in time compared to the standard tones (table 4.1). Figure 4.3 shows the grand averaged ERP response to the duration deviant tone, the standard tone, and the computed duration deviant MMN. The figure shows that compared to standard ERP, the N100 component of the ERP response to the duration deviant is larger in amplitude and has a longer duration. As a result, a significant difference and a MMN response with a peak before 200ms is generated.

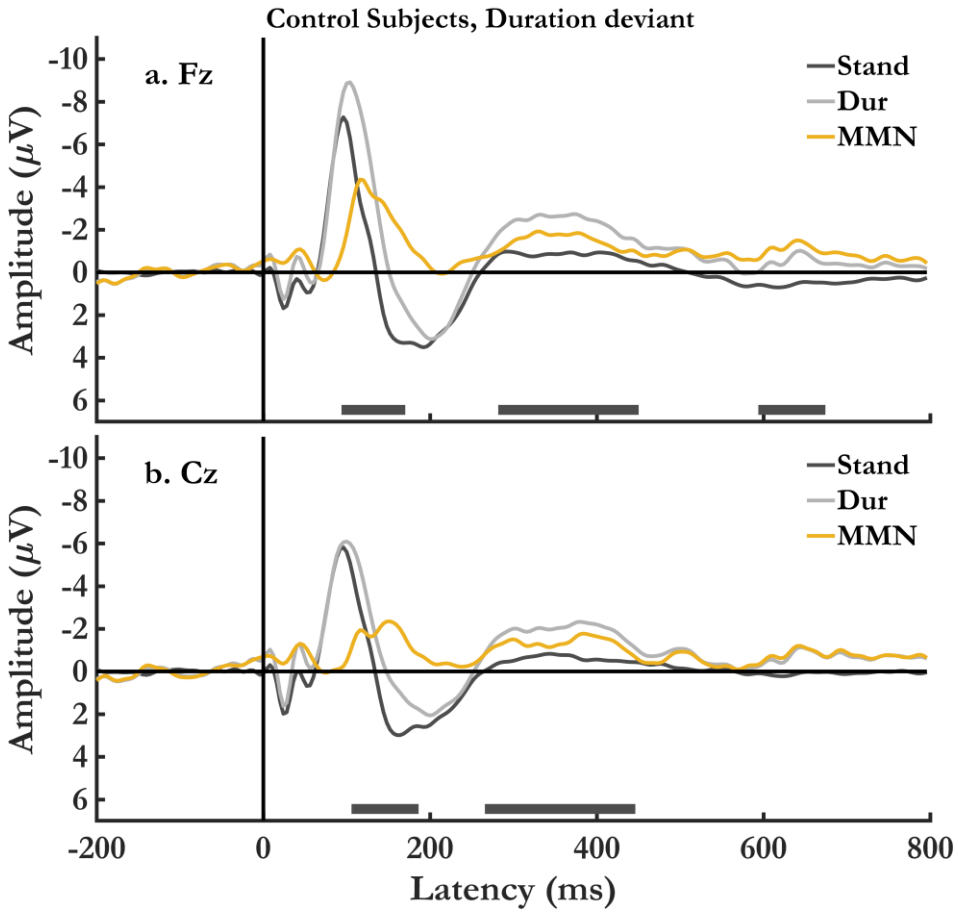


Figure 4.3 Grand average standard ERP, duration deviant ERP, and duration MMN in control group (n = 17). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz, b. Electrode Cz.

There is a secondary, but significant, negativity at a later interval. This negativity is likely a result of the N200 component of ERP, which is believed to be an indicator of initial discrimination between stimuli when subjects are actively attending to the tone (D. S. G. Umbricht et al., 2006; Winterer & McCarley, 2010). Though such a response is not expected in a passive auditory oddball experiment, a similar response was observed for most deviant types in the paper that proposed the optimal paradigm adapted in this experiment (Näätänen et al., 2004). We also see that the negative peak of MMN decreases from Fz to Cz electrodes and has a longer latency at Cz. This is reflected in the duration MMN peak amplitude and peak latency measures reported in table 4.2.

The standard and duration deviant ERP responses and corresponding duration MMN from individual subjects in the patient group are shown in figure 4.4 for

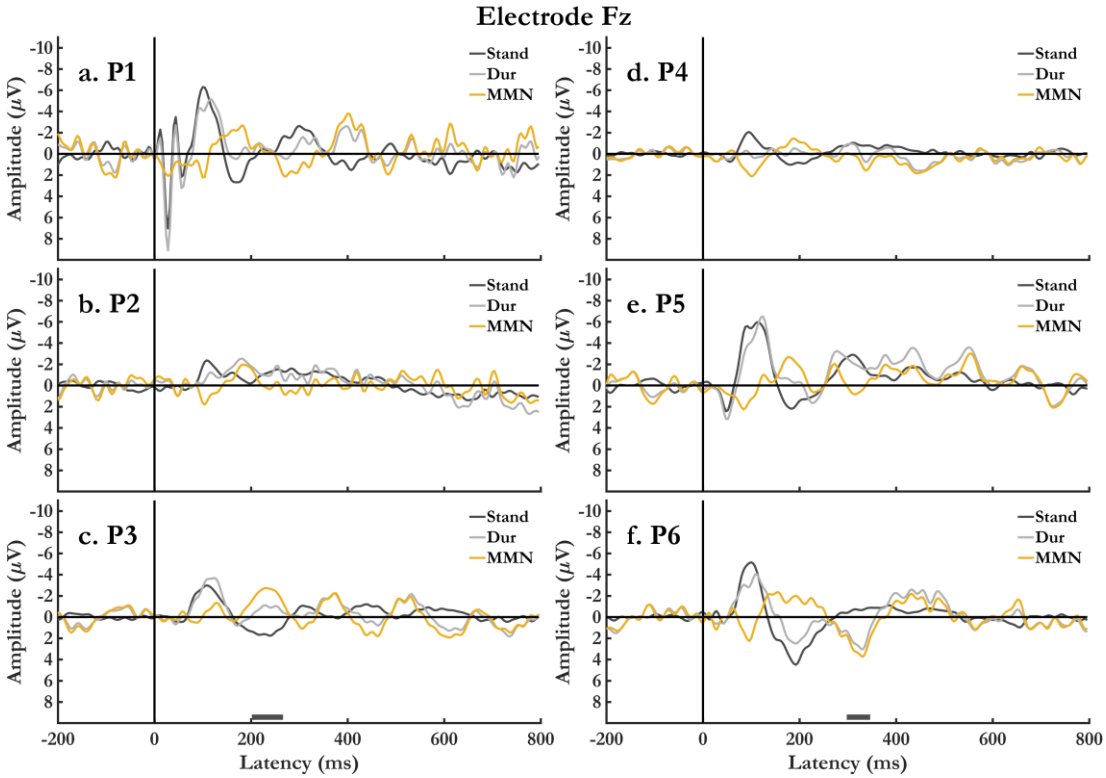


Figure 4.4 Average standard ERP, duration deviant ERP, and duration MMN at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot represent periods of significant difference.

electrode Fz and figure 4.5 for electrode Cz. From these figures, we see that the ERP responses for both the standard tone and duration deviant tone are smaller in amplitude across each subject. We also see that only a few of the plots show any significant differences between the two responses. Resulting from the diminished ERP amplitude in both standard and duration deviant, and the similarity between them, the MMN response in each patient is diminished. For example, the ERP response from patients P2 and P4 is only marginally different from the baseline activity. It should also be noted that unlike the ERP for duration deviant in control subjects, the N100 component, when present in patients, closely follows, and in many cases is smaller than the N100 component of the standard tone. As a result, we see a positivity in the MMN response earlier in the trial, followed by the negative peak later. This peak in the MMN amplitude is a result of the difference in the ERP responses after the N100 component. Therefore, the duration MMN peak latency is delayed in the patient group.

The duration MMN peak amplitudes and latencies for individual patients are recorded in table 4.2.

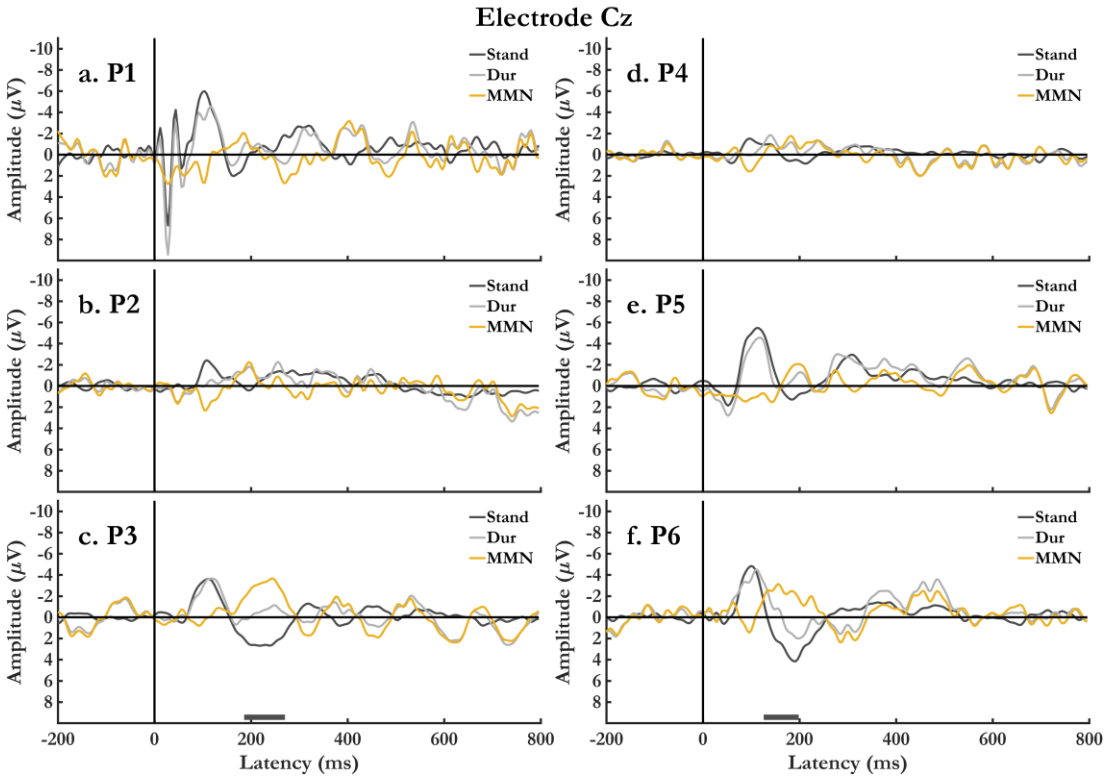


Figure 4.5 Average standard ERP, duration deviant ERP, and duration MMN at Cz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot represent periods of significant difference.

The ERP results from the groups of patients based on their clinical diagnosis are presented in figure 4.6 for electrode Fz and figure 4.7 for electrode Cz. Both these figures also show control group response for the respective electrodes taken from figure 4.3. This is followed by grand average ERP responses from schizophrenia patients, schizoaffective disorder patients, and all patients combined. From these figures, we see that the difference between duration deviant and standard response is significant only for a small period at electrode Cz in schizophrenia and schizoaffective disorder patients. Similar to individual patient plots, all the ERP responses and the computed MMN are diminished compared to control subjects. Unlike the control group, the MMN response shows initial positivity and later negativity in both the patient groups. In the grand averaged response from all patients grouped together (fig

4.6d, 4,7d) there are significant differences at both Fz and Cz electrodes, and the MMN peak amplitudes are observed within the period of this significant difference. The duration MMN peak amplitude and peak latency for all the patient groups are presented in table 4.2. Compared to the healthy control group, the duration MMN peak amplitude is smaller, and the peak latency is longer in each of the patient groups.

Table 4.2 MMN peak amplitude and latency measures for duration deviant.

	Peak Amplitude (μVolts)		Peak Latency (ms)	
	Fz	**Cz**	**Fz**	**Cz**
Control Subjects (n = 17)				
Grand Average	-4.35	-2.35	116	152
Patients				
P1	-2.65	-2.06	184	184
P2	-1.98	-2.26	184	196
P3	-2.73	-3.67	232	244
P4	-1.46	-1.75	188	180
P5	-2.66	-2.07	176	196
P6	-2.35	-3.15	156	156
Schizophrenia Patients (n = 3)				
Grand Average	-1.93	-2.01	188	184
Schizoaffective Disorder Patients (n = 3)				
Grand Average	-1.73	-1.92	184	192
All Patients (n = 6)				
Grand Average	-1.82	-1.92	184	188

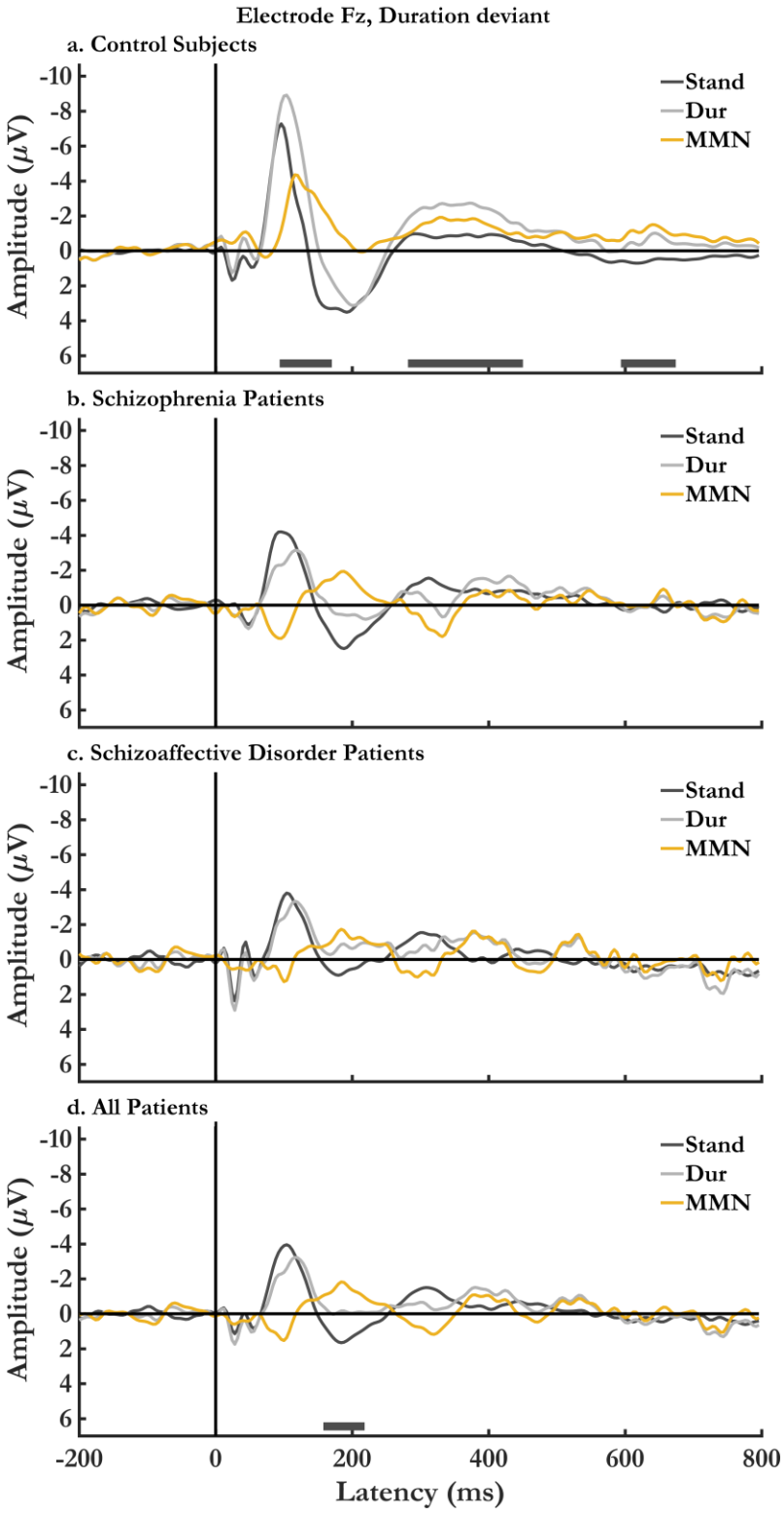


Figure 4.6 Grand average standard ERP, duration deviant ERP, and duration MMN at electrode Fz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.3a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

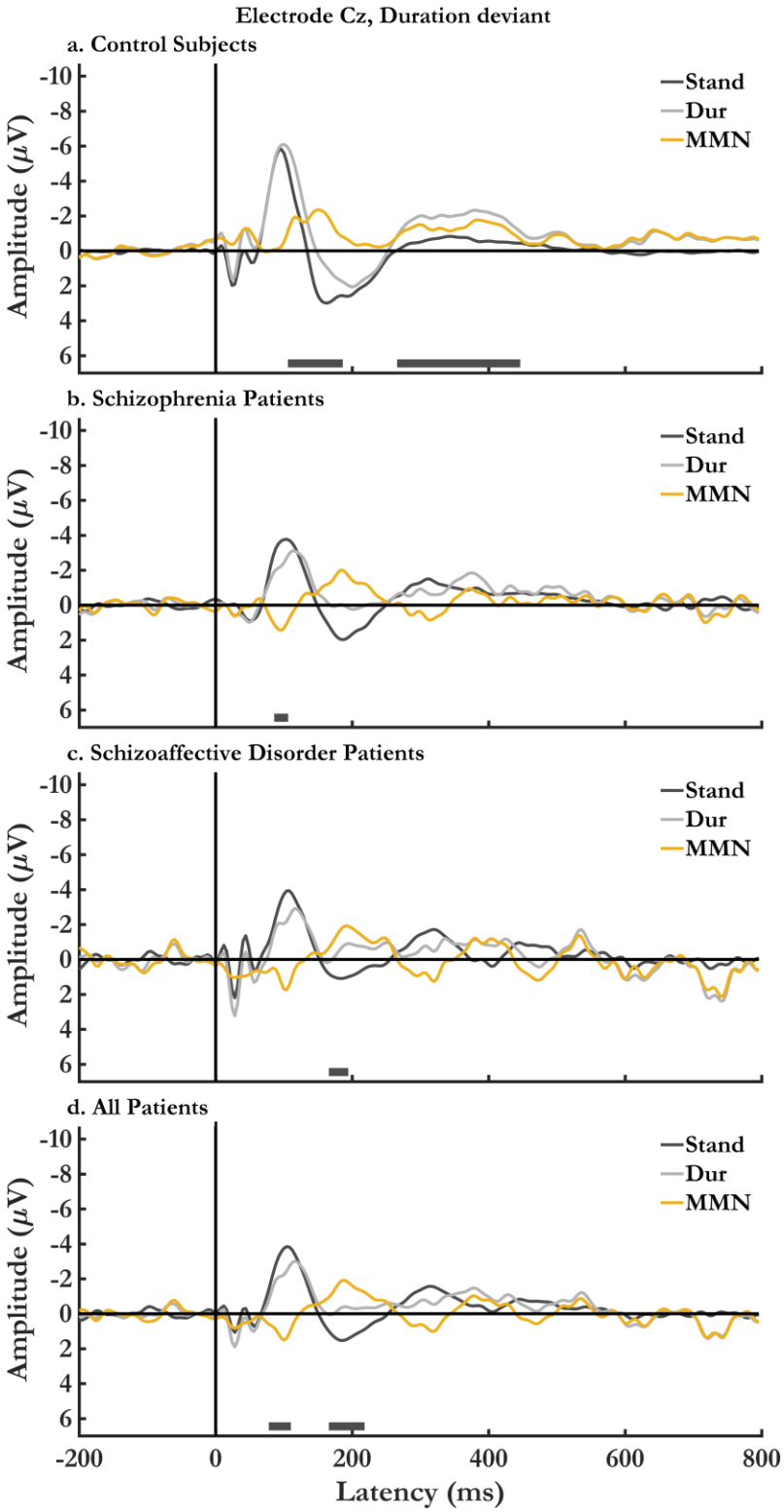


Figure 4.7 Grand average standard ERP, duration deviant ERP, and duration MMN at electrode Cz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.3b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

4.5.1.2 TIME-FREQUENCY ANALYSIS – DURATION DEVIANT

The healthy control group ERSP responses to the standard and duration deviant tones, and the difference ERSP are shown in figure 4.8. The figure shows an initial synchronisation (i.e. an increase in power, represented by blue) of lower frequencies up to approximately 16Hz in both the standard and deviant response. The duration deviant ERSP response has a relatively stronger synchronisation (darker blue) around 100ms time point, with a peak in the 4-8Hz region. This response closely matches the duration MMN peak latency seen in figure 4.3. The responses at both the Fz and Cz electrodes show similar pattern with the synchronisation at Fz being stronger. The synchronisation of the lower frequencies gradually decreases to the baseline level 200ms post-stimulus. The right column in the figure with the plot of the difference

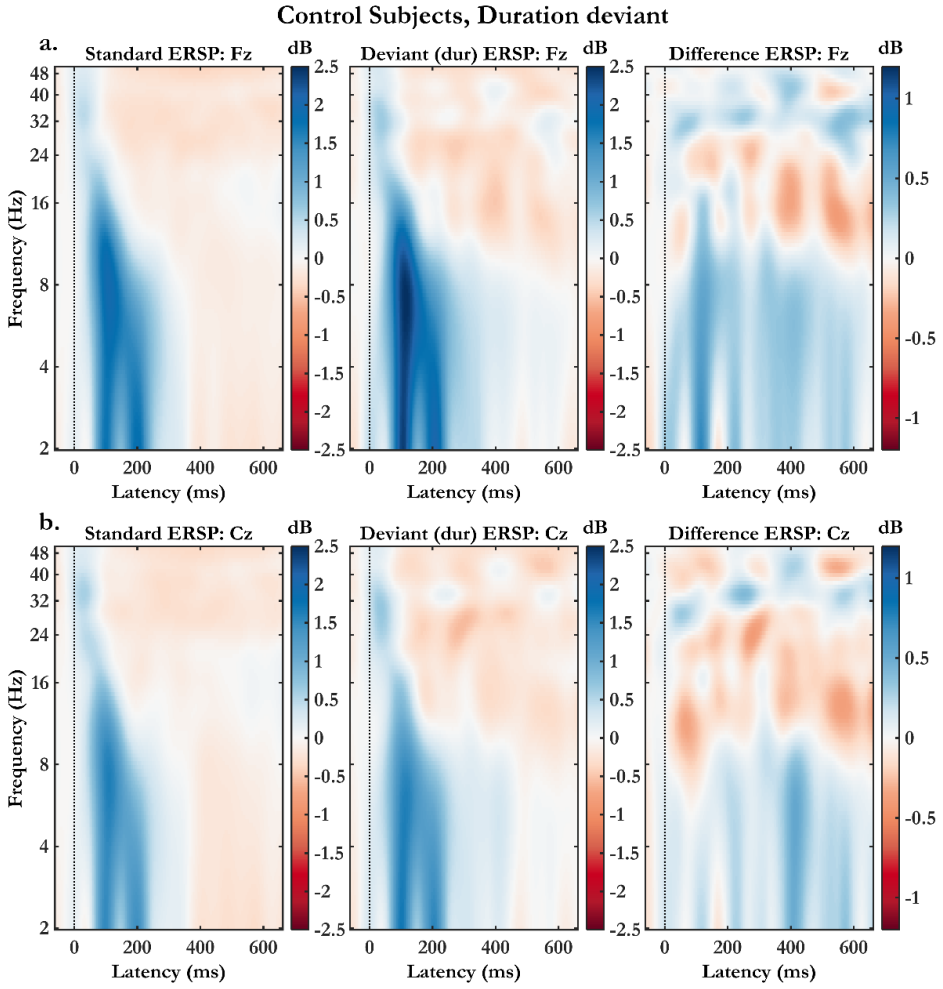


Figure 4.8 Grand average standard ERSP, duration deviant ERSP, and difference ERSP in control group (n = 17). a. Electrode Fz, b. Electrode Cz. Each row represents three plots (left to right): standard ERSP, duration deviant ERSP, difference ERSP. There are no significant difference regions ($p<0.05$).

ERSP shows that the lower frequencies are more synchronised during the duration deviant trials. We also see a desynchronisation (i.e. decrease in power, represented by red) of higher frequency in the range around 16Hz. The permutation statistical test along with the cluster-based multiple comparisons correction did not show any significant differences between the standard and deviant tone response at either Fz or Cz electrodes.

The average difference ERSP responses from individual patients are shown in the figures 4.9 and 4.10 for electrodes Fz and Cz, respectively. From these plots, we see that most of the patients do not show a pattern of synchronisation and desynchronisation as observed in the averaged difference ERSP plots (fig 4.8) from the control subjects. Patients P1, P3, and P5 show a strong desynchronisation at lower frequencies during the duration deviant relative to the standard tone. Some similarity

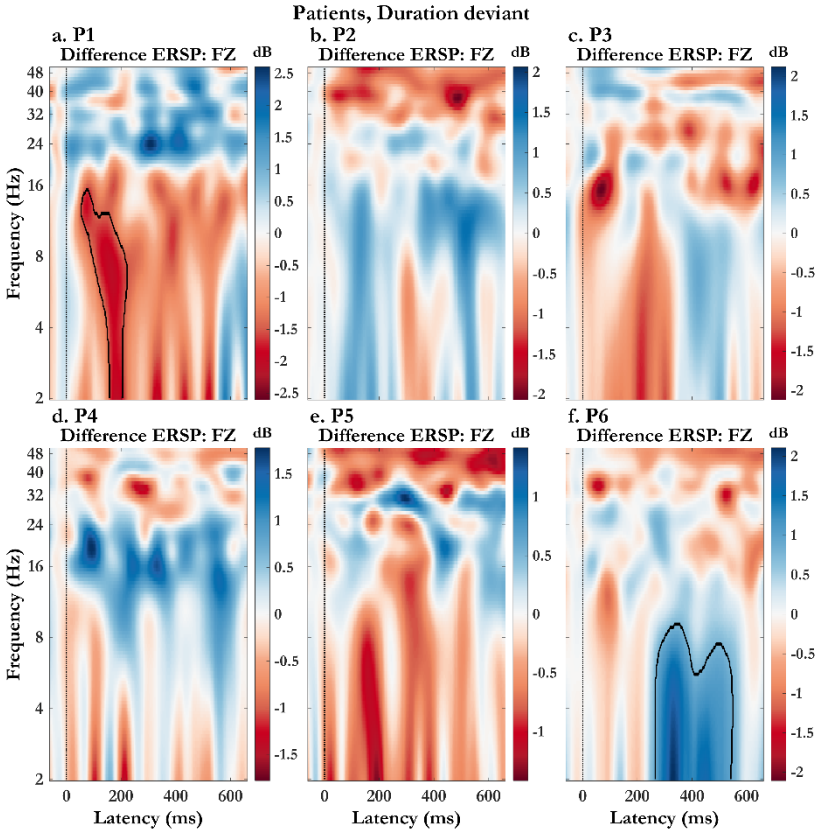


Figure 4.9 Average difference ERSP between duration deviant and standard tone at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

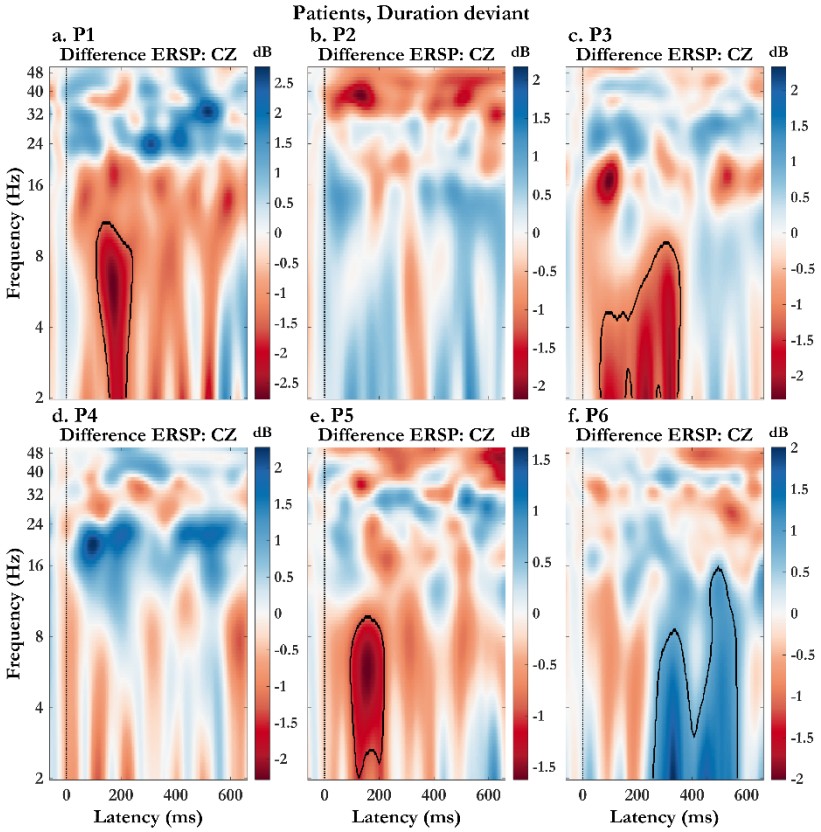


Figure 4.10 Average difference ERSP between duration deviant and standard tone at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

is observed between the plots from patient P2 and the control subjects, but a desynchronisation of lower frequencies is observed later in the trial. However, in patient P6, following an initial desynchronisation, a strong synchronisation of the lower frequency bands is observed later in the trial. In some plots, we see clusters of regions where standard and duration deviant ERSP are significantly different from each other (overlaid black contours). In the figures 4.9 and 4.10, we also see that the responses at electrodes Fz and Cz from each subject exhibit similar patterns.

The difference ERSP plots for individual patients show considerable variability both within and between subjects. To get a better understanding of the patient group responses

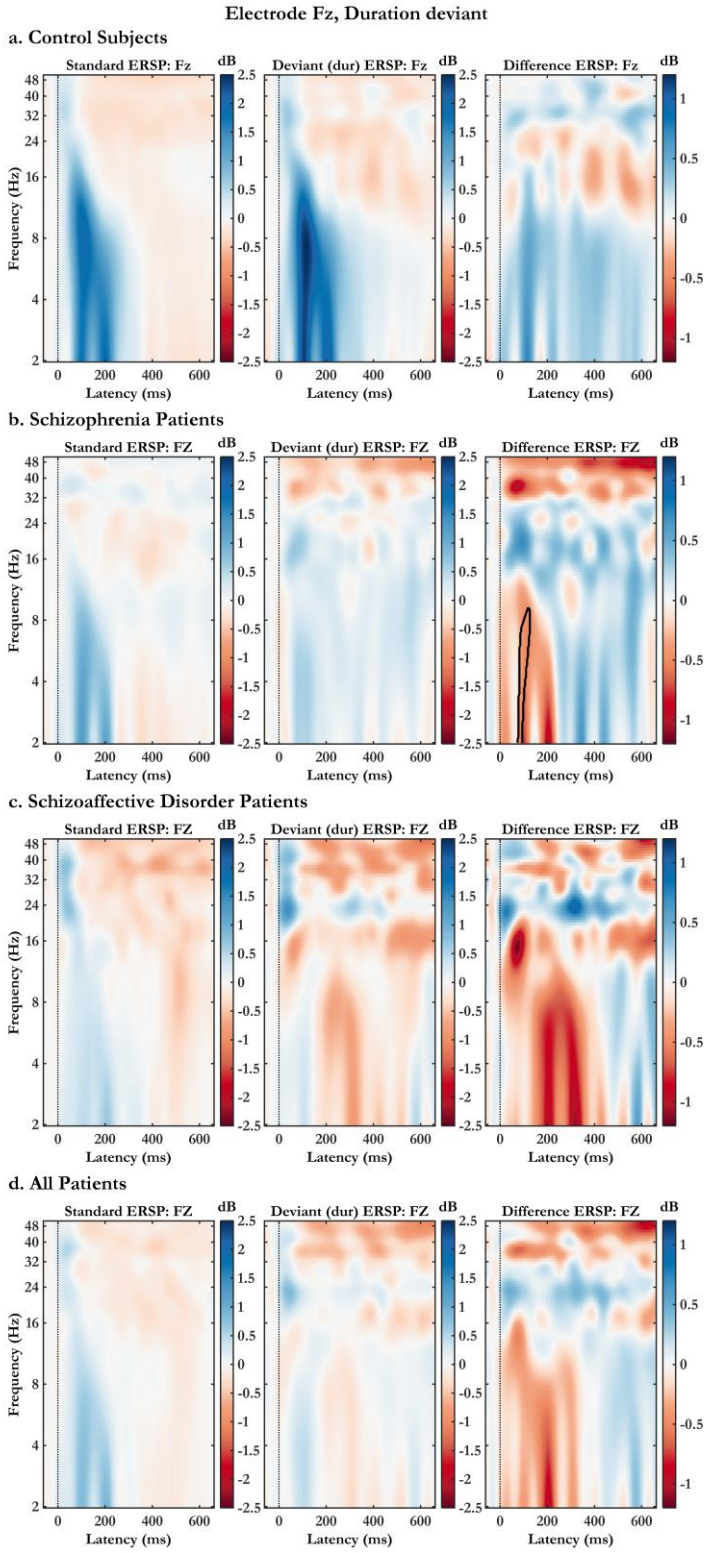


Figure 4.11 Grand average standard ERSP, duration deviant ERSP, and difference ERSP at electrode Fz in subject groups. a. Control subject response from Figure 4.8a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ are presented by black contours.

to the duration deviant, the average ERSP response at electrode Fz and electrode Cz are shown in figure 4.11 and figure 4.12, respectively. Both these figures show ERSP responses from control subjects, followed by schizophrenia patients, schizoaffective disorder patients, and all patients grouped together. All the plots use the same range of colour scale as seen in figure 4.8. The ERSP response to standard and duration deviant tones are plotted with ±2.5dB range and the average difference ERSP is plotted with ±1.2dB range.

In schizophrenia patients (figs 4.11b and 4.12b), the ERSP response to the standard tone is similar to that of the control group but comparatively smaller in magnitude. The duration deviant on the other hand results in small changes in the time-frequency signals and is close to the baseline. This is in contrast to the control group where the duration deviant tone elicited a stronger initial synchronisation in the low frequency region compared to that of the standard tone. Due to a relatively lower magnitude of response to the duration deviant, we see a desynchronisation of lower frequencies that peaks around a latency of 200ms as seen in difference ERSP of schizophrenia patient group.

A different pattern is observed in the patients diagnosed with schizoaffective disorder (figs 4.11c, 4,12c). In this case, the response to the standard tone looks similar to that of the control group, however the range is even lower than schizophrenia patients. Due to this, the response looks barely different from the baseline period before the trial onset. In the duration deviant ERSP however, we see that the lower frequency region is desynchronised in schizoaffective disorder patients. This also results in a difference plot that has a strong desynchronisation. It is also interesting to note that the peak of the desynchronisation in the difference plot is observed at latency longer than 300ms.

In the grand averaged ERSP response from the whole patient group (figs 4.11d, 4.12d) we see that, patients have a lower overall response magnitude (synchronisation or desynchronisation) to both the standard tone and duration deviant tone. We also see that the response to the duration deviant is small and is close to the pre-stimulus baseline period.

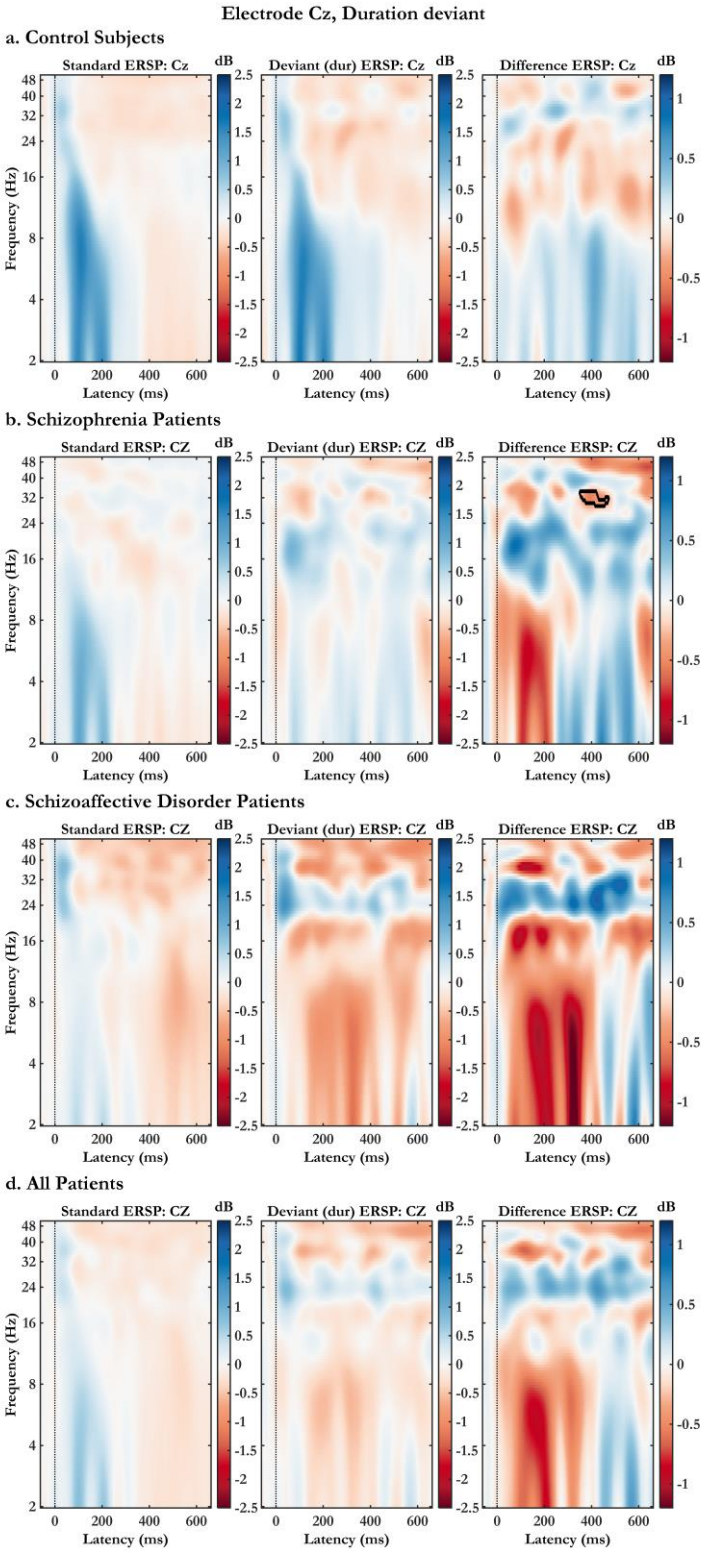


Figure 4.12 Grand average standard ERSP, duration deviant ERSP, and difference ERSP at electrode Cz in subject groups. a. Control subject response from Figure 4.8b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

4.5.1.3 KEY FINDINGS – DURATION DEVIANT

1. The control subject group showed a large and significant duration deviant MMN response at both electrode Fz and Cz.
2. The patient groups showed a diminished duration deviant MMN response which was significant only for a short duration at electrode Cz.
3. The duration deviant ERSP response in control subject group showed stronger synchronization compared to standard tone ERSP response around 100ms post-stimulus however, the difference was not significant at either Fz or Cz electrodes.
4. The ERSP responses to both standard tone and duration deviant were diminished in patient groups and did not show the synchronization pattern observed in control subjects.

4.5.2 FREQUENCY DEVIANT MMN

The frequency deviant in the auditory oddball task was created by using sinusoidal partials that differed in their frequencies, when compared to the standard tone partials. Expanding on the description given in table 4.1, half of the frequency deviants had 10% decrease in the partial sinusoidal frequency (450Hz, 900Hz, 1350Hz) and the other half had a 10% increase in the partial's frequencies (550Hz, 1100Hz, 1650Hz).

4.5.2.1 EVENT RELATED POTENTIAL ANALYSIS – FREUQENCY DEVIANT

The grand average ERP response from the healthy control group to frequency deviant stimuli is shown in figure 4.13. This figure also shows the standard tone response for comparison and the frequency MMN response computed by taking the difference between the frequency deviant and the standard tone.

The ERP response to the frequency deviant shows a larger N100 component compared to that of the standard tone. This component is also boarder in duration . As a result, we see the MMN response starting to increase around 100ms and peak after the N100 component. The peak of the MMN is seen around the time of the positive peak in the standard tone ERP. Both the Fz and Cz electrodes show a similar MMN response, with a larger peak on the frontal electrode. The values of frequency MMN peak amplitudes and peak latencies are outlined in table 4.2. Similar to the duration deviant response, the black bar at the bottom of each plot in figure 4.13 represent

statistically significant differences between the responses to the frequency deviant and standard tones during the 100-200ms post-stimulus period,. The secondary significant negativity is present in this case too.

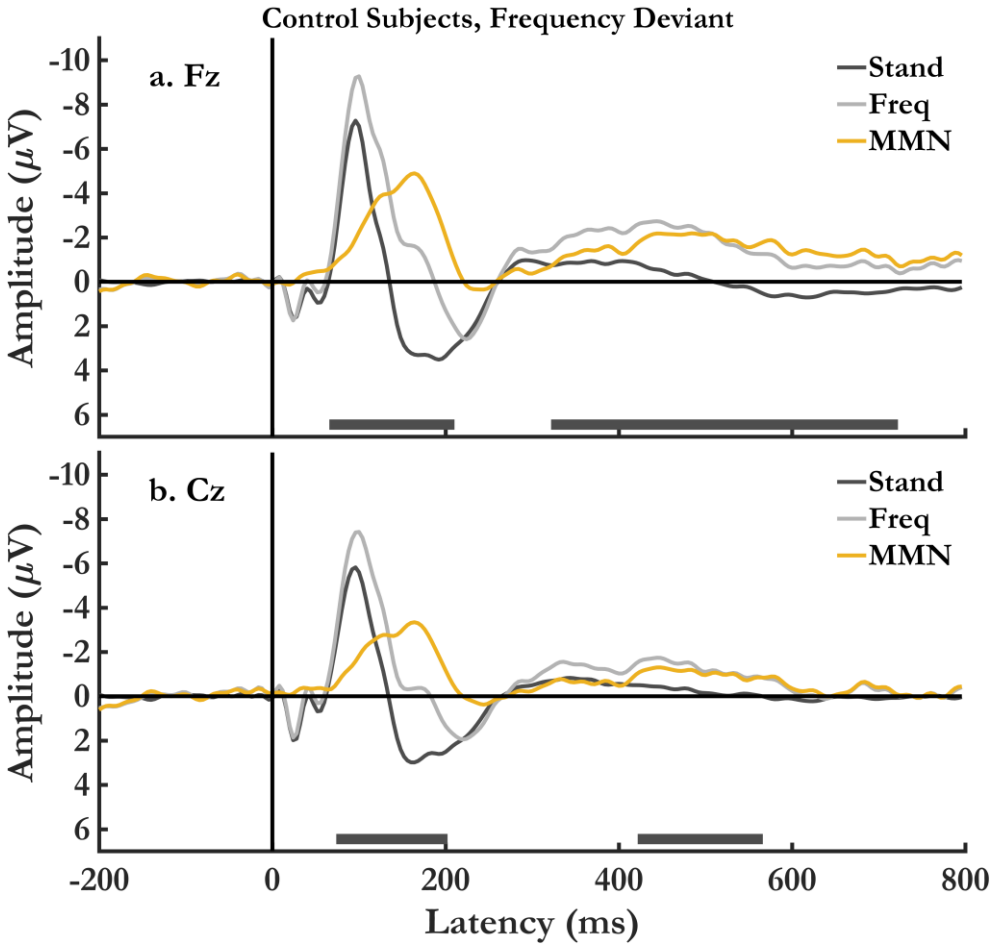


Figure 4.13 Grand average standard ERP, frequency deviant ERP, and frequency MMN in control group (n = 17). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz, b. Electrode Cz.

The frequency deviant ERP response and MMN from individual patients, is shown in figure 4.14 for electrode Fz and in figure 4.15 for electrode Cz. We see from these plots that for most of the patients, the MMN response shows small fluctuations that are barely distinguishable from that of the pre-stimulus baseline period. Only patient P6 at electrode Cz showed a significant difference between the standard tone and frequency deviant in the region where the peak of the MMN is expected. The frequency MMN peak amplitude and peak latency values for individual patients are shown in table 4.3. We see from this table that on average compared to control

subjects, each patient showed a decreased MMN peak amplitude which occurred at a longer peak latency. The relatively shorter latency in patient P3 (92ms at Cz) resulted from not having a clearly defined MMN peak.

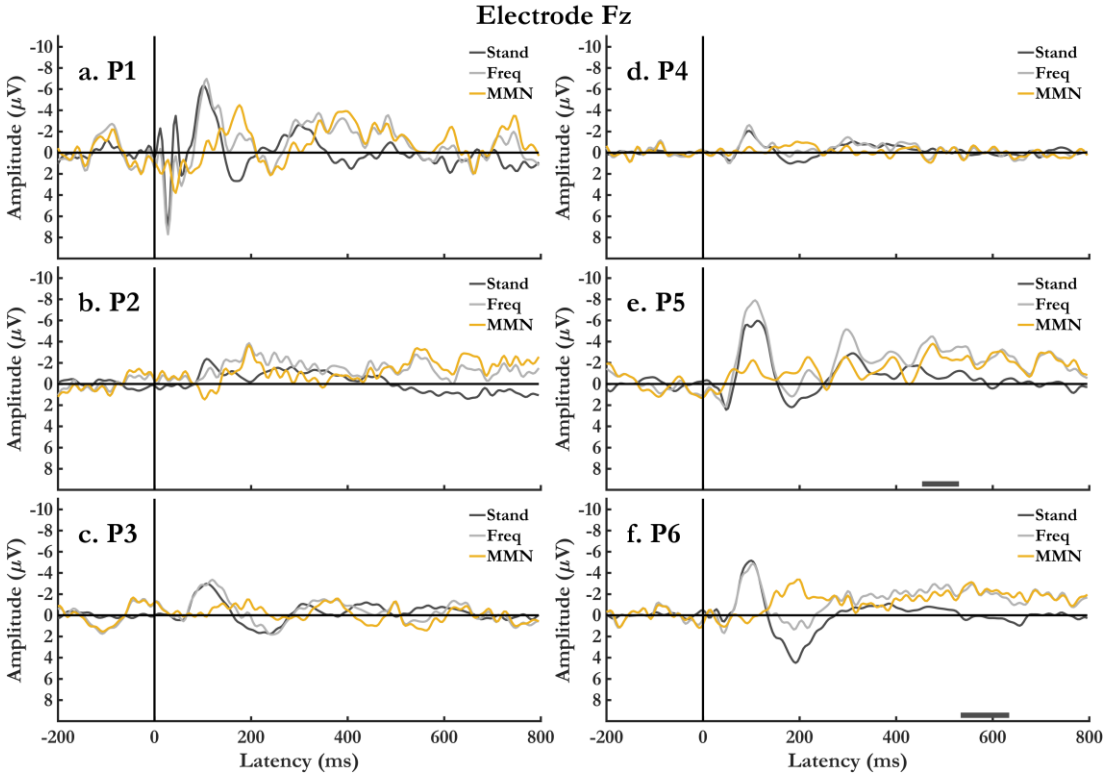


Figure 4.14 Average standard ERP, frequency deviant ERP, and frequency MMN at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

Individual patients showed considerable variability between each other and do not represent the group response to the frequency deviant tone. The grand average ERP responses from the schizophrenia and schizoaffective disorder patient groups, to frequency deviant and the frequency MMN, are shown in figures 4.16 for electrode Fz and 4.17 for electrode Cz. In both these figures the ERP response from control subjects from figure 4.13 is presented at the top. This is followed by the ERP response from the two clinically diagnosed groups of patients and then by the ERP response from all patients grouped together.

In schizophrenia patients (fig 4.16b, 4.17b) we see the frequency deviant N100 component peak is a little higher than the standard tone ERP response. However, this

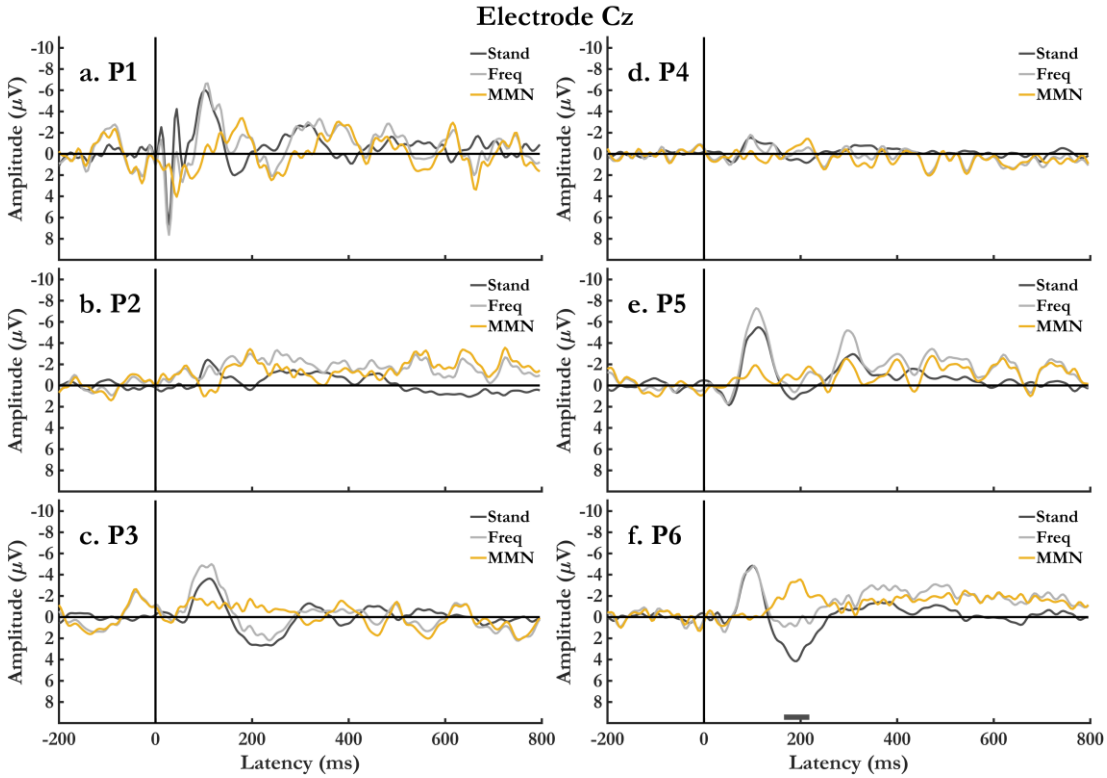


Figure 4.15 Average standard ERP, frequency deviant ERP, and frequency MMN at Cz electrode in individual patients. The six patient (P1to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

ERP response has a smaller positivity leading to the peak of the MMN in the time region following the N100 component. As can be inferred from the individual patient plots, there is an overall reduction in the ERP response, and thus the MMN. In patients with schizoaffective disorder, the ERP response to the frequency deviant (fig 4.16c, 4.17c) closely follows the standard tone response, until a little after the N100 peak. The deviant ERP, unlike the standard tone response, stays negative for most of the trial period and shows positivity only for a short period. As a result, the MMN peak in schizoaffective disorder group is little higher than the schizophrenia group, but still lower than the control group. In both the patient groups we do not see significant differences between the two ERP signals. In the grand averaged response from all the patients (fig 4.16d, 4,17d) we see a significant difference at electrode Fz, however, the MMN peak amplitude is still smaller than the control subject group. Like in the individual patient case, the MMN peak amplitudes and peak latencies for patient groups are presented in table 4.3.

Table 4.3 MMN peak amplitude and latency measure for frequency deviant.

	Peak Amplitude (μVolts)		Peak Latency (ms)	
	Fz	**Cz**	**Fz**	**Cz**
Control Subjects(n = 17)				
Grand Average	-4.89	-3.34	164	164
Patients				
P1	-4.48	-3.37	176	180
P2	-3.65	-3.43	196	196
P3	-1.49	-1.72	192	92
P4	-1.04	-1.42	196	216
P5	-2.52	-1.90	216	108
P6	-3.40	-3.54	196	200
Schizophrenia Patients (n = 3)				
Grand Average	-1.88	-1.83	200	208
Schizoaffective Disorder Patients (n = 3)				
Grand Average	-2.38	-2.23	192	196
All Patients (n = 6)				
Grand Average	-2.10	-1.94	196	196

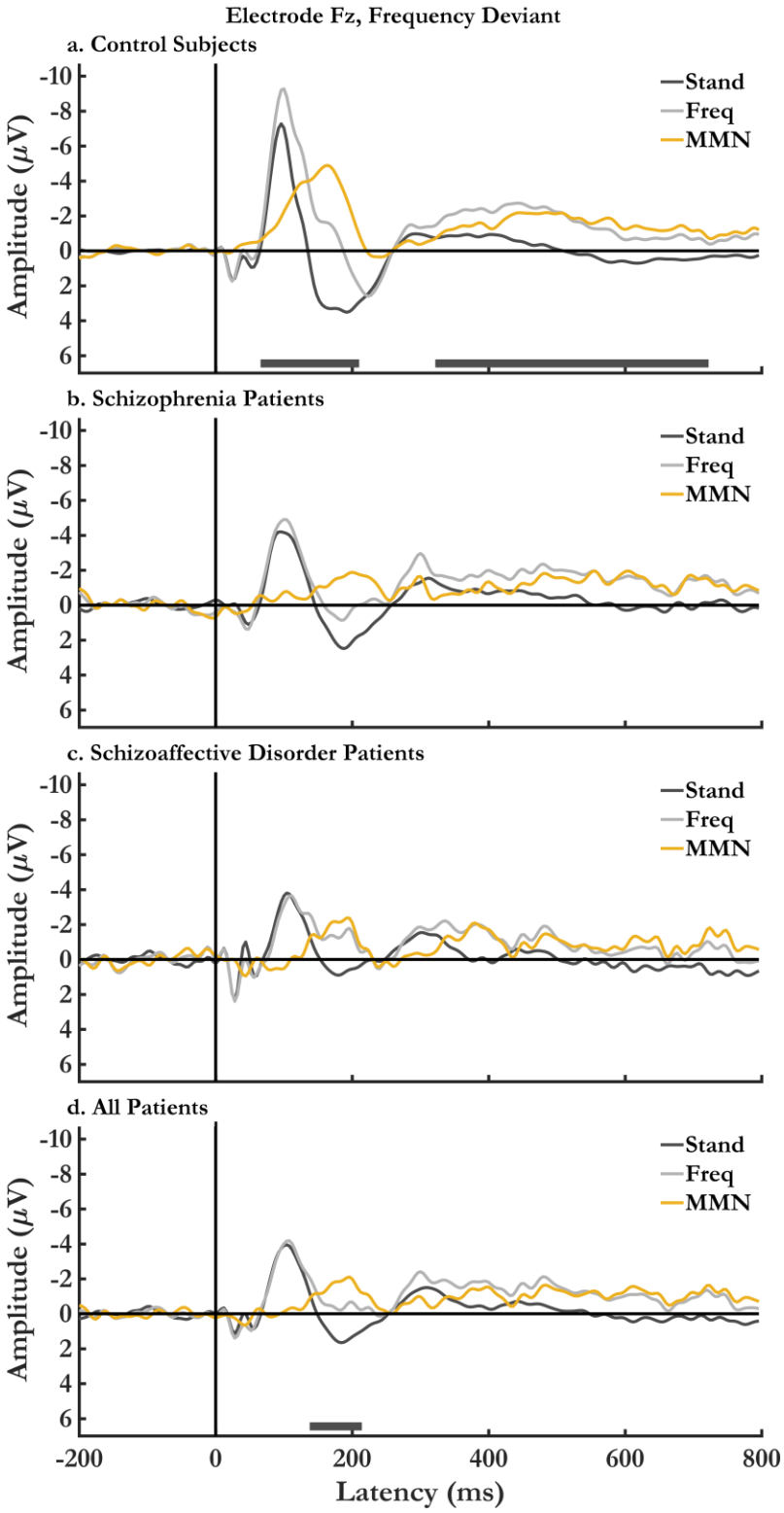


Figure 4.16 Grand average standard ERP, frequency deviant ERP, and frequency MMN at electrode Fz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.13a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

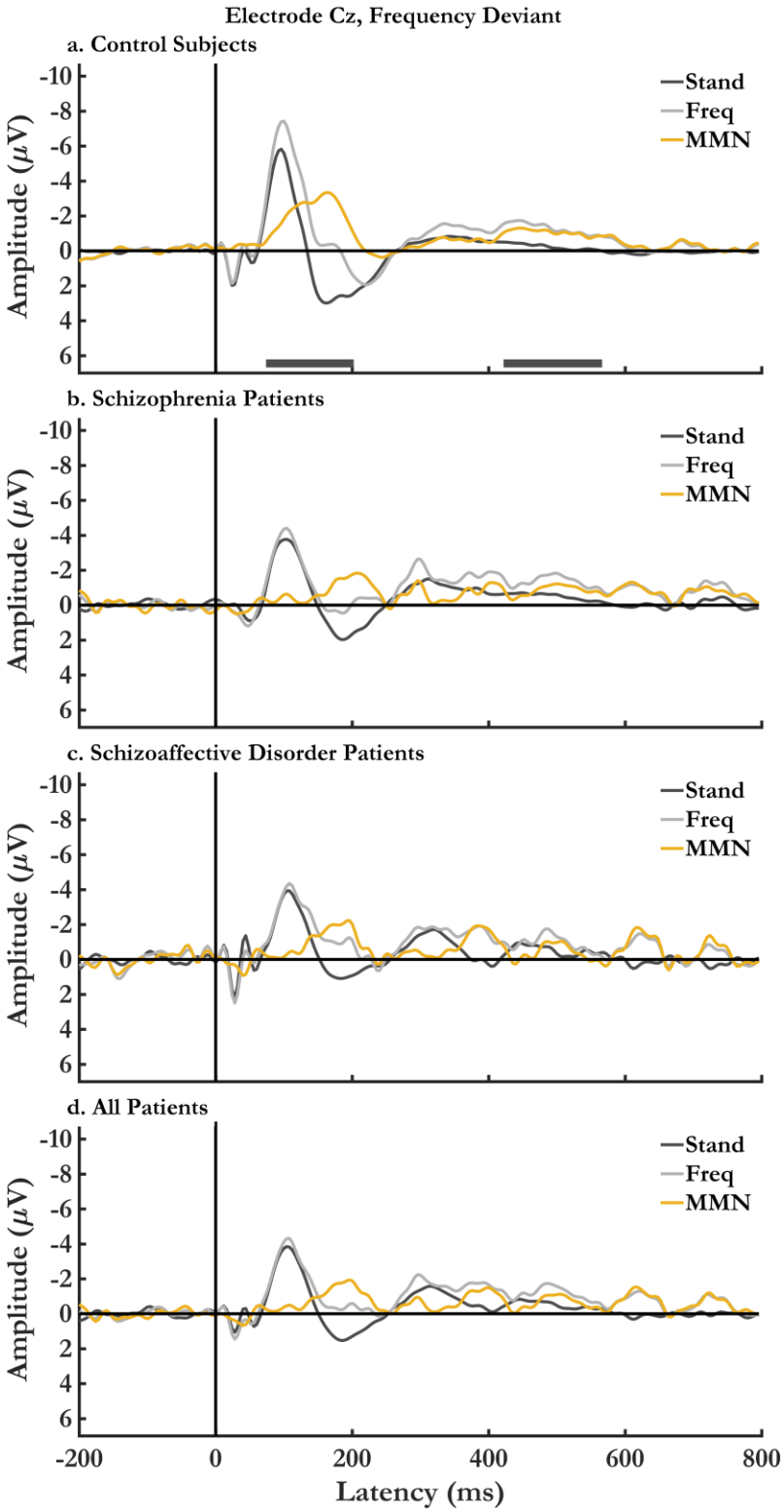


Figure 4.17 Grand average standard ERP, frequency deviant ERP, and frequency MMN at electrode Cz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.13b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

4.5.2.2 TIME-FREQUENCY ANALYSIS – FREUQENCY DEVIANT

The ERSP plots for electrodes Fz and Cz from control subjects are shown in figure 4.18. Compared to the standard tone ERSP we see a strong synchronisation of the lower frequencies from 2Hz to 16Hz. This synchronisation peaks approximately 100ms after trial onset. We also see a smaller secondary synchronisation around 200ms latency. The power during the frequency deviant response is significantly higher than the standard tone response only at electrode Fz. The region of significant difference after multiple comparisons correction ($p<0.05$) is marked by the black contours overlaid on the difference ERSP plot in the right column. A significant difference is observed during the primary peak of synchronisation. Other regions in the time frequency plot show little to no difference between the two stimuli.

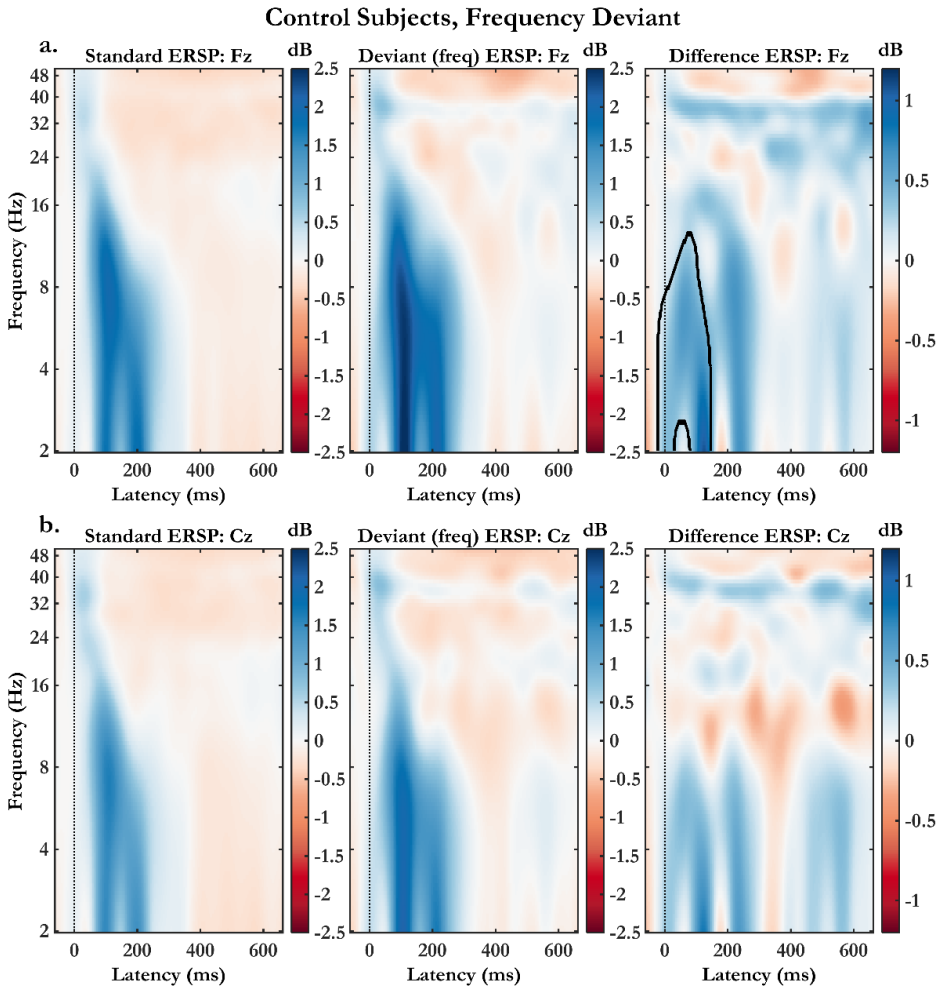


Figure 4.18 Grand average standard ERSP, frequency deviant ERSP, difference ERSP in control group (n = 17). a. Electrode Fz, b. Electrode Cz. Each row has three plots (left to right): standard ERSP, frequency deviant ERSP, difference ERSP. The significantly different region ($p<0.05$) is marked by black contours in the right column.

The average difference ERSP responses from individual patients for the frequency deviant, are shown in figure 4.19 for electrode Fz, and figure 4.20 for electrode Cz. For electrode Fz, we see that patients P1, P2, and P5 show some regions of initial synchronisation of lower frequencies from 2Hz to 16Hz, as seen in the difference plot for control subjects in figure 4.18a. However, the synchronisation is not consistent across the whole region till 200ms post-stimulus. Also, patients P2 and P5 respectively have a significant region of synchronisation and desynchronisation towards the end of the trial period. This type of late effect was not observed in control subjects and is not expected in response to a frequency deviant during an auditory oddball task. Patients P3, P4 and P6 show large areas of desynchronisation that are distributed across the time-frequency region. For electrode Cz, from the difference ERSP shown in figure 4.20, we again observe variability across individual patients. In this case, patients P1 and P3 show synchronisation of low-frequency bands while others show no clear pattern. Overall, for both the electrodes, we see more

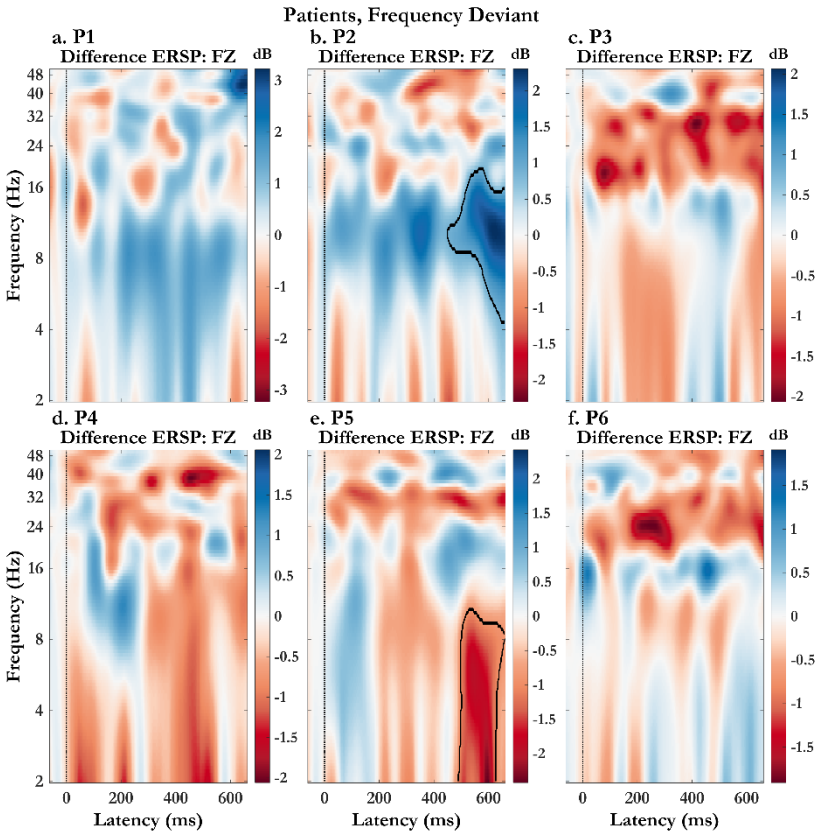


Figure 4.19 Average difference ERSP between frequency deviant and standard tone at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

desynchronisation in activity than synchronisation, during the deviant trials. The desynchronisation is also stronger than the average synchronisation in each case. This again is different from the control group where a more synchronised low-frequency response was observed during the deviant trials.

The individual patient difference ERSP plots are highly variable, and there is no clear pattern within the schizophrenia and schizoaffective disorder patient groups. The group average ERSP plots are shown in figures 4.21 and 4.22 for electrodes Fz and Cz, respectively. In these plots, the ERSP response of control subjects taken from figure 4.18 is shown at the top. The figures also show group averaged ERSP from schizophrenia patients, schizoaffective disorder patients, and all patients grouped together.

Figures 4.21b and 4.22b show that on average, schizophrenia patients (P4, P5, and P6) have a smaller change from the pre-stimulus baseline period during any type of stimulus. This is expected as a similar pattern was observed in the ERP response.

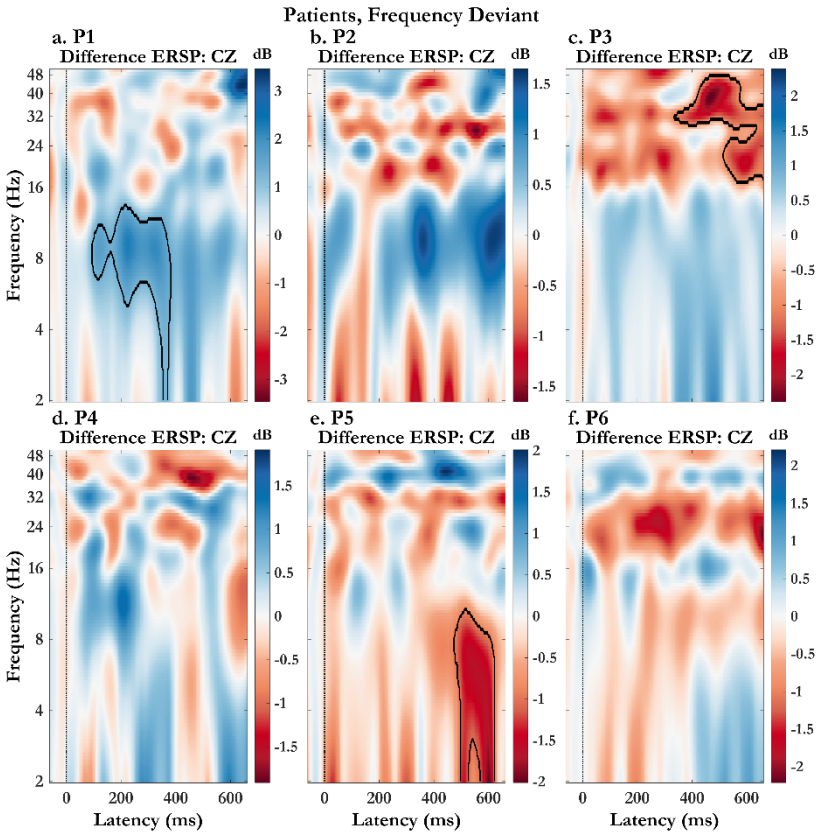


Figure 4.20 Average difference ERSP between frequency deviant and standard tone at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

Similar to the control subjects, we see a synchronisation before 200ms in the lower frequency signals up to 16Hz. However, later in the frequency deviant trials, 300ms post-stimulus at Fz and 400ms post-stimulus at Cz, we see an overall desynchronisation of the frequency spectrum, which was not observed in controls. The difference ERSP further shows us that, compared to the standard tone, response during the frequency deviant exhibited lower synchronisation of the frequencies below 8Hz. We also see regions of desynchronisation in higher 16Hz to 32Hz range. None of the differences in this group were significant, and unlike the control subjects, desynchronisation was stronger than the synchronisation.

In schizoaffective disorder patients (figs 4.21c, 4.22c) we see a relatively stronger and consistent synchronisation of lower frequencies in the deviant trials. This stronger synchronisation compared to the standard tone ERSP is seen in the difference plots, with peaks at approximately 8Hz. However, these peaks are observed around 400ms post-stimulus and none of them satisfy the significance criteria. This 400ms latency is much longer than the typically observed MMN peak latency, which occurs between 100ms and 200ms. The grand average response from all the patients to the frequency deviant (fig 4.21d, 4.22d) shows a relative synchronisation of low frequencies from 2Hz to 16Hz, and desynchronisation of higher frequencies. No significant differences are seen in this case either.

4.5.2.3 KEY FINDINGS – FREQUENCY DEVIANT

1. The frequency deviant MMN response in control subject group resulted from a larger and broader N100 component in the ERP response to the frequency deviant compared to standard tone.
2. The frequency deviant MMN response in patient groups was diminished and significant differences between the frequency deviant ERP and standard tone ERP was observed only in all patient group at electrode Fz.
3. The frequency deviant ERSP response in control subject group showed stronger synchronization compared to standard tone ERSP response before 200ms post-stimulus. This increase in synchronization to the frequency deviant tone was significant at electrode Fz.
4. The ERSP responses to frequency deviant was diminished in patient groups and did not show any significant difference from the standard tone ERSP.

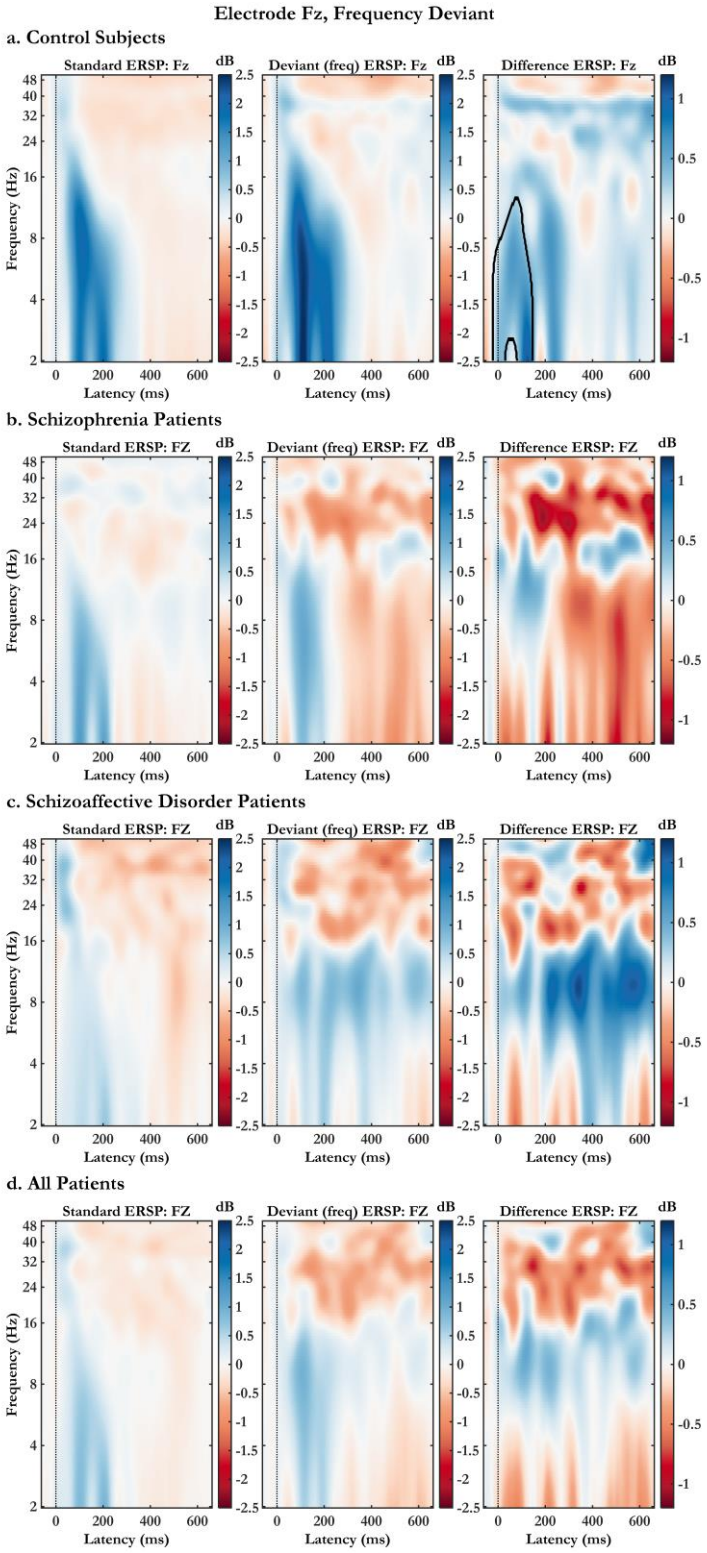


Figure 4.21 Grand average standard ERSP, frequency deviant ERSP, and difference ERSP at electrode Fz in subject groups. a. Control subject response from Figure 4.18a (n = 17),b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

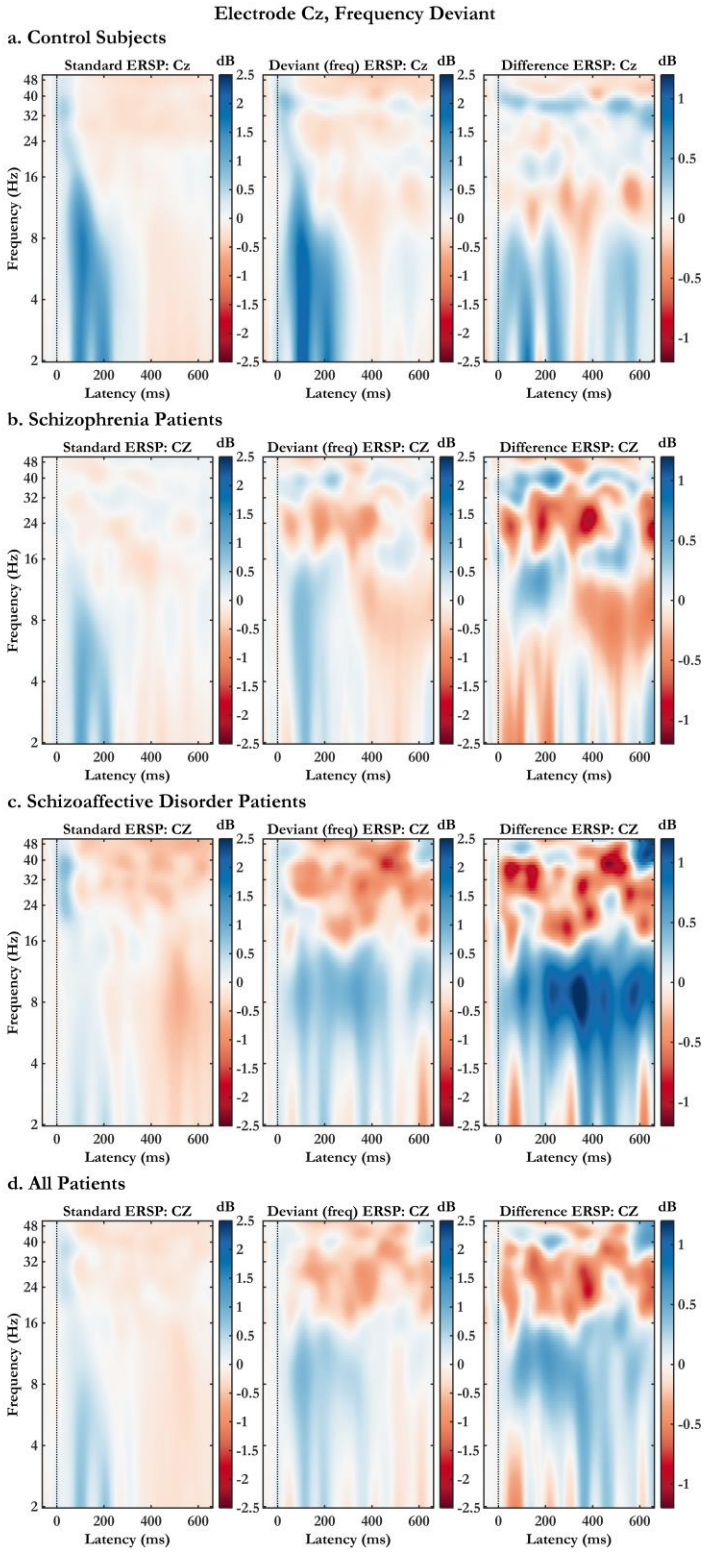


Figure 4.22 Grand average standard ERSP, frequency deviant ERSP, and difference ERSP at electrode Cz in subject groups. a. Control subject response from Figure 4.18a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients. (n = 6) Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP.

4.5.3 INTENSITY DEVIANT MMN

The intensity deviant tone used in the auditory oddball experiment was either 10dB below or above the standard tone intensity. Both higher and lower intensity deviants were presented with 50% probability each. In this section, the MMN response generated by this tone is studied in both healthy controls and patients.

4.5.3.1 EVENT RELATED POTENTIAL ANALYSIS – INTENSITY DEVIANT

Figure 4.23 compares the ERP response to the intensity deviant with the standard tone and plots the intensity MMN in the control group. This figure shows responses at both Fz and Cz electrode. The ERP response to the intensity deviant shows a significant deviation from the standard tone. We see from the figure 4.23 that at both the Fz and Cz electrodes, the peak of the N100 component is a little larger in the

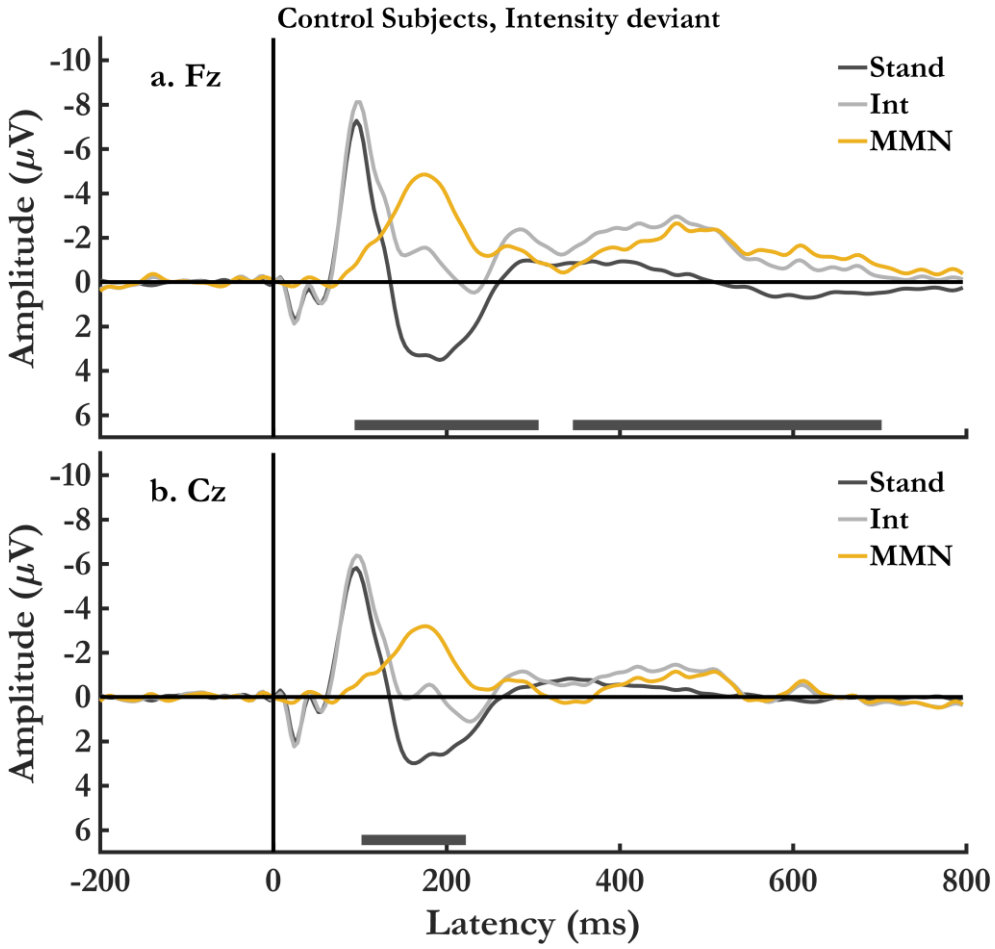


Figure 4.23 Grand average standard ERP, intensity deviant ERP, and intensity MMN in control group (n = 17). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz, b. Electrode Cz.

intensity deviant response. However, the MMN peak due to this deviant is a result of the difference between the ERP responses after the N100 peak. The ERP response for the intensity deviant in the control group does not have a significant positivity throughout the trial period. Therefore, we see that the MMN peak occurs in the period where the standard tone response is at the peak of its positive amplitude. During this period, we see that both the electrodes meet the significance criteria, marked by the black bars at the bottom. Electrode Fz also shows significant difference between the two tones later in the trial period. This is a result of the secondary negativity observed during the intensity deviant, but not during the standard tone. A similar MMN response from frontal electrode was shown in the paper by Näätänen and colleagues in 2004 (Näätänen et al., 2004). Like the previous two deviant tones, we also see a decrease in the MMN peak from Fz to Cz electrode. The MMN peak latencies at both the electrodes are the same. The values for the intensity deviant MMN peak amplitudes and peak latencies are shown in table 4.4.

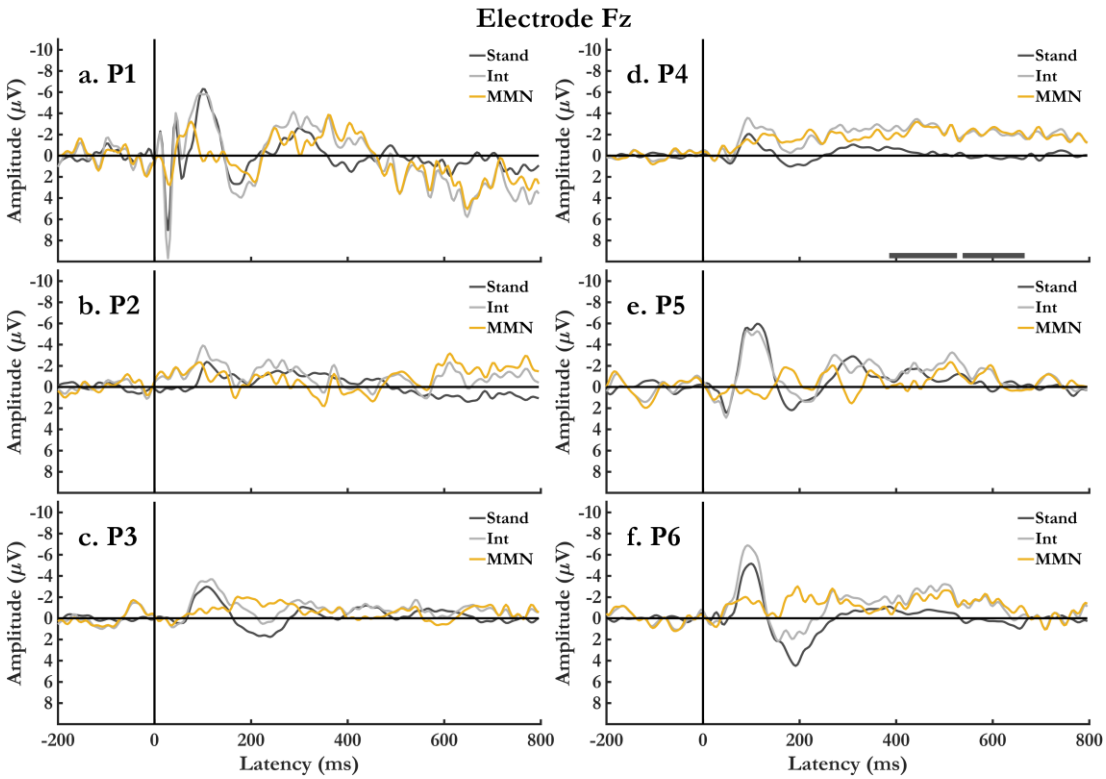


Figure 4.24 Average standard ERP, intensity deviant ERP, and intensity MMN at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

Figures 4.24 and 4.25 respectively show the intensity deviant responses at electrodes Fz and Cz from individual patients. Like the ERP response to standard tone, intensity deviant response is diminished in the patient group. Except for one patient P4, we do not see significant differences between the responses in any other patients. In patient P1, though the ERP signals from both tone types are relatively large, they closely follow each other resulting in a small MMN response. In patient P2 the small N100 ERP response due to intensity deviant, is larger than that of the standard tone, resulting in an earlier peak of the intensity MMN (<100ms latency, table 4.4). In patients P3 and P6 the ERP signals show a similar pattern to the control subjects. In these patients, the largest difference between the ERP signals comes due to the smaller positivity after N100 peak during the intensity deviant. Patient P4 shows a constantly negative intensity deviant ERP. This leads to an MMN response that is significant at a later period at electrode Fz and starting from about 200ms at electrode Cz. In patient P5, the ERP signals are relatively large but are similar in their time course. In this case,

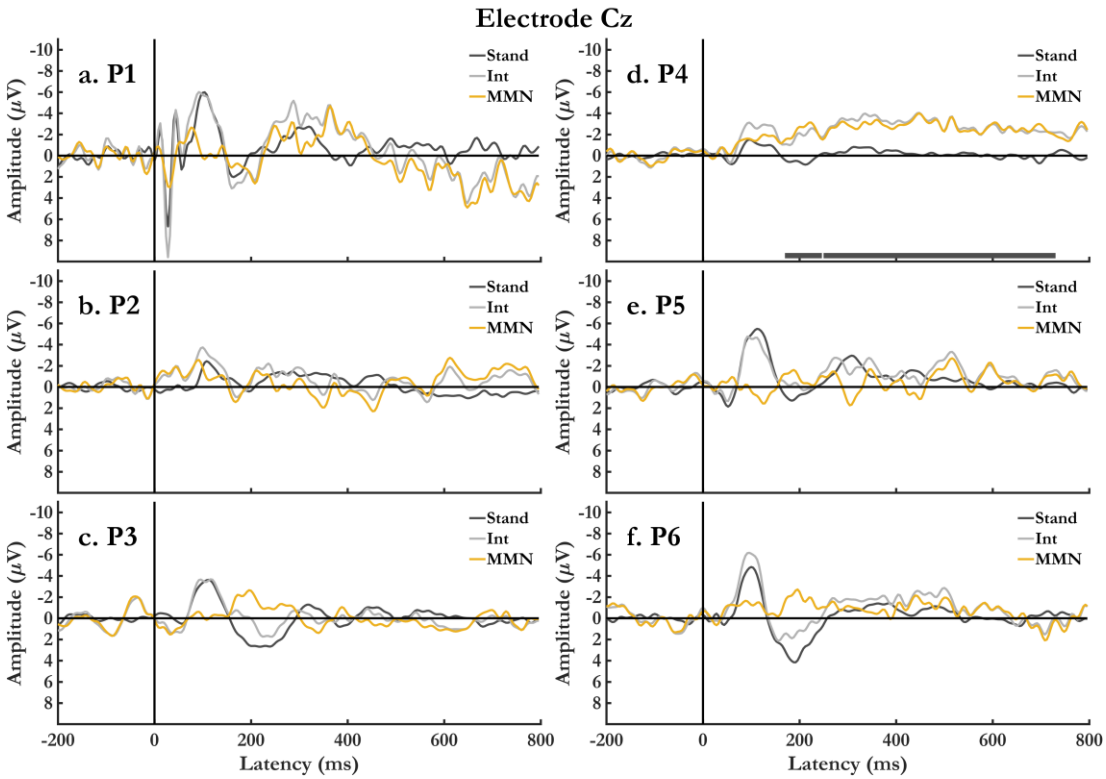


Figure 4.25 Average standard ERP, intensity deviant ERP, and intensity MMN at Cz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

the MMN response is barely present as a random fluctuation around the baseline. From the intensity MMN peak amplitude and latency data in table 4.4, we see that all patients have a smaller intensity MMN peak amplitude compared to control subjects.

Table 4.4 MMN peak amplitude and latency measures for intensity deviant.

	Peak Amplitude (μVolts)		Peak Latency (ms)	
	Fz	**Cz**	**Fz**	**Cz**
Control Subjects (n = 17)				
Grand Average	-4.85	-3.19	176	176
Patients				
P1	-2.62	-2.82	248	248
P2	-2.34	-2.55	92	92
P3	-2.04	-2.65	172	196
P4	-2.46	-3.13	220	224
P5	-1.85	-1.60	172	188
P6	-3.01	-2.72	196	196
Schizophrenia Patients (n = 3)				
Grand Average	-1.85	-2.16	192	196
Schizoaffective Disorder Patients (n = 3)				
Grand Average	-1.50	-1.34	244	92
All Patients (n = 6)				
Grand Average	-1.38	-1.33	248	196

The response variability in individual patients is large. To get a broader understanding on these patients, the grand average responses were computed from patient groups with distinct clinical diagnosis. The grand average ERP from the schizophrenia patients (P4, P5, and P6), schizoaffective disorder patients (P1, P2, and P3), and all patients grouped together are shown in figure 4.26 for electrode Fz and figure 4.27 for electrode Cz. These figures also show grand average ERP response from control subjects (figs 4.26a, 4.27a) taken from figure 4.23. Schizophrenia patients (figs 4.26b, 4.27b) show a similar ERP response and MMN profile as that of control subjects. The overall response is smaller compared to the control subjects, but we see a small increase in the N100 peak followed by a small or no positivity during the intensity deviant.

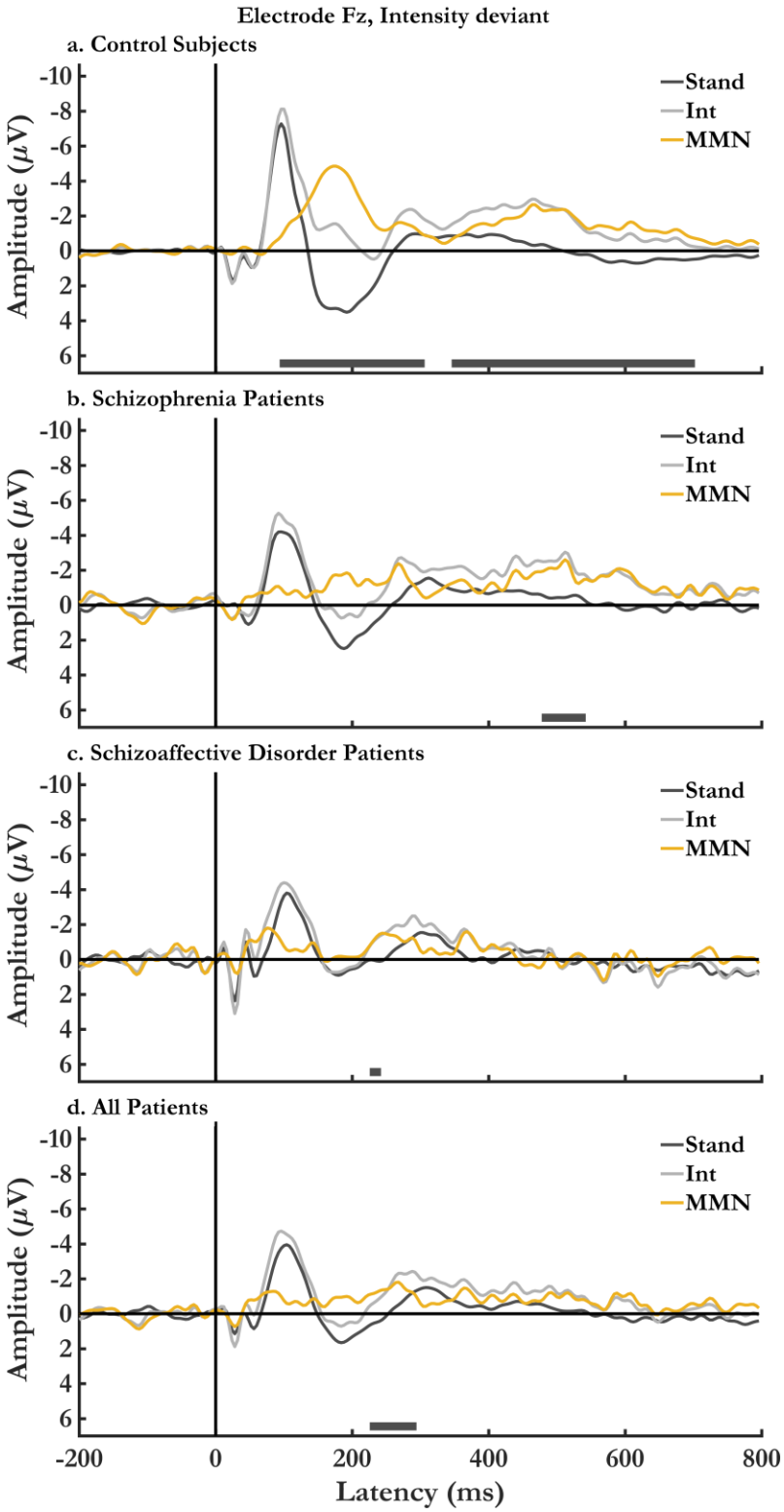


Figure 4.26 Grand average standard ERP, intensity deviant ERP, and intensity MMN at electrode Fz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.23a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

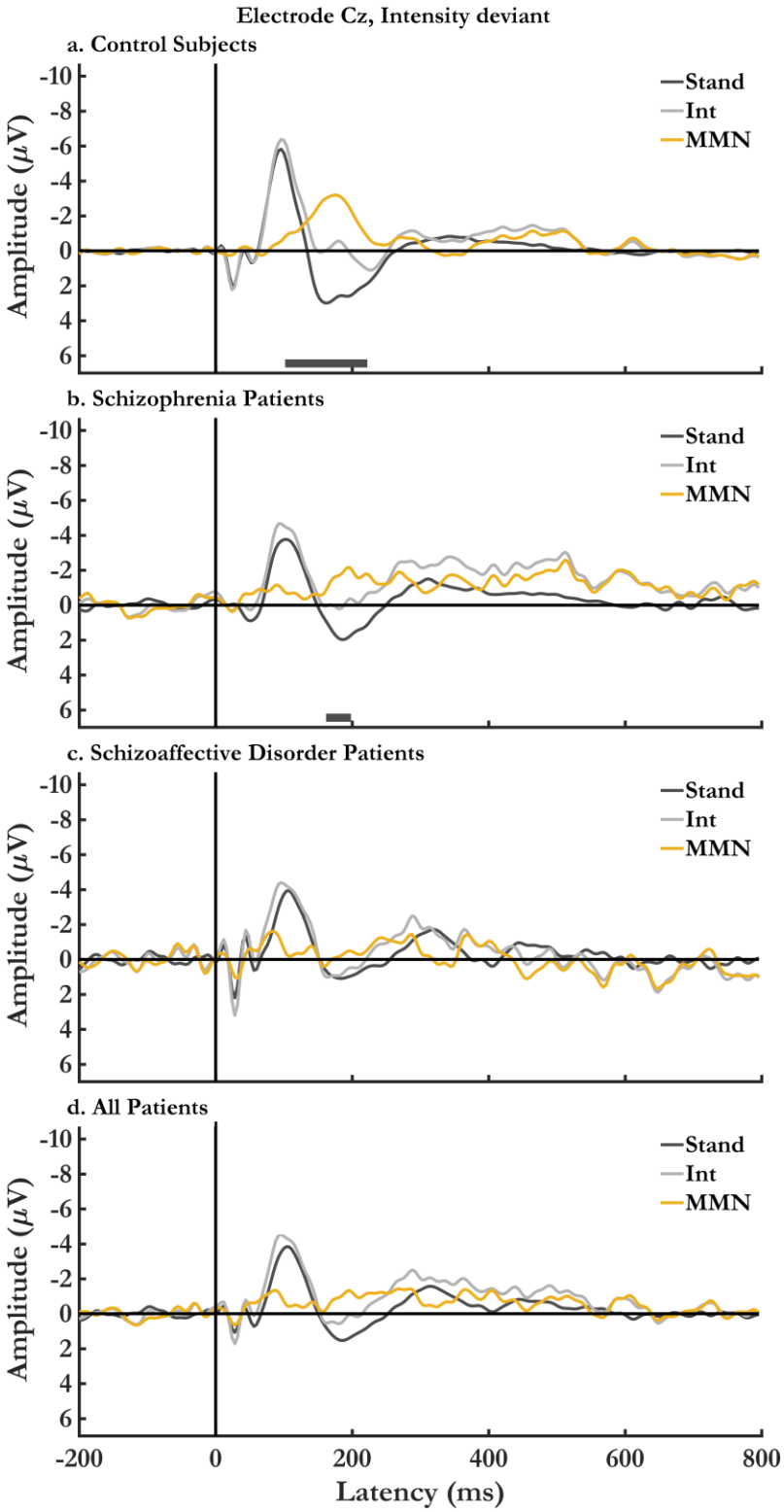


Figure 4.27 Grand average standard ERP, intensity deviant ERP, and intensity MMN at electrode Cz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.23b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

Besides the smaller amplitude we also see a longer MMN peak latency in schizophrenia patients. Only small periods of significant differences are observed on either electrode; marked on the plots with black bars. The ERP response from the schizoaffective disorder patients (figs 4.26c, 4.27c) shows a different pattern with a broader N100 component during the intensity deviant. The positivity after N100 component in this group closely follows the standard tone response. The MMN peak occurs due to the later negativity of the intensity deviant ERP at Fz. However, the MMN peak at Cz is observed at a shorter latency due to the earlier intensity deviant N100 response. The grand average response from the whole patient group (figs 4.26d, 4.27d) shows a MMN response that is relatively constant between the 90ms to 250ms interval. The peaks are observed at a longer latency compared to control subjects. The details of intensity MMN peak amplitudes and latencies for each patient group are provided in table 4.4.

4.5.3.2 TIME-FREQUENCY ANALYSIS – INTENSITY DEVIANT

The results of the ERSP analysis for the control subject group are shown in figure 4.28. From this figure we see that for both Fz and Cz electrodes the ERSP response for the intensity deviant is similar to that of the standard tone. This is further confirmed in the difference plot that shows a relatively weak desynchronisation and synchronisation of various frequencies. The power range of this plot is smallest of all the 5 deviant types that were used in this experiment. Also, the lack of contours on this difference plot states that none of the time-frequency regions satisfied the significance criteria of $p<0.05$, after multiple comparisons correction was applied. However, looking at the changes for both the electrodes, we can see similar patterns exhibited in the difference plots. In the lower frequencies from 2Hz to 12Hz, we see an initial synchronisation from the beginning of the trial. This gradually transitions into a desynchronisation that peaks little before 200ms in the lowest frequency bin. There is also a characteristic short time desynchronisation and synchronisation in the lowest frequency bins of 2-3Hz at approximately 100ms, which happens before the larger desynchronisation is observed. Outside this region, that is beyond 200ms for all frequencies, and above 12Hz before 200ms, we see only small relative changes in the

difference plot. There is a desynchronisation of frequencies between 8Hz and 24Hz and a weak synchronisation at other regions.

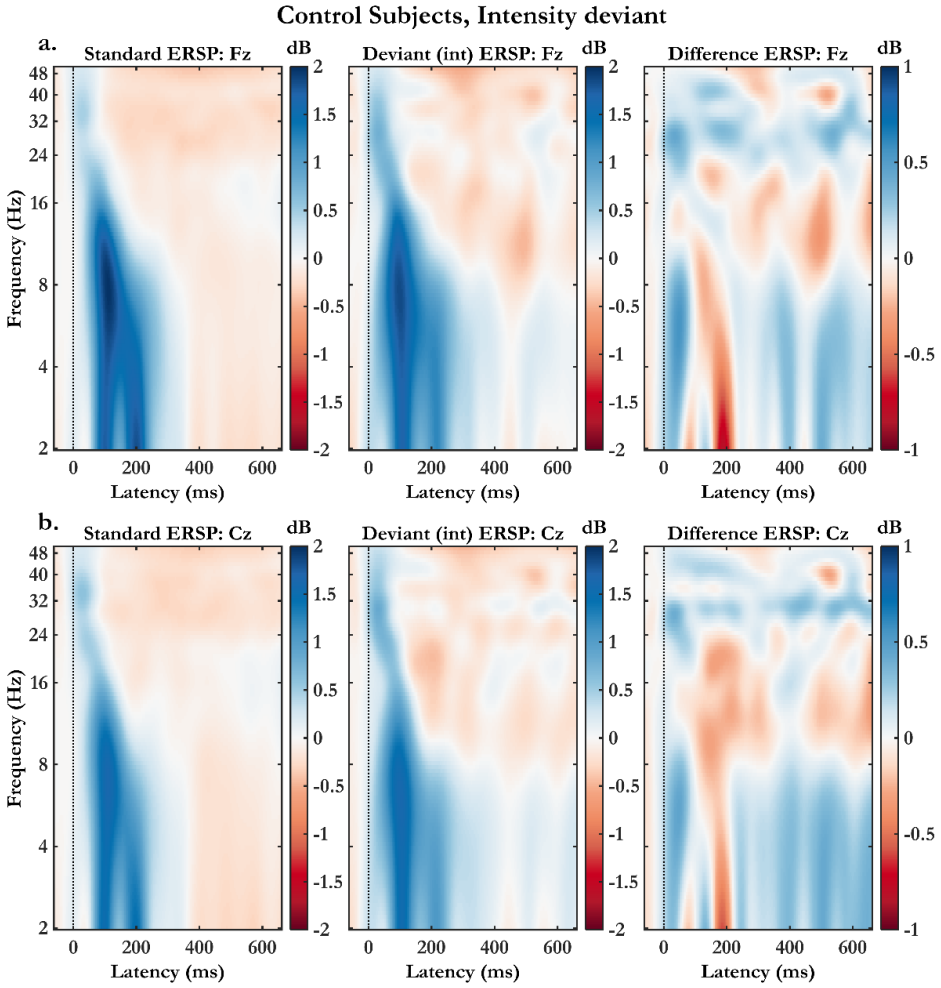


Figure 4.28 Grand average standard ERSP, intensity deviant ERSP, difference ERSP in control group (n = 17). a. Electrode Fz, b. Electrode Cz. Each row has three plots (left to right): standard ERSP, intensity deviant ERSP, difference ERSP. There are no significant difference regions ($p<0.05$).

Though no significant differences were observed between the ERSP plots in the control group, the ERSP response from patients was still investigated. The average responses from individual patients are plotted in figures 4.29 and 4.30 for electrodes Fz and Cz, respectively. In these figures only the difference ERSP is shown for each patient, corresponding to the right column in figure 4.28 for control subjects.

In patient P1 the lower frequency bins at electrode Fz show a pattern that switches between desynchronisation and synchronisation until 200ms. This pattern is opposite to what is seen in control subjects. We also see a strong synchronisation of

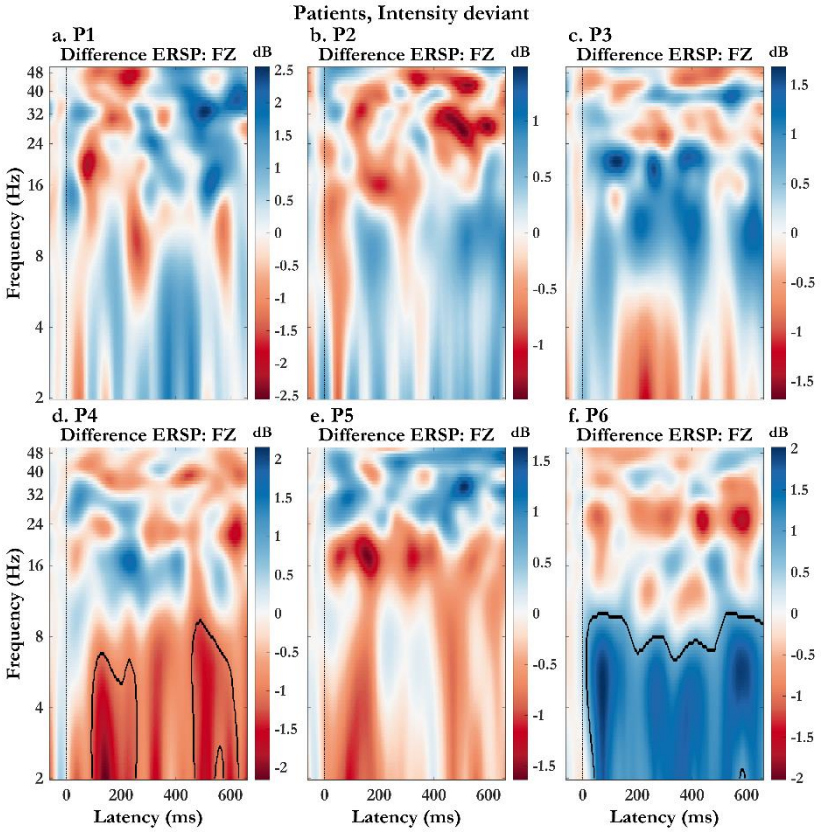


Figure 4.29 Average difference ERSP between intensity deviant and standard tone at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

frequencies from 2Hz to 8Hz around 400ms, that is significant at electrode Cz. Patient P2 mostly showed a broadband synchronisation of all the frequency bins through the trial period with small regions of desynchronisation. The desynchronisation region includes the frequencies 2Hz to 16Hz in the beginning of the trial at electrode Fz. This is similar to the pattern observed from patient P1 at Fz, however the scales of the two plots are different. The ERSP response from patient P3 maybe considered the most similar to the control group. Here, we see an initial synchronisation followed by a desynchronisation of the lower frequency range. While the desynchronisation in this case lasts for a longer period and is observed at both the electrodes, the synchronisation is only observed at Fz, with initial Cz response close to the baseline. Patient P4 shows a large desynchronisation of frequencies 2Hz to approximately 12Hz throughout the trial period at both electrodes. Two clusters of significant differences at electrode Fz are also observed. One of these clusters is around 200ms latency where the peak of the MMN was observed for patient P4. In patient P5 we see a desynchronisation of 2Hz

to 12Hz frequencies until 200ms at both the electrodes. Patient P6 shows a pattern that is opposite of patient P4 with a synchronisation of 2Hz to 12Hz frequencies throughout the trial period. This synchronisation is significant at both the electrodes Fz and Cz. Overall, the figures 4.29 and 4.30 demonstrate that there was considerable variability across the individual patients.

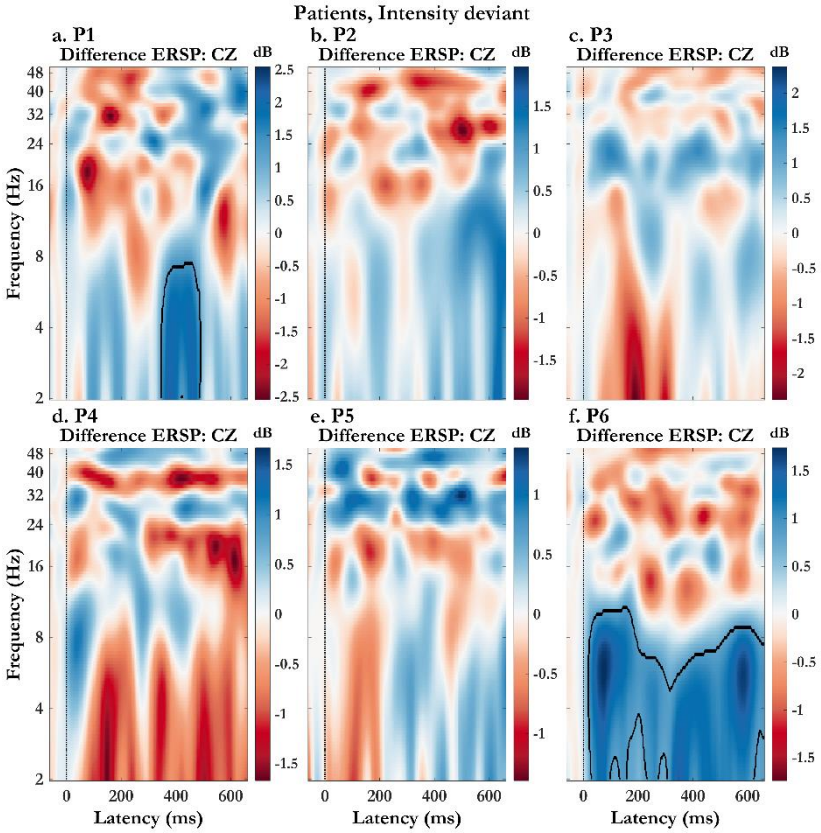


Figure 4.30 Average difference ERSP between intensity deviant and standard tone at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

To better understand the group dynamics of response to intensity deviant, the grand average ERSP responses from the patients diagnosed with schizophrenia, schizoaffective disorder, and all patients grouped together were examined. The figures 4.31 and 4.32 show these plots for electrodes Fz and Cz, respectively. The ERSP response from control subjects in also shown in these figures (figs 4.31a, 4.32a) to easily visualize the differences in group responses. The standard tone and intensity

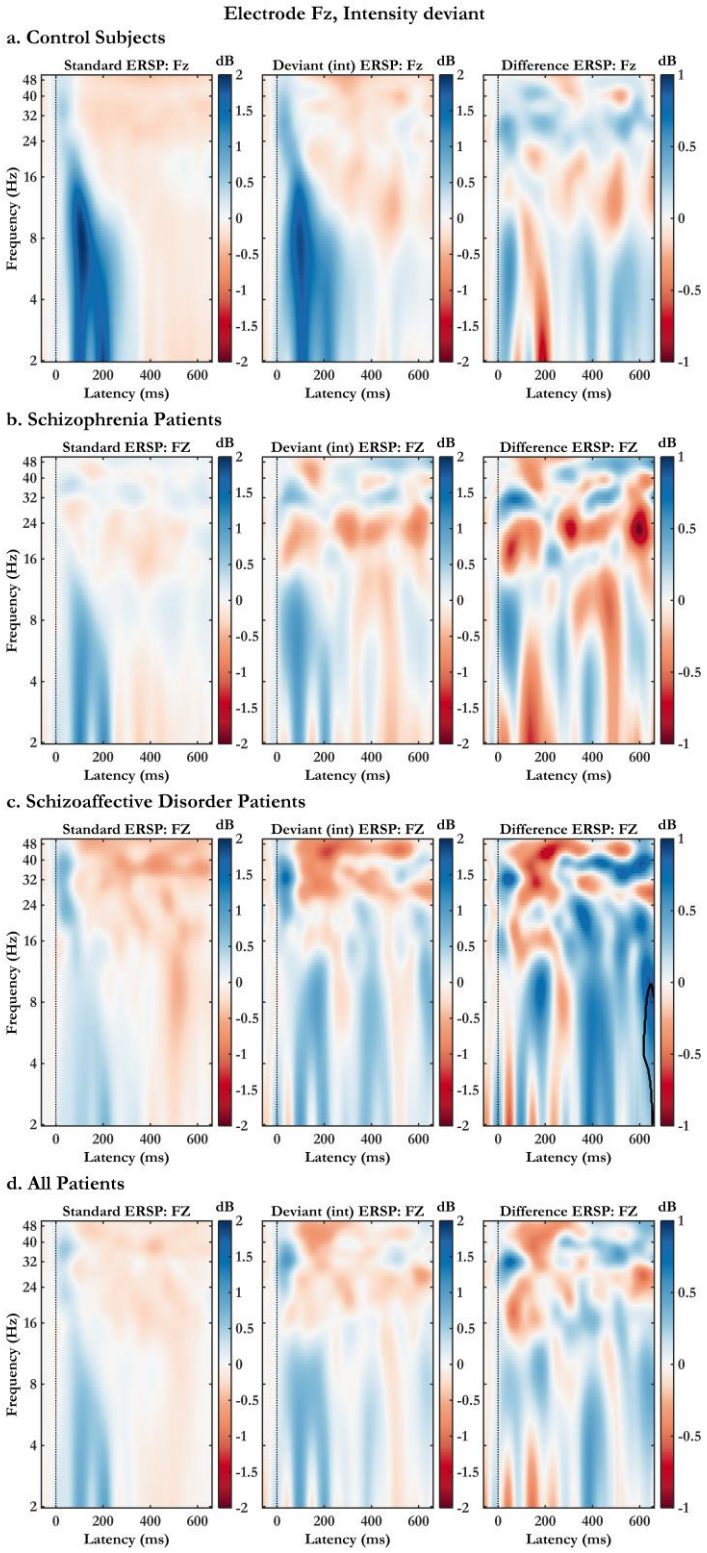


Figure 4.31 Grand average standard ERSP, intensity deviant ERSP, and difference ERSP at electrode Fz in subject groups. a. Control subject response from Figure 4.28a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

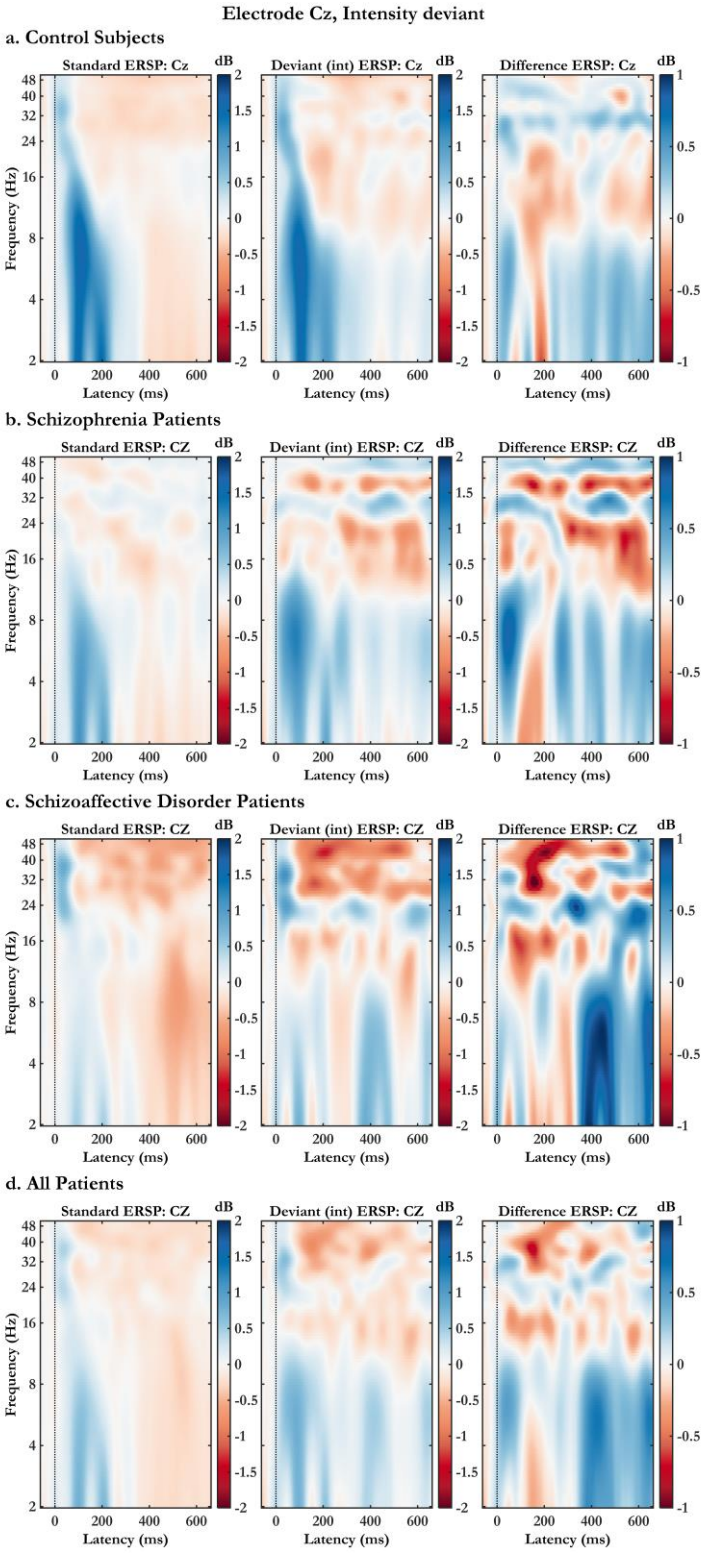


Figure 4.32 Grand average standard ERSP, intensity deviant ERSP, and difference ERSP at electrode Cz in subject groups. a. Control subject response from Figure 4.28b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP.

deviant ERSP response plots all use the same colour-scale of ±2dB while the difference ERSP plots all use the colour-scale ±1dB. In schizophrenia patients (P4, P5, and P6) we see that the grand average ERSP (figs 4.31b, 4.32b) for intensity deviant show smaller changes from baseline compared to the control group. The difference ERSP show a pattern that does show similarity to control group with an initial synchronisation of frequencies below 12Hz that transitions into desynchronisation. The healthy controls and schizophrenia patients do not share any further similarity.

In schizoaffective disorder patients (P1, P2, and P3) the ERSP response (figs 4.31c, 4.32c) to the deviant again show smaller changes from the pre-stimulus baseline period compared to the control subjects. The difference ERSP do not show any similarity with the control subjects in this group. We see a strong synchronisation of lower frequencies, especially at electrode Cz, that was not see in control subjects. The results from the whole patient group (figs 4.31d, 4.32d) show that the grand average ERSP response were close to the pre-stimulus baseline activity. The difference ERSP has some similarity to the control group, but it is not very clearly seen. Except for a small region in schizoaffective disorder patients at electrode Fz, no regions of significant differences were seen in these group plots. This is expected as no significant difference between ERSP responses of standard and intensity deviant tones were observed in the control subject group as well.

4.5.3.3 KEY FINDINGS – INTENSITY DEVIANT

1. The intensity deviant MMN response had a longer peak latency of 176ms in control subject group. This resulted from significant differences between in ERP response to the intensity deviant and standard tone after the N100 component.
2. The intensity deviant MMN response in patient groups was diminished with longer peak latencies of greater than 190ms in all cases except for schizoaffective disorder patients at electrode Cz.
3. The intensity deviant ERSP response in control subject group was similar to standard tone ERSP response and there were no significant differences between the two.
4. The ERSP responses to intensity deviant was diminished in patient groups and did not show any significant difference from the standard tone ERSP as well.

4.5.4 LOCATION DEVIANT MMN

The location deviant tone was created by introducing a time difference of 800µs between the left and right channel of the headphones. This resulted in a perceived change in the location of the tone coming from either 90º to the right or left of the standard tone. On average, half the tones were placed on the right, and other half on the left of the standard tone location. These details have also been outlined in table 4.1.

4.5.4.1 EVENT RELATED POTENTIAL ANALYSIS – LOCATION DEVIANT

The ERP response and the MMN response generated due to the location deviant in healthy controls group are shown in figure 4.33. The control group elicited the largest N100 peak in the location deviant ERP, compared to any other tone type. We see from the figure that, the N100 component is broader compared to the standard tone.

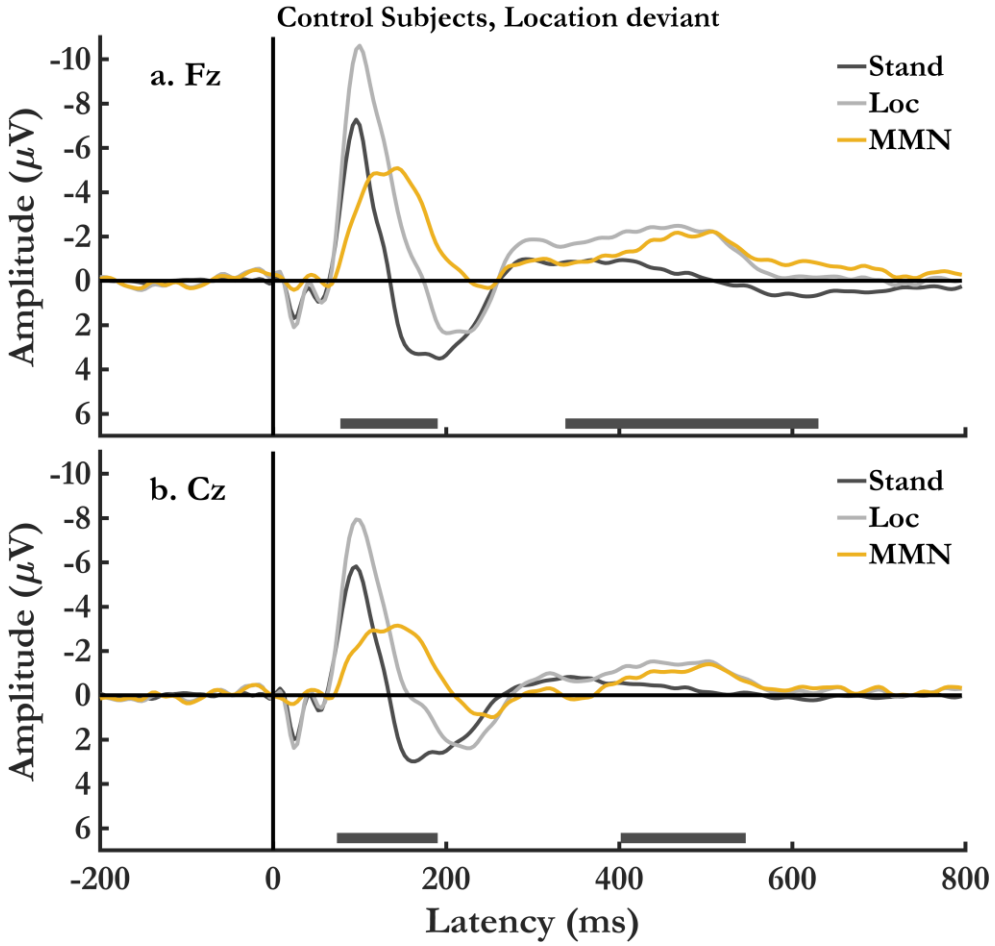


Figure 4.33 Grand average standard ERP, location deviant ERP, and location MMN in control subject group (n = 17). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz, b. Electrode Cz.

Following the N100 peak, the ERP response has a significant, but smaller positivity. These dynamics of the time series lead to a large location MMN with peak latency of 144ms, at both the Fz and Cz electrodes. The black bars at the bottom of each plot indicate that this peak occurs within the time window of significant differences between the ERP response to the two tone-types. As has been seen in previous deviant types, there is a sharp decrease in the MMN peak amplitude as we move from the frontal to central electrode location. Similar to other deviant MMNs, a secondary significant negativity which occurs at a longer latency is also observed.

The ERP responses and location MMN of individuals from the patient group are shown in figure 4.34 for electrode Fz, and figure 4.35 for electrode Cz. For the location deviant we see some relatively large MMN response from a few patients. In these cases, the location deviant ERP is significantly large when compared with the standard tone ERP. A large N100 component is elicited by the location deviant in patient P1 at both the Fz and Cz electrodes. This component is similar to that seen in control

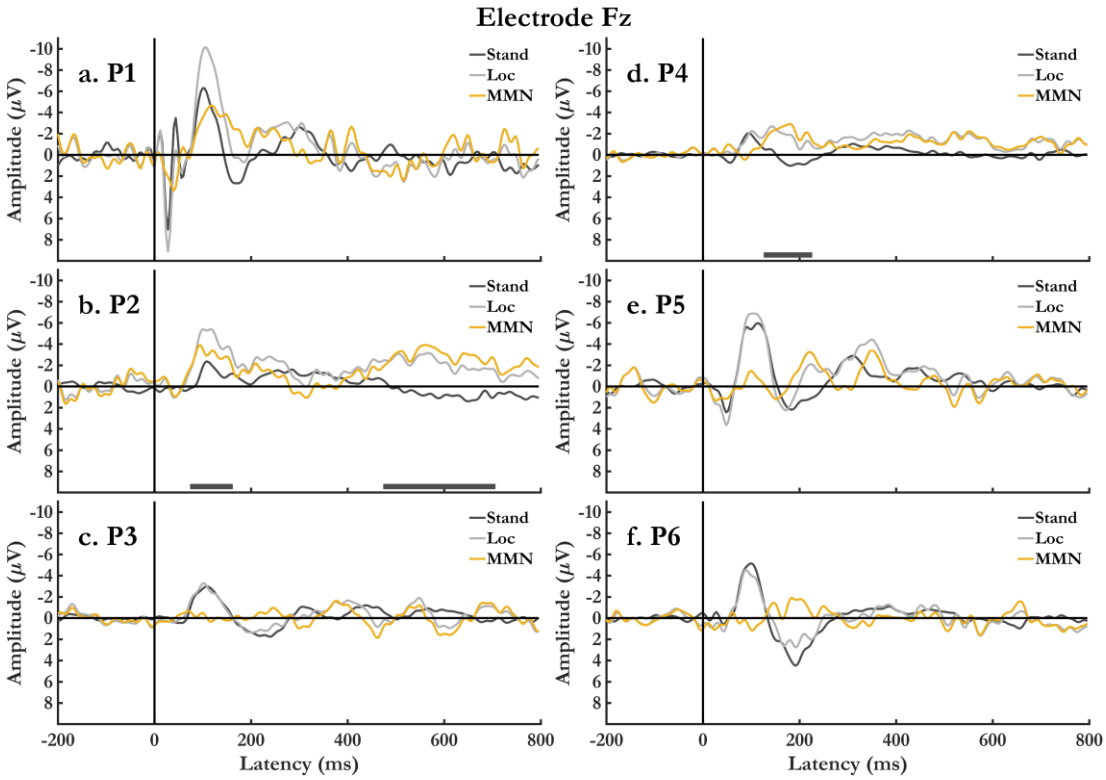


Figure 4.34 Average standard ERP, location deviant ERP, and location MMN at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

subjects, with a wider profile and a peak larger than standard tone response. However, the difference between the ERP responses did not satisfy the significance criteria in this case. This could be due to the relatively small number of trials (Standard tone: 273, location deviant: 68) that were used for calculating the average responses in patient P1. A similar response is observed in patient P2 that is also significantly different from the standard tone ERP. This patient even shows a significant secondary negativity in the MMN response, as seen in the control subjects. In patients P3, P5, and P6 the N100 component of the location deviant ERP closely follows the standard tone response. The peak of the location MMN in these subjects is observed due to the difference between the positive component of the ERP following the N100 wave. In patient P3 the MMN peak is close to the baseline (zero) in the 90ms to 250ms region. We do see a significant difference for a short duration at electrode Cz for this patient, but it occurs at a longer latency than is expected for the peak MMN. In patient P4, the negative peak of ERP for the location deviant occurs at a longer latency than in the

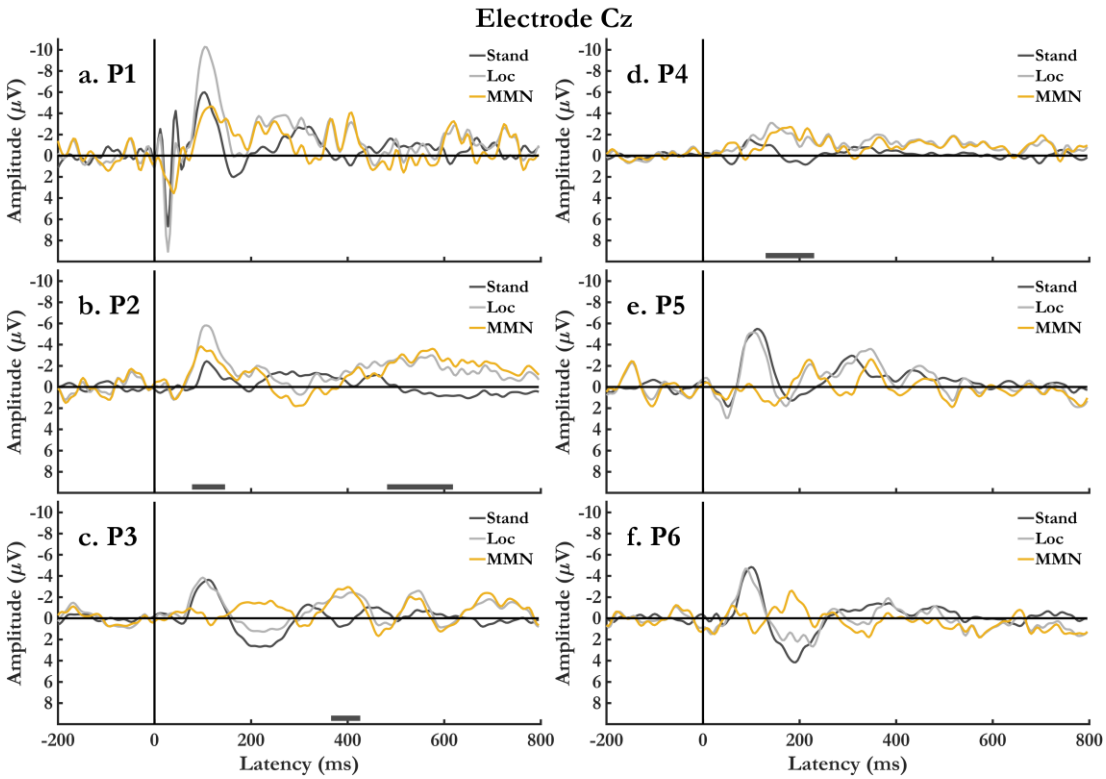


Figure 4.35 Average standard ERP, location deviant ERP, and location MMN at Cz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

standard ERP response. This resulted in a significant difference between the signals, and location MMN peak at a latency little longer than what was observed in control subjects.

Table 4.5 MMN peak amplitude and latency measures for location deviant.

	Peak Amplitude (μVolts)		Peak Latency (ms)	
	Fz	**Cz**	**Fz**	**Cz**
Control Subjects (n = 17)				
Grand Average	-5.08	-3.14	144	144
Patients				
P1	-4.64	-4.65	120	116
P2	-3.88	-3.84	96	96
P3	-0.96	-1.66	244	240
P4	-2.93	-2.71	180	180
P5	-3.25	-2.58	220	220
P6	-1.91	-2.61	184	184
Schizophrenia Patients (n = 3)				
Grand Average	-2.13	-1.90	212	212
Schizoaffective Disorder Patients (n = 3)				
Grand Average	-2.58	-2.73	120	100
All Patients (n = 6)				
Grand Average	-1.90	-2.01	212	212

The grand averaged group ERP response from patients with different clinical diagnosis is shown in figures 4.36 for electrode Fz and 4.37 for electrode Cz. To help visualize the differences in group responses, each of these two figures also include the grand average ERP response from the control subjects taken from figure 4.33. We see that in schizophrenia patients (figs 4.36b, 4.37b), the N100 component of the response to the location deviant closely follows the standard tone response. The location MMN peak is observed due to the differences during the period following the N100 peak. This resulted in a smaller MMN peak that occurs at longer latency compared to the control subjects. In schizoaffective disorder patients (figs 4.36c, 4.37c), a different pattern is observed due to the large N100 peaks in response to the location deviant. As seen in the individual patient plots (fig 4.34 and 4.35), patients P1 and P2 show a similar response which translates into this pattern observed in the schizoaffective group. Due to this, the location MMN peak in this group is larger than the

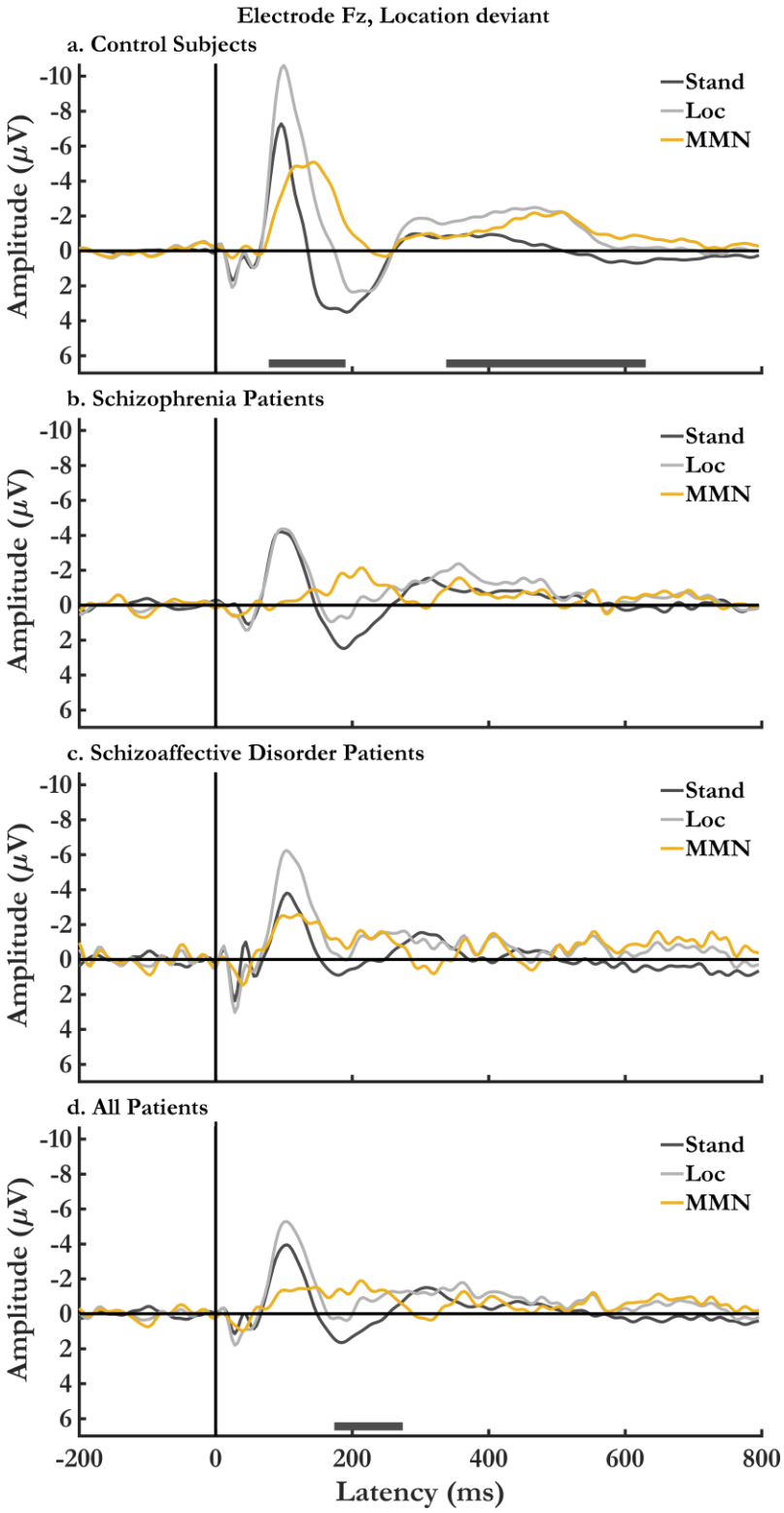


Figure 4.36 Grand average standard ERP, location deviant ERP, and location MMN at electrode Fz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.33a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

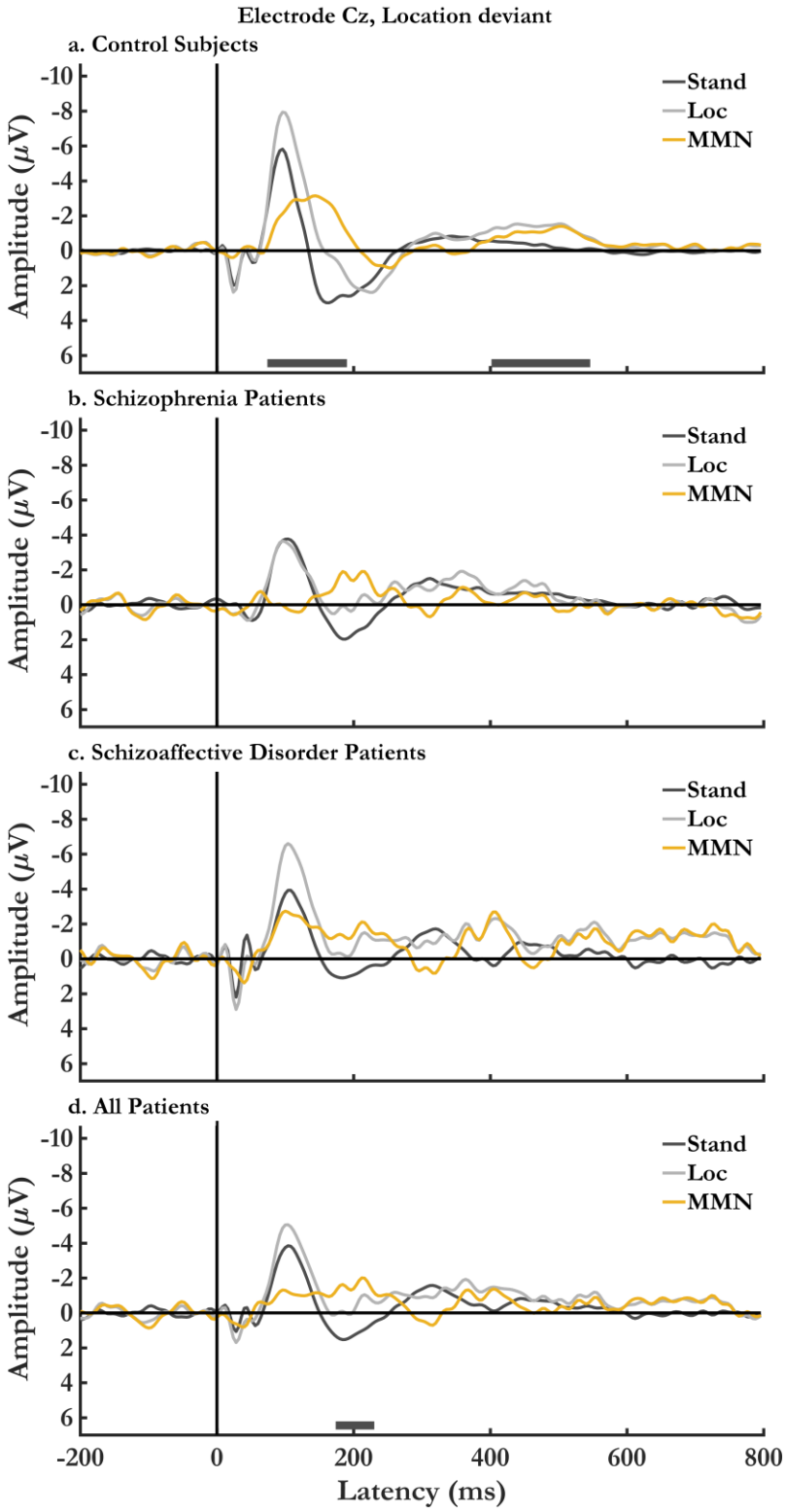


Figure 4.37 Grand average standard ERP, location deviant ERP, and location MMN at electrode Cz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.33b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

schizophrenia patients and occurs at a shorter latency compared to the control subjects. Neither of the groups showed any time periods with significant differences.

The grand average ERP response from the all the patients (figs 4.36d, 4.37d), as expected, is an average of the two groups segregated by the clinical diagnosis. The MMN response shows a longer period of negativity that lasts for approximately 200ms. This negativity spans from a few milliseconds before the N100 peak to the time when the positivity of the standard tone ERP returns to baseline. At both Fz and Cz electrodes we see a window of significant negativity with the peak of the MMN occurring within this window. The values of the location MMN peak amplitudes and peak latencies are shown in table 4.5.

4.5.4.2 TIME-FREQUENCY ANALYSIS – LOCATION DEVIANT

The time-frequency or ERSP response to the location deviant in control subjects is shown, and compared with the standard tone response, in figure 4.38. Both the standard and location deviant ERSP responses are plotted with a colour scale of ±3dB, which was used to visualize all grand average ERSP responses shown in this section. The right column plots the difference ERSP with the colour scale of ±1.5dB. From this figure we see that there is a strong synchronisation of the lower frequencies starting from 2Hz and extending to almost 16Hz during the first 200ms of the location deviant trials. The peak of this synchronisation occurs at approximately 100ms latency, directly corresponding to the N100 peak observed in the ERP analysis (fig 4.33). There is also a secondary peak at approximately 200ms which spans 2Hz to 8Hz frequencies. This effect is stronger on the frontal Fz electrode compared to the central Cz electrode. The difference plot shows that for location deviant, this synchronisation is significantly stronger than the synchronisation in the standard tone response. The plot also shows that the significance criteria is met for a wider range of frequencies on the frontal electrode compared to the central electrode.

The ERSP response to the location deviant in individual patients is examined in the following figures. Figure 4.39 shows the ERSP difference plot for each patient for electrode Fz and figure 4.40 for electrode Cz. The plots for individual patients look quite different from each other and from the average control group. In control subjects there are no regions in the time-frequency difference plots that show a strong desynchronisation through the trial period. This is unlike what we see from the

individual patient ERSPs in previous sections, where every patient exhibits regions of strong desynchronisation in time range and frequency spectrum.

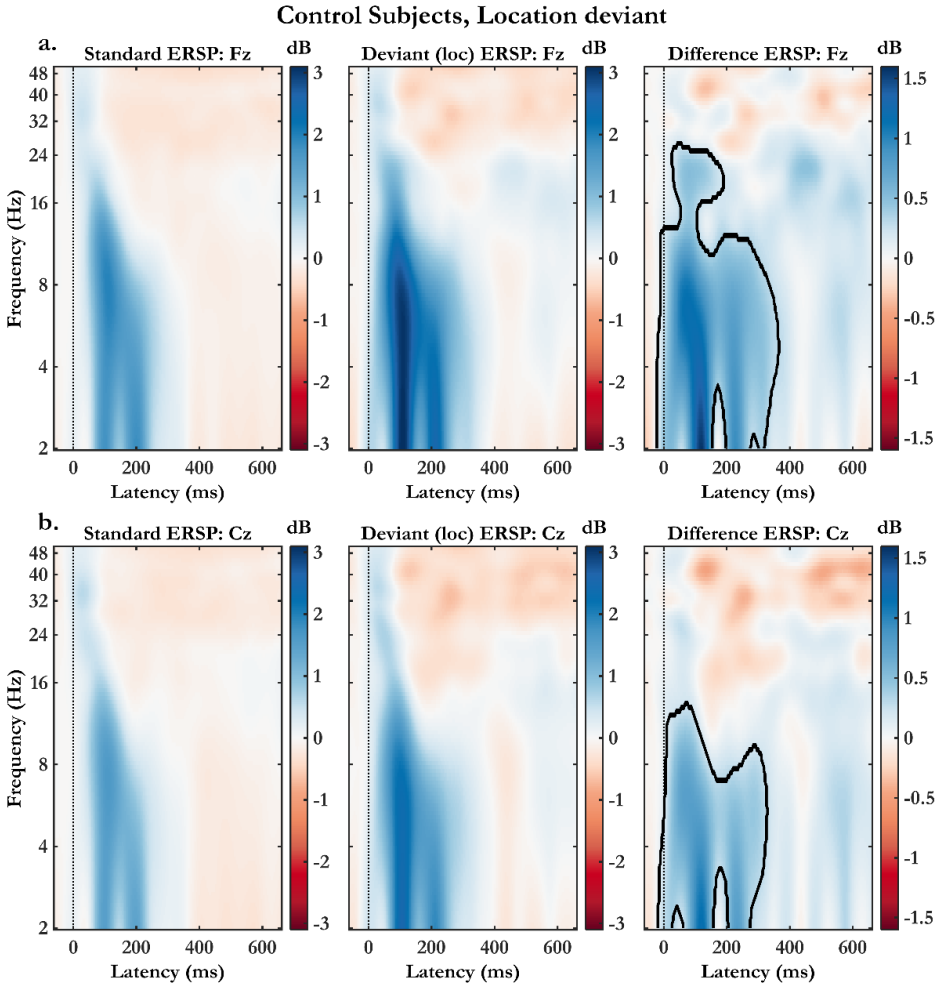


Figure 4.38 Grand average standard ERSP, location deviant ERSP, and difference ERSP in control subject group (n = 17). a. Electrode Fz, b. Electrode Cz. Each row has three plots (left to right): standard ERSP, location deviant ERSP, difference ERSP. The significantly different region ($p<0.05$) is marked by black contours in the right column.

Similar to the control subjects, patient P1 shows an initial synchronisation of frequencies lower than 24Hz. However, this synchronisation lasts less than 200ms. In the later time bins, we also see a desynchronisation of frequencies centred approximately at 8Hz, with a stronger effect observed at electrode Fz. Patient P2 is the only patient to show any significant difference between the standard tone response and the location deviant response, though at a latency much longer than expected for location MMN. This patient also shows short periods of low frequency

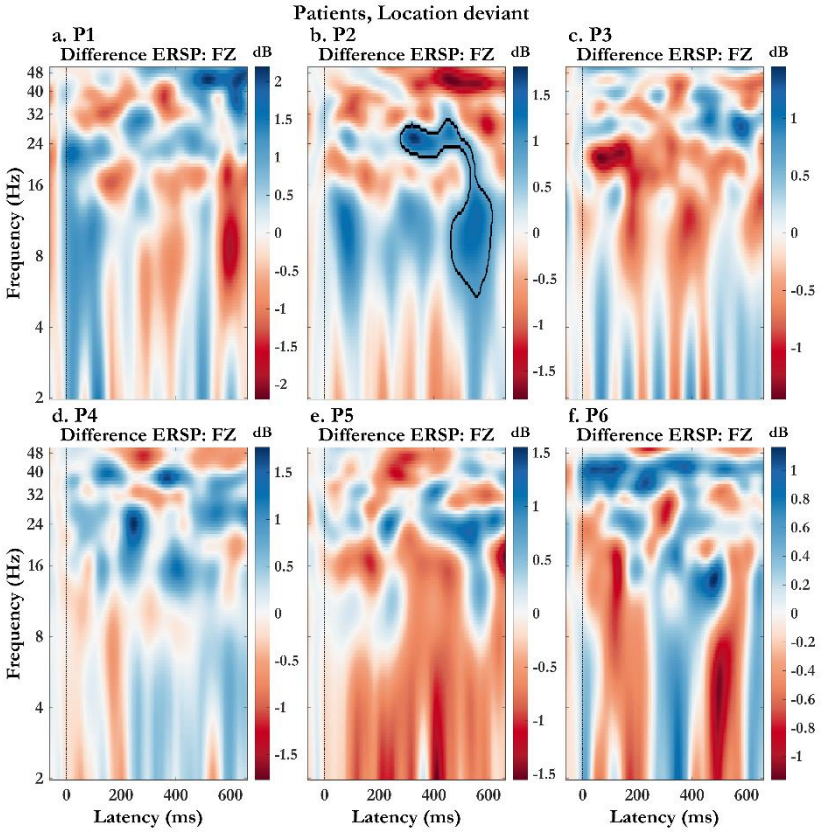


Figure 4.39 Average difference ERSP between location deviant and standard tone at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

desynchronisation that range from 2Hz to 8Hz, unlike the control group. Like patient P1, patient P3 also shows shorter latency synchronisation of low frequencies. This synchronisation lasts longer at electrode Cz and is followed by desynchronisation of these bands at both the electrodes. In patient P4 the response is more variable between the frontal and central electrodes. At electrode Fz we see an initial desynchronisation of frequencies below 16Hz, which then transitions to an average synchronisation of the time-frequency plot, with a few small regions of desynchronisation. At electrode Cz we do not see the initial desynchronisation, but only synchronisation across most of the time-frequency plots. Patient P5's difference ERSP response shows an average desynchronisation of the whole time-frequency plot, except for some small regions of synchronisation. This effect is observed at both the frontal and central electrodes and is opposite to control group. The difference ERSP response from patient P6 also shows variability between electrodes, as seen in patient P4. At electrode Fz there is

desynchronisation of frequencies below 16Hz from the beginning of the trial to 200ms post-stimulus, which transitions into synchronisation for approximately another 200ms, and then desynchronisation again lasting till 600ms post-stimulus. On the central Cz electrode however, we see an average synchronisation of these frequencies, and a few short time windows during which frequencies close to 2Hz are desynchronised.

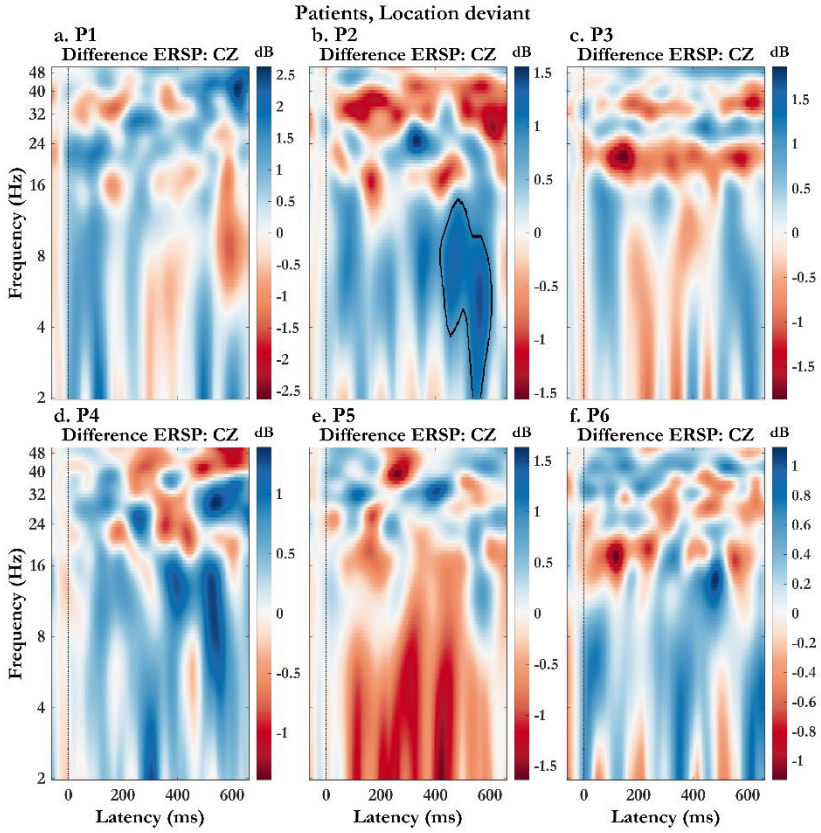


Figure 4.40 Average difference ERSP between location deviant and standard tone at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

We have seen from figures 4.39 and 4.40 that the ERSP responses from individual patients vary significantly. In the proceeding figures the patients are grouped based on their clinical diagnosis and their responses are investigated. Figures 4.41 and 4.42 show group averaged ERSP responses at electrodes Fz and Cz, respectively. The ERSP responses from control subjects are taken from figure 4.38 and included in these figures. The colour-scales used in these plots are also same as the ones used in figure 4.38 (±3dB for standard and location deviant ERSP and ±1.5dB

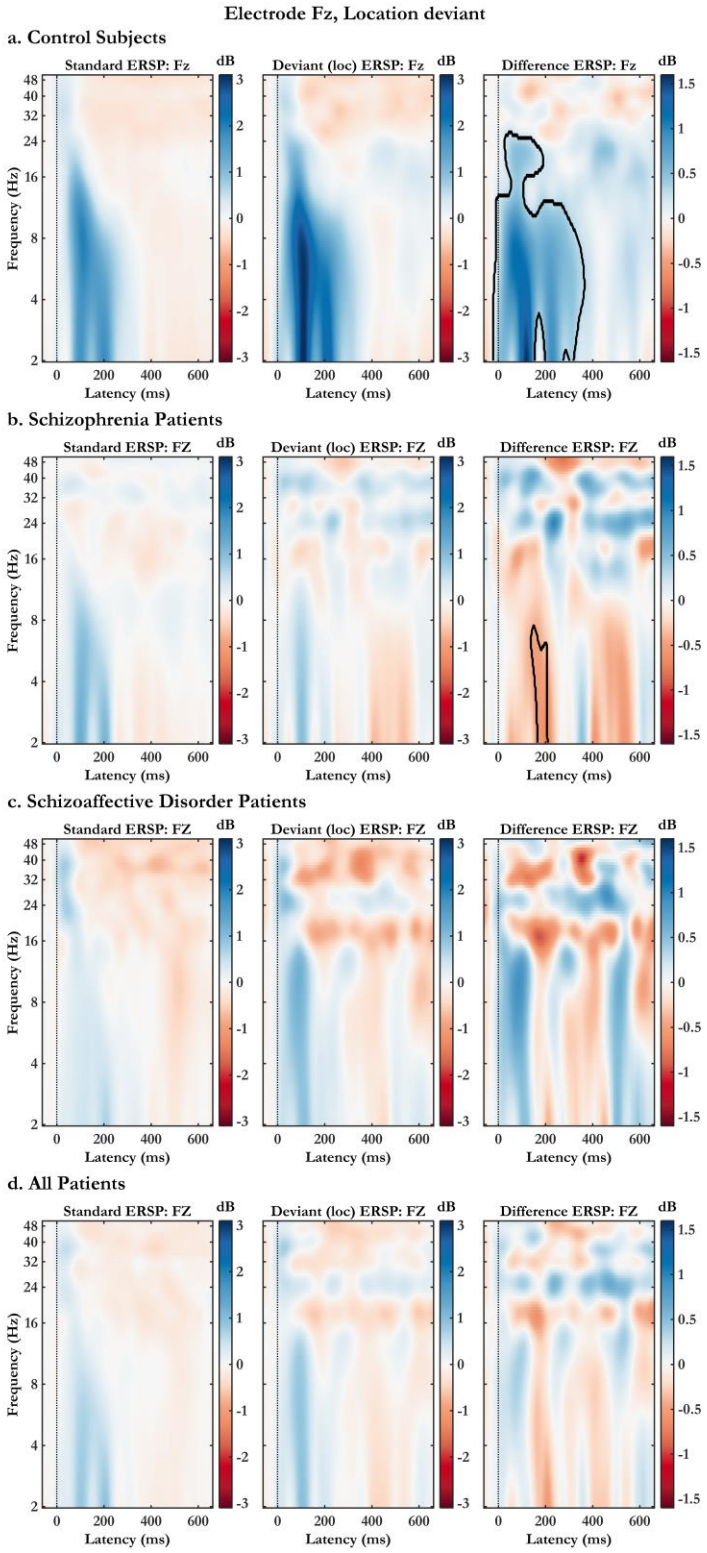


Figure 4.41 Grand average standard ERSP, location deviant ERSP, and difference ERSP at electrode Fz in subject groups. a. Control subject response from Figure 4.38a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

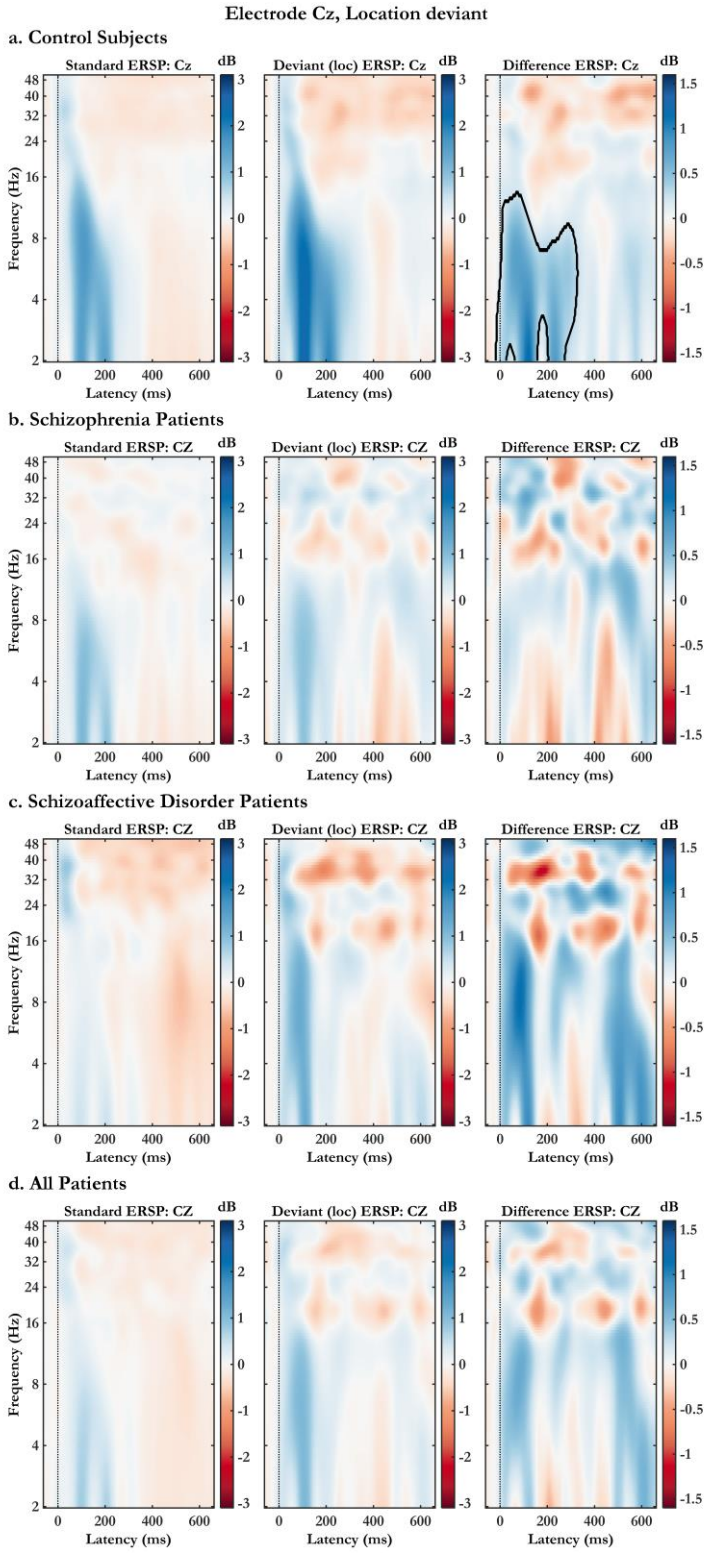


Figure 4.42 Grand average standard ERSP, location deviant ERSP, and difference ERSP at electrode Cz in subject groups. a. Control subject response from Figure 4.38b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

for difference ERSP). We have seen from previous ERSP plots for both the groups of patients that, the relative increase/decrease in power across the time-frequency plot is smaller in patients when compared to the control group. This applies to average response to the standard tone as well as the deviant tones. Location deviant ERSP response also shows this pattern in both the patient groups.

In schizophrenia patients (figs 4.41b, 4.42b) we see a weak synchronisation of frequencies below 16Hz during the location deviant stimulus and a desynchronisation of these frequencies at latencies greater than 400ms. The difference plot demonstrates that the initial synchronisation seen in the location deviant ERSP is weaker than that of standard tone response. This leads to a relatively desynchronised response in the difference plot. This desynchronisation also meets significance criteria during a short time window close to 200ms at electrode Fz. This is in contrast with what was seen in the control group. The schizoaffective disorder patients (figs 4.41c, 4.42c) show a stronger initial synchronisation of frequency signals below 16Hz during the location deviant trials. This synchronisation is marginally stronger at electrode Cz. However, unlike the control group, this synchronisation lasts for a shorter duration and does not meet the significance criteria. We also see desynchronisation of these frequencies at longer latencies, particularly at electrode Fz.

The grand averaged response from all the patients (figs 4.41d, 4.42d) for location deviant does show a synchronisation of frequencies below 16Hz that is relatively stronger than the standard tone response. As expected, this is also observed for a shorter duration compared to the control group and does not meet the significance criteria of $p<0.05$ after multiple comparisons correction.

4.5.4.3 KEY FINDINGS – LOCATION DEVIANT

1. The location deviant ERP had the largest N100 component which also resulted in a large significant MMN response in control subject group.
2. The location deviant MMN response in patient groups was diminished and significant differences between the location deviant ERP and standard tone ERP were observed only for a short duration at electrodes Fz and Cz.
3. The location deviant ERSP response in control subject group had significantly stronger synchronization of 2-16Hz frequencies from the beginning of the trial to approximately 300ms post-stimulus at both electrodes Fz and Cz.

4. The ERSP responses to location deviant was diminished in patient groups and only a small cluster of significant difference with the standard tone ERSP response was observed in schizophrenia patients at electrode Fz.

4.5.5 GAP DEVIANT MMN

4.5.5.1 EVENT RELATED POTENTIAL ANALYSIS – GAP DEVIANT

The gap deviant tone was created by introducing a 7ms silence in the middle of the 75ms standard tone signal. The grand average ERP response from the control subject group to this deviant tone is shown in figure 4.43. This figure also shows the standard tone response, and the gap MMN response calculated from subtracting the standard response from the gap deviant response.

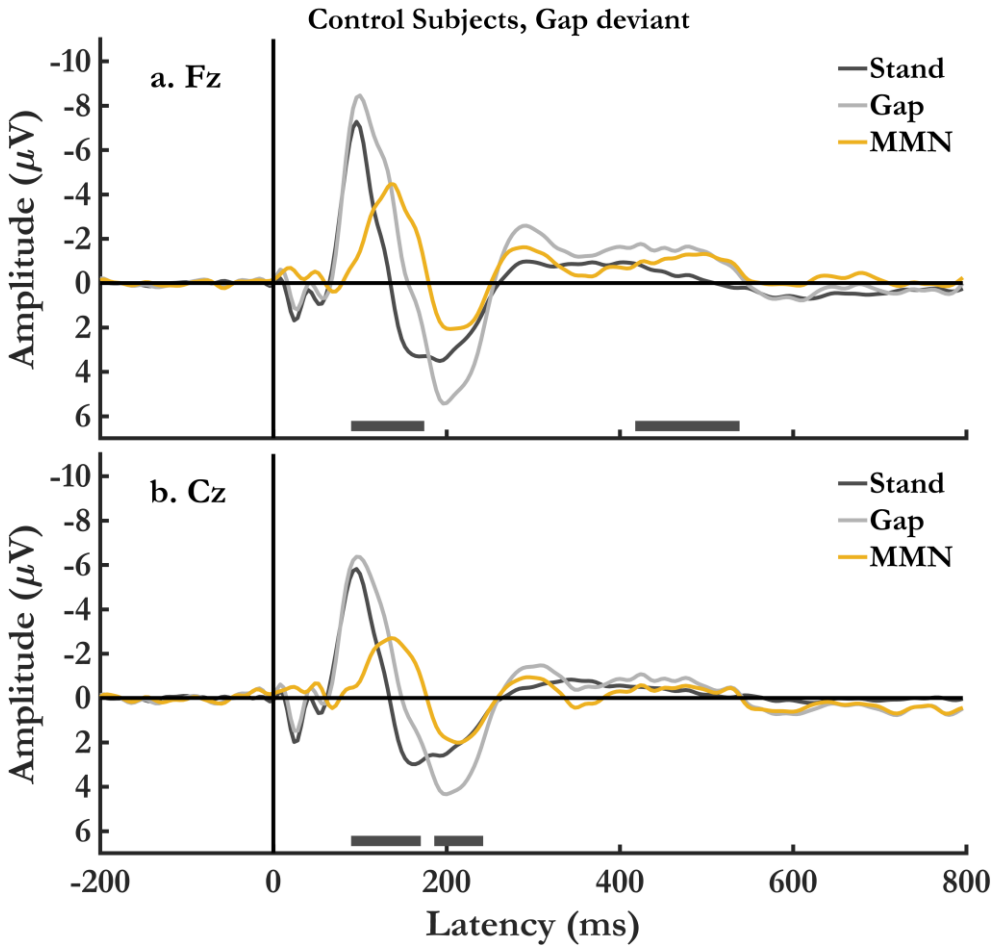


Figure 4.43 Grand average standard ERP, gap deviant ERP, and gap MMN in control subject group (n = 17). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz, b. Electrode Cz.

The gap deviant elicits an ERP response with a relatively higher N100 peak compared to other deviants, and a broader time-course. Following the N100 negativity, we see a positivity in the ERP signal that is larger than the positivity exhibited by the ERP response to the standard tone stimulus. This is unlike what is observed for any other deviant type where, the positive response is either smaller than standard tone ERP or is even absent (fig 4.23a., intensity deviant, Fz electrode). Due to this larger negativity in the ERP response, the resulting MMN response has a positive peak close to 200ms along with the usual negative peak earlier in the signal time-course. From the black bars at the bottom of each plot in figure 4.43, we see that the MMN amplitude is significantly different from the baseline during multiple periods of the trial. At electrode Fz we see a primary significant negativity that peaks at 136ms. There is also a secondary significant negativity observed at a latency longer than 400ms. At electrode Cz we observe that along with the primary negativity, the positivity around

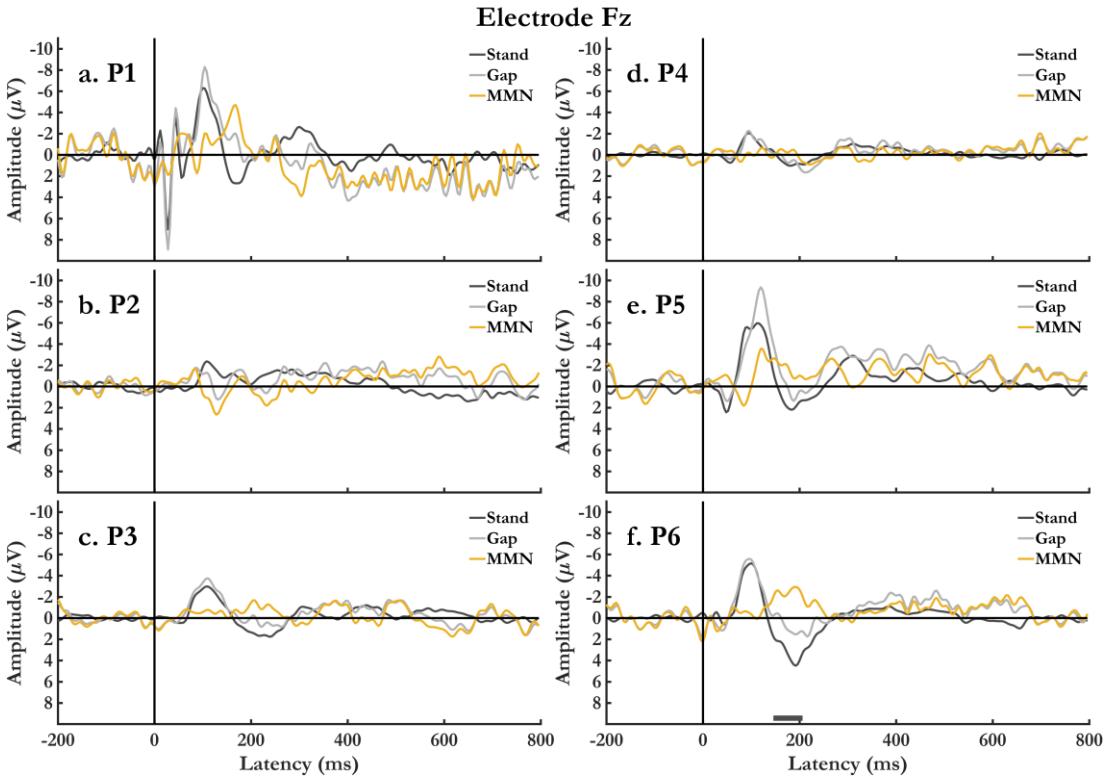


Figure 4.44 Average standard ERP, gap deviant ERP, and gap MMN at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

200ms latency is also significantly different from the baseline. The gap MMN peak amplitudes and peak latencies for each electrode are tabulated in table 4.6.

The average ERP response and gap MMN were computed to study the individual patient responses to the gap deviant tone. Figures 4.44 and 4.45 provide these responses at electrodes Fz and Cz, respectively. Similar to the previous deviant stimuli, there is a considerable variability in the response to gap deviant across the patient group. In none of the patients we see an increase in the positivity of the deviant ERP response compared to the standard response, like seen in the control group.

In patient P1, we see a marginally higher N100 peak in response to the gap deviant stimuli. This peak is more prominent at electrode Fz than at Cz. The MMN peak in this case, however, is observed after the N100 peak, when the standard tone response exhibits positivity. The gap deviant ERP in patient P1 also shows a positivity at longer latencies of the trial, unlike other deviant responses. In patient P2, we see a small positivity in the gap deviant ERP when the standard tone ERP is in the N100

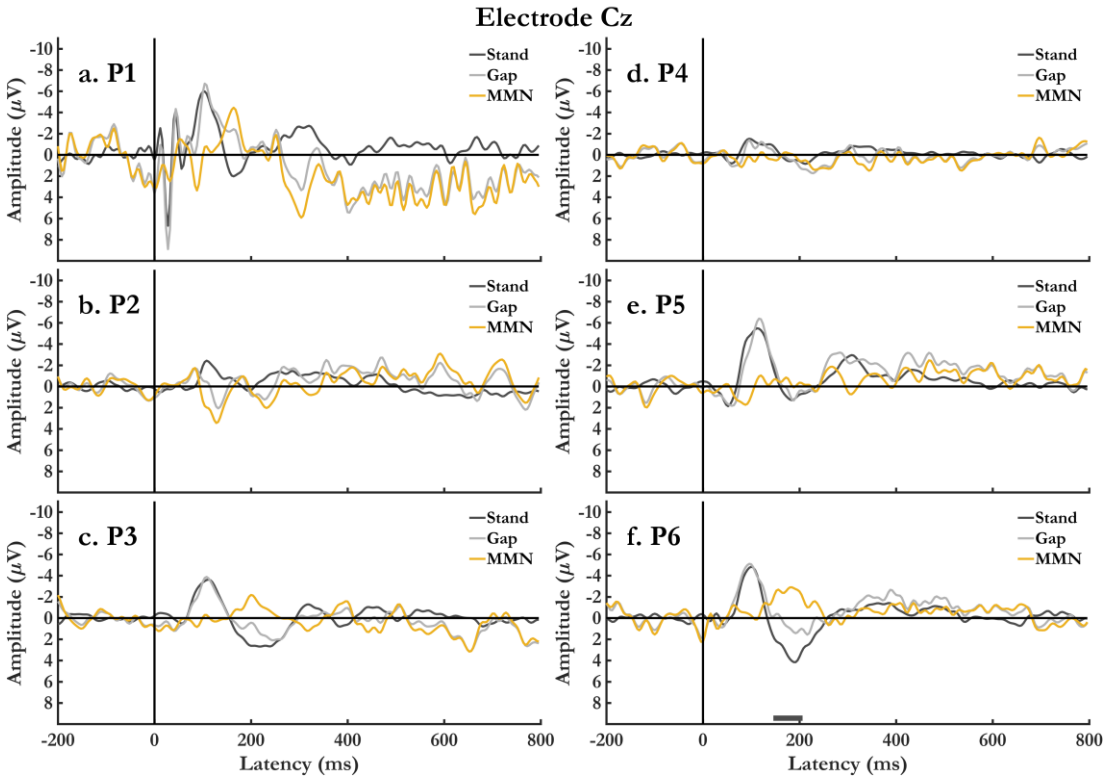


Figure 4.45 Average standard ERP, gap deviant ERP, and gap MMN at Cz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom of each plot, when present, represent periods of significant difference.

wave period. The MMN peak in this patient is seen because of a later negativity in gap deviant ERP response. In patient P3, the gap deviant ERP closely follows the standard tone ERP with the difference occurring after the N100 response. We observe the peak of the MMN in this patient during the period close to 200ms. In patient P4, like the standard ERP response, the gap deviant ERP response is also diminished. These two ERP are close to each other in amplitude, leading to an MMN response which shows small random fluctuation around the baseline. In patient P5, the gap deviant ERP has larger N100 peak at the frontal electrode. This results in the MMN peak at electrode Fz to occur at 120ms latency. At Cz electrode, both the standard and gap deviant ERP N100 peaks are closer to each other, however the MMN peak in the 90 to 250ms period is still observed at the same latency. Patients P6 is the only patient in the group that meets the significance criteria for difference between the gap deviant and standard tone ERP responses. The significant period occurs after the peak in N100 component and due to the difference in the positivity of the ERP signals. The peak of the MMN responses, at both the electrodes, are also observed during this period of the trial. The values of gap MMN peak amplitudes and peak latencies for individual patients at both the electrodes are shown in table 4.6.

The ERP responses were further analysed from the groups of patients in the study based on their clinical diagnosis. The grand average ERP responses from schizophrenia, schizoaffective disorder, and all patient groups are plotted in figures 4.46 for electrode Fz and 4.47 for electrode Cz. The figures also include the ERP responses from control group. From these figures we see that similar average pattern of ERP responses to the gap deviant stimuli are exhibited by both the patient groups. The peak of the N100 component is a little higher than that in the standard tone response at electrode Fz. At both the frontal and central electrodes, the peak of the MMN is observed after the N100 peak. This is a result of the difference between the time course of the ERPs, and the smaller positivity during the gap deviant response.

Table 4.6 MMN peak amplitude and latency measures for gap deviant

	Peak Amplitude (μVolts)		Peak Latency (ms)	
	Fz	**Cz**	**Fz**	**Cz**
Control Subjects (n = 17)				
Grand Average	-4.49	-2.70	136	136
Patients				
P1	-4.70	-4.44	168	164
P2	-0.96	-0.96	180	184
P3	-1.67	-2.18	204	200
P4	-0.66	-0.24	124	172
P5	-3.56	-1.03	120	120
P6	-2.95	-2.90	192	184
Schizophrenia Patients (n = 3)				
Grand Average	-1.73	-1.22	152	176
Schizoaffective Disorder Patients (n = 3)				
Grand Average	-1.95	-1.77	168	168
All Patients (n = 6)				
Grand Average	-1.72	-1.43	168	168

The values of the gap MMN peak amplitudes and peak latencies shown in table 4.6 clearly demonstrate the variability across individual patients. We also see that for grand averages of the 2 clinically different patient groups, the values do not differ much from each other, or when all patients are grouped together. It is also evident from the plots that MMN response in patients is diminished when compared to the control group. This is also reflected in the smaller MMN peak amplitudes shown in table 4.6, in almost all individual patients, and the patient groups. The table also shows that the peak latency in patient groups is longer compared to the control group.

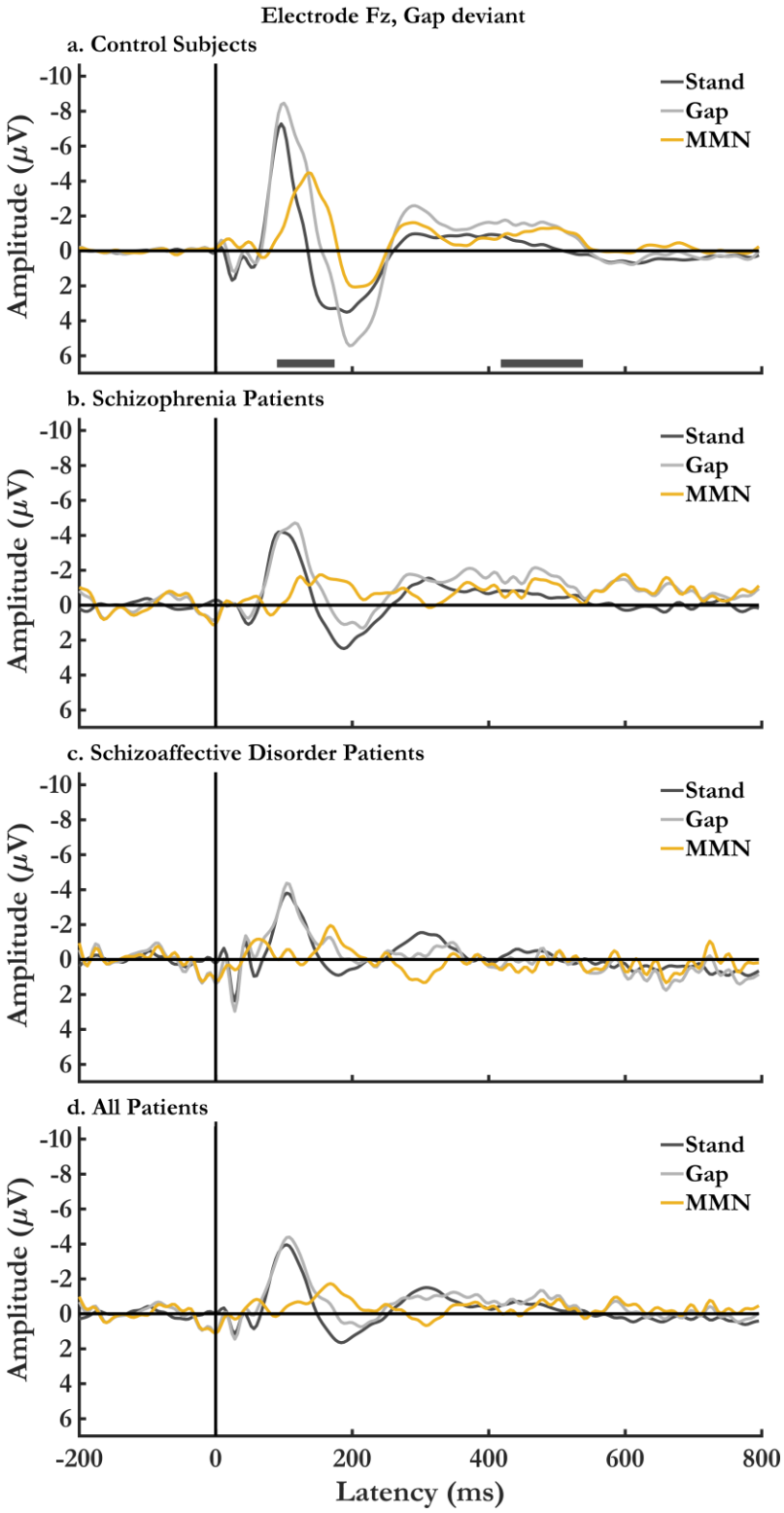


Figure 4.46 Grand average standard ERP, gap deviant ERP, and gap MMN at electrode Fz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.43a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

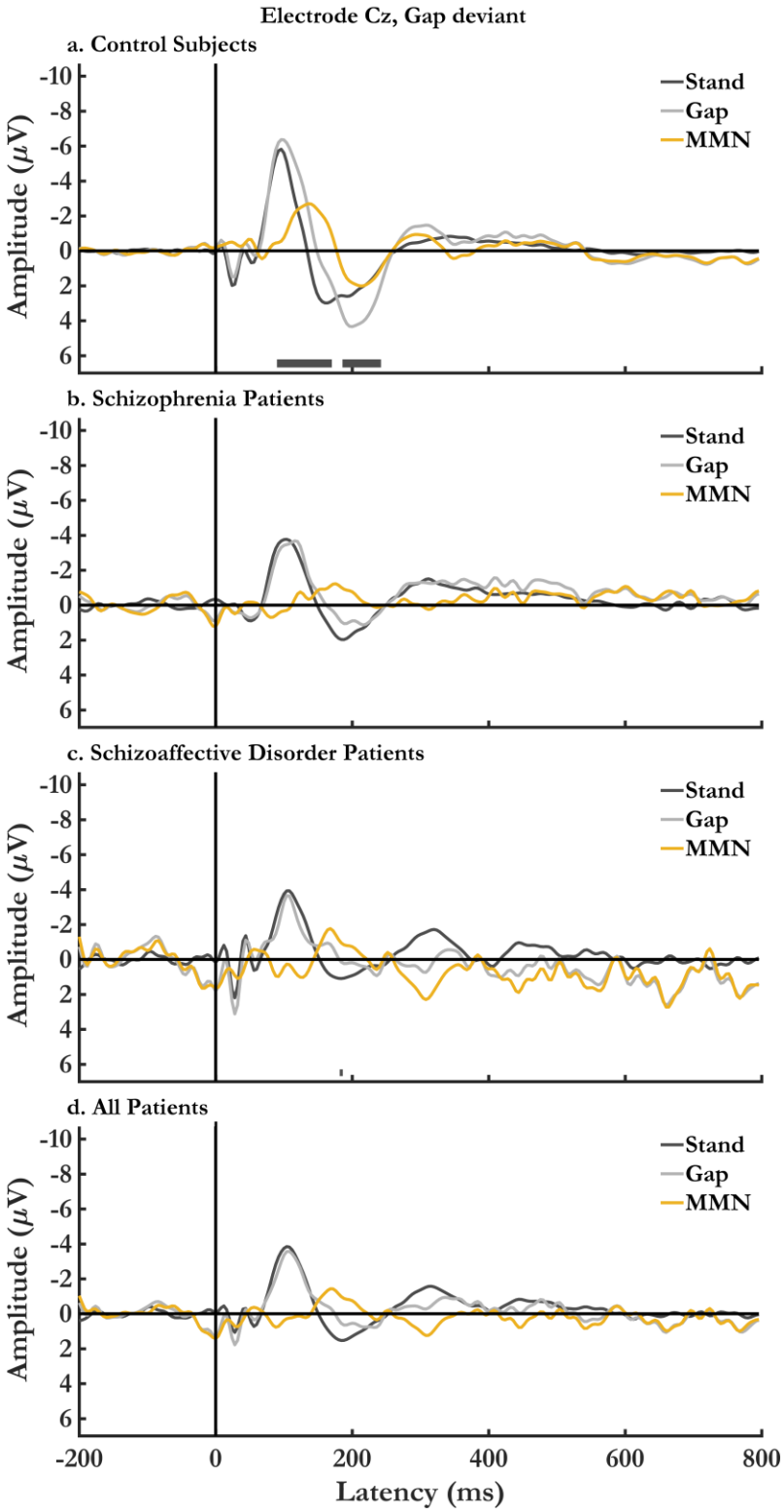


Figure 4.47 Grand average standard ERP, gap deviant ERP, and gap MMN at electrode Cz in subject groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Control subject response from Figure 4.43b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6).

4.5.5.2 TIME-FREQUENCY ANALYSIS – GAP DEVIANT

Figure 4.48 shows the control group ERSP response from standard tone stimulus (left), gap deviant stimulus (middle), and the difference between the two (right), for both Fz and Cz electrode. The standard and gap deviant responses are plotted using a colour scale of approximately ±3dB and the difference ERSP is made with ±1.5 dB scale. These scales are chosen to accommodate the plots from all the groups, including control subjects and patients. Comparing the standard and gap deviant ERSP response from both the electrodes we see that the synchronisation of frequencies below 16Hz is relatively stronger for the gap deviant. In the deviant plot, we observe two peaks at the lower end of the spectrum at approximately 100ms and 200ms. These peaks closely line-up with the negative (N100) and positive peaks in the gap deviant ERP shown in

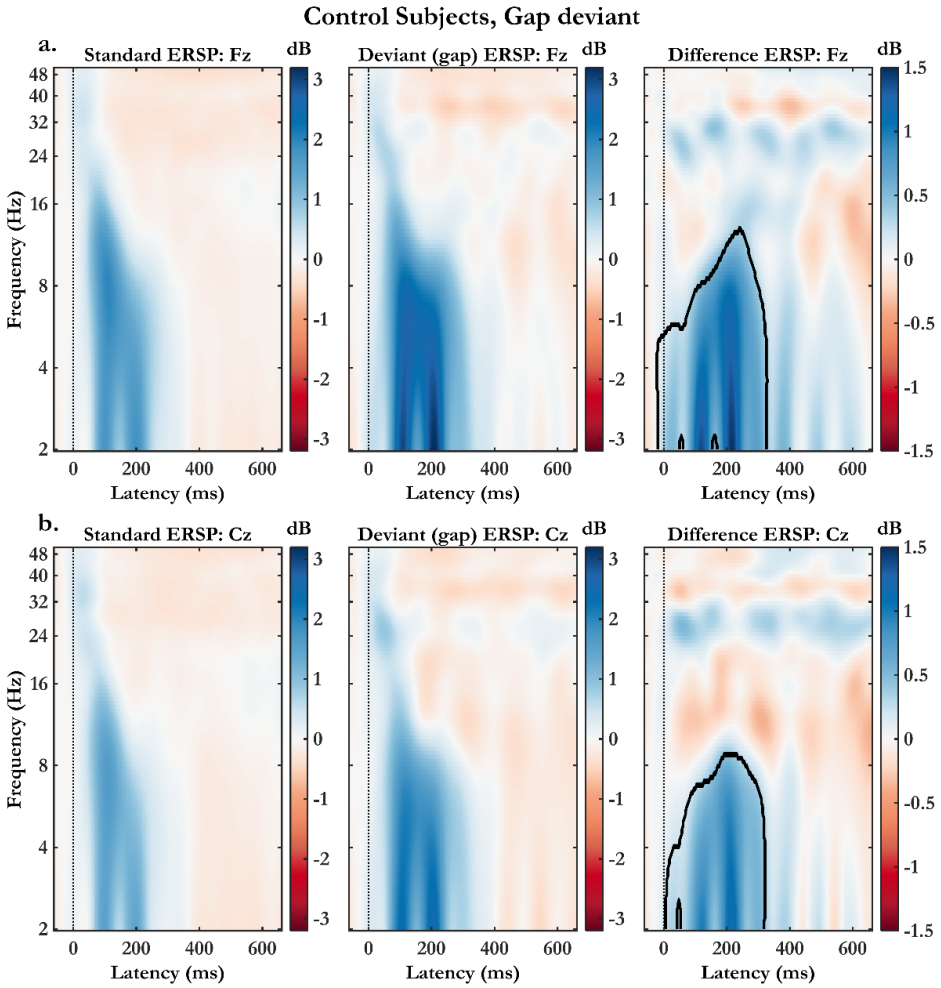


Figure 4.48 Grand average standard ERSP, gap deviant ERSP, and difference ERSP in control subject group (n = 17). a. Electrode Fz, b. Electrode Cz. Each row has three plots (left to right): standard ERSP, gap deviant ERSP, difference ERSP. The significantly different region ($p<0.05$) is marked by black contours in the right column.

figure 4.43. We also see in the gap deviant ERSP, specifically at electrode Fz, that the second peak around 200ms is higher than the first peak. This is unlike what is seen in the standard tone ERSP and other deviant plots where the earlier peak is higher. This can be clearly seen for the standard tone response in figure 4.28, where different colour-scale limits are used. The difference ERSP plots further show us that the synchronisation of the 2-16Hz frequency for the gap deviant is significantly stronger than that of the standard tone. The plot shows that at the beginning of the trial, frequencies below 6Hz on the frontal electrode and below 4Hz of the central electrode are significantly synchronised. As the latency increases, we see the range of synchronised frequencies also increasing, reaching approximately 16Hz on the frontal Fz electrode and 8Hz of the central Cz electrode. In this plot we also observe that the peak at 200ms is higher than the lower latency peak. This peak is in the period during the positivity of the MMN response observed in figure 4.43. The other regions of the

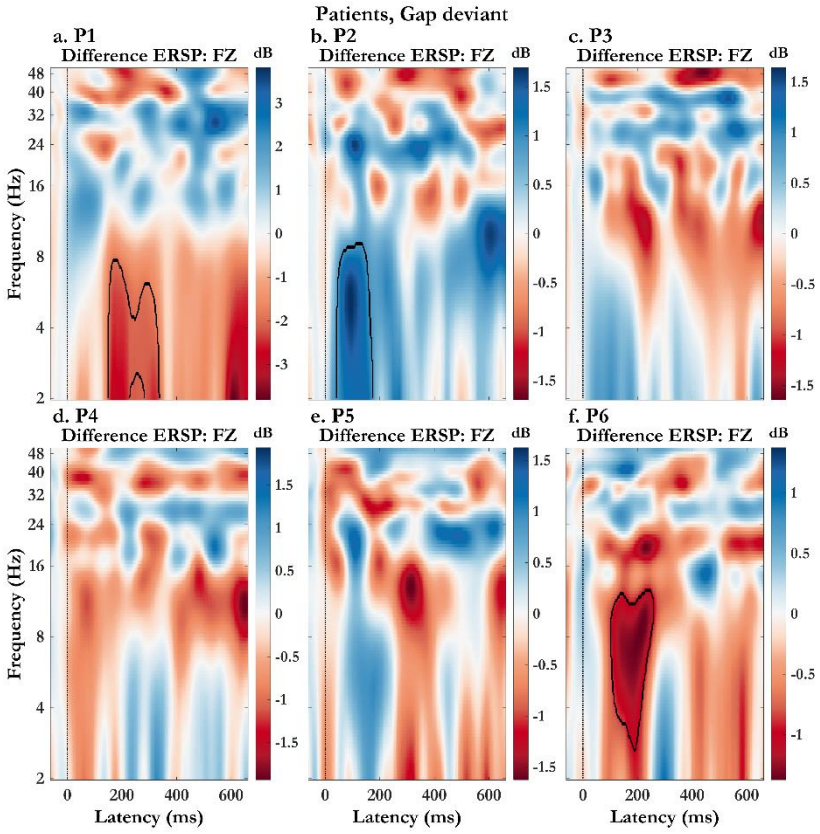


Figure 4.49 Average difference ERSP between gap deviant and standard tone at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

ERSP plots show weaker synchronisation and desynchronisation that do not pass the significance criteria of $p<0.05$ after multiple comparisons correction.

The difference ERSP response from individual patients is shown in figures 4.49 for electrode Fz and 4.50 for electrode Cz. As we have previously seen for other deviant stimuli, there is a substantial variability between patients. In patient P1, we predominately see a desynchronisation of low-frequency signal approximately below 12Hz. At electrode Fz this relative desynchronisation during the gap deviant response is also significant in 100-300ms range. In patient P2, the pattern of response is relatively close to that of the control subjects. A significant synchronisation of frequencies below 8Hz is observed at electrode Fz with the peak observed in the 4Hz to 8Hz frequency range. We do see a relative synchronisation of this band at electrode Cz too, but it does not satisfy the significance criteria. In this case significant difference is seen at the end of the trial centred around 8Hz. In patient P3, we see early synchronisation of lower frequencies until 200ms post-stimulus period at electrode Fz.

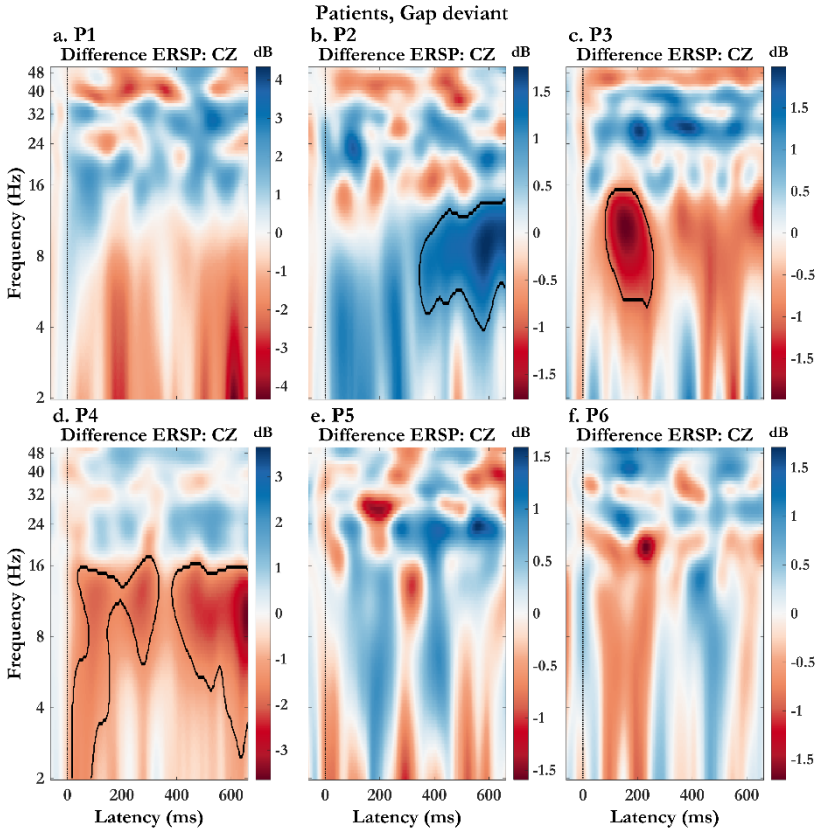


Figure 4.50 Average difference ERSP between gap deviant and standard tone at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

At electrode Cz however, we see a strong desynchronisation during this time which is centred at approximately 8Hz. In patient P4, like P1, the difference plot again shows an overall desynchronisation of the frequencies below 16Hz. At electrode Fz this occurs for the first 200ms and does not satisfy the significance criteria. It is followed by synchronisation for about 200ms. At electrode Cz the desynchronisation of these frequencies is much more prominent and is also significantly smaller than the standard tone response for most of the trial period. Patient P5 exhibits synchronisation of lower frequencies from a few milliseconds after trial onset to about 200ms at both electrode Fz and Cz. This synchronisation is followed by desynchronisation which is stronger at electrode Fz. None of the changes seen in the two difference plots meets the significance criteria. In patient P6, we see a region of significant desynchronisation at electrode Fz. This region occurs at a latency that also showed significant MMN response as seen in figures 4.47 and 4.48. At electrode Cz we do not see a significant difference. However, we see a similar pattern of desynchronisation as observed at Fz that lasts until 200ms post-stimulus.

To study the grand averaged response from the schizophrenia and schizoaffective disorder patient groups, and all patients grouped together, their ERSP responses to the gap deviant are plotted in figure 4.51 for electrode Fz, and figure 4.52 for electrode Cz. These figures also include the responses at these electrodes from control group shown in figure 4.43 and use the same colour scales for the patient groups.

In schizophrenia patients, we have seen earlier that the response to the standard tone is diminished across the whole time-frequency plot. From the middle columns of figures 4.51b and 4.52b, we see that this holds true for the gap deviant ERSP as well. Similar to the control subjects (figs 4.51a, 4.52a), the gap deviant ERSP in schizophrenia patients also exhibit synchronisation of lower frequency signals with two peaks around 100ms and 200ms respectively. However, unlike the control subjects, the frequency range of this synchronisation is smaller and extends only from 2Hz to 8Hz. We can tell from the difference plot that, relative to the standard tone response, the synchronisation in gap deviant response is smaller, hence leading to a negative value in the difference plots. We also see that electrode Cz exhibits a larger

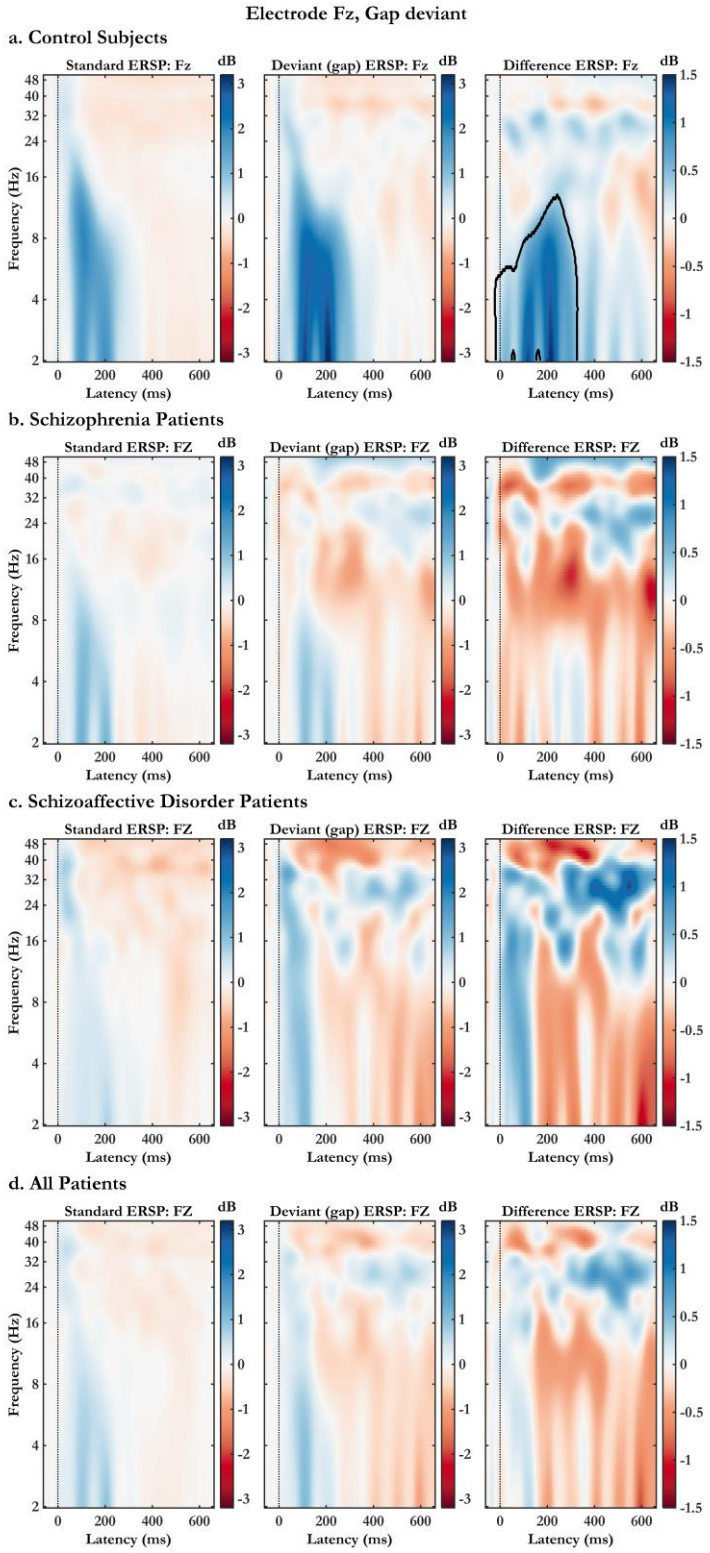


Figure 4.51 Grand average standard ERSP, gap deviant ERSP, and difference ERSP at electrode Fz in subject groups. a. Control subject response from Figure 4.48a (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

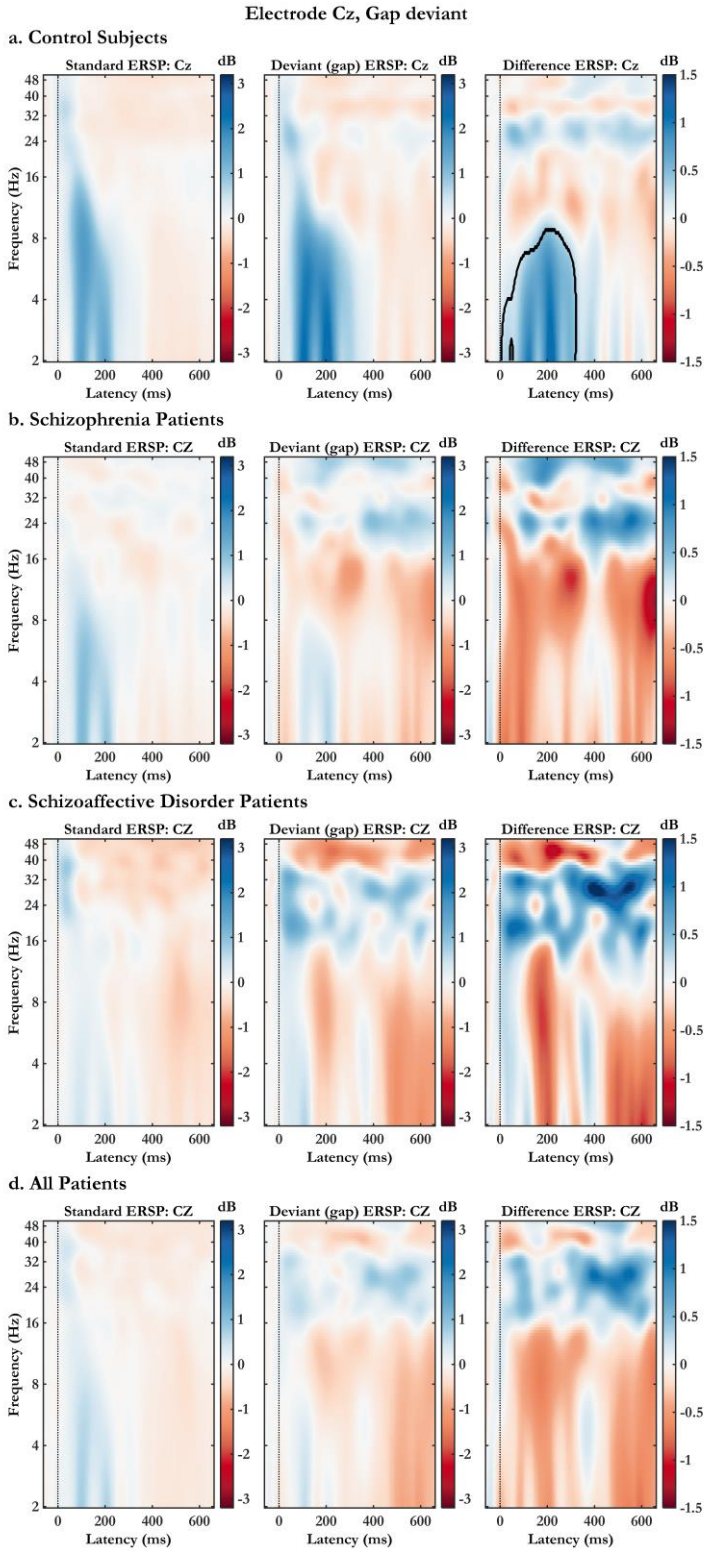


Figure 4.52 Grand average standard ERSP, gap deviant ERSP, and difference ERSP at electrode Cz in subject groups. a. Control subject response from Figure 4.48b (n = 17), b. Schizophrenia patients (n = 3), c. Schizoaffective disorder patients (n = 3), d. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

decrease from standard to gap deviant tone response, when compared to the Fz electrode. None of the regions in these plots satisfied the significant difference criteria.

In schizoaffective disorder we again see a diminished response to the gap deviant stimulus (figs 4.51c, 4.52c). However, in these patients there is an initial phase of synchronisation in the gap deviant response that is larger than the standard tone response. We also see that this initial synchronisation period is exhibited by wider frequency spectrum extending from 2Hz to about 32Hz. The relative synchronisation is stronger at electrode Fz compared to Cz. This initial period of synchronisation is like what is exhibited in control subject group but lasts for a shorter period. It is followed by a relatively stronger desynchronisation of the 2Hz to 16Hz frequency spectrum for almost the whole remaining trial. In this case too, none of the regions of the plot satisfy the criteria of significance.

The grand averaged results from all the patients grouped together (figs 4.51d, 4.52d) show that the electrode Fz shows an initial period of relative synchronisation. This period is shorter than what is exhibited by control subjects and is followed by stronger desynchronisation, which is not seen in control subjects. At electrode Cz, we see that through the whole trial, the gap deviant response for frequencies below 16Hz is smaller than the standard tone response. Similar to the observations from the two patient groups, and unlike control subjects, none of the regions in the patient group ERSP plots are significantly different between the two types of stimuli.

4.5.5.3 KEY FINDINGS – GAP DEVIANT

1. The significant gap deviant MMN response was observed in control subject group and was the only MMN with a prominent positive peak around 200ms at both electrodes Fz and Cz.
2. The gap deviant MMN response in patient groups was diminished and no significant differences were observed between the gap deviant ERP and standard tone ERP responses at electrodes Fz or Cz.
3. The gap deviant ERSP response in control subject group had a strong synchronization of lower frequencies with two prominent 2Hz peaks at 100ms and 200ms post stimulus. This synchronization was also significantly stronger that the standard tone ERSP response from beginning of the trial to approximately 300ms post-stimulus.

4. The ERSP responses to gap deviant was diminished in patient groups and no significant differences were found relative to the standard tone ERSP response.

4.5.6 STATISTICAL ANALYSIS OF EEG MEASURES

The results presented in sections 4.5.1 to 4.5.5 show that the MMN response for each deviant type in patients is diminished when compared to the control group. This is further illustrated by figure 4.53 showing MMN elicited by the five deviant types in both healthy control and patient groups. A variability in the MMN peak latency between control and patient groups is also observed in tables 4.2 to 4.6. In the previous sections, each deviant type is analysed individually. In this section, an overall picture of the differences seen in patient group is constructed by considering all the deviant types together, and through visualization and statistical analysis of EEG measures.

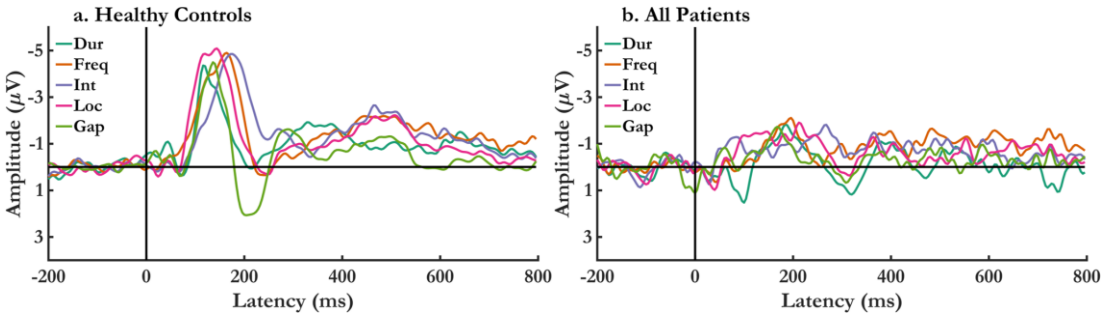


Figure 4.53 Grand Average MMN at electrode Fz elicited by the five deviant tones. a. Healthy control subject group, b. All patients group.

The MMN peak amplitude and peak latency measures computed from grand average of heathy control subjects and patients grouped by their clinical diagnosis are presented in figure 4.54. These results are graphically presented to effectively compare the subject groups, deviant types, and responses at the midline electrodes. Figure 4.54a to 4.54e represent the duration, frequency, intensity, location, and gap deviants, respectively. In each plot within the figure, the x-axis represents the five electrodes Fz, FCz, Cz, CPz, and Pz, in sequence from the frontal scalp region to the parietal region. In each figure, the left side plots the MMN peak amplitude. On the right side the MMN peak latencies are plotted. Each plot has three lines for control group, schizophrenia patient group, and schizoaffective disorder patient group. It should be noted that all the values plotted in these figures are measures computed from the grand averaged signal. They are computed, for each group, from MMN response obtained by taking

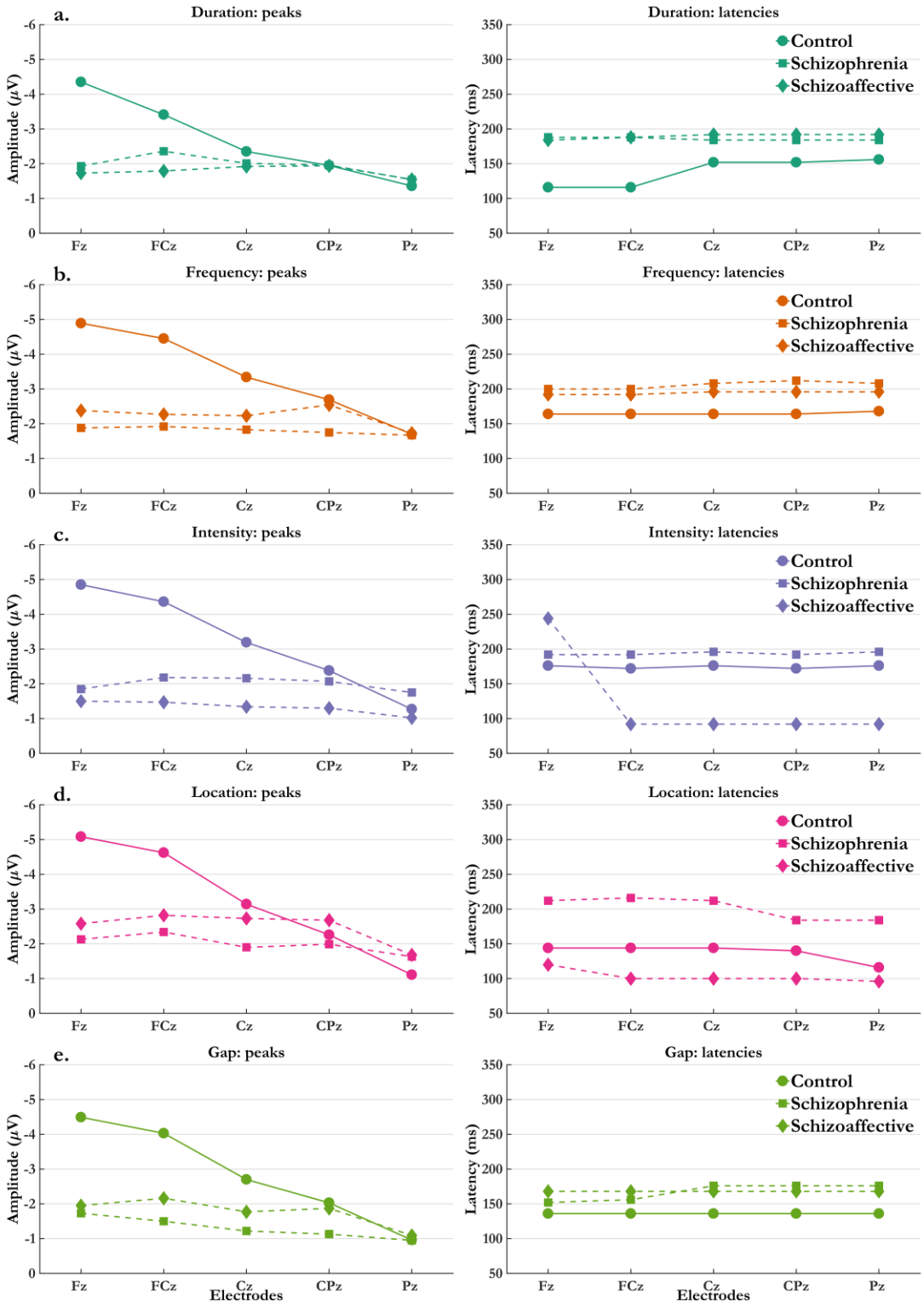


Figure 4.54 Grand average MMN measures across midline electrodes in control and patient groups for all deviant types. a. Duration deviant, b. Frequency deviant, c. Intensity deviant, d. Location deviant, e. Gap deviant. Left column: MMN peak amplitudes, Right column: MMN peak latencies. Solid lines and circle markers represent healthy controls. Dotted lines are used for patients with square markers for schizophrenia and diamond markers for schizoaffective disorder, respectively. The peak latency plots have a non-zero y-axis as the purpose of them is to visualize the patterns in the data.

the difference between the grand average ERPs of the deviant and the standard tone. Therefore, each point is a single value and not an average of values obtained from individual subjects in the group. For this reason, there are no statistical comparisons to be computed for the measures shown in this figure.

From the plots on the left side of figure 4.54, we see that in control subjects there a is gradual decrease in the MMN peak, going from the frontal region of the scalp to the parietal region. This decrease in observed in all the deviant types (fig 4.54a to fig 4.54e). On the other hand, the patient groups do not show any such pattern. In this case a diminished MMN is observed on the frontal electrodes and it does not change much across the midline electrodes. We do see some small differences between the patient groups across the deviant types. For example, the MMN peak amplitudes are higher in schizoaffective disorder patient group for frequency, location, and gap deviant, when compared to the schizophrenia patient group. For the intensity deviant, the amplitudes are higher in schizophrenia patient group compared to the schizoaffective disorder patient group.

The plots on the right side of figure 4.54 show the variation of MMN peak latencies. The peak latencies do not show any specific pattern in control group across the midline electrodes from Fz to Pz. The only variations we see are in the duration deviant where the peak latency increases at electrode Cz (staying constant after that) and in the location deviant where there is a small decrease at electrode Pz. This increase in peak latency during duration deviant can be explained from plot of duration deviant ERPs and duration MMN response in figure 4.3. We see a double peak at electrode Cz with the latter peak higher than the earlier. It is also interesting to note that the initial smaller peak at electrode Cz occurs close to the MMN peak latency at electrode Fz. The MMN peak latencies across the midline electrodes are relatively constant for the patient groups as well. However, we see longer peak latency in schizophrenia patients in intensity and location deviants, compared to control subjects. Even more interesting observation is that schizoaffective disorder patients have shorter intensity and location MMN peak latencies compared to the control group. In the other three deviant types, we see an increase of peak latencies in both the patient groups.

The figure 4.54 shows how the grand average responses in the patient groups differ from that of the control subjects. These grand average responses give a big

picture of the different group, however, to determine the statistical differences between the groups, measures that were computed from average responses from individual subjects were used. The results of the mixed factor 3x5x5 ANOVA for the average MMN amplitude, MMN peak amplitude, and MMN peak latencies are presented below.

For the average MMN amplitude, a significant main effect was observed in all the three group ($F(2, 532) = 46.08$, $p < 0.0001$), electrode location ($F(4, 532) = 9.66$, $p < 0.0001$), and deviant type ($F(4, 532) = 2.95$, $p = 0.0198$) variables. There was also a significant interaction between the group and electrode location variables ($F(8, 532) = 5.47$, $p < 0.0001$). Multiple comparisons analysis revealed that the average MMN amplitude was significantly larger in control subjects when compared to both schizophrenia patients ($p < 0.0001$) and schizoaffective disorder patients ($p < 0.0001$). There was no significant difference between the two patient groups. For the electrode locations, average MMN amplitude at both electrode Fz and FCz was significantly larger than the amplitude at electrode CPz (Fz: $p = 0.0282$, FCz: $p = 0,0410$) and Pz (both Fz and FCz: $p < 0.0001$). The average amplitude at Cz was also larger than at electrode Pz ($p = 0.0088$). Location deviant elicited a larger average MMN amplitude than the gap deviant ($p = 0.0078$).

The results from the analysis of MMN peak amplitudes showed a significant main effect only in the group ($F(2, 532) = 46.85$, $p < 0.0001$) and the electrode location ($F(4, 532) = 9.21$, $p < 0.0001$) variables. Similar to the average MMN amplitude, there was also a significant interaction between the group and electrode location variables for MMN peak amplitude ($F(8, 532) = 5.49$, $p < 0.0001$). Multiple comparisons analysis revealed that, the MMN peak amplitude was significantly larger in control subjects compared to schizophrenia patients ($p < 0.0001$) and schizoaffective disorder patients ($p < 0.0001$). There were no significant differences between the two patient groups. For the electrode locations, MMN peak amplitude at CPz was significantly lower than the peak at Fz ($p = 0.0287$) and FCz ($p = 0.0391$). The peak at electrode Pz was significantly lower than the peak at electrodes Fz ($p < 0.0001$), FCz ($p < 0.0001$), and Cz ($p = 0.0141$).

The interaction effect between the group and electrode locations, was similar for both MMN peak amplitude and average MMN amplitude. This interaction is best

understood from the plot for MMN peak amplitude interaction in figure 4.55a. Each point in the plot is the mean of the MMN peak amplitude, with the standard error of mean represented by the error bars. The points are jittered in x dimension for the ease

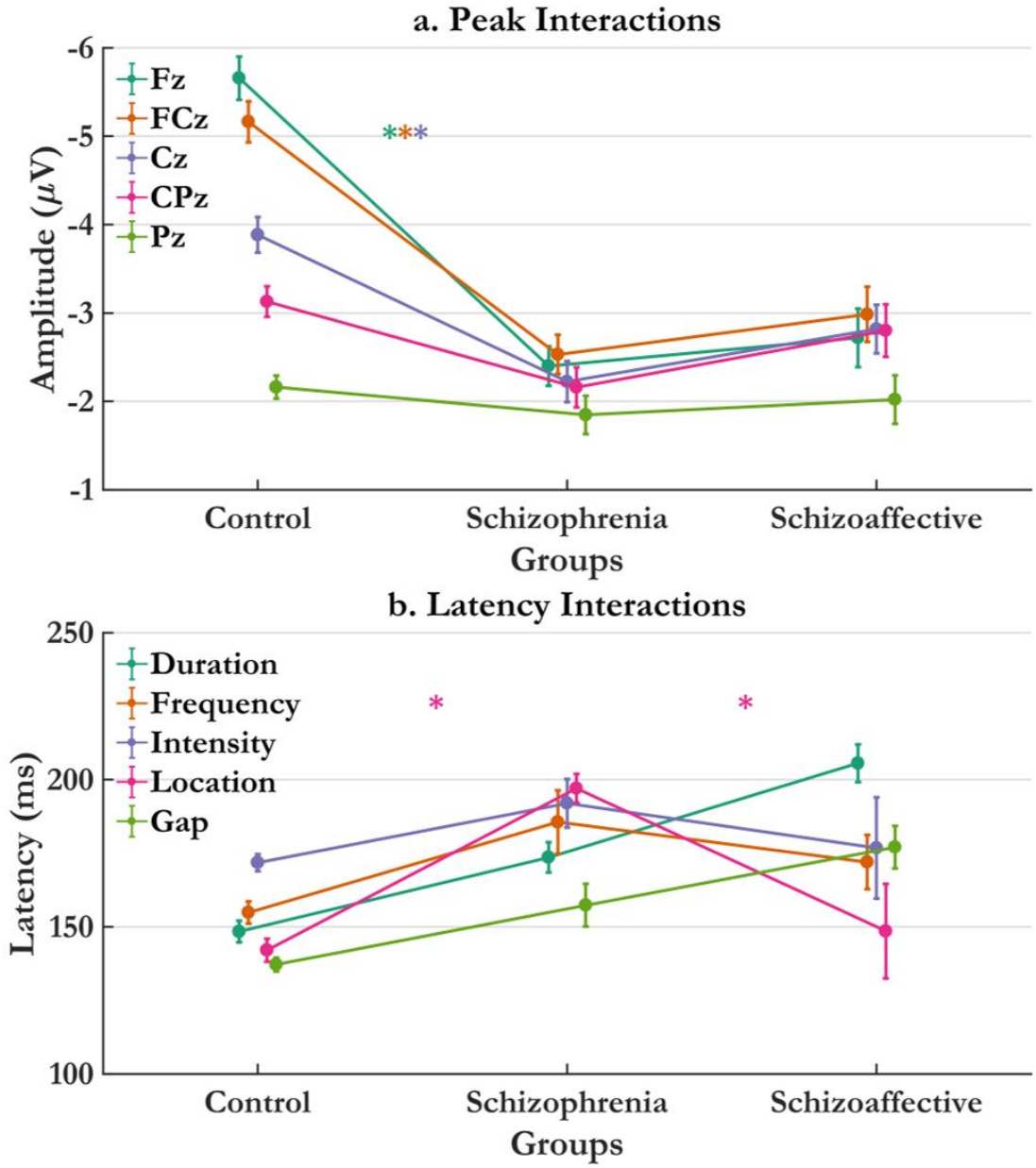


Figure 4.55 Interacting factors observed from ANOVA analysis of MMN measures. a. Interaction plot between subject groups and electrode locations in determining MMN peak amplitudes. b. Interaction plot between subject groups and deviant in determining MMN peak latency. The asterisk (*) represents significant differences ($p<0.05$) between adjacent groups and are coloured by the corresponding factors in the plot legends. Points are jittered in x dimension for the ease of visualization. The plots have non-zero y-axis as we mainly focus on the patterns in values of data presented.

of visualization of each value. The plot shows that though significant main effects were seen in both group and electrode locations, the variation of MMN peak amplitude cannot be determined by either factor individually. The asterisks on the plot represent the results of the multiple comparisons test. The MMN peak amplitude was significantly larger in control subjects compared to schizophrenia patients at electrodes Fz ($p < .0001$), FCz ($p < 0.0001$), and Cz ($p < 0.0386$). Not shown in the plot, this pattern was observed between control subjects and schizoaffective disorder patients too, but only for electrodes Fz ($p < 0.0001$) and FCz ($p = 0.0005$). The plot also shows that for the CPz and Pz electrodes, while there were small changes between the control and patient groups, the differences were not significant.

The ANOVA analysis of the MMN peak latencies revealed a significant main effect in the group ($F(2, 532) = 38.12$, $p < 0.0001$) and deviant type ($F(4, 532) = 4.89$, $p = 0.0007$) variables. A multiple comparisons analysis of the results showed that peak latencies were significantly longer in both schizophrenia patients ($p < 0.0001$) and schizoaffective disorder patients ($p < 0.0001$) compared to control subjects. There was no significant difference between the two patient groups. There was also a significant interaction between the deviant type and subject group variables ($F(8, 532) = 4.45$, $p < 0.0001$). The interaction plot between them is shown in figure 4.55b. Each point in the plot is the mean of the MMN peak latencies, with the standard error of mean represented by the error bars. The points are jittered in x dimension for the ease of visualization of each value. The plot shows that the peak latency changes between the subject groups are dependent on the type of deviant. The asterisks in the plot represent significantly longer peak latency in schizophrenia patients for location deviant compared to both healthy controls ($p < 0.0001$) and schizoaffective disorder patients ($p = 0.0067$). In duration and gap deviants, the latency is longer in patient groups compared to healthy controls. However, only schizoaffective patients showed significantly longer peak latency when compared to control subjects (duration: $p < 0.0001$, gap: $p = 0.0021$). Though schizoaffective patients had a longer peak latency compared to the schizophrenia patients in these two deviants, the increase was not significant.

4.5.7 CORRELATIONS WITH DEMOGRAPHIC DATA

All the patients in the study were scored using two questionnaires on the day of the auditory oddball experiment; a. Positive and Negative Syndrome Scale (PANSS) which measure the symptom severity in schizophrenia patient (Kay et al., 1987), and b. Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) used to rate the severity of the depression in patients. The scores obtained from these two scales were compared with the MMN peak amplitude and peak latency measurements of MMN for each deviant types. As seen from figure 4.54 the MMN

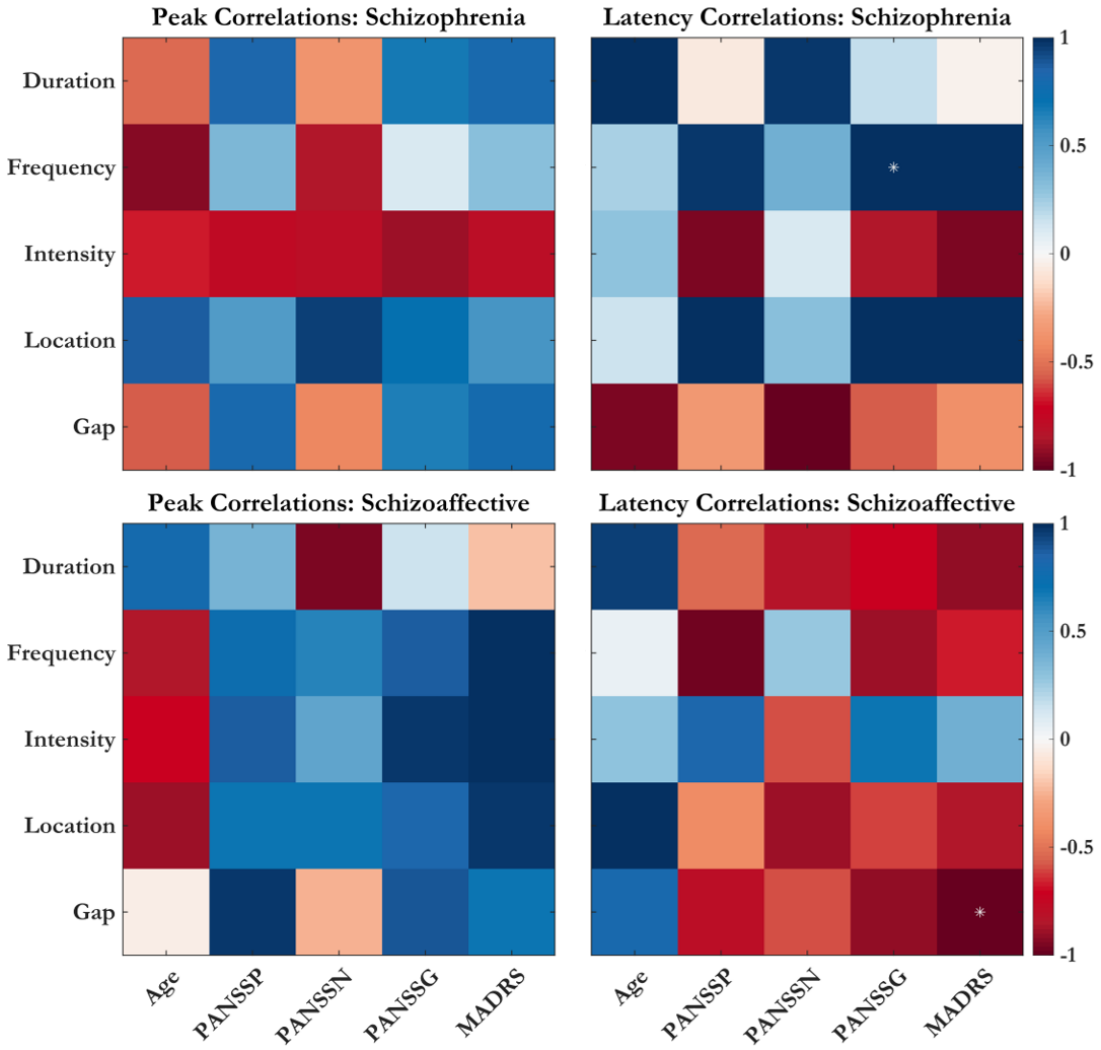


Figure 4.56 Correlations between MMN measures at electrode Fz and symptom severity scores in patients. Left column: correlations with absolute MMN peak amplitudes, right column: correlations with MMN peak latency. Top raw: schizophrenia patients, bottom row: schizoaffective disorder patients. Asterisk (*) represent $p<0.05$. The vertical and horizontal axis labels are shared by the plots in the rows and columns, respectively.

response is most prominent on the frontal midline electrodes. Therefore, the measures at electrode Fz in patient group were used to calculate the correlations.

Figure 4.56 shows the correlations between these scales and the absolute MMN peak amplitude (left columns) and peak latency (right column) for both the schizophrenia (top row) and schizoaffective disorder (bottom row) patients. The significant correlations are marked with an asterisk. As seen from the plots, though there are some positive and negative correlations, most of them are not significant. The correlations between the MMN peak amplitude and the various measurements from PANSS and MADRS mostly show a positive value. Only in a few cases, like intensity deviant MMN in schizophrenia patients, the correlations show an expected negative value; meaning the severity of the symptoms leads to a reduction in the MMN amplitude. Previous studies have shown significant correlations with the MMN peak amplitude and cognitive functioning scores assigned to patients using different types of measures (Kärgel et al., 2014; Light & Braff, 2005; Rissling et al., 2014). When comparing the MMN peak latency, we see an increased peak latency in schizophrenia patients with more severe symptoms (positive correlation) in frequency and location deviants. This agrees with the previous findings, but only one correlation (frequency MMN peak latency and PANSSG) is significant (Kathmann et al., 1995; Näätänen et al., 2012). This pattern is reversed in patients diagnosed schizoaffective disorder. This is an interesting observation because schizoaffective disorder patients are often grouped with schizophrenia patient in studies involving subjects diagnosed within the schizophrenia spectrum of disorders.

The correlations of MMN measures with the age of patients are also shown in the first column of each plot of figure 4.56. Though none of the correlations with the patient age are significant, in most cases we do see a negative correlation with the MMN peak amplitudes and a positive correlation with the MMN peak latency. The negative correlation with the age of the patients is expected as MMN amplitude has been documented to reduce with age (Näätänen et al., 2012). The MMN peak amplitude and peak latency correlations with age of healthy control subjects was also calculated. Negative correlations were found between MMN peak amplitudes for each deviant type and age but none of them were significant. The correlations between MMN peak latencies were positive for frequency, intensity, and location deviants,

consistent with previously observed results (Näätänen et al., 2012). Only the correlation with location deviant was relatively high and significant (r=0.545, p=0.0238).

4.6 Discussion and Conclusion

This chapter investigated the EEG response to an auditory oddball task in both healthy controls and patients diagnosed within the schizophrenia spectrum of disorders; as determined by Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013a). The experimental paradigm was adapted from a 2004 article by Näätänen *et.al.* (Näätänen et al., 2004). This paradigm incorporated five different types of deviant tones in a single sequence of auditory tones. The usage of this experimental paradigm (table 4.1), along with the EEG recording setup, enabled a reliable recording of the neural response to the auditory tones from the whole scalp. The recorded data was analysed using an event related potential analysis and a time-frequency analysis. The former provided with a broad-spectrum time course of the stimulus locked EEG signals and corresponding MMN response calculated for each deviant. The latter, time-frequency response, gave a granular insight into the contribution of each frequency bin between 2Hz and 50Hz.

The ERP analysis showed a clear MMN response for each deviant type in the control subject group. However, the average ERP plots of individual patients showed that most of them did not elicit significant MMN responses to the deviant stimuli. The grand-averaged ERP analysis of the schizophrenia and schizoaffective patient groups also showed an overall reduction in the MMN amplitude in each deviant type. These findings agreed with the literature and have also been reported in recent studies like the one by Hirt et al (Hirt et al., 2019). While the significant regions of MMN responses were highlighted in figures from sections 4.5.1 to 4.5.5, the differences between the control and patient groups were studied in section 4.5.6. The statistical results in this section were aligned with the previous observations in patients categorized within the schizophrenia spectrum. Hirt et. al. showed a significant decrease in duration and frequency MMN amplitude in early-stage and chronic schizophrenia patients compared to healthy control subjects (Hirt et al., 2019). The statistical analysis results from their study agreed with the ANOVA results in section 4.5.6 that demonstrated a

significant decrease in MMN peak amplitude in patients when compared to control subjects at frontal electrodes. These ANOVA results took the findings a step further and showed that MMN responses exhibited differences even between the patient groups (fig 4.55). In most of the studies employing patients with schizophrenia spectrum disorder, patients diagnosed with specific type of disorder within the spectrum were grouped together (Hermens et al., 2010; Michie et al., 2002; D. Umbricht et al., 2003). In the Hirt et al. study patients were a diagnosed with the schizophrenia spectrum of disorders meeting different ICD-10 codes for paranoid-hallucinatory, acute psychotic, schizoaffective disorder, etc (Hirt et al., 2019). It is also evident from the literature on MMN that, fewer studies like the one from Hermens and colleagues (Hermens et al., 2010) reported findings about the variations in peak latencies. The results from the preceding section demonstrated that both MMN peak amplitude and peak latency were affected in patients with schizophrenia and schizoaffective disorder. It was also seen from figure 4.55b that peak latency variations in the patient groups were dependent on the deviant type. A significantly longer location MMN peak latency was seen in schizophrenia patients compared to both control and schizoaffective disorder groups. Also, only schizoaffective disorder patients showed a significantly longer duration and gap MMN peak latency when compared to control subjects. These findings were promising with respect to the hypothesis that auditory oddball experiments with multiple deviant types provide more specific information about the clinical diagnosis of the patients. The results of the statistical analysis demonstrated that extracted measures like mean and peak amplitude, and latency, can be reliably used as measures of comparison between healthy controls and patient groups. Further investigation with larger patient groups could lead to the discovery of more robust and specific measures within each group. These could eventually be used as biomarkers for preliminary screening of people showing symptoms of psychosis.

In the results obtained from time-frequency analysis of each deviant type, as a general trend in control subjects, a significant synchronisation of lower frequencies (2Hz to 16Hz) was seen in response to the deviant stimuli. This synchronisation in the range of theta/alpha band frequencies was significant for frequency, location, and gap deviant stimuli. In the case of duration deviant, the synchronisation was not significant,

and for the intensity deviant stimuli the earlier (<100ms) synchronisation was followed by a desynchronisation. In all the cases, the difference between deviant and standard stimuli were observed in the initial 200-300ms post-stimulus. These findings from the healthy control subjects were consistent with previously reported time-frequency response findings (Javitt et al., 2018; Ko et al., 2012; M. Lee et al., 2017). In the patient group, like the ERP response, the ERSP response to the deviants was smaller, resulting in differences that were insignificant with respect to the standard stimuli. This has been recently reported by other researchers too (Javitt et al., 2018; Ko et al., 2012; M. Lee et al., 2017). The results obtained from the experiment in this chapter incorporated gap and location deviant types, which have not been extensively studied previously, particularly using the ERSP analysis. Also, differences have been reported between the time-frequency response from schizophrenia and schizoaffective disorder patients, something that has not been thoroughly studied previously but larger number of patients is needed to confirm this.

The major limitation of the experiment presented here is the small group of recruited patients. This was further exacerbated by the diagnostic difference between patients. This also likely resulted in non-significant and unexpected correlations between the MMN measures and clinical rating of patients (fig 4.56). Another limitation of this experiment was that source localization was not used to determine the generators of the observed EEG activity in response to the auditory oddball task. One of the reasons for this was the smaller number of EEG recording electrodes in the patient group which would have resulted in incorrect or blurry localizations (Michel & Brunet, 2019). This is further elaborated in Chapter 9, section 9.1.3. The use of source localization would have been helpful in comparing our observations to the previously published research (Alho, 1995; Csépe, 1995; Näätänen et al., 2007, 2012; Rissling et al., 2014) on neural processes involved in the generation of MMN. Despite these drawbacks, with multiple other significant findings from this single auditory oddball experiment, it can be confidently said that the experimental paradigm can serve as a powerful tool in the diagnostic protocol. As has been mentioned earlier, the literature survey indicated a pattern of grouping patients that fall within the schizophrenia spectrum. The experimental findings in this chapter, however, showed that, while there were similarities within the group, there were also differences

between patients diagnosed with different pathologies. Therefore, we postulate that a deeper dive with larger patient groups, with specific clinical diagnosis, is necessary.

The various measures computed from the EEG response are promising candidates for biomarkers that could be significant in diagnosis of patients. These and other similar measures extracted from the experimental paradigm can be used to create a high-dimensional landscape of individual subjects. Creating such a data rich, high-dimensional picture with larger size groups of healthy controls and patients could likely be used as a preliminary diagnostic tool to categorize a new test subject based on where they are "located" in this landscape. These ideas are further explored in Chapters 8 and 9.

CHAPTER 5. STROOP TASK

5.1 Introduction

James M. Cattell first observed in 1886 that it took longer for subjects to name the colour of an object than to read the colour names (Cattell, 1886). This was one of the first observations that led J. Riddley Stroop to create one of most widely known experiments in Psychology, by his name; the Stroop effect (Stroop, 1935). In its simplest form, Stroop effect is the delay in response observed when conflicting stimuli are present. For example, people take significantly longer to name the colour of ink a colour word is written in when the two do not match (the word "RED" written in blue ink) when compared to a case where the two matches ("GREEN" written in green ink).

5.1.1 TYPES OF STROOP TASKS

Over the past century, researchers have extensively studied the Stroop effect with experimental designs using different types of stimuli. However, each of these experiments shares certain characteristics that make them a version of the same task. These characteristics include subjects presented with stimuli with two dimensions or aspects and asked to respond to only one of them. In different conditions within the task, the two dimensions of stimuli could either be in harmony with each (congruent) or contradicting each other (incongruent). Most of the experiments also incorporate a third control condition where one of the stimuli is irrelevant and does not either contradict or agree with the other.

The most common type of Stroop task, which was also used by J. Riddley Stroop in his study, is the colour-word task. As described briefly, this task uses a colour word written in either same or different colour as its meaning. In his experiment, Stroop used a sheet of paper with hundred words either written in black (control case) or in a colour different from its meaning (incongruent). Stroop carried out several different experiments and found out that it took longer for subjects to finish reading the incongruent colour-word stimuli (Stroop, 1935). Over the years, as progress has been made in experimental design, and technology has been incorporated in the carrying out psychological experiments, researchers have moved to precise measurements of response to single stimuli. Other types of Stroop tasks have included colour-object task, counting Stroop task, emotional Stroop task, etc. The colour-object task is like the colour-word task with the replacement of words with objects that typically have a

specific colour (*e.g.* red apple). This task has been useful in testing subjects like pre-school children (Cramer, 1967) who haven't learned how to read yet but, have developed object-colour associations. The counting Stroop task uses number words printed a different number of times (*e.g.* "three" printed thrice for congruent and twice or incongruent) and was designed to study subjects in an MRI (Bush et al., 1998). Emotional Stroop task uses words associated with neutral (table, desk, etc), positive (holidays, success, etc), and negative (slaughter, failure, etc) emotions presented in different ink colours. The subjects are instructed to identify the colour of the word. This task has been used to test patients with different psychopathologies (Williams et al., 1996) like depression, schizophrenia (Demily et al., 2010), etc to assess if the emotion words caused interference compared to neutral words.

5.1.2 OBSERVATIONS AND PSYCHOLOGY OF THE STROOP TASK

The different types of Stroop task described above do not only share specific characteristics in their design but also in the behavioural responses observed in subjects. As stated earlier, Stroop observed that subjects took significantly longer to read colour-names written in conflicting ink colours when compared to colour-names written in black. He called this the *"Effect of Interfering Colour Stimuli"* and is now widely recognized as *interference* in the psychology literature. This effect is shared by all the different types of Stroop tasks where one dimension of the stimuli interferes with processing and thus results in longer response times. Comalli et. al. showed that varying degrees of interference was observed in subject age groups ranging from 7 to 80 years (Comalli Jr et al., 1962). Phebe Cramer showed this effect in preschool children in a colour-object task as they had not learned to read words yet (Cramer, 1967). The interference of conflicting stimuli is also observed in counting Stroop task, where counting the number of conflicting number words takes longer when compared to counting neutral words (Bush et al., 1998).

These tasks not only present with the primary effect of *interference* but also have other effects that are consistently seen across different types. The experimenters that have used congruent stimulus dimensions have observed an *enhancement* (opposite of *interference*) when compared to neutral or control stimulus. Different studies have also seen practice effects in subjects that result in decreased *interference* (Bush et al., 1998; Stroop, 1935). Another interesting observation from several different studies has

indicated that certain dimensions of stimulus are more dominant compared to others. For example, it has been observed that humans are more inclined towards reading a word than towards processing the colour of the ink the word is written in. In other words, there is a certain degree of automaticity in paying attention to certain aspects of stimuli. Comalli et. al. observed that across the whole age range of 7 to 80 years, subjects were faster in reading a colour word written in black than in naming the colour of a rectangular patch (Comalli Jr et al., 1962). In her 1967 paper, Cramer observed that preschool kids showed no significant difference in naming the form of the object irrespective of it being in its native (*e.g.* red apple) or non-native (*e.g.* blue apple) colour. However, the difference between naming the colour of a rectangular patch and naming the colour of an object in its non-native colour was significant (Cramer, 1967). This observation, like in the colour-word task, implied the dominance of the form of the object when compared to its colour.

The human mind is continuously making decisions as it interacts with its environment. We react to various stimuli presented to us through our sensory organs throughout our day-to-day life. The decisions we take can be as simple as choosing between coffee and tea, and as complex as deciding between what's right and wrong when conflicting opinions are presented. The brain is processing all the information presented to it and has only a certain amount of capacity. The processing system is also sequential in nature and thus has an additional task of prioritizing between different sources. Hence, when multiple sources of information are presented to it, the mind can often get overwhelmed, leading to a bottleneck situation (Sahinoglu & Dogan, 2016). This especially becomes difficult when different sensory sources are presenting contradicting information. In such a situation, we tend to process and respond quicker to processes that we are more familiar with (automatic processing) than the ones that do not occur in our daily life (Sahinoglu & Dogan, 2016). For example, humans are used to reading words and are almost never presented with the task of naming the colour of the ink they are written in. This complexity of human's reaction to multi-dimensional stimuli is simplified by the easy to administer Stroop task. It helps in assessing how different psychopathologies affect information processing and conflict resolution systems in the human brain. For this reason, it has become a powerful research tool.

5.1.3 NEUROPHYSIOLOGY OF THE STROOP TASK

The previous sections have discussed the different types of laboratory tasks that invoke the Stroop effect in humans. Studies that examine the psychological aspect of the effect and theorize how the brain works to produce it were also discussed. This section dives deeper into decades of research on Stroop effect with an emphasis on experiments that study both the behavioural and neurological aspects. A Google Scholar search of articles citing the 1935 Stroop paper shows that there are a few thousand papers that have documented the neurophysiology of this task. It is also found that different neuroimaging techniques like EEG, PET and fMRI have been used by researchers. This section briefly describes a few of these papers with an emphasis on studies using EEG.

Duncan-Johnson and Kopell conducted one of the first studies to understand how the brain processes the stimulus during a Stroop task (Duncan-Johnson & Kopell, 1981). It was previously established that the EEG P300 wave marks the time it takes to evaluate a stimulus. The theory was that comparing the P300 latency and response time (RT) of different task conditions within the Stroop task would provide an insight into the interference effect. This study found that the P300 latency recorded at Pz electrode did not significantly change between congruent, neutral, and incongruent trials. However, as it was repeatedly observed, the subjects showed significant differences in RT. This was the first observation that led to the conclusion that the interference effect in the Stroop task occurred due to conflicting responses and not due to stimulus evaluation. In another study by Ilan and Polich, this observation was confirmed using key-press responses; as opposed to vocalization in the previous one (Ilan & Polich, 1999). The results from these two studies concurrently showed that the latency of P300 response during the Stroop task is independent of the type of stimulus. The Ilan and Polich study also included recordings from Fz and Cz electrodes along with Pz. It showed that the amplitude of the P300 wave and the difference in congruency related activation increased going from the Fz to Cz to the Pz electrode.

In the 1990s several different studies were conducted by various research groups using neuroimaging techniques like PET and fMRI. These techniques provided an opportunity to study the involvement of regions of the brain that were difficult to observe using EEG electrodes. Pardo et. al. used PET recordings of healthy subjects

while performing the colour-word Stroop task with incongruent and congruent trials (Pardo et al., 1990). They looked at the difference in the activation between the two types of trials and found that anterior cingulate cortex (ACC) showed the most significant increase in activation from congruent to incongruent trials. This was further confirmed by the previously mentioned study that introduced the counting Stroop task (Bush et al., 1998). Bush et. al. also showed that practice effects observed in the behavioural results were mimicked in the fMRI activation changes of the ACC.

West and Bell compared the Stroop effect between younger and older healthy subject groups (West & Bell, 1997) using EEG recordings. They found that the older subjects exhibited significantly greater interference effect when compared to the younger. These differences were also seen in EEG signals with significant differences in activation of frontal medial, frontal lateral and parietal regions. Stroop task demands the involvement of anterior attention system including the prefrontal cortex, which had been previously shown to decline with age. The researchers thus concluded that a decline in performance was consistent with age-related changes in the brain.

Schack et. al. used coherence between pairs of electrodes to understand the changes in neural activity during congruent and incongruent Stroop trials (Schack et al., 1999). They found that 13-20 Hz band was most significant in discriminating between the two trials conditions. The incongruent trials exhibited higher coherence values on the left hemisphere in and between the frontal and parietal areas, when compared to congruent. They also found that time of maximal coherence was a predictor of reaction times. The correlations between the two were significant for all the 4 fronto-parietal combinations in the incongruent case. Whereas, in the congruent case, significant correlations were restricted to right hemisphere fronto-parietal pair of electrodes.

Some of the more recent studies with EEG recordings have tried to understand how the brain detects, resolves, and adapts to different conflicting stimuli. A 2009 study by Badzakova-Trajkov *et.al.* used global field power from all the recorded electrodes and LORETA source localization to study the difference between the congruent, incongruent, and control conditions (Badzakova-Trajkov et al., 2009). They found that the difference between control and both congruency conditions exhibited similar properties. The peak in the difference waveform was seen in an

earlier time window between 260ms and 430ms and the source was in the middle cingulate. However, in the case of incongruent versus congruent the peak difference waveform was found between 370ms and 480ms with the source mainly located in the anterior cingulate. The researchers attributed the former to allocation of attention and the later to conflict identification and resolution.

Another interesting study from 2011 used a modified version of the Stroop task that manipulated the onset time of the two stimuli (colour and word) (Coderre et al., 2011). There were three types of trials presented; one where both stimuli were presented simultaneously, another where colour was presented 400ms before the word and a third one with word presented before the colour. This was done to study which of the different components of the event related to EEG potentials (ERP) were responsible for conflict detection and which for conflict resolution. They concluded that an early negative ERP component (N450) present around 350-450ms was responsible only for conflict detection. They also concluded, though with some speculation, that a late positive component (LPC) helped with the resolution of the conflicting stimuli.

The various EEG studies of Stroop effect with healthy subjects have given an insight into how the brain responds to conflicting stimuli. The common theme emerging from these studies is the predominant use of the word-colour Stroop paradigm. The locations of the recorded electrodes by different authors are also common and is concentrated at Fz, Cz and Pz electrode regions. Finally, source localization has strongly concluded that anterior cingulate cortex is the primary area of the brain involved in performing the Stroop task (Badzakova-Trajkov et al., 2009).

5.1.4 STROOP EFFECT IN SCHIZOPHRENIA RESEARCH

Patients with schizophrenia often display cognitive deficits. They have been shown to face difficulty in maintaining and executing a set of instructions. Patients also suffer from attention deficits, abnormal language performance, and inability to suppress irrelevant stimulus (Keefe & Harvey, 2012). For these reasons, Stroop task has been extensively used to study the psychological and neurophysiological aspects of schizophrenia. This section describes some of these studies.

Henik and Salo reviewed around 50 years of schizophrenia research using the Stroop task (Henik & Salo, 2004). Though they limited themselves mainly to

behavioural and psychological studies, their 2004 article gives a deep insight into this pathology and its effect on the performance in the task. Schizophrenia patients seem to exhibit longer interference times with the card version of the task. This version however has become obsolete as computerized single-trial versions of Stroop task can measure responses more accurately, especially when accompanied with neurophysiological measures. The differences in symptomology of patients can also affect their performance in the task. Hepp *et. al.* showed that chronic, acute, and schizoaffective patients showed significantly larger interference than patients with recurrent episodes (Hepp et al., 1996). However, Henik and Solo observed inconsistencies in the interference patterns exhibited by schizophrenia patients across studies. They postulate that the inconsistent results across studies are mainly due to the version of task used (card vs. single-trial) and other differences in methodology. Another trend that Henik and Salo observed is that the inter-trial interval had a significant effect on the performance of the patients when compared to healthy subjects. It was noted that longer inter-trial intervals led to higher error rates in schizophrenia patients. This was attributed to the inability of these patients to maintain attention for an extended period (Henik & Salo, 2004).

Markela-Lerenc *et. al.* published one of the first studies that used EEG signals to study the schizophrenia patients during a Stroop task (Markela-Lerenc et al., 2009). They employed 15 patients and 15 age/sex matched control subjects to study the ERP signals while performing two blocks of computerized version of the colour-word Stroop task. They used congruent, incongruent, and neutral conditions. They used EEG signals from four midline electrodes and pooled a set of three electrodes for each of the right frontal, left frontal, right parietal, and left parietal regions. The grand average ERP signals of control subjects from all these electrode locations showed significant differences between congruency conditions. The frontal regions showed greater negativity (N450) in the 350-450ms time window in the incongruent trials. In the parietal regions, this translated to greater sustained positivity in 600-1000ms time window. The patient group did not show these differences in the first block of trials. However, in the second block, patients showed similar ERP time courses in the parietal region. Moreover, the incongruent-congruent difference was negatively correlated with error rate in patients. This denotes that this difference in ERP activity is crucial

for conflict resolution during the task. The group also looked at the spatial difference of the ERP signal at 400ms and found it to be significantly lower in the patients.

Kim *et. al.* conducted a similar study with female Korean college students that exhibited schizotypal traits (Kim et al., 2012). This study also used a computerized colour-word Stroop task, but with Korean words. The researchers conducted ERP analysis with the Fz and Pz electrodes. They found that control subjects showed a significant frontal negativity (FN or N450) difference in the 300-400ms time window between incongruent and congruent trials. This FN was not observed in subjects with schizotypal traits. However, like the previous study, both the groups showed significant differences between the two task conditions with the sustained positivity on the Pz electrode. The researchers conducted a source localization analysis using the LORETA algorithm. The current density in the left cingulate gyrus and medial frontal gyrus was found to be significantly lower in schizotypal trait subjects. They also observed with regression analysis that schizotypal-trait subjects showed a significant correlation between left cingulate activation and accuracy of the incongruent trials. These results are consistent with the Markela-Lerenc study (Markela-Lerenc et al., 2009) and also with imaging studies (Bush et al., 1998; Pardo et al., 1990) that have showed involvement of anterior cingulate cortex and prefrontal cortex in performing Stroop like tasks.

In one of most recent studies Popov et. al. used brain oscillatory dynamics techniques to study the differences between controls subjects and schizophrenia patients (Popov et al., 2018). They analysed behavioural data during a computerized Stroop task with 4-7 Hz (theta) and 10-30Hz (alpha/beta) EEG oscillations. As expected, they observed an overall higher response time in patients. However, they did not observe a larger Stroop effect on patients. With the theta oscillation they observed that patients produced less enhancement compared to control subjects during incongruent trials in the dorsal anterior cingulate gyrus (dACC) and the superior frontal gyrus. They also observed that the central alpha/beta suppression closely tracked the reaction time (RT) with higher suppression signifying longer RT. This effect was consistent in both patient and control groups. They also looked at theta phase coherence between dACC and sensorimotor regions to quantify the communication between the two regions. Schizophrenia patients were observed to

show poor coherence during incongruent trials. The authors concluded that poor communication between the two areas lead to impaired motor preparation and hence poorer performance by the patient population.

5.2 Aims of Study

The above sections have highlighted the important aspects for Stroop task along with expected behavioural results in both healthy subjects and schizophrenia patients. The neurophysiological findings studies involving Stroop task have also been outlined. The study described in this chapter used this knowledge to design a Stroop task experiment. Along with behavioural results and observations from EEG analysis, a set of outcomes that can be used to diagnose subjects in a clinical setting, are also presented. Following were the aims of this study:

1. To use a computerized Stroop task to observe behavioural response along with simultaneous EEG recordings in both healthy control subjects and patients diagnosed with the schizophrenia spectrum of disorders.
2. To compute behavioural response measures and determine if Stroop effect was observed using the task design used in this study.
3. To compute the ERP and ERSP responses to each trial condition and study the similarities and differences between them. Based on previous research described in section 5.1.3, we hypothesized to see significant differences between the congruent and incongruent task conditions. These differences were predicted to be observable in both the time and frequency domain of EEG data.
4. To visualize and calculate statistical differences between the response from healthy control group and patient groups. We hypothesized that unlike healthy control subjects, the patient group would show smaller or insignificant differences between the congruent and incongruent task conditions.
5. To compute the correlations of patient symptom severity with behavioural performance and EEG measures like P300 peak amplitude and peak latency. We hypothesized that patients with more severe symptoms were likely to show larger deficits in behavioural performance

and smaller differences between the congruent and incongruent task conditions.

5.3 Experimental Methods

5.3.1 TASK DESCRIPTION

A computerized version of the Stroop task was used in this study. The Stim^2 software (NeuroScan Inc.) was used to generate the stimuli and the triggers were interfaced with NeuroScan 4.5 Acquire software using the Stim^2 hardware. The task consisted of two types of stimuli. The congruent trials were four colour words namely green, blue, red, and yellow written in the same colour ink as the meaning of the word. The incongruent trials were the words written in a different colour ink as their meaning; for example, the word "blue" written in the colour yellow. Subjects were instructed to press the "Match" button for congruent and "No Match" button for the incongruent trials using a response pad (Compumedics NeuroScan Switch and Response Pad). A "Match"/"No Match" response was chosen to make the task easier for the patient group, instead of a traditional Stroop task response where subjects were asked to indicate the colour of ink the colour-word is written in. Before beginning the test phase of the task, subjects were given a practice phase of 24 trials.

Figure 5.1 shows the timing diagram of the computerized Stroop task. Every trial began with a word presented for a set time referred to as the "Stimulus Duration" (SD). From the beginning of the trial the subjects had a window of time to respond; the "Response Window" (RW). If the subject pressed a button within this window, the time elapsed from the onset of stimulus to the button press was recorded as the

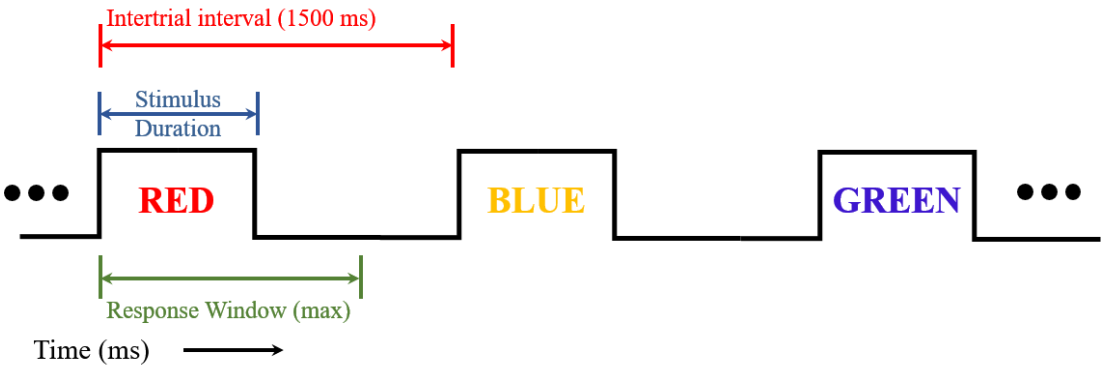


Figure 5.1 Timing diagram for Stroop task. Intertrial interval: 1500ms. Stimulus Duration for Controls: 150ms, Patients: 200ms. Response Window for Controls: 1000ms, Patients: 1200ms.

"Latency" (LT). The trial was recorded as either correct or incorrect depending on the response. If, however, the subject did not press any button within the RW, the trial was recorded as "no response" and LT was recorded as equal to RW. The subjects were not given any feedback if the trial was correct, incorrect, or no response. After the "Inter Trial Interval" (ITI), a new word was presented.

All the subjects performed the task in blocks of trials with approximately 25% congruent and 75% incongruent trials generated using a pseudo-random generator. The seed used for the generator was not always the same value, leading to small differences in the exact number of congruent and incongruent trials presented to each subject. For the control subjects, the task was carried out in 2 blocks of 400 trials each. This took approximately 10 minutes per block. The SD was set at 150ms and the RW at 1000ms. When the first patient (P1) was presented with this setting, the subject had considerable difficulty in performing the task. For that reason, the task parameters were modified for patients which were approved as minor amendment by the West of Scotland Research Ethics Service. The ITI was kept the same at 1500ms but, the SD was increased to 200ms and RW was increased to 1200ms. The trials were presented in 4 blocks of 200 trials each. This took 5 minutes per block. This task was carried out on the same day as, and following the, MMN task in both the patients and control subjects.

The change in task parameters between the healthy control and patient groups raised a major concern regarding making direct comparisons between them. Therefore in this chapter we present the performances and EEG analysis of control and patient groups separately, unlike the previous and following experiments.

5.3.2 SUBJECTS

All the recruited healthy control subjects (n = 19) performed the auditory oddball task. However, 1 subject was excluded from the analysis due to noise and corrupted data. Therefore, data collected from 18 healthy control subjects were used for analysis. All the recruited patients performed the Stroop task, however, for the reasons mentioned in the last section modifications were made to the task parameters after recording from patient P1. The results are presented for individual patients as well as three groups of patients including schizophrenia patients (P4, P5, P6), schizoaffective disorder patients (P1, P2, P3), and all patients grouped together.

5.3.3 BEHAVIOURAL ANALYSIS

The behavioural performance in the Stroop task was quantified by the percent correct of and the response latency to both the congruent and incongruent stimuli. The percent change in the response latency between the congruent and incongruent trial response was also analysed. Several studies that use the Stroop task, also incorporate a "neutral" set of trials where the colour words are written in black ink. The latencies in these trials can be used to study the "enhancement" (decreased latency) in congruent trials and "interference" (increased latency) in the incongruent trials. Due to the restrictions imposed by the Stim^2 software, "neutral" trials were not incorporated in this experiment. Therefore, to study the interference caused by the irrelevant stimuli in the incongruent condition, the latencies obtained in the congruent trials were used as a surrogate to the "neutral" trials. The percentage increase in the incongruent latencies with respect to the congruent latencies is calculated using the simple formula:

$$\%\, Change = 100 * \ (Lat_{incong} - Lat_{cong})/Lat_{cong} \qquad \textbf{(5.1)}$$

5.3.4 EEG MEASUREMENT

The standard EEG recording and pre-processing pipeline described in Chapter 3 was used during this experiment, except for a common average reference (CAR) compared to the mastoid reference used during the auditory odd ball task. The epoch was defined as -200ms to +1300ms relative to stimulus onset and the average amplitude in the 200ms pre-stimulus window was used for baseline correction. After the artefact rejection, cleaning of EEG data, and dropping the trials with incorrect responses, an average of 85% trials were retained in healthy control subjects. In patients this number was approximately 50% with a significant percentage of trials getting dropped due to incorrect response. This is elaborated further in the section 5.4.

The EEG pre-processing and cleaning was followed by the ERP and ERSP analysis of the congruent and incongruent trial response. Based on the commonly studied electrodes in the literature on Stroop task with EEG recording, these analyses were carried out and visualized at the midline electrodes Fz, Cz, and Pz.

The EEG measures P300 peak amplitude and peak latency were computed for the ERP response to the congruent trials, incongruent trials, and the difference between

the two ERPs (incongruent – congruent). The time-period defined for the calculations of the peak and latencies varies across research studies. The studies that use the P300 terminology, also use either a broad window (280-600ms) across the midline electrodes (Ilan & Polich, 1999) or only focus on the Pz electrode (Duncan-Johnson & Kopell, 1981). In other studies where the N450 terminology is used, different smaller window sizes are used to average the response at each electrode. The time-periods are earlier for frontal electrodes (350-450ms) and later for central electrodes (450-550ms) (Markela-Lerenc et al., 2009). These studies also define a late positive component (LPC) or a sustained potential at the parietal electrodes in the 600-900ms range, where the incongruent ERP response amplitude is higher than the congruent EPR response (Coderre et al., 2011; Kim et al., 2012; Markela-Lerenc et al., 2009). From the observation in our data and considering the methodology followed by previous studies, the post-stimulus time-period of 300-600ms was chosen to calculate the P300 peak amplitude and peak latency.

5.3.5 STATISTICAL ANALYSIS

The statistical differences between the behavioural response to congruent and incongruent trials of the Stroop task were determined using t-tests. The statistical differences between the EEG responses to the congruent and incongruent trial conditions were determined using the non-parametric permutation tests and cluster-based multiple comparisons correction. These tests were carried out to compare both the ERP and ERSP responses. Both these statistical analysis were done separately for the healthy control and patient groups. As mentioned earlier, due to the differences between the task parameters in control and patient groups, no direct statistical comparisons were carried out between them.

5.4 Results and Comparisons

5.4.1 BEHAVIOURAL RESULTS

This section describes the behavioural performance outcomes of Stroop task in both control subjects and patients. Decades of literature on Stroop task, shows that the Stroop effect is expected to be observed in both the control subjects and patients.

Table 5.1 Patient performance in Stroop task.

Patient	P1	P2	P3	P4	P5	P6
Colour	●	●	●	●	●	●
Gender	M	M	M	M	M	M
Age	35	26	57	64	59	47
Clinical Diagnosis*	SA	SA	SA/BSD	S	S	S
PANSS						
Positive	27	8	7	7	16	9
Negative	10	14	7	23	21	7
General	34	21	16	19	50	18
MADRS	9	7	4	2	18	5
Blocks (200 trials each)	2	4	3	4	4	4
Response Latency:						
Congruent (ms)	469.68	751.21	741.91	820.19	585.00	846.43
Incongruent (ms)	516.18	661.76	646.31	670.27	533.47	826.36
Percent Increase (%)	9.90	-11.91	-12.89	-18.28	-8.81	-2.37
Percent Correct:						
Congruent	23.2	76.5	20.5	56.4	8.3	60.3
Incongruent	21.7	96.8	68.0	76.5	38.4	67.5
All	22.1	91.6	55.8	71.4	30.8	65.6

* S: Schizophrenia, SA: Schizoaffective Disorder, BSD: Bipolar Spectrum Disorder

Table 5.1 outlines the different measures that were gathered from the patients recruited for the study. The columns in the table represent individual patients P1 to P6. The coloured dots show the colours assigned to each subject and used throughout the different figures in this section. The first few rows give the PANSS (Kay et al., 1987) and MADRS (Montgomery & Asberg, 1979) scores of each patient on the day of Stroop task. Following this, the number of blocks performed by each patient are listed. We see from the table that patients P2, P4, P5, and P6 completed 4 blocks of 200 trials each, P1 completed 2 blocks, and P3 completed 3 blocks. As mentioned previously,

patient P1 was presented with the same task parameters as the control subjects. The difficulty in performing the task is seen from the various measures presented in the table. Trials from all the blocks were combined before calculating various task outcomes. The table provides the mean congruent response latencies, incongruent response latencies, percent increase in response latency, and percentage of correct congruent, incongruent, and all trials.

Figure 5.2 shows the percent correct performance measure in Stroop task for healthy control subjects and patients. The plot is constructed using the overall percentage correct after combining all blocks of trials performed by each subject. All the healthy control subjects are marked using green dots distributed around the centre of their x-label to visualize overlapping values. The individual patients are represented by their assigned colours. Even though the task was altered to be easier for patients (except P1 in orange), the figure clearly shows that patients had extreme difficulty in performing the task. All the control subjects were able to perform the task at greater than 90% accuracy while only one patient accuracy was above 90%.

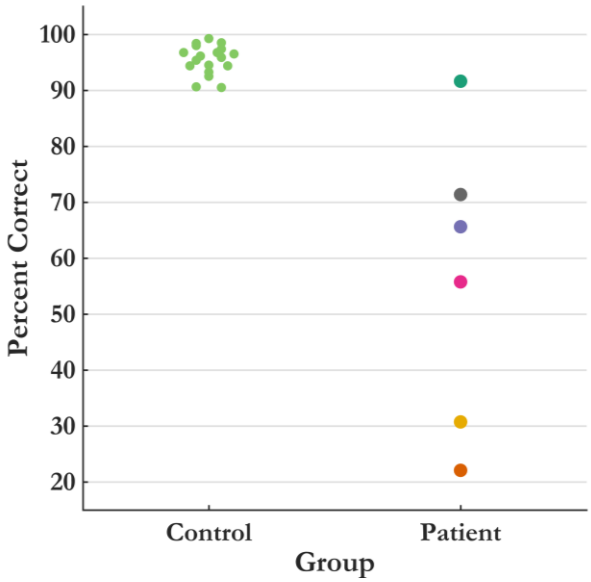


Figure 5.2 Total percent correct in Stroop task. Scatter plot showing the total percentage of correct trials in control subjects (n=18) and patients (n=6). Non-zero y-axis is used to clearly visualize the spread of percentage of correct trials.

Figure 5.3 shows the differences between the response latencies to congruent and incongruent trials. The goal of the plots is to observe the Stroop effect in both

control subjects (fig 5.3a.) and patients (fig 5.3b.). In both the plots the mean congruent and incongruent response latencies for every subject are paired and connected with a line. In figure 5.3a., green colour is used for the subjects which showed an increase in response latency and red colour is used for those that showed a decrease. We see that only 5 out of the 18 subjects show the increase in response latency from congruent to incongruent trials. Patient-assigned colours are used for the figure 5.3b. Even in the patient group, only one patient (P1) shows an increase in response latency going from

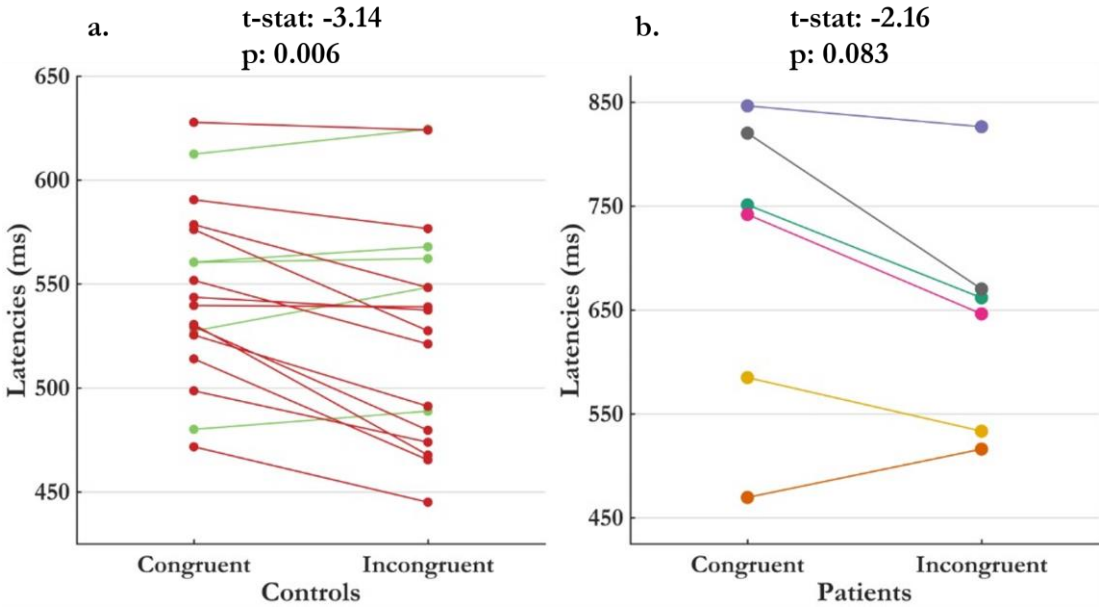


Figure 5.3 Comparison of congruent and incongruent response latencies in Stroop task. a. Healthy control subjects (n = 18). Individual subjects are connected by lines; green: increase, red: decrease, in response latency. b. Patients (n = 6). Individual patients connected by lines of colour assigned to them. t-stat: paired t-test statistic, p: significance level of difference between paired values not zero. The non-zero y-axis is used to clearly visualize the spread of latencies.

congruent to incongruent trials.

The y-axes of the two plots in figure 5.3 show that patients are overall much slower than control subjects in performing the Stroop task (also shown in table 5.2 below). To quantify the Stroop effect by studying the differences in the response latencies of congruent and incongruent trials, a paired t-test was performed within the control and patient groups. This test was ideal for this purpose as each point in the congruent set had a corresponding point in the incongruent set. In figure 5.3, the details of paired t-test output for each group are shown on top of each plot. The t-statistic

gives a measure of the deviation between the pairs of samples compared to a zero-mean distribution. The p-value represents the significance level of the difference between the pairs being distinct from zero. Based on the p-values seen in the figure we can say that the control subjects had a significantly smaller mean response latency to the incongruent trials compared to the congruent trials. The effect was not significant in the patient group. In the patient group, 5 out of 6 patients showed a decrease in latency during incongruent trials. Measuring the statistical differences within the schizophrenia patient group (P4, P5, and P6) and the schizoaffective patient group (P1, P2, and P3) also did not show any significant differences.

Table 5.2 Group performance averages in Stroop task.

	Response Latency (ms)		Percent Correct (%)		
	Congruent	Incongruent	Congruent	Incongruent	All
Healthy Control Subjects (n = 18)	545.51	527.17	88.5	97.9	95.5
Schizophrenia Patients (n = 3)	750.54	676.70	41.7	60.8	55.9
Schizoaffective Disorder Patients (n = 3)	654.27	608.09	40.0	62.2	56.5
All Patients (n = 6)	702.40	642.39	40.9	61.5	56.2

Table 5.2 shows the mean performance measures across groups of subjects. The measures are provided for the healthy control subjects, schizophrenia patients, schizoaffective disorder patients, and all patients grouped together. In all the groups we see a decrease in mean response latency from congruent trials to incongruent trials. All the groups are also observed to have higher percentage of correct incongruent trials when compared to the congruent condition. These effects are in contrast with what is traditionally seen in a Stroop task. As discussed in section 5.1, Stroop effect is always observed when conflicting stimuli are presented (Bush et al., 1998; Comalli Jr et al., 1962; Cramer, 1967; Demily et al., 2010; Williams et al., 1996). Also, certain dimensions of stimuli are easier (reading the colour word) to process than others (correctly responding to the colour of ink) (Comalli Jr et al., 1962; Cramer, 1967; Sahinoglu & Dogan, 2016). However, there has been previous research which has shown that under certain experimental conditions, congruent trials can have a higher average response latency when compared to incongruent trials (Logan & Zbrodoff,

1979). Two factors likely caused this behavioural response in our Stroop task (for both healthy control and patient groups): a. higher percentage of incongruent trials (approximately 75%), b. Using a "Match"/"No Match" response instead of indicating the colour of the ink. These factors and other likely causes for the behavioural observations are discussed in detail in sections 5.5.1.

The distribution of percent change in the response latency from congruent to incongruent trials for control and patient groups is shown in figure 5.4. On the left side is the distribution of percent change in the control subjects and on the right side is the distribution in patients. The plot shows that the percent change in response latencies is negative in most subjects, meaning a decreased response latency was seen in incongruent trials. The figure also shows a large variability in the patient group. This is further investigated by analysing the EEG data collected during the Stroop task.

The observations from figure 5.4 further show that in this experiment instead of observing an increase in the incongruent mean response latency, we saw a decrease. Only 5 control subject, and 1 patient showed an increase in incongruent mean response

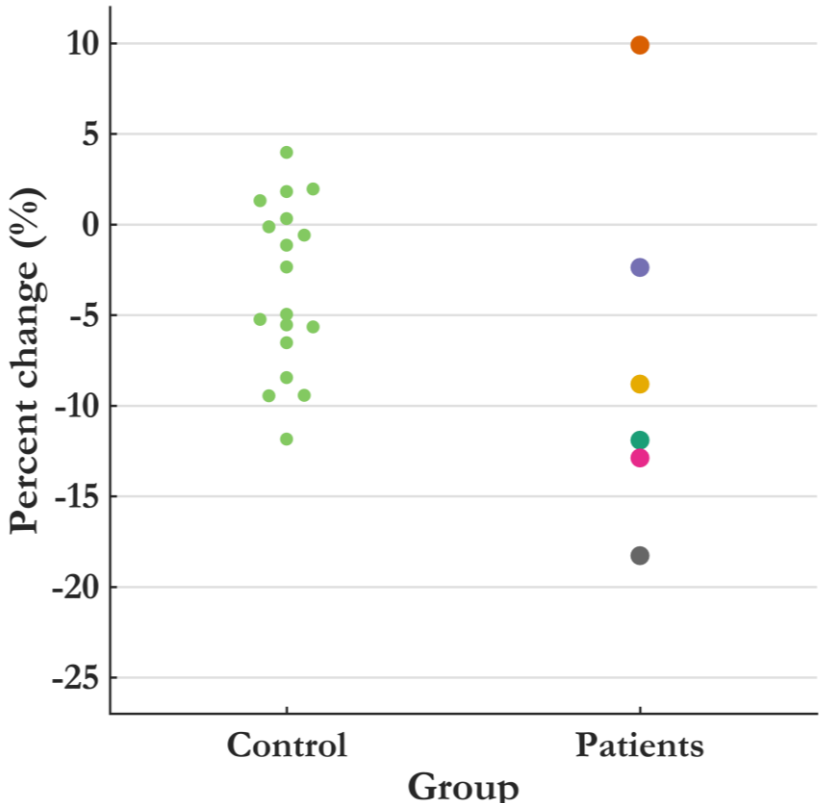


Figure 5.4 Percent change in latencies from congruent to incongruent trials in Stroop task performed by healthy control (n = 18) and patient (n = 6) groups.

latency. Also, the decrease in incongruent response latency was relatively higher than the increase observed in few subjects. Patients in the experiments showed this effect to a larger extent. The data collected during the experiment was studied carefully to find any mistakes that could have occurred in specifying the task conditions during analysis. No such mistakes were found.

5.4.2 EVENT RELATED POTENTIAL ANALYSIS

The grand averaged ERP responses calculated from control subjects are presented in figure 5.5. The individual plots represent ERP responses at Fz, Cz, and Pz (fig 5.5a to fig 5.5c). The congruent trial response is plotted in blue, while the incongruent is in red. The black vertical line in each plot marks the trial onset and separates the pre-stimulus baseline and post-stimulus response. To represent the period of significant difference between the congruent and incongruent response, a black bar at the bottom of plot is used. The significance level was set at $p<0.05$ after accounting for multiple comparisons using permutation cluster-based correction method.

In each of the ERP waveforms we see the N100, P200, and N200 components (marked in fig 5.5a) elicited at the beginning after stimulus onset (N100-P200-N200 complex). These components are typically observed at frontocentral electrodes in any EEG experiment where an auditory or visual stimulus is presented (Luck, 1995; Woodman, 2010). The N100 component is observed to peak between 90 and 200ms, followed by the larger P200 peak in the 100-250ms period, and the N200 component peaking at approximately 200ms (Sur & Sinha, 2009). These are exogenous components that are obligatory and are triggered by the presence of a stimulus. They are also seen in most individual patient responses and patient group responses shown later in figures 5.6 to 5.10. We see that these components are independent of stimulus condition at each of the three midline electrodes. They are followed by the endogenous components that are task dependent and represent the underlying neural processes (Luck, 2012).

As expected with a Stroop task, a large positive ERP component is elicited after the N100-P200-N200 complex in both congruent and incongruent conditions, with congruent stimulus resulting in a higher amplitude response. This response is referred as either the P300 (Duncan-Johnson & Kopell, 1981; Ilan & Polich, 1999) or N450 (Coderre et al., 2011; Kim et al., 2012; Markela-Lerenc et al., 2009) component in the

studies that were reviewed in section 5.1.3 and 5.1.4. The P300 (marked in fig 5.5a) naming convention is used through this chapter as the elicited response is positive on all the midline electrodes.

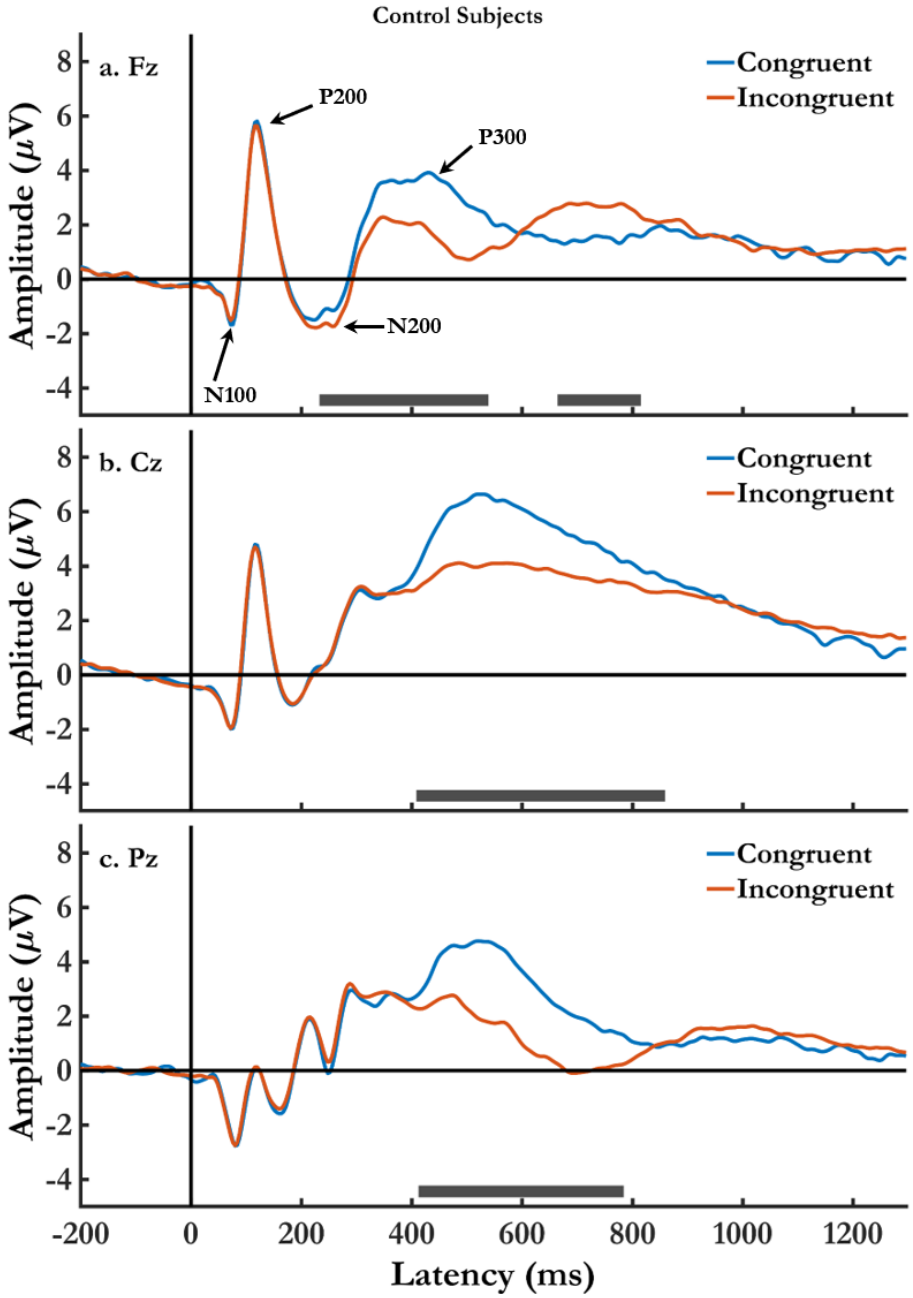


Figure 5.5 Grand average ERP response to Stroop Task conditions in control subject group (n = 18). Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Electrode Fz with the N100, P200, N200, and P300 components marked. b. Electrode Cz, c. Electrode Pz.

To quantify the differences in the task conditions more precisely, the P300 peak amplitude and peak latency were calculated as described in section 5.3.4. From the observation in figure 5.5, the ERP at Pz is observed to peak earlier than 600ms with larger congruent ERP amplitude and no difference between the incongruent and congruent condition beyond 800ms. At electrode Fz there is a second time-window of significant difference, however this difference was only weakly significant at p=0.025. The P300 peak amplitude and peak latency measures are presented in table 5.3.

The data in table 5.3 shows that most of the peaks lie within the window where the difference between the task conditions was significant. Compared to the mean response latency of the congruent (545.51ms) and incongruent (527.17ms) trials, the peak P300 response occurred earlier. It should be noted that the absolute value of the peak amplitude of the difference waveform consistently increases going from frontal to parietal midline electrodes (Fz to Pz). This shows that parietal Pz electrode was the most informative in distinguishing between the two trial types. The same pattern is also observed in the peak latency.

Table 5.3 Stroop P300 response measures for control subject group (n = 18).

	Peak Amplitude (μVolts)			**Peak Latency (ms)**		
	Cong	**Incong**	**Diff**	**Cong**	**Incong**	**Diff**
Fz	3.91	2.28	-2.41	432	348	472
Cz	6.64	4.11	-2.68	520	484	520
Pz	4.76	2.88	-2.95	520	352	540

Cong: Congruent, **Incong**: Incongruent, **Diff**: Difference

The ERP responses in patients were first computed individually as any diagnosis protocol would need to be applied to one patient at a time. Table 5.4 outlines the details of attempted trials and the trials finally averaged during EEG analysis after cleaning the data and dropping trials with incorrect response. Comparing the percentage of trials used for EEG analysis in this table to the percentage of correct trials in table 5.1, we see that small number of trials available for EEG analysis was primarily due to the poor performance of patients in the Stroop task. Based on the ERP book by Steven J. Luck (Luck, 2014b), the number of trials available to average for the congruent condition in patients P1, P3, and P5 is too small. The small number of trials result in a

noisy estimate of the average waveform biasing the amplitudes to either higher or lower than an estimate derived from more number of trials. This also affects the estimation of peak amplitude and peak latency in individual subjects. Despite these issues we have presented the results from each patient in the following figures.

Table 5.4 Number of Stroop trials in EEG analysis for individual patients.

		P1	P2	P3	P4	P5	P6
Total Trials Attempted	**Congruent**	164	204	156	204	204	204
	Incongruent	456	596	444	596	596	596
Correct and Cleaned Trials	**Congruent**	29	155	27	113	17	122
	Incongruent	90	562	279	432	229	401
Percentage	**Congruent**	17.7	76.0	17.3	55.4	8.3	59.8
	Incongruent	19.7	94.3	62.8	72.5	38.4	67.3

The ERP waveforms for each patient are shown in figures 5.6, 5.7, and 5.8 for electrodes Fz, Cz, and Pz, respectively. Unpaired permutation statistics followed by the cluster-based multiple comparisons correction was used to compute the statistical difference between the task conditions for individual patients. This was different from computing the statistics for the group of control subjects, where paired average responses from each subject were available. The P300 peak amplitudes and latencies from individual patients are shown in Table 5.5.

As outlined before, patient P1 started with the same time parameters as the control subjects and had difficulty in doing the experiment. This patient thus had very few correct trials and was also the only one with an increase in the latency from congruent to incongruent trials. The difficulty in correctly responding to the task is also reflected in the ERP response from the patient. Both the stimulus conditions show nearly identical responses from all the electrodes. However, we do still see a significant N100-P200-N200 complex after stimulus onset at electrodes Fz and Cz (fig 5.6a, 5.7a), similar to the average ERP responses in control subjects.

Patient P2 was one of the best performing patients with 91.6% correct trials overall. We see significant differences between the congruent and incongruent trials across all the electrodes in this patient. However, at the frontal electrode Fz (fig 5.6b)

the ERP response is negative in both conditions, with congruent ERP showing larger negative amplitude. Figures 5.7b and 5.8b show that at electrodes Cz and Pz the congruent response amplitude is larger than that of the incongruent response. The mean trial response latency for patient P2 was 661.76ms for incongruent and 751.21ms for congruent trials, which is greater than the peak latency at both Cz and Pz electrode (shown in table 5.5). We also see an increase in the absolute peak of the difference from Cz to Pz.

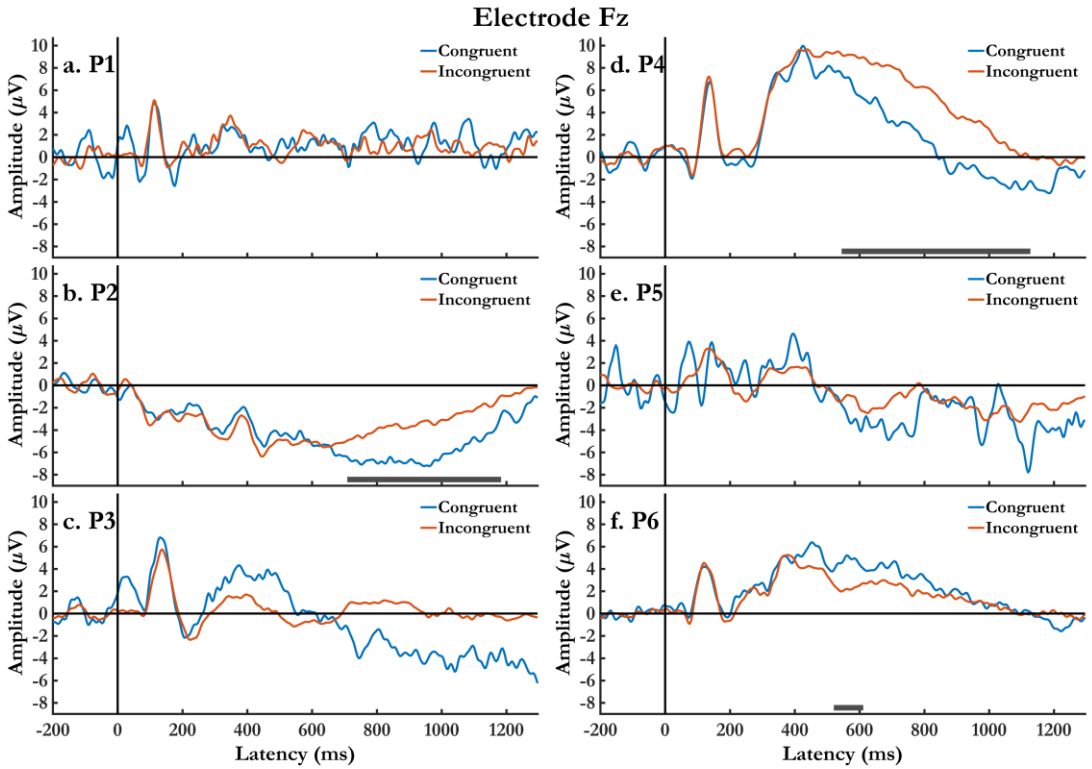


Figure 5.6 Average ERP response to Stroop task conditions at Fz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference.

In Patient P3, there were not many trials in the congruent condition (27, from table 5.4) and that could be one of the reasons we do not see significant differences at electrodes Fz and Pz. However, we see a significantly large P300 response during the congruent trials at electrode Cz, which points to the internal mechanisms controlling the frontal and parietal activation being affected.

Patient P4, like P2, had a large number of correct and clean trials and shows significant differences between task conditions across all three electrodes. At Fz and

Cz electrodes, we see a larger P300 response in the incongruent condition compared to congruent condition. The difference is much larger at Fz compared to Cz. At the Pz electrode the ERP response is negative almost throughout the trial period for both stimuli.

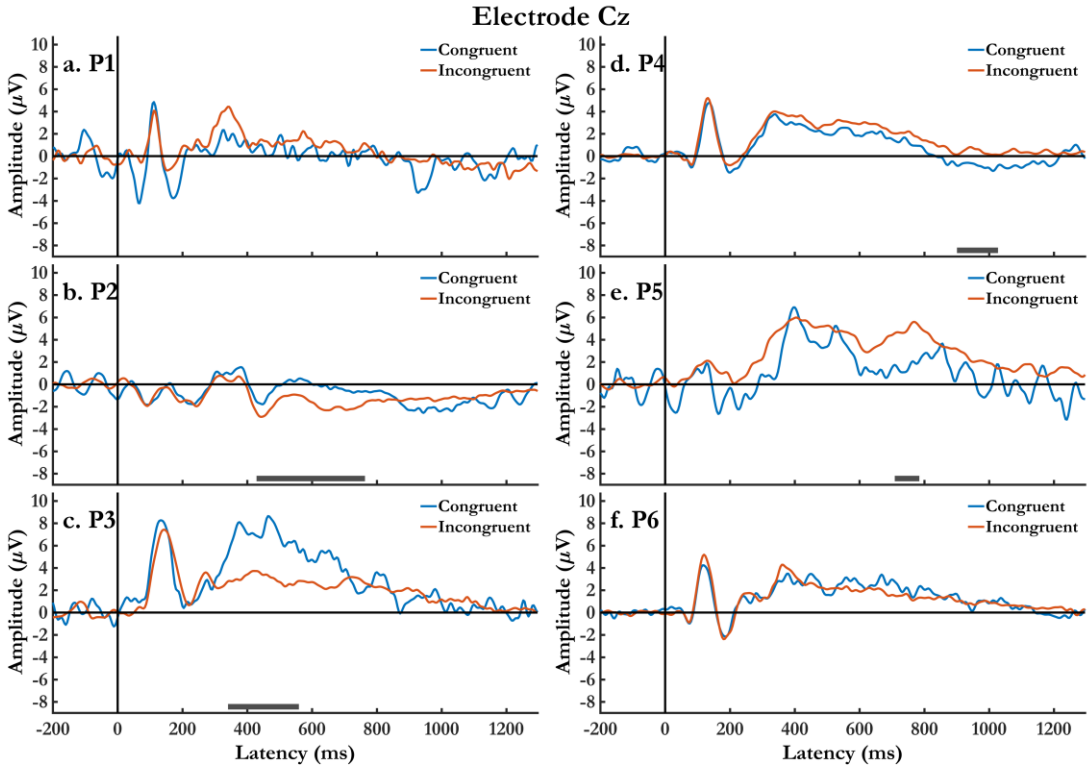


Figure 5.7 Average ERP response to Stroop task conditions at Cz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference.

Patient P5 had very few trials in the congruent condition and shows significant difference for a short duration only at the Cz electrode. However, the significance window is after the mean trial response latency of 585.00ms and 533.47ms for both congruent and incongruent trials, respectively.

Patient P6 performed relatively well in the task and more than 50% correct and cleaned trials were available for both congruent and incongruent conditions. The patient shows a P300 response in both task conditions at electrodes Fz and Cz. However, the congruent P300 response was larger than the incongruent P300 response only at electrode Fz, and the significance window was relatively short. It should be

noted that the significance window was observed about 200ms before the mean trial response latency in patient P6.

The ERP response from individual patients is useful, however, the group averaged ERP response were also computed from the two patient groups based on their clinical diagnosis, schizophrenia and schizoaffective disorder. A group averaged ERP response was also computed using all the 6 patients. The patient group averaged ERP responses are shown in figure 5.9 for electrode Fz, figure 5.10 for electrode Cz, and figure 5.11 for electrode Pz.

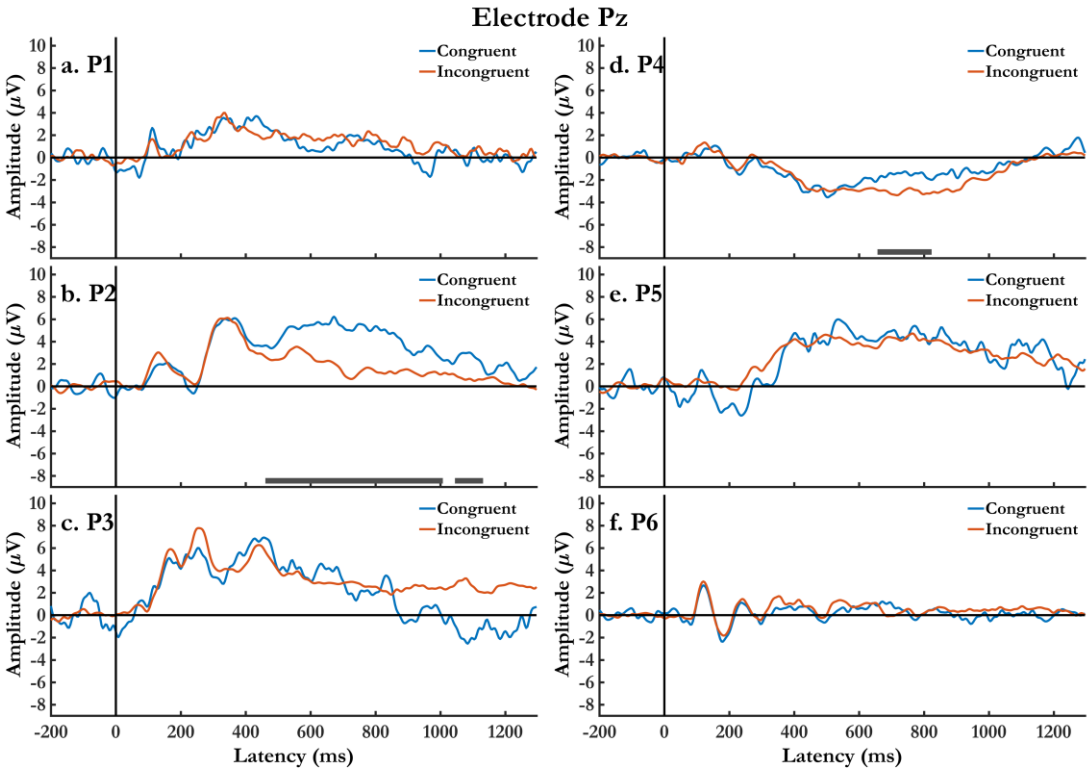


Figure 5.8 Average ERP response to Stroop task conditions at Pz electrode in individual patients. The six patient (P1 to P6) responses are plotted on 3x2 grid from a to f. Vertical and horizontal black lines in each plot represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference.

Table 5.5 Stroop P300 response measures for individual patients and patient groups.

		Peak (μVolts)			Peak Latency (ms)		
		Cong	**Incong**	**Diff**	**Cong**	**Incong**	**Diff**
P1	**Fz**	2.79	3.73	-2.15	324	348	508
	Cz	2.33	4.42	-0.85	328	344	504
	Pz	3.70	3.99	-1.65	432	336	436
P2	**Fz**	-1.93	-2.70	-1.32	388	384	416
	Cz	1.54	0.78	-1.70	380	316	592
	Pz	6.09	6.12	-2.62	368	344	596
P3	**Fz**	4.32	1.71	-3.48	376	396	464
	Cz	8.64	3.73	-5.38	464	420	468
	Pz	6.94	6.26	-1.68	456	440	380
P4	**Fz**	9.97	9.65	-0.66	424	440	332
	Cz	3.75	4.00	0.20	340	336	472
	Pz	-0.81	-0.36	-0.63	312	328	596
P5	**Fz**	4.63	1.66	-3.02	396	408	396
	Cz	6.90	5.99	-1.00	400	404	396
	Pz	5.99	4.61	-1.64	536	496	532
P6	**Fz**	6.39	5.25	-3.01	452	380	560
	Cz	3.48	4.28	-1.09	380	360	584
	Pz	0.79	1.69	-0.07	388	352	584
Schizophrenia patients (n = 3)	**Fz**	6.00	5.14	-0.87	436	408	436
	Cz	4.16	4.39	0.11	388	364	532
	Pz	1.32	1.41	-0.44	548	356	580
Schizoaffective disorder patients (n = 3)	**Fz**	1.33	0.32	-1.82	368	372	504
	Cz	3.50	2.52	-1.98	372	344	500
	Pz	4.71	4.73	-1.14	380	336	468
All patients (n = 3)	**Fz**	3.41	2.62	-0.98	392	380	436
	Cz	3.79	3.32	-0.78	388	364	468
	Pz	2.85	2.99	-0.72	384	340	464

Cong: Congruent, **Incong**: Incongruent, **Diff**: Difference

From the figures 5.9, 5.10, and 5.11 we see that none of the conditions or electrodes showed significant differences in the patient groups. We do see that in schizophrenia patients, there is a P300 response at both frontal (Fz, fig 5.9a) and central (Cz, fig 5.10a) electrodes, but is missing at the parietal electrode (Pz, fig 5.11a). Even though the difference is not significant, we do see that at both Fz and Cz, the

average ERP response in incongruent condition is larger than that of the congruent condition. The schizoaffective patients show a different pattern. In the frontal region (Fz, fig 5.9b) there is an overall suppression of ERP relative to the baseline. The average P300 response increases as we go from the frontal to parietal electrodes (fig 5.9b, 5.10b, 5.11b). We do not see any significant differences in this patient group

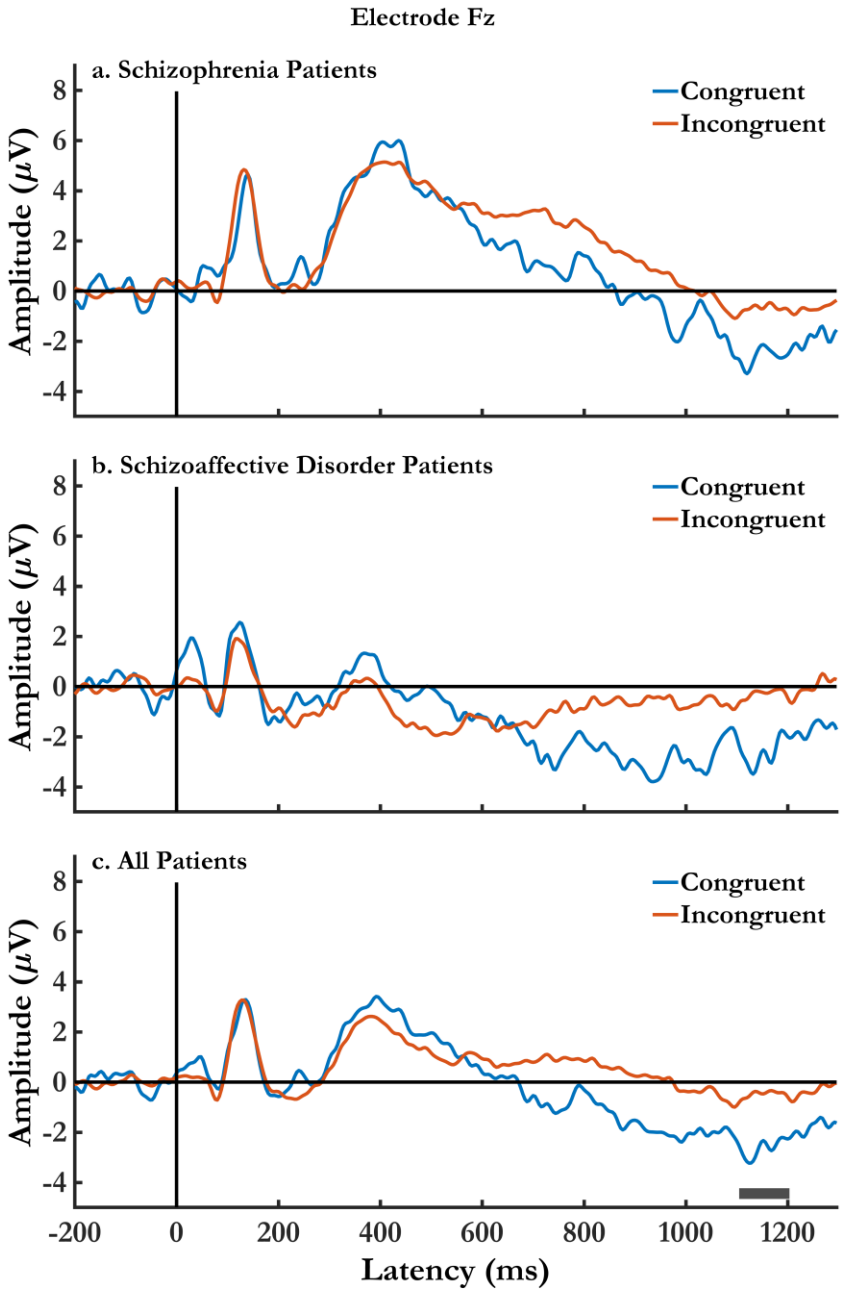


Figure 5.9 Grand average ERP response to Stroop task conditions at electrode Fz in patient groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6).

either. The congruent P300 is larger than incongruent at both Cz and Pz electrodes. Interestingly, at both these electrodes, the ERP response to incongruent stimuli is however larger than congruent response after approximately 800ms. This is similar to the LPC response observed in some papers (Coderre et al., 2011; Markela-Lerenc et al., 2009). It should be noted that the difference between the ERP responses to the two

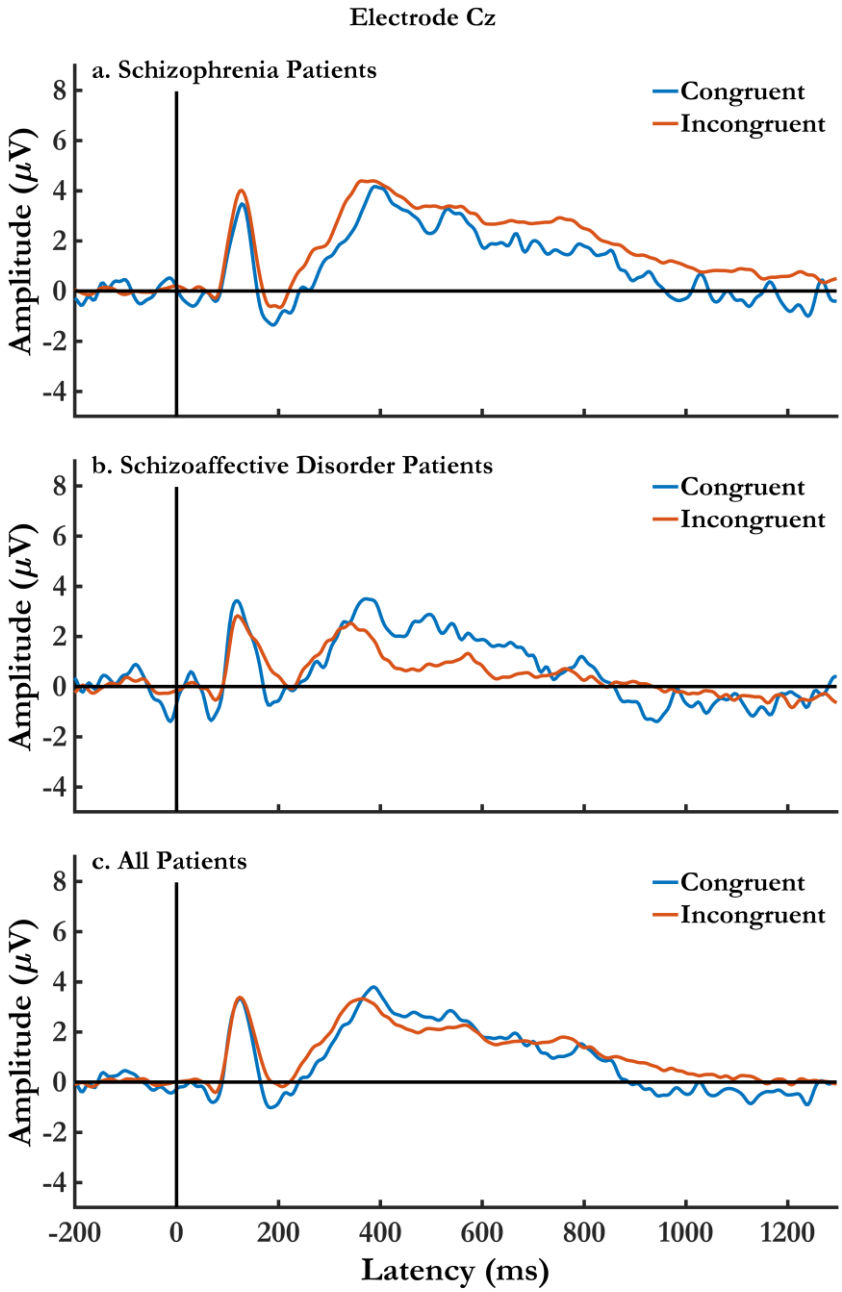


Figure 5.10 Grand average ERP response to Stroop task conditions at electrode Cz in patient groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6).

task conditions is not significant. The grand averaged ERP from the whole patient group is shown in figures 5.9c, 5.10c, and 5.11c. As expected from the patient group responses, no significant differences are observed between the task conditions except for a small window at electrode Fz (fig 5.9c) towards the end of the trial. The P300 peak amplitudes and peak latencies computed from the grand averaged ERP responses

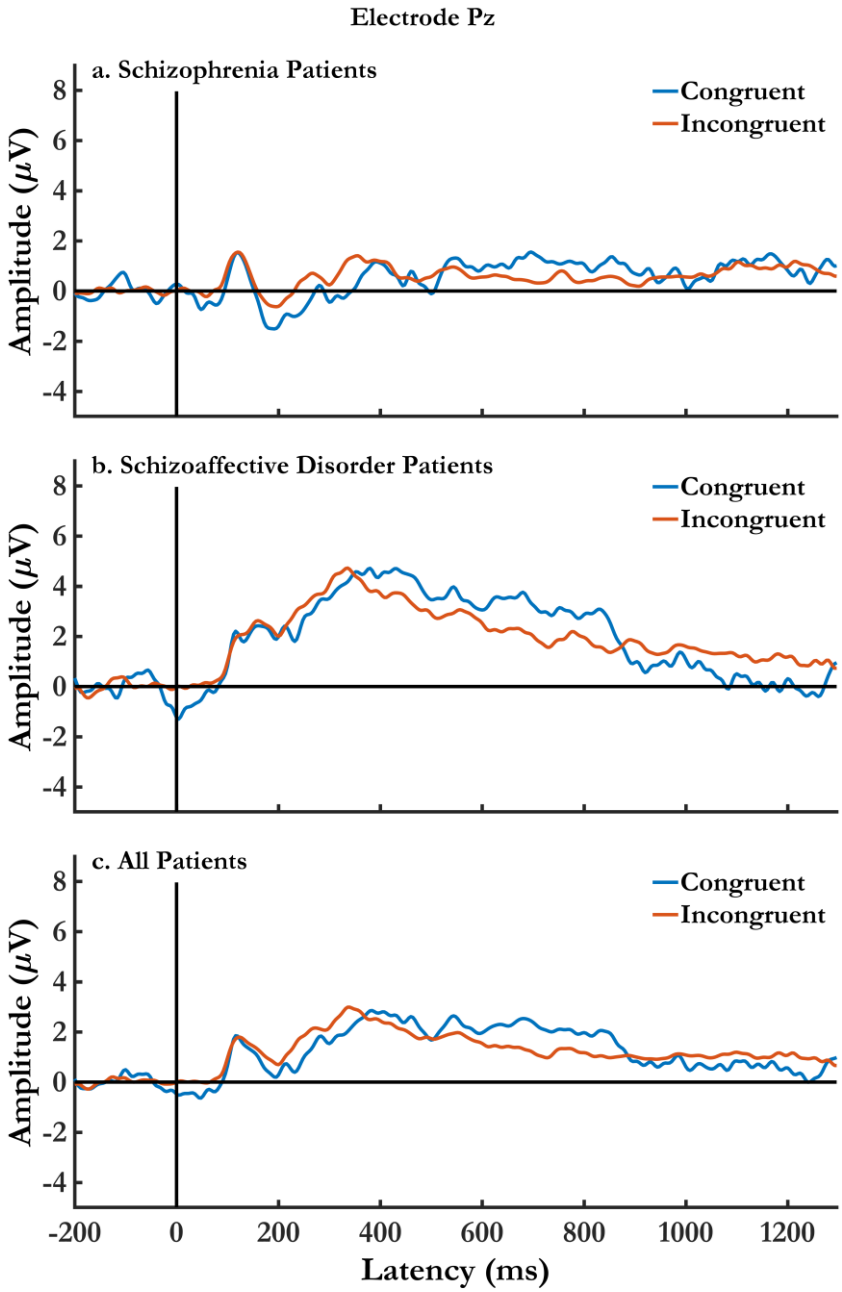


Figure 5.11 Grand average ERP response to Stroop task conditions at electrode Pz in patient groups. Vertical and horizontal black lines represent trial onset and baseline, respectively. Black bars at the bottom represent periods of significant difference. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6).

to congruent and incongruent conditions, and the difference waveform for each patient group is also recorded in table 5.5.

5.4.3 TIME-FREQUENCY ANALYSIS

Figure 5.12 shows the grand average ERSP responses at electrodes Fz, Cz, and Pz in control subjects. For each electrode there is a response for the congruent trials, incongruent trials, and a difference of the two (incongruent – congruent). The difference responses on the right are also overlaid with the output of the permutation statistics with cluster-based correction. The region inside the black line boundaries was significantly different between congruent and incongruent trials at $p<=0.05$.

The plots show that, relative to baseline, there is an initial broadband synchronisation for 100-200ms. After this initial period, the frequencies below 8Hz (delta/theta band) continue to be synchronised, but the frequencies above 8Hz are desynchronised. Both the synchronisation and desynchronisation are relatively stronger in the congruent trials compared to the incongruent. Across all the three electrodes we see that the desynchronisation in frequency range of 8-24Hz peaks (alpha/beta band) around 500ms. These desynchronisation patterns reflect event related movement preparation and execution (button press in Stroop task) and have been extensively studied in motor neuroscience literature (Kilavik et al., 2013; Nakayashiki et al., 2014; Pfurtscheller & Lopes da Silva, 1999; Tan et al., 2013). From the difference plot of each electrode, we see a significant sustained relative synchronisation starting at frequencies above 8Hz and continuing to lower frequencies in the second half of the trial period. The synchronisation of lower frequencies in incongruent trials relative to congruent trials is significantly weaker only in the frontal region at electrode Fz and is seen as negative (red) values in the difference plots.

As each of the plots in figure 5.12 show a clean pattern of synchronisation and desynchronisation, the peaks and troughs were calculated for these ERSP responses. The latency and frequency of these measures were also determined. This set of measures from figure 5.12 are like the analysis of ERP plots (shown in table 5.3) and are recorded in table 5.6. For each electrode, the maxima (peak) and minima (trough) of the power distribution is recorded.

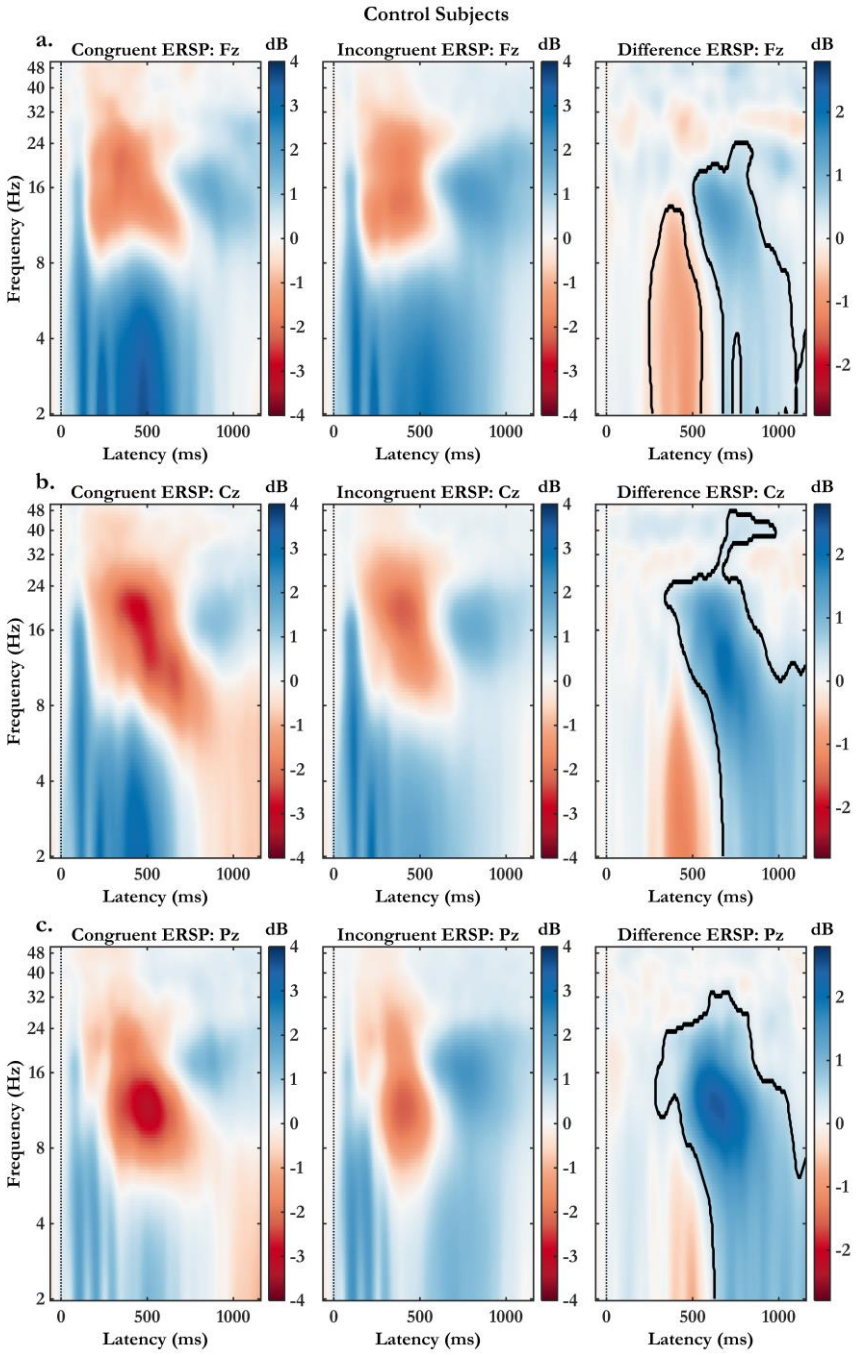


Figure 5.12 Grand average ERSP response to Stroop Task conditions in control subject group (n = 18). a. Electrode Fz, b. Electrode Cz, c. Electrode Pz. Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. The black contours in the right column represent areas of significant difference at $p<0.05$.

The table shows that the peaks in spectral power occur at lower end of the spectrum in both task conditions. Another point to be noted is that the latency of these peaks is found to be earlier than that of the mean trial response latencies in control

subjects (545.51ms for congruent and 527.17ms for incongruent). However, for the incongruent trials and at electrode Pz, the lower frequency is approximately at baseline level before 500ms post-stimulus. It should also be noted that the peak power decreases from frontal to parietal electrodes in both task conditions. The valley or the trough regions (red) of the images show a clearer pattern. The absolute power decrease (desynchronisation) from baseline is lower in the frontal regions and gradually increases towards the parietal electrode. The minima occur at higher frequency in the range of 11-20Hz. From the difference ERSP plot, the initial desynchronisation in incongruent trials when compared to congruent trials, has a minimum at lower frequency close to 2Hz. On the other hand, the relative sustained synchronisation in the incongruent trials (compared to congruent trials) is observed to occur after 600ms post-stimulus and peaks at approximately 12Hz.

Table 5.6 Stroop ERSP measures from control subject group.

	Power (dB)			**Latency (ms)**			**Frequency (Hz)**		
	Cong	**Incong**	**Diff**	**Cong**	**Incong**	**Diff**	**Cong**	**Incong**	**Diff**
Peak									
Fz	3.63	3.17	1.44	472	232	660	2.00	2.00	12.76
Cz	3.07	2.91	2.07	472	220	684	2.00	2.00	11.96
Pz	1.92	2.27	2.49	104	776	644	2.00	16.02	11.96
Trough									
Fz	-2.02	-1.95	-1.02	348	380	464	20.12	14.07	2.00
Cz	-2.90	-2.28	-1.25	448	396	416	19.47	19.47	2.95
Pz	-3.31	-2.28	-0.75	508	404	496	11.58	11.58	2.00

Cong: Congruent, **Incong**: Incongruent, **Diff**: Difference

The time-frequency analysis and the ERSP response from individual patients is presented in the figures 5.13, 5.14, and 5.15 for electrodes Fz, Cz, and Pz, respectively. However, unlike figure 5.12, only the difference plots are shown for each patient. Also, like the ERP analysis in single patient subjects, unpaired permutation statistics with cluster-based multiple comparisons correction were used to generate the ERSP plots. The results of the statistical tests are overlaid on each figure with the black lines

marking the boundaries of the regions that were significantly different in congruent and incongruent trials.

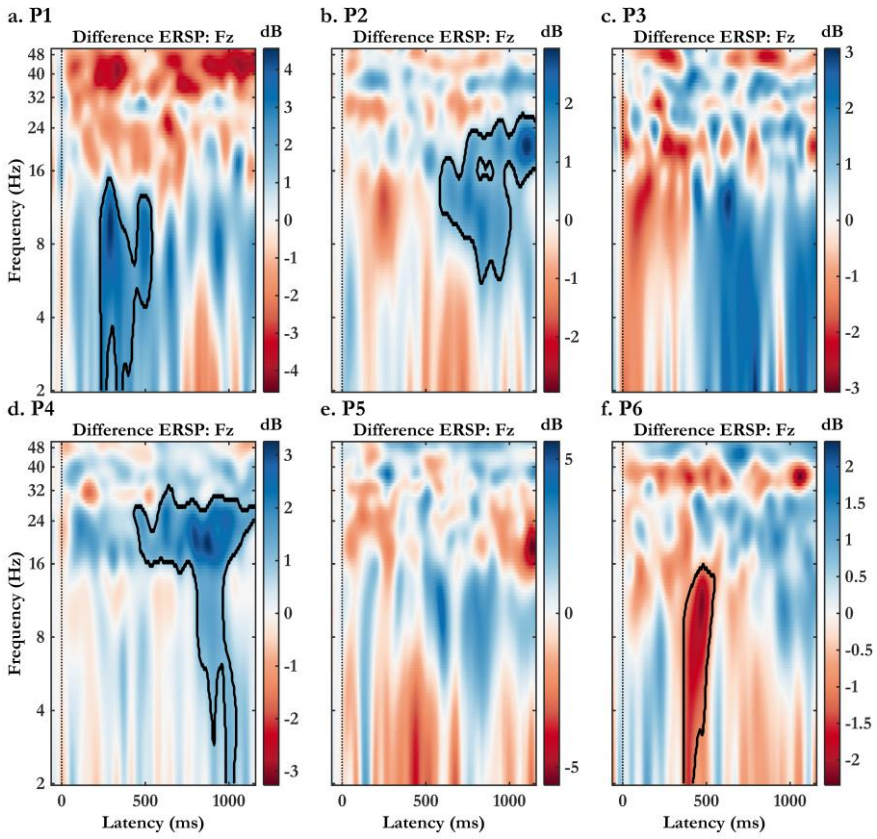


Figure 5.13 Average ERSP response difference between Stroop task conditions at Fz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

The individual patient figures show a considerable variability. We also see that the ERSP plots show significant differences even in the cases where ERP signals did not show any significant differences (e.g. patient P1). Largely, patients exhibit a pattern of synchronisation across the spectrum throughout the trial period at the three electrodes. The synchronisation is more prominent in later period of the trial and is widespread in both time and frequency. Most patients show a significant synchronisation effect. The desynchronisation of lower frequency is observed only in a few plots, like patient P6 at electrode Fz and Cz. In each plot we see several peaks and valleys in the time-frequency space. This could be attributed to variability within each patient and to the fact that these plots are from a single subject and not a group.

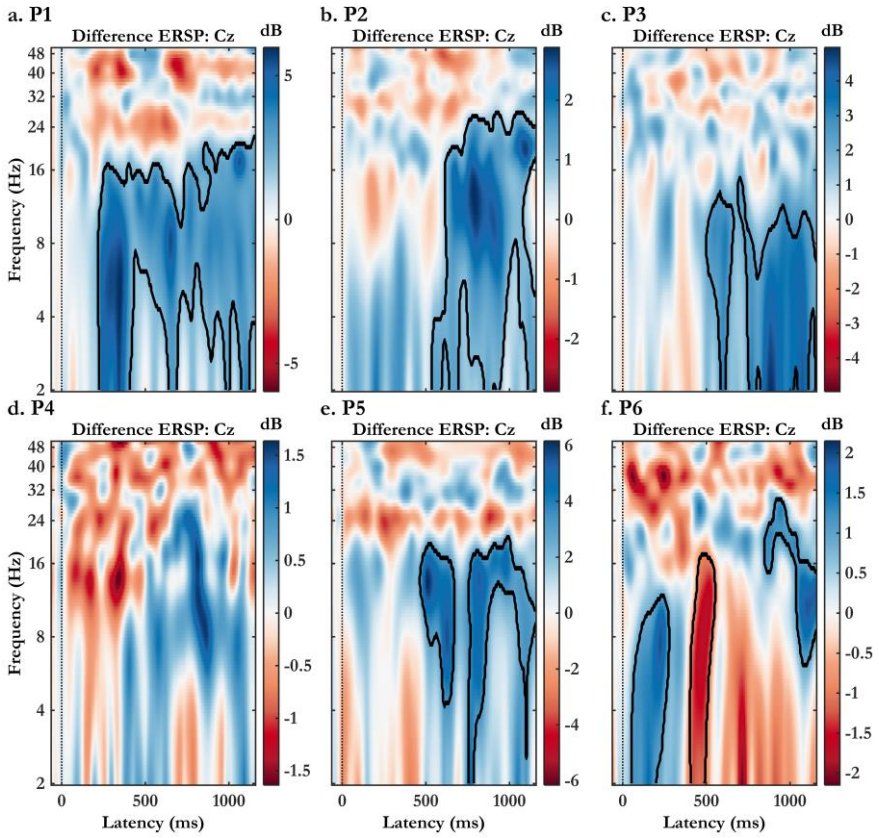


Figure 5.14 Average ERSP response difference between Stroop task conditions at Cz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

The grand average group ERSP from schizophrenia and schizoaffective disorder patient groups are presented in figure 5.16 for electrode Fz, figure 5.17 for electrode Cz, and figure 5.18 for electrode Pz. Each of these figures also show the grand average ERSP response from all patients grouped together. From these figures some patterns can be observed. Schizophrenia patients (fig 5.16a, 5.17a, 5.18a) show a wider spectral desynchronisation of frequencies in the 4-24Hz range, sometimes going as high as 32Hz. The time-frequency region of synchronisation (blue) in schizophrenia patients is small with weak synchronisation compared relative to the per-stimulus baseline. On the contrary the desynchronisation of the higher frequencies is relatively stronger in schizophrenia group. We see multiple valleys or troughs even in the group ERSP of schizophrenia patients. The large variation in the trial response latencies of patients could account for the time latency of these troughs. However, we also see multiple frequencies in the plots that are desynchronised. This most likely indicates to

difference in neural mechanisms of the individual subjects during the trial periods. It should be noted that the significant differences between the congruent and incongruent trials were found only in a small region at electrode Fz (fig 5.16b).

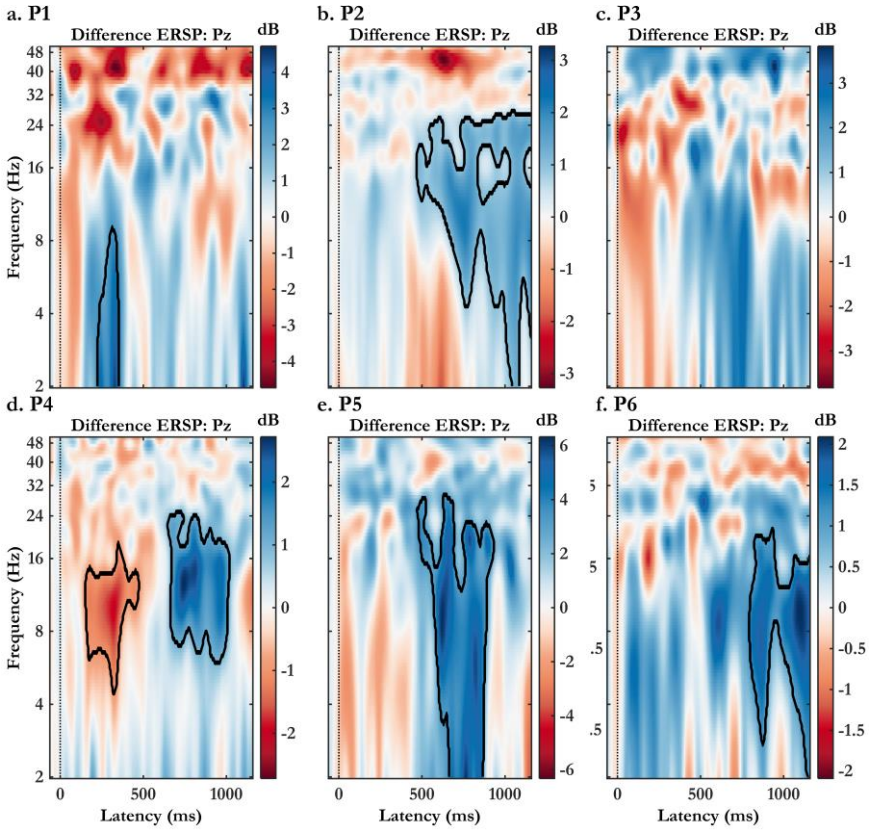


Figure 5.15 Average ERSP response difference between Stroop task conditions at Pz electrode in individual patients. The six patient (P1 to P6) response differences are plotted on 2x3 grid from a to f. In each plot, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

The ERSP response from schizoaffective disorder patients (fig 5.16b, 5.17b, 5.18b) shows larger absolute changes in the spectral power over the trial period relative to the baseline period. This can be clearly seen from the wider colour scales in panel b of figures 5.16, 5.17, and 5.18. We see that the activity desynchronisation is strongest in 8-16Hz region. Similar to schizophrenia patients, the desynchronisation is widespread in both frequency and time dimension. This is likely due to the variation within the schizoaffective disorder patients. The desynchronisation of 8-16Hz band is strongest at channel Cz (fig 5.17b) and the differences between congruent and incongruent trials are significant at the Fz and Cz electrodes (fig 5.16b and 5.17b, right

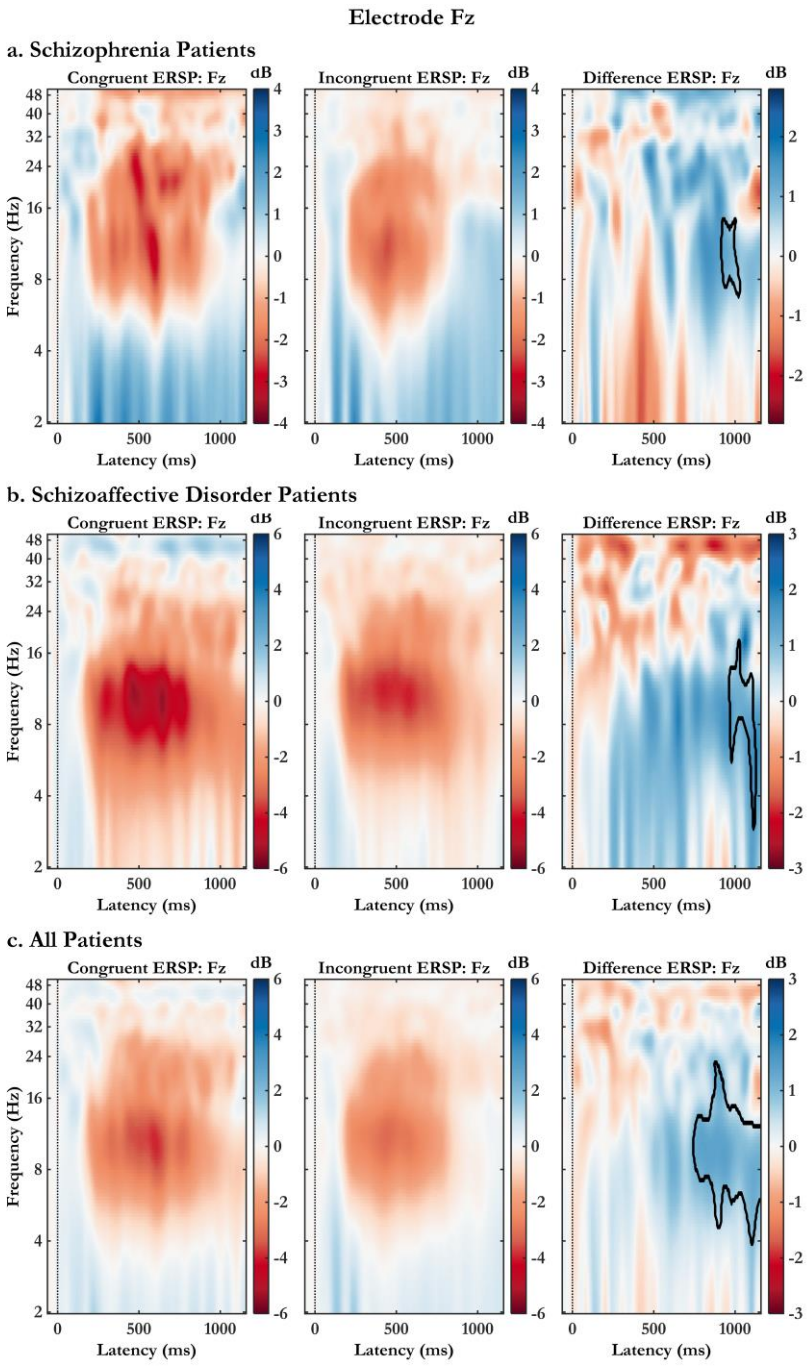


Figure 5.16 Grand average ERSP response to Stroop task conditions at electrode Fz in patient groups. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

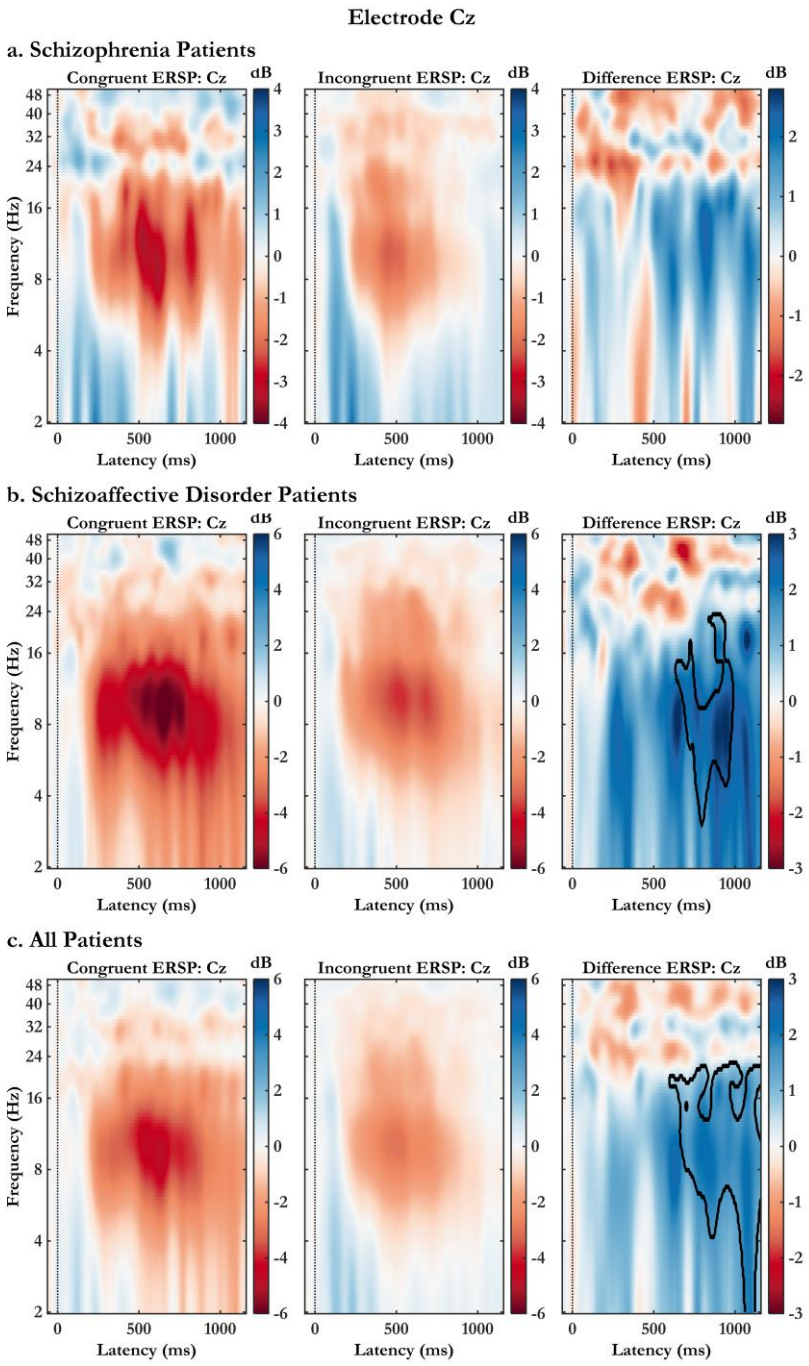


Figure 5.17 Grand average ERSP response to Stroop task conditions at electrode Cz in patient groups. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

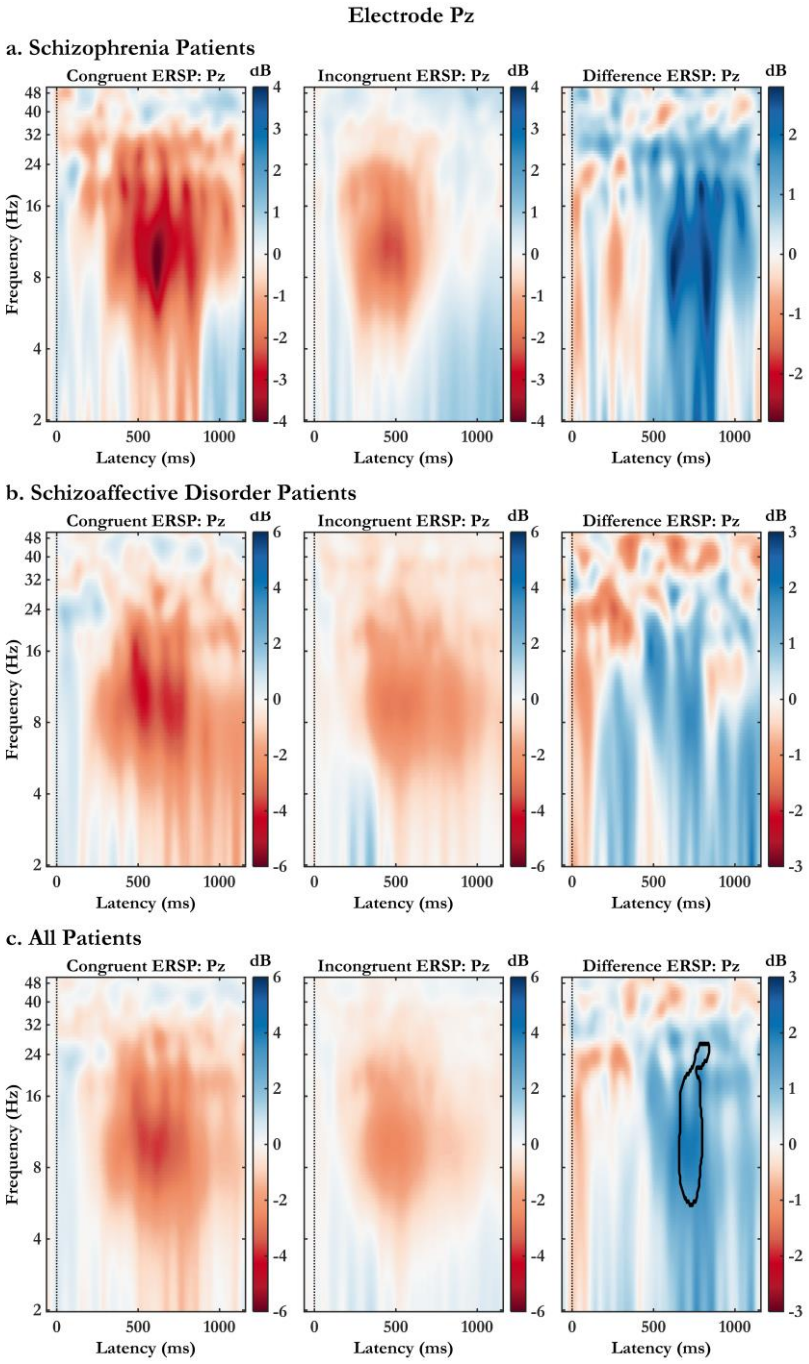


Figure 5.18 Grand average ERSP response to Stroop task conditions at electrode Pz in patient groups. a. Schizophrenia patients (n = 3), b. Schizoaffective disorder patients (n = 3), c. All patients (n = 6). Each row has three plots (left to right): congruent ERSP, incongruent ERSP, difference ERSP. In the difference plots on the right, areas of significant difference at $p<0.05$ (if present) are presented by black contours.

columns). Like the schizophrenia patients, we again see a lack of synchronisation in frequencies less than 8Hz and most of the response is a desynchronisation of higher frequency activity. Lastly, the grand averaged ERSP from the whole patient group is

presented in figures 5.16c, 5.17c, and 5.18c. In these plots too, we see that the lower frequency signals do not change much from the pre-stimulus baseline or between task conditions at any of the electrodes. The comparatively higher frequency signals in the range of 8-16Hz show an overall desynchronisation during each task condition with a significantly stronger desynchronisation of this activity in congruent trials.

5.4.4 ANANLYSIS OF EEG MEASURES

The grand average ERP signals from control subjects and the patients were presented in figures 5.5, 5.9, 5.10, and 5.11. The features extracted from these ERP responses, namely the P300 peak amplitude and peak latency, at the three midline electrodes were also tabulated. The changes in these values across the midline electrodes are plotted for visual inspection in figure 5.19. Here, two more intermediate electrodes FCz and CPz, are also included. The figure shows measures from congruent trials (5.19a.), incongruent trials (5.19b.), and the difference (incongruent – congruent) waveform (5. 19c.). In each of these, the plot on the left shows the P300 peak amplitudes and the plot on the right shows the P300 peak latencies. The purpose of these plots is to visualize the patterns of EEG measures in the control and patient groups. While the change in task parameters between control and patient groups prevents us making direct comparisons between them, these plots help with visualizing the differences within the patient groups.

From the plots we observe that in control subjects the congruent peak amplitudes are largest at the Cz electrode with a decrease observed both towards frontal and parietal directions. The decrease is steeper towards the frontal region. The incongruent peak amplitudes have smaller variation over the midline electrodes compared to congruent peak amplitudes, however the largest peak amplitude is still seen at electrode Cz. The absolute value of difference peak amplitude in control subjects increases from frontal (Fz) to parietal (Pz) region. It should be noted that the peaks in this plot (fig 5. 19c) were calculated from the waveform obtained by subtracting the congruent grand averaged ERP from the incongruent grand averaged ERP. For this reason, the values of peak amplitudes are negative, and are different from the value incongruent peak amplitude – congruent peak amplitude.

In both the congruent and incongruent trials, we see a decrease in peak amplitudes across the midline electrodes in schizophrenia patients and an increase in

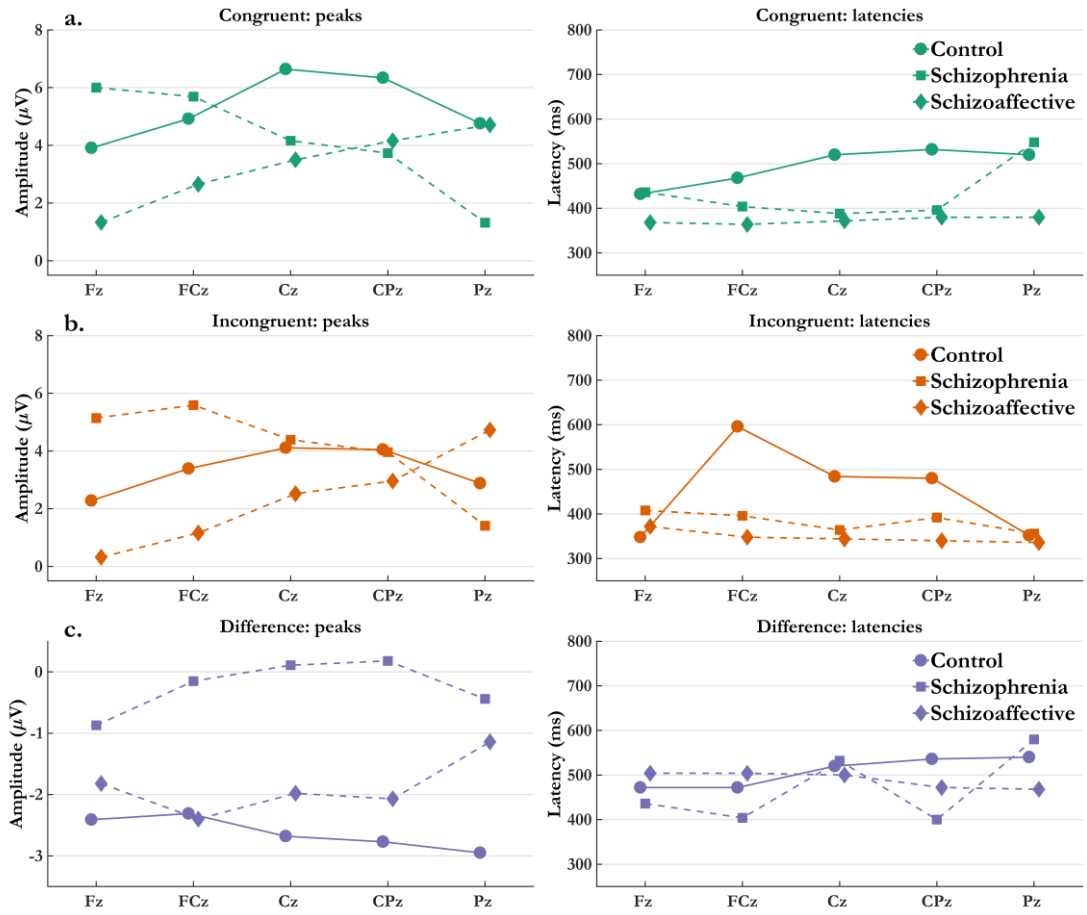


Figure 5.19 Grand average ERP measures across midline electrodes in control and patient groups during Stroop task. a. Congruent ERP, b. Incongruent ERP, c. Difference (incongruent – congruent) ERP. Left column: Peak amplitudes, Right column: Peak latencies. Solid lines and circle markers represent healthy controls (n = 18). Dotted lines are used for patients with square markers for schizophrenia (n = 3) and diamond markers for schizoaffective disorder (n = 3). Non-zero axis is used to better visualize the patterns in the values of peak latencies.

peak amplitudes in schizoaffective disorder patients. The difference peak amplitudes indicate that, except at electrode Pz, schizoaffective disorder patients show relatively consistent peak amplitudes across the midline electrodes. In the schizophrenia patient group, the difference peak amplitudes are much smaller than the schizoaffective disorder patients. The peak amplitudes on three midline electrodes FCz, Cz, and CPz are remarkably close to zero, meaning both the congruent and incongruent P300 responses were almost identical in the 300-600ms post-stimulus period.

The P300 peak latencies plotted on the right side of figure 5. 20, except in few cases, do not vary a lot across the midline electrodes. The congruent peak latencies in control subjects are lower in the frontal region when compared to the parietal

electrodes. In the incongruent condition the control subjects show a decrease in peak latencies from FCz to Pz electrode, with Fz electrode showing the shortest peak latency. The difference peak latency across the midline electrodes is observed to show a small increase from Fz to Pz electrodes, as seen in the congruent condition. In schizophrenia patients, the peak latency values for both congruent and incongruent response are consistent across the midline electrodes except for the congruent trials at Pz electrodes. This can be explained by observing the ERP response at Pz from figure 5.11, which does not fluctuate much around the baseline, thus leading to a peak latency that can occur anywhere during the 300-600ms window. In the difference peak latency for schizophrenia patients, we see an increase from electrode FCz to Cz. This can be attributed to earlier mentioned fact that in these cases the difference waveform was close to baseline. In schizoaffective disorder patients, the peak latency values are stable across both the task conditions, difference ERP, and through the midline electrodes.

5.4.5 CORRELATIONS BETWEEN EEG MEASURES AND BEHAVIOURAL MEASURES

In section 5.4.1 the behavioural performance of each subject in terms of percentage of correct trials and mean response latency of trials was computed. Similarly the P300 peak amplitude and peak latency for the both the task conditions for all the subjects was calculated across the 5 midline electrodes (Fz, FCz, Cz, CPz, Pz). The pair-wise combinations of these trial measures and P300 measures were used to compute the correlations shown in table 5.7. For example, the first column represents the correlations between congruent response latencies and P300 peak amplitudes. The correlations are also coloured by their relative values for ease of visualization; darker blue colours represent more positive correlations while darker red colours represent more negative correlations. Significant correlations have been marked with an asterisk (*) symbol.

In control subjects, we see overall low correlations between various measures, none of which were significant. However, we do see expected relationships between the various pairs. For example, P300 peak amplitudes in both task conditions are negatively correlated with the mean trial response latency, meaning subjects that had a larger P300 response were also, on average, quicker at responding to the trial. The positive correlation between the P300 peak latency with the average trial response

latency can be theorized as subjects taking longer to make a decision and thus needing more time to respond to the trial. The correlations with the percentage of correct trials are relatively lower in control subjects. Unlike the average trial response latency, there is no intuition between how the P300 measures that were calculated from correct trials, could be informative of the percentage of correct trials. Also, these correlations are even smaller than those seen with the average trial response latency and likely a spurious effect.

Table 5.7 Correlations between behavioural data and ERP response measures from Stroop task.

Trial	Response Latency				Percent Correct			
P300	Peak Amplitude		Peak Latency		Peak Amplitude		Peak Latency	
Cond	Cong	Incong	Cong	Incong	Cong	Incong	Cong	Incong
Control subjects (n = 18)								
Fz	-0.15	0.06	0.43	-0.08	0.10	0.05	0.38	0.22
FCz	-0.12	-0.11	0.23	-0.07	0.00	-0.01	0.01	-0.07
Cz	-0.32	-0.28	0.17	-0.04	-0.24	-0.01	0.16	0.01
CPz	-0.38	-0.25	0.05	0.02	-0.24	-0.06	0.16	-0.15
Pz	-0.19	-0.15	-0.07	-0.31	-0.21	-0.06	0.00	0.20
Schizophrenia patients (n = 3)								
Fz	0.69	0.41	0.91	-0.50	0.71	0.94	0.90	0.27
FCz	-0.30	0.06	0.91	-0.72	-0.28	0.75	0.90	-0.01
Cz	-1.00*	-0.77	-0.69	-0.61	-1.00*	-0.99	-0.71	-0.99
CPz	-0.98	-0.96	-0.69	-0.59	-0.98	-0.87	-0.71	-0.99
Pz	-0.95	-0.55	-0.91	-0.77	-0.96	-0.98	-0.92	-1.00
Schizoaffective disorder patients (n = 3)								
Fz	-0.31	-0.80	0.99	0.94	-0.98	-0.94	0.61	0.81
FCz	-0.06	-0.76	0.81	0.79	-0.90	-0.92	-0.12	0.58
Cz	0.38	-0.72	0.77	0.16	-0.62	-0.89	-0.18	-0.13
CPz	0.20	-0.77	0.74	0.26	-0.76	-0.92	-0.22	-0.03
Pz	0.96	0.99	-0.28	0.48	0.22	0.90	-0.97	0.20

Cond: Condition; **Cong**: Congruent, **Incong**: Incongruent; *p<0.05

The correlation values were higher in both the patient groups. One of the reasons for this could be the high degree of variability that was seen in these subjects. It should be noted that, though the numbers were higher, the expected patterns were observed only in few cases. For example, in schizophrenia patients we see an expected negative

correlation between the P300 peak amplitudes and mean trial response latencies at almost all electrodes, except Fz. This correlation is also significant at electrode Cz for congruent trials. The P300 peak latency and mean trial response latency exhibited an expected positive correlation only in the congruent trials at electrodes Fz and FCz. There were some strong negative and positive correlations between the P300 measures and percent correct in schizophrenia patients which cannot be intuitively explained. The correlation numbers in some of cells have an absolute value of 1 due to rounding them to two significant digits. Like the schizophrenia patient group, the schizoaffective disorder patient group also exhibited some expected correlations between the P300 measures and trial measures. For example, expected negative correlations were seen for incongruent trials between P300 peak amplitude and mean trial response latency on all electrodes expect Pz. It was interesting to see that, as we had in figures 5.19, an opposite pattern is exhibited in some cases when comparing the two groups of patients. For example, the P300 peak latency and mean trial response latencies for both task conditions show an expected positive correlation in schizoaffective disorder patients. However, except in 2 cases, these correlations are negative in schizophrenia patients.

Table 5.8 Correlations between percentage change in trial latency and difference ERP measures from Stroop task.

	Control		**Schizophrenia**		**Schizoaffective**	
	DPA w/ PCL	**DPL w/ PCL**	**DPA w/ PCL**	**DPL w/ PCL**	**DPA w/ PCL**	**DPL w/ PCL**
Fz	0.32	0.45	-0.91	0.94	0.17	0.83
FCz	0.06	0.41	-0.86	0.93	0.55	-0.06
Cz	0.08	0.15	-0.94	0.50	0.67	-0.20
CPz	0.03	0.05	-0.79	0.51	0.72	-0.74
Pz	0.03	0.09	0.25	-0.28	0.49	-0.23

DPA: **D**ifference **P**eak **A**mplitude; **DPL**: **D**ifference **P**eak **L**atency

PCL: **P**ercent **C**hange in Response **L**atency

In section 5.4.1 the relative interference in the incongruent trials was calculated using the percentage change in response latency (PCL) from congruent trials. We have seen from section 5.4.1 that in most of the subjects there was a percent decrease in mean trial response latency from congruent to incongruent trial. From tables 5.3 and 5.5 we have seen that the difference (incongruent – congruent) ERP peak amplitudes,

in the 300-600ms post-stimulus period, are also negative in most subjects. This is because the congruent ERP amplitude is higher than the incongruent ERP amplitude. Correlation analysis was used to determine the relationship between PCL and the difference peak amplitude (DPA) and latency (DPL) measures. A negative correlation between DPA and PCL is expected as this would signify that larger differences in ERP resulted in subjects making faster decisions and responding to both trial at a similar relative mean trial response latency. Positive correlation between PCL and DPL are expected as this would signify that the time it took to differentiate between the type of trial translated into longer differences in trial response latencies between the task conditions. The correlations between PCL and difference ERP measures are shown in table 5.8. The cells are also coloured for ease of visualization, like in table 5.7. As seen in table 5.7, the correlations in control subjects are lower and non-significant and all the values were seen to be positive.

The absolute values of correlations in patient groups are again observed to be high. In schizophrenia patients DPA values from all midline electrodes except Pz are negatively correlated with PCL. The DPL were positively correlated with PCL at all electrodes except Pz. In schizoaffective disorder patients, positive correlations between DPA and PCL are observed. The correlations with peak latency are also mostly negative except on the frontal Fz electrode. These differences in the patients show that schizophrenia patient group mostly showed expected correlation, but the schizoaffective patient group did not. It should be noted however, none of the correlation in table 5.8 were significant.

5.4.6 CORRELATION WITH DEMOGRAPHIC DATA

In figure 5.20 we computed the correlations between the difference ERP measures and the various scores assigned to each patient using the PANSS (Kay et al., 1987) and MADRS (Montgomery & Asberg, 1979) questionnaires along with their age. The significant correlation values are marked with an asterisk (*). The difference ERP measures were used with the rationale that patients with more severe symptoms would not be able to differentiate between the two types of trials and likely have similar ERP response. Thus, the absolute values of difference ERP peak amplitudes are expected to show negative correlations with age, and with the scores on various scales. The schizophrenia patients show the expected results with age and with PANSSN scale

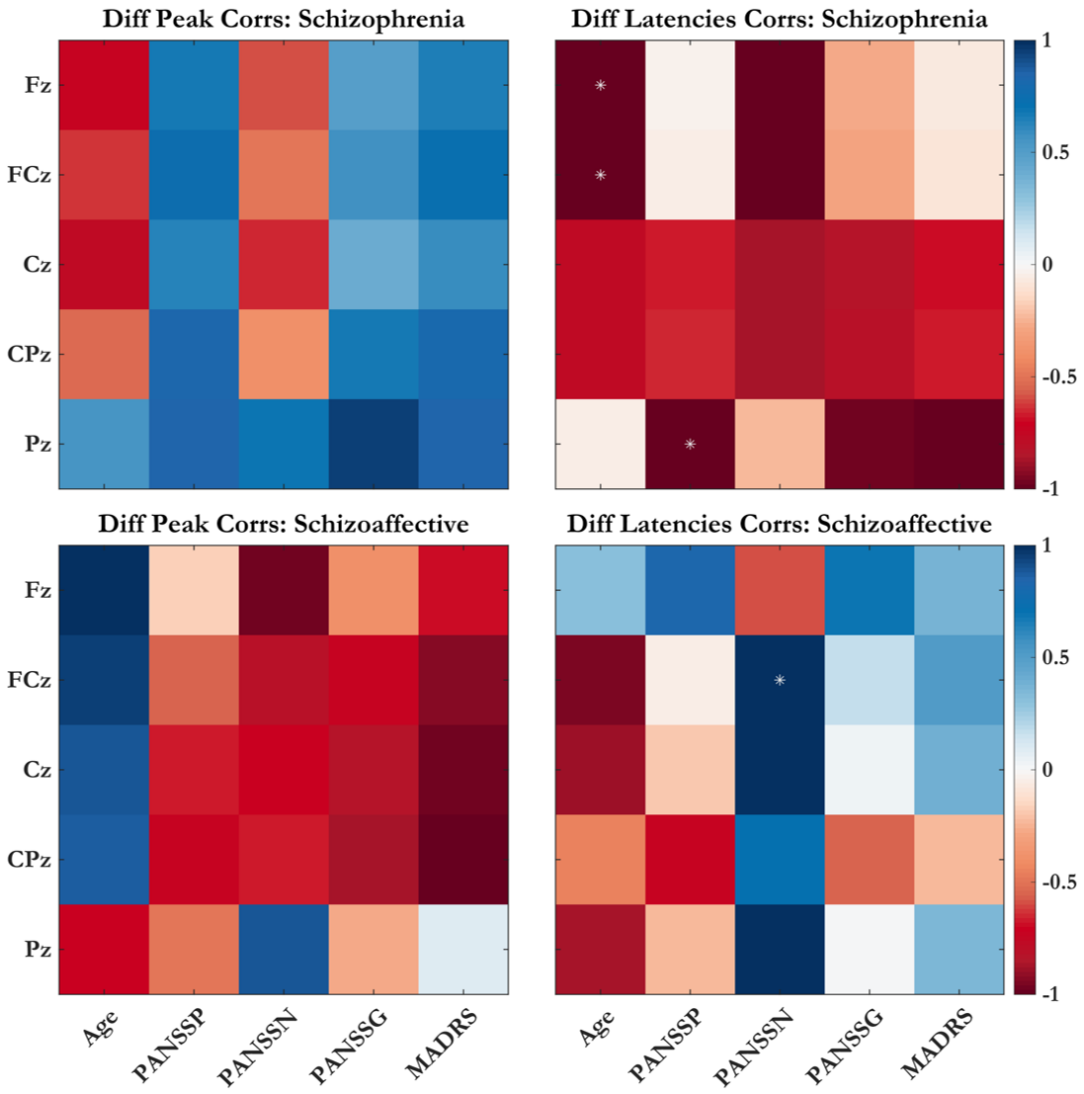


Figure 5.20 Correlations between difference ERP measures from Stroop task and symptom severity scores in patients. Left column: correlations with difference ERP peak amplitudes, Right column: correlations with difference ERP peak latency. Top raw: schizophrenia patients (n = 3), bottom row: schizoaffective disorder patients (n = 3). Asterisk (*) represent $p<0.05$. The vertical and horizontal axis labels are shared by the plots in the rows and columns, respectively.

on all electrodes except Pz. All the other correlations are positive. In schizoaffective disorder patients, we see negative correlations in most cases except with the age variable. With the difference ERP peak latency, a positive correlation is expected with the hypothesis that patients who took longer to differentiate between congruent and incongruent trials are also likely to score higher on the symptom severity scales. In schizophrenia patients however all the correlation values are negative. In schizoaffective disorder patients, positive correlations are seen with the PANSSN and

MADRS scores at four out of five electrodes. Electrode Fz shows smaller positive correlation for all measures except PANNSN values. All other correlation were negative.

The correlations between age and difference ERP measures in control subjects were also computed. It was found that all electrodes showed negative correlations between difference ERP absolute peak amplitude and age. These values decreased moving from the frontal to the parietal electrodes (Fz: -0.46; Pz: -0.09), with none of the values being significant. The correlations between difference ERP peak latency and age of control subjects were positive at electrodes FCz, and Cz and negative on

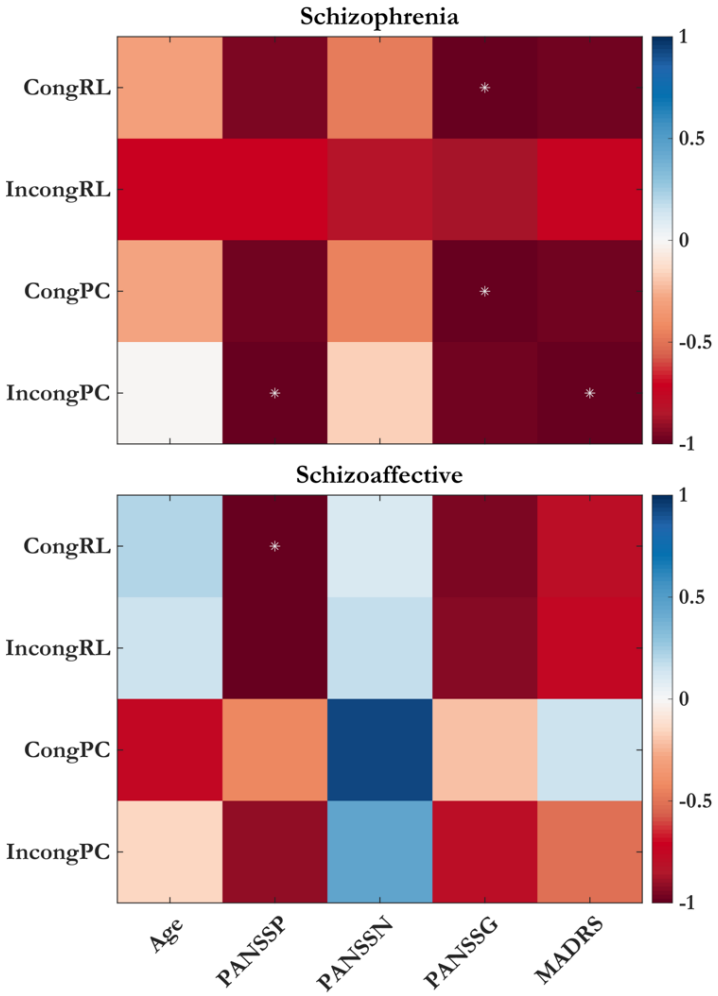


Figure 5.21 Correlations between behavioural performance measures from Stroop task and symptom severity scores in patients. Top row: schizophrenia patients (n = 3), Bottom row: schizoaffective disorder patients (n = 3). RL: mean trial response latency, PC: percent correct. Asterisk (*) represent $p<0.05$. The horizontal axis labels are shared by both plots.

the other three electrodes. The correlations were significant at electrode FCz ($r = 0.49$, $p = 0.04$).

Correlations between the behavioural measures and the scores assigned to patients using the PANNNS and MADRS scales were also computed. These correlations are shown in figure 5.21. As before, a negative correlation between the severity score and the percentage of correct trials is expected, meaning patients with more severe symptoms performed poorly. This also means that positive correlations between the severity score and mean trial response latency are expected. In schizophrenia patients all the correlations are found to be negative with a few correlations meeting the significance criteria of $p<0.05$. In schizoaffective disorder patients age is negatively correlated with both the percent correct measures and positively correlated with both the mean trial response latency measures. PANSSN scores in this group are all shown to have positive correlations, while almost all other correlation measures are negative. The correlations between behavioural performance measures and age in control subjects were also computed. A significant positive correlation was found between age and percent correct of congruent trials ($r = 0.48$, $p = 0.05$).

5.5 Discussion

The Stroop experiment described in this chapter showed a contradictory result to the expected increase in latency with the presence of conflicting stimuli in incongruent condition (Stroop effect). The behavioural analysis showed that, on average, subjects had a higher response latency to the congruent condition (table 5.2). In this section this finding is further explored using previous research. The goal is to determine why such an effect was observed and what changes can be made to the experimental paradigm to elicit the Stroop effect.

5.5.1 TASK DESIGN LIMITATIONS

A computerized Stroop task was used in the experiments presented in this chapter. To summarize, subjects were presented with two types of trials, namely: a. congruent trials: colour-word matches the ink its written in (e.g. “RED” written in red ink), b. incongruent trials: colour-word is conflicting with the ink its written in (e.g. “RED” written in blue ink). Traditionally, the subjects are asked to respond to the

colour of the ink by choosing one of the four options (red, blue, green, yellow), and ignore the meaning of the colour-word. As reading words is a more automatic process for humans and interpreting colour of the ink requires employment of selective attention (Comalli Jr et al., 1962), it takes longer for subjects to respond to incongruent trials where a conflicting information is present.

The task presented in this chapter used an approximate congruent to incongruent ratio of 25:75. Also, subjects were instructed to pay attention to the colour of the ink and ignore the colour word. However, instead of using a standard type of response, they were asked to respond with either a "MATCH" response for congruent trials, or a "NO MATCH" response to incongruent trials. This was done to make the task easier for patients. We have seen from section 5.4.1 that the task parameters used in the experiment led to an increased mean response latency in congruent trials when compared to incongruent trials, an opposite effect than what is traditionally expected. Two likely causes for this observation are investigated in this section.

Firstly, practice effect in task was investigated. In previous literature, the interference in Stroop task is seen to reduce as subjects complete more trials (Bush et al., 1998). As a result, the response time to the incongruent trials is reduced. A moving average of the trial response latency was computed to investigate if the practice effect dominated the average results presented in section 5.4.1. If this were the case, we would see that subjects initially had larger latencies to incongruent trials but eventually were able to respond to them faster than the congruent trials. The practice effect in

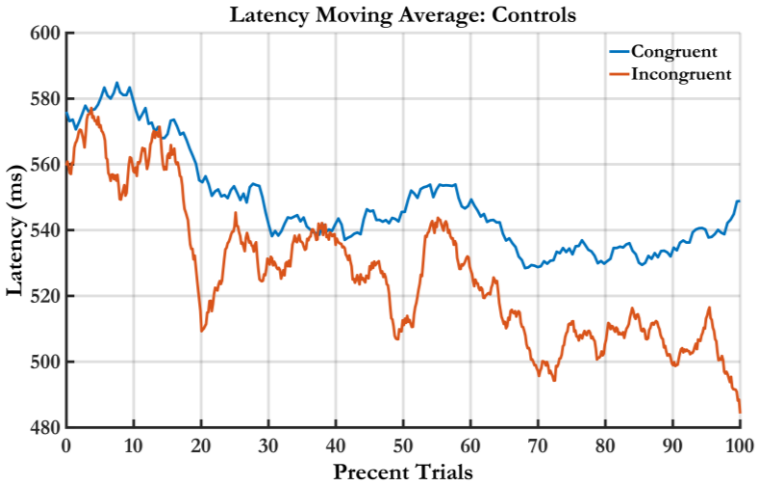


Figure 5.22 Moving average of trial latencies in healthy control subjects performing the Stroop task.

such a scenario can be strong enough that mean latencies calculated for all trials could show a smaller value for incongruent condition compared to the congruent condition.

The moving average of response latency computed for all control subjects is shown in figure 5.22. The x-axis shows the percentage of completed trials and the y-axis shows a 30-trial moving average of the response latencies. We see from this figure that subjects had shorter response latencies to incongruent trials from the beginning of the experiment. A practice effect is observed in both task conditions with decreasing latencies as more trials are completed. A similar effect was seen in patients. Even in the 24-trial practice phase before the experiment began, the average response latency in the incongruent trials was smaller than congruent trials. These observations show that the observed results were not a consequence of a practice effect.

Secondly, it is likely that the observed behavioural response to the task was a result of a combination of the smaller percentage of congruent trials, and the use of "MATCH"/"NO MATCH" response in the experiment. A previous study by Logan and Zbrodoff demonstrated how a higher percentage of incongruent condition can lead to lower average response latency in incongruent trials when compared to congruent trials (Logan & Zbrodoff, 1979). They used a Stroop-like task with words "ABOVE" and "BELOW" presented either above or below the fixation point. In the congruent condition the words matched with the location, and in the incongruent condition they did not. The percentage of incongruent trials within a block of trials was varied between 10% and 90%, with the rest of the trials being congruent. They observed that reporting the position of the word was the faster/automatic process and did not show significant interference. However, reading the word required selective attention and showed interference effect only when the incongruent conditions were infrequent. In other words, response latencies were smaller for incongruent trials when they were more frequent. They observed that the cross-over in average trial response latency happened at approximately 40:60 congruent to incongruent trial ratio. That is, when the incongruent trials were more than 60% of the total trials in the task, the average response latency was higher in congruent trials. This is similar to what was observed in the experiment presented in this chapter with approximately 75% of the trials being incongruent.

Logan and Zbrodoff drew a few conclusions from their observations regarding the strategies used by subjects to perform the task. They interpret the observations as a result of a weighted combination of automatic processing and selective attention. The automatic processing of the stimulus is involuntary and not under the control of the subjects. The selective attention towards one of the two dimensions of the stimulus is a voluntary process that the subject can weigh differently based on the cues observed while performing the task. To minimize response latency, the weight assigned to the unreported dimension can be increased if it helps in making the decision. For example, when incongruent trials are more frequent, a word appearing below the fixation point is more likely to be "ABOVE" and vice-versa. So, the subject can increase the weight assigned to position of the word and select "ABOVE" more frequently when it appears below the fixation point.

The interpretations drawn by Logan and Zbrodof are complicated to adapt to a task where more combinations of stimuli are present. However, it is possible that in the computerized Stroop task presented in this chapter, subjects were able to choose "NO MATCH" faster by reading the word first and then making a decision if it matched the ink, it was written in. Also, because the incongruent trials were more frequent, the subjects were probably ready to respond "NO MATCH" by default. If a congruent trial was presented, they had to switch their default response and respond using the "MATCH" button. As mentioned before, this type of response was chosen to make the task easier for patients. However, if the subjects were required to respond to the colour of the ink by choosing one of the four options, they would be forced to pay attention to the colour and reading the words would not help much in making the decision. In that case, they would not have been able to use the strategy of reading the word first to facilitate their response latency.

Other papers have used Stroop tasks with varying percentages of incongruent trials and have always seen interference with conflicting stimuli trials, irrespective of their frequency (Lansbergen & Kenemans, 2008; Tillman & Wiens, 2011). All the papers reviewed in introduction of this chapter also reported increased latency in the incongruent trials. The Logan and Zbrodof study showed how increased frequency of incongruent trials in this experiment could have led to their smaller response latencies.

It is likely that the use of “MATCH”/“NO MATCH” response type further facilitated the subjects in responding faster to incongruent trials.

Two changes to the task can likely help in observing the expected Stroop effect. Firstly, the relative number of congruent trials should be kept equal or higher than incongruent trials. Secondly, subjects should be asked to respond to the colour of the ink by choosing one of the four colour options as opposed to responding if the trial is congruent (“MATCH”) or incongruent (“NO MATCH”). Though this would make the task harder for patients, it is more likely to produce the desired Stroop effect.

5.5.2 EEG RESPONSE

The grand averaged ERP analysis showed statistical differences between the congruent and incongruent trials on the midline electrodes for the control group (fig 5.5). Conducting the same analysis on each individual patient did not show statistical differences in most cases (fig 5.6, 5.7, and 5.8). This analysis demonstrated that neural time course in the patient group for both the congruent and incongruent trials was indistinguishable in most cases, thus likely leading to poorer task performance (even with task parameters modified to make the task easier). The lack of statistical difference between task conditions was also shown in the grand averaged ERPs of the two patient groups (figs 5.9, 5.10, 5.11). Visualizing the changes in EEG measures P300 peak amplitude and peak latency showed that though both the patient groups had difficulty in performing the tasks, the change in performance likely resulted from different neural mechanisms. The plot in figure 5.19 showed that the schizophrenia patients showed diminished activity on the parietal electrodes while the schizoaffective disorder patients showed a diminished activity on the frontal electrodes. This could be an indicator of schizophrenia patients having difficulty in motor response preparation, while schizoaffective disorder patients being unable to reliably process the interfering stimuli.

The ERSP response to the Stroop task conditions in healthy controls was shown in figure 5.12. In this figure we saw an early synchronisation of the delta/theta activity (frequencies below ~8Hz) followed by the desynchronisation of alpha/beta frequencies (8-24 Hz). These frequency changes were seen during both congruent and incongruent trials, with stronger synchronisation and desynchronisation in the former. It was also observed that the delta/theta synchronisation was stronger on the frontal electrode

while the alpha/beta desynchronisation was stronger on the vertex and parietal midline electrodes (Cz and Pz). These EEG oscillatory dynamics have been previously investigated in the context of Stroop task (Popov et al., 2018). The delta/theta synchronisation is associated with the frontal processing of the different types of stimuli, while the alpha/beta desynchronisation is associated with the motor response preparation and execution (Kilavik et al., 2013; Nakayashiki et al., 2014; Pfurtscheller & Lopes da Silva, 1999; Tan et al., 2013).

In the ERSP responses from patients, differences were found between the schizophrenia patients and schizoaffective disorder patients. In schizophrenia patients the delta/theta frequencies showed a weak synchronisation while the alpha/beta frequencies showed a strong desynchronisation. In schizoaffective disorder patients the delta/theta band synchronisation was negligible, and the alpha/beta desynchronisation was stronger than the schizophrenia patient group. As the delta/theta band activity represents frontal processing, the absence of activity in this band in schizoaffective disorder patients further confirmed the observations from figure 5.19. The previously mentioned Popov *et. al.* study (Popov et al., 2018) did not provide the specific diagnosis of their patient group. However, in their patient group, they reported a weaker theta synchronisation and a weaker desynchronisation of the alpha/beta band. Though we saw a similar effect with the theta band from patients in this study, we did not see the weaker desynchronisation of alpha/beta activity. Another behavioural study by Hepp *et. al.* had seen difference in interference caused due to incongruent trials between recurrent schizophrenia patients and schizoaffective psychosis patients (Hepp et al., 1996). As the results in this chapter also point towards differences between the two patient groups, a further investigation of various pathologies within the schizophrenia spectrum of diseases is warranted.

5.6 Conclusion

The Stroop experiment in this study had two major limitations. Firstly the task design did not elicit the traditionally observed Stroop effect, but an opposite effect where response to congruent stimulus was longer in latency than the response to incongruent stimulus. In section 5.5.1 we discussed the causes of this phenomenon and described how the task design could be modified to elicit a traditional response.

Secondly, due to the difficulty faced by the first patient to perform the task, the task parameters were altered to make the task easier for that group. Due to the differences in task parameters between the control and patient groups we could not make direct comparisons between them. Despite these drawbacks we analysed the behaviour and EEG response to the task and made statistical comparisons between responses to congruent and incongruent conditions within each subject group. Also, comparisons of patients diagnosed with schizophrenia and schizoaffective disorder showed differences between in both ERP and ERSP responses. For this reason we believe that the measures from a Stroop task with appropriate task parameters have the potential in probing cognitive deficits in schizophrenia spectrum of disorder patients and should be included in a protocol that targets different aspects of the disease pathology.

CHAPTER 6. STANDARDIZED COGNITIVE TESTING WITH CANTAB

6.1 Introduction

Cambridge Neuropsychological Test Automated Battery (CANTAB) was developed in the 1980s (Barnett et al., 2010, 2015; Levaux et al., 2007). It was created with the rationale of incorporating technological innovations (in the 1980s) in computerized control and touch sensitive displays, into experimental neuropsychology. Use of these technologies had found success in animal studies and provided a platform to translate them into human testing (Barnett et al., 2015). In the last 30 years, CANTAB has gained tremendous popularity and has been used in hundreds of studies worldwide. The CANTAB bibliography currently lists over 2200 articles with studies in several different types of disorders like psychotic, personality, cardiovascular, cancer, genetic, neurological, etc (*CANTAB Bibliography*, 2021).

CANTAB is comprised of several different tests for memory, attention, and executive function. The initial development of these tests was driven by animal studies (non-human primates) of cognitive dysfunction introduced through chemical or anatomical lesions to the brain (Barnett et al., 2015; Levaux et al., 2007; Strauss et al., 2006). Researchers were interested in carrying out similar tests in humans with different types of disabilities, while keeping it readily accessible and easy to use. However, as advances were made is neurophysiological testing methods, newer tests were also incorporated (Levaux et al., 2007). Currently, CANTAB provides with several different test batteries which combine a unique set of cognitive tests specific for a disorder. It also provides the flexibility of creating test batteries that can be used to assess several subjects, which is a common practice in research community. The non-verbal nature of most of the tests also introduces an ease of use by overcoming the barriers of language and culture (Barnett et al., 2010; Green et al., 2019).

In the recent years, CANTAB has moved out of research environment and has been made available in clinical setting. Adapting to the technological advances and ease of access to tablets, CANTAB has been developed into a mobile tablet version that can easily be used by primary care providers with basic knowledge of psychological testing. The tests have been standardized across large population of patients and healthy individuals (Strauss et al., 2006). The interface also provides scores for different test outcome relative to the normative data collected from healthy population. This feature is extremely helpful for the clinicians. The relation to

normative data provides an instant insight into subject's current psychological state without the need of, or bias due to, their medical history.

Along with all the benefits, CANTAB also comes with some weaknesses. Most of the tasks can only be used to test visuo-spatial aspects of cognition. This hinders the test of verbal functioning of subjects which is an important aspect of patients with schizophrenia and similar pathologies. Verbal interactions are a big part of anyone's daily life, and patients with schizophrenia like disorders suffer from a decreased quality of social life. However, the battery has recently added two tests for verbal memory: Graded Naming Test (GNT) and Verbal Recognition Memory (VRM). There is also a lack of comparison available with standard neurological tests, and some studies have shown a marginal correlation between CANTAB tests and traditional neurophysiological measures. The test-retest reliability of CANTAB has also been under question and needs further testing (Levaux et al., 2007; Smith et al., 2013).

Despite the drawbacks mentioned above, CANTAB remains a strong cognitive testing platform. The aim of the research presented in this thesis was to create hybrid protocol that uses different modalities of testing. Schizophrenia is a complex disorder and manifests in several different ways in individuals. With the use of a set of easily accessible tests (administered through CANTAB), in conjunction with other experiments collecting neurophysiological response to specifically selected tasks, the severity of subject's disorder can be quantified by measuring statistical difference between patient's outcome and the healthy control subjects. This chapter describes the CANTAB tests that were used in the protocol to compare healthy control subjects and schizophrenia spectrum disorder patients. As expected with schizophrenia patients, a general decrease in performance was observed across all patients (Rupchev et al., 2017).

6.2 Task Descriptions

All the subjects performed five standardized cognitive tests. This section provides the detailed description of each task and the rationale behind using them in this experiment. A brief overview of these tests is provided in table 6.1, with the details of each test described below.

Table 6.1 Brief overview of CANTAB Tasks.

Test	Purpose	Task description	Time (min)
Motor Screening (**MOT**)	Visuo-motor coordination and comprehension difficulties	Touch the centres of crosses appearing at random locations on the screen	2
Reaction Time **(RTI)**	Speed of response and movement	Simple and 5-choice variant; touch the circle where yellow dot appeared	5
Paired Associate Learning **(PAL)**	Episodic visuo-spatial memory, learning and association abilities	Associate visual patterns with locations on the screen	8
Spatial Working Memory **(SWM)**	Recognition memory for spatial locations	Self-ordered search task for tokens without returning to token locations	4
Verbal Recognition Memory **(VRM)**	Immediate free recall, and recognition memory for verbal information	Verbal list learning; free recall of presented list and recognition of presented words among distractors	10

6.2.1 MOTOR SCREENING TEST (MOT)

The Motor Screening Test was the first CANTAB test performed by each subject. This test was useful in getting the participants familiarized with the computerized testing interface. It also provided a baseline measure of sensorimotor deficits and comprehension ability of the subject that could limit the outcomes of other tests.

The task consisted of coloured crosses appearing at random locations on the screen; as shown in figure 6.1. The participants were instructed to touch the centre of the cross with the forefinger of their dominant hand. Thirteen trials were presented to each subject with the last ten being assessed. The outcome of the task measured the speed of response and accuracy of touching the cross. The task took 2 minutes.

Figure 6.1 The Motor Screening task (MOT).

6.2.2 REACTION TIME (RTI)

The Reaction Time task (RTI) was first introduced by Sahakian et. al. in 1993 (Sahakian et al., 1993). This task was designed to the asses the speed of response to a visual stimulus which can either be predictable or unpredictable. In the latter case, the task also provides a measure of processing speed and attention of the participant (Barnett et al., 2010).

In this task, the subjects had to press and hold a button at the bottom of the screen to begin each trial. White circles were presented on the top of the screen and a yellow dot appeared in centre of one of the circles after a random pre-stimulus duration. The subjects were then told to touch the circle where the dot appeared as quickly as possible. Subjects were instructed to use the same hand to press the bottom button and to touch the screen. In the predictable or the simple RTI variant of the task, only one

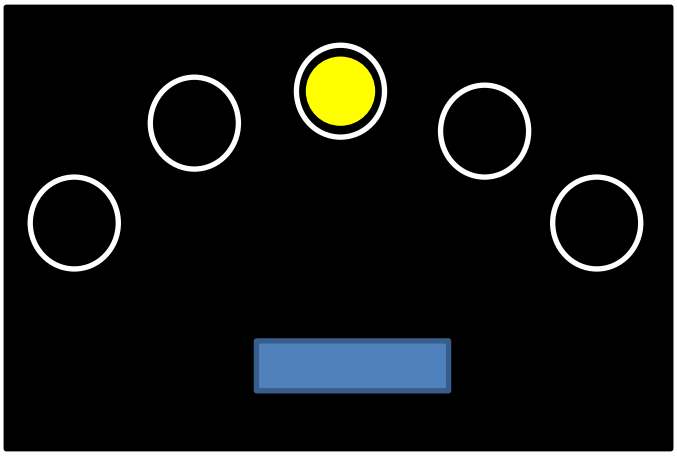


Figure 6.2 Five-choice stage of the Reaction Time task.

white circle was displayed. In the unpredictable or 5-choice variant of the task (fig 6.2) five circles were displayed, and the subject had to touch the circle where the dot appeared to get the trial correct.

Each subject started with 10 non-assessed trials of simple RTI to familiarize and give feedback. If 9 or more out of these 10 trials were incorrect, this stage was repeated. Following this, the subject performed 30 assessed trials of simple RTI. The subject then performed 10 non-assessed trials, this time of 5-choice RTI, with the same criterion of stage being repeated if 9 or more out of 10 trials were incorrect. A set of 30 assessed 5-choice RTI trials was then performed. No feedback was provided during the assessed trials. The whole task took about 5 minutes to complete. The outcomes produced quantified the subject's accuracy, reaction time, and movement time in both the simple and 5-choice variants of the task.

6.2.3 PAIRED ASSOCIATES LEARNING (PAL)

The Paired Associates Learning (PAL) task for CANTAB was first designed and presented by Sahakian et. al. in 1988 (Sahakian et al., 1988). This task tests the participant's short term visuo-spatial memory, visual association, and learning abilities (Barnett et al., 2010).

The task consisted of a few filled white boxes (squares) displayed around the centre of the screen. Each box was "opened" (unfilled) for approximately 3 seconds in a random order and was either empty or consisted of a visual pattern (fig 6.3). The patterns were designed in a way that they could not be verbalized with the location on

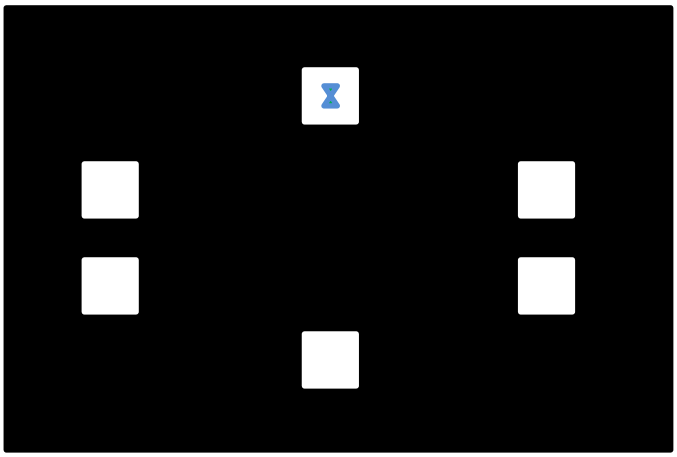


Figure 6.3 Paired Associates Learning (PAL) task showing a pattern in an open box.

the screen. After all the boxes were opened, each of the patterns present in the squares were presented randomly (with respect to the order presented in the boxes) in the centre of the screen. The subject was asked to choose the box that the pattern was previously observed in. If the subject was unable to make the correct selections for all the patterns, the boxes were opened again in random order and the whole trial was repeated with all the patterns presented randomly at the centre. The trial ended when all the patterns were correctly paired with their respective boxes or if the maximum number of attempts was reached without the subject correctly pairing the patterns and square locations. After the first sequence of "opening" the boxes to show the patterns in them, the boxes were opened only for approximately 2 seconds each.

To familiarize with the task, each subject started with a practice trial with 6 boxes and 2 patterns. The difficulty of the task was varied by the number of boxes and patterns presented. After the practice trial the subjects started with 6 boxes and 2 patterns and went on to 3, 4, 5, 6, and 8 patterns. Eight boxes were used in the 8-pattern stage. The patterns were not repeated between stages. At each stage, the subject had a maximum of 6 attempts to choose all the pattern-square pairs correctly. The whole task took about 8 minutes. The outcome from this task quantified the total errors and errors made in the 6-pattern stage.

6.2.4 SPATIAL WORKING MEMORY (SWM)

The Spatial Working Memory Task (SWM) was first presented by Owen et. al. in 1990 (A. M. Owen et al., 1990). This task was designed to test the ability of the subject to retain spatial information and manipulate remembered items in the working memory.

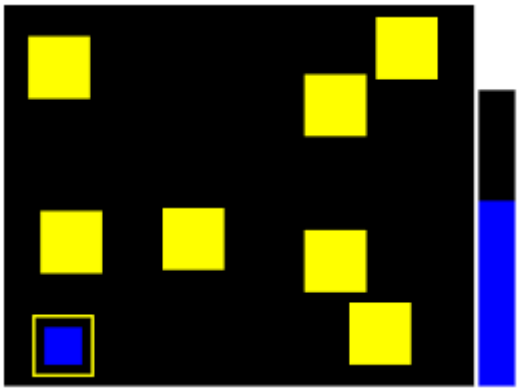


Figure 6.4 Spatial Working Memory task (SWM) screen, 8 boxes.

The objective of this task was to “search” through a number of coloured boxes to find a “blue token”. The goal of the task was to find all the tokens and use them to fill up the column on the left (fig 6.4). The test began with a few boxes randomly displayed on the screen. The number of boxes was equal to the total number of tokens needed to fill the column. At any given time, only one of the boxes contained the token. The subjects were instructed to touch each box in any sequence to “open” and find the token. Once a token was found, the participant was asked to move it to the column. At this point the next token would be hidden and must be found to proceed. The key instruction given to the participants was that same box would never be used to hide the token more than once. Once all the tokens were found and the column was filled, the task ended.

In this task, the difficulty of the task was varied by using 4, 6, and 8 number of boxes/tokens (fig 6.4). For each difficulty level, 2 trials were conducted. The subjects were familiarised with the task using a 3-box problem for 3 trials. The whole task took about 4-5 minutes. Two scores were computed to assess the performance of the participants in the task. The first score was the between search error which was the number of times the subject looked for the token in the same box. The other score was the measure of strategy. The efficient strategy to perform this task was to use the same search sequence to find all the tokens. This efficiency can be approximated by counting the number of times the subject started a search sequence with a new box. A higher strategy score, that is, many searches beginning with a different box, implies a poorer use of strategy and vice-versa. (A. M. Owen et al., 1990; Robbins et al., 1998). This score was computed only for the 6 and 8 shape stage.

6.2.5 VERBAL RECOGNITION MEMORY (VRM)

The verbal Recognition Memory task (VRM) was designed to assess the subject’s memory of verbal information. The assessment was performed under two conditions: free recall and recognition in a two-alternative forced choice paradigm.

The task began with participants being shown a list of 12 words on the screen. The words appeared one at a time for 3 seconds, with an interval of 2 second in between. The subjects were instructed to say the word out loudly and remember it, without any need to remember the sequence of presentation. Once the subject had seen all the words, the screen was turned towards the experimenter and the subjects were

asked to recall as many words as possible while the experimenter recorded them. Following this free recall phase, the subjects were randomly shown the words again, one at a time, along with an equal number of distractor words. The subject was asked to make a forced choice if they had seen the word on the screen before or not. The whole task took about 10 mins. The performance of the participant was assessed based on number of words recalled and the number of correct choices made in the recognition phase.

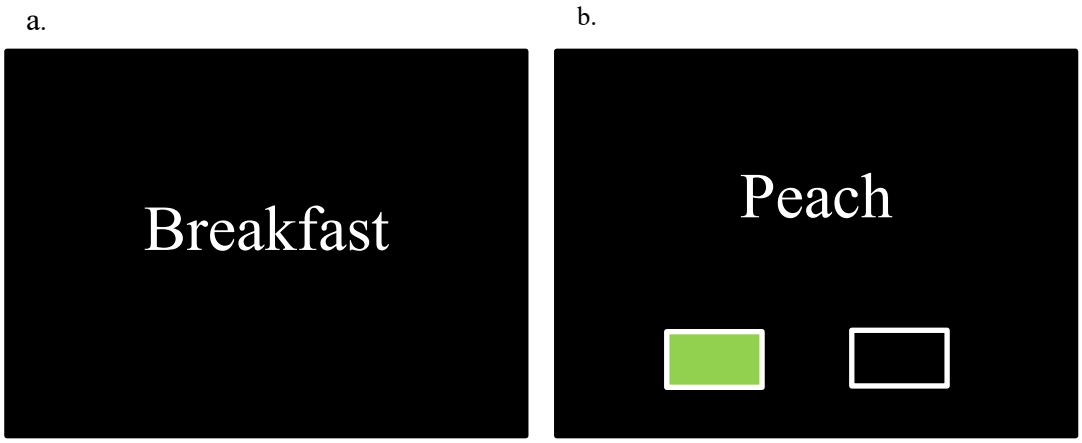


Figure 6.5 Verbal Recognition Memory task (VRM). a. Presentation Phase, b. Recognition Phase.

6.3 Results and Comparisons

The main goal of using CANTAB in this study was to quantify the various cognitive deficits present in patients in the schizophrenia spectrum. As described above, five different cognitive tests were administered to 17 control subjects and 6 recruited patients. The CANTAB interface computed some basic statistics for each test and produced a comprehensive report with set of outcomes for every subject. Table 6.2 shows the average outcomes for healthy control subject and patient groups. Table 6.3 lists different task outcomes for all the 6 patients, individually. It also presents the demographic information of the patients, like their age, gender, PANSS (Kay et al., 1987), and MADRS (Montgomery & Asberg, 1979) scores on the day of CANTAB experiments. The coloured dots at the top of the table show the colours assigned to each patient. These colours have been used throughout this section to show differences within the patient group. In the following subsections, all the outcomes in the table are summarised and a comparison with the control group is presented.

Table 6.2 Average group performances in CANTAB tasks.

Groups	Healthy Controls	All Patients
Motor Screening task:		
Median latency (ms): mean (std)	570.41 (93.04)	989.17 (353.32)
Mean error: mean (std)	9.23 (1.65)	11.06 (3.27)
Reaction Time Task Simple:		
Accuracy: median (std)	30 (2.12)	28 (3.06)
Reaction time (ms): mean (std)	289.50 (26.09)	423.43 (143.83)
Movement time (ms): mean (std)	168.43 (38.06)	342.96 (113.63)
Five-Choice:		
Accuracy: median (std)	30 (1.15)	29 (2.65)
Reaction time (ms): mean (std)	305.69 (23.39)	392.37 (83.50)
Movement time (ms): mean (std)	184.94 (41.05)	339.98 (110.25)
Paired Associates Learning:		
Total adjusted errors: median (std)	6 (7.63)	71.50 (44.83)
Total adjusted errors: median (std) (6 shapes)	1 (2.41)	22.50 (10.39)
Last Stage Reached: median (std) (number of shapes)	8 (0)	6.50 (2.04)
Spatial Working Memory:		
Between errors: median (std)	8 (8.75)	28 (14.40)
Strategy: median (std)	16 (4.20)	20 (4.79)
Verbal Recognition Memory:		
Immediate free recall correct: median (std)	10 (1.80)	4 (2.40)
Immediate free recall novel: median (std)	0 (0.56)	0 (0.84)
Immediate recognition correct: median (std)	24 (0.62)	20.50 (1.79)
Immediate recognition false positives: median (std)	0 (0.56)	1 (1.64)

Table 6.3 Performance of patients in CANTAB tasks.

Patient	P1	P2	P3	P4	P5	P6
Colour						
Gender	M	M	M	M	M	M
Age	35	26	57	64	59	47
PANSS						
Positive	28	8	7	7	18	26
Negative	27	9	10	12	20	23
General	38	19	17	17	49	59
MADRS	3	4	2	0	22	26
Motor Screening task:						
Median latency (ms)	1,139.00	611.50	1,561.00	1,089.50	875.00	659.00
Mean error	6.92	10.82	8.09	15.1	11.04	14.39
Reaction Time Task Simple:						
Accuracy	29	30	27	24	23	30
Reaction time: (ms) mean (std)	339.93 (94.27)	299.50 (32.54)	672.33 (311.64)	519.50 (181.48)	339.30 (61.77)	370.03 (85.30)
Movement time: (ms) mean (std)	275.76 (39.25)	203.53 (16.22)	517.48 (65.95)	372.58 (75.82)	412.26 (51.45)	276.17 (58.51)
Five-Choice:						
Accuracy	29	30	23	30	29	29
Reaction time: (ms) mean (std)	334.48 (26.65)	352.10 (37.41)	543.74 (138.67)	437.93 (92.57)	340 (48.17)	345.97 (43.1)
Movement time: (ms) mean (std)	280.07 (44.39)	203.90 (34.57)	418.91 (79.80)	391.13 (58.48)	490.52 (79.04)	255.38 (45.02)
Paired Associates Learning:						
Total adjusted errors	43	21	116	123	100	36
Total adjusted errors (6 shapes)	15	15	30	30	30	6
Last Stage Reached (number of shapes)	8	8	4	4	5	8

Spatial Working Memory:						
Between errors	10	0	31	27	38	29
Strategy	15	10	23	21	20	20
Verbal Recognition Memory:						
Immediate Free recall correct	6	9	3	3	3	5
Immediate Free recall novel	0	0	1	0	2	0
Immediate Recognition correct	20	24	22	19	20	21
Immediate Recognition false positives	3	0	1	1	4	0

6.3.1 MOTOR SCREENING TASK

Motor screening task (MOT) has been used in several studies to get the subjects acquainted with the interface. This task is also helpful in assessing if a subject can comprehend and follow instructions. It provides a baseline expectation of how the subject is going to perform in the other tasks.

Figure 6.6 compares the performance of control subjects with patients in MOT. Each green dot in the figures represents a single healthy subject; with them overlapping on each other when the values are same or close. The red lines represent the trend by linking the medians of the data from each group. The asterisks on top of the line mark the significance level of the two-sample t-test with one asterisk representing a p-value of less than 0.05 and two representing a p-value of less than 0.001. Similar approach has been used throughout this section.

In 6.6a., latency is defined by the time take to reach the cross after it was displayed on the screen. We see that patients are significantly slower than control subjects when reaching the coloured crosses on the screen. However, we also see from figure 6.6b that errors between controls and patients do not differ significantly (0.088). The error was calculated as the distance in pixel units between the centre of the cross and the point of touch. The lack of significant increase in error in patients, is an

indication that they are able to understand the basics of using the interface and are able to follow instructions.

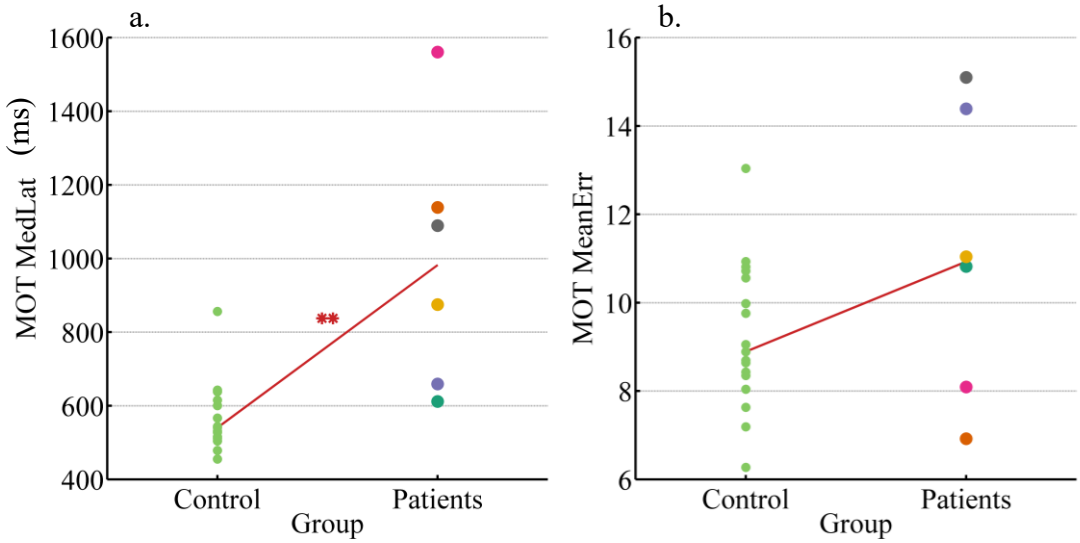


Figure 6.6 Comparison of performance between healthy controls and patients in Motor Screening Task (MOT). a. Median Latency (ms) in MOT, patients show a significant increase (two-sample t-test, $p<.001$) in latency to touch to the cross. b. Error in MOT, patients made more errors compared to the control group but, the difference is not significant. Non-zero y-axes are used for better visualization of data.

6.3.2 REACTION TIME TASK

The reaction time task (RTI) was designed to quantify the visual processing speed and motor function of the subjects. The task had two variants: simple RTI and 5-choice RTI. The outcomes of the task were grouped by type of subject; control or patient and a comparison was performed. For both the variants three different measures were computed and are presented in the figures below.

Figure 6.7 compares the accuracy between controls and patients in both the variants of the task. The accuracy score is the number of correct responses by each subject. It is observed that the patient group does not significantly differ from the control group in both the simple ($p=0.222$) and 5-choice RTI ($p=0.259$). This is an indicator of intact visual processing and ability to integrate information to accurately choose the correct response. In the case of 5-choice RTI, the accuracy also demonstrates the attention of the subject as it does not only involve reacting to the presentation of the visual stimulus, but also attending to its location.

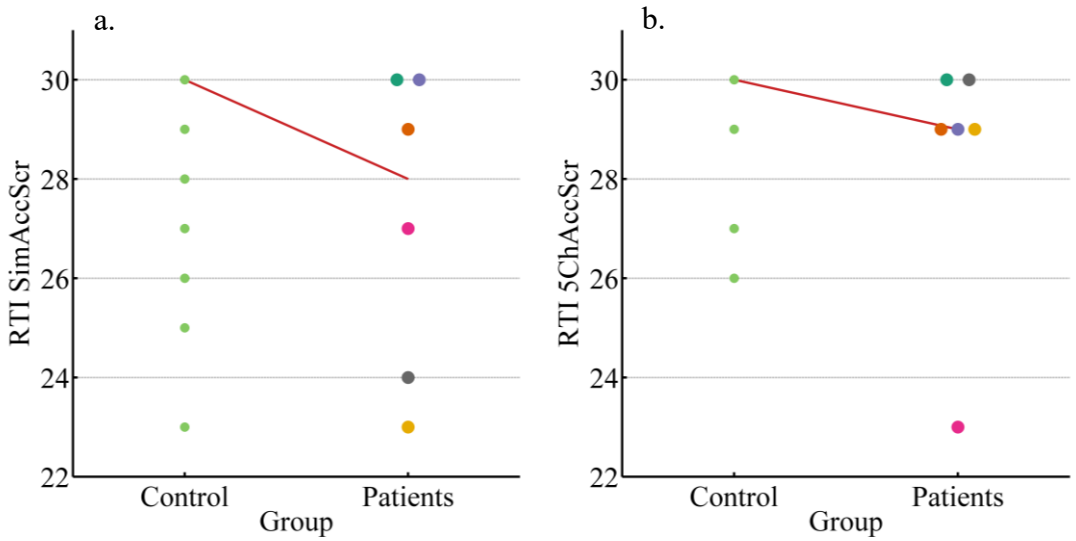


Figure 6.7 Comparison of accuracy between healthy controls and patients in Reaction Time Task (RTI). a. Accuracy in Simple RTI. b. Accuracy in 5-Choice RTI. Patients show a small decrease in accuracy in both the variants of the task, which is not statistically significant. Non-zero y-axes are used for better visualization of data.

The other measures of performance in RTI are the reaction time and movement time. Reaction time is calculated as the mean time taken to release the button after the stimulus is presented. Movement time is the mean time taken to move from the button

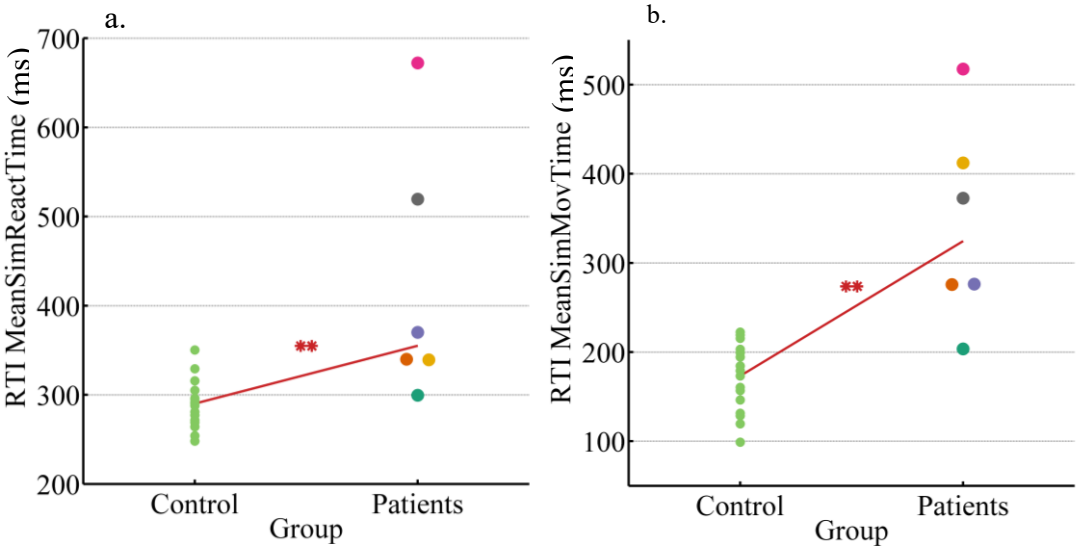


Figure 6.8 Comparison of performance between healthy controls and patients in Simple Reaction Time Task (RTI). a. Simple Reaction time (ms) in RTI, patients react significantly slower (two-sample t-test, $p<.001$) than control subjects. b. Simple Movement Time (ms), patients are further slower to move when compared to the control group, with higher level of significance (two-sample t-test, $p<0.0001$). Non-zero y-axes are used for better visualization of data.

to the location where the stimulus is presented. Figures 6.8 and 6.9 present these two outcomes for simple and 5-choice RTI, respectively.

From the results observed in MOT, it is evident that patients are much slower in moving to the target and their latency is significantly different from the control subjects. Similar outcome is observed in the movement times in both the simple (fig 6.8b.) and 5-choice RTI (fig 6.9b.).

The reaction times in the two tasks are shown in figures 6.8a and 6.9a. In this instance, we again notice a significant increase in reaction times of patients when compared to control subjects. This reaction time entails the time taken by the subject to integrate the visual information of stimulus being presented and then making a decision to execute an action. The slowing of response in patients shows that this integration process of visual processing to motor reaction is diminished in the group. This result when combined with the results of figure 6.7, portrays that the patients are trading speed for accuracy. That is, to obtain the same level of accuracy, patients took much longer to make a decision.

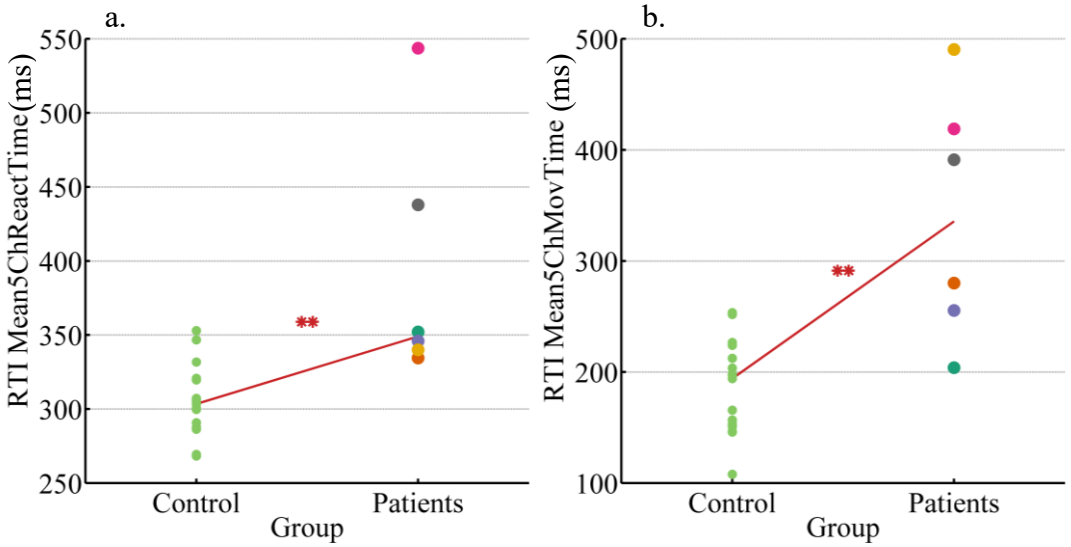


Figure 6.9 Comparison of performance between healthy controls and patients in 5-Choice Reaction Time Task (RTI). a. 5-Choice Reaction time (ms) in RTI, patients react significantly slower (two-sample t-test, $p<.001$) than control subjects. b. 5-Choice Movement Time (ms), patients are further slower to move when compared to the control group, with higher level of significance (two-sample t-test, $p<0.0001$). Non-zero y-axes are used for better visualization of data.

6.3.3 PAIRED ASSOCIATES LEARNING TASK

The paired associates learning task (PAL) required the subjects to learn and maintain an association between visual patterns and their location. The performance in this task has been extensively studied in patients with different pathologies such as Alzheimer's disease, Parkinson's Disease (Sahakian et al., 1988; Swainson et al., 2001), and schizophrenia (Kéri et al., 2012). In these studies, the task performance has been shown to be a strong indicator of diminished functioning of hippocampal region of the medial temporal lobe.

The comparison of performance between the control and patients is carried out using two types of error metrics. The first metric calculated the total errors in the task. It is to be noted that not all subjects were able to finish or reach to all the levels of the task. This was due to termination caused by failure to complete any stage in the maximum number of allowed trials (6). An adjustment to the errors is performed for every stage that was not reached. The adjustment error is calculated using the formula:

$$Err_{adj} = (n_{patterns} - n_{patterns}/n_{boxes}) * n_{\max\ \_trials} \quad \textbf{(6.1)}$$

The above equation states that for any stage, the adjusted error (Err_{adj}) is equal to the maximum number of allowed trials ($n_{\max\ \_trials}$), multiplied by the difference between the number of patterns ($n_{patterns}$) in the stage and the relative number of patterns to the number of boxes (n_{boxes}). For example, the adjusted error of not reaching a stage with 5 patterns, 6 boxes and, 6 maximum trials would be (5 – 5/6) *6 = 25. This number is less than the total number of errors possible in this stage (5*6 = 30). So, the total adjusted error metric is equal to the total number of errors in the stages that the subject reached added to the adjusted error of all the stages the subject did not participate in. This metric is presented in figure 6.10a. We can see that there is a highly significant difference in the performance of the control and patients. Though there are a few control subjects that are unable to complete the last stage with 8 patterns, all the controls did reach the final stage. This is not the case with all the patients and therefore we see high numbers in that column.

The second metric calculated is the adjusted error in stage with 6 shapes and is shown in figure 6.10b. In this figure, we again see a highly significant difference between control and patients. All the control subjects are able to reach and successfully complete this stage. On the other hand, 3 out of the 6 patients are unable to complete this stage and had the adjusted error of 30 (= (6- 6/6) *6).

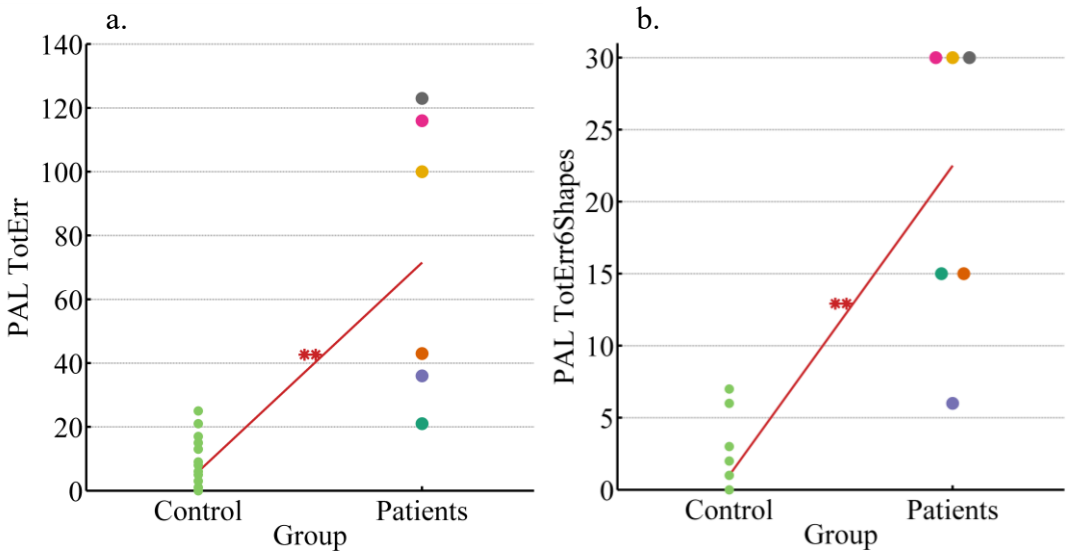


Figure 6.10 Comparison of performance between healthy controls and patients in Paired Associates Learning Task (PAL). a. Total number of adjusted errors in PAL task, patients perform significantly worse (two-sample t-test, p<1e-5) than control subjects. b. Adjusted errors in the 6-shape stage of PAL task, patients again perform significantly worse (two-sample t-test, p<1e-6) than controls with some failing to reach this stage.

6.3.4 SPATIAL WORKING MEMORY TASK

The spatial working memory task was first introduced and studied in patients with frontal lobe lesions (A. M. Owen et al., 1990). Since then it has been used in several studies with pathologies that cause dysfunction of the frontal lobe (A. M. Owen et al., 1996; Robbins et al., 1998). It has also been verified as a marker of risk of psychosis (Wood et al., 2003).

To compare the performance of control and patient subjects in the SWM task, two different scores are used (fig 6.11). The “between error” scores are calculated as the number of times the subject looked for a token in the same box. Figure 6.11a. shows that patients showed a significant increase in the “between error” when compared to control subjects (p=0.013). It should also be noted that the control

subjects with the "between error" score greater than 25 are the oldest subjects in the control group (ages 48 and 55), indicating the age dependence of SWM task performance.

The second score used to compare the performance is the strategy score of the subjects, with higher number representing poorer use of strategy. The minimum strategy in this task is 1 for each trial in stages with 6 and 8 boxes, which is 4. The maximum strategy score is 1 for each search which adds up to 28. From figure 6.11b. we can see that patients are significantly poorer in performing the SWM task when compared to the controls; with 4 out of 6 subjects with strategy scores of greater than or equal to 20. The gap seen in the control column on figure 6. 11b. divides the group almost equally in half with a significant correlation with age (Pearson's r=0.59, p=0.01) (fig 6.14a).

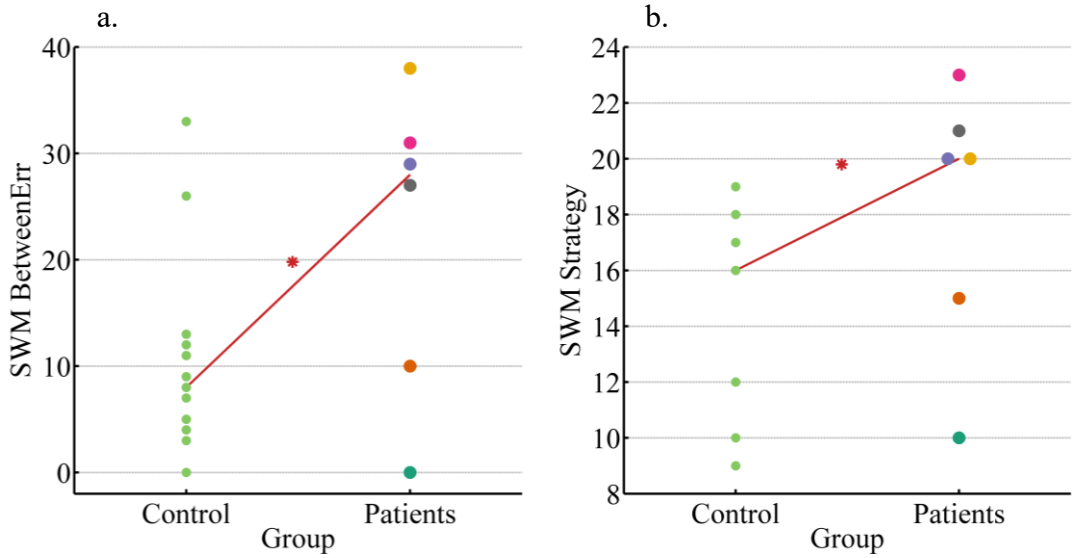


Figure 6.11 Comparison of performance between healthy controls and patients in Spatial Working Memory Task (SWM). a. Number of between errors in SWM task, typically, patients make more errors with the distributions being different with low significance (two-sample t-test, p=0.013). b. Strategy score for SWM task (lower scores are better), patients are marginally worse (two-sample t-test, p=0.047) than control subjects. Non-zero y-axis is used for better visualization of data.

6.3.5 VERBAL RECOGNITION MEMORY

The verbal recognition memory task has been a relatively new addition to CANTAB as one of the two tasks that are not language independent. Patients with schizophrenia have been shown to have extensive verbal memory deficits

(Chemerinski & Siever, 2010) and this test was used to quantify that cognitive impairment.

In the VRM task, the subject performance is tested in two phases after a list of 12 words is presented to them, one word at a time. The first phase is of free recall immediately after the list presentation. The performance here is measured using the total number of words recalled by the subjects. Figure 6.12a. shows that patients performed significantly worse than the control subjects. The CANTAB interface also accounted for any novel words that the subjects imagined having seen in the presented list. In this case (fig 6.12b) the control subjects and patients showed no significant differences (p=0.392).

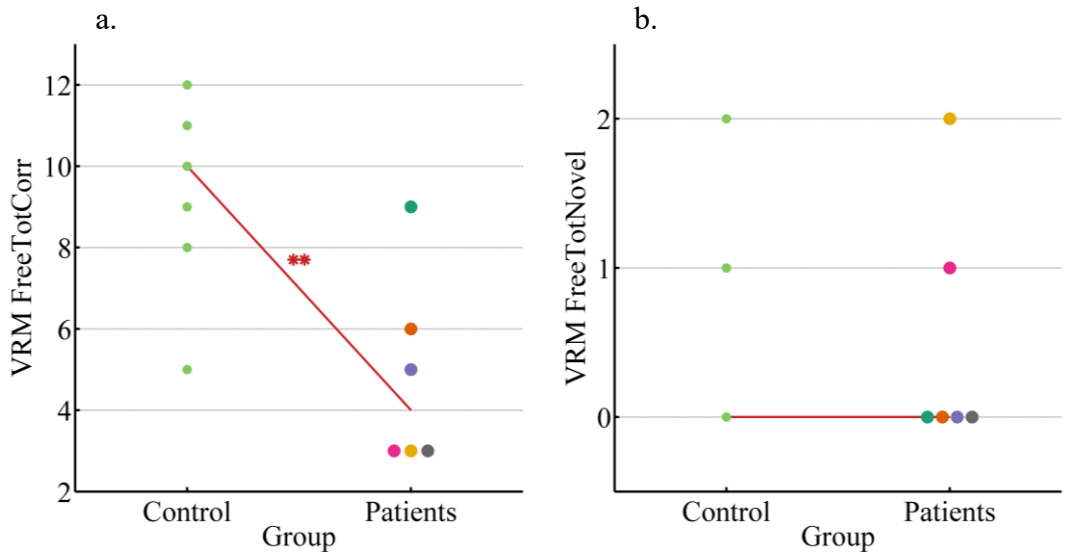


Figure 6.12 Immediate free recall of words in healthy controls and patients in Verbal Recognition Memory Task (VRM). a. Number of words recalled in VRM task after list presentation, compared to control subjects, patients are able to remember significantly less (two-sample t-test, p<1e-4) number of words. Non-zero y-axis is used for better visualization of data. b. Number of novel words recalled, very few subjects recalled words that are not shown in the initial list. No difference is observed between control subjects and patients.

After the free recall phase subjects are tested under an immediate recognition phase shown in figure 6.13. In this phase, subjects had to correctly recognise the presented words amongst an equal number of distractors. Figure 6.13a. compares the total number of correct choices made by controls and patient group. With 12 words presented earlier and equal number of distractors, the maximum number of correct choices are 24. Patients are observed to perform significantly worse with most control

subjects getting a perfect score. The number of false positives are calculated as the number of words that the subject reported to have seen but were not a part of the original list. It is observed that patients made significantly greater number of false positive choices.

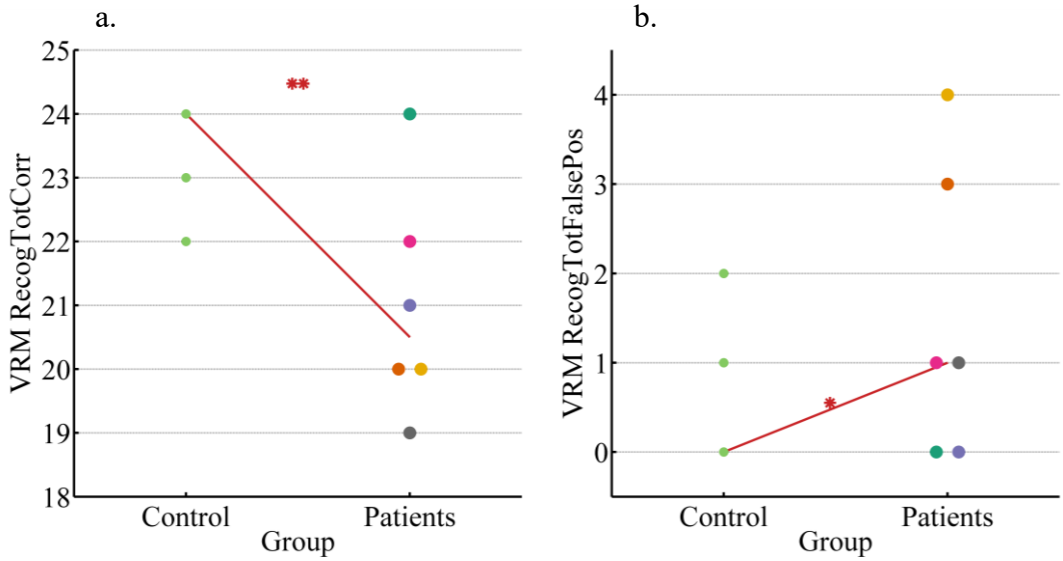


Figure 6.13 Immediate recognition of words in healthy controls and patients in Verbal Recognition Memory Task (VRM). a. Number of words correctly recognised to be seen or unseen, compared to control subjects, patients classified fewer words correctly but, the small difference is significant (two-sample t-test, p<1e-4. b. Number of words that are classified as seen but were not present in the original list, patients are marginally worse (two-sample t-test, p=0.01) than control subjects. Non-zero y-axis is used for better visualization of data.

6.3.6 INTER-TASK CORRELATIONS

After observing the outcomes of individual tasks, relationship between task performance measurements was analysed for both control subjects and patients. Performance of subjects across and within tasks were correlated using Pearson's correlation. Figure 6.14 shows the significant correlations for control subjects (a.) and patients (b.). In the case of control subjects, we see significant correlations between measures that represent similar cognitive features. For example, we see correlations between simple and 5-choice accuracies, reaction times, and movement times. This spans across tasks as well in correlations between RTI movement times and MOT latencies. The correlation patterns seen in patients are more complex. It is interesting to note however, that the SWM measures are correlated with age of both controls and

patients. As mentioned earlier, the interpretation of SWM measures should therefore account for the age factor and treated with caution.

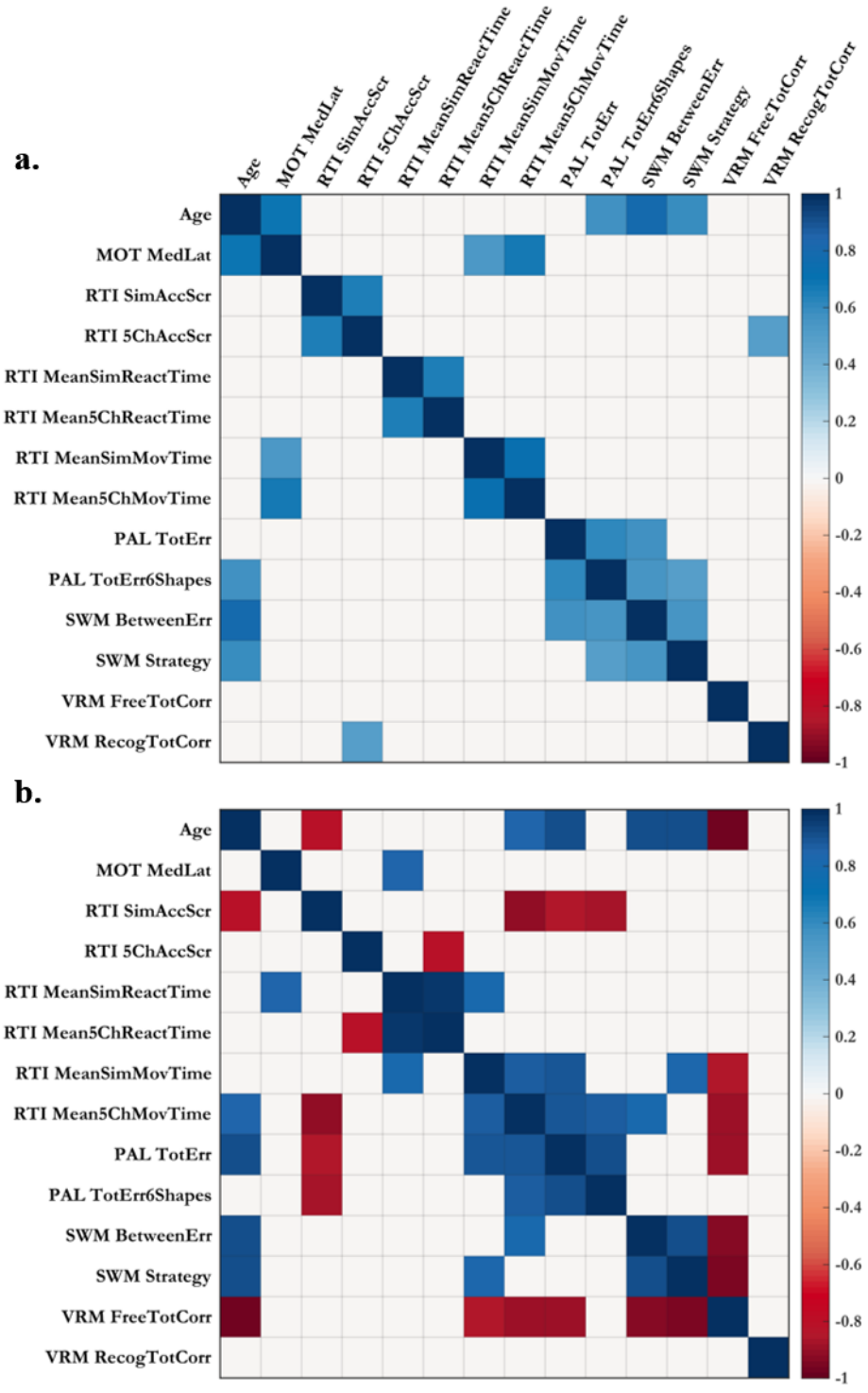


Figure 6.14 Inter-task correlations from CANTAB tasks. a. Control subjects b. Patients. Only significant correlation with $p<0.05$ are shown with others set equal to 0. Diagonal lines are equal to 1 as they represent correlation of the measure with itself. The square matrix is symmetric around the diagonal.

6.3.7 CORRELATIONS WITH DEMOGRAPHIC DATA

In table 6.3 the scores assigned to patients based on two different questionnaires used by clinical research team are provided. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) measure the symptom severity in schizophrenia patients. The second questionnaire is the Montgomery–Åsberg Depression Rating Scale (Montgomery & Asberg, 1979) used to rate the severity of the patient's depression. These scores were compared with a few outcomes of the different tasks that the patients performed.

Several different outcomes from all the CANTAB tasks were correlated with the three PANSS sub scores and MADRS score. Though the figure 6.15 shows a few higher absolute values of correlations, none of them are found to be significant. One of the reasons behind this could be the small number of patients in the study.

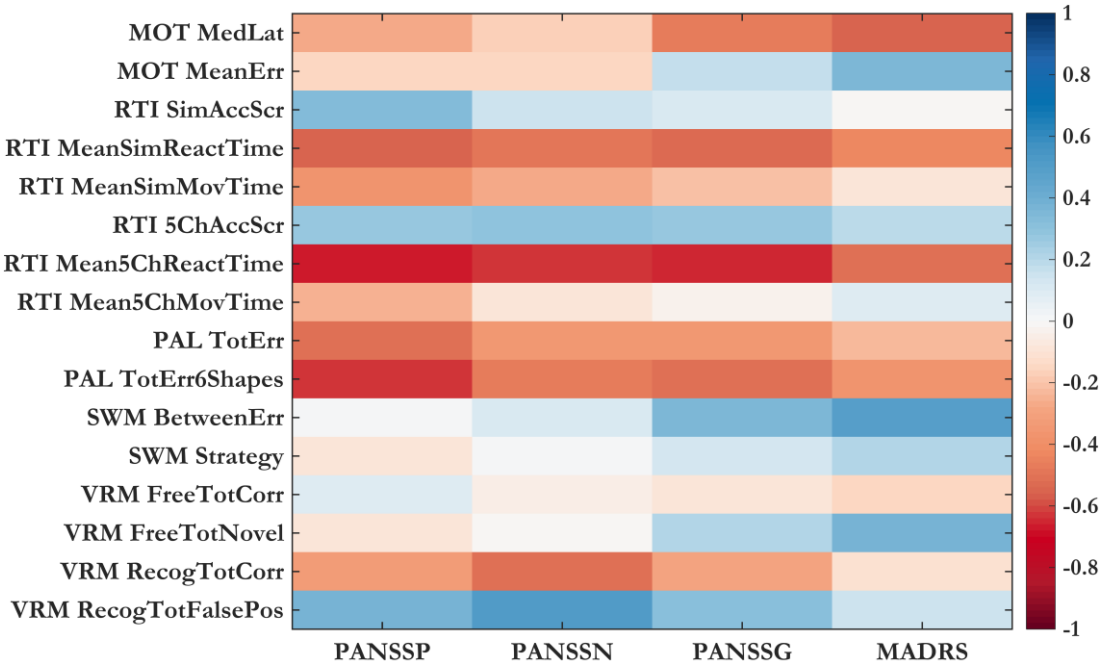


Figure 6.15 Correlations between CANTAB task outcome and PANSS and MADRS scores in patients.

6.4 Discussion and Conclusion

The previous section described performance of patients in individual tasks and compared it with the group of control subjects. A general observation from all the tasks was that subjects with schizophrenia spectrum disorders showed an overall deficit in cognitive processing. This confirmed the observations of several different studies with

similar disorder (Levaux et al., 2007). In this study, at least one of outcome measures that was calculated on any specific task, showed a significant difference between the patient and control groups. This was particularly encouraging to see with only a small set of 6 patients. This section discusses the implications of these findings on the neurophysiological deficits in our patient group.

The first two task administered to the subjects (MOT and RTI) tested their visual-motor coordination and processing. RTI specifically was designed to segregate the time taken to process the visual input (reaction time) and the time taken to move to the target (movement time). MOT has been primarily used as a familiarisation task by all the studies that make the use of the CANTAB interface. However, very few studies have reported the performance of subjects in this task (Saykin et al., 1994; Stip et al., 2005). A highly significant increase in patient group latency period in the MOT task was observed, while no difference was seen in the error score (fig 6.6). This implied that patients with schizophrenia spectrum disorders did not show any deficit in movement accuracy, however, they did show slowed motor response. A similar pattern was observed in the outcome of the RTI task too (figures 6.7 to 6.9). In addition, the response time outcome of RTI pointed at an additional deficit in the visual-motor processing in the patient group. This time signified that patients were trading speed for accuracy of performance. A similar pattern has been previously observed in Alzheimer's patients with and without medication. (Sahakian et al., 1993). It was also of significance that the RTI performance deficits were identified with only 6 patients.

The third cognitive task was the paired associates learning (PAL) task. This task was first used to study patients with Alzheimer's (AD) and Parkinson's disease (PD) (Sahakian et al., 1988). Since then, the task has been extensively used to study deficits in subjects with neurodegenerative disorders, different types of dementias, and in different age groups (Barnett et al., 2015; H Barnett et al., 2005). The test was also successfully used as marker to distinguish mild AD patients from other types of dementia and depression (Swainson et al., 2001).

The above studies have established the use of PAL in assessing cognitive deficits observed in different pathologies. However, PAL has also been used in animal and human studies to investigate the neurophysiological changes in the brain. To

accomplish the task successfully, the subject needed to associate the visual information of the pattern with the spatial information of its location. This association has long been shown to involve the entorhinal cortex and associated hippocampal regions of the brain. Thus, animal studies in primates and mice and human studies using imaging and subjects with brain lesions, have confirmed the importance of these brain areas in PAL performance. These studies have also shown an involvement of the frontal lobe (Barnett et al., 2015). Particularly in case of schizophrenia patients, Kéri et al. showed that loss in hippocampal volume led to poor performance in PAL task (Kéri et al., 2012). One of the important aspects of these findings was that PAL task could be used to quantify these deficits in subjects that had not shown any signs of psychosis or were in early stages of schizophrenia spectrum (Bartók et al., 2005). Therefore, as in the case of AD, PAL task performance is a strong candidate to be considered as an early marker of disease manifestation of schizophrenia.

The fourth task that the subjects performed was spatial working memory (SWM). This task demanded the subject to maintain an easily retrievable representation of the spatial information. This task was first designed and studied by Owen et. al. in subjects with frontal lobe lesions. This early study showed a significant deficit in these subjects when compared to controls. The performance was also seen to diverge further away as the difficulty of the task was increased (A. M. Owen et al., 1990). Wood and colleagues have used this task to show that working memory deficits were present in young individuals who were at a high risk of developing psychosis. A similar observation was presented in a Hungarian study with subjects presenting pre-psychotic symptoms (Bartók et al., 2005). In another recent study comparing young schizophrenia patients with age matched healthy individuals, significant deficit was observed in the SWM task (Rupchev et al., 2017). In experiments presented in this chapter, unlike other tasks, differences in SWM measures showed lower significance of $p<0.05$ instead of $p<0.001$. Also, only in SWM task, the performances were found to be significantly correlated to the age of both controls (Between errors: $r=0.79$, $p=1e-4$ and Strategy: $r=0.59$, $p=0.01$) and patients (Between errors: $r=0.89$, $p=0.01$ and Strategy: $r=0.92$, $p=0.009$). With these observations, and that of the recent studies, it is important to be cautious while interpreting the results from SWM. Though the task

does have a potential of being a cognitive marker for early diagnosis of schizophrenia, the age of the subject would need to be incorporated into the diagnostic process.

The final task performed by the subjects was the Verbal Recognition Memory task (VRM). It has been well established that schizophrenia patients suffer from verbal hallucinations and disorganized thoughts (American Psychiatric Association, 2013b). Therefore, it is not surprising that patients would have significant difficulty remembering a set of words while many other thoughts and voices are likely occluding their mind. However, there have not been many studies with VRM, as it is a more recent addition to the CANTAB battery. Also, as this task is language dependent, the performance of this task can be reliably used as a marker only when the task language matches the patient's native tongue. All the subjects in this chapter's study were selected with the requirement of English as their first language. Thus, the results obtained here were not confounded by the language factor. In both the free recall and recognition phase of the task, patients were significantly worse than the control subjects. In the free recall phase especially, 3 out of 6 patients recalled only 25% (3) of the words, while only 3 out of 17 control subjects performed worse than 75%.

In conclusion, these set of 5 tests along with the cognitive evaluations (PANSS and MADRS) presented in table 6.3, can quantitively define the cognitive deficits of any schizophrenia patient. It is also important to note that this set of tests were specifically selected with the intension of obtaining the most information in the least amount of time. To enable this, shortened versions of the tasks that incorporated a wide variety of difficulty levels were chosen. The measures thus obtained, encompass a wide range of each deficit that is expected to be observed in patients with a risk of psychosis. This, therefore, resulted in a comprehensive list that can serve as a measure of the subject's cognitive deficits, as shown in each column of table 6.3.

CHAPTER 7. EMOTION RECOGNITION TASK

7.1 Introduction

The complexity of the schizophrenia spectrum of disorders has been well demonstrated through the reviewed literature and findings of the previous chapters. The previous chapters have demonstrated that the recruited patients exhibit significant deficits in the automatic pre-attentive processing (Chapter 4), selective attention (Chapter 5), and in several cognitive mechanism like working memory, verbal memory, etc (Chapter 6). Patients within this spectrum of disorders also exhibit emotional deficits like blunt affect and anhedonia. This directly impacts their social well-being and quality of life.

In this chapter the emotional deficits in the patient group were studied with a facial emotion recognition task. The following section reviews the research literature on behavioural and neurophysiological aspects of this deficit. This is followed by the description of the experimental task, and the behavioural and neurophysiological observations made from it.

7.2 Facial Emotion Recognition

Facial expression of emotions is the primary form of non-verbal communication in everyday life. Paired along with affective prosody, a person can use facial expressions to convey different meanings to the recipient while speaking the same sequence of words (Becker & Rojas, 2020; Garrido-Vásquez et al., 2018; Meconi et al., 2018). This works both ways in a conversation, with the recipient conveying the understanding of the context with their facial expressions (Crivelli & Fridlund, 2018; Garrido-Vásquez et al., 2018). Recognizing, interpreting, and expressing emotions through facial movements, is therefore particularly important aspect of any social interaction. All these aspects have been studied in patients within the schizophrenia spectrum of disorders (American Psychiatric Association, 2013b; Bonfils et al., 2019; World Health Organization (WHO), 2022). This section focuses on facial expression recognition research that examines the behavioural responses and their neurophysiological basis.

7.2.1 BEHAVIOURAL FINDINGS

Early studies of facial expression recognition with schizophrenia patients primarily looked at the behavioural deficits. With the development of computerized

testing, and better understanding of schizophrenia patients exhibiting emotional deficits, study designs improved in the 1990's and larger curated groups were being recruited. These studies used standardized tasks, inclusion/exclusion criteria, etc. to better quantify the emotional deficits observed in schizophrenia patients (Kohler et al., 2010). Mandal and colleagues published one of the first review of experiments conducted in this field (Mandal et al., 1998). They reviewed studies that tested both the emotion recognition and expression abilities in schizophrenia patients. They observed a generalized deficit in facial emotion recognition in schizophrenia patients, with little to no evidence of differences between the subtypes. Some studies in the review found a global emotion recognition deficit, while other found specific decrement in the negative emotion detection with positive emotions being detected comparable to healthy control subjects. The review also pointed out that there were some variations in the type of stimulus across studies. One of the interesting observations was that schizophrenia patients were better able to recognize emotions with parts of face (upper, middle, lower) used as stimuli. This was probably one of the first indications that impairment in facial expression recognition was linked to face processing deficits in these patients.

Kohler and colleagues were interested in examining the effect of facial emotion intensity and studying the error patterns made by schizophrenia patients (Kohler et al., 2003). They used stimuli with neutral, happy, sad, angry, fear, and disgust emotions. These stimuli were previously recorded in a dataset by Gur and colleagues (Gur et al., 2002) where subjects exhibited all the facial emotions (except neutral) either with low or high intensity. Kohler and colleagues found that patients made higher errors in fear, disgust, and neutral recognition. High intensity emotions were recognized better but, the increase in intensity resulted in a smaller increase in percent correct responses in patients when compared to the control subjects. This difference between patients and control subjects was most pronounced in fearful emotions. The error pattern in neutral emotion recognition was also different in patients compared to that of control subjects. The pattern revealed that patients were more prone to perceive neutral emotions as disgust and fear, compared to control subjects that attributed neutral emotions as either happy or sad. The researchers also reported a significant correlation between

performance and negative symptoms score for flattening, alogia, avolition, and anhedonia, as assigned by the Scale for Assessment of Negative symptoms (SANS).

To study the link between emotion recognition and facial processing, Martin and colleagues (Martin et al., 2005) orthogonally varied the emotion and identity of the face stimulus in Stroop like task (Stroop, 1935). Participants were asked to press one button if the identity (or facial emotion) of the two presented stimuli was same and another button if it was different. In the identity comparison experiment, the emotions were either kept same or varied. In the emotion comparison experiment, the identity was kept same or varied. A similar study was conducted by Bediou and colleagues where they also reported emotion specific error (Bediou et al., 2005). Both these studies found a significant correlation between the performance on identity and emotion tasks. Bediou study reported significantly worse performance in patients compared to control subjects, while identifying sad and angry emotions but not happy, fear, and disgust. Martin and colleagues reported schizophrenia patients were impaired in recognizing both identity and emotion, with larger impairment in the later. When the identity was varied in the emotion task, some schizophrenia patients even performed at chance levels in the Martin study. Bediou and colleagues also reported that the emotion matching performance in patients was worse when identity was varied. This is similar to performance deficit in Stroop effect observed in schizophrenia patients, related to the inability in selectively suppressing interfering stimuli (Henik & Salo, 2004) (Chapter 5). Martin study reported that negative symptoms were significantly correlated with the performance on emotion matching task, specifically when the identity was varied. Bediou study did not see any correlations between performance and negative or positive symptom scores.

To disentangle the facial emotion recognition deficit in schizophrenia patients, and the quantify how factors like, task type, hospitalization, medication, etc. effected the performance, Kohler and colleagues conducted a meta-analytic review. This review examined the findings of eighty-six studies between 1970-2007 (Kohler et al., 2010). They found that facial emotion perception showed a significant deficit in schizophrenia patients when compared to control subjects. The effect size was not dependent on the type of task (identification or matching). Impairment in inpatient schizophrenia subjects was significantly larger than outpatients. A more recent meta-

analytic review (Savla et al., 2013) of broader social cognition deficits in schizophrenia patients, also found this larger effect in inpatient subjects (62 studies). Kohler review also found that the effect size was largest in unmedicated patients. There were few (15/86) studies that had patients with both schizophrenia and schizoaffective disorder diagnosis. The effect size in these studies were not significantly different from studies with only schizophrenia patients.

7.2.2 NEUROPHYSIOLOGICAL FINDINGS

The studies investigating neurophysiology of facial emotion recognition, particularly in schizophrenia patients, are relatively new. Experimental evidence from functional magnetic resonance imaging (fMRI) suggest that schizophrenia patients show a reduced activation of areas typically related to emotion processing, such as, amygdala, fusiform gyrus, and frontal cortex (Taylor et al., 2012). There has also been evidence of possibly compensatory increase of activation of other areas that are typically not associated with emotion processing in healthy controls (Taylor et al., 2012). However, how these differences in cortical and sub-cortical activations manifest as electrical activity recorded with EEG, is still an active area of research with the first related study published in 2001 (Streit et al., 2001).

Streit and colleagues used a blurred face categorization task and a facial affect recognition task, while recording EEG signals from healthy controls and schizophrenia patients. They found that patients were significantly worse at correctly recognizing emotions, with the fear recognition most impaired. No significant behavioural difference was observed between the two groups in categorizing faces from objects. Statistical analysis of EEG peak amplitudes in the 180ms-250ms time window during affect recognition task, showed a significant higher amplitude in controls and on temporal recording sites. They also found a significant correlation between performance and frontal amplitude in this period across the subjects. However, no significant relation was found between the amplitudes, clinical ratings, and performance in patient group(Streit et al., 2001).

Hermann and colleagues (Herrmann et al., 2004) investigated the hypothesis that, early face-processing deficits in schizophrenia patients leads to poor emotional affect recognition. They used a classification task between faces and buildings to compare the activation of temporal recordings sites. The post-stimulus period from

113ms to 230ms was considered. They found that the negative ERP component N170 was significantly larger for face stimuli compared to buildings. Schizophrenia patients showed a significantly lower amplitude difference between faces and buildings. It was also observed that the N170 amplitude was higher on right hemisphere. These results were consistent with earlier fMRI and electrophysiological studies showing processing of facial features occurs at an early stage of approximately 170ms after stimulus. These studies had also reported involvement of fusiform gyrus, which is reduced in volume in schizophrenia patients, in N170 generation (Herrmann et al., 2004).

The findings from the Herrmann study were further investigated by Campanella and colleagues for the specificity of N170 deficit, along with its dependence on the visual P100 ERP component (Campanella et al., 2006). They also wanted to determine relationship between the deficit and symptom severity in patients, scored using PANSS (Kay et al., 1987). They used a deviant face-detection task that presented neutral faces as a frequent stimulus, with differing identity or facial expressions as the deviants. The study found a significant temporal N170 (electrodes T5 and T6) deficit in patients with high PANSS score. This reduction in amplitude was present both in identity and emotion deviants. The reduction in N170 amplitude was also preceded by a significant reduction in P100 amplitude at electrodes O1 and O2. The study also investigated the longer latency P300 (electrodes Pz, CP1, and CP2) and N400 (electrodes T5, Oz, T6) components, and found similar amplitude reduction in schizophrenia patients with high PANSS score. The P300 component peak was also found to be significantly delayed in patients. The study thus provided a compelling evidence of overall face-processing deficit in patients, along with a significant correlation of N170 amplitude with the positive symptom sub-scores from the PANSS scale.

To probe the time-course of facial affect recognition and the relationship between early and late ERP components, Turetsky and colleagues used a short 100ms duration stimulus. This reduced stimulus enabled the researchers to specifically target early visual processing and observe its effect on the later ERP components. The stimuli were happy, neutral, and sad faces with two levels of intensities. While patients were overall worse at the task, their performance towards happy faces was found to be correlated with severity of negative symptoms. This study also used the global field

power (GFP) (Skrandies, 1990), which is a measure of variability of the potentials across the scalp, to identify various components of the ERP response. Four components, namely P100, N170, N250m and P300 were uncovered using the GFP, during the emotion classification task. The earlier P100 component was observed to be modulated by the intensity of the emotions. The N170 component was significantly smaller in patients and during neutral stimuli. In patients, positive symptom severity was correlated with the N170 amplitude during sad faces. While no significant effects were observed for N250 component, P300 exhibited similar trends to that of the N170. In patients, variance in the P300 component was captured by N170, thus leading the researchers to speculate that the P300 modulation could be a downstream effect (Turetsky et al., 2007).

The N170 response to emotional stimuli has been further studied in more detail in the recent years. For example, Akbarfahimi and colleagues studied both the peak amplitude and latency of the N170 component, recorded at occipito-temporal sites P7 (left-hemisphere) and P8 (right-hemisphere). They found significant hemisphere effect on amplitude, with right hemisphere exhibiting larger peaks. The left hemisphere amplitude was also significantly correlated with positive symptom severity in patients defined by the PANSS positive scale. The peak latency was observed to be higher in patients and had a significant interaction with facial expression type. In patients, the N170 peak latency for fearful expression was higher compared to that of happy and neutral faces. An opposite relationship was seen in control subjects (Akbarfahimi et al., 2013).

An interesting study was published by Maher and colleagues in 2016 where they investigated the relationship between the ERP signal and fMRI response (Maher et al., 2016). Even though this study was primarily investigating only the face-processing deficiency in schizophrenia patients, it was included in this review. This was warranted by the fact that, most of the previously described research has argued that deficit in facial expression recognition is directly related to a high-level face-processing deficit (Campanella et al., 2006; Herrmann et al., 2004; Turetsky et al., 2007). Maher and colleagues used line drawings of faces and trees mixed with scrambled lines as stimuli. The subjects had to indicate which side of the screen the object was on. Four different contrast values were used for the stimuli (0%, Th%, 2 times Th%, and 100%). The

contrast threshold (Th) for individual subjects was determined from an earlier experiment as the threshold at which the subjects could detect the object on the screen with 80% accuracy. EEG recordings were primarily taken from right hemisphere P8 electrode, and an average of ERP signal between 120ms and 220ms was used. P7 electrode recording from left hemisphere was used as the control electrode. Control subjects had a significantly larger N170 response to faces compared to trees. This was not true in patients. This was also one of the studies that compared schizophrenia and schizoaffective patients within its patient group but did not find any significant differences. The researchers found significant correlation between the ERP amplitude and the fMRI response from the fusiform face area (FFA) at approximately 170ms latency in control subjects. This correlation was also missing in patients, thus indicating that N170 component observed in patients was generated from other sources. This hypothesis was strengthened by the significant correlation of N170 response with the face detection threshold in control subjects, but not in patients. In patients, a weakly significant correlation was observed between the PANSS negative score and N170 response (Maher et al., 2016).

Two recent meta-analytic review on face-processing ERP components provided an overall view of EEG deficit in schizophrenia patients. Earls and colleagues reviewed twelve studies (328 patients and 330 controls) involving early face-processing component P100 (Earls et al., 2016). An overall significant decrease in P100 amplitude was observed in patients. They also compared the relationship between facial affect type and P100 amplitude, finding a significant reduction in patients for the happy and neutral stimuli, but not for fearful stimuli. McCleery and colleagues analysed twenty-one studies with N170 component (438 patients, 418 controls) and six (149 patients, 151 controls) with N250 (McCleery et al., 2015). They found significant reduction in both component amplitudes in schizophrenia patients, when compared to control subjects. For the N170 component, they concluded that the deficit was independent of emotional or non-affective stimuli, bolstering the hypothesis of higher-level face-processing deficit. They did not draw any specific conclusion for N250 component due to the small number of studies analysed.

The various studies described in this section show that patients within the schizophrenia spectrum exhibit both behavioural, and neurophysiological deficits in

face processing and facial affect recognition. All the neurophysiological studies reported deficits in the early visual component like P100 and N170 (Akbarfahimi et al., 2013; Herrmann et al., 2004; Maher et al., 2016; Streit et al., 2001), while fewer studies discussed deficits in longer latency components like N250 and P300 (Campanella et al., 2006; Turetsky et al., 2007). The lack of understanding of longer latency ERP components (N250), especially in case of affect recognition, was also concluded by McCleery (McCleery et al., 2015).

7.3 Aims of Study

This chapter describes the findings from an emotion recognition task conducted on healthy controls and patients diagnosed within the schizophrenia spectrum of disorders. Behavioural and neurophysiological findings are presented from both, early visual and a late cognitive deficit standpoint. Following were the aims of this study:

1. To use a facial emotion recognition task to observe behavioural response along with simultaneous EEG recordings in both healthy control subjects and patients diagnosed with the schizophrenia spectrum of disorders.
2. To compute behavioural response measures and compare the performance between healthy control subjects and patients. We hypothesized that patients would show performance deficit in categorizing facial emotions compared to healthy control subjects.
3. To compute and compare the ERP response to each emotion type between healthy control subjects and patients. We hypothesized to see deficits in early facial processing components and cognitive response at frontal electrodes in patients compared to healthy control subjects.
4. To use the observations from the ERP analysis to compute specific EEG measures and ERSP response at selected electrodes.
5. To compute correlations of patient symptom severity with behavioural performance and EEG measures. We hypothesized that patients with more severe symptoms would exhibit larger deficits in both behavioural performance and EEG measures.

7.4 Experimental Methods

7.4.1 TASK DESCRIPTION

In this experiment, a computerized facial emotion recognition task was used to study the behavioural and neurophysiological deficits in the patient group. The participants were presented with schematic faces with four different types of expressions namely, neutral, happy, angry, and sad. The stimuli were presented using the Stim^2 Gentask software and the triggers were interfaced with the NeuroScan 4.5 Acquire module using the Stim^2 hardware. Each trial began with the schematic appearing on screen for 200ms. Participants had 2500ms to choose their response by pressing one of the four buttons on a response pad (Compumedics NeuroScan Switch and Response Pad) labelled "O.K" for neutral, and "happy", "angry", and "sad", for

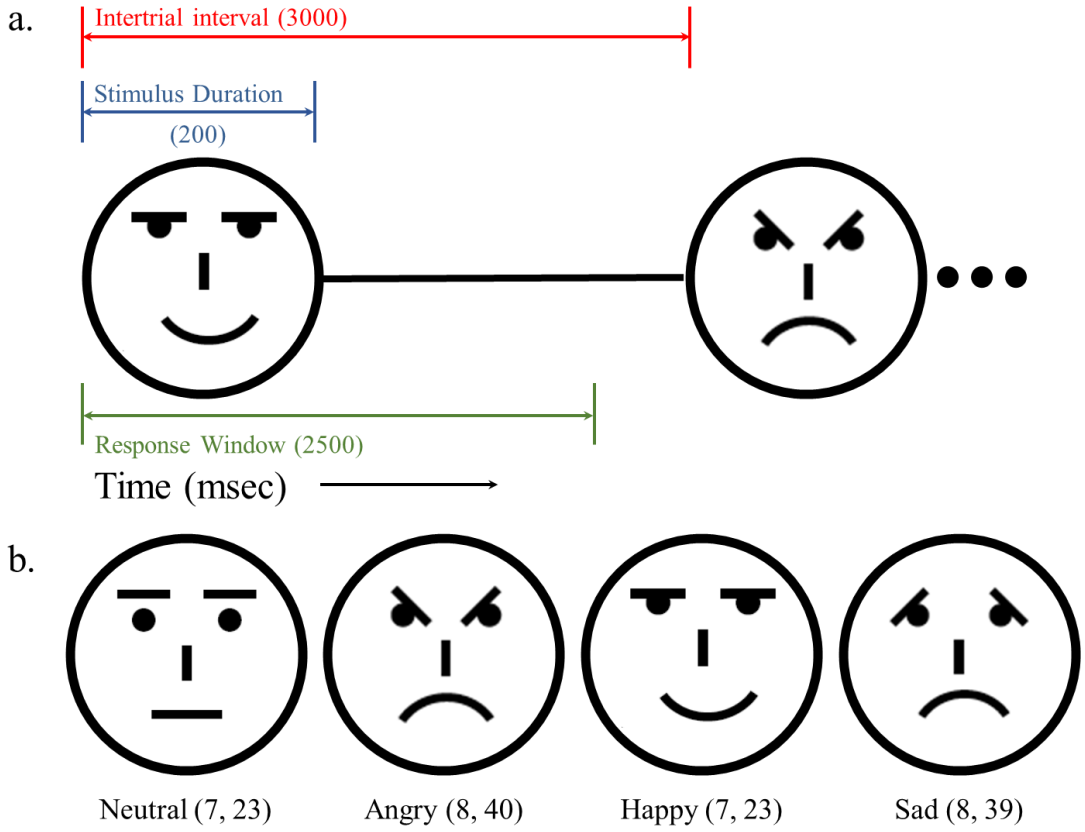


Figure 7.1 Facial emotion recognition task. a. Timing diagram of task trial. Trials began with presentation of stimulus for 200ms. The subjects a maximum of 2500ms to respond with a 3000ms inter-trial interval. b. Face schematic selected for stimuli based on participant's selection and rating (1-5). Expression for four chosen stimuli is shown below each schematic. The first number in bracket shows how many subjects out of 8 chose the schematic followed by the total score from all subjects (max value: 8 (subjects) * 5 (rating) =40).

the corresponding schematic expression. The response window was set to a maximum of 2500ms after the stimulus onset, and the intertrial interval was set to 3000ms. The timing diagram of the task is shown in figure 7.1a.

The four face schematics used for stimuli were chosen from eight schematics previously shown to eight randomly chosen healthy subjects who were not a part of the study (Appendix D). The subjects were asked to categorise each schematic as one of the four types, neutral, happy, angry, and sad. The subjects were also asked to rate their categorization on a scale of 1-5 with 1 denoting least convincing and 5 being most convincing. The face schematics that were selected for each category are shown in figure 7.1b. Below each of the chosen stimuli, the expression type followed by number of participants that chose the response, and the total score assigned (maximum score = number of participants*5 = 8*5 = 40). Schematic representation of faces with emotions were chosen instead of faces from datasets of real humans with expressions, to avoid any adverse reactions from the patients.

All subjects performed two blocks of 180 trials each. Each of the four facial expressions were randomly presented with an equal likelihood. Each block took approximately 10 mins. With a 5 min break between the two blocks, the task took about 25 mins in total. The experiment was performed during the second session following the cognitive testing through CANTAB. During the experiment, EEG was recorded from each subject. The recording setup (described in Chapter 3 and previously used in MMN and Stroop experiments) was carried out after the CANTAB experiment was completed.

7.4.2 SUBJECTS

All 19 healthy control subjects performed the facial emotion recognition task. However only one block of data was recorded from one of the control subjects. Therefore, this subject was excluded from analysis in this study leaving 18 healthy control subjects. All the 6 patients performed the facial emotion recognition task. The results from this study are presented for the healthy control group, and the two patient groups diagnosed with schizophrenia (P4, P5, P6) and schizoaffective disorder (P1, P2, P3).

7.4.3 BEHAVIOURAL ANALYSIS

The behavioural performance of each subject was quantified by the percentage of correct responses and mean trial response latency. These measures were calculated for each of the four emotion types after combining data from both the blocks of trials performed by the subjects.

7.4.4 EEG MEASUREMENT

The general steps of EEG pre-processing pipeline have been described in Chapter 3. A common average reference (CAR) was used in pre-processing the EEG recordings during this study. The trial epoch was defined starting from 500ms pre-stimulus baseline period to 2500ms post-stimulus. Any offset or small fluctuations were removed from each trial by subtracting the average baseline activity from each electrode. A baseline period of 500ms (longer than the other two EEG experiments) was used due to the longer duration of the trial. Even with a longer baseline period, a low frequency swing was observed in the data. This was reduced by using a higher high-pass filter cut-off of 0.5Hz in in pre-processing pipeline, compared to 0.05Hz in other experiments. The higher filter cut-off frequency was also helpful in producing a more stable ICA decomposition (Winkler et al., 2015) which was used for artefact rejection and cleaning the data (Chapter 3, Section (3.2.4). After artefact rejection and dropping the incorrect trial responses, approximately 95% of all trials were retained in healthy control subjects and 82% in patients.

The artefact suppression was followed by computation of event related potentials (ERP) of each electrode. Grand average ERP were computed for each subject group (healthy controls, schizophrenia patients, and schizoaffective disorder patients) after data from both the blocks performed by each subject was combined. The ERP responses to each emotional expression stimuli were compared between healthy control group and patient groups. The comparisons were made for all the electrodes that were common across the two groups, excluding the two mastoid electrodes (M1 and M2).

Based on the observations from the ERP analysis, comparison of ERSP response to each facial emotion type was conducted at electrodes FP1 and P8. The comparisons were made between the healthy control group and whole patient group as we did not

observe significant differences between the ERP response of schizophrenia patient and schizoaffective disorder patients.

Also based on the observations from ERP analysis, EEG measures were computed from electrodes P8, FP1, and FP2. P100 and N170 components associated with early face processing were observed at the P8 electrode. The peak amplitude and latency of these components were computed for statistical analysis. The peak amplitude and latency of the P100 component was determined by finding the maximum amplitude of a subject's ERP response at electrode P8 in the 50ms-200ms post-stimulus interval. Similarly, the peak amplitude and latency of N170 component was determined by finding the minimum amplitude of ERP response at P8 in the 50ms-250ms post-stimulus interval. At electrodes FP1 and FP2 significant differences between healthy control and patient groups were observed in the P300 region lasting approximately 200ms. Therefore, the mean amplitude in the 400-600ms post-stimulus interval was computed, instead of determining the peak amplitude.

7.4.5 STATISTICAL ANALYSIS

A multi-factor analysis of variance (ANOVA) was carried out for both the behavioural performance measures (percentage of correct trials and average trial response latency) using the group of the subject (control, schizophrenia, or schizoaffective) as the between subject factor, and the task condition (neutral, happy, angry, or sad) as the within subject factor. This led to a 3x4 design with 96 data-points (24 subjects*4 task conditions). ANOVA with all the patients in one group was also computed using a 2x4 design with the same 96 data-points.

Permutation statistics were used to determine the periods of significant differences between the ERP responses from control group and two patient groups. A cluster-based correction method was used to account for the multiple comparisons problem arising due to all the time points of the signal. These statistics were also used to compare the ERSP responses at P8 and FP1 between the control group and the whole patient group.

A multi-factor ANOVA was also used to analyse the EEG measures from the P100 and N170 at electrode P8 and the mean amplitude of P300 component at electrode FP1 and FP2. Similar to the behavioural analysis, the group of the subjects (control, schizophrenia, and schizoaffective disorder) was used as the between subject

factor, and the task condition (neutral, happy, angry, and sad) as the within subject factor. This led to a 3x4 design with 96 data-points (24 subjects*4 task conditions). A 2x4 design ANOVA was also conducted with all patients grouped together.

7.5 Results and Comparisons

7.5.1 BEHAVIOURAL RESULTS

The behavioural results from each of these patients are presented in table 7.1. The table contains the mean trial response latency and percent correct for each task condition. The table also shows the symptom severity of each patient assessed by a trained clinical staff, on the day of the experiment. The patients were scored based on two questionnaires: Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), scoring the positive, negative, and general symptoms of the patient, and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), rating the severity of depression in patients.

The behavioural performance results for each group of subjects are graphically shown in figure 7.2. Figure 7.2a shows the percentage of correct responses for each type of emotion. Each point represents the mean, with the error bars showing the standard error of mean. The plot shows that patients had smaller number of correct recognitions overall. An interesting pattern emerges within the patient group when segregated by their clinal diagnosis. Schizophrenia patients are observed to have a much higher error rate compared to schizoaffective disorder patients; whose performance is relatively close to the control group. Schizophrenia patients are also seen to make the highest number of errors in recognizing angry facial expression.

The mean trial response latency to the four types of stimuli is plotted in figure 7.2b, with the standard error of the mean represented by error bars. Control subjects are again found to have the best performance in recognizing each type of facial expression. This is represented by the shorter response latencies observed in the control group compared to the patient groups. The response of schizoaffective patients is relatively slower with a large variability within the group. Schizophrenia patients are the slowest in their response, with average response latency several 100ms longer in most cases. Within each group, latency differences are also seen between task

conditions; for example, healthy controls are quickest at responding to neutral stimulus and slowest at recognizing the sad stimulus.

Table 7.1 Patient performance in emotion recognition task.

Patient	P1	P2	P3	P4	P5	P6
Gender	M	M	M	M	M	M
Age	35	26	57	64	59	47
Clinical Diagnosis*	SA	SA	SA/BSD	S	S	S
PANSS						
Positive	28	8	7	7	18	26
Negative	27	9	10	12	20	23
General	38	19	17	17	49	59
MADRS	3	4	2	0	22	26
Response Latency (ms)						
Neutral	716.34	465.39	1245.97	888.33	1057.10	865.73
Happy	774.93	565.68	1151.83	1293.08	1151.28	1114.56
Angry	638.78	513.61	1231.55	1221.89	1051.25	1136.67
Sad	837.97	641.14	1460.33	1216.04	1306.90	1038.46
Percent Correct:						
Neutral	100.0	100.0	77.2	87.1	96.0	100.0
Happy	98.8	98.8	90.4	77.1	69.9	92.88
Angry	96.8	94.7	80.0	58.9	71.6	54.7
Sad	98.8	97.5	59.3	59.3	71.6	97.5

* S: Schizophrenia, SA: Schizoaffective Disorder, BSD: Bipolar Spectrum Disorder

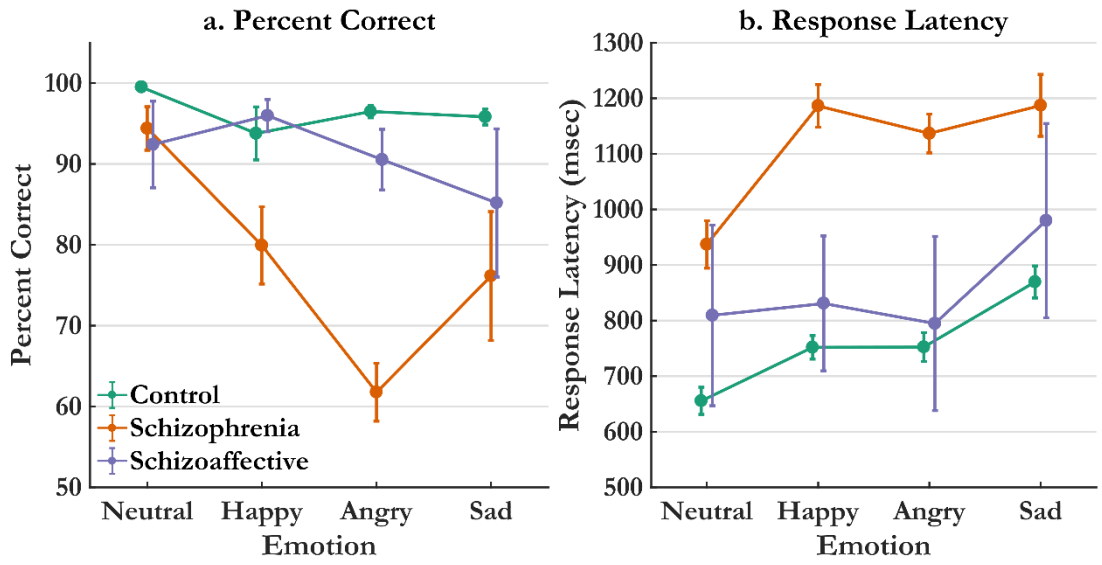


Figure 7.2 Performance comparison in emotion recognition task. a. Percentage of correct trials for each type of emotion. b. Average trial response latency to each type of emotion. Non-zero y-axes are used for better visualization of data.

The 3x4 ANOVA on percentage of correct trials showed a significant main effect in both the group ($F(2, 84) = 21.74$, $p << 0.0001$) and task condition variables ($F(3, 84) = 4.53$, $p = 0.0054$). There was also a significant interaction between the 2 factors ($F(6, 84) = 2.93$, $p = 0.012$), which can be already seen in figure 7.2a. Multiple comparisons analysis on the group factor showed that, schizophrenia patients got significantly smaller number of trials correct compared to both control subjects ($p << 0.0001$) and schizoaffective disorder patients ($p = 0.002$), while there was no significant difference between control subjects and schizoaffective disorder patients. Comparison on the task condition variable showed a significantly lower number of angry ($p = 0.0046$) and sad ($p = 0.0422$) trials recognised correctly, compared to neutral trials. Analysing both the group and task condition together showed that schizophrenia patients were significantly worse at recognising angry expressions compared to both control subjects ($p << 0.0001$) and schizoaffective disorder patients ($p = 0.0098$). Schizophrenia patients were also significantly worse at recognizing sad expressions compared to control subjects ($p = 0.0341$). Similar results were seen from 2x4 ANOVA for percentage of correct trials for main effects of both group ($F(1, 88) = 25.9$, $p << 0.0001$) and task conditions ($F(3, 88) = 3.57$, $p = 0.0172$). No significant interactions were found in this case. Multiple comparison analysis for this design

showed that patients performed significantly worse at recognizing angry ($p = 0.0009$) and sad ($p = 0.0333$) expressions compared to the control group.

For the mean response latency of correct trials, the 3x4 ANOVA showed a significant main effect in both the group ($F(2, 84) = 26.64$, $p << 0.0001$) and task condition variables ($F(3, 84) = 3.84$, $p = 0.0126$). There was no significant interaction between the 2 factors. Multiple comparison analysis on the group factor showed that, schizophrenia patients were significantly slower in their response compared to both control subjects ($p << 0.0001$) and schizoaffective disorder patients ($p = 0.004$), while there was no significant difference between control subjects and schizoaffective disorder patients. Comparison on the task condition variable showed a significantly slower response to sad ($p = 0.0063$) trials compared to neutral trials. Considering both the group and task condition together showed that in control subjects response to sad expressions was significantly slower ($p = 0.0052$) compared to neutral trials. Schizophrenia patients were significantly slower at responding to happy ($p = 0.0016$) and angry ($p = 0.0092$) expressions compared to control subjects. Results from 2x4 ANOVA for average response latency of correct trials similarly showed main effects in both group ($F(1, 88) = 31.87$, $p << 0.0001$) and task conditions ($F(3, 88) = 4.75$, $p = 0.0041$). No significant interactions were found in this case either. Multiple comparison analysis for this design showed that patient group was significantly slower at responding to happy ($p = 0.0370$) expressions compared to the control group.

7.5.2 EVENT RELATED POTENTIAL ANALYSIS

The ERP responses to the four types of facial emotion stimuli are presented in figures 7.3 to 7.6. Each figure plots the ERP response of 35 electrodes laid out on a grid closely following their relative positions on the scalp. Each plot shows three grand average ERP responses, namely: healthy control group (green), schizophrenia patient group (orange), and schizoaffective disorder patient group (purple). Responses are shown only in the -200ms to 1300ms time window relative to the stimulus onset, as the ERPs were relatively stable outside this period. The periods of significant difference between the control group and whole patient group are represented by the grey patches. The periods of significant difference between control group and schizophrenia patient group are presented as orange bars and for the control group and schizoaffective disorder patient group using purple bars at the bottom of each plot.

The response to the neutral facial emotion stimuli is shown in figure 7.3. Surprisingly, the periods of significant differences between the control and patient groups are seen at largest number of electrodes for this condition, when compared to other task conditions. However, it should be noted from the figure that several frontal, temporal, and occipital electrodes show these significant difference periods later in the trial. The mean response latencies of all groups to the neutral stimuli were less than 1000ms (fig 7.2b). Taking this into consideration, we see that except for a few

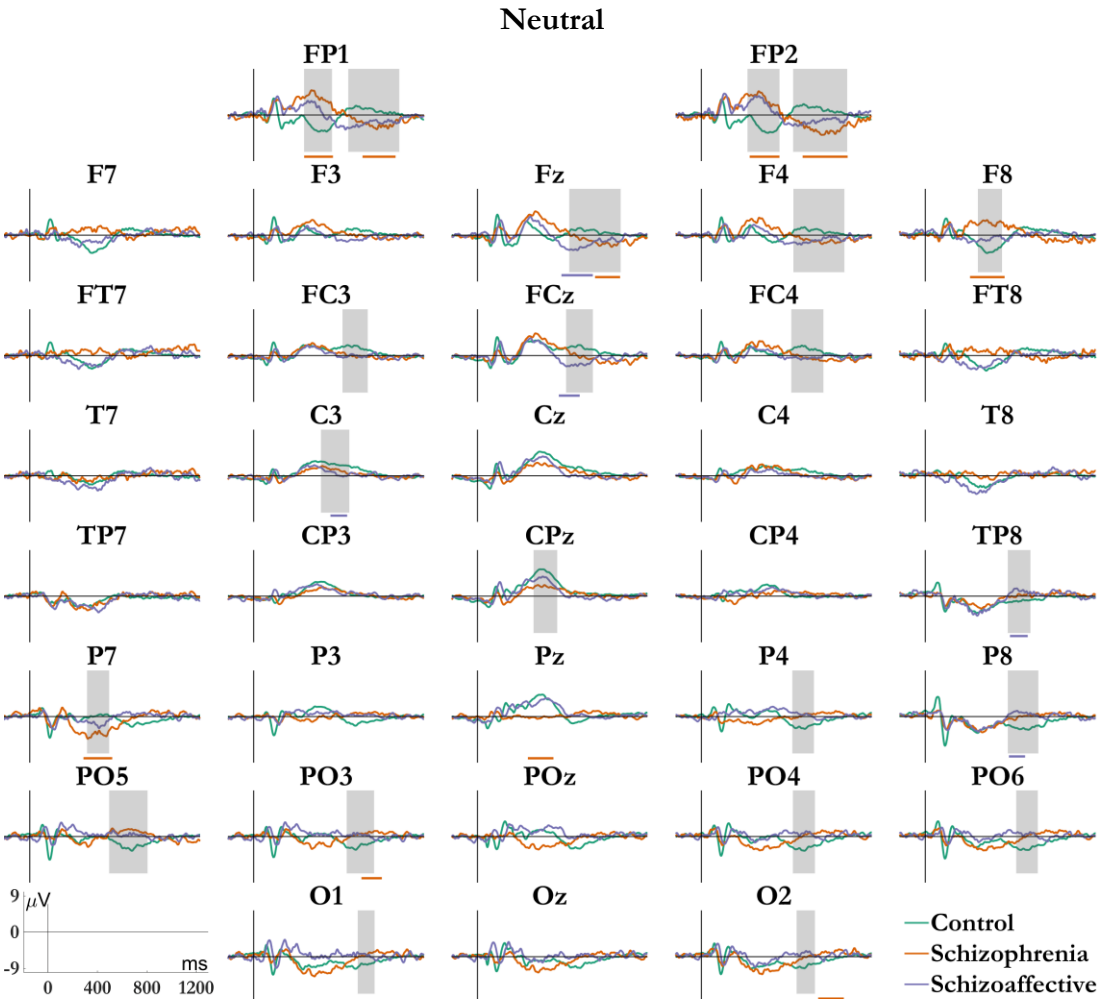


Figure 7.3 Grand average ERP response to Neutral emotion stimuli. Each plot shows the response of a single electrode from control subjects (green, n=18), schizophrenia patients (orange, n=3), and schizoaffective disorder patients (purple, n=3). Gray patches represent regions of significant difference between healthy control subjects and patients. Significant differences between control and schizophrenia are shown by orange bar and between control and schizoaffective disorder are shown by purple bar at the bottom of each plot. Electrodes are arranged based on their location on the scalp. The axis on the bottom left shows the time and amplitude range of each plot.

electrodes, the grey patches indicating significant differences in figure 7.3 occur after the mean response latency. As patients with schizophrenia spectrum of disorders have trouble focusing and paying attention to tasks when compared to healthy control subjects (Chapter 2, Section 2.1), it can be speculated that patients were distracted after responding to the trial. This could have led to a deviation in the ERP response in patients when compared to the control subjects. The earlier differences at the frontal FP1 and FP2 electrodes approximately in the 400-600ms post-stimulus period are

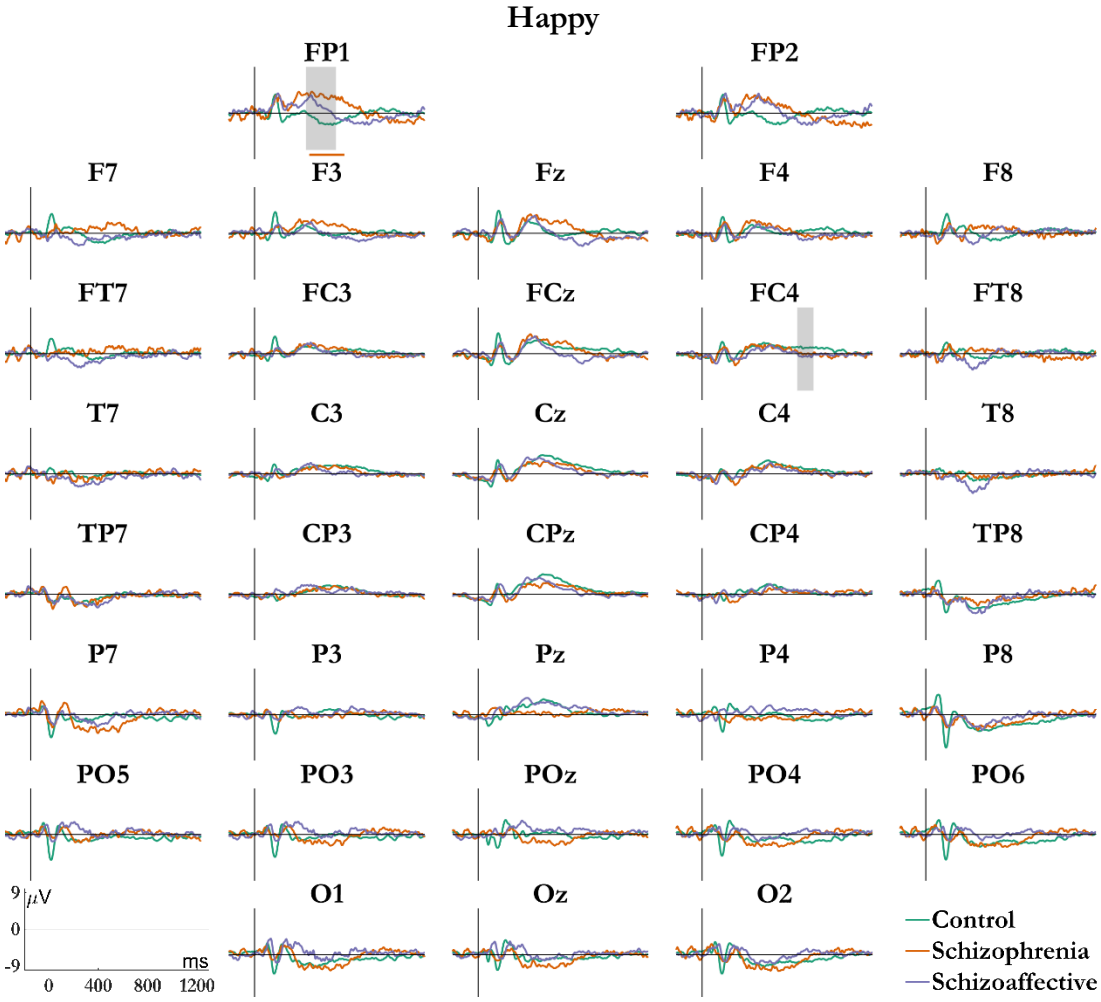


Figure 7.4 Grand average ERP response to Happy emotion stimuli. Each plot shows the response of a single electrode from control subjects (green, n=18), schizophrenia patients (orange, n=3), and schizoaffective disorder patients (purple, n=3). Gray patches represent regions of significant difference between healthy control subjects and patients. Significant differences between control and schizophrenia are shown by orange bar at the bottom of each plot. Electrodes are arranged based on their location on the scalp. The axis on the bottom left shows the time and amplitude range of each plot.

noteworthy and further investigated later in the section. Control group also showed large P100 and N170 components on the P8 electrode which is not seen in either of the patient groups.

Figure 7.4 shows the response to the happy facial emotion stimuli. Significant difference is seen only at electrodes FP1 and FC4. The difference at electrode FP1 is also significant between control and schizophrenia patient groups, but not between control and schizoaffective disorder patient groups. Though the average response at

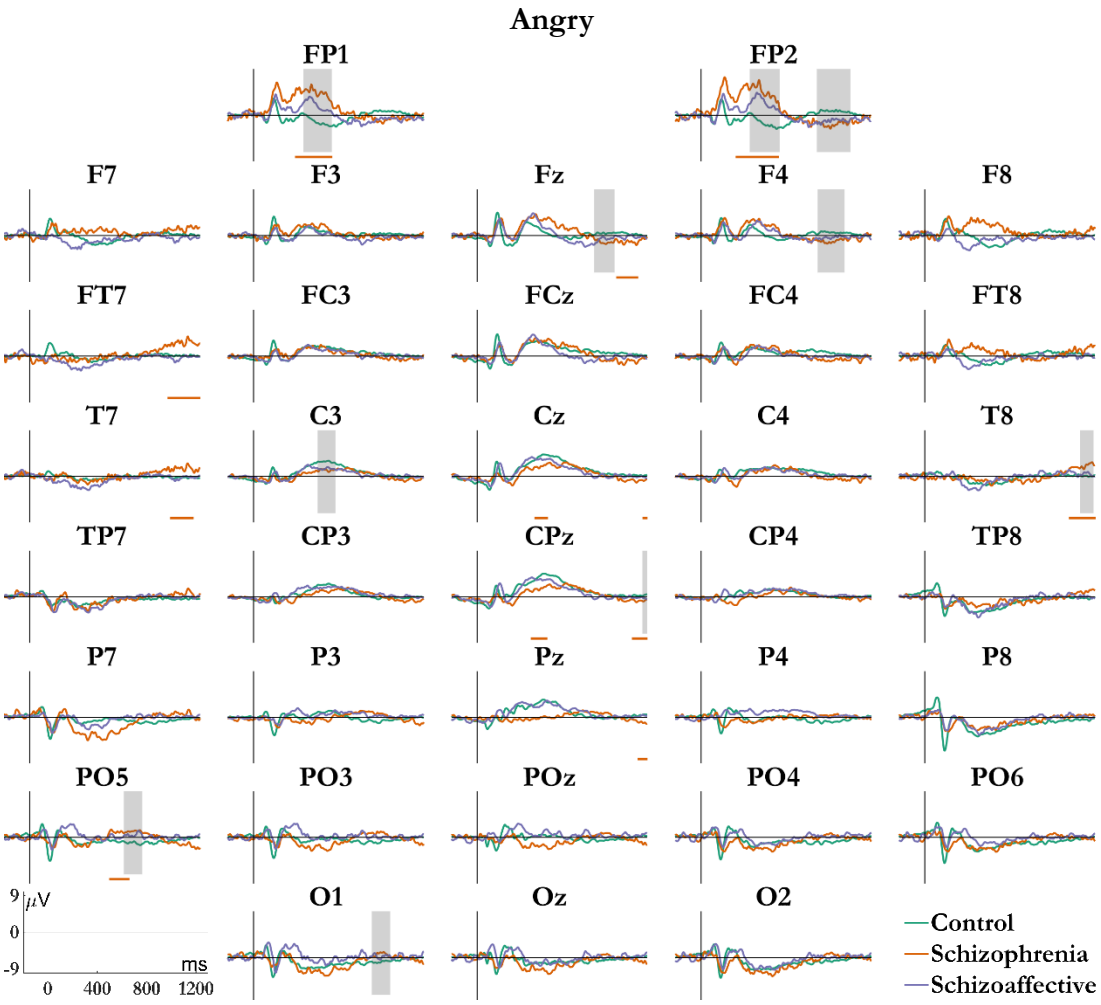


Figure 7.5 Grand average ERP response to Angry emotion stimuli. Each plot shows the response of a single electrode from control subjects (green, n=18), schizophrenia patients (orange, n=3), and schizoaffective disorder patients (purple, n=3). Gray patches represent regions of significant difference between healthy control subjects and patients. Significant differences between control and schizophrenia are shown by orange bar and between control and schizoaffective disorder are shown by purple bar at the bottom of each plot. Electrodes are arranged based on their location on the scalp. The axis on the bottom left shows the time and amplitude range of each plot.

the FP2 electrode has a large difference between the control and patient groups, it did not satisfy the significance criteria. The responses at these frontal electrodes deviated between the subject groups approximately during the same time window of 400-600ms post-stimulus period. In the control group we also observed large P100 and N170 components at P8 electrode representative of early face processing. These early components are diminished in both patient groups.

Responses to angry facial emotion stimuli are plotted in figure 7.5. A few more electrodes show significant difference periods to this stimulus. Specifically, both FP1

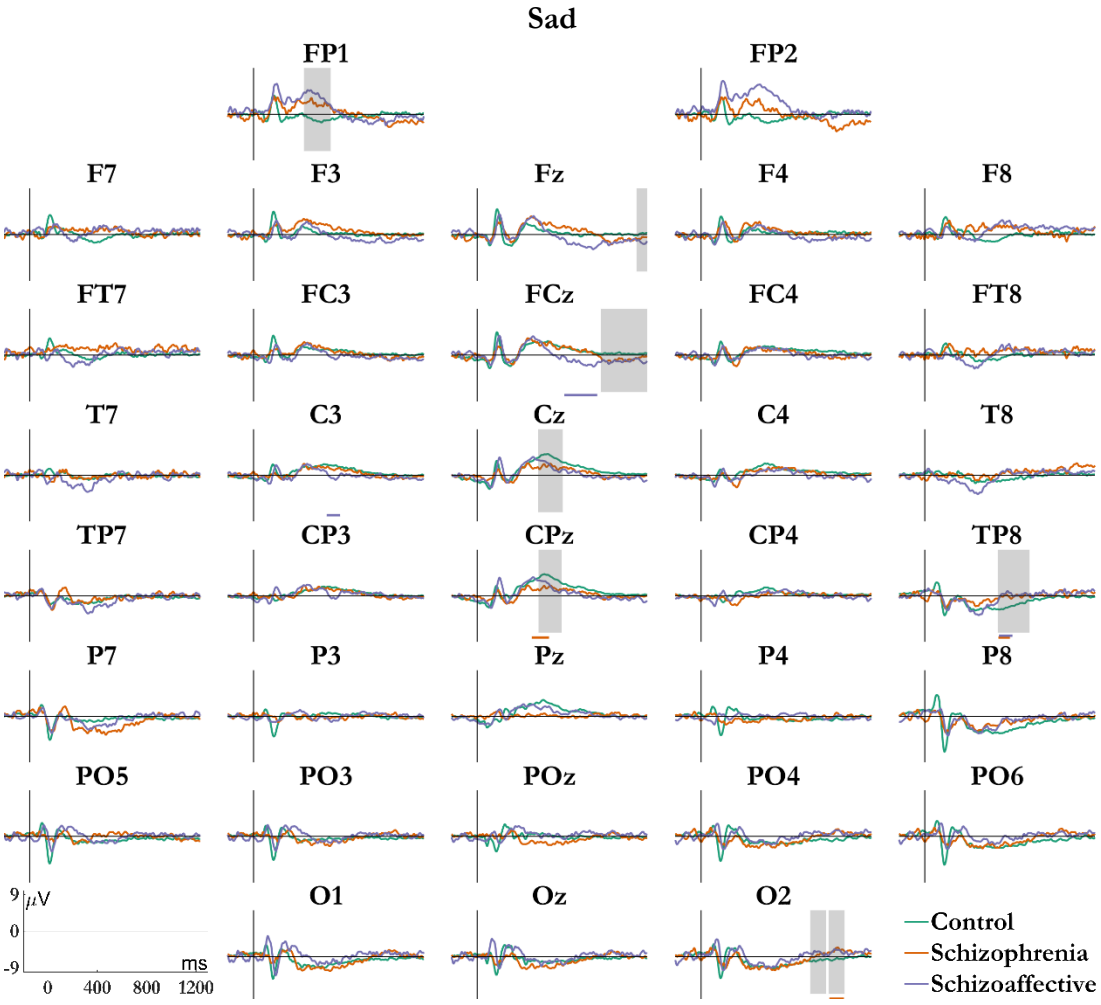


Figure 7.6 Grand average ERP response to Sad emotion stimuli. Each plot shows the response of a single electrode from control subjects (green, n=18), schizophrenia patients (orange, n=3), and schizoaffective disorder patients (purple, n=3). Gray patches represent regions of significant difference between healthy control subjects and patients. Significant differences between control and schizophrenia are shown by orange bar and between control and schizoaffective disorder are shown by purple bar at the bottom of each plot. Electrodes are arranged based on their location on the scalp. The axis on the bottom left shows the time and amplitude range of each plot.

and FP2 electrodes show significant differences in 400-600ms post-stimulus period. These significant differences are also present when only control and schizophrenia patient groups are compared with each other.

The response to the sad facial emotion stimuli shown in figure 7.6 are found to be significantly different between the subject groups at electrode FP1, along with a few mid-line electrodes. The difference at FP1 is largest among the electrodes and is approximately during the 400-600ms post-stimulus time window. As with neutral and happy stimuli, both angry and sad stimuli elicited a large P100 and N170 component at electrode P8 only in the control group.

Figures 7.3 to 7.6 demonstrate a common pattern across responses to all the facial emotion stimuli. Firstly, we observe large P100 and N170 components at electrode P8 in controls. These components have been shown to represent the early facial processing and are diminished in patients within the schizophrenia spectrum of disorders (Earls et al., 2016; McCleery et al., 2015). Secondly, we see difference between control and patient groups at electrodes FP1 and FP2 in all the four task conditions. The difference in ERP waveforms is large in the P300 region, specifically 400-600ms time window post-stimulus, and is also significant in most cases. Multi-factor analysis of variance (ANOVA) was used to establish a simpler and quantifiable measure to distinguish between the groups.

The 3x4 ANOVA on P100 peak amplitude showed a significant main effect only in the group variable ($F(2, 84) = 22.05$, $p << 0.0001$). No significant main effect was observed in the task condition variable, and no interaction effect was observed between the two variables. Multiple comparisons analysis of the group variable indicated that when compared to control subjects, peak amplitude of P100 component was significantly smaller in both schizophrenia ($p << 0.0001$) and schizoaffective disorder ($p = 0.0001$) patients. The peak amplitudes between the two patient groups did not differ significantly. As expected, the 2x4 ANOVA design yielded similar results with a significant main effect on the group variable ($F(1, 88) = 44.44$, $p << 0.0001$). No main or interactions effects were observed in the ANOVA conducted on P100 peak latency. However, the average P100 peak latency in patients was shorter than in control subjects.

The test on N170 peak amplitude produced results similar to that of P100, albeit with a smaller effect size. The 3x4 ANOVA showed a significant main effect in the group variable ($F(2, 84) = 5.57$, $p = 0.0053$). Multiple comparisons analysis of the group variable indicated that when compared to control subjects, the absolute peak amplitude of N170 component was significantly smaller only in schizophrenia ($p = 0.0192$) patients. In schizoaffective disorder patients, the absolute amplitude was smaller than control subjects as well. However, it did not meet the significance criteria of $p < 0.05$. There was no significant difference between the two patient groups. The 2x4 ANOVA design yielded similar results, with a significant main effect on the group variable ($F(1, 88) = 11.49$, $p = 0.001$).

The results for the ANOVA on N170 peak latency were different from that of the P100 peak latency. The 3x4 ANOVA showed a significant main effect in the group variable ($F(2, 84) = 11.63$, $p << 0.0001$). No significant main effect was seen in the task conditions variable, and no interaction effect was seen between the two variables. Multiple comparisons analysis of the group variable indicated that when compared to control subjects, N170 peak latency was significantly higher in both schizophrenia ($p = 0.0017$) and schizoaffective disorder ($p = 0.0010$) patients. There was no significant difference between the two patient groups. Similarly, the 2x4 ANOVA showed a significant main effect in the group variable ($F(1, 88) = 24.13$, $p << 0.0001$) and no other main or interaction effects.

Lastly, the 3x4 ANOVA on the mean P300 amplitude at electrode FP1 also showed a significant main effect only in the group variable ($F(2, 84) = 17.93$, $p << 0.0001$). No main effect in the task condition, or an interaction between the task condition and subject group was observed. The multiple comparisons analysis of group variable showed that the mean P300 amplitude in patients was significantly higher than control subjects (schizophrenia: $p << 0.0001$, schizoaffective disorder: $p = 0.0008$). The 2x4 ANOVA design also showed same results with significant main effect in the group variable ($F(1, 88) = 35.37$, $p << 0.0001$). These tests were also conducted on the average P300 amplitudes at electrode FP2, and similar results were observed.

7.5.3 TIME-FREQUENCY ANALYSIS

The ERP analysis of the whole electrode array, followed by the statistical tests, produced an understanding of how the time course of the electrical activity on certain

electrodes differed between subject groups. The differences in activity were mainly observed at the frontal FP1 electrode, and the early face processing related components were most prominent on the occipito-temporal P8 electrode. The event related spectral perturbation (ERSP) or time-frequency decomposition from these electrodes are discussed in this section.

A grand averaged ERSP was computed for each type of facial emotion stimuli. As seen from the ERP analysis, this response was compared between the groups of subjects. The statistical tests conducted on the ERP waveforms did not show any significant difference between the two patient groups. For this reason, and for the ease of visualizing the results, statistical comparison of ERSP was computed between the control subject group and the whole patient group.

The grand averaged ERSP response at the electrodes FP1 and P8 are visualized in figures 7.7 and 7.8, respectively. The rows a-d in the figure correspond to the four different facial emotion stimuli. In each row, the plot on the left is the response from the control group, while the plot in the middle is the response from the patient group. The plot on the right is the difference between the two responses (patient – control), with the black contour lines representing the areas of significantly different activity. The time-frequency plot had 100 logarithmically spaced frequency bins from 2Hz to 50Hz, and approximately 200 linearly spaced time bins. Like the ERP plots, activity between -200ms and 1300ms relative to the trial onset has been shown.

Figure 7.7 shows the grand average ERSP activity at the electrode FP1. At every facial emotion stimulus onset, control subjects show a synchronisation of the 2-8Hz delta/theta band power, relative to the baseline period. This synchronisation of delta/theta power is observed to be sustained approximately for 1500ms, after which it returns to the baseline levels (period after 1300ms not shown in plots). There is also a desynchronisation of the frequencies approximately 8-24Hz alpha/beta band range. This desynchronisation peaks around 12Hz and 500ms which is likely associated with response preparation and execution (button press) and has been previously studied in motor neuroscience literature (Kilavik et al., 2013; Nakayashiki et al., 2014; Pfurtscheller & Lopes da Silva, 1999; Tan et al., 2013). The activity desynchronisation lasts for a few 100ms and is followed by the synchronisation of frequencies up to 24Hz while the higher frequencies stay at baseline levels. The ERSP activity in the patient

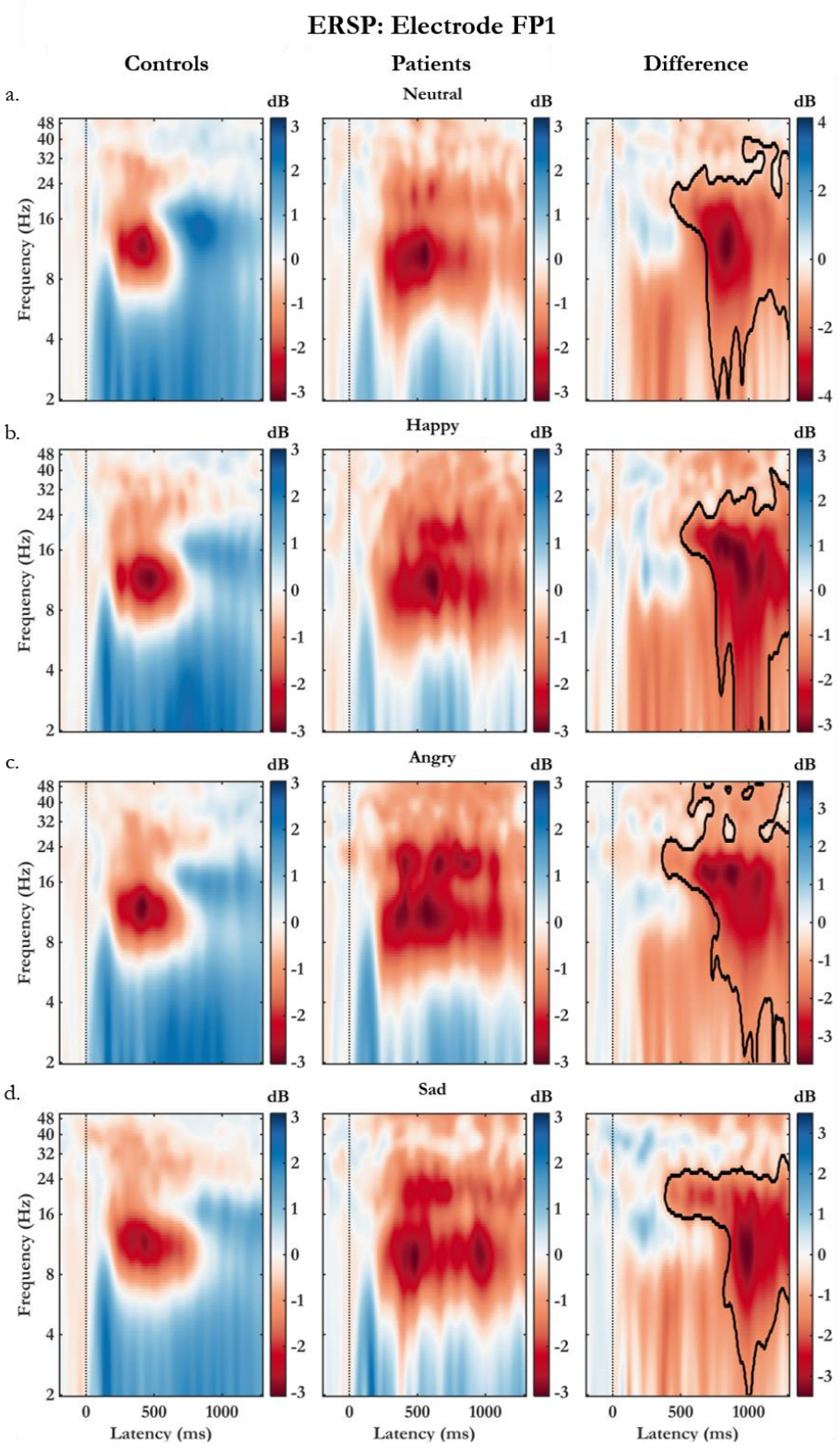


Figure 7.7 ERSP response to various emotion stimuli at electrode FP1 in healthy control group (n = 18), patient group (n = 6), and the difference between them. a. Neutral, b. Happy, c. Angry, and d. Sad. For each stimulus control ERSP is plotted on the left, patient ERSP in middle, and patient – control on the right. The black contours in the difference plots on the right represent areas of significant difference at $p<0.05$.

group is different from the control group in a few aspects. Firstly, the sustained synchronisation of delta/theta band after trial onset is relatively weaker than control group. Secondly, the alpha/beta desynchronisation spread over a broader frequency range and for longer duration. The longer duration is likely a result of the large response variability in the patient group. The smaller variability in the neutral stimulus response latency, is reflected in the smaller duration of the strong desynchronisation in the alpha/beta band activity. In other stimuli, the desynchronisation lasts longer and even shows multiple peaks. Lastly, the synchronisation of frequencies below 24Hz, is not seen. Following the desynchronisation period, the broadband activity returns to the baseline levels after approximately 1500ms. From the plots on the right of figure 7.7, it is observed that the difference between control and patient groups is statistically significant over a broad range of frequencies, later in the trial. This period is when the patient group has a sustained activity desynchronisation, while the control group exhibits a synchronisation of frequencies below 24Hz.

Figure 7.8 shows the grand averaged ERSP activity at electrode P8. Control subjects show a strong initial synchronisation of the 2-16Hz spectrum. This synchronisation is seen in all task conditions, and corresponds well in time with the large P100, and N170 face processing components seen in the ERP waveform. This increase in power for approximately 200ms is followed by a desynchronisation of the frequencies in alpha/beta band and a return to baseline of frequencies below 6Hz. The alpha/beta desynchronisation occurs at around the same time window as electrode FP1, and likely is representative of neutral dynamics involved in response preparation and execution. A weaker wide band sustained synchronisation is seen before all the activity returns to baseline after approximately 1500ms (not shown in the figure). In patient group, the initial synchronisation of lower spectrum is much weaker than the control group, and even weaker than what is seen on the frontal electrodes. This again ties well with the significantly diminished P100 and N170 components seen in the ERP plots. The desynchronisation of activity in patients is seen to begin around 200ms, and peaks at approximately 8Hz frequency and 500ms post stimulus. Unlike the control subjects, the desynchronisation in patients is widespread in both time and frequency space, and no broadband synchronisation is seen later in the trial. The differences in the ERSP response between control and patients are also clear from the difference plot, and the

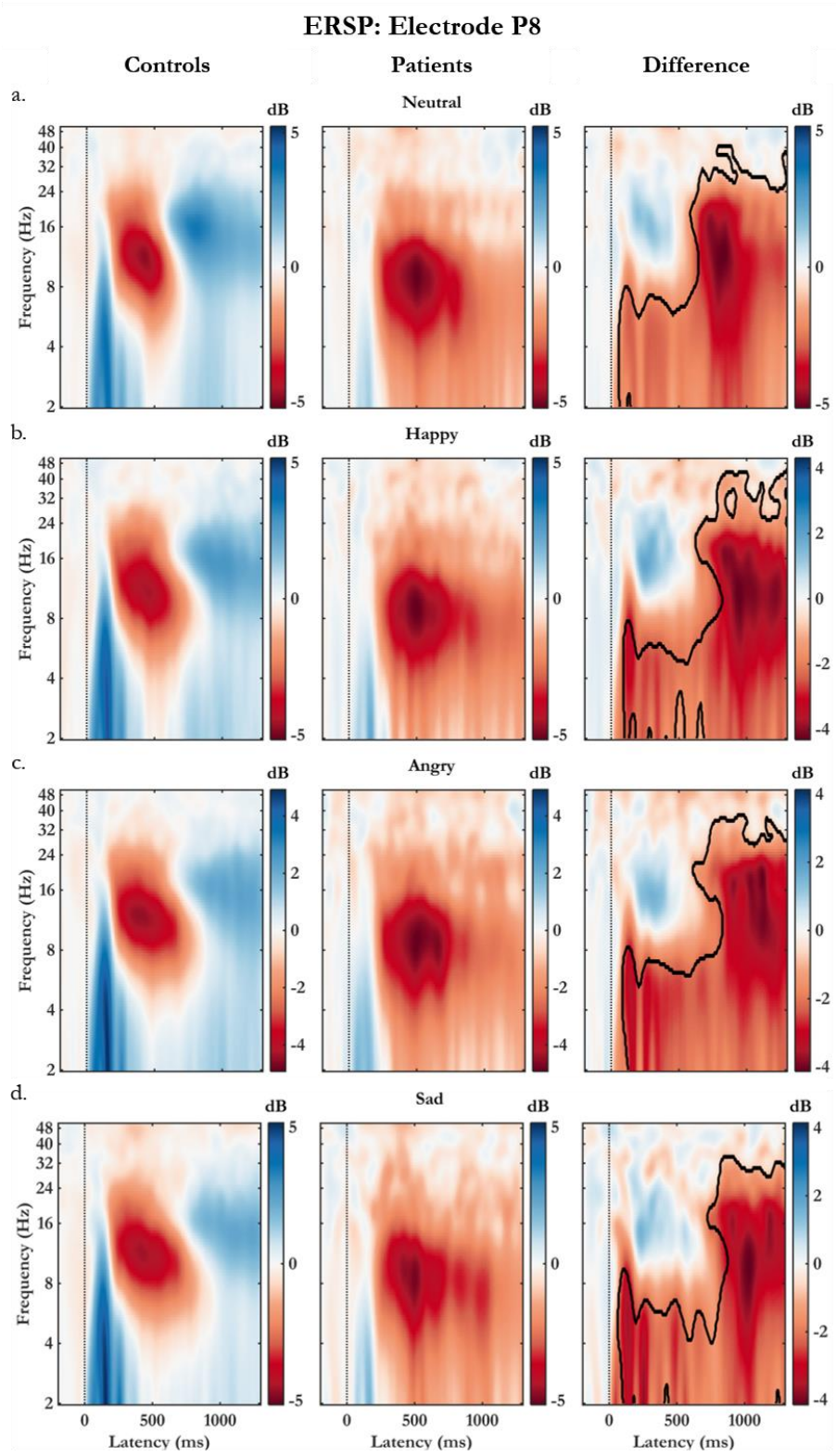


Figure 7.8 ERSP response to various emotion stimuli at electrode P8 in healthy control group (n = 18), patient group (n = 6), and the difference between them. a. Neutral, b. Happy, c. Angry, and d. Sad. For each stimulus control ERSP is plotted on the left, patient ERSP in middle, and patient – control on the right. The black contours in the difference plots on the right represent areas of significant difference at $p<0.05$.

contours surrounding the significant regions. There is a large difference in the initial delta/theta band synchronisation between control and patient groups. Due to this, a significant difference is observed from the beginning of the stimulus onset. This is unlike what is observed in the ERSP response at FP1 electrode.

7.5.4 CORRELATIONS BETWEEN EEG MEASURES AND BEHAVIOURAL MEASURES

In section 7.5.1 the behavioural performance was measured using the percent correct and mean trial response latency measures for each task condition and group of subjects. In the following section 7.5.2, the ERP waveforms at electrodes FP1 and P8 were analysed to compute peak and latency of P100 and N170 components at electrode P8, and the mean amplitude of P300 component (400-600ms post-stimulus) at FP1. Table 7.2 shows the correlation between these two sets of measurements. Each cell in the table is also coloured based on its value with darker blue cells representing higher positive correlation and darker red cells representing higher negative correlations. Some correlations have an absolute value of one, as a result of rounding them to two significant digits. Significant correlations have been marked with an asterisk (*) symbol.

The correlations in the control group are relatively low across all combinations of measurements. The correlation values in both the patient groups were higher. However, it should be noted that with only three subjects in each of the schizophrenia and schizoaffective disorder groups, the correlation needs to be almost equal to one to be significant. As seen from the papers reviewed earlier in the chapter, the components P100 and N170 from the P8 electrode are reliably elicited while looking at human facial stimuli. They are also an important part of the neural dynamics of facial emotion recognition. With that knowledge, a better performance, that is, higher percentage of correct trial (PC) and a shorter average trial response latency (RL), is expected with larger component peaks and shorter component latencies. The P300 activity at FP1 electrode was seen only in the patients. It is likely that if the patients were unable to use the face-processing components, which were diminished, they were compensating with frontal processing to recognize and categorize the stimuli. With that hypothesis an improvement in performance measures is expected with higher mean FP1 P300 amplitude, specifically in patients.

Table 7.2 Correlations between behavioural data and ERP response measures from emotion recognition task.

Type[§]	Percent Correct				Response Latency			
	N	H	A	S	N	H	A	S
Control subjects								
P100								
Peak	0.18	0.14	0.28	0.16	-0.08	-0.50*	-0.29	-0.24
Lat	0.01	-0.08	0.00	-0.06	0.30	0.34	0.49*	0.33
N170								
Peak	-0.46	-0.19	-0.20	-0.23	-0.26	-0.16	-0.26	-0.44
Lat	-0.42	0.03	0.05	0.37	0.05	0.01	-0.01	0.00
FP1 P300								
Mean	-0.37	-0.03	-0.14	-0.22	0.13	-0.02	0.24	0.15
Schizophrenia patients								
P100								
Peak	-0.56	1.00*	-0.88	0.16	-0.89	-0.44	0.96	-0.73
Lat	-0.52	0.03	0.53	-0.46	-0.90	0.91	0.20	0.91
N170								
Peak	0.27	0.39	0.23	0.96	-0.93	-1.00*	-0.84	-0.93
Lat	0.39	-0.74	0.95	-0.13	0.96	-0.32	-0.90	0.71
FP1 P300								
Mean	-0.38	0.80	-1.00*	0.80	-0.96	0.24	0.75	-1.00*
Schizoaffective disorder patients								
P100								
Peak	0.55	0.20	-0.40	0.71	-0.78	-0.53	0.13	-0.87
Lat	0.93	0.40	0.22	0.62	-1.00*	-0.70	-0.48	-0.80
N170								
Peak	-0.45	-0.32	-0.11	-0.79	0.71	0.63	0.38	0.92
Lat	0.00	0.14	0.08	-0.63	-0.31	-0.48	-0.35	0.41
FP1 P300								
Mean	-0.94	-0.95	-0.94	-0.98	1.00*	1.00*	1.00	1.00*

[§]**N:** Neutral, **H:** Happy, **A:** Angry, **S:** Sad

The P100 peak in control subjects shows the expected positive correlations with PC and negative correlation with RL. However, the correlations are low and satisfy significance level only with happy emotion RL. In schizophrenia patients there is a variability between task conditions. Expected and significant positive correlation with PC is observed with happy facial stimuli but is either lower or negative for other trials. All the task conditions except angry stimuli show the expected negative correlations with RL. In schizoaffective disorder patients, none of the correlation between the P100

amplitude and behavioural data are significant. However, they exhibit the expected trends except with behavioural measures from angry stimuli.

The P100 peak latency has close to zero correlations with PC and as expected, positive values with RL. In schizophrenia patients there are no significant correlation with either PC or RL. However, longer RL are seen with higher peak latency in all task conditions except the neutral stimuli. In schizoaffective disorder the correlation patters are opposite of what is expected and even significant with neutral average response latency.

As the N170 component produces a negative peak at P8 electrode, absolute values were used to compute the correlations. In control subjects, the N170 peak amplitude does not show the expected correlation trends with PC. However, an expected pattern is observed between N170 peak amplitude and RL. In schizophrenia patients, a clear pattern of increased PC and shorter RL is seen for larger N170 amplitudes. The correlations are low in most cases but are significant with happy stimuli RL. Schizoaffective disorder patients show exactly opposite and unexpected patterns that are not significant. The N170 peak latency has low correlation with all measures from the control group. None of the correlation from the patient groups are significant and show mixed relationships across task conditions.

The mean P300 amplitude at FP1 has small correlation with the performance measures in control subjects. In the patient groups, some of the correlations are significant, but most do not agree with the hypothesis previously mentioned. In schizophrenia patients, the desirable pattern is seen with PC of happy and sad stimuli and RL of neutral and sad stimuli. In schizoaffective disorder patients the pattern is completely opposite of what is hypothesized.

7.5.5 CORRELATIONS WITH DEMOGRAPHIC DATA

All the patients were scored by the clinical staff on the day of experiment using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) questionnaires. The PANSS scale has three different sub scales rating the patient's negative (PANSSN), positive (PANSSP), and general (PANSSG) symptoms. The scores of all the patients have already been shown in table 7.1.

Figure 7.9 shows the correlations between the ERP measures extracted in the section 7.5.2, and the various scores assigned using the PANSS and MADRS scale, along with the age of the patients. The rows from top to bottom in the figure represent correlation with a. P100 peak, b. P100 latency, c. N170 peak, d. N170 latency, and e. P300 mean. In each row, the plot on the left depicts correlation values for schizophrenia patients, while the plot on the right is for schizoaffective disorder patients. Each image plot has values for pairwise correlations between the four task conditions and five demographic measures. The significant correlation values are marked with an asterisk (*).

No significant correlations are seen in either patient groups with the P100 peak amplitude (fig 7.9a). However, most correlations are negative which implies that patients who are older and with more severe symptoms have smaller P100 peak amplitude. In a few cases the P100 peak amplitude exhibit positive correlations. In schizophrenia patient, positive correlations are seen between happy stimuli and symptom scores. In schizoaffective disorder patients, correlations are positive between all task conditions and MADRS score. No significant correlations are observed with the P100 peak latency (fig 7.9b) either. Positive values are expected in these plots. These signify that older patients and patients with more severe symptoms also exhibit longer P100 peak latency. This is seen only with the age factor of schizophrenia patients and MADRS score of schizoaffective disorder patients.

Like in correlation with behavioural measures, the absolute values of N170 peaks are used while computing the correlations in figure 7.9c. In schizophrenia patients, older age is associated with smaller N170 amplitude, while all the other symptom measures show an unexpected positive correlation. The values are also significant in the case of happy stimulus. In schizoaffective disorder patients, negative correlation values are observed with only the MADRS score. The N170 latency is longer in schizophrenia patients that are older and have severe symptoms, but the correlations are small, and do not meet the significance criteria. In schizoaffective disorder patients, longer N170 latency is mainly seen in patients with higher MADRS score.

The mean P300 amplitude at electrode FP1 is smaller in schizophrenia patients with more severe symptoms, except in the sad stimuli case. Also, older schizophrenia

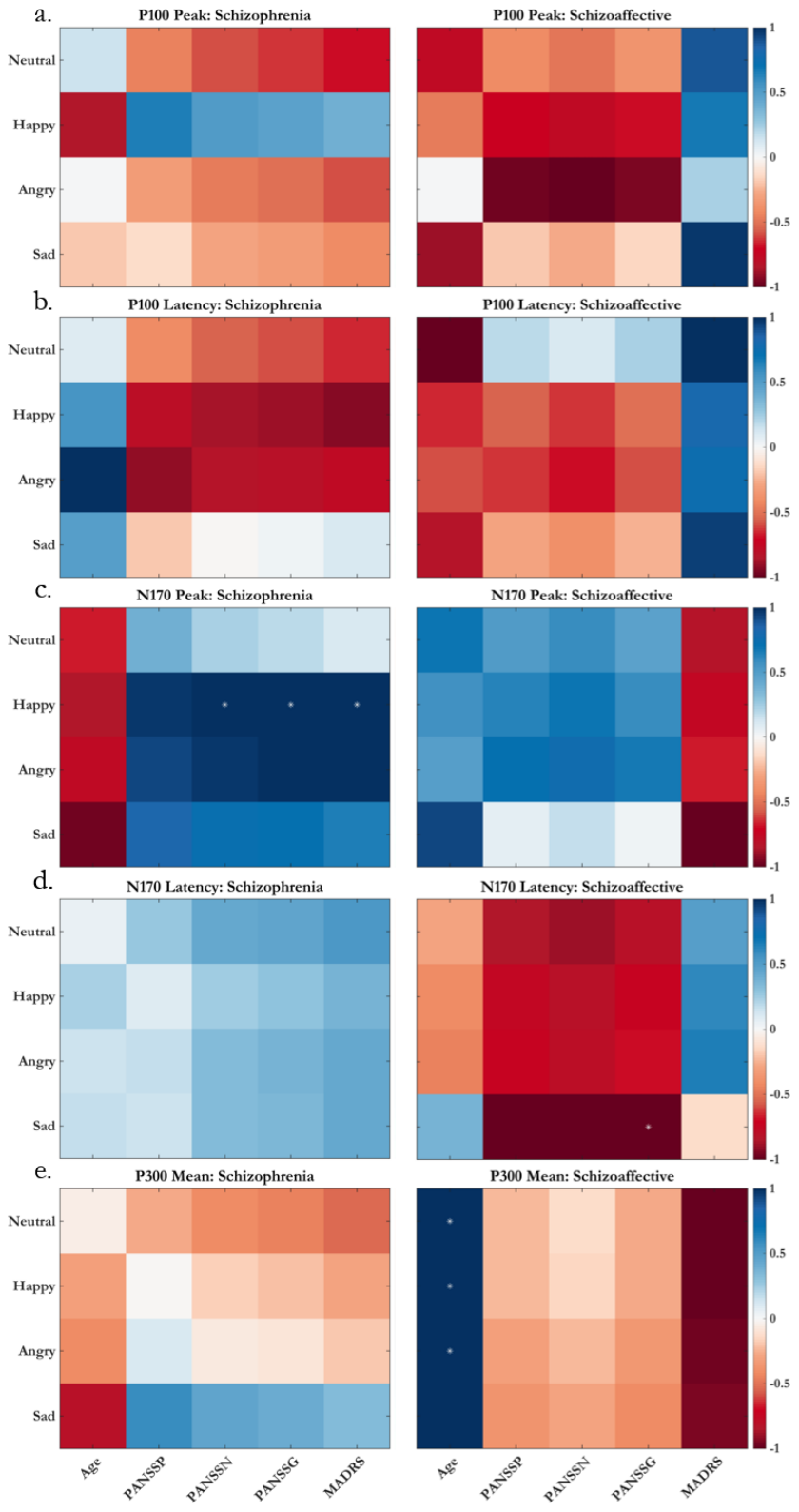


Figure 7.9 Correlations between ERP measures from emotion recognition task and symptom severity scores in patients.

patients have smaller P300 amplitudes. However, all the correlation values are relatively small and do not meet the significance criteria. In schizoaffective disorder patients, the PANSS scores show small negative correlation and the MADRS scores show a larger negative correlation. The age of the schizoaffective disorder patients, however, show unexpected positive and significant correlations with mean P300 amplitudes.

The correlations between age of the control group, and the various ERP components were also measured. Most of the correlations were not significant, but weak negative correlations with both P100 and N170 peak amplitudes implied that, older control subjects were likely to have smaller peak amplitudes. There were also small positive correlations between age and P100 peak latency. N170 peak latency correlation with age in control subjects were the only measure showing significant correlations. N170 peak latency had a significant positive correlation with age during the angry ($r = 0.54$, $p = 0.019$) and sad trials ($r = 0.66$, $p = 0.003$), while a significant negative correlation during the happy ($r = -0.59$, $p = 0.009$) trials. Correlations between age and P300 mean amplitude in control subjects were small and non-significant.

Lastly, correlations between the behavioural measures and the symptom severity measures in patients were also computed. These correlations are plotted in figure 7.10 with the patient groups in two columns, percent correct measures in the top row, and the mean trial response latency measure in the bottom row. The significant correlations are marked with an asterisk (*). Both groups of patients show smaller accuracy with older age, except in the case of angry stimuli in schizophrenia patients. The correlations of percentage of correct trials with the PANSS and MADRS scores are positive and not significant. It is expected that patients with more severe symptoms would likely be worse at performing the task, but this is not the case. The mean trial response latency also show an expected relationship with the age of patients. In all cases older patients are slower in their response and correlation are also significant in schizoaffective disorder patients. The trial latency does not show the expected relationship with the PANSS and MADRS scores. That is, patients with more severe symptoms exhibiting shorter average trial response latencies. No significant

correlations were found between the performance measures and age of the control group.

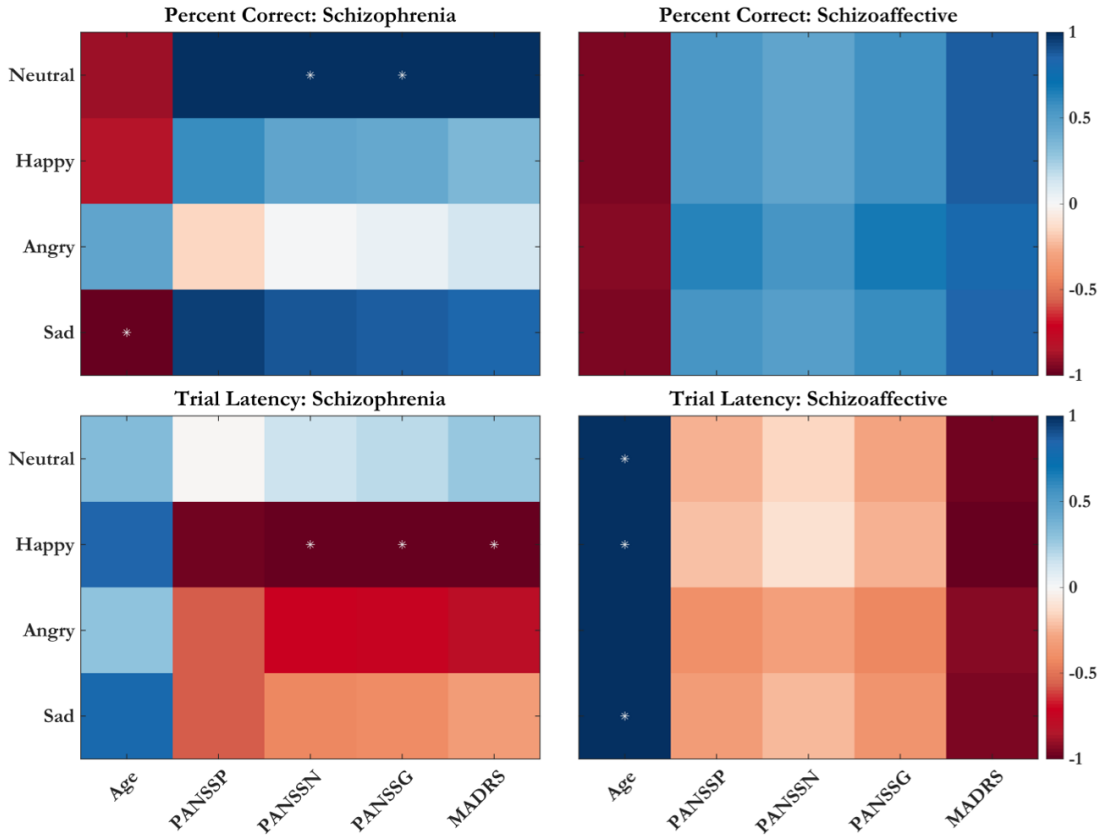


Figure 7.10 Correlations between behavioural performance measures from emotion recognition task and symptom severity scores in patients. Left column: schizophrenia patients, right column: schizoaffective disorder patients, top row: percentage of correct trials, bottom row: average trial response latency.

7.6 Discussion and Conclusion

In this chapter a computerized facial emotion recognition task was used to study deficits in the patients diagnosed within the schizophrenia spectrum of disorders. To limit any exaggerated reactions from patients, schematic faces were used instead of real human faces displaying various emotions. The task used only four primary emotions—neutral, happy, angry, and sad, which could be easily represented by schematic diagrams. Both behavioural and neurophysiological data was collected and analysed to study the differences between healthy control group and patients.

The behavioural analysis revealed that patient had significant deficit in correctly recognizing emotions and were also slower in their response. A statistical analysis of

the data pointed towards larger differences within the patient group, between the two clinical diagnoses of schizophrenia and schizoaffective disorder. Schizophrenia patients made significantly more errors than both the control, and schizoaffective disorder patients. These errors were further pronounced in the angry and sad task conditions. The mean trial response latency in schizophrenia group was also much longer, compared to both the control subjects and schizoaffective disorder patients. There has been variability in literature about how behavioural performance is dependent on emotion type. Both the earlier mentioned studies with meta-analysis on behaviour response (Kohler et al., 2010; Savla et al., 2013), did not account for the task condition as a factor in their analysis. These studies also found that patients with different clinical diagnosis within the schizophrenia spectrum, were either lumped together in experiments or did not show significant differences in performance. Therefore, the findings from this chapter need to be further investigated with larger group size.

The ERP response from this experiment was visualized over the whole grid of electrodes on the scalp. The differences between the control and patient groups were compared for each task condition. Statistical tests conducted on the ERP waveforms, showed significant differences between control and patient groups, on a variable set of electrodes for each task condition. It was interesting to see that the frontal FP1 (and to certain extent FP2) electrode was always a part of the set. This electrode was especially prone to artefacts from eye movement and blinks, due to its proximity. Therefore, when it was found that the activity on this electrode was significantly different between healthy control and patients, the inspection of EEG signals before and after ICA artefact rejection was revisited. This second pass at visually inspecting the time series, and studying the changes after artefact suppression, assured that any eye related components from all the test subjects were greatly reduced or eliminated. For these reasons, the difference observed at electrode FP1 in this experiment were very unlikely to be a result of artefact in the EEG data.

The ERP plots showed large face processing related P100 and N170 components at the P8 electrode, specifically in control subjects. The component amplitudes were lower for patients in the ERP plots, but the statistical analysis on the time series data did not find significant differences in that region. One likely explanation to this could

be that the components occurred for a short duration, and the time series signal rapidly changed its polarity from large positive to large negative value. Therefore, to further determine the statistical differences between healthy subjects and patients, the peak amplitude and latency values were extracted for both P100 and N170 components at electrode P8. The mean amplitude of the P300 region at electrode FP1 was also computed. All these extracted measures were analysed using ANOVA. The results of ANOVA showed all measures except P100 latency were significantly different in patients. Both P100 and N170 peak amplitudes were significantly smaller in patients, compared to the control group. N170 peak latency was significantly longer, and P300 mean amplitudes were significantly larger in patients. Though there were small differences between the schizophrenia and schizoaffective disorder patients, none of the measures derived from ERP responses were significantly different between the two groups. Except for the FP1 P300 results, which were not found in our search of published studies on the topic, the results in this chapter were found to be consistent with the findings from earlier research (Earls et al., 2016; McCleery et al., 2015).

To study the spectral variation in the EEG activity, ERSP analysis was conducted at the FP1 and P8 electrodes. Differences in the delta/theta band synchronisation at the P8 electrode were found, with healthy controls showing significantly strong synchronisation early in the trial compared to patients. To our knowledge there has been only one recent study that has reported analysis of time frequency signals during a face perception and emotion recognition task (Marosi et al., 2019). The paper by Marosi and colleagues reported a significantly weaker theta synchronisation in patients from the parieto-occipital region of scalp in the 140-200ms post-stimulus. These results agree with the observations in this chapter. Significant differences at FP1 electrode ERSP were also found in this chapter, which were not found in our search of the literature on facial emotion recognition tasks with EEG recordings.

The correlation analysis conducted across the behavioural, neurophysiological, and demographic measures, yielded less than satisfactory results. This was likely a result of smaller number of subjects, especially in the patient groups. It should also be noted that, several of the papers reviewed earlier in this chapter, did not find concrete correlations between similar measures extracted from either behavioural performance or EEG data, and symptom severity in patients quantified by clinical assessment scales.

The experiment carried out in this chapter was conducted on small healthy control and patient groups. Also, face schematic stimuli was used instead of real human faces. Even with these factors, statistically significant deficits in patients were observed. Moreover, large behavioural differences were also seen between the patient groups based on their clinical diagnosis. Addressing the drawbacks in the experiment can further tease apart subtle differences between the patients within the schizophrenia spectrum of disorders, but diagnosed with different specific clinical categories. Using either more realistic face schematic, or real human faces could potentially show more precise differences in the EEG activity. The results from this study showcased that a facial emotion recognition task could be an important part of an early diagnostic protocol for schizophrenia spectrum of disorders. This task provided insights into a set of deficits experienced by patients that directly affect their daily social interactions and quality of life, quite unlike the other experiments described in this thesis.

CHAPTER 8. KEY FINDINGS

The current protocol was studied across healthy control subjects and patients diagnosed within the schizophrenia spectrum who can be considered as chronic patients. Schizophrenia is a multidimensional disorder that encompasses a multitude of symptoms like, positive symptoms (hallucination, delusions, etc.), negative symptoms (diminished emotional expressions, lack of motivation, etc.), and cognitive deficits (poor working memory, lack of insight, etc.). The protocol studied in this thesis aimed at quantifying different deficits in a small and heterogenous patient group. Three of the patients included in this study had the clinical diagnosis of schizophrenia, while the other three had the diagnosis of schizoaffective disorder. The age of the patients also ranged from 26 to 64 years. This chapter summarizes the findings from the different experiments that were carried out and describes a basic approach to how findings from different experiments can be combined to be more informative than a single experiment.

8.1 Mismatch Negativity

Chapter 4 described the results and observations from the auditory oddball experiment conducted in the healthy control and patient groups. The auditory oddball paradigm was based on a widely accepted paradigm proposed in (Näätänen et al., 2004). This paradigm efficiently used standard tones and five different types of auditory oddball or deviant tones (duration, frequency, intensity, location, gap) in a single experiment that lasted approximately 25 mins long. The mismatch negativity (MMN) signal obtained from the difference of ERP response to standard and deviant stimuli during an auditory oddball experiment is a representation of automatic pre-attentive alerting mechanism observed in healthy subjects. It has been used as an index for attention switching capacity, loss of grey matter, etc; more so in patients demonstrating psychotic behaviour than other neuropathologies (Näätänen et al., 2012).

Using the multiple-deviant paradigm proved advantageous as the analysis of the EEG recordings during the task showed differences in the responses to the 5 deviant tones. Event-related potentials analysis (ERP) showed that each deviant type produced unique responses. As a result, MMNs obtained from comparing the deviant ERPs with standard tone ERP were observed to exhibit variable time domain characteristics

including average/peak amplitude and peak latency. These ERP measures were extracted from each deviant type, from both the healthy control and patient group subjects and at multiple recording locations from the midline electrodes (Fz, FCz, Cz, CPz, Pz). This generated a large and comprehensive dataset of objective measurements from each single experiment. Applying analysis of variance (ANOVA) on these measurements, statistical differences were seen based on multiple factors including the deviant type, subject group (control, schizophrenia, schizoaffective), and recording location. The average MMN amplitudes for all deviant types were found to be largest at the frontal electrodes Fz and FCz. Both the schizophrenia and schizoaffective disorder patients showed a significant decrease in average MMN amplitude when compared to healthy control subjects. For the MMN peak amplitude, an interaction was also observed between the subject groups and electrode location. Compared to the control subject group, the peak amplitude was significantly reduced in patient groups only at the first three midline electrodes (Fz, FCz, and Cz). The MMN peak latencies were also found to be significantly longer in both the patient groups, when compared to healthy control subjects. The MMN peak latencies showed an interaction between the deviant type and subject group factors. The location deviant MMN peak latency was found to be significantly longer in schizophrenia group compared to both control and schizoaffective disorder group. On the other hand, duration and gap deviant MMN peak latencies were significantly longer than control group only in the schizoaffective disorder patients. This analysis displayed the importance of recording from multiple locations and using multiple deviant types. The analysis also highlighted that there were differences, not only between healthy controls and patient groups, but also within the patient group.

The observations of the EEG response to the auditory oddball task were furthered by studying the time-frequency decomposition or event related spectral perturbation (ERSP) of standard and deviant tones. Visualizing the average control group ERSP at the Fz and Cz electrodes showed a synchronisation of the delta/theta band (2-16Hz) within the first 200-300ms of stimuli. It also showed that this synchronisation was stronger when deviant tones were presented. Though all the deviant ERSP responses showed these similarities, they also showed differences in the synchronisation patterns and relative timing. When compared to the standard tone

ERSP, the intensity deviant ERSP response showed a desynchronisation of delta/theta band activity following the initial synchronisation. Similar to the MMN amplitude, the relative delta/theta band synchronisation to deviant stimuli were weaker or absent at a group level in patients. Also, similar to the MMN response, there were subtle differences between the patients diagnosed with schizophrenia and schizoaffective disorder. These differences varied across the deviant types and have been detailed in Chapter 4. Statistical comparisons were made between the standard and each deviant ERSP, but the higher-level features like peaks and latencies were not extracted from the ERSP response. The ERSP response was visualized to better understand the underlying frequency contribution to the time-domain signal. Extracting higher level features would have only diminished the granularity provided by the analysis.

The MMN peak amplitude and peak latency measures computed at electrode Fz were correlated with the patient PANSS (Kay et al., 1987) and MADRS (Montgomery & Asberg, 1979) scores. The results from this analysis were not encouraging as we did not find many significant correlations or that agreed with the previously reported literature. While this analysis would benefit from larger patient population, it also likely signified that the MMN response was a result of complex processes and interactions in the brain. Thus, it was unlikely to be completely defined with correlations computed between high level features extracted from experimental measurements and clinical ratings of patients using the PANSS and MADRS questionnaires. Each type of analysis provided with different insights about a subject and added to a multi-dimensional descriptor that defined their neuropathology. Same was applicable to behavioural measures computed from other tasks in this thesis. These objective measurements from the subjects defined a set of physiological and behavioural response measures that incorporated a more holistic view of an individual. New subjects can be studied in the context of their position in the high-dimensional distribution created by these measurements, taken from either healthy control subjects or patients with known clinical diagnosis. This could provide a suitable starting point for physicians diagnosing these subjects within a clinical setting. This idea is further explored in section 8.5 and Chapter 9.

The statistically significant results from the auditory oddball experiment were encouraging. The task is especially important in diagnosing patients within the

schizophrenia spectrum of disorders as it does not involve active participation of the subjects. Having observed statistical differences between patient groups in measures computed from EEG response increased the significance of the experiment, and further justified its inclusion within a diagnostic test protocol like DeSIPhER.

8.2 Stroop Task

Chapter 5 outlined the findings from administering a computerized Stroop task. This type of task has long been used in psychology and neuroscience research to study the information processing and conflict resolution capabilities. It has also been extensively used in studying the decline in these processes caused due to various neuropathologies. In this experiment the subjects were presented with two types of trial: congruent (colour name written in same colour ink), and incongruent (colour name written in a conflicting colour ink). The subjects were instructed to select the correct trial type within a set response period. EEG activity was also simultaneously recorded while the subjects were performing the task. One of the major drawbacks of this experiment was the change in task parameters between healthy control subjects and patients which was done to make the task easier to perform for the patients. This was done after the experiment was conducted with the first patient P1 and it was observed that he had significant difficulty in performing the task (22% accuracy). An amendment was made to the protocol and the stimulus duration was increased from 150ms to 200ms, and the response window was increased from 1000ms to 1200ms for rest of the patients. This change prevented us from making any direct comparisons between the control and patients groups. The analysis was focused on studying the differences between the response to congruent and incongruent task conditions within each group. We also grouped the schizophrenia and schizoaffective disorder patients separately to examine any differences in their response.

The first analysis for this experiment was conducted on behavioural performances of healthy controls and patients. Upon this analysis, the second major drawback of the experiment was encountered. Stroop effect – that is an increase in the response time during incongruent trials compared to the congruent trials, was not observed in both the groups. Instead, 18 out of the 24 total subjects (18 healthy controls, 6 patients) control showed an increased average response latency to the

congruent trials. It is likely that the larger number of incongruent trials (approximately 75%), and the use of "MATCH"/"NO MATCH" response, were the reasons why the traditional Stroop effect was not elicited. Section 5.5.1 investigated the behavioural results and discussed the changes that could be made to observe the desired results. The behavioural analysis of the task showed that despite making the task easier for the patient group, patients had significant difficulty in performing the task with only one patient with accuracy greater than 90%. All control subjects had an accuracy of greater than 90%.

EEG data was analysed using ERP and ERSP measurements. Statistical tests revealed significant differences between congruent and incongruent trials in healthy control subjects. In patients these differences were not significant which likely also resulted in the decline in behavioural performance of the group. EEG measures P300 peak amplitude and P300 peal latency were computed from both the control and patient groups. The P300 peak amplitude showed a pattern across the five midline electrodes (Fz, FCz, Cz, CPz, and Pz) which was opposite between patients diagnosed with schizophrenia and schizoaffective disorder. Similar to the MMN findings from Chapter 4, this finding pointed towards differences between the patient groups based on their clinical diagnosis. Specifically, from the Stroop task, it was demonstrated that the poor performance in schizophrenia patients was likely a result of difficulty in motor preparation, while in schizoaffective disorder patient a result of lack of frontal processing of interfering stimuli.

The ERSP analysis in healthy control group showed a stronger frontal synchronisation of delta/theta band activity, associated with distinguishing the type of stimuli, was seen earlier in the trial. This was followed by a larger parietal desynchronisation of alpha/beta activity, representing the motor response preparation and execution. This pattern of response was observed in both congruent and incongruent trials, with congruent trials showing both stronger synchronisation of the delta/theta band, and stronger desynchronisation of the alpha/beta band. The two patient groups showed differences in their ERSP measures. In schizophrenia patients, the delta/theta synchronisation was weak, and alpha/beta desynchronisation was strong. In schizoaffective disorder patients, delta/theta synchronisation was absent in both task conditions, and alpha/beta desynchronisation was stronger compared to the

schizophrenia patients. This further indicated that there may be a lack of frontal processing in schizoaffective disorder patients, while the motor preparation and execution activity was not affected. In both the patient groups the desynchronisation of activity had a wide spread both time and frequency dimensions.

Correlation analysis was used to establish a relationship between behavioural response, EEG activity, and demographic data of healthy controls and patients. Significant relationships were found only in a few cases. This was not very encouraging and could benefit from data collected from larger groups of both healthy control subjects and patients, and a more robust Stroop task design.

8.3 Cognitive Testing Using CANTAB

In Chapter 6 the healthy control subjects and patients were subjected to a set of behavioural tests designed for cognitive assessment. Patients diagnosed within the schizophrenia spectrum suffer from moderate to severe cognitive decline, with cognitive impairments even preceding the onset of psychosis (Keefe & Harvey, 2012). The computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) was used for administering the cognitive tests. Five tests were chosen to assess motor coordination (Motor screening or MOT), speed of response (Reaction time or RTI), visuo-spatial memory and association (Paired associate learning or PAL), spatial working memory (SWM), and verbal memory (Verbal recognition memory or VRM). Shortened versions of the tests were chosen to obtain a quantitative measurement of these cognitive abilities in a relatively short time. On average the experiment took a total of approximately 40 minutes.

Based on the task, different measures of cognitive performance were computed for both the healthy control subjects and patients. Several conclusions were drawn using t-test statistical comparisons between the group performances. The MOT and RTI task outcomes demonstrated that although the patients were able to grasp the task objective, they had a slower response and longer movement durations. In the PAL task, the patients made significantly more errors than the control subjects. These observations have been previously shown to be indicative of hippocampal loss (Kéri et al., 2012), and an early sign of psychosis (Bartók et al., 2005). The spatial working memory task quantified how efficiently a subject was able to retain and access the

information needed to perform the task. The results from the experiments suggested that patients had significantly more difficulty in strategically carrying out the task. The spatial working memory performance was also found to be dependent on the age of both controls and patient groups. In the VRM task, patients were observed to have significantly more difficulty in recalling the words previously presented to them. Compared to the healthy control subjects, they were also more likely to pick the wrong word when presented with a choice between a previously presented word and a distractor.

Further, correlations across the different task performances were computed to determine if they were informative of each other. In both control subjects and patients, similar measures like the error and strategy scores in SWM task were significantly correlated. In patients, compared to healthy controls a relatively greater number of significant relationships between task performances were seen. This was likely due to the overall decline in performance on all tasks in the patient group. Tasks chosen in the CANTAB experiment were selected to capture different cognitive abilities of the subjects. The results from the inter-task correlations further strengthened our confidence that performance in any given task could not be reliably inferred from another. Correlations were also calculated between task measures and the scores assigned by the PANSS and MADRS assessments of patients. No significant relationships were found, indicating that the two assessments carried out by clinically trained staff contained important information not easily captured by the cognitive tests. Unlike the two previous experiments, extensive comparison within the patient group based on their differing clinical diagnosis was not reported. This was because no statistical differences were observed between the schizophrenia and schizoaffective disorder patients, except in the case of mean error in MOT task (two-sample t-test, $p=0.045$).

8.4 Emotion Recognition Task

Facial emotion recognition task elaborated in Chapter 7 was the final experiment conducted in the pursuit of a comprehensive diagnostic protocol. This experiment was included in the protocol to specifically study and quantify the emotional deficits exhibited by patients within the schizophrenia spectrum of disorders. In this

experiment, subjects had to perform a simple facial emotion recognition task by categorizing the facial schematic images presented on the screen as either neutral, happy, angry, or sad, by using a button press response. The behavioural responses along with the EEG activity during the experiment were recorded for post-hoc analysis.

The behavioural response to the task showed a large deficit in patients when compared to the control subjects (fig 7.2). The deficit in schizophrenia patients was significantly larger than the deficit in schizoaffective disorder patients. Schizophrenia patients had the highest error rates in the angry and sad trials. The average trial response latency in schizophrenia patients was also much longer, while the schizoaffective disorder patients exhibited response latencies that were closer to that of control subjects. It was interesting to see significant behavioural differences between the two patient groups, unlike in previous experiments.

A different approach was taken in the analysis of EEG data collected during this experiment, when compared to the auditory odd-ball and Stroop tasks. Those two tasks have been widely researched for decades and a standardized set of analysis already exists. The study of emotion deficits in schizophrenia spectrum of disorders is relatively new, and researchers have been exploring different tasks, types of stimuli, analysis methods, etc. in this field. This was evident from research papers reviewed in Chapter 7. Due to the novelty of the task employed by the research community, the EEG activity from all the electrodes was analysed, unlike the previous two EEG experiments. Also, as opposed to looking for differences in responses between task conditions, which is critical both in auditory oddball and Stroop tasks, the group level differences were targeted for each type of facial emotion stimuli.

The time-series ERP analysis of all the electrodes on the scalp (fig 7.3 to 7.6) led to the finding that frontal electrodes FP1 and FP2 showed statistical differences between control subjects and patients for every facial emotion stimulus (neutral, happy, angry, or sad). Large facial perception related ERP components, namely: P100 and N170, were also observed at electrode P8 in control subjects. These components were diminished in the patients. Measures were extracted for statistical analysis from the facial perception components, and frontal FP1 electrode. Significant results were found in all the cases, which reinforced the findings from literature and added a new

finding from the activity observed at FP1. Unlike the previous two EEG experiments, the measures extracted from the ERP waveforms did not show statistical differences between the schizophrenia and schizoaffective disorder patients.

ERSP analysis was also conducted on the FP1 and P8 electrodes. Due to the lack of difference in the ERP response between the schizophrenia and schizoaffective disorder patients, all patients were grouped together. Statistical comparisons made between healthy control subjects and patients showed significant differences. The response at electrode FP1 in patients showed a weaker delta/theta synchronisation when compared to the control subjects. Similar patterns were observed in the response at P8 electrode with very weak or absent delta/theta synchronisation in patients when compared to the control subjects. The absence of delta/theta synchronisation reflected the diminished P100 and N170 components in the patient group. At both the FP1 and P8 electrodes, patients had a wider time and frequency spread in alpha/beta desynchronisation when compared to the control group alpha/beta desynchronisation.

The attempts at establishing relationships between behavioural measures, EEG measures, and subject demographic data, were mostly unsuccessful. This could be attributed to factors like smaller patient group (more so when it is split by clinical diagnosis), complex relationships between the EEG dynamics and manifestation of behaviour, and subjective variability in how the symptom severity scores were assigned. However, the results obtained from a small number of subjects for this simple facial emotion recognition task, were encouraging. Also, this task gave a perspective of the emotional deficits in patients, which was missing from the other experiments in the protocol. All these reasons warrant for a study with larger sample size, more specifically with patients spanning the spectrum of schizophrenia disorders.

8.5 Combined Analysis

In the chapters of this thesis, and as summarized in the previous sections, behavioural and/or neurophysiological responses were investigated from individual experiments. However, a kitchen-sink analysis of observations from all experiments has the potential of being more informative than each individual experiment. While an extensive study on combining and analysing the various behavioural and EEG measures is out of the scope of this thesis, we used Principal Component Analysis

(PCA), a popular dimensionality reduction technique, on measures computed across the experiments. PCA can be used to visualize the high-dimensional heterogeneous distributions of data collected from different experiments by projecting it in 2 or 3 dimensions.

Table 8.1 Experimental measures used as features in PCA analysis.

Experiment	Number of Features	List of Features
Mismatch Negativity	10	• MMN peak amplitude at Fz from all deviants (5) • MMN peak latencies at Fz from all deviants (5)
CANTAB	13	• MOT (1) – Median latency • RTI (6) – Simple accuracy score – Five-choice accuracy score – Mean simple reaction time – Mean five-choice reaction time – Mean simple movement time – Mean five-choice movement time • PAL (2) – Total adjusted errors – Total adjusted errors (6 shapes) • SWM (2) – Between errors – Strategy • VRM (2) – Immediate Free recall correct – Immediate Recognition correct
Facial Emotion Recognition Task	28	• N170 peak amplitudes (4 emotions) • N170 peak latencies (4 emotions) • P100 peak amplitudes (4 emotions) • P100 peak latencies (4 emotions) • P300 at FP1 mean amplitude (4 emotions) • Behavioural measures: (8) – Percent Correct (4 emotions) – Response Latency (4 emotions)
Total	51	

Table 8.1 lists all the 51 experimental measures that were used to as input features to the PCA algorithm. Only the measures computed from 3 out of the 4 experiments were used for this analysis as a direct comparison between control and

patient groups could not be made for the computerized Stroop task. We can see from the table 3.2 in Chapter 3 that 15 out of the 19 healthy control subjects recruited for this study completed the mismatch negativity experiment, CANTAB, and emotion recognition tasks successfully. Therefore, data collected from 15 control subjects and all 6 recruited patients was used to compute the principal components with the PCA technique.

The reduced 2-dimensional visualization of the 51 features is shown in figure 8.1. Figure 8.1a shows the plot of cumulative variance of the 21 principal components (restricted to 21 by the total number of observations), and figure 8.1b visualizes the distribution of all subjects in first and second principal component. The gradual increase in the cumulative variance (fig 8.1a) signifies that the data collected by the experiments is varied and cannot be captured by a few dimensions. The figure 8.1b shows that even with only 56% of the variance accounted by the first two principal components, the patient distribution can be easily separated from the control subjects. The distribution shows some interesting patterns. The first principal component that accounts for approximately 43% of variance in the data splits the subjects in two groups with all control subjects on the left side of the x-axis. All the patients except Patient P2 are separated from the control subjects on the right side of x-axis. The second principal component which accounts for an additional 13% of the variance in

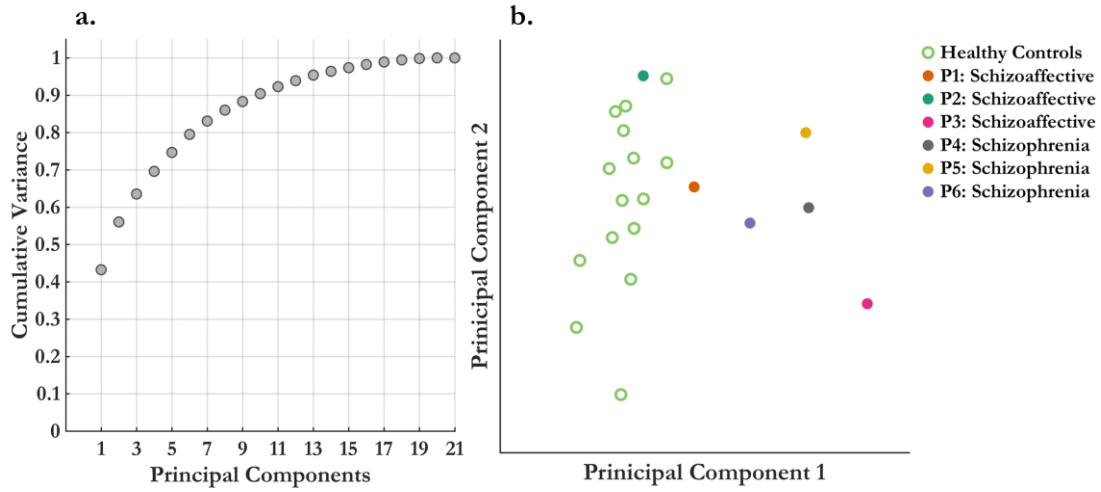


Figure 8.1 Dimensionality reduction and visualization using PCA computed on measures obtained across experiments in the protocol. a. Cumulative variance captured by PCA components. b. Subject distribution in two-dimensional space created by first and second principal components.

the data is observed to capture the differences across the control subjects. This is shown by the lighter green (no-fill) circles for individual control subjects spanning the y-axis of the plot in figure 8.1b. Patient P2 who was the youngest patient in our group is seen at upper end of this component. The three patients with schizophrenia diagnosis (P4, P5, and P6), are seen close to one another in the plot. Finally, Patient P3, who is seen furthest away from both healthy controls and other patients, was a patient of schizoaffective disorder with a likelihood of bipolar syndrome disorder.

The results shown in figure 8.1 provide a preliminary demonstration of how data can be combined across the experiments in our protocol. It also shows the benefits of conducting experiments that target different aspects of the pathology exhibited by the schizophrenia spectrum of disorders.

CHAPTER 9. LIMITATIONS, FUTURE WORK AND CONCLUSION

This chapter discusses the limitations of the study, while proposing possible improvements to the protocol. Further, it is outlined how this protocol could benefit from a larger clinical study and be useful for early diagnosis of high-risk patients. The chapter is concluded with suggestions of ways in which the multi-dimensional diverse data obtained from the experiments, can be efficiently used to aid, and guide the physicians in making a diagnosis.

9.1 Limitations and Suggestions for Future Work

The experiments conducted for this study were limited by the number of clinically diagnosed patients recruited within the scope of the study. Only six patients could be recruited within the time frame allotted for the study. Although it was not intentional, all the recruited patients were male. The power of the results and analysis was further reduced due to smaller sample size created by the difference in clinical diagnosis of the patient group. Coincidently, the patient group was split into 50% with three patients with the clinical diagnosis of schizophrenia and the other three categorized as schizoaffective disorder. Therefore, after the data was collected from the patients, it was decided to conduct analysis on the two patient groups based on their clinical diagnosis. As mentioned previously, this led to a lower power in the results. But it also resulted in finding differences in the EEG activity between the patient groups. Data from all the patients as a group on its own was also analysed. Another limitation to note was that the scoring for PANSS (Kay et al., 1987) and MADRS (Montgomery & Asberg, 1979) were not conducted by a single research nurse. Chapter 5 showed that in the Stroop experiment, a traditional Stroop effect was not elicited in both healthy controls and patients. This discrepancy was due to the design parameters of the task. The changes that would be required to observe the desired traditional Stroop effect have been discussed in section 5.4.1.

Having observed differences between the two clinical groups across multiple experiments, it becomes necessary to study larger groups of patients within the schizophrenia spectrum. It is also important to explore the whole spectrum of patients in the study with specific disorders like schizophrenia, schizotypal, schizoaffective disorder, delusional disorder, etc, because each sub-type manifests itself differently in its patients.

One of the major limitation of the study was that the patient group was not age or sex matched with the healthy control group. The effect of difference between the groups on the observations from various experiments is discussed in subsection 9.1.1. There are few other areas where the study could have been improved. These either come in the form of improvements to the methodology, or a deeper investigation into different ways of analysing the collected data. This is discussed in the subsections 9.1.2 to 9.1.4.

9.1.1 LIMITATIONS DUE TO AGE AND SEX

The average age of the patient group recruited into the study was comparatively higher than the average age of healthy control group. The patient group had an age distribution of 48.0 ± 13.6 years (mean ± std) while the healthy control group had an age distribution of 30.4 ± 8.5 years. Also, while the distribution of control group had females (n=9) along with males (n=10), the patient group comprised only of males (n=6). The experiments in this thesis used auditory and visual stimulus while recording behavioural and EEG response in subjects. With the inclusion criteria of normal or corrected vision and the exclusion criteria of colour blindness in both control and patient groups, it can be safely assumed that differences in sight of the two groups were insignificant. While only subjects with normal hearing were included in the study, there were still age and sex related differences in hearing (Roth et al., 2011; Wiley et al., 2008) that were potential confounding factors in the observations made from the auditory oddball task. Also, an age-associated cognitive decline (Deary et al., 2009; Salthouse, 2009) and differences in cognitive functioning between males and females (Miller & Halpern, 2014; Weiss et al., 2003) have been reported. This section highlights how the age and sex differences between our healthy control and patient groups could have biased the observations experiments carried out in this thesis. The observations across all experiments were mentioned except for the Stroop task as no comparison was made between healthy control and patient groups in that task.

9.1.1.1 MISMATCH NEGATIVITY

In the correlation analysis of MMN peak amplitude and peak latency with the age of patients and control subjects (Section 4.5.7) we found results consistent with the published literature. All the deviant MMN peak amplitudes in control subjects were

negatively correlated with their age. This was true for most of the deviant types in patients as well. This indicated an age-related decline in MMN peak amplitude which was consistent with the literature, albeit only for duration and frequency deviants (Cheng et al., 2013; Cooper et al., 2006; Näätänen et al., 2012; Nowak et al., 2016; Pekkonen, 2000; Tsolaki et al., 2015). Therefore, age was one of the confounding factors in the observation of significantly decreased MMN peak amplitudes in the patient groups. A similar argument could be made for the significantly longer MMN peak latency in the patient group, as it has also been shown to increase with the age of subjects (Cooper et al., 2006; Näätänen et al., 2012; Nowak et al., 2016; Tsolaki et al., 2015). In this study, we also found a positive correlation between the age of control subjects and frequency, intensity, and location MMN peak latencies. There was a positive correlation between peak latencies and age of patients in the schizophrenia patient group across all the deviants except for the gap MMN; implying that older the patient, the later the peak of the MMN due to duration, frequency, intensity, and location deviants. In schizoaffective disorder patient group, a positive correlation between the age and peak latencies was observed across all the deviants.

There have been inconsistent reports about the effect of sex on MMN peak amplitude and peak latency (Matsubayashi et al., 2008). Kasai et al. showed no effect of sex on MMN (Kasai et al., 2002). Brossi et al. found significantly shorter frequency MMN latency in females compared to males, and non-significant but larger frequency MMN amplitude in females (Bortoleto Brossi et al., 2007). Toufan et. al found significantly longer MMN latency due to frequency deviant in females than males. Although, larger frequency MMN amplitude were observed in the females than males, the results were non-significant (Toufan et al., 2021). Given the inconsistencies in these results, it is unclear if the presence of females in our control group was a confounding factor. It can be speculated that because females are likely to have larger MMN amplitude based on studies by Brossi et al. and Toufan et al., the differences between the MMN amplitudes of control and patient groups was exacerbated due to absence of female patients.

9.1.1.2 COGNITIVE TESTING USING CANTAB

CANTAB was used to administer standardized cognitive tests to control and patients groups. The effect of age and sex on these tasks is discussed here.

The results from both the motor screening (MOT) and reaction time (RTI) tasks showed that patients were slower in their reaction and movement times when compared to control subjects. Though we did not find significant correlations with most of these measures and ages of our control or patient groups, older individuals consistently show slower reaction times (Berchicci et al., 2013). This is true for both simple reaction tasks and choice-reaction tasks (R. A. Abbott et al., 2019; Falkenstein et al., 2006). This indicated that age factor played a role in the longer reaction times observed in our patient group. The effects of sex were difficult to detect – with some studies finding no significant differences between reaction times of males and females (R. A. Abbott et al., 2019; Keshavarz & Dehghanizade, 2020) and others finding faster reaction times in males (Adam, 1999; Karia et al., 2012). Therefore, it was unlikely that the absence of females in the patient group contributed to any significant difference in the results.

The paired associate learning (PAL) task that tested visuo-spatial episodic memory showed no significant correlation between the age of either control or patient group and the total error. However, Abbott et al. showed a significant effect of the age variable in their linear regression model fitting the PAL total error score (R. A. Abbott et al., 2019). Other studies on episodic memory have also shown an age related decline in middle-aged (48-62) and older (71-83) subjects (Kinugawa et al., 2013; Korkki et al., 2020). This suggested that age was a confounding factor because older healthy subjects showed larger PAL total error. Differences in episodic memory have also been observed in sex-based comparison. Although the study by Abbott et al. did not find sex as a significant factor in their correlation model for PAL total error (R. A. Abbott et al., 2019), other studies have shown males to have a better visuo-spatial episodic memory while females had a better verbal episodic memory. (Herlitz et al., 1997; Herlitz & Rehnman, 2008; Pauls et al., 2013). These observations suggested that with only male patients in the patient group, the increase in PAL total errors likely was not confounded by the sex factor.

The spatial working memory (SWM) task that assessed the spatial memory in control and patient groups resulted in a significant positive correlation of SWM between error and SWM strategy measures with age. A similar observation was made by Abbott et al. with healthy control subjects (R. A. Abbott et al., 2019) and age-associated decline in spatial memory have been previously demonstrated (Barnes, 1988; León et al., 2016). This denoted that performance on this task was confounded by the age of the subjects. Sex-associated differences in spatial memory across multiple studies showed that males are better at spatial memory tasks than females (León et al., 2016; Persson et al., 2013; Postma et al., 2004). The study by Abbott et al. also found males to be better at the SWM task (R. A. Abbott et al., 2019). Also, the observations of better visuo-spatial episodic memory in males compared to females from previously cited research (Herlitz et al., 1997; Herlitz & Rehnman, 2008; Pauls et al., 2013) further confirmed the sex-associated differences. Therefore, the absence of females in the patient group was unlikely to be a confounding factor contributing to the higher SWM error and SWM strategy measures in the patient group.

Lastly, the verbal recognition memory (VRM) task assessed the verbal memory based on free recall of presented words and recognition of presented words in presence of a distractor. While a significantly poor performance in the patient group compared to the control group was observed, no significant correlations of the performance measures with the age of subjects were found. However, published literature has shown an age-associated decline in verbal memory of healthy subjects (Bleecker et al., 1988; Kramer et al., 2003; Lamar et al., 2003). Verbal memory has also been shown to be better in females compared to males (Bleecker et al., 1988; Lamar et al., 2003; Sundermann et al., 2016), with age-sex interactions indicating that younger females do not show age-related decline (Kramer et al., 2003). The most recent meta-analysis pointed to potential bias in the publications, however it concluded that females have a slight advantage over males in specific types of verbal fluency, recall, and recognition (Hirnstein et al., 2022). These observations from published research on verbal memory indicated that age and sex were likely significant confounding factors in the results obtained from the VRM task. The patient group was all male and the mean age of patients was higher than the healthy control group that comprised of both males and

females. Therefore, both the age and sex factors played a role in contributing to the poorer performance on the VRM task.

9.1.1.3 EMOTION RECOGNITION TASK

In Chapter 7 we studied the behavioural response to the emotion recognition (ER) task and observed a deficit in patient group in both the percentage of correct trials and trial response latency. We also found that our patient group (and more specifically the schizophrenia subgroup) were worse at recognizing angry and sad expressions compared to the control group. The patients were also observed to be significantly slower at recognizing happy expressions compared to control subjects. The correlation of the percentage of correct trials and trial response latency measures with age of patients showed that older patients had smaller percent of correct trials, and longer trial response latencies. Age-related decline in facial emotion recognition has been demonstrated in several published studies (Isaacowitz et al., 2007; Khawar et al., 2014; Orgeta & Phillips, 2007; Sasson et al., 2010; Sullivan et al., 2007). There is also evidence of older healthy subjects having more difficulty in recognising negative emotions such as sadness, anger, and fear. Sex-related differences have also been observed in emotion recognition. Female subjects have been shown to be more accurate (Montagne et al., 2005; Sasson et al., 2010; Saylik et al., 2018; Wingenbach et al., 2018) and faster (Saylik et al., 2018; Wingenbach et al., 2018) at emotion recognition. There have also been studies with schizophrenia patients showing sex-related differences (Erol et al., 2013; Weiss et al., 2003). From these previously observed age and sex related effects it was highly likely that both age and absence of females in the patient group were confounding factors in the behavioural observation from the ER task.

The face processing P100 and N170 components measured at electrode P8 in our experiment were significantly larger in amplitudes in control group compared to the patient group. The N170 component peak latency in patient group was also observed to be significantly longer than the N170 peak latency in control group. There is evidence of age (Boutet et al., 2021; Rousselet et al., 2010) and sex (Choi et al., 2015; S. A. Lee et al., 2017; Sun et al., 2017) related differences in these early face processing components. Larger N170 (Choi et al., 2015) and P100 (S. A. Lee et al., 2017) peak amplitudes have been observed in females compared to males. Females

have been shown to have shorter N170 and P100 peak latencies compared to males (Sun et al., 2017). Therefore, similar to the behavioural response in the ER task, it was likely that the deficits observed in face processing components recorded from patient group were confounded by both their age and absence of females in the group.

9.1.2 EEG RECORDING SETUP

In Chapter 3 the recording setup used in the EEG experiments was described. Setting up the EEG recording involved putting the cap on, connecting the electrodes, and using a conductive gel to reduce the impedance for a cleaner recording. The electrodes used in the experiments were passive, meaning the recorded signal had to be transmitted to an external amplifier through cables. Generally, wet passive electrodes record a relatively good quality of signal, however, they have the following drawbacks. The use of conductive gel increases the setup time and is later inconvenient for the subjects, as it needs to be washed off. One of the primary reasons only half the electrodes were used for recording in patients compared to the healthy subjects, was to reduce the setup time. Secondly, as the electrodes are passive, the cables are prone to pick up line noise, and other kinds of artefact before the signal even reaches the first stage of amplification.

In the recent years, active electrodes with built-in amplifiers are becoming more popular. There are also dry-active electrode setups that do not require any kind of conductive material to be applied at the recording site. Several studies have been conducted to compare the performance of active electrodes and even dry active electrodes, with the more traditional wet passive electrode setup. As newer electrodes designs have come forward, the gap between the wet electrodes and dry electrode has reduced (Di Flumeri et al., 2019; Mathewson et al., 2017; Radüntz, 2018). The dry active electrodes also come with an additional advantage of reduced setup time, and no requirement of post-recording clean-up. For these reasons, usage of dry active electrode setup in the experiments could have significantly reduced the setup time, without a significant sacrifice in signal quality. The minor reduction in signal quality could be mitigated with increased number of trials incorporated within the same total duration of the experiment. The reduced setup time would also help with reducing the anxiety and lack of patience, more likely to be observed in patient groups. This would

lead to a more reliable experimental outcome, that is not significantly affected due to the longer wait times before the recording can begin.

9.1.3 EEG SOURCE LOCALIZATION

The EEG activity recorded from the scalp electrodes is a result of many localized regions of neural activity generating the signal. Depending on where in the brain these sources reside, and how strongly they are activated, they all contribute to the activity observed on the scalp electrodes. In the experiments presented in this thesis, the observed scalp activity was analysed for its time-course and time-frequency decomposition. Some conclusions on the region of the activity were also drawn based on the electrode position and activation patterns. However, as the observed scalp activity on any electrode is a combination of many distributed sources (variably influencing it), decomposing and localizing the signal into these underlying sources can be more insightful.

There have been several different techniques and algorithms designed to accomplish these decompositions. Algorithms like minimum norm (MN), LORETA, etc. perform localization directly on the observed EEG activity. These result in smooth source activation maps, either on the surface of the brain, or distributed through its 3D volume (Michel & He, 2019). Another approach is to first decompose the EEG signals using independent component analysis (ICA), followed by fitting dipoles to these components (Delorme et al., 2012). These localization algorithms have been shown to work better with higher density EEG recordings of 64 electrodes to 256 electrodes. Though sources deduced from lower density recordings with <32 electrode arrays can still provide valuable insight, they often result in incorrect or blurred localizations (Michel & Brunet, 2019). Using approximately 32 electrodes for recording EEG from the patient group was one of the reasons source localizations was not pursued in the study. Being able to conduct such type of analysis is another reason in the favour of using high-density (>64 electrodes), dry active electrode arrays with low setup times.

9.1.4 MULTI-VARIATE HIGH-DIMENSIONAL DATA ANALYSIS

Schizophrenia or schizophrenia spectrum disorders manifest in the form of diverse and complex symptomology. Patients suffer from positive symptoms like delusions and hallucination, negative symptoms like diminished emotional expression

and avolition, and cognitive decline. The diversity in the neurophysiology within the patient group participating in this study, was also observed in the analyses carried out on individual patients. The goal in collecting data from multiple experiments for each subject, was to create a holistic picture of the patient's psychological, neurophysiological, and cognitive state.

Several features were observed and extracted from the different experiments, like the performance on various CANTAB tasks, MMN peak amplitudes and peak latencies for different deviant types, etc. Multi-variate statistical analysis on subsets of these features were also carried out, and significant relationships, that were informative of the subjects' behavioural and neurophysiological state, were found. Such analyses can provide the knowledge of feature distributions with respect to a group of subjects, for example patients diagnosed with schizophrenia. However, in a clinical setting, when a new subject/patient is encountered, and similar tests are administered, a prediction needs to be made. This prediction needs to be informative to the physician or the clinical staff, giving them an objective measure about where this new subject lies in the spectrum of healthy individuals, schizophrenia, schizoaffective disorder, etc.

There are several emerging methodologies in the field of data analytics and machine learning that are being adapted in the field of healthcare and medical diagnostics (G. Cho et al., 2019; Foster et al., 2014; Miotto et al., 2018; Mohr et al., 2017; Rahman et al., 2020; Rajkomar et al., 2019; Shatte et al., 2019; Waring et al., 2020). From the data obtained from different experiments conducted in this thesis, for example, a classification model can be created to predict if the subject is healthy, or in the schizophrenia spectrum. This model can then be used on any new subject undergoing clinical diagnosis due to suspected pathology. Another method of using the data would be to apply clustering algorithms like k-means, to differentiate between healthy controls and patient groups. Subsequently, a new subject can be studied in this high-dimensional space. A diagnosis can then be made based on their nearest neighbour among the previously studied subjects. In section 8.5 of Chapter 8 we demonstrated a preliminary analysis visualizing these high-dimensional heterogeneous distributions projected in 2 dimensions using PCA.

The types of data analytic techniques briefly outlined here can only be reliable with larger groups of healthy controls and patients. The larger numbers are required to populate the high-dimensional feature space. With a long-term clinical collection of data from larger group of subjects, an informative database can be created. Such a database, on one hand can be used to make reliable and robust diagnosis of any new subject. On the other hand, it can also be useful in investigating subtle differences between different diagnosis within the schizophrenia spectrum, possibly leading to specific diagnosis and individually tailored treatments for each patient. As the database increases with time, it can potentially lead to new discoveries in the field that were previously impossible due to only a part of the whole being investigated.

9.2 Conclusion

The aim of this thesis was to design a protocol with relatively easy tasks that investigated the heterogeneity in the schizophrenia spectrum of disorders. This heterogeneity manifests itself as a combination of positive, negative, and cognitive deficits observed in patients. Encouraging results were seen with a small sample group of patients when compared to healthy control subjects, giving an assurance that a step in the right direction was taken. The observations from figure 8.1 further reinforced our confidence that a protocol with assessments targeting various aspects of the pathology captured more information than a single diagnostic test.

Currently, the clinical diagnosis of schizophrenia is based on interviews conducted by a mental healthcare professional, such as a psychiatrist, to make a diagnosis based on the set of criteria defined in DSM-5 or ICD-11. These criteria have been evolving over the years, have been set by experts in the field, and tested in studies. However, these criteria do not have a neurophysiological basis and do not require any objective measurements of changes in behaviour or brain function. The major challenges to translate such a diagnostic protocol in a clinical setting would be to firstly incorporate data measures from a larger and more diversified group of healthy subjects and patients. Secondly, standardization of the various steps from collecting the data, to an automated analysis, and interpretation of results will be required. This standardization and automation would reduce the time and expertise needed to collect the data, resulting in minimal overhead in time needed and additional training of the

clinical staff. Thirdly, the biggest challenge would be to collaborate with mental healthcare professional who are inclined to use such a protocol with objective measures to supplement their current method of diagnosis. This would require a larger research study that could be furthered into a country-wide clinical study in this population of patients. Although, this might sound ambitious, the overall idea to have a diagnostic method that can be used for an early intervention for schizophrenia was the primary focus of this work.

The need for standardizing the experimental paradigm, analysis pipeline, and guidance for clinical assessment through questionnaires like PANSS and MADRS, is to reduce the ambiguity and differences between subjects for diagnostic purpose. Further, use of automated data analytics techniques will provide a better understanding of how the multi-dimensional measures are distributed among the population of healthy subjects and patients with varying degrees of pathology. This protocol would be useful with other groups such as, high-risk individuals, individuals in their prodromal phase of schizophrenia, patients who have more pronounced positive symptoms (e.g. auditory hallucinations), etc., to find defining and definitive biomarkers through the various EEG experiments and CANTAB. This can eventually lead to a better understanding of the complex neuropathology of schizophrenia spectrum of disorders. A heterogeneous diagnostic protocol as presented in this thesis, can be a promising tool for mental healthcare professionals who encourage the use of a holistic approach of diagnosis that involves clinical assessment of patient's history, environmental factors, and an objective measurement of behavioural and neurological manifestations in schizophrenia.

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APPENDICES

APPENDIX A - ETHICS APPROVALS

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Professor Robert Hunter
NHS Greater Glasgow and Clyde
Gartnavel Royal Hospital
1055 Great Western Road
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West of Scotland REC 1
Ground Floor - Tennent Building
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G11 6NT

Date 01 June 2015
Direct line 0141 211 6270
E-mail WoSREC1@ggc.scot.nhs.uk

Dear Professor Hunter

Study title: **Developing Schizophrenia Identification using Physiological EEG Response (DeSIPhER)**
REC reference: **15/WS/0083**
Protocol number: **GN15AM117**
IRAS project ID: **103549**

Thank you for your letter (e-mail) of 29 May 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 25 May 2015

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant consent form [Consent Form - Patients]	1.2	28 May 2015
Participant information sheet (PIS) [Participant Information Sheet - Patients]	1.2	28 May 2015
Participant information sheet (PIS) [Participant Information Sheet - Controls]	1.2	28 May 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [control poster]		

Document	*Version*	*Date*
Covering letter on headed paper [CoveringLetterREC200515]	v1	20 May 2015
GP/consultant information sheets or letters [Letter to GP_revised]	v1.1	12 May 2015
Non-validated questionnaire [Medical controls]	1.0	12 March 2015
Non-validated questionnaire [Screening controls]	1.0	12 March 2015
Participant consent form [Consent Form - Patients]	1.2	28 May 2015
Participant consent form [Control consent form]	v1.1	12 May 2015
Participant information sheet (PIS) [Participant Information Sheet - Patients]	1.2	28 May 2015
Participant information sheet (PIS) [Participant Information Sheet - Controls]	1.2	28 May 2015
REC Application Form [REC_Form_13042015]		13 April 2015
Research protocol or project proposal [Project Proposal]	v1.0	12 March 2015
Summary CV for Chief Investigator (CI) [Chief Investigators CV]		
Summary CV for student [Student Researcher CV]		
Summary CV for supervisor (student research) [Conway]		
Summary CV for supervisor (student research) [Lakany]		30 July 2014
Summary CV for supervisor (student research) [Reid]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study Flowchart]	v1.0	12 March 2015
Validated questionnaire [MADRS]		
Validated questionnaire [PANSS]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/WS/0083 **Please quote this number on all correspondence**

Yours sincerely

Abibat Adewumi

Abibat Adewumi
Coordinators Assistant

Copy to: *Dr Erica Packard, NHS Greater Glasgow & Clyde*

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

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West of Scotland REC 1
Research Ethics
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
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(Formerly Yorkhill Childrens Hospital)

Date 20 July 2016
Direct line 0141 232 1807
E-mail WoSREC1@ggc.scot.nhs.uk

Dear Professor Hunter

Study title: **Developing Schizophrenia Identification using Physiological EEG Response (DeSIPhER)**
REC reference: **15/WS/0083**
Protocol number: **GN15AM117**
Amendment number: **Amendment number 1 dated 07/07/2016 (REC Ref AM02)**
Amendment date: **07 July 2016**
IRAS project ID: **103549**

The above amendment was reviewed by the Sub-Committee in correspondence. The amendment relates to the change in the entry criteria from 18-55 years to 18-65 years.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Amendment number 1 dated 07/07/2016 (REC Ref AM02)	07 July 2016
Research protocol or project proposal [Highlighted]	1.1	05 July 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/WS/0083:	**Please quote this number on all correspondence**

Yours sincerely

Abibat Adewumi

On behalf of
Dr Malcolm Booth
Chair

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Erica Packard, NHS Greater Glasgow and Clyde*

West of Scotland REC 1

Attendance at Sub-Committee of the REC meeting on 18 July 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Malcolm Booth	Consultant in Anaesthesia and Intensive Care (Chair)	Yes	Chair of Meeting
Dr Iain Macpherson	Clinical Senior Lecturer in Medical Oncology (Clinical Trials Research)	Yes	
Mr Robin Sim	Investments (Retired)	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Abibat Adewumi-Ogunjobi	Co-ordinators Assistant

APPENDIX B - INFORMATION SHEETS AND CONSENT FORMS

Healthy Control Information Sheet

Participant Information Sheet

Name of department: Biomedical Engineering Department
Title of the study: DeSIPhER-Developing Schizophrenia Identification using Physiological EEG Response

Introduction

Schizophrenia affects about 1% of the global population. Living with a mental illness like schizophrenia is not only very challenging for the patients but also for their family members. It has many symptoms which make diagnosing it very challenging. This study aims to evaluate a set of new experiments which could be useful for early diagnosis in high risk patients.

The set of experiments are designed to study the brain activity of healthy adults using electroencephalography (EEG). Participants should have no previous history of psychiatric, medical, or neurological disorders and no previous history of drug or alcohol abuse.

The experiment will be conducted by researcher Sibani P Mohanty, EngD (doctoral) student at the University of Strathclyde, Biomedical engineering department, as part of her research project.

Sibani P Mohanty, B.E, MSc
Neurophysiology Lab, Biomedical Department, University of Strathclyde

Version 1.2 28/05/2015

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What is the purpose of this investigation?

To understand any abnormalities that patients with schizophrenia might display during the experiments, it is important to understand how a healthy brain functions during the same experiments. This study involves a set of experiments designed to understand cognitive development, emotional responses, and responses to auditory stimuli. This study will help us form a picture of average performance in a healthy population and the data collected from the healthy controls will be used to form a database of healthy subjects before the study is taken to a clinical set up for testing in patients with schizophrenia. The aim is to establish if this experiment is a useful early diagnostic measure for high risk patients of schizophrenia.

Do you have to take part?

Participation is completely voluntary. You are completely free to decide if you want to participate or not. There will be no consequences if you refuse to participate or if you withdraw from participation at any time before or during the experiment, for any reason. Choosing not to participate in this project will in no way influence your standing or relationship with the University.

Why have you been invited to take part?

We are looking to recruit healthy participant in the age group 18-55 years for this study. Participants should have normal or corrected sight, normal hearing and normal upper limb function. Only participants with English as their first language will be included. No specific skill is required for the experiment.

Participants with any neurological, psychiatric, or musculoskeletal impairment or disease; or history of drug or alcohol abuse will be excluded. You will be asked to fill out a screening questionnaire to determine if you meet the inclusion criteria listed in the first paragraph, and that you do not fall under any of the exclusion criteria mentioned in this paragraph.

What are the potential risks to you in taking part?

The recording equipment devices are of medical grade, electrically isolated and periodically inspected. Consequently no risk is predicted regarding the electrical or recording aspects. A skin patch test will be conducted to find out if you are allergic to EEG conductive gel or abrasive gel. If you are found to be allergic, you will not have to go through any further procedures and any of your data will be removed from the study.

The data collected from you will not be used to make any clinical judgements or diagnoses based on the information you provide or the data we record from you.

What will you do in the project?

Before we begin with the sessions, we need to make sure that you meet our inclusion criteria: you will be asked to fill out a screening questionnaire and send it through the e-mail to the researcher Sibani P Mohanty. If you meet our criteria, appointment to conduct sessions 1 and 2 will be fixed with you. Before the commencement of session 1, you will be asked to consent for the study by signing the consent form and then fill in a short medical questionnaire, answering a few questions about your general health and habits before we begin with the experiments in session 1.

During the experiments, the activity from your scalp will be recorded using electrodes on the cap that will be put on your head. A conductive gel is used to fill the gap between the electrodes and your scalp. This is done to obtain a good signal from the scalp. You are requested to wash your hair and towel-dry your hair before you come in for the experiment in order to remove any oil from the scalp. Also, you are requested to make sure to have a good nights' sleep the night before the experiment in order to avoid any tiredness during the experiment.

You will be seated for the entire experiment. We will attach the electrode cap on the scalp and a few electrodes around the eyes. The conductive gel will be inserted through the top of the electrode. To

help improve the signals we will lightly rub the scalp under the electrode using an abrasive gel. This may cause slight discomfort at the time, but is not painful and has no lasting effects. The gel itself is water soluble and easy to wash out. It is highly unlikely that you will have an allergic reaction to the gel or the swabs, and we will test your skin before continuing. If you have a reaction at this point, or at any point during the experiment we will remove the cap and electrodes and you can wash the gel off quickly and easily.

The disposable, single-use earphones are foam inserts, similar to ear plugs, with a small channel for the sound to pass through. The foam is compressed before insertion into the ear canal. Once in place it expands to form a seal against the ear, reducing external noises. The sound levels of the tones that you will hear are carefully controlled and are within safe levels so will not cause any damage to your ears. If you have any problems with in-ear headphones or with your hearing in general, please let us know before starting the experiment.

After the experiment facilities will be provided for washing your hair and scalp to remove the electrode gel.

Session 1:

Task 1: Mismatch Negativity task; Task duration: 25 minutes

You will listen to a series of short tones. The tones will occur every second. The first 10 tones are the standard tone, after which the

standard tones will alternate with tones that have been slightly altered (e.g. different length or frequency). You do not have to pay attention to the tones; you should pay attention to the video you are watching.

Task 2: Stroop task; Task duration: 25 minutes

You will be presented with two blocks (10 minutes each) of a computerized stroop task where in the names of colours written either in the same colour or in a different colour. For example: RED / RED (colour red written in green or in red). You are asked to press response button '**No Match**' for incongruent condition, that is when the name of the colour does not match the meaning of the correct colour on the screen (for example: the word red appearing in the colour green). Similarly, press button '**Match**' for congruent condition. This is a standardized task to study the relationship between speed of processing and executive functioning with working memory and cognitive development. You will be provided with a practice phase of 24 stimuli each before you take up the test phase.

Session 2:

Task 3: CANTAB task; Task duration: 40 minutes

You will then be asked to perform several standardised cognitive tests using CANTAB (Cambridge Neurophysiological Test

Automated Battery), a touch screen tablet. There will be a total of 5 tests not lasting more than 5-10 mins each.

Task 4: Emotional response task; Task duration: 45 minutes

The part 1 of the final task involves viewing faces expressing a number of emotions. You will be presented with a series of schematic faces with standard emotions (happy, sad, angry and neutral/O.K). You need to categorise these as happy, angry, neutral/O.K and sad by pressing buttons on a response pad corresponding to that emotion. The buttons are labelled as 'happy', 'sad', 'angry' and 'O.K'. This task consists of 2 blocks of 10 minutes each with a 5 minute break in between. You will be provided with a practice phase of 24 stimuli before the actual experiment. EEG will be recorded during this task.

In the second part of the experiment, we show you the same happy, sad or angry cartoon faces and you will first need to mimic these expressions back and then imagine an incident where you personally experienced the emotion expressed by the schematic face. While you are performing the above tasks, EEG will be recorded and your facial expressions will be recorded on video and by electrodes on your facial muscles. This experiment will last 15 minutes in total.

Site: University of Strathclyde, Biomedical department, Neurophysiology Lab, Level 3.

Version 1.2 28/05/2015

Duration: 2 hours per session

Compensation/Payments: You will also be given £10 per study session to cover any out of pocket expenses. Also, any travel expenses will be covered by the research team.

Breaks and refreshments will be provided in between each task during both sessions.

What happens to the information in the project?

All the information you provide will be treated as strictly confidential, and will only be accessed by the researchers named on this information sheet. Your data will be anonymised so that only the researchers will be able to identify your data. You will be assigned a unique study identification number when you express an interest in this study, and this number will be used in all subsequent documentation to anonymise any personal or sensitive information. The key that relates your personal details such as name and age will be stored separately and securely from the study data, and will be destroyed at the end of the study so that no one can identify you from the data. Paper copies of the screening questionnaire and medical questionnaire will be securely destroyed once your data has been anonymously added to the study. All data will be encrypted and securely stored on University servers in password protected folders. The University of Strathclyde is registered with the Information Commissioner's Office who implements the Data Protection Act

1998. All personal data on participants will be processed in accordance with the provisions of the Data Protection Act 1998.

Thank you for reading this information – please ask the researcher (Sibani P Mohanty) or Dr Campbell Reid if you have any questions or if you are unsure about what is written here.

What happens next?

If you are interested in taking part, please complete the screening questionnaire and email it back to Sibani P Mohanty. Sibani P Mohanty will then organise a time for you to attend your first session. You will be able to ask any questions you have at this stage. If you are happy with the information you have read, and that your questions have been satisfactorily answered you will be asked to sign the consent form and fill out the medical questionnaire. If you chose not to take part in the study at this, or any other stage, all your data will be removed from the study and any paper documents securely destroyed. You can ask for more details about the study when you have finished both sessions, and you can also ask to be informed if the results are published.

Chief Investigator Details:

Bernard A. Conway, PhD, Professor
Biomedical Department, University of Strathclyde

Version 1.2 28/05/2015

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Prof. Robert Hunter, BSc (Hons); MBChB; MD; MRCPsych; FRCPsych
Consultant Psychiatrist, Clinical Director PsyRING at University of Glasgow, Associate Director R&D NHS Greater Glasgow and Clyde
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E-mail: robert.hunter@ggc.scot.nhs.uk

Researcher:
Sibani P Mohanty, B.E, MSc

Version 1.2 28/05/2015

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This investigation was granted ethical approval by the Department of Biomedical Engineering ethics committee.

If you have any questions/concerns, during or after the investigation, or wish to contact an independent person to whom any questions may be directed or further information may be sought from, please contact:

Linda Gilmour
Secretary to the Departmental Ethics Committee
National Centre for Prosthetics and Orthotics
Department of Biomedical Engineering
Curran Building, 131 St James Road
Glasgow G4 0LS
Telephone: 0141 548 3298
Email: linda.gilmour@strath.ac.uk

Version 1.2 28/05/2015

Screening questionnaire for Healthy Controls

Study Identification Number: _____

Screening Questionnaire

The information in this questionnaire will be used to determine if you are suitable for this study. The researcher will assess your answers, and may ask you for more details depending on the responses you give. This information is entirely confidential and will only be seen by the researchers involved in the study.

1.	Do you, or does anyone in your family, have any history of psychiatric/neurological disorders?	Yes/No/Do not know
2.	Have you ever had a head injury (including neurosurgery)?	Yes/No/Do not know
3.	Do you, or does anyone in your family, have epilepsy?	Yes/No/Do not know
4.	Do you have any implants, such as a cochlear implant?	Yes/No
5.	Are you colour blind?	Yes/No
6.	Do you suffer from any medical condition?	Yes/No
	If yes, are you currently on medication?	Yes/No
7.	Have you ever had a stroke?	Yes/No
8.	Have you experienced any faintness, light-headedness, or blackouts?	Yes/No
9.	Have you had any severe headaches or migraines?	Yes/No
10.	Have you ever experienced seizures or fainting spells?	Yes/No
11.	If you are female, is there a chance you are you pregnant?	Yes/No/ NA
12.	Do you have normal or corrected vision?	Yes/No
13.	Do you have normal hearing?	Yes/No
14.	Do you have normal upper limb function?	Yes/No
15.	Is English your first language?	Yes/No

Date: _____

Medical questionnaire for Health Controls

Study Identification Number:_____

Medical Questionnaire

Date of Birth: _____ Gender: Male / Female _____

This questionnaire will gather data that may be correlated to your performance during the experiments that you take part in during this study. The data will be treated entirely anonymously and no clinical judgements will be made based on this information or your performance during the experiments.

1. What level of education have you obtained? _____
2. What is your current employment status? _____
3. What is your handedness preference? Left/Right
4. Do you smoke? Yes/No
   If yes, how many cigarettes do you smoke a day? _____
   If yes, how many cigarettes have you had today? _____
5. Do you consume alcohol? Yes/No
   If yes, how many units do you consume on average each week? _____
6. Are you aware of feeling low in a past few weeks? Yes/No
   If yes, for how long? _____
7. How many cups of tea/coffee/caffeine drinks do you normally drink a day? _____
8. How many cups of tea/coffee/caffeine drinks have you had today? _____
9. How many hours do you usually sleep a night? _____
10. How many hours sleep did you get last night? _____
11. On average, how would you rate your sleep on a scale of 1-5, 1 being very poor and 5 being absolutely fine? _____

Date: _____

Healthy Control Consent Sheet

Department of Biomedical Engineering
106, Rottenrow East
Glasgow

Study Identification Number:

DeSIPhER: Developing Schizophrenia Identification using Physiological EEG Response

Consent Form

Please initial the BO X

1. I confirm that I have read and understood the information sheet for the above project and the researcher has answered any queries to my satisfaction.	☐
2. I understand that the data collected during this research will be used to form a healthy control anonymised database and stored for research purposes.	☐
3. I understand that my participation is voluntary and that I am free to withdraw from the project at any time, without having to give a reason and without any consequences.	☐
4. I understand that I can withdraw my data from the study at any time.	☐
5. I understand that any information recorded in the investigation will remain confidential and no information that identifies me will be made publicly available.	☐
6. I consent to my video being taken as part of the project, and I understand that no-one other than the researchers named on the participant information sheet will have access to the video.	☐
7. I understand that participating or withdrawing from the project will in no way influence my standing or relationship within the University.	☐
8. I consent to being a participant in the project.	☐

Name of the participant:	Signature of the participant:	Date:
Name of the witness:	Signature of the witness:	Date:

Version 1.1 12/05/2015

Prof. Robert Hunter
Department of Biomedical Engineering
106, Rottenrow East
Glasgow
Phone no: +44 (0) 141 211 3600

NHS
Greater Glasgow and Clyde

DeSIPhER:

Developing Schizophrenia Identification using Physiological EEG Response

Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. If you decide to take part in the study, your GP will be informed about your participation.

Who is conducting the research?

The research is being carried out by Prof. Robert Hunter (Consultant Psychiatrist, Associate Director R&D NHS Greater Glasgow and Clyde) and researcher Sibani P Mohanty from the Department of Biomedical Engineering, University of Strathclyde.

What is the purpose of the study?

We are undertaking this study to help understand differences in how the brain functions in people who have suffered with psychosis and healthy people who have not had mental health problems. Hopefully our research may help doctors reach better conclusions about the sort of mental health problems people have. You can help us by performing a few simple tasks that will help us to assess your memory and concentration, emotional responses and by listening to a series of quiet sounds while we record your brain waves.

Why have I been invited?

As someone who has experienced mental health problems and suffered with psychosis, you have been invited to take part in this study, to help us understand how the brain functions during the set of tasks mentioned above. This may help us take a step forward towards developing better diagnostic criteria for schizophrenia at an earlier stage.

Do I have to take part?

It is up to you to decide if you would want to be the part of our study. The study pattern will be described to you by the research nurse and any questions will be clarified. If you are interested in taking part, but need more time to think or discuss, then that will be fine. You will then be asked to sign a consent form to show you have agreed to take part in our study. Your GP will be informed about your participation in this study. You are free to withdraw at any time, without giving reason. This will not affect the standard of care you receive or your future treatment. You will also be given £25 per study session to cover any out of pocket expenses. Also, any travel expenses will be covered by the research team.

What does taking part involve?

There will be two sessions spread over two weeks. Each session will last for about 2 hours in total. Before each session begins, the research nurse will go through the standard interviews with you. This should take only about an hour of your time. The next stage involves EEG recording wherein we place a cap on your head (more like a beanie hat) and a few electrodes around your eyes and forehead. Using a water soluble gel we can get a good recording from your scalp. Before we use the gel, we will check for allergy. However, these gels cause no harm and can be easily washed off.

In the first task of session 1, you will be listening to a series of beeps using disposable foam ear phones while watching a video of your favourite movie. You just need to pay attention to the movie. In the second task, you will be presented with the names of colours written either in the same colour or in a different colour. For example: RED/RED (colour red written in green or in red). You press response button (as quickly as possible) '**No Match**' when the name of the colour does not appear in the correct colour on the screen (for example: the word red appearing in the colour green/yellow/blue) and button '**Match**' when the colour and its meaning match (for example: the word red appearing in the colour red itself). You will be given some time to practice before you do the task.

In the first task of the session 2, we have a few touch screen tests for you. They are more like games and will need all your attention in performing the tests. In the second task, you will be presented with series of cartoon faces and you just have to identify the emotions they express as happy, sad, and angry or O.K by pressing the corresponding buttons. In the next experiment of the second task, we show you the same happy, sad or angry cartoon faces and you will first need to mimic these expressions back and then imagine an incident where you personally experienced the emotion

expressed by the cartoon face. While you are performing these tasks with the cartoon faces, **we will record a video to capture your facial expressions as well.**

We will provide you with breaks in between the tasks and refreshments at the end of every session. You can always let us know if you find the task too demanding or tiring and we shall suspend the task immediately.

What happens to the information?

You will be assigned a study identification number to keep your data and personal information confidential. As mentioned earlier all **your information** will be **anonymised** and known only to the researcher. The information (study data and videos) obtained will remain confidential and stored within a locked filing cabinet at University of Strathclyde. The data are held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission.

What are the possible benefits of taking part?

It is hoped that by taking part in this research, you will help to provide valuable information regarding the functioning of the brain in schizophrenia during the various tasks.

Who has reviewed the study?

This study has been reviewed by the NHS West of Scotland Research Ethics Committee.

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact **Stephen Mulholland**.

Contact:

Stephen Mulholland
Kelvin House, Gartnavel Royal Hospital
Phone no: 0141 211 3608

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher Sibani P Mohanty in the first instance but the normal NHS complaint mechanisms is also available to you.

Contact:

Sibani P Mohanty
Doctoral Post Graduate Student
Biomedical Engineering
University of Strathclyde
Phone no: 0141 548 4691

Thank-you for taking the time to read this and for your cooperation. It is much appreciated.

Patients Consent Sheet

Department of Biomedical Engineering
106, Rottenrow East
Glasgow

Subject Identification Number:

DeSIPhER: Developing Schizophrenia Identification using Physiological EEG Response

Consent Form

Please initial box

1. I confirm that I have read and understand the information sheet dated 25/01/2016 (version 1.3) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records. ☐
4. I understand that my GP has been informed about my participation in this research study. ☐
5. I consent to my video being taken as part of the project, and I understand that no-one other than the researchers named on the participant information sheet will have access to the video. ☐
6. I understand that any information recorded in the investigation will remain confidential and no information that identifies me will be made publicly available. ☐
7. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the study team, from regulatory authorities or from the NHS Greater Glasgow and Clyde, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. I agree to take part in the above study. ☐

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Name of Participant	Date	Signature
----------	----------	----------
Name of Witness	Date	Signature

Version 1.3 25th January 2016

APPENDIX C - PANSS AND MADRS

Positive And Negative Syndrome Scale (PANSS) Rating Criteria

GENERAL RATING INSTRUCTIONS

Data gathered from this assessment procedure are applied to the PANSS ratings. Each of the 30 items is accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology, as follows:

1- absent

2- minimal

3- mild

4- moderate

5- moderate severe

6- severe

7- extreme

In assigning ratings, one first considers whether an item is at all present, as judging by its definition. If the item is absent, it is scored 1, whereas if it is present one must determine its severity by reference to the particular criteria from the anchoring points. The highest applicable rating point is always assigned, even if the patient meets criteria for lower points as well. In judging the level of severity, the rater must utilise a holistic perspective in deciding which anchoring point best characterises the patient's functioning and rate accordingly, whether or not all elements of the description are observed.

The rating points of 2 to 7 correspond to incremental levels of symptom severity:

- A rating of 2 (minimal) denotes questionable or subtle or suspected pathology, or it also may allude to the extreme end of the normal range.
- A rating of 3 (mild) is indicative of a symptom whose presence is clearly established but not pronounced and interferes little in day-to- day functioning.
- A rating of 4 (moderate) characterises a symptom which, though representing a serious problem, either occurs only occasionally or intrudes on daily life only to a moderate extent .
- A rating of 5 (moderate severe) indicates marked manifestations that distinctly impact on one's functioning but are not all-consuming and usually can be contained at will.

- A rating of 6 (severe) represents gross pathology that is present very frequently, proves highly disruptive to one's life, and often calls for direct supervision.
- A rating of 7 (extreme) refers to the most serious level of psychopathology, whereby the manifestations drastically interfere in most or all major life functions, typically necessitating close supervision and assistance in many areas.

Each item is rated in consultation with the definitions and criteria provided in this manual. The ratings are rendered on the PANSS rating form overleaf by encircling the appropriate number following each dimension.

PANSS RATING FORM

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/ persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgment and insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

SCORING INSTRUCTIONS

Of the 30 items included in the PANSS, 7 constitute a **Positive Scale**, 7 a **Negative Scale**, and the remaining 16 a **General Psychopathology Scale**. The scores for these scales are arrived at by summation of ratings across component items. Therefore, the potential ranges are 7 to 49 for the Positive and Negative Scales, and 16 to 112 for the General Psychopathology Scale. In addition to these measures, a Composite Scale is scored by subtracting the negative score from the positive score. This yields a bipolar index that ranges from –4 2 to +42, which is essentially a difference score reflecting the degree of predominance of one syndrome in relation to the other.

POSITIVE SCALE (P)

P1. **DELUSIONS** - Beliefs which are unfounded, unrealistic and idiosyncratic.

Basis for rating - Thought content expressed in the interview and its influence on social relations and behaviour.

1 **Absent** - Definition does not apply

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits

3 **Mild** - Presence of one or two delusions which are vague, uncrystallised and not tenaciously held. Delusions do not interfere with thinking, social relations or behaviour.

4 **Moderate** - Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations or behaviour.

5 **Moderate Severe** - Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations and behaviour.

6 **Severe** - Presence of a stable set of delusions which are crystallised, possibly systematised, tenaciously held and clearly interfere with thinking, social relations and behaviour.

7 **Extreme** - Presence of a stable set of delusions which are either highly systematised or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardise the safety of the patient or others.

P2. **CONCEPTUAL DISORGANISATION -** Disorganised process of thinking characterised by disruption of goal-directed sequencing, e.g. circumstantiality, loose associations, tangentiality, gross illogicality or thought block.

Basis for rating - Cognitive-verbal processes observed during the course of interview.

1 **Absent** - Definition does not apply

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits

3 **Mild** - Thinking is circumstantial, tangential or paralogical. There is some difficulty in directing thoughts towards a goal, and some loosening of associations may be evidenced under pressure.

4 **Moderate** - Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.

5 **Moderate Severe** - Generally has difficulty in organising thoughts, as evidenced by frequent irrelevancies, disconnectedness or loosening of associations even when not under pressure.

6 **Severe** - Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.

7 **Extreme** - Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which result in total failure of communication, e.g. "word salad" or mutism.

P3. **HALLUCINATORY BEHAVIOUR -** Verbal report or behaviour indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms.

Basis for rating - Verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour.
4 **Moderate** - Hallucinations occur frequently but not continuously, and the patient's thinking and behaviour are only affected to a minor extent.
5 **Moderate Severe** - Hallucinations occur frequently, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behaviour. Patient may have a delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.
6 **Severe** - Hallucinations are present almost continuously, causing major disruption of thinking and behaviour. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.
7 **Extreme** - Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behaviour. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioural responses, including obedience to command hallucinations.

P4 **EXCITEMENT -** Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance or excessive mood lability.

Basis for rating - Behavioural manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Tends to be slightly agitated, hypervigilant or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.
4 **Moderate** - Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.
5 **Moderate Severe** - Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.
6 **Severe** - Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating or sleeping.
7 **Extreme** - marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

P5. **GRANDIOSITY -** Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power and moral righteousness.

Basis for rating - Thought content expressed in the interview and its influence on behaviour.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.
4 **Moderate** - Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.
5 **Moderate Severe** - Clear-cut delusions concerning remarkable abilities, status or power are expressed and influence attitude but not behaviour.
6 **Severe** - Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc) are expressed, notably influence interactions and may be acted upon.
7 **Extreme** - Thinking, interactions and behaviour are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power and/or moral stature, which may take on a bizarre quality.

P6. **SUSPICIOUSNESS/PERSECUTION -** Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, ad distrustful attitude, suspicious hypervigilance or frank delusions that others mean harm.

Basis for rating – Thought content expressed in the interview and its influence on behaviour.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Presents a guarded or even openly distrustful attitude, but thoughts, interactions and behaviour are minimally affected.
4 **Moderate** - Distrustfulness is clearly evident and intrudes on the interview and/or behaviour, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5 **Moderate Severe** - Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behaviour.
6 **Severe** - Clear-cut pervasive delusions of persecution which may be systematised and significantly interfere in interpersonal relations.
7 **Extreme** - A network of systematised persecutory delusions dominates the patient's thinking, social relations and behaviour.

P7. **HOSTILITY -** Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and assualtiveness.

Basis for rating – Interpersonal behaviour observed during the interview and reports by primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions and occasional irritability.
4 **Moderate** - Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5 **Moderate Severe** - Patient is highly irritable and occasionally verbally abusive or threatening.
6 **Severe** - Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assualtive towards others.
7 **Extreme** - Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault towards others.

NEGATIVE SCALE (N)

N1. **BLUNTED AFFECT -** Diminished emotional responsiveness as characterised by a reduction in facial expression, modulation of feelings and communicative gestures.

Basis for rating - Observation of physical manifestations of affective tone and emotional responsiveness during the course of the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Changes in facial expression and communicative gestures seem to be stilted, forced, artificial or lacking in modulation.
4 **Moderate** - Reduced range of facial expression and few expressive gestures result in a dull appearance
5 **Moderate Severe** - Affect is generally 'flat' with only occasional changes in facial expression and a paucity of communicative gestures.
6 **Severe** - Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage or inappropriate uncontrolled laughter.
7 **Extreme** – Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or 'wooden' expression.

N2. **EMOTIONAL WITHDRAWAL -** Lack of interest in, involvement with, and affective commitment to life's events.

Basis for rating - Reports of functioning from primary care workers or family and observation of interpersonal behaviour during the course of the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Usually lack initiative and occasionally may show deficient interest in surrounding events.
4 **Moderate** - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.
5 **Moderate Severe** - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6 **Severe** - Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.
7 **Extreme** – Patient is almost totally withdrawn, uncommunicative and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

N3. **POOR RAPPORT -** Lack of interpersonal empathy, openness in conversation and sense of closeness, interest or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication.

Basis for rating - Interpersonal behaviour during the course of the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Conversation is characterised by a stilted, strained or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4 **Moderate** - Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.
5 **Moderate Severe** - Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6 **Severe** - Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7 **Extreme** - Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

N4. PASSIVE/APATHETIC SOCIAL WITHDRAWAL - Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living.

Basis for rating – Reports on social behaviour from primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4 **Moderate** – Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5 **Moderate Severe** - Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6 **Severe** - Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7 **Extreme** – Profoundly apathetic, socially isolated and personally neglectful.

N5. DIFFICULTY IN ABSTRACT THINKING - Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalisations and proceeding beyond concrete or egocentric thinking in problem-solving tasks.

Basis for rating - Responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Tends to give literal or personalised interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.
4 **Moderate** - Often utilises a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.
5 **Moderate Severe** - Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.
6 **Severe** - Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features and idiosyncratic interpretations.
7 **Extreme** - Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

N6. **LACK OF SPONTANEITY AND FLOW OF CONVERSATION** - Reduction in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal interactional process.

Basis for rating - Cognitive-verbal processes observed during the course of interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** – Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.
4 **Moderate** – Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.
5 **Moderate Severe** - Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.
6 **Severe** - Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (e.g. "I don't know", "I'm not at liberty to say"). Conversation is seriously impaired as a result and the interview is highly unproductive.
7 **Extreme** - Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.

N7. **STEREOTYPED THINKING** - Decreased fluidity, spontaneity and flexibility of thinking, as evidenced in rigid, repetitious or barren thought content.

Basis for rating - Cognitive-verbal processes observed during the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Some rigidity shown in attitude or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.
4 **Moderate** - Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.
5 **Moderate Severe** - Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.
6 **Severe** – Uncontrolled repetition of demands, statements, ideas or questions which severely impairs conversation.
7 **Extreme** - Thinking, behaviour and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness and restrictiveness of patient's communication.

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1. **SOMATIC CONCERN -** Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease.

Basis for rating - Thought content expressed in the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Distinctly concerned about health or bodily malfunction, but there is no delusional conviction and overconcern can be allayed by reassurance.
4 **Moderate** - Complains about poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.
5 **Moderate Severe** - Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.
6 **Severe** - Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.
7 **Extreme** – Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect or thinking.

G2. **ANXIETY -** Subjective experience of nervousness, worry, apprehension or restlessness, ranging from excessive concern about the present or future to feelings of panic.

Basis for rating - Verbal report during the course of interview and corresponding physical manifestations.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Expresses some worry, overconcern or subjective restlessness, but no somatic and behavioural consequences are reported or evidenced.
4 **Moderate** - Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.
5 **Moderate Severe** - Patient reports serious problems of anxiety which have significant physical and behavioural consequences, such as marked tension, poor concentration, palpitations or impaired sleep.
6 **Severe** - Subjective state of almost constant fear associated with phobias, marked restlessness or numerous somatic manifestations.
7 **Extreme** - Patient's life is seriously disrupted by anxiety, which is present almost constantly and at times reaches panic proportion or is manifested in actual panic attacks.

G3. **GUILT FEELINGS** - Sense of remorse or self-blame for real or imagined misdeeds in the past.

Basis for rating - Verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** – Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.
4 **Moderate** - Patient expresses distinct concern over his responsibility for a real incident in his life but is not pre-occupied with it and attitude and behaviour are essentially unaffected.
5 **Moderate Severe** - Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.
6 **Severe** - Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he should receive harsh sanctions as such punishment.
7 **Extreme** - Patient's life is dominated by unshakable delusions of guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.

G4. **TENSION** -Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating and restlessness.

Basis for rating - Verbal report attesting to anxiety and thereupon the severity of physical manifestations of tension observed during the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.
4 **Moderate** - A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.
5 **Moderate Severe** - Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating and restlessness, but can conduct in the interview is not significantly affected.
6 **Severe** - Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.
7 **Extreme** - Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

G5. **MANNERISMS AND POSTURING –** Unnatural movements or posture as characterised be an awkward, stilted, disorganised, or bizarre appearance.

Basis for rating - Observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Slight awkwardness in movements or minor rigidity of posture
4 **Moderate** – Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.
5 **Moderate Severe** - Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.
6 **Severe** - Frequent repetition of bizarre rituals, mannerisms or stereotyped movements, or a contorted posture is sustained for extended periods.
7 **Extreme** - Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

G6. **DEPRESSION** - Feelings of sadness, discouragement, helplessness and pessimism.

Basis for rating - Verbal report of depressed mood during the course of interview and its observed influence on attitude and behaviour.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Expresses some sadness of discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4 **Moderate** - Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behaviour or social functioning and the patient usually can be cheered up.
5 **Moderate Severe** - Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and some interference in appetite and sleep. The patient cannot be easily cheered up.
6 **Severe** - Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness and worthlessness. In addition, there is major interference in appetite and or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7 **Extreme** - Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self neglect, possible depressive or nihilistic delusions and/or possible suicidal thoughts or action.

G7. **MOTOR RETARDATION –** Reduction in motor activity as reflected in slowing or lessening or movements and speech, diminished responsiveness of stimuli, and reduced body tone.

Basis for rating - Manifestations during the course of interview as well as reports by primary care workers as well as family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.
4 **Moderate** - Patient is clearly slow in movements, and speech may be characterised by poor productivity including long response latency, extended pauses or slow pace.
5 **Moderate Severe** – A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.
6 **Severe** - Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.
7 **Extreme** - Patient is almost completely immobile and virtually unresponsive to external stimuli.

G8. **UNCOOPERATIVENESS -** Active refusal to comply with the will of significant others, including the interviewer, hospital staff or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility or belligerence.

Basis for rating - Interpersonal behaviour observed during the course of the interview as well as reports by primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.
4 **Moderate** - Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programmes, etc. The patient may project a hostile, defensive or negative attitude but usually can be worked with.
5 **Moderate Severe** - Patient frequently is incompliant with the demands of his milieu and may be characterised by other as an "outcast" or having "a serious attitude problem". Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.
6 **Severe** - Patient is highly uncooperative, negativistic and possibly also belligerent. Refuses to comply with the most social demands and may be unwilling to initiate or conclude the full interview.
7 **Extreme** - Active resistance seriously impact on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff and participate even briefly in an interview.

G9. **UNUSUAL THOUGHT CONTENT** - Thinking characterised by strange, fantastic or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical and patently absurd.

Basis for rating - Thought content expressed during the course of interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Thought content is somewhat peculiar, or idiosyncratic, or familiar ideas are framed in an odd context.
4 **Moderate** - Ideas are frequently distorted and occasionally seem quite bizarre.
5 **Moderate Severe** - Patient expresses many strange and fantastic thoughts, (e.g. Being the adopted son of a king, being an escapee from death row), or some which are patently absurd (e.g. Having hundreds of children, receiving radio messages from outer space from a tooth filling).
6 **Severe** - Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g. having three heads, being a visitor from another planet).
7 **Extreme** - Thinking is replete with absurd, bizarre and grotesque ideas.

G10. **DISORIENTATION** - Lack of awareness of one's relationship to the milieu, including persons, place and time, which may be due to confusion or withdrawal.

Basis for rating - Responses to interview questions on orientation.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address, knows hospital staff names but not their functions, knows the month but confuses the day of the week with an adjacent day, or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the mayor, governor, or president.
4 **Moderate** - Only partial success in recognising persons, places and time. For example, patient knows he is in a hospital but not its name, knows the name of the city but not the borough or district, knows the name of his primary therapist but not many other direct care workers, knows the year or season but not sure of the month.
5 **Moderate Severe** - Considerable failure in recognising persons, place and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly but not know the current month, day of week or even the season.
6 **Severe** - Marked failure in recognising persons, place and time. For example, patient has no knowledge of his whereabouts, confuses the date by more than one year, can name only one or two individuals in his current life.
7 **Extreme** - Patient appears completely disorientated with regard to persons, place and time. There is gross confusion or total ignorance about one's location, the current year and even the most familiar people, such as parents, spouse, friends and primary therapist.

G11. **POOR ATTENTION** - Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining or shifting focus to new stimuli.

Basis for rating – Manifestations during the course of interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Limited concentration evidenced by occasional vulnerability to distraction and faltering attention toward the end of the interview.
4 **Moderate** - Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.
5 **Moderate Severe** - Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately..
6 **Severe** - Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.
7 **Extreme** - Attention is so disrupted that even brief conversation is not possible.

G12. **LACK OF JUDGEMENT AND INSIGHT** - Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognise past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalisation or treatment, decisions characterised by poor anticipation or consequences, and unrealistic short-term and long-range planning.

Basis for rating – Thought content expressed during the interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Recognises having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.
4 **Moderate** - Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganised thinking, suspiciousness and social withdrawal. The patient may rationalise the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension and sleep difficulty.
5 **Moderate Severe** - Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognised.
6 **Severe** - Patient denies ever having had a psychiatric disorder. He disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalisation.
7 **Extreme** - Emphatic denial of past and present psychiatric illness. Current hospitalisation and treatment are given a delusional interpretation (e.g. as punishment fro misdeeds, as persecution by tormentors, etc), and the patient thus refuse to cooperate with therapists, medication or other aspects of treatment.

G13. **DISTURBANCE OF VOLITION** – Disturbance in the wilful initiation, sustenance and control of one's thoughts, behaviour, movements and speech.

Basis for rating - Thought content and behaviour manifested in the course of interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.
4 **Moderate** - Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alteration in thinking, and in consequence, verbal and cognitive functioning are clearly impaired.
5 **Moderate Severe** - Disturbance of volition interferes in thinking as well as behaviour. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidence in halting speech.
6 **Severe** - Disturbance of volition interferes in the execution of simple automatic motor functions, such as dressing or grooming, and markedly affects speech.
7 **Extreme** – Almost complete failure of volition is manifested by gross inhibition of movement and speech resulting in immobility and/or mutism.

G14. **POOR IMPULSE CONTROL** - Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary or misdirected discharge of tension and emotions without concern about consequences.

Basis for rating – Behaviour during the course of interview and reported by primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.
4 **Moderate** - Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.
5 **Moderate Severe** - Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.
6 **Severe** - Patient frequently is impulsive aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assualtive behaviour and may also be sexually offensive and possibly respond behaviourally to hallucinatory commands.
7 **Extreme** - Patient exhibits homicidal, sexual assaults, repeated brutality, or self-destructive behaviour. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

G15. **PREOCCUPATION -** Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour.

Basis for rating - Interpersonal behaviour observed during the course of interview.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concerned exhibited toward others.
4 **Moderate** - Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.
5 **Moderate Severe** - Patient often appears to be engaged in autistic experiences, as evidenced by behaviours that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.
6 **Severe** - Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.
7 **Extreme** - Gross absorption with autistic experiences, which profoundly affects all major realms of behaviour. The patient constantly may be responding verbally or behaviourally to hallucinations and show little awareness of other people or the external milieu.

G16. **ACTIVE SOCIAL AVOIDANCE** - Diminished social involvement associated with unwarranted fear, hostility, or distrust.

Basis for rating - Reports of social functioning primary care workers or family.

1 **Absent** - Definition does not apply
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits
3 **Mild** - Patient seems ill at ease in the presence of others of others and prefers to spend time alone, although he participates in social functions when required.
4 **Moderate** - Patient begrudgingly attends all or most social activities but may needs to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.
5 **Moderate Severe** - Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.
6 **Severe** - Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he tends to isolate himself from others.
7 **Extreme** - Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others.

Montgomery–Åsberg Depression Rating Scale (MADRS) Rating Criteria

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1,3,5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise but this must be recorded.

---

1. Apparent Sadness
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture.

Rate by depth and inability to brighten up.

0 No sadness.
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

---

2. Reported sadness
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3. Inner tension
Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.

Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic

---

4. Reduced sleep
Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep

---

5. Reduced appetite
Representing the feeling of a loss of appetite compared with when well.

Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

6. Concentration Difficulties
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

---

7. Lassitude
Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

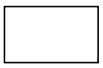
---

8. Inability to feel
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings or friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

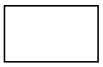
0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.



10. Suicidal thoughts
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparation for suicide.



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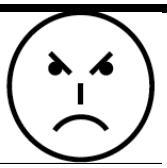
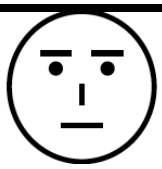
**** Correspondence.***
(Received 24 April; revised 30 August 1978)

APPENDIX D - FACE SCHEMATICS TESTED FOR EMOTION RESPONSE

(Number of participants, Total scores), Maximum total score: 8*5 = 40

Faces	Happy	Sad	Neutral	Angry	Chosen
		(8, 39)			Sad
		(5, 19)	(3, 6)		
				(8, 40)	Angry
	(7, 23)		(1, 3)		Happy
	(1, 3)		(7, 23)		Neutral
	(5, 20)	(3, 9)			
				(8, 39)	

APPENDIX E - MATLAB CODES: MISMATCH NEGATIVITY

Optimal MMN Stimulus Generation

```
clear all

output_filename = 'optimal_MMN_paradigm_1000msITI';

output_file = [output_filename, '.seq'];
[fid_out, message] = fopen(deblank(output_file),'wt');

% Format the header for the output file
fprintf(fid_out,'Version 4.0.08012003\n');
fprintf(fid_out,'Numevents 1510\n');
fprintf(fid_out,'label\tmode\tdur\twin\titi\trdB\tldB\tresp\ttype\tfilename\
n'),
fprintf(fid_out,'-----\t-------\t-------\t-------\t-------\t--------\t------
--\t----\t----\t--------\n');

%define first 8 columns
common_columns = {'0','SND','0.00','0.00','1000','80','80','-1'};

%define file location of standard tone and trigger code
standard = 'D:\MSc Projects 2012\Sound Files\standard.wav';
standard_code = '1';

%define file location of durantion deviant tone and trigger code
duration_deviant = 'D:\MSc Projects 2012\Sound Files\duration_deviant.wav';
duration_code = '12';

%define file location of lower frequency deviant tone and trigger code
lower_frequency_deviant = 'D:\MSc Projects 2012\Sound
Files\lower_frequency_deviant.wav';
lower_frequency_code = '9';

%define file location of upper frequency deviant tone and trigger code
upper_frequency_deviant = 'D:\MSc Projects 2012\Sound
Files\upper_frequency_deviant.wav';
upper_frequency_code = '9';

%define file location of lower intensity deviant tone and trigger code
lower_intensity_deviant = 'D:\MSc Projects 2012\Sound Files\standard.wav';
lower_intensity_code = '4';
lower_dB = '70';

%define file location of upper intensity deviant tone and trigger code
upper_intensity_deviant = 'D:\MSc Projects 2012\Sound Files\standard.wav';
upper_intensity_code = '4';
upper_dB = '90';

%define file location of left location deviant tone and trigger code
```

```
left_location_deviant = 'D:\MSc Projects 2012\Sound
Files\left_location_deviant.wav';
left_location_code = '5';

%define file location of right location deviant tone and trigger code
right_location_deviant = 'D:\MSc Projects 2012\Sound
Files\right_location_deviant.wav';
right_location_code = '5';

%define file location of gap deviant tone and trigger code
gap_deviant = 'D:\MSc Projects 2012\Sound Files\gap_deviant.wav';
gap_code = '8';

%first 10 stimuli are standard tones
for i=1:10

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},standard_code,standard);
end

%alternate standard tones with randomly selected deviants
for ii=1:1500
    check_even = ii/2;
    if floor(check_even)==check_even                %for even numbered
trials
        a=rand;                                     %senerate a random
number
                if a<=0.2
                %write duration deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},duration_code,duration_de
viant);
                end
                if a>0.2 && a<=0.3
                %write lower frew deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},lower_frequency_code,lowe
r_frequency_deviant);
                end
                if a>0.3 && a<=0.4
                %write upper freq deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},upper_frequency_code,uppe
r_frequency_deviant);
                end
```

```
                if a>0.4 && a<=0.5
                %write lower int deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},low
er_dB,lower_dB,common_columns{8},lower_intensity_code,lower_intensity_devian
t);
                end
                if a>0.5 && a<=0.6
                %write upper int deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},upp
er_dB,upper_dB,common_columns{8},upper_intensity_code,upper_intensity_devian
t);
                end
                if a>0.6 && a<=0.7
                %write left loc deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},left_location_code,left_l
ocation_deviant);
                end
                if a>0.7 && a<=0.8
                %write right loc deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},right_location_code,right
_location_deviant);
                end
                if a>0.8
                %write gap deviant line

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},gap_code,gap_deviant);
                end
    elseif floor(check_even)<check_even
        %write standard

fprintf(fid_out,'%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\t%s\n',common_columns{1}
,common_columns{2},common_columns{3},common_columns{4},common_columns{5},com
mon_columns{6},common_columns{7},common_columns{8},standard_code,standard),
    end
end

fclose all
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Healthy Controls

```
data_dir = 'E:\EngD Data\Sibani\Pilot\PILOT\';
% data_files = strcat(data_dir, '*MMN*.cnt');
dataset_dir = strcat(data_dir, 'datasets\mmn\withICA\');
% files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};

load mmn_controls.mat

for i = 2:length(subjects)
    data_files = strcat(data_dir, subjects{i}, '*MMN*.cnt');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end

    f_name = split(files(1).name, '.');
    f_name = f_name{1};

    disp('Prepocessing:')
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load data
    cnt_file = strcat(data_dir, files(1).name);
    try
        EEG = pop_loadcnt(cnt_file, 'keystroke', 'off');
        EEG.setname = f name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_cnt = [skipped_cnt; f_name];
        continue
    end

    % Import channel info
    EEG = pop_chanedit(EEG, 'lookup', ...
                       'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit2.3\standard_BESA\standard-10-5-
cap385.elp', ...
                       'eval','chans = pop_chancenter( chans, [],[]);');

    % Re-reference data to M1, M2 (33, 43)
    EEG = pop_reref(EEG, [33 43]);

    % Resample data
    EEG = pop_resample(EEG, 250);

    % Filter data
    % High-pass
    EEG = pop_eegfiltnew(EEG, .1, []);
    % Low-pass
    EEG = pop_eegfiltnew(EEG, [], 40);

    % Remove line noise using CleanLine
    EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                        'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                        'verb', 1, 'winsize', 4, 'winstep', 4);
    % Run ICA
    EEG = pop_runica(EEG, 'icatype', 'runica');

    % Extract Epoch
    try
        EEG = pop_epoch(EEG, {1, 12, 9, 4, 5, 8}, [-.2 .8]);
```

```
    catch
        disp('Skipping epoching:')
        disp(f name)
        disp(' ')
        disp(' ')
        skipped_epoch = [skipped_epoch; f_name];
        continue
    end
    EEG = pop_rmbase(EEG, [-200, 0]);
    EEG.setname = [f_name '_Fs250_LP40'];
    EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40' '_ds'], 'filepath',
dataset_dir);

    clear EEG
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient Data\';
data_files = strcat(data_dir, '*MMN*.cnt');
dataset_dir = strcat(data_dir, 'datasets\mmn\withICA');
files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};

for i = 1:length(files)
    f_split = split(files(i).name, '_');
    f_name = split(files(i).name, '.');
    f_name = char(f_name(1));
    sub_id = char(f_split(1));
    sub_date = char(f_split(2));

    disp('Prepocessing:')
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load data
    cnt_file = strcat(data_dir, files(i).name);
    try
        EEG = pop_loadcnt(cnt_file, 'keystroke', 'on');
        EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_cnt = [skipped_cnt; f_name];
        continue
    end

    % Import channel info
    EEG = pop_chanedit(EEG, 'lookup', ...
                       'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit2.3\standard_BESA\standard-10-5-
cap385.elp', ...
                       'eval','chans = pop_chancenter( chans, [],[]);');

    % Re-reference data to M1, M2 in patients (36, 37)
    EEG = pop_reref(EEG, [36 37]);

    % Resample data
    EEG = pop_resample(EEG, 250);

    % Filter data
    % High-pass
    EEG = pop_eegfiltnew(EEG, .1, []);
    % Low-pass
    EEG = pop_eegfiltnew(EEG, [], 40);
```

```
    % Remove line noise using CleanLine
    EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                        'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                        'verb', 1, 'winsize', 4, 'winstep', 4);
    % Run ICA
    EEG = pop_runica(EEG, 'icatype', 'runica');

    % Extract Epoch
    try
        EEG = pop_epoch(EEG, {1, 12, 9, 4, 5, 8}, [-.2 .8]);
    catch
        disp('Skipping epoching:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_epoch = [skipped_epoch; f_name];
        continue
    end
    EEG = pop_rmbase(EEG, [-200, 0]);
    EEG.setname = [f_name '_Fs250_LP40'];
    EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40' '_ds'], 'filepath',
dataset_dir);

    clear EEG
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\mmn\withICA\withMarked\withRejectEpochs\';
%Directory where mmn datasets are saved
byType_dir = strcat(data_dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType_dir, 'dir')
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event_type = [1, 12, 9, 4, 5, 8];
type_name = {'stand', 'dur', 'freq', 'int', 'loc', 'gap'};

skipped_set = {};
skipped_split = {};
% return;

load mmn_controls.mat
type_total_trials = zeros(6, length(subjects));  % Trials by type (1, :) cong; (2, :)
incong
type_accepted_trials = zeros(6, length(subjects)); % Correct Trials by type (1, :)
cong; (2, :) incong

for i = 1:length(subjects)

    data_files = strcat(data_dir, subjects{i}, '*MMN*.set');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end

    f_name = split(files(1).name, '.');
    f_name = f_name{1}(1:end-3);

    rej files = strcat(data dir, 'rej mats\', f name, ' rej.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
```

```
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load dataest
    try
        ALLEEG = [];
        EEG = pop loadset(files(1).name, files(1).folder);

        type = extractfield(EEG.event, 'type');
        [C,ia,ic] = unique(type);
        a_counts = accumarray(ic,1);
        type_total_trials(:, i) = a_counts([1,2,6,3,4,5]);
        disp(['Rejected epochs: ', rej_files(1).name])
        load([rej_files(1).folder, '\', rej_files(1).name])
        tot_epochs = length(rej.rejmanual);
        EEG.reject.rejmanual = rej.rejmanual;
        EEG = pop_rejepoch( EEG, EEG.reject.rejmanual ,0);
        [ALLEEG, EEG, index] = eeg_store(ALLEEG, EEG);
%         EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
        continue
    end

    % Create datasets by types

    for j = 1:length(event_type)

        % Name of the new dataset with event_type and type_name appended
        set_name = strcat(f_name, '_', num2str(event_type(j)), '_',
char(type_name(j)));

        % Selecting one event at a time
        try
            [EEG_type evnt_ind_test] = pop_selectevent(EEG, 'type', event_type(j));
            type_accepted_trials(j, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
        catch
            disp('Skipping split:')
            disp(set_name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG_type = pop_saveset(EEG_type, 'filename', set_name, 'filepath',
byType_dir);
        clear EEG_type
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\mmn\withICA\withMarked\withRejectEpochs\';   %Directory where mmn
datasets are saved
data_files = strcat(data_dir, '*MMN*.set');
files = dir(data_files);

byType dir = strcat(data dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType_dir, 'dir')
```

```
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event_type = [1, 12, 9, 4, 5, 8];
type_name = {'stand', 'dur', 'freq', 'int', 'loc', 'gap'};

skipped set = {};
skipped_split = {};
% return;

type_total_trials = zeros(6, length(files));  % Trials by type (1, :) cong; (2, :)
incong
type_accepted_trials = zeros(6, length(files)); % Correct Trials by type (1, :) cong;
(2, :) incong

for i = 1:length(files)

    f_name = split(files(i).name, '.');
    f_name = f_name{1}(1:end-3);

    rej_files = strcat(data_dir, 'rej_mats\', f_name, '_rej.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load dataest
    try
        ALLEEG = [];
        EEG = pop_loadset(files(i).name, files(i).folder);

        % Droping EOG channels
        drop_chans = [36, 37];
        EEG = pop_select(EEG, 'nochannel', drop_chans);
        % Capitalizing channel labels to avoid conflicts between subjects
        EEG = capitalize_chan_labels(EEG);


        type = extractfield(EEG.event, 'type');
        [C,ia,ic] = unique(type);
        a_counts = accumarray(ic,1);
        type_total_trials(:, i) = a_counts([1,2,6,3,4,5]);
        disp(['Rejected epochs: ', rej_files(1).name])
        load([rej_files(1).folder, '\', rej_files(1).name])
        tot_epochs = length(rej.rejmanual);
        EEG.reject.rejmanual = rej.rejmanual;
        EEG = pop_rejepoch( EEG, EEG.reject.rejmanual ,0);
        [ALLEEG, EEG, index] = eeg_store(ALLEEG, EEG);
%         EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
        continue
    end

    % Create datasets by types

    for j = 1:length(event_type)

        % Name of the new dataset with event_type and type_name appended
        set_name = strcat(f_name, '_', num2str(event_type(j)), '_',
char(type_name(j)));

        % Selecting one event at a time
        try
            [EEG_type evnt_ind_test] = pop_selectevent(EEG, 'type', event_type(j));
            type_accepted_trials(j, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
```

```
        catch
            disp('Skipping split:')
            disp(set name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG_type = pop_saveset(EEG_type, 'filename', set_name, 'filepath',
byType_dir);
        clear EEG_type
    end
end

function EEG = capitalize_chan_labels(EEG)
    for i = 1:length(EEG.chanlocs)
        EEG.chanlocs(i).labels = upper(EEG.chanlocs(i).labels);
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\mmn\withICA\withMarked\withRejectEpochs\byType\';
%Directory where mmn datasets are saved
data_files = strcat(data_dir, '*MMN*.set');
files = dir(data_files);

% Event types to compare in the study
types_toComp = {'stand', 'dur', 'freq', 'int', 'loc', 'gap'};
commands = {};

for i = 1:length(files)
    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_MMN');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
end

% Create the study

name = 'control_MMN_wICA';
[STUDY ALLEEG] = std_editset([], [], 'name', name,...
        'task', 'Oddball',...
        'filename', name, ...
        'filepath', 'E:\EngD Data\Sibani\Studies\MMN\',...
        'commands', commands);

% Duration deviant, make and compute components
std_dirpath = 'E:\EngD Data\Sibani\Studies\MMN\controls_wICA';
if ~exist(std_dirpath)
  mkdir(std_dirpath);
end
CURRENTSTUDY = 1; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_MMN_standVsdur', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'dur'}, ...
                       'filepath', std dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
```

```
                              'recompute','off', ...
                              'erp','on',...
                              'ersp', 'on', 'itc', 'on', ...
                              'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Frequency deviant, make and compute components
CURRENTSTUDY = 2; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_MMN_standVsfreq', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'freq'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                              'recompute','off', ...
                              'erp','on',...
                              'ersp', 'on', 'itc', 'on', ...
                              'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Intensity deviant, make and compute components
CURRENTSTUDY = 3; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_MMN_standVsint', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'int'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                              'recompute','off', ...
                              'erp','on',...
                              'ersp', 'on', 'itc', 'on', ...
                              'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Location deviant, make and compute components
CURRENTSTUDY = 4; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_MMN_standVsloc', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'loc'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                              'recompute','off', ...
                              'erp','on',...
                              'ersp', 'on', 'itc', 'on', ...
                              'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Gap deviant, make and compute components
CURRENTSTUDY = 5; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_MMN_standVsgap', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'gap'}, ...
                       'filepath', std dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                              'recompute','off', ...
                              'erp','on',...
                              'ersp', 'on', 'itc', 'on', ...
                              'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});


%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\mmn\withICA\withMarked\withRejectEpochs\byType\';   %Directory where
mmn datasets are saved
data_files = strcat(data_dir, '*MMN*.set');
files = dir(data_files);

% Event types to compare in the study
types_toComp = {'stand', 'dur', 'freq', 'int', 'loc', 'gap'};
commands = {};

for i = 1:length(files)
    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_MMN');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
end

% Create the study
name = 'patient_MMN_wICA';
[STUDY ALLEEG] = std_editset([], [], 'name', name,...
        'task', 'Oddball',...
        'filename', name, ...
        'filepath', 'E:\EngD Data\Sibani\Studies\MMN\',...
        'commands', commands);

% Duration deviant, make and compute components
std_dirpath = 'E:\EngD Data\Sibani\Studies\MMN\patients_wICA';
if ~exist(std_dirpath)
  mkdir(std_dirpath);
end
CURRENTSTUDY = 1; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'patient_MMN_standVsdur', ...
                       'variable1', 'condition', ...
                       'values1', {'stand' 'dur'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', 'savetrials', 'on', ...
                             'erp','on',...
                             'erpim', 'on', ...
                             'erpimparams', {'nlines', 50, 'smoothing', 10}, ...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Frequency deviant, make and compute components
CURRENTSTUDY = 2; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'patient_MMN_standVsfreq', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'freq'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', 'savetrials', 'on', ...
                             'erp','on',...
                             'erpim', 'on', ...
                             'erpimparams', {'nlines', 46, 'smoothing', 10}, ...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Intensity deviant, make and compute components
```

```
CURRENTSTUDY = 3; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'patient MMN standVsint', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'int'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', 'savetrials', 'on', ...
                             'erp','on',...
                             'erpim', 'on', ...
                             'erpimparams', {'nlines', 46, 'smoothing', 10}, ...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Location deviant, make and compute components
CURRENTSTUDY = 4; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'patient_MMN_standVsloc', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'loc'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', 'savetrials', 'on', ...
                             'erp','on',...
                             'erpim', 'on', ...
                             'erpimparams', {'nlines', 50, 'smoothing', 10}, ...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

% Gap deviant, make and compute components
CURRENTSTUDY = 5; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'patient_MMN_standVsgap', ...
                       'variable1','condition', ...
                       'values1',{'stand' 'gap'}, ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', 'savetrials', 'on', ...
                             'erp','on',...
                             'erpim', 'on', ...
                             'erpimparams', {'nlines', 27, 'smoothing', 10}, ...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Healthy Controls

```
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\MMN\control_MMN_wICA.study');

chan_names = {};
for i = 1:length(ALLEEG(1).chanlocs)
    chan_names{i} = ALLEEG(1).chanlocs(i).labels;
end

imp_chan_array = [10, 28];
disp('Plots made for channels:')
disp(chan_names(imp_chan_array));

scales = [2.5, 2.5, 2, 3.1, 3.2];
diff_scales = [1.2, 1.2, 1.0, 1.6, 1.5];
for design num = 1:5

    for i = imp_chan_array
```

```
        STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
        disp(STUDY.design(design_num).name)
        disp('')
        std_name = STUDY.design(design_num).name;
        dev_type = split(std_name, 'Vs');
        dev_type = dev_type{2};
        channels = chan_names(i);

        stat_method = 'montecarlo';
        stat_corr = 'cluster';
        stat_cluster = '''clusterstatistic'',''maxsum''';
        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                              'mode', 'fieldtrip', ...
                              'fieldtripmethod', stat_method, ...
                              'fieldtripalpha', 0.05, ...
                              'fieldtripmcorrect', stat_corr, ...
                              'fieldtripclusterparam', stat_cluster);

        [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
            std_erpplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        stand_erp =  mean(erpdata{1}, 2);
        dev_erp = mean(erpdata{2}, 2);
        mmn = mean(erpdata{2} - erpdata{1}, 2);

        mmn_plot(stand_erp, dev_erp, mmn, dev_type, ...
                 erptimes, pcond, .05, 1, fig_title);
        set_fig_props();

        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                              'mode', 'fieldtrip', ...
                              'fieldtripmethod', stat_method, ...
                              'fieldtripnaccu', 5000, ...
                              'fieldtripalpha', 0.05, ...
                              'fieldtripmcorrect', stat_corr, ...
                              'fieldtripclusterparam', stat_cluster);

        [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
           std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        mmn_ersp_plot_scaled(erspdata, ersptimes, erspfreqs, pcond, ...
                             dev_type, channels, scales(design_num),
diff_scales(design_num))
        set_fig_props();
    end

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Individual Patients

```
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\MMN\patient_MMN_wICA.study');

chan_names = {};

for j = 1:length(ALLEEG(1).chanlocs)
    chan_names{j} = ALLEEG(1).chanlocs(j).labels;
end

imp_chan_array = [5, 15];
disp('Plots made for channels:')
disp(chan_names(imp_chan_array));
load mmn_patients.mat

for s_ind = 1:6
    s = subjects{s_ind};
    for design_num = 1:5
        save([fig_dir 'pcond_ersp_mmn_patient'], 'pcond_ersp_mmn_patient')
        for i = imp_chan_array  %[5, 15, 25]   % 1:length(chan_names)
```

```
            STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
            disp(STUDY.design(design_num).name)
            disp(chan names(i))
            std_name = STUDY.design(design_num).name;
            dev_type = split(std_name, 'Vs');
            dev_type = dev_type{2};
            channels = chan_names(i);

            stat_method = 'montecarlo';
            stat_corr = 'cluster';
            stat_cluster = '''clusterstatistic'',''maxsum''';
            STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                                   'mode', 'fieldtrip', ...
                                   'singletrials', 'on', ...
                                   'fieldtripmethod', stat_method, ...
                                   'fieldtripalpha', 0.05, ...
                                   'fieldtripmcorrect', stat_corr, ...
                                   'fieldtripclusterparam', stat_cluster);

            [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
                std_erppplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on',
'subject', s);

            stand_erp =  mean(erpdata{1}, 2);
            dev_erp = mean(erpdata{2}, 2);
            mmn = dev_erp - stand_erp;

            mmn_plot(stand_erp, dev_erp, mmn, dev_type, ...
                     erptimes, pcond, .05, 1, fig_title);
            set_fig_props();

            STUDY = pop_statparams(STUDY, 'condstats', 'off', ...
                                   'mode', 'fieldtrip', ...
                                   'singletrials', 'on', ...
                                   'fieldtripmethod', stat_method, ...
                                   'fieldtripalpha', 0.05, ...
                                   'fieldtripmcorrect', stat_corr, ...
                                   'fieldtripclusterparam', stat_cluster);

            [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
               std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on',
'subject', s);

            erspdata = norm_ersp(erspdata, ersptimes);
            disp('Finished first go...')
            [pcond, pgroup, pinter] = std_stat(erspdata, 'condstats', 'on', ...
                                               'mode', 'fiedtrip', ...
                                               'fieldtripmethod', stat_method, ...
                                               'fieldtripalpha', 0.05, ...
                                               'fieldtripmcorrect', stat_corr, ...
                                               'fieldtripclusterparam', stat_cluster,
...
                                               'paired', {'off', 'off'});

            mmn_ersp_plot(erspdata, ersptimes, erspfreqs, pcond, dev_type, channels)
            set_fig_props();

        end

    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Patients Groups

```
% For schizophrenia patients use this comment others
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\MMN\patient MMN wICA SchizOnly.study');

% For schizoaffective disorder patients use this comment others
```

```
% [STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\MMN\patient_MMN_wICA_NonSchizOnly.study');

% For all patients use this comment others
% [STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\MMN\patient_MMN_wICA.study');

chan names = {};

for j = 1:length(ALLEEG(1).chanlocs)
    chan_names{j} = ALLEEG(1).chanlocs(j).labels;
end
imp_chan_array = [5, 15];
disp('Plots made for channels:')
disp(chan_names(imp_chan_array));
load mmn_patients.mat

scales = [2.5, 2.5, 2, 3.1, 3.2];
diff_scales = [1.2, 1.2, 1.0, 1.6, 1.5];
for design_num = 1:5

    for i = imp_chan_array  %[5, 15, 25]   % 1:length(chan_names)
        STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
        disp(STUDY.design(design_num).name)
        disp(chan_names(i))
        disp(newline)
        std_name = STUDY.design(design_num).name;
        dev_type = split(std_name, 'Vs');
        dev_type = dev_type{2};
        channels = chan_names(i);

        stat_method = 'montecarlo';
        stat_corr = 'cluster';
        stat_cluster = '''clusterstatistic'','maxsum'''';
        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripmcorrect', stat_corr, ...
                               'fieldtripclusterparam', stat_cluster);

        [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
            std_erpplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        stand_erp =  mean(erpdata{1}, 2);
        dev_erp = mean(erpdata{2}, 2);
        mmn = dev_erp - stand_erp;
        mmn_plot(stand_erp, dev_erp, mmn, dev_type, ...
                 erptimes, pcond, .05, 1, fig_title);
        set_fig_props();

        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripmcorrect', stat_corr, ...
                               'fieldtripclusterparam', stat_cluster);

        [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
           std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        mmn_ersp_plot_scaled(erspdata, ersptimes, erspfreqs, pcond, ...
                             dev_type, channels, scales(design_num),
diff_scales(design_num))
        set_fig_props();
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

MMN Peak and Latency Plots

```
% Load data
control_stats = import_mmn_erp_stats('control_mmn.csv');
schiz_stats = import_mmn_erp_stats('schizOnly_mmn.csv');
nonschiz_stats = import_mmn_erp_stats('nonschiz_mmn.csv');

% Plot MMN Peaks
for i=1:5
    figure('Position', [1 41 1536 748.8000]);

    hold on;
    colors = brewermap(5, 'Dark2');

    plot(table2array(control_stats(i, 2:6)), '-o', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(schiz_stats(i, 2:6)), '--s', ...
                    'color', colors(i,:), 'Linewidth', 3,...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(nonschiz_stats(i, 2:6)), '--d', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    ax = gca;
    ax.YDir = 'reverse';

    set(gca, 'Ygrid', 'on')
    set(gca, 'xlim', [.5, 5.5]);
    set(gca, 'ylim', [-6, 0]);
    set(gca, 'XTick', [1,2,3,4,5], 'XTickLabel', str2mat('Fz', 'FCz', 'Cz', 'CPz',
'Pz'));

    if i==5
        set( get(gca,'XLabel'), 'String', 'Electrodes');
    end
    set( get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
    x_lab = get(gca, 'xlabel');
    set(x_lab, 'Units', 'normalized');
    set(x_lab, 'Position', [0.5, -0.06, 0]);

    title([char(control_stats.Deviant(i)), ': peaks']);

    set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
        'FontWeight', 'Bold', 'LineWidth', 2)

    % Format the labels of different boxes
    txt = findobj(gca,'Type','text');
    set(txt,'VerticalAlignment', 'Middle', ...
        'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
end

% Plot MMN Latencies
for i=1:5
    figure('Position', [1 41 1536 748.8000]);

    hold on;
    colors = brewermap(5, 'Dark2');

    plot(table2array(control_stats(i, 7:end)), '-o', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);
```

```
    plot(table2array(schiz_stats(i, 7:end)), '--s', ...
                    'color', colors(i,:), 'Linewidth', 3,...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(nonschiz stats(i, 7:end)), '--d', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    set(gca, 'Ygrid', 'on')
    set(gca, 'xlim', [.5, 5.5]);
    set(gca, 'ylim', [50, 350]);
    set(gca, 'XTick', [1,2,3,4,5], 'XTickLabel', str2mat('Fz', 'FCz', 'Cz', 'CPz',
'Pz'));

    if i==5
        set( get(gca,'XLabel'), 'String', 'Electrodes');
    end
    set( get(gca,'YLabel'), 'String', 'Latency (ms)');
    x_lab = get(gca, 'xlabel');
    set(x_lab, 'Units', 'normalized');
    set(x_lab, 'Position', [0.5, -0.06, 0]);

    title([char(control_stats.Deviant(i)), ': latencies']);

    set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
        'FontWeight', 'Bold', 'LineWidth', 2)

    % Format the labels of different boxes
    txt = findobj(gca,'Type','text');
    set(txt,'VerticalAlignment', 'Middle', ...
        'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
    legend({'Control', 'Schizophrenia', 'Schizoaffective'}, ...
           'FontSize', 42)
    legend('boxoff')
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

MMN ANOVA Analysis

```
control_dir = 'E:\EngD Data\Sibani\Studies\MMN\extracted_data\controls\';
schiz_dir = 'E:\EngD Data\Sibani\Studies\MMN\extracted_data\schiz_patients\';
nonSchiz_dir = 'E:\EngD Data\Sibani\Studies\MMN\extracted_data\nonSchiz_patients\';
all dir = 'E:\EngD Data\Sibani\Studies\MMN\extracted data\all patients\';

condition_names = {'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'};
conditions = {'standVsdur'; 'standVsfreq'; 'standVsint'; 'standVsloc'; 'standVsgap'};
electrodes = {'Fz'; 'FCz'; 'Cz'; 'CPz'; 'Pz'};
groups = {'Control'; 'Schizophrenia'; 'Schizoaffective'}; % 'All_patients'};

% MMN mean/peak amplitude
mmn_mean = [];
group_var = {};
elec_var = {};
cond_var = {};
age_var = [];

for g = 1:length(groups)
    disp(newline)
    disp(newline)
    disp(['Processing group: ' groups{g}])
    for e = 1:length(electrodes)
        disp(['Processing electrode: ' electrodes{e}])
        for c = 1:length(conditions)
            disp(newline)
            disp(['Processing condition: ' conditions{c}])
```

```
            if strcmp(groups{g}, 'Control')
                erp file = [control dir, 'control MMN ', conditions{c}, ' ',
electrodes{e}];
            elseif strcmp(groups{g}, 'Schizophrenia')
                erp_file = [schiz_dir, 'schiz_patient_MMN_', conditions{c}, '_',
electrodes{e}];
            elseif strcmp(groups{g}, 'Schizoaffective')
                erp_file = [nonSchiz_dir, 'nonSchiz_patient_MMN_', conditions{c},
'_', electrodes{e}];
            elseif strcmp(groups{g}, 'All_patients')
                erp_file = [all_dir, 'all_patient_MMN_', conditions{c}, '_',
electrodes{e}];
            end

            disp(['Loading: ', erp_file])
            erp_data = load(erp_file);
            mmn_data = erp_data.erpdata{2} - erp_data.erpdata{1};
            erptimes = erp_data.erptimes;
            time_ind = erptimes>89 & erptimes<251;

            curr_means = min(mmn_data(time_ind, :)); %, 1);
%           [~, curr_ind] = min(mmn_data(time_ind, :));
%               curr_times = erptimes(time_ind);
%               curr_latencies = curr_times(curr_ind);
%               curr_means = [];
%               for i = 1:length(curr_latencies)
%                   curr_time_logical = erptimes>(curr_latencies(i)-21) &
erptimes<(curr_latencies(i)+21);
%                   curr_erp_times = erptimes(curr_time_logical);
%                   curr_means = [curr_means, mean(mmn_data(curr_time_logical,
i))];
%               end
            mmn_mean = [mmn_mean, curr_means];

            curr_groups = repmat(groups(g), length(curr_means), 1);
            group_var = {group_var{:}, curr_groups{:}};

            curr_elecs = repmat(electrodes(e), length(curr_means), 1);
            elec_var = {elec_var{:}, curr_elecs{:}};

            curr conds = repmat(conditions(c), length(curr means), 1);
            cond_var = {cond_var{:}, curr_conds{:}};
        end
    end
end

clc
[p,tbl,stats,terms] = anovan(mmn_mean,{group_var,elec_var,cond_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes','Condition'});

% MMN Peak interactions
results = multcompare(stats,'Dimension',[1, 2]);
figure('Position', [1 41 1536 748.8000]);
hold on;
colors = brewermap(5, 'Dark2');

for e = 1:length(electrodes)
    disp(newline)
    disp(['Processing electrode: ' electrodes{e}])
    cond_mean = [];
    cond_stderr = [];
    x_vals = [.91, 1.91, 2.91] + e*.03;
    text_x_vals = [.85, 1.85, 2.85] + e*.05;
    for g = 1:length(groups)
        disp(['Processing group: ' groups{g}])
        curr_ind = strcmp(electrodes{e}, elec_var) & strcmp(groups{g}, group_var);
        curr_data = mmn_mean(curr_ind);
```

```
        cond_mean = [cond_mean, mean(curr_data)];
        cond_stderr = [cond_stderr, std(curr_data)/sqrt(length(curr_data))];

        result_num = 3*(e-1) + (g-1);
        result_cond = results(:, 1)==result_num & results(:, 6)<0.05 & ...
                      results(:, 2)-results(:,1)<2 & mod(results(:,1),3)~=0;
        if ~isempty(results(result_cond, :))
            disp(results(result cond, :))
            text(text_x_vals(g-1)+.5, -5, '*', ...
                'Color',colors(e,:))
        end
    end

    err = errorbar(x_vals, cond_mean, cond_stderr, '-o', ...
             'color', colors(e,:), 'Linewidth', 3, ...
             'MarkerEdgeColor',colors(e,:),...
             'MarkerFaceColor',colors(e,:), ...
             'MarkerSize', 10);
end

ax = gca;
ax.YDir = 'reverse';
set(gca, 'Ygrid', 'on')
set(gca, 'xlim', [.5, 3.5]);
set(gca, 'ylim', [-6, -1]);
set(gca, 'XTick', [1,2,3], 'XTickLabel', {'Control', 'Schizophrenia',
'Schizoaffective'});


set(get(gca,'XLabel'), 'String', 'Groups');
set(get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
x_lab = get(gca, 'xlabel');
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

legend({'Fz'; 'FCz'; 'Cz'; 'CPz'; 'Pz'}, ... % 'All Patients'}, ...
       'FontSize', 32)
legend('boxoff')
legend('Location', 'northwest')
title('a. Peak Interactions')
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
f_name = 'peak_interactions';
print(f_name, '-dpng', '-r300', '-painters');
close

% MMN peak latencies
mmn_latencies = [];
group_var = {};
elec_var = {};
cond_var = {};

for g = 1:length(groups)
    disp(newline)
    disp(newline)
    disp(['Processing group: ' groups{g}])
    for e = 1:length(electrodes)
        disp(['Processing electrode: ' electrodes{e}])
        for c = 1:length(conditions)
            disp(newline)
            disp(['Processing condition: ' conditions{c}])

            if strcmp(groups{g}, 'Control')
                erp_file = [control_dir, 'control_MMN_', conditions{c}, '_',
electrodes{e}];
            elseif strcmp(groups{g}, 'Schizophrenia')
                erp_file = [schiz_dir, 'schiz_patient_MMN_', conditions{c}, '_',
electrodes{e}];
            elseif strcmp(groups{g}, 'Schizoaffective')
                erp_file = [nonSchiz_dir, 'nonSchiz_patient_MMN_', conditions{c},
'_', electrodes{e}];
            elseif strcmp(groups{g}, 'All_patients')
```

```
                erp_file = [all_dir, 'all_patient_MMN_', conditions{c}, '_',
electrodes{e}];
            end

            disp(['Loading: ', erp_file])
            erp_data = load(erp_file);
            mmn_data = erp_data.erpdata{2} - erp_data.erpdata{1};
            erptimes = erp data.erptimes;
            time_ind = erptimes>89 & erptimes<251;

            [~, curr_ind] = min(mmn_data(time_ind, :));
            curr_times = erptimes(time_ind);
            curr_latencies = curr_times(curr_ind);
            mmn_latencies = [mmn_latencies, curr_latencies];

            curr_groups = repmat(groups(g), length(curr_latencies), 1);
            group_var = {group_var{:}, curr_groups{:}};

            curr_elecs = repmat(electrodes(e), length(curr_latencies), 1);
            elec_var = {elec_var{:}, curr_elecs{:}};

            curr_conds = repmat(conditions(c), length(curr_latencies), 1);
            cond_var = {cond_var{:}, curr_conds{:}};
        end
    end
end

clc
[p,tbl,stats,terms] = anovan(mmn_latencies,{group_var,elec_var,cond_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes','Condition'});

% MMN Latency interactions
results = multcompare(stats,'Dimension',[1, 3]);
figure('Position', [1 41 1536 748.8000]);
hold on;
colors = brewermap(5, 'Dark2');

for c = 1:length(conditions)
    disp(newline)
    disp(['Processing condition: ' conditions{c}])
    cond_mean = [];
    cond_stderr = [];
    x_vals = [.91, 1.91, 2.91] + c*.03;
    text_x_vals = [.85, 1.85, 2.85] + c*.05;
    for g = 1:length(groups)
        disp(['Processing group: ' groups{g}])
        curr_ind = strcmp(conditions{c}, cond_var) & strcmp(groups{g}, group_var);
        curr_data = mmn_latencies(curr_ind);
        cond_mean = [cond_mean, mean(curr_data)];
        cond_stderr = [cond_stderr, std(curr_data)/sqrt(length(curr_data))];

        result_num = 3*(c-1) + (g-1);
        result_cond = results(:, 1)==result_num & results(:, 6)<0.05 & ...
                      results(:, 2)-results(:,1)<2 & mod(results(:,1),3)~=0;
        if ~isempty(results(result_cond, :))
            disp(results(result_cond, :))
            text(text x vals(g-1)+.5, 225, '*', ...
                'Color',colors(c,:))
        end
    end
    err = errorbar(x_vals, cond_mean, cond_stderr, '-o', ...
             'color', colors(c,:), 'Linewidth', 3, ...
             'MarkerEdgeColor',colors(c,:),...
             'MarkerFaceColor',colors(c,:), ...
             'MarkerSize', 10);
end

set(gca, 'Ygrid', 'on')
set(gca, 'xlim', [.5, 3.5]);
set(gca, 'ylim', [100, 250]);
set(gca, 'XTick', [1,2,3], 'XTickLabel', {'Control', 'Schizophrenia',
'Schizoaffective'});
```

```
set(get(gca,'XLabel'), 'String', 'Groups');
set(get(gca,'YLabel'), 'String', 'Latency (ms)');
x_lab = get(gca, 'xlabel');
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

legend({'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'}, ... % 'All
Patients'}, ...
       'FontSize', 32)
legend('boxoff')
legend('Location', 'northwest')
title('b. Latency Interactions')
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
f_name = 'latency_interactions';
print(f_name, '-dpng', '-r300', '-painters');
close

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

MMN Correlations with Demographic data

```
% Load Demographic data
load_patient_demo_data

% Load saved EEG measures
patient_dur_data = import_mmn_patient_byDeviant('dur_patient_mmn.csv');
patient_dur_data = sortrows(patient_dur_data, 'Codes');

patient_freq_data = import_mmn_patient_byDeviant('freq_patient_mmn.csv');
patient_freq_data = sortrows(patient_freq_data, 'Codes');

patient_int_data = import_mmn_patient_byDeviant('int_patient_mmn.csv');
patient_int_data = sortrows(patient_int_data, 'Codes');

patient_loc_data = import_mmn_patient_byDeviant('loc_patient_mmn.csv');
patient_loc_data = sortrows(patient_loc_data, 'Codes');

patient_gap_data = import_mmn_patient_byDeviant('gap_patient_mmn.csv');
patient_gap_data = sortrows(patient_gap_data, 'Codes');


patient_peak_data = [patient_dur_data{:,'PeakFz'}, patient_freq_data{:,'PeakFz'}, ...
                     patient_int_data{:,'PeakFz'}, patient_loc_data{:,'PeakFz'}, ...
                     patient_gap_data{:,'PeakFz'}];

patient_latency_data = [patient_dur_data{:,'LatencyFz'},
patient_freq_data{:,'LatencyFz'}, ...
                        patient_int_data{:,'LatencyFz'},
patient_loc_data{:,'LatencyFz'}, ...
                        patient_gap_data{:,'LatencyFz'}];

patient_scores = patient_demo_data{:, {'Age', ...
                                       'PANSSP_session1', 'PANSSN_session1', ...
                                       'PANSSG_session1', ...
                                       'MADRS_session1'}};
patient_peak_schiz = abs(patient_peak_data(4:end, :));
patient_latency_schiz = patient_latency_data(4:end, :);
patient_scores_schiz = patient_scores(4:end, :);

patient_peak_nonSchiz = abs(patient_peak_data(1:3, :));
patient_latency_nonSchiz = patient_latency_data(1:3, :);
patient_scores_nonSchiz = patient_scores(1:3, :);

% Peak correlation
% Computing and plotting correlations for Schizophrenia patients
[task_score_corr, p] = corr(patient_peak_schiz, patient_scores_schiz);
```

```
c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

condition_names = {'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:10)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', condition_names)
axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Peak Correlations: Schizophrenia')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'demo_peak_corrs_schiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

% Computing and plotting correlations for Schizoaffective patients
[task_score_corr, p] = corr(patient_peak_nonSchiz, patient_scores_nonSchiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

condition_names = {'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:10)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', condition_names)
axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Peak Correlations: Schizoaffective')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'demo_peak_corrs_nonSchiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close

% Latency correlation
% Computing and plotting correlations for Schizophrenia patients
[task_score_corr, p] = corr(patient_latency_schiz, patient_scores_schiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

condition_names = {'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
```

```
              'MADRS'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:10)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', condition_names)
axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Latency Correlations: Schizophrenia')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'demo_latency_corrs_schiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

% Computing and plotting correlations for Schizoaffective patients
[task_score_corr, p] = corr(patient_latency_nonSchiz, patient_scores_nonSchiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

condition_names = {'Duration'; 'Frequency'; 'Intensity'; 'Location'; 'Gap'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:10)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', condition_names)
axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Latency Correlations: Schizoaffective')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'demo_latency_corrs_nonSchiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Figure Formatting Function

```
function set_fig_props()
    set(findall(gcf,'-property','FontSize'),'FontSize',24)
    set(findall(gcf,'-property','FontName'),'FontName','Garamond')
    set(findall(gcf,'-property','FontWeight'),'FontWeight','Bold')
    set(findall(gcf,'-property','LineWidth'),'LineWidth',2)
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

ERSP Averaging and Normalization function

```
function ersp_norm = norm_ersp(erspdata, ersptimes)
    P = squeeze(erspdata{1});
    base_t = find(ersptimes<0);
    mbase = mean(P(base_t, :, :), 1);
    mbase = mean(mbase, 3);
    P_norm = P./mbase;

    ersp_norm = {};
    ersp_norm{1,1} = P_norm;

    P = squeeze(erspdata{2});
    base_t = find(ersptimes<0);
    mbase = mean(P(base_t, :, :), 1);
    mbase = mean(mbase, 3);
    P_norm = P./mbase;

    ersp_norm{2,1} = P_norm;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for MMN ERP Plots

```
function mmn_plot(stand_erp, dev_erp, mmn, dev_type, ...
    erptimes, pcond, p_thresh, reverse, fig_title)

    figure('Position', [1 41 1536 748.8000]);

    max_y = max(max(stand_erp), max(dev_erp));
    max_y = floor(max_y + 2);
    min_y = min(min(stand_erp), min(dev_erp));
    min_y = ceil(min_y - 2);

    max_y = 7;
    min_y = -11;

    plot(erptimes, stand_erp, 'linewidth', 1., 'color', [0.3 0.3 0.3])
    hold on; plot(erptimes, dev_erp, 'linewidth', 1., 'color', [0.7 0.7 0.7])
    plot(erptimes, mmn, 'linewidth', 2)
    plot(erptimes, zeros(length(erptimes), 1), 'k', 'linewidth', 1)


    if ~reverse
        patch_y = [min_y+.4 min_y+.7];
    else
        patch y = [max y-.4 max y-.7];
    end

    patch_c = [0.3 0.3 0.3];
    times = erptimes;
    regions = pcond{1};

    if sum(regions)>0
        r_ind = find(regions==1);
        r_ind_change = find(diff(r_ind)>1);
        r_ind_change = sort([r_ind_change' r_ind_change'+1]);
        r_ind_change = [1 r_ind_change length(r_ind)];

        for i = 1:2:length(r_ind_change)-1
            tmp_t = [times(r_ind(r_ind_change(i))) ...
                     times(r_ind(r_ind_change(i+1)))];
            tmp_p = patch([tmp_t(1) tmp_t(2) tmp_t(2) tmp_t(1)], ...
                          [patch_y(1) patch_y(1) patch_y(2) patch_y(2)], ...
                          patch_c);
            set(tmp_p, 'edgecolor', patch_c);
        end
    end
```

```
    box off
    set(gca,'FontSize',36, 'fontname','times')
    legend('stand', dev type, 'MMN')
    legend('boxoff')
    yticks(min_y+1:2:max_y-1);
    plot([0, 0], [min_y max_y], 'k', 'linewidth', 0.5)
    ylim([min_y, max_y]);
    title(fig title);
    set( get(gca,'XLabel'), 'String', 'Latency (ms)');
    set( get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
    legend('Stand', first_upper(dev_type), 'MMN', 'Location', 'northeast')
    legend('boxoff')
    if reverse
        ax = gca;
        ax.YDir = 'reverse';
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for MMN ERSP Plots

```
function mmn_ersp_plot_scaled(erspdata, ersptimes, erspfreqs, pcond, dev_type,
channels, ersp_scale, diff_scale)
    figure('Position', [1 41 1536 748.8000]);
    rdbu_map = brewermap(200,'RdBu');
    c_val_esrp = [max(max(abs(mean(erspdata{1}, 4)))), ...
                  max(max(abs(mean(erspdata{2}, 4))))];
    c_val_esrp = max(c_val_esrp);
    disp(['Cal for 1,2 ' num2str(c_val_esrp)])
    c_val_esrp = ersp_scale;
    erspfreqs = log(erspfreqs);

    fticks = [2 4 8 16 24 32 40, 48];

    p1 = subplot('Position', [.075, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{1}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal');
    set( get(p1,'XLabel'), 'String', 'Latency (ms)');
    set( get(p1,'YLabel'), 'String', 'Frequency (Hz)');
    set(gca,'ytick',log(fticks));
    set(gca,'yticklabel', string(fticks))
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Standard ERSP: ', cell2mat(join(channels, ', '))])

    p2 = subplot('Position', [.375, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{2}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p2,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Deviant (' dev_type ') ERSP: ' cell2mat(join(channels, ', '))])

    p3 = subplot('Position', [.675, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{2} - erspdata{1}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p3,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(brewermap(200,'RdBu'));
```

```
    hcb = colorbar;
    title(hcb, 'dB')
    c_val = max(max(abs(mean(erspdata{2} - erspdata{1}, 4))));
    disp(['Cal for 3 ' num2str(c_val)])
    c_val = diff_scale;
    caxis([-c_val, c_val])
    hold on;
    x = linspace(ersptimes(1), ersptimes(end), length(ersptimes));
    y = linspace(erspfreqs(1), erspfreqs(end), length(erspfreqs));
    contour(x, y, pcond{1}~=1, 'k')
    title(['Difference ERSP: ', cell2mat(join(channels, ', '))])

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for Single Patient MMN ERSP Plots

```
function mmn_ersp_plot(erspdata, ersptimes, erspfreqs, pcond, dev_type, channels,
fig_title)
    figure('Position', [1 41 1536 748.8000]);
    rdbu_map = brewermap(200,'RdBu');

    P_db{1,1} = 10*log10(mean(erspdata{1}, 3));
    P_db{2,1} = 10*log10(mean(erspdata{2}, 3));
    c_val_esrp = [max(max(abs(P_db{1}))), ...
                  max(max(abs(P_db{2})))];
    c_val_esrp = max(c_val_esrp);

    erspfreqs = log(erspfreqs);

    fticks = [2 4 8 16 24 32 40, 48];

    p1 = subplot('Position', [.075, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{1}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal');
    set( get(p1,'XLabel'), 'String', 'Latency (ms)');
    set( get(p1,'YLabel'), 'String', 'Frequency (Hz)');
    set(gca,'FontSize', 24, 'fontname','times')
    set(gca,'ytick',log(fticks));
    set(gca,'yticklabel', string(fticks))
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Standard ERSP: ', cell2mat(join(channels, ', '))])

    p2 = subplot('Position', [.375, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{2}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set(gca,'FontSize', 24, 'fontname','times')
    set( get(p2,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Deviant (' dev_type ') ERSP: ' cell2mat(join(channels, ', '))])

    p3 = subplot('Position', [.675, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{2}' - P_db{1}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set(gca,'FontSize', 24, 'fontname','times')
    set( get(p3,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
```

```
    colormap(brewermap(200,'RdBu'));
    hcb = colorbar;
    title(hcb, 'dB')
    c_val = max(max(abs(P_db{2} - P_db{1})));
    caxis([-c_val, c_val])
    hold on;
    x = linspace(ersptimes(1), ersptimes(end), length(ersptimes));
    y = linspace(erspfreqs(1), erspfreqs(end), length(erspfreqs));
    contour(x, y, pcond{1}'~=1, 'k')
    title(['Difference ERSP: ', cell2mat(join(channels, ', '))])

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

APPENDIX F - MATLAB CODES: STROOP TASK

Stroop Task Behavioural Plots

```
% Load Data
load('stroop control combined')
load('stroop_patient_combined')
strooppatient = strooppatient09032020;

schiz_inds = [3, 5, 6];
non_schiz_inds = [2, 1, 4];

schiz_patients = strooppatient(schiz_inds, :);
non_schiz_patients = strooppatient(non_schiz_inds, :);

% Comparing percent correct between control and patients
clc
values = [stroopcontrol.TotalPercentCorrect; ...
          strooppatient.TotalPercentCorrect];
groups = [1*ones(size(stroopcontrol.TotalPercentCorrect)); ...
          2*ones(size(strooppatient.TotalPercentCorrect))];
label = {'Control', 'Patient'};
make rawplot colored stroop(values, groups, label, 'Percent Correct');
ylim([15, 105])

% Patient compare cong and incong latencies
clc
label = {'Congruent', 'Incongruent'};
compare_within_patients(strooppatient.CongLatency, strooppatient.IncongLatency,
label, 'Latencies (ms)');
[h,p,ci,stats] = ttest(strooppatient.IncongLatency, strooppatient.CongLatency)
[h,p,ci,stats] = ttest(strooppatient.IncongLatency, strooppatient.CongLatency,
'tail', 'right')
ylim([425, 875]);
yticks([450, 550, 650, 750, 850]);

% Control compare cong and incong latencies
clc
label = {'Congruent', 'Incongruent'};
compare_within_controls(stroopcontrol.CongLatency, stroopcontrol.IncongLatency,
label, 'Latencies (ms)');
[h,p,ci,stats] = ttest(stroopcontrol.IncongLatency, stroopcontrol.CongLatency)
[h,p,ci,stats] = ttest(stroopcontrol.IncongLatency, stroopcontrol.CongLatency,
'tail', 'right')
ylim([425, 650]);
yticks([450, 500, 550, 600, 650]);

% Compare percent change in latency between controls and patients
clc
control_perc_change = (stroopcontrol.IncongLatency-
stroopcontrol.CongLatency)*100./stroopcontrol.CongLatency;
patient_perc_change = (strooppatient.IncongLatency-
strooppatient.CongLatency)*100./strooppatient.CongLatency;

values = [control_perc_change; patient_perc_change];
```

```
groups = [1*ones(size(control_perc_change)); 2*ones(size(patient_perc_change))];
label = {'Control', 'Patients'};
make rawplot colored stroop(values, groups, label, 'Percent change (%)');
ylim([-12, 27])

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function to compare Controls and Patients

```
function fig_handle = make_rawplot_colored_stroop(values, groups, label, y_label)
%Make a boxplot for the values with grouping
%   values:   vector of all the data thats used to create the boxplot
%   groups:   vector representing how the data is grouped; same number is
%             assigned to the values in the same group. The data can have
%             any number of groups
%   label:    labels that will be shown for each group in the plot. Make
%             sure the number of labels is same as diffenret number of
%             groups.
%   y label:  label for y-axis.


% Get colors for raw data
c_data = brewermap(20, 'RdYlGn');
color_data = brewermap(8, 'Dark2');
color_data = color_data([1,2,3,4,6,8], :);
% Set Figure position and size
figure('Units' , 'normalized', ...
       'Position', [0., 0., .9, .9]);
% figure('Position', [1 41 1536 748.8000])
hold on;

unique_groups = unique(groups);

x_controls = groups(groups==1);
values_controls = values(groups==1);

x_patients = groups(groups==2);
values_patients = values(groups==2);
values_patients_5 = values_patients([1,3,4,5,6]);

% Calculating p-values between adjacent groups
dist1 = values_controls;
dist2 = values_patients_5;
% dist2 = values_patients;

[h, p] = ttest2(dist1, dist2);
[hk, pk] = kstest2(dist1, dist2);
medians(1) = median(dist1);
medians(2) = median(dist2);

% put a * mark if p<0.05
if p < 0.05
    plot(mean(unique_groups)-0.025, mean(medians)*1.1, ...
         '*', 'Color', c_data(2, :),...
         'LineWidth', 2, 'MarkerSize', 10)
end

% put another * mark if p<0.005
if p < 0.005
    plot(mean(unique_groups)+0.025, mean(medians)*1.1, ...
         '*', 'Color', c_data(2, :),...
         'LineWidth', 2, 'MarkerSize', 10)
end

% plot a line between medians of group data
plot(unique_groups, medians, 'Color', c_data(2, :), 'LineWidth', 2)
set(gca,'xtick',unique(groups),'xticklabel',label)

disp(['Ttest p = ', num2str(p, '%1.4e\n')])
disp(['Ktest p = ', num2str(pk, '%1.4e\n')])
```

```
%  Plot and format raw values

% Add noise to x values so that values that are close dont overlap
x = groups; % + (rand(size(groups)) - .5)/5;
x_controls = x(groups==1);
values_controls = values(groups==1);
% x_controls = x_controls + (rand(size(x_controls)) - .5)/5;

% Seperate overlapping data for controls
unique_vals = unique(ceil(values_controls));
for i=1:length(unique_vals)
    n = length(values_controls(ceil(values_controls)==unique_vals(i)));
    if n==1
        continue;
    else
        x_controls(ceil(values_controls)==unique_vals(i)) = 1 + linspace(-.025*n,
0.025*n, n);
    end
end

% Plot the raw values for controls
plot(x_controls, values_controls, 'o', 'MarkerSize', 10, ...
     'MarkerEdgeColor', c_data(15, :), ...
     'MarkerFaceColor', c_data(15, :), 'LineWidth', 1)

hold on;

% Plot raw values for patients with their individual colours
x_patients = x(groups==2);
values_patients = values(groups==2);

% Seperate overlapping data
unique_vals = unique(ceil(values_patients));
for i=1:length(unique_vals)
    n = length(values_patients(ceil(values_patients)==unique_vals(i)));
    if n==1
        continue;
    else
        x_patients(ceil(values_patients)==unique_vals(i)) = 2 + linspace(-.025*n,
0.025*n, n);
    end
end


for i=1:length(x_patients)
    plot(x_patients(i), values_patients(i), 'o', ...
         'MarkerSize', 15,'MarkerEdgeColor', color_data(i, :), ...
         'MarkerFaceColor', color_data(i, :), 'LineWidth', 1)
end

xlim([unique_groups(1) - 0.5, unique_groups(end) + 0.5]);
% change fonts for the axis
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

% set labels for x and y axis
xlabel('Group')
x lab = get(gca, 'xlabel');
set(x_lab, 'Units', 'normalized');
set(x_lab, 'Position', [0.5, -0.07, 0]);
ylabel(y_label)

box 'off'
set(gca, 'Ygrid', 'on')

% Format the labels of different boxes
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');

axis('square')
fig_handle = gcf;
```

```
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function to compare within Healthy Controls

```
function fig_handle = compare_within_controls(cong, incong, label, y_label)
%Make a boxplot for the values with grouping
%   cong:   vector of all the cong values
%   incong: vector of all the incong values
%   label:  text label for x-axis
%   y_label:  label for y-axis.


% Get colors for raw data
c_data = brewermap(20, 'RdYlGn');
% Set Figure position and size
figure('Units' , 'normalized', ...
       'Position', [0., 0., .9, .9]);
hold on;

data = [cong incong];
x = [ones(size(cong)) 2*ones(size(incong))];

data_pos = data(incong-cong>0, :);
x_pos = x(incong-cong>0, :);

data_neg = data(incong-cong<=0, :);
x_neg = x(incong-cong<=0, :);
% Plot the raw values

plot(x_pos', data_pos', 'o-', 'Color',  c_data(15, :), ...
     'MarkerSize', 10, 'MarkerEdgeColor', c_data(15, :), ...
     'MarkerFaceColor', c_data(15, :), 'LineWidth', 2)
hold on;

plot(x_neg', data_neg', 'o-', 'Color',  c_data(2, :), ...
     'MarkerSize', 10, 'MarkerEdgeColor', c_data(2, :), ...
     'MarkerFaceColor', c_data(2, :), 'LineWidth', 2)


xlim([0.5, 2.5]);
% change fonts for the axis
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

% set labels for x and y axis
xlabel('Controls')
x_lab = get(gca, 'xlabel');
set(x_lab, 'Units', 'normalized');
set(x_lab, 'Position', [0.5, -0.07, 0]);
set(gca,'xtick',[1 2],'xticklabel',label)
ylabel(y_label)

box 'off'
set(gca, 'Ygrid', 'on')

% Format the labels of different boxes
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');

axis('square')
fig_handle = gcf;

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function to compare within Patients

```
function fig_handle = compare_within_patients(cong, incong, label, y_label)
%Make a boxplot for the values with grouping
%   cong:   vector of all the cong values
%   incong: vector of all the incong values
%   label:  text label for x-axis
%   y_label:  label for y-axis.


% Get colors for raw data
c_data = brewermap(20, 'RdYlGn');
color_data = brewermap(8, 'Dark2');
color_data = color_data([1,2,3,4,6,8], :);
% Set Figure position and size
figure('Units' , 'normalized', ...
       'Position', [0., 0., .9, .9]);
hold on;


% Plot the raw values for cong
for i=1:length(cong)
    plot([1 2], [cong(i) incong(i)], 'o-', 'Color',  color_data(i, :), ...
         'MarkerSize', 15, 'MarkerEdgeColor', color_data(i, :), ...
         'MarkerFaceColor', color_data(i, :), 'LineWidth', 2)
    hold on;
end

xlim([0.5, 2.5]);
% change fonts for the axis
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

% set labels for x and y axis
xlabel('Patients')
x_lab = get(gca, 'xlabel');
set(x_lab, 'Units', 'normalized');
set(x_lab, 'Position', [0.5, -0.07, 0]);
set(gca,'xtick',[1 2],'xticklabel',label)
ylabel(y_label)

box 'off'
set(gca, 'Ygrid', 'on')

% Format the labels of different boxes
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');

axis('square')
fig_handle = gcf;

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Healthy Controls

```
data_dir = 'E:\EngD Data\Sibani\Pilot\PILOT\';
% data_files = strcat(data_dir, '*Stroop*B*.cnt');
dataset_dir = strcat(data_dir, 'datasets\stroop\withICA');
% files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};
load stroop_controls.mat

for i = 1:length(subjects)
    disp(' ');
    disp(' ');
    disp(['Subject:' subjects{i}]);
```

```
    data_files = strcat(data_dir, subjects{i}, '*Stroop*B*.cnt');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end

    % Load data
    for j = 1:length(files)
        f_name = split(files(j).name, '.');
        f_name = f_name{1};

        disp('Prepocessing:')
        disp(f_name)
        disp(' ')
        cnt_file = strcat(data_dir, files(j).name);
        try
            EEG = pop_loadcnt(cnt_file, 'keystroke', 'on');
            EEG.setname = f_name;
        catch
            disp('Skipping loading:')
            disp(f_name)
            disp(' ')
            disp(' ')
            skipped_cnt = [skipped_cnt; f_name];
            continue
        end

        % Import channel info
        EEG = pop_chanedit(EEG, 'lookup', ...
                           'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit2.3\standard_BESA\standard-10-5-
cap385.elp', ...
                           'eval','chans = pop_chancenter( chans, [],[]);');

        % Re-reference data to common average excluding EOG
        EEG = pop_reref(EEG, [], 'exclude', [65, 66]);

        % Resample data
        EEG = pop_resample(EEG, 250);

        % Filter data
        EEG = pop_eegfiltnew(EEG, .1, []);
        % Low-pass
        EEG = pop_eegfiltnew(EEG, [], 40);

        % Remove line noise using CleanLine
        EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                            'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                            'verb', 1, 'winsize', 4, 'winstep', 4);
        % Run ICA
        EEG = pop_runica(EEG, 'icatype', 'runica');

        % Extract Epoch
        try
            EEG = pop epoch(EEG, {8, 9}, [-.2 1.3]);
        catch
            disp('Skipping epoching:')
            disp(f_name)
            disp(' ')
            disp(' ')
            skipped_epoch = [skipped_epoch; f_name];
            continue
        end
        EEG = pop_rmbase(EEG, [-200, 0]);
        EEG.setname = [f_name '_Fs250_LP40'];
        EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40' '_ds'], 'filepath',
dataset_dir);

        clear EEG
    end
```

```
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient Data\';
data_files = strcat(data_dir, '*Stroop*B*.cnt');
dataset_dir = strcat(data_dir, 'datasets\stroop\withICA\');
files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};

for i = 1:length(files)
    f_split = split(files(i).name, '_');
    f_name = split(files(i).name, '.');
    f_name = char(f_name(1));
    sub_id = char(f_split(1));
    sub date = char(f split(2));
    sub_block = split(f_split(4), '.');
    sub_block = char(sub_block(1));

    disp('Prepocessing:')
    disp(f_name)

    % Load data
    cnt_file = strcat(data_dir, files(i).name);
    try
        EEG = pop_loadcnt(cnt_file, 'keystroke', 'on');
        EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_cnt = [skipped_cnt; f_name];
        continue
    end

    % Import channel info
    EEG = pop_chanedit(EEG, 'lookup', ...
                       'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit2.3\standard_BESA\standard-10-5-
cap385.elp', ...
                       'eval','chans = pop_chancenter( chans, [],[]);');

    % Re-reference data to Cz in patients (15)
    EEG = pop_reref(EEG, [], 'exclude', [38, 39]);

    % Resample data
    EEG = pop_resample(EEG, 250);

    % Filter data
    EEG = pop_eegfiltnew(EEG, .1, []);
    % Low-pass
    EEG = pop_eegfiltnew(EEG, [], 40);

    % Remove line noise using CleanLine
    EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                        'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                        'verb', 1, 'winsize', 4, 'winstep', 4);
    % Run ICA
    EEG = pop_runica(EEG, 'icatype', 'runica');

    % Extract Epoch
    try
        EEG = pop epoch(EEG, {8, 9}, [-.2 1.3]);
    catch
        disp('Skipping epoching:')
```

```
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_epoch = [skipped_epoch; f_name];
        continue
    end
    EEG = pop_rmbase(EEG, [-200, 0]);
    EEG.setname = [f name ' Fs250 LP40'];
    EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40' '_ds'], 'filepath',
dataset_dir);
    clear EEG
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\stroop\withICA\withMarked\withRejectEpochs\';
%Directory where Stroop datasets are saved
byType_dir = strcat(data_dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType_dir, 'dir')
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event_type = [9, 8];
type_name = {'cong', 'incong'};

resp_type = {'keypad2', 'keypad1'};

skipped_set = {};
skipped_split = {};

load stroop_controls.mat
type_total_trials = zeros(2, length(subjects));
type_clean_trials = zeros(2, length(subjects));  % Trials by type (1, :) cong; (2, :)
incong
type_correct_trials = zeros(2, length(subjects)); % Correct Trials by type (1, :)
cong; (2, :) incong

for i = 1:length(subjects)

    data_files = strcat(data_dir, subjects{i}, '*Stroop*.set');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end
    f_name = split(files(1).name, '_B');
    f_name = char(f_name(1));

    rej_files = strcat(data_dir, 'rej_mats\', subjects{i}, '*Stroop*.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
    disp(f_name)

    % Load and concatenate datasets
    try
        ALLEEG = [];
        for j = 1:length(files)
            % Print file names being concatenated to verify correct file
            % are being processed for the give subject. Delete any datasets
            % that are incorrect from folder
            disp(' ')
            disp('Loading')
            disp(['File: ', files(j).name])
            disp(['Rejected epochs: ', rej files(j).name])

            load([rej_files(j).folder, '\', rej_files(j).name])
```

```
            tot_epochs = length(rej.rejmanual);
            disp(['Total epochs: ', num2str(tot_epochs)])
            num_rejected = sum(rej.rejmanual);
            disp(['Retianed epochs: ', num2str(tot_epochs-num_rejected)])

            EEG_block = pop_loadset(files(j).name, files(j).folder);

            type = extractfield(EEG block.event, 'type');
            [C,ia,ic] = unique(type);
            a_counts = accumarray(ic,1);
            for k = 1:2
                type_total_trials(k, i) = type_total_trials(k, i) +
a_counts(contains(C, num2str(event_type(k))));
            end
            EEG_block.reject.rejmanual = rej.rejmanual;
            EEG_block = pop_rejepoch( EEG_block, EEG_block.reject.rejmanual ,0);
            [ALLEEG, EEG_block, index] = eeg_store(ALLEEG, EEG_block);
        end
        EEG_block = pop_mergeset(ALLEEG, 1:length(files), 0);
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
        continue
    end

    % Create datasets by types
    for k = 1:length(event_type)

        % Name of the new dataset with event_type and type_name appended
        set_name = strcat(f_name, '_', num2str(event_type(k)), '_',
char(type_name(k)));

        % Selecting one event at a time
        try
            % Selecting all epochs
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_block, 'type',
event_type(k));
            type_clean_trials(k, i) = length(EEG_type.epoch);
            % Further keeping epochs with correct response and within max
            % resp time
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_type, 'type',
resp_type(k), 'latency', '0<=1000');
            type_correct_trials(k, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
        catch
            disp('Skipping split:')
            disp(set_name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG type = pop saveset(EEG type, 'filename', set name, 'filepath',
byType_dir);
        clear EEG_type
    end
    clear *EEG*
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\stroop\withICA\withMarked\withRejectEpochs\';   %Directory where Stroop
datasets are saved
```

```
byType_dir = strcat(data_dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType dir, 'dir')
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event type = [9, 8];
type_name = {'cong', 'incong'};

resp_type = {'keypad2', 'keypad1'};

skipped_set = {};
skipped_split = {};

load stroop_patients.mat
type_total_trials = zeros(2, length(subjects));
type_clean_trials = zeros(2, length(subjects));  % Trials by type (1, :) cong; (2, :)
incong
type_correct_trials = zeros(2, length(subjects)); % Correct Trials by type (1, :)
cong; (2, :) incong

for i = 1:length(subjects)

    data_files = strcat(data_dir, subjects{i}, '*Stroop*.set');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end
    f_name = split(files(1).name, '_B');
    f_name = char(f_name(1));

    rej_files = strcat(data_dir, 'rej_mats\', subjects{i}, '*Stroop*.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
    disp(f_name)

    % Load and concatenate dataset
    try
        ALLEEG = [];
        for j = 1:length(files)
            % Print file names being concatenated to verify correct file
            % are being processed for the give subject. Delete any datasets
            % that are incorrect from folder
            disp(' ')
            disp('Loading')
            disp(['File: ', files(j).name])
            disp(['Rejected epochs: ', rej_files(j).name])

            load([rej_files(j).folder, '\', rej_files(j).name])
            tot_epochs = length(rej.rejmanual);
            disp(['Total epochs: ', num2str(tot_epochs)])
            num_rejected = sum(rej.rejmanual);
            disp(['Retianed epochs: ', num2str(tot_epochs-num_rejected)])

            EEG_block = pop_loadset(files(j).name, files(j).folder);

            % Droping EOG channels
            drop_chans = [38, 39];
            disp('Dropping EOG channels: VEOG, HEOG...')
            EEG_block = pop_select(EEG_block, 'nochannel', drop_chans);
            % Capitalizing channel labels to avoid conflicts between subjects
            disp('Capitalizing channel labels...')
            EEG_block = capitalize_chan_labels(EEG_block);

            type = extractfield(EEG_block.event, 'type');
            [C,ia,ic] = unique(type);
            a_counts = accumarray(ic,1);
            for k = 1:2
                type_total_trials(k, i) = type_total_trials(k, i) +
a_counts(contains(C, num2str(event_type(k))));
            end
```

```
            EEG_block.reject.rejmanual = rej.rejmanual;
            EEG_block = pop_rejepoch( EEG_block, EEG_block.reject.rejmanual ,0);
            [ALLEEG, EEG block, index] = eeg store(ALLEEG, EEG block);
        end
        EEG = pop_mergeset(ALLEEG, 1:length(files), 0);
    catch
        disp('Skipping loading:')
        disp(f name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
        continue
    end

    % Create datasets by types
    for k = 1:length(event_type)

        % Name of the new dataset with event_type and type_name appended
        set_name = strcat(f_name, '_', num2str(event_type(k)), '_',
char(type_name(k)));

        % Selecting one event at a time
        try
            % Selecting all epochs
            [EEG_type evnt_ind_test] = pop_selectevent(EEG, 'type', event_type(k));
            type_clean_trials(k, i) = length(EEG_type.epoch);
            % Further keeping epochs with correct response and within max
            % resp time
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_type, 'type',
resp_type(k), 'latency', '0<=1200');
            type_correct_trials(k, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
        catch
            disp('Skipping split:')
            disp(set_name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG_type = pop_saveset(EEG_type, 'filename', set_name, 'filepath',
byType_dir);
        clear EEG_type
    end
    clear *EEG*
end

function EEG = capitalize_chan_labels(EEG)
    for i = 1:length(EEG.chanlocs)
        EEG.chanlocs(i).labels = upper(EEG.chanlocs(i).labels);
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\stroop\withICA\withMarked\withRejectEpochs\byType\';
%Directory where Stroop datasets are saved
data_files = strcat(data_dir, '*Stroop*.set');
files = dir(data_files);

% Event types and their names to append to file name before saving
event_type = [9, 8];
type_name = {'cong', 'incong'};

commands = {};
```

```
for i = 1:length(files)
    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_Stroop');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
end

std_dirpath = 'E:\EngD Data\Sibani\Studies\Stroop\controls_wICA';
if ~exist(std_dirpath)
  mkdir(std_dirpath);
end

name = 'control_Stroop_wICA';
[STUDY ALLEEG] = std_editset([], [], 'name', name, ...
                             'task', 'Stroop', ...
                             'filename', name, ...
                             'filepath', 'E:\EngD Data\Sibani\Studies\Stroop\', ...
                             'commands', commands);
STUDY = std_makedesign(STUDY, ALLEEG, 1, ...
                       'name','control_CongVsIncong', ...
                       'filepath',std_dirpath);

[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');

[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','off', ...
                             'erp','on',...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\stroop\withICA\withMarked\withRejectEpochs\byType\';   %Directory where
Stroop datasets are saved
data_files = strcat(data_dir, '*Stroop*.set');
files = dir(data_files);

% Event types and their names to append to file name before saving
event_type = [9, 8];
type_name = {'cong', 'incong'};

commands = {};

for i = 1:length(files)

    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_Stroop');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
end

std_dirpath = 'E:\EngD Data\Sibani\Studies\Stroop\patients_wICA';
if ~exist(std dirpath)
  mkdir(std_dirpath);
end
```

```
name = 'patient_Stroop_wICA';
[STUDY ALLEEG] = std editset([], [], 'name', name, ...
                             'task', 'Stroop', ...
                             'filename', name, ...
                             'filepath', 'E:\EngD Data\Sibani\Studies\Stroop\', ...
                             'commands', commands);
STUDY = std makedesign(STUDY, ALLEEG, 1, ...
                       'name','patient_CongVsIncong', ...
                       'filepath', std_dirpath);

[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');

[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','on', 'savetrials', 'on', ...
                             'erp','on',...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 200});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Healthy Controls

```
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\Stroop\control_Stroop_wICA.study');

chan_names = {};
for i = 1:length(ALLEEG(1).chanlocs)
    chan_names{i} = ALLEEG(1).chanlocs(i).labels;
end
imp_chans = [10, 28, 48];
disp(chan_names(imp_chans))

for design_num = 1
    for i = imp_chans
        STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
        disp(STUDY.design(design_num).name)
        disp('')
        std_name = STUDY.design(design_num).name;
        channels = chan_names(i);

        stat_method = 'montecarlo';
        stat_corr = 'cluster';
        stat_cluster = '''clusterstatistic'',''maxsum''';
        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripmcorrect', stat_corr, ...
                               'fieldtripclusterparam', stat_cluster);

        [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
            std_erpplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');
        cong_erp =  mean(erpdata{1}, 2);
        incong_erp = mean(erpdata{2}, 2);
        fig_title = ['ERP Cong Vs Incong: ', cell2mat(join(channels, ', '))];

        stroop_plot(cong_erp, incong_erp, ...
                 erptimes, pcond, .05, 0, fig_title);
        set_fig_props();

        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripmcorrect', stat_corr, ...
                               'fieldtripclusterparam', stat_cluster);

        [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
           std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');
```

```
        stroop_ersp_plot(erspdata, ersptimes, erspfreqs, pcond, channels)
        set fig props();
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Individual Patients

```
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\Stroop\patient_Stroop_wICA.study');

chan names = {};

for j = 1:length(ALLEEG(3).chanlocs)
    chan_names{j} = ALLEEG(3).chanlocs(j).labels;
end
imp chan array = [5, 15, 25];
disp('Plots made for channels:')
disp(chan_names(imp_chan_array));
load stroop_patients.mat

for s_ind = [3,4,5,6,1,2]
    s = subjects{s_ind};
    for design_num = 1
        for i = imp_chan_array
            disp('')
            disp([s ' ' chan_names(i)])
            STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
            disp(STUDY.design(design_num).name)
            disp('')
            std_name = STUDY.design(design_num).name;
            channels = chan_names(i);

            stat_method = 'montecarlo';
            stat_corr = 'cluster';
            stat_cluster = '''clusterstatistic'',''maxsum''';
            STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                                   'mode', 'fieldtrip', 'singletrials', 'on', ...
                                   'fieldtripmethod', stat_method, ...
                                   'fieldtripalpha', 0.05, ...
                                   'fieldtripmcorrect', stat_corr, ...
                                   'fieldtripclusterparam', stat_cluster);
            [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
                std_erpplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on',
'subject', s);

            cong_erp =  mean(erpdata{1}, 2);
            incong_erp = mean(erpdata{2}, 2);
            fig_title = [s ' ERP Cong Vs Incong: ', cell2mat(join(channels, ', '))];
            stroop_plot(cong_erp, incong_erp, ...
                     erptimes, pcond, .05, 0, fig_title);

            set_fig_props();

            STUDY = pop_statparams(STUDY, 'condstats', 'off', ...
                                   'mode', 'fieldtrip','singletrials', 'on', ...
                                   'fieldtripmethod', stat_method, ...
                                   'fieldtripalpha', 0.05, ...
                                   'fieldtripmcorrect', stat_corr, ...
                                   'fieldtripclusterparam', stat_cluster);
            [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
               std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on',
'subject', s);

            erspdata = norm_ersp(erspdata, ersptimes);
            [pcond, pgroup, pinter] = std_stat(erspdata, 'condstats', 'on', ...
                                               'mode', 'fiedtrip', ...
                                               'fieldtripmethod', stat_method, ...
                                               'fieldtripalpha', 0.05, ...
```

```
                                                    'fieldtripmcorrect', stat_corr, ...
                                                    'fieldtripclusterparam', stat_cluster,
...
                                                    'paired', {'off', 'off'});

            stroop_ersp_plot_patient(erspdata, ersptimes, erspfreqs, pcond, channels)
            set_fig_props();
        end
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Plots: Patients Groups

```
% For schizophrenia patients use this comment others
[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\Stroop\patient_Stroop_wICA_SchizOnly.study');

% For schizoaffective disorder patients use this comment others
% [STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\Stroop\patient_Stroop_wICA_NonSchizOnly.study');

% For all patients use this comment others
% [STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\Stroop\patient_Stroop_wICA.study');

chan_names = {};

for j = 1:length(ALLEEG(1).chanlocs)
    chan_names{j} = ALLEEG(1).chanlocs(j).labels;
end
imp_chan_array = [5, 15, 25];
disp('Plots made for channels:')
disp(chan_names(imp_chan_array));
load stroop_patients.mat

for design_num = 1

    for i = imp_chan_array
        STUDY = std_selectdesign(STUDY, ALLEEG, design_num);
        disp(STUDY.design(design_num).name)
        disp('')
        std_name = STUDY.design(design_num).name;
        channels = chan_names(i);

        stat_method = 'montecarlo';
        stat_corr = 'cluster';
        stat_cluster = '''clusterstatistic'',''maxsum''';
        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripmcorrect', stat_corr, ...
                               'fieldtripclusterparam', stat_cluster);
        [STUDY, erpdata, erptimes, pgroup, pcond, pinter] = ...
            std_erpplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        cong_erp =  mean(erpdata{1}, 2);
        incong_erp = mean(erpdata{2}, 2);
        fig_title = ['ERP Cong Vs Incong: ', cell2mat(join(channels, ', '))];
        stroop_plot(cong_erp, incong_erp, ...
                 erptimes, pcond, .05, 0, fig_title);
        set_fig_props();

        STUDY = pop_statparams(STUDY, 'condstats', 'on', ...
                               'mode', 'fieldtrip', ...
                               'fieldtripmethod', stat_method, ...
                               'fieldtripalpha', 0.05, ...
                               'fieldtripnaccu', 5000, ...
                               'fieldtripmcorrect', stat_corr, ...
```

```
                                'fieldtripclusterparam', stat_cluster);
        [STUDY, erspdata, ersptimes, erspfreqs, pgroup, pcond, pinter] =  ...
           std_erspplot(STUDY, ALLEEG, 'channels', channels, 'noplot', 'on');

        stroop_ersp_plot(erspdata, ersptimes, erspfreqs, pcond, channels)
        set_fig_props();
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for Stroop ERP Plots

```
function stroop_plot(stand_erp, dev_erp, ...
    erptimes, pcond, p_thresh, reverse, fig_title)

    figure('Position', [1 41 1536 748.8000]);

    max_y = max(max(stand_erp), max(dev_erp));
    max_y = floor(max_y + 2);
    min_y = min(min(stand_erp), min(dev_erp));
    min_y = ceil(min_y - 2);

    max_y = 9;
    min_y = -5;

    plot(erptimes, stand_erp, 'linewidth', 2.)
    hold on; plot(erptimes, dev_erp, 'linewidth', 2.)
    plot(erptimes, zeros(length(erptimes), 1), 'k', 'linewidth', 2.)

    if ~reverse
        patch_y = [min_y+.4 min_y+.7];
    else
        patch_y = [max_y-.4 max_y-.7];
    end

    patch_c = [0.3 0.3 0.3];
    times = erptimes;
    regions = pcond{1};

    if sum(regions)>0
        r_ind = find(regions==1);
        r_ind_change = find(diff(r_ind)>1);
        r_ind_change = sort([r_ind_change' r_ind_change'+1]);
        r_ind_change = [1 r_ind_change length(r_ind)];

        for i = 1:2:length(r_ind_change)-1
            tmp_t = [times(r_ind(r_ind_change(i))) ...
                     times(r_ind(r_ind_change(i+1)))];
            tmp_p = patch([tmp_t(1) tmp_t(2) tmp_t(2) tmp_t(1)], ...
                          [patch_y(1) patch_y(1) patch_y(2) patch_y(2)], ...
                          patch_c);
            set(tmp_p, 'edgecolor', patch_c);
        end
    end

    box off
    set(gca,'FontSize',36 , 'fontname','times')
    yticks(min_y+1:2:max_y-1);
    plot([0, 0], [min_y max_y], 'k', 'linewidth', 2.)
    ylim([min_y, max_y]);
    xlim([min(erptimes) max(erptimes)])
    title(fig_title, 'Interpreter', 'none');
    set( get(gca,'XLabel'), 'String', 'Latency (ms)');
    set( get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
    legend('Congruent', 'Incongruent', 'Location', 'northeast')
    legend('boxoff')
    if reverse
        ax = gca;
```

```
        ax.YDir = 'reverse';
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for Stroop ERSP Plots

```
function stroop_ersp_plot(erspdata, ersptimes, erspfreqs, pcond, channels)
    figure('Position', [1 41 1536 748.8000]);
    rdbu_map = brewermap(200,'RdBu');
    c_val_esrp = [max(max(abs(mean(erspdata{1}, 4)))), ...
                  max(max(abs(mean(erspdata{2}, 4))))];
    c_val_esrp = max(c_val_esrp);
    disp(['Cal for 1,2 ' num2str(c_val_esrp)])
    c_val_esrp = 4;
    erspfreqs = log(erspfreqs);
    fticks = [2 4 8 16 24 32 40, 48];

    p1 = subplot('Position', [.075, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{1}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal');
    set( get(p1,'XLabel'), 'String', 'Latency (ms)');
    set( get(p1,'YLabel'), 'String', 'Frequency (Hz)');
    set(gca,'ytick',log(fticks));
    set(gca,'yticklabel', string(fticks))
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Congruent ERSP: ', cell2mat(join(channels, ', '))])

    p2 = subplot('Position', [.375, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{2}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p2,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Incongruent ERSP: ' cell2mat(join(channels, ', '))])

    p3 = subplot('Position', [.675, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, mean(erspdata{2} - erspdata{1}, 4));
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p3,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(brewermap(200,'RdBu'));
    hcb = colorbar;
    title(hcb, 'dB')
    c_val = max(max(abs(mean(erspdata{2} - erspdata{1}, 4))));
    disp(['Cal for 3 ' num2str(c_val)])
    c_val = 2.8;
    caxis([-c_val, c_val])
    hold on;
    x = linspace(ersptimes(1), ersptimes(end), length(ersptimes));
    y = linspace(erspfreqs(1), erspfreqs(end), length(erspfreqs));
    contour(x, y, pcond{1}~=1, 'k')
    title(['Difference ERSP: ', cell2mat(join(channels, ', '))])
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting function for Single Patient Stroop ERSP Plots

```
function stroop_ersp_plot_patient(erspdata, ersptimes, erspfreqs, pcond, channels)
    figure('Position', [1 41 1536 748.8000]);
    rdbu_map = brewermap(200,'RdBu');

    P_db{1,1} = 10*log10(mean(erspdata{1}, 3));
    P_db{2,1} = 10*log10(mean(erspdata{2}, 3));
    c_val_esrp = [max(max(abs(P_db{1}))), ...
                  max(max(abs(P_db{2})))];
    c_val_esrp = max(c_val_esrp);

    erspfreqs = log(erspfreqs);

    fticks = [2 4 8 16 24 32 40, 48];

    p1 = subplot('Position', [.075, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{1}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal');
    set( get(p1,'XLabel'), 'String', 'Latency (ms)');
    set( get(p1,'YLabel'), 'String', 'Frequency (Hz)');
    set(gca,'FontSize',20, 'fontname','times')
    set(gca,'ytick',log(fticks));
    set(gca,'yticklabel', string(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Congruent ERSP: ', cell2mat(join(channels, ', '))])

    p2 = subplot('Position', [.375, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{2}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set(gca,'FontSize', 24, 'fontname','times')
    set( get(p2,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title(['Incongruent ERSP: ' cell2mat(join(channels, ', '))])

    p3 = subplot('Position', [.675, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, P_db{2}' - P_db{1}');
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p3,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'FontSize', 24, 'fontname','times')
    set(gca,'ytick',log(fticks)); %(inds(1:2:end)));
    colormap(brewermap(200,'RdBu'));
    hcb = colorbar;
    title(hcb, 'dB')
    c_val = max(max(abs(P_db{2} - P_db{1})));
    caxis([-c_val, c_val])
    hold on;
    x = linspace(ersptimes(1), ersptimes(end), length(ersptimes));
    y = linspace(erspfreqs(1), erspfreqs(end), length(erspfreqs));
    contour(x, y, pcond{1}'~=1, 'k')
    title(['Difference ERSP: ', cell2mat(join(channels, ', '))])
    set(findall(gcf,'-property','FontSize'),'FontSize',24)
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Stroop Peak and Latency Plots

```
control_stats = import_stroop_erp_stats('control_stroop.csv');
schiz_stats = import_stroop_erp_stats('schiz_stroop.csv');
nonschiz_stats = import_stroop_erp_stats('nonSchiz_stroop.csv');

% Plot Stroop Peaks
y_max = [7, 7, 4];
for i=1:3
    figure('Position', [1 41 1536 748.8000]);
    hold on;
    colors = brewermap(5, 'Dark2');

    plot(table2array(control_stats(i, 2:6)), '-o', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(schiz_stats(i, 2:6)), '--s', ...
                    'color', colors(i,:), 'Linewidth', 3,...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(nonschiz stats(i, 2:6)), '--d', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    ax = gca;
    set(gca, 'Ygrid', 'on')
    set(gca, 'xlim', [.5, 5.5]);
    set(gca, 'ylim', [-.5, y_max(i)]);
    set(gca, 'XTick', [1,2,3,4,5], 'XTickLabel', str2mat('Fz', 'FCz', 'Cz', 'CPz',
'Pz'));

    if i==5
        set( get(gca,'XLabel'), 'String', 'Electrodes');
    end
    set( get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
    x_lab = get(gca, 'xlabel');
    set(x_lab, 'Units', 'normalized');
    set(x_lab, 'Position', [0.5, -0.06, 0]);

    title([char(control_stats.Type(i)), ': peaks']);

    set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
        'FontWeight', 'Bold', 'LineWidth', 2)

    % Format the labels of different boxes
    txt = findobj(gca,'Type','text');
    set(txt,'VerticalAlignment', 'Middle', ...
        'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
end

% Plot Stroop Latencties
for i=1:3
    figure('Position', [1 41 1536 748.8000]);
    hold on;
    colors = brewermap(5, 'Dark2');

    plot(table2array(control_stats(i, 7:end)), '-o', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(schiz_stats(i, 7:end)), '--s', ...
                    'color', colors(i,:), 'Linewidth', 3,...
                    'MarkerEdgeColor',colors(i,:),...
```

```
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    plot(table2array(nonschiz_stats(i, 7:end)), '--d', ...
                    'color', colors(i,:), 'Linewidth', 3, ...
                    'MarkerEdgeColor',colors(i,:),...
                    'MarkerFaceColor',colors(i,:), ...
                    'MarkerSize', 20);

    set(gca, 'Ygrid', 'on')
    set(gca, 'xlim', [.5, 5.5]);
    set(gca, 'ylim', [175, 1400]);
    set(gca, 'XTick', [1,2,3,4,5], 'XTickLabel', str2mat('Fz', 'FCz', 'Cz', 'CPz',
'Pz'));

    if i==5
        set( get(gca,'XLabel'), 'String', 'Electrodes');
    end
    set( get(gca,'YLabel'), 'String', 'Latency (ms)');
    x_lab = get(gca, 'xlabel');
    set(x_lab, 'Units', 'normalized');
    set(x_lab, 'Position', [0.5, -0.06, 0]);

    title([char(control_stats.Type(i)), ': latencies']);

    set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
        'FontWeight', 'Bold', 'LineWidth', 2)

    % Format the labels of different boxes
    txt = findobj(gca,'Type','text');
    set(txt,'VerticalAlignment', 'Middle', ...
        'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
    legend({'Control', 'Schizophrenia', 'Schizoaffective'}, ... % 'All Patients'},
...
           'FontSize', 42, 'Location','northwest')
    legend('boxoff')
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Stroop ANOVA Analysis

```
control_dir = 'E:\EngD Data\Sibani\Studies\Stroop\extracted_data\controls\';
schiz_dir = 'E:\EngD Data\Sibani\Studies\Stroop\extracted_data\schiz_patients\';
nonSchiz_dir = 'E:\EngD
Data\Sibani\Studies\Stroop\extracted_data\nonSchiz_patients\';
all_dir = 'E:\EngD Data\Sibani\Studies\Stroop\extracted_data\all_patients\';

condition_names = {'Congruent'; 'Incongruent'};
electrodes = {'Fz'; 'FCz'; 'Cz'; 'CPz'; 'Pz'};
groups = {'Control'; 'Schizophrenia'; 'Schizoaffective'}; % 'All_patients'};

erp_mean = [];
erp_latencies = [];
group_var = {};
elec_var = {};
cond_var = {};
age_var = [];

diff_mean = [];
diff_latencies = [];
diff_group_var = {};
diff_elec_var = {};
diff_age_var = [];

for g = 1:length(groups)
    disp(newline)
    disp(newline)
    disp(['Processing group: ' groups{g}])
    for e = 1:length(electrodes)
        disp(['Processing electrode: ' electrodes{e}])
```

```
        disp(newline)

        if strcmp(groups{g}, 'Control')
            erp_file = [control_dir, 'control_CongVsIncong_', electrodes{e}];
        elseif strcmp(groups{g}, 'Schizophrenia')
            erp_file = [schiz_dir, 'schiz_patient_CongVsIncong_', electrodes{e}];
        elseif strcmp(groups{g}, 'Schizoaffective')
            erp file = [nonSchiz dir, 'nonSchiz patient CongVsIncong ',
electrodes{e}];
        end

        disp(['Loading: ', erp_file])
        erp_data = load(erp_file);
        cong_data = erp_data.erpdata{1};
        incong_data = erp_data.erpdata{2};
        diff_data = incong_data - cong_data;
        erptimes = erp_data.erptimes;
        time_ind = erptimes>300 & erptimes<600;

        % Congruent condition
        [curr_means, curr_ind] = max(cong_data(time_ind, :));
%         curr_means = mean(cong_data(time_ind, :), 1);
        erp_mean = [erp_mean, curr_means];
        curr_times = erptimes(time_ind);
        curr_latencies = curr_times(curr_ind);
        erp_latencies = [erp_latencies, curr_latencies];

        curr_groups = repmat(groups(g), length(curr_means), 1);
        group_var = {group_var{:}, curr_groups{:}};
        curr_elecs = repmat(electrodes(e), length(curr_means), 1);
        elec_var = {elec_var{:}, curr_elecs{:}};
        curr_conds = repmat(condition_names(1), length(curr_means), 1);
        cond_var = {cond_var{:}, curr_conds{:}};

        % Incongruent condition
        [curr_means, curr_ind] = max(incong_data(time_ind, :));
%         curr_means = mean(incong_data(time_ind, :), 1);
        erp_mean = [erp_mean, curr_means];
        curr_times = erptimes(time_ind);
        curr_latencies = curr_times(curr_ind);
        erp_latencies = [erp_latencies, curr_latencies];

        curr_groups = repmat(groups(g), length(curr_means), 1);
        group_var = {group_var{:}, curr_groups{:}};
        curr_elecs = repmat(electrodes(e), length(curr_means), 1);
        elec_var = {elec_var{:}, curr_elecs{:}};
        curr_conds = repmat(condition_names(2), length(curr_means), 1);
        cond_var = {cond_var{:}, curr_conds{:}};
%
%         % Difference condition
        [curr_means, curr_ind] = max(diff_data(time_ind, :));
%         curr_means = mean(diff_data(time_ind, :), 1);
        diff_mean = [diff_mean, curr_means];
        curr_times = erptimes(time_ind);
        curr_latencies = curr_times(curr_ind);
        diff_latencies = [diff_latencies, curr_latencies];
        curr_groups = repmat(groups(g), length(curr_means), 1);
        diff group var = {diff group var{:}, curr groups{:}};
        curr_elecs = repmat(electrodes(e), length(curr_means), 1);
        diff_elec_var = {diff_elec_var{:}, curr_elecs{:}};
    end
end

% ANOVA of Amplitudes
clc
[p,tbl,stats,terms] = anovan(erp_mean,{group_var,elec_var,cond_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes','Condition'});
% ANOVA of Diff Amplitudes
clc
[p,tbl,stats,terms] = anovan(diff_mean,{diff_group_var,diff_elec_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes'});
```

```
% ANOVA of Latencies
clc
[p,tbl,stats,terms] = anovan(erp_latencies,{group_var,elec_var,cond_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes','Condition'});
% ANOVA of Diff latencies
clc
[p,tbl,stats,terms] = anovan(diff_latencies,{diff_group_var,diff_elec_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes'});

% Amplitudes interaction plot
clc
[p,tbl,stats,terms] = anovan(erp_mean,{group_var,elec_var,cond_var}, ...
                             'model','interaction', ...
                             'varnames',{'Group','Electrodes','Condition'});

results = multcompare(stats,'Dimension',[1, 2]);
figure('Position', [1 41 1536 748.8000]);
hold on;
colors = brewermap(5, 'Dark2');

for g = 1:length(groups)
    disp(newline)
    disp(['Processing group: ' groups{g}])
    cond_mean = [];
    cond_stderr = [];
    x_vals = [.90, 1.90, 2.90, 3.90, 4.90] + g*.05;
    text_x_vals = [.85, 1.85, 2.85, 3.85, 4.85] + g*.05;
    for e = 1:length(electrodes)
        disp(['Processing electrode: ' electrodes{e}])
        curr_ind = strcmp(electrodes{e}, elec_var) & strcmp(groups{g}, group_var);
        curr_data = erp_mean(curr_ind);
        cond_mean = [cond_mean, mean(curr_data)];
        cond_stderr = [cond_stderr, std(curr_data)/sqrt(length(curr_data))];

        result_num = 3*(e-1) + (g-1);
        result_cond = results(:, 1)==result_num & results(:, 6)<0.05 & ...
                      results(:, 2)-results(:,1)<2 & mod(results(:,1),3)~=0;
        if ~isempty(results(result_cond, :))
            disp(results(result_cond, :))
            text(text_x_vals(e-1)+.5, -5, '*', ...
                'Color',colors(g,:))
        end
    end

    err = errorbar(x_vals, cond_mean, cond_stderr, '-o', ...
              'color', colors(g,:), 'Linewidth', 3, ...
              'MarkerEdgeColor',colors(g,:),...
              'MarkerFaceColor',colors(g,:), ...
              'MarkerSize', 10);
end

ax = gca;
set(gca, 'Ygrid', 'on')
set(gca, 'xlim', [.5, 5.5]);
set(gca, 'ylim', [.5, 8]);
set(gca, 'XTick', [1,2,3,4,5], 'XTickLabel', electrodes);

set(get(gca,'XLabel'), 'String', 'Electrodes');
set(get(gca,'YLabel'), 'String', 'Amplitude (\muV)');
x_lab = get(gca, 'xlabel');
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

h = legend(groups, ...
       'FontSize', 32);
legend('boxoff')
pos = get(h,'Position');
posx = 0.6;
posy = 0.2;
set(h,'Position',[posx posy pos(3) pos(4)]);
```

```
title('Peak Interactions')
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
f_name = 'peak_interactions';
print(f_name, '-dpng', '-r300', '-painters');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Measures Correlations with Patient Demographic data

```
load_patient_demo_data


patient_scores = patient_demo_data(:, {'PatientCode', 'Age', ...
                                       'PANSSP session1', 'PANSSN session1', ...
                                       'PANSSG_session1', ...
                                       'MADRS_session1'});


patient_scores_schiz = patient_scores(4:end, :);
% Sorting the rows alphabetically as thats how the data is stored in STUDY
patient_scores_schiz = sortrows(patient_scores_schiz, 'PatientCode');
patient_scores_schiz = patient_scores_schiz{:, 2:end};
patient_scores_nonSchiz = patient_scores(1:3, :);
patient_scores_nonSchiz = sortrows(patient_scores_nonSchiz, 'PatientCode');
patient_scores_nonSchiz = patient_scores_nonSchiz{:, 2:end};

% Schizophrenia patients

schiz_diff_inds = ismember(diff_group_var, {'Schizophrenia'});

schiz_diff_mean = diff_mean(schiz_diff_inds);
schiz_diff_latencies = diff_latencies(schiz_diff_inds);
schiz_diff_elec = diff_elec_var(schiz_diff_inds);
plot_stroop_demo_corrs(schiz_diff_mean, patient_scores_schiz, ...
                       'Diff Peak Corrs: Schizophrenia',
'demo_diff_peak_corrs_Schiz.png')
plot_stroop_demo_corrs(schiz_diff_latencies, patient_scores_schiz, ...
                       'Diff Latencies Corrs: Schizophrenia',
'demo_diff_latencies_corrs_Schiz.png')

% Schizoaffective disorder patients

nonSchiz_diff_inds = ismember(diff_group_var, {'Schizoaffective'});

nonSchiz_diff_mean = diff_mean(nonSchiz_diff_inds);
nonSchiz_diff_latencies = diff_latencies(nonSchiz_diff_inds);
nonSchiz_diff_elec = diff_elec_var(nonSchiz_diff_inds);
plot_stroop_demo_corrs(nonSchiz_diff_mean, patient_scores_nonSchiz, ...
                       'Diff Peak Corrs: Schizoaffective',
'demo_diff_peak_corrs_nonSchiz.png')
plot_stroop_demo_corrs(nonSchiz_diff_latencies, patient_scores_nonSchiz, ...
                       'Diff Latencies Corrs: Schizoaffective',
'demo_diff_latencies_corrs_nonSchiz.png')

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Correlation plotting function

```
function plot_stroop_demo_corrs(mat1, mat2, fig_title, f_name)
mat1 = reshape(mat1, [], 5);

[task_score_corr, p] = corr(mat1, mat2);
c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
```

```
              'MADRS'};
electrodes = {'Fz'; 'FCz'; 'Cz'; 'CPz'; 'Pz'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', electrodes)
axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title(fig_title)
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
print(f_name, '-dpng', '-r300', '-painters');
close;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Behavioural data Correlations with Patient Demographic data

```
load_patient_demo_data


patient_scores = patient_demo_data(:, {'PatientCode', 'Age', ...
                                       'PANSSP_session1', 'PANSSN_session1', ...
                                       'PANSSG_session1', ...
                                       'MADRS_session1'});

patient_scores_schiz = patient_scores(4:end, :);
% Sorting the rows alphabetically as thats how the data is stored in STUDY
patient_scores_schiz = sortrows(patient_scores_schiz, 'PatientCode');
patient_scores_schiz = patient_scores_schiz{:, 2:end};
patient_scores_nonSchiz = patient_scores(1:3, :);
patient_scores_nonSchiz = sortrows(patient_scores_nonSchiz, 'PatientCode');
patient_scores_nonSchiz = patient_scores_nonSchiz{:, 2:end};

load('stroop_patient_combined')
strooppatient = strooppatient09032020;

% Putting schiz and nonSchiz alphabetically as thats how the data is stored in STUDY
schiz_inds = [3, 5, 6];
non_schiz_inds = [2, 1, 4];
schiz_patients = strooppatient{schiz_inds, 2:end-2};
non_schiz_patients = strooppatient{non_schiz_inds, 2:end-2};


% Schizophrenia patients
[task_score_corr, p] = corr(schiz_patients, patient_scores_schiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

metric_names = {'CongRL'; 'IncongRL'; 'CongPC'; 'IncongPC'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
```

```
set(gca, 'YTickLabel', metric_names)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Schizophrenia')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'behaviour_demo_corrs_schiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

% Schizoaffective disorder patients
[task_score_corr, p] = corr(non_schiz_patients, patient_scores_nonSchiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

metric_names = {'CongRL'; 'IncongRL'; 'CongPC'; 'IncongPC'};

score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
set(gca, 'YTickLabel', metric_names)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Schizoaffective')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'behaviour_demo_corrs_nonSchiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

APPENDIX G - MATLAB CODES: CANTAB

Control and Patient comparison plots

```
load('cantab_data_thesis')

groups = [1*ones(size(control_data(2,:))), ...
          2*ones(size(patient_data(2, :)))];
patient_diag = patient_subjects(2,:);
label = {'Control', 'Patients'};
mot = [3, 4];
rti = [5, 6, 9, 12, 13, 16];
pal = [19, 20];
swm = [21, 22];
vrm = 23:26;

all_metrics = [mot, rti, pal, swm, vrm];
for metric = all_metrics  % Select which metrics to plot
    y_label =  cell2mat(task_rows(metric,4));
    fprintf('\n%s\n', y_label)
    values = [control_data(metric,:), patient_data(metric, :)];
    make_rawplot_colored_cantab(values, groups, label, patient_diag, y_label);
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Plotting Function

```
function fig_handle = make_rawplot_colored_cantab(values, groups, label,
patient_diag, y_label)
%Make a boxplot for the values with grouping
%   values:   vector of all the data thats used to create the boxplot
%   groups:   vector representing how the data is grouped; same number is
%             assigned to the values in the same group. The data can have
%             any number of groups
%   label:    labels that will be shown for each group in the plot. Make
%             sure the number of labels is same as diffenret number of
%             groups.
%   y_label:  label for y-axis.


% Get colors for raw data
c_data = brewermap(20, 'RdYlGn');
color_data = brewermap(8, 'Dark2');
color_data = color_data([1,2,3,4,6,8], :);

% Get patient groups
nonSchiz_inds = find(contains(patient_diag, 'SA'));
schiz_inds = setdiff(1:6, nonSchiz_inds);

% Set Figure position and size
figure('Units' , 'normalized', ...
       'Position', [0.2, 0.2, .7, .7]);
hold on;

unique_groups = unique(groups);

% Calculating p-values between adjacent groups
for i=1:length(unique_groups)-1
    dist1 = values(groups==unique_groups(i));
    dist2 = values(groups==unique_groups(i+1));
    dist_schiz = dist2(schiz_inds);
    dist_nonSchiz = dist2(nonSchiz_inds);
%     dist_schiz =
    [h(i), p(i)] = ttest2(dist1, dist2);
    [hs(i), ps(i)] = ttest2(dist1, dist_schiz);
    [hsa(i), psa(i)] = ttest2(dist1, dist_nonSchiz);
    [hp(i), pp(i)] = ttest2(dist_schiz, dist_nonSchiz);
%     [hk(i), pk(i)] = kstest2(dist1, dist2);
    medians(i) = median(dist1);
    medians(i+1) = median(dist2);

    % put a * mark if p<0.05
    if p(i) < 0.05
        plot(mean(unique_groups(i:i+1))-0.025, mean(medians(i:i+1))*1.1, ...
             '*', 'Color', c_data(2, :),...
             'LineWidth', 2, 'MarkerSize', 10)
    end

    % put another * mark if p<0.005
    if p(i) < 0.005
        plot(mean(unique_groups(i:i+1))+0.025, mean(medians(i:i+1))*1.1, ...
             '*', 'Color', c_data(2, :),...
             'LineWidth', 2, 'MarkerSize', 10)
    end

end

% plot a line between medians of group data
plot(unique_groups, medians, 'Color', c_data(2, :), 'LineWidth', 2)
set(gca,'xtick',unique(groups),'xticklabel',label)

disp(['Ttest Control vs Patient p = ', num2str(p(i), '%1.4e\n'), ', <0.05:',
num2str(p(i)<0.05), ', <0.01:', num2str(p(i)<0.01)])
disp(['Ttest Control vs Schiz p  = ', num2str(ps(i), '%1.4e\n'), ', <0.05:',
num2str(ps(i)<0.05), ', <0.01:', num2str(ps(i)<0.01)])
disp(['Ttest Control vs nonSchiz p  = ', num2str(psa(i), '%1.4e\n'), ', <0.05:',
num2str(psa(i)<0.05), ', <0.01:', num2str(psa(i)<0.01)])
```

```
disp(['Ttest Schiz vs nonSchiz p  = ', num2str(pp(i), '%1.4e\n'), ', <0.05:',
num2str(pp(i)<0.05), ', <0.01:', num2str(pp(i)<0.01)])
% disp(['Ktest p = ', num2str(pk(i), '%1.4e\n')])

% Plot and format raw values

% Add noise to x values so that values that are close dont overlap
x = groups; % + (rand(size(groups)) - .5)/5;
x_controls = x(groups==1);
values_controls = values(groups==1);
% x_controls = x_controls + (rand(size(x_controls)) - .5)/5;

% Seperate overlapping data for controls
unique_vals = unique(ceil(values_controls));
for i=1:length(unique_vals)
    n = length(values_controls(ceil(values_controls)==unique_vals(i)));
    if n==1
        continue;
    else
        x_controls(ceil(values_controls)==unique_vals(i)) = 1 + linspace(-.025*n,
0.025*n, n);
    end
end

% Plot the raw values for controls
plot(x_controls, values_controls, 'o', 'MarkerSize', 7, ...
     'MarkerEdgeColor', c_data(15, :), ...
     'MarkerFaceColor', c_data(15, :), 'LineWidth', 1)
hold on;

% Plot raw values for patients with their individual colours
x_patients = x(groups==2);
values_patients = values(groups==2);

% Seperate overlapping data
unique_vals = unique(ceil(values_patients));
for i=1:length(unique_vals)
    n = length(values_patients(ceil(values_patients)==unique_vals(i)));
    if n==1
        continue;
    else
        x_patients(ceil(values_patients)==unique_vals(i)) = 2 + linspace(-.025*n,
0.025*n, n);
    end
end


for i=1:length(x_patients)
    plot(x_patients(i), values_patients(i), 'o', ...
         'MarkerSize', 10,'MarkerEdgeColor', color_data(i, :), ...
         'MarkerFaceColor', color_data(i, :), 'LineWidth', 1)
end

xlim([unique_groups(1) - 0.5, unique_groups(end) + 0.5]);
% change fonts for the axis
set(gca, 'FontSize', 14, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

% set labels for x and y axis
xlabel('Group')
x_lab = get(gca, 'xlabel');
set(x_lab, 'Units', 'normalized');
set(x_lab, 'Position', [0.5, -0.07, 0]);
ylabel(y_label)

box 'off'
set(gca, 'Ygrid', 'on')

% Format the labels of different boxes
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 18, 'FontName', 'Garamond', 'FontWeight', 'Bold');
```

```
axis('square')
fig_handle = gcf;

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Task correlation plot

```
load('cantab_data_thesis')
type = 'Pearson';

% Patients
[task score corr, p] = corr(patient data', 'type', type);

% Controls
% [task_score_corr, p] = corr(control_data', 'type', type);

% Select metrics to correlate
task_inds = [1, 3, 5, 12, 6, 13, 9, 16, 19, 20, 21, 22, 23, 25];

task_score_corr = task_score_corr(task_inds, task_inds);
p = p(task_inds, task_inds);
c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);

figure('Position', [100, 25, 900, 900]);
subplot('Position', [.28, .02, .7, .7])
imagesc(task_score_corr, [-1 1])
hold on;

% Find sginificant correlations
sig = find(p<0.05);
sig_more = find(p<0.005);
sig = setdiff(sig, sig_more);
[sig_i, sig_j] =  ind2sub(size(task_score_corr), sig);
[sig_more_i, sig_more_j] =  ind2sub(size(task_score_corr), sig_more);

% Plot
test = eye(length(task_inds)) - .01;
test(sig) = task_score_corr(sig);
test(sig_more) = task_score_corr(sig_more);
imagesc(test, [-1 1])
hold on;

colormap(c_inv)

set(gca, 'YTick', .5:length(task_inds))

% set(gca, 'YTickLabel', task_rows(task_inds, 4))

set(gca, 'XTick', .5:length(task_inds))

hx = get(gca,'XLabel');  % Handle to xlabel
set(hx,'Units','data');
pos = get(hx,'Position');
y = pos(3) - .7 ;
X = 1:length(task_inds);
set(gca, 'XTickLabel', [])
% Place the new labels
for i = 1:length(task_inds)
  t(i) = text(X(i),y,task_rows(task_inds(i),4));
end
set(t,'Rotation',60,'HorizontalAlignment','left',...
    'FontSize', 14, 'FontName', 'Garamond', 'FontWeight', 'Bold')

set(gca, 'YTickLabel', [])
% Place the new labels
for i = 1:length(task inds)
  t(i) = text(y,X(i),task_rows(task_inds(i),4));
end
```

```
set(t,'VerticalAlignment', 'middle', 'HorizontalAlignment','right',...
    'FontSize', 14, 'FontName', 'Garamond', 'FontWeight', 'Bold')

set(gca, 'TickLength', [0,0])
colorbar
set(gca, 'FontSize', 14, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
axis('square')
grid('on')

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Demographic data correlation plot

```
load('demographic_data_new')
load('cantab_data_thesis')

age = 1;
mot = [3, 4];
rti = [5, 6, 9, 12, 13, 16];
pal = [19, 20];
swm = [21, 22];
vrm = 23:26;
all_metrics = [mot, rti, pal, swm, vrm];
[task_score_corr, p] = corr(patient_data(all_metrics, :)', patient_scores([1:3, 5],
:)');

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
figure('Position', [100, 25, 1100, 700]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', patient_score_type([1:3, 5]))
set(gca, 'YTick', 1:length(all_metrics))
set(gca, 'YTickLabel', task_rows(all_metrics, 4))
colorbar
set(gca, 'FontSize', 18, 'FontName', 'Garamond', ...
    'LineWidth', 1, 'FontWeight', 'Bold')

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

APPENDIX H - MATLAB CODES: EMOTION RECOGNITION

Facial Emotion Recognition Task Behavioural Response Plots

```
load('ER_control_data.mat')
load('ER_patient_data.mat')

% Latency Compare plot
lat_data = [ERcontrol.latency_neutral, ERcontrol.latency_happy,
ERcontrol.latency_angry, ERcontrol.latency_sad];
lat_data_patient = [ERpatient.latency_neutral, ERpatient.latency_happy,
ERpatient.latency_angry, ERpatient.latency_sad];
lat patient diag = {'Schizoaffective'; 'Schizoaffective'; 'Schizophrenia';
'Schizoaffective'; 'Schizophrenia'; 'Schizophrenia'};
lat_data_nonSchiz = lat_data_patient(contains(lat_patient_diag, 'Schizoaffective'),
:);
lat_data_schiz = lat_data_patient(contains(lat_patient_diag, 'Schizophrenia'), :);

figure('Position', [1 41 800 748.8000]);
hold on;
colors = brewermap(5, 'Dark2');
x_vals = [.95,1.95,2.95,3.95];
data_mean = mean(lat_data, 1);
data_stderr = std(lat_data, 1)/sqrt(length(lat_data));
err = errorbar(x_vals, data_mean, data_stderr, '-o', ...
```

```
            'color', colors(1,:), 'Linewidth', 3, ...
            'MarkerEdgeColor',colors(1,:),...
            'MarkerFaceColor',colors(1,:), ...
            'MarkerSize', 10);
x_vals = [.95,1.95,2.95,3.95] + .05 ;
data_mean = mean(lat_data_schiz, 1);
data_stderr = std(lat_data_schiz, 1)/sqrt(length(lat_data_schiz));
err = errorbar(x vals, data mean, data stderr, '-o', ...
            'color', colors(2,:), 'Linewidth', 3, ...
            'MarkerEdgeColor',colors(2,:),...
            'MarkerFaceColor',colors(2,:), ...
            'MarkerSize', 10);
x_vals = [.95,1.95,2.95,3.95] + 0.1;
data_mean = mean(lat_data_nonSchiz, 1);
data_stderr = std(lat_data_nonSchiz, 1)/sqrt(length(lat_data_nonSchiz));
err = errorbar(x_vals, data_mean, data_stderr, '-o', ...
            'color', colors(3,:), 'Linewidth', 3, ...
            'MarkerEdgeColor',colors(3,:),...
            'MarkerFaceColor',colors(3,:), ...
            'MarkerSize', 10);
label = {'Neutral', 'Happy', 'Angry', 'Sad'};
groups = {'Control', 'Schizophrenia', 'Schizoaffective'};
ax = gca;
set(gca, 'Ygrid', 'on')
set(gca, 'xlim', [.5, 4.5]);
set(gca, 'ylim', [500, 1300]);
set(gca, 'XTick', [1,2,3,4], 'XTickLabel', label);


set(get(gca,'XLabel'), 'String', 'Emotion');
set(get(gca,'YLabel'), 'String', 'Response Latency (ms)');
x_lab = get(gca, 'xlabel');
set(gca, 'FontSize', 28, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

title('b. Response Latency')
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 28, 'FontName', 'Garamond', 'FontWeight', 'Bold');
f_name = 'response_latency';
print(f_name, '-dpng', '-r300', '-painters');
close

% Percent Correct Compare plot
perc_data = [ERcontrol.perc_corr_neutral, ERcontrol.perc_corr_happy,
ERcontrol.perc_corr_angry, ERcontrol.perc_corr_sad];
perc_data_patient = [ERpatient.perc_corr_neutral, ERpatient.perc_corr_happy,
ERpatient.perc_corr_angry, ERpatient.perc_corr_sad];
perc_patient_diag = {'Schizoaffective'; 'Schizoaffective'; 'Schizophrenia';
'Schizoaffective'; 'Schizophrenia'; 'Schizophrenia'};
perc_data_nonSchiz = perc_data_patient(contains(perc_patient_diag,
'Schizoaffective'), :);
perc_data_schiz = perc_data_patient(contains(perc_patient_diag, 'Schizophrenia'), :);

figure('Position', [1 41 800 748.8000]);
hold on;
colors = brewermap(5, 'Dark2');
x vals = [.95,1.95,2.95,3.95];
data_mean = mean(perc_data, 1);
data_stderr = std(perc_data, 1)/sqrt(length(perc_data));
err = errorbar(x_vals, data_mean, data_stderr, '-o', ...
            'color', colors(1,:), 'Linewidth', 3, ...
            'MarkerEdgeColor',colors(1,:),...
            'MarkerFaceColor',colors(1,:), ...
            'MarkerSize', 10);
x_vals = [.95,1.95,2.95,3.95] + .05 ;
data_mean = mean(perc_data_schiz, 1);
data_stderr = std(perc_data_schiz, 1)/sqrt(length(perc_data_schiz));
err = errorbar(x_vals, data_mean, data_stderr, '-o', ...
            'color', colors(2,:), 'Linewidth', 3, ...
            'MarkerEdgeColor',colors(2,:),...
            'MarkerFaceColor',colors(2,:), ...
            'MarkerSize', 10);
```

```
x_vals = [.95,1.95,2.95,3.95] + 0.1;
data_mean = mean(perc_data_nonSchiz, 1);
data_stderr = std(perc data nonSchiz, 1)/sqrt(length(perc data nonSchiz));
err = errorbar(x_vals, data_mean, data_stderr, '-o', ...
             'color', colors(3,:), 'Linewidth', 3, ...
             'MarkerEdgeColor',colors(3,:),...
             'MarkerFaceColor',colors(3,:), ...
             'MarkerSize', 10);
label = {'Neutral', 'Happy', 'Angry', 'Sad'};
groups = {'Control', 'Schizophrenia', 'Schizoaffective'};
ax = gca;
set(gca, 'Ygrid', 'on')
set(gca, 'xlim', [.5, 4.5]);
set(gca, 'ylim', [50, 105]);
set(gca, 'XTick', [1,2,3,4], 'XTickLabel', label);


set(get(gca,'XLabel'), 'String', 'Emotion');
set(get(gca,'YLabel'), 'String', 'Percent Correct');
x_lab = get(gca, 'xlabel');
set(gca, 'FontSize', 28, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)

h = legend(groups, ... % 'All Patients'}, ...
       'FontSize', 28);
legend('boxoff')
pos = get(h,'Position');
posx = 0.15;
posy = 0.15;
set(h,'Position',[posx posy pos(3) pos(4)]);

title('a. Percent Correct')
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 28, 'FontName', 'Garamond', 'FontWeight', 'Bold');
f_name = 'percent_corect';
print(f_name, '-dpng', '-r300', '-painters');
close

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Facial Emotion Recognition Task Behavioural ANOVA

```
load('ER_control_data.mat')
load('ER_patient_data.mat')

% Latencies ANOVA test
lat_data = [ERcontrol.latency_neutral, ERcontrol.latency_happy,
ERcontrol.latency_angry, ERcontrol.latency_sad];
lat_type = {'Neutral', 'Happy', 'Angry', 'Sad'};
lat_type = repmat(lat_type, length(lat_data), 1);
lat_type = reshape(lat_type, 1, []);
lat_data = reshape(lat_data, 1, []);
lat_group = repmat({'Control'}, 1, length(lat_type));

lat_data_patient = [ERpatient.latency_neutral, ERpatient.latency_happy,
ERpatient.latency_angry, ERpatient.latency_sad];
lat_patient_diag = {'Schizoaffective'; 'Schizoaffective'; 'Schizophrenia';
'Schizoaffective'; 'Schizophrenia'; 'Schizophrenia'};
lat_patient_diag = repmat(lat_patient_diag, 1, size(lat_data_patient,2));
lat_type_patient = {'Neutral', 'Happy', 'Angry', 'Sad'};
lat_type_patient = repmat(lat_type_patient, length(lat_data_patient), 1);
lat_type_patient = reshape(lat_type_patient, 1, []);
lat_data_patient = reshape(lat_data_patient, 1, []);
lat_patient_diag = reshape(lat_patient_diag, 1, []);
lat_group_patient = repmat({'Patient'}, 1, length(lat_type_patient));


lat data = [lat data, lat data patient];
lat_type = [lat_type, lat_type_patient];
lat_group = [lat_group, lat_group_patient];
```

```
% Uncomment to include two types of patients
% lat_group = [lat_group, lat_patient_diag];

[p,tbl,stats,terms] = anovan(lat_data,{lat_type,lat_group}, ...
                             'model','interaction', ...
                             'varnames',{'Type','Group'});

% Percent Correct ANOVA test
perc_data = [ERcontrol.perc_corr_neutral, ERcontrol.perc_corr_happy,
ERcontrol.perc_corr_angry, ERcontrol.perc_corr_sad];
perc_type = {'Neutral', 'Happy', 'Angry', 'Sad'};
perc_type = repmat(perc_type, length(perc_data), 1);
perc_type = reshape(perc_type, 1, []);
perc_data = reshape(perc_data, 1, []);
perc_group = repmat({'Control'}, 1, length(perc_type));

perc_data_patient = [ERpatient.perc_corr_neutral, ERpatient.perc_corr_happy,
ERpatient.perc_corr_angry, ERpatient.perc_corr_sad];
perc_patient_diag = {'Schizoaffective'; 'Schizoaffective'; 'Schizophrenia';
'Schizoaffective'; 'Schizophrenia'; 'Schizophrenia'};
perc_patient_diag = repmat(perc_patient_diag, 1, size(perc_data_patient,2));
perc_type_patient = {'Neutral', 'Happy', 'Angry', 'Sad'};
perc_type_patient = repmat(perc_type_patient, length(perc_data_patient), 1);
perc_type_patient = reshape(perc_type_patient, 1, []);
perc_data_patient = reshape(perc_data_patient, 1, []);
perc_patient_diag = reshape(perc_patient_diag, 1, []);
perc_group_patient = repmat({'Patient'}, 1, length(perc_type_patient));

perc_data = [perc_data, perc_data_patient];
perc_type = [perc_type, perc_type_patient];
perc_group = [perc_group, perc_group_patient];
% Uncomment to include two types of patients
% perc_group = [perc_group, perc_patient_diag];

[p,tbl,stats,terms] = anovan(perc_data,{perc_type,perc_group}, ...
                             'model','interaction', ...
                             'varnames',{'Type','Group'});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Healthy Controls

```
data_dir = 'E:\EngD Data\Sibani\Pilot\PILOT\';
data_files = strcat(data_dir, '*ER*B*.cnt');
dataset_dir = strcat(data_dir, 'datasets\ER\withICA_1Hz\');
files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};

for i = 1:length(files)
    f_split = split(files(i).name, '_');
    f_name = split(files(i).name, '.');
    f_name = char(f_name(1));
    sub_id = char(f_split(1));
    sub_date = char(f_split(2));
    sub_block = split(f_split(4), '.');
    sub_block = char(sub_block(1));

    disp('Prepocessing:')
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load data
    cnt_file = strcat(data_dir, files(i).name);
    try
        EEG = pop_loadcnt(cnt_file, 'keystroke', 'on');
        EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
```

```
        disp(' ')
        disp(' ')
        skipped_cnt = [skipped_cnt; f_name];
        continue
    end

    % Import channel info
    EEG = pop_chanedit(EEG, 'lookup', ...
                       'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit3.3\standard_BESA\standard-10-5-
cap385.elp', ...
                       'eval','chans = pop_chancenter( chans, [],[]);');

    % Re-reference data to common average excluding EOG
    EEG = pop_reref(EEG, [], 'exclude', [65, 66]);

    % Resample data
    EEG = pop_resample(EEG, 250);

    % Filter data
    EEG = pop_eegfiltnew(EEG, 1, []);
    % Low-pass
    EEG = pop_eegfiltnew(EEG, [], 40);

    % Remove line noise using CleanLine
    EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                        'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                        'verb', 1, 'winsize', 4, 'winstep', 4);
    % Run ICA
    EEG = pop_runica(EEG, 'icatype', 'runica');

    % Extract Epoch
    try
        EEG = pop_epoch(EEG, {53, 20, 28, 40}, [-.5 2.5]);
    catch
        disp('Skipping epoching:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_epoch = [skipped_epoch; f_name];
        continue
    end
    EEG = pop_rmbase(EEG, [-500, 0]);
    EEG.setname = [f_name '_Fs250_LP40_HP1_ICA'];
    EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40_HP1' '_ICA'], 'filepath',
dataset_dir);

    clear EEG
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Pre-processing and Epoch extraction: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient Data\';
data_files = strcat(data_dir, '*ER*B*.cnt');
dataset_dir = strcat(data_dir, 'datasets\ER\withICA\');
files = dir(data_files);
skipped_cnt = {};
skipped_epoch = {};

for i = 3:length(files)
    f_split = split(files(i).name, '_');
    f_name = split(files(i).name, '.');
    f_name = char(f_name(1));
    sub_id = char(f_split(1));
    sub_date = char(f_split(2));

    disp('Prepocessing:')
```

```
    disp(f_name)
    disp(' ')
    disp(' ')

    % Load data
    cnt_file = strcat(data_dir, files(i).name);
    try
        EEG = pop loadcnt(cnt file, 'keystroke', 'on');
        EEG.setname = f_name;
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_cnt = [skipped_cnt; f_name];
        continue
    end

    % Import channel info
    EEG = pop_chanedit(EEG, 'lookup', ...
                       'C:\Users\Sibani
Mohanty\Documents\MATLAB\eeglab14_1_2b\plugins\dipfit3.3\standard_BESA\standard-10-5-
cap385.elp', ...
                       'eval','chans = pop_chancenter( chans, [],[]);');

    % Re-reference data to common average excluding EOG
    EEG = pop_reref(EEG, [], 'exclude', [38 39]);

    % Resample data
    EEG = pop_resample(EEG, 250);

    % Filter data
    % High-pass
    EEG = pop_eegfiltnew(EEG,1, []);
    % Low-pass
    EEG = pop_eegfiltnew(EEG, [], 40);

    % Remove line noise using CleanLine
    EEG = pop_cleanline(EEG, 'bandwidth', 2,'chanlist', [1:EEG.nbchan],
'computepower', 0, 'linefreqs', [50 100 150],...
                        'normSpectrum', 0, 'p', 0.01, 'pad', 2, 'plotfigures', 0,
'scanforlines', 1, 'sigtype', 'Channels', 'tau', 100,...
                        'verb', 1, 'winsize', 4, 'winstep', 4);
    % Run ICA
    EEG = pop_runica(EEG, 'icatype', 'runica');

    % Extract Epoch
    try
        EEG = pop_epoch(EEG, {53, 20, 28, 40}, [-.5 2.5]);
    catch
        disp('Skipping epoching:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_epoch = [skipped_epoch; f_name];
        continue
    end
    EEG = pop rmbase(EEG, [-500, 0]);
    EEG.setname = [f_name '_Fs250_LP40_HP1'];
    EEG = pop_saveset(EEG, 'filename', [f_name '_Fs250_LP40_HP1' '_ICA'], 'filepath',
dataset_dir);

    clear EEG
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\ER\withICA_1Hz\withMarked\withRejectEpochs\';
%Directory where ER datasets are saved
byType_dir = strcat(data_dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType_dir, 'dir')
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event_type = [53, 20, 28, 40];
type_name = {'Neutral', 'Angry', 'Happy', 'Sad'};

resp_type = {'keypad1', 'keypad2', 'keypad4', 'keypad8'};

skipped_set = {};
skipped_split = {};

load er_controls.mat
type_total_trials = zeros(4, length(subjects));
type_clean_trials = zeros(4, length(subjects));  % Trials by type (1, :) cong; (2, :)
incong
type_correct_trials = zeros(4, length(subjects)); % Correct Trials by type (1, :)
cong; (2, :) incong

for i = 1:length(subjects)

    data_files = strcat(data_dir, subjects{i}, '*ER*.set');
    files = dir(char(data_files));
    if isempty(files)
        disp('Skipping Subject:')
        disp(subjects{i})
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end
    f_name = split(files(1).name, '_B');
    f_name = char(f_name(1));

    rej_files = strcat(data_dir, 'rej_mats\', subjects{i}, '*ER*.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
    disp(f_name)

    % Load and concatenate datasets
    try
        ALLEEG = [];
        for j = 1:length(files)
            % Print file names being concatenated to verify correct file
            % are being processed for the give subject. Delete any datasets
            % that are incorrect from folder
            disp(' ')
            disp('Loading')
            disp(['File: ', files(j).name])
            disp(['Rejected epochs: ', rej_files(j).name])

            load([rej_files(j).folder, '\', rej_files(j).name])
            tot_epochs = length(rej.rejmanual);
            disp(['Total epochs: ', num2str(tot_epochs)])
            num_rejected = sum(rej.rejmanual);
            disp(['Retianed epochs: ', num2str(tot_epochs-num_rejected)])

            EEG_block = pop_loadset(files(j).name, files(j).folder);

            type = extractfield(EEG_block.event, 'type');
            [C,ia,ic] = unique(type);
            a_counts = accumarray(ic,1);
            for k = 1:length(event_type)
```

```
                type_total_trials(k, i) = type_total_trials(k, i) +
a_counts(contains(C, num2str(event_type(k))));
            end
            EEG_block.reject.rejmanual = rej.rejmanual;
            EEG_block = pop_rejepoch( EEG_block, EEG_block.reject.rejmanual ,0);
            [ALLEEG, EEG_block, index] = eeg_store(ALLEEG, EEG_block);
        end
        EEG block = pop mergeset(ALLEEG, 1:length(files), 0);
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
        continue
    end

    % Create datasets by types

    for k = 1:length(event_type)

        % Name of the new dataset with event_type and type_name appended
        set_name = strcat(f_name, '_', num2str(event_type(k)), '_',
char(type_name(k)));

        % Selecting one event at a time
        try
            % Selecting all epochs
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_block, 'type',
event_type(k));
            type_clean_trials(k, i) = length(EEG_type.epoch);
            % Further keeping epochs with correct response and within max resp time
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_type, 'type',
resp_type(k), 'latency', '0<=2500');
            type_correct_trials(k, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
        catch
            disp('Skipping split:')
            disp(set_name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG_type = pop_saveset(EEG_type, 'filename', set_name, 'filepath',
byType_dir);
        clear EEG_type
    end
    clear *EEG*
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Data Splitting by Trial Type: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\ER\withICA_1Hz\withMarked\withRejectEpochs\';   %Directory where ER
datasets are saved
byType_dir = strcat(data_dir, 'byType');
% Create the byType folder for datasets by type, if it doesn't exist already.
if ~exist(byType_dir, 'dir')
  mkdir(byType_dir);
end

% Event types and their names to append to file name before saving
event_type = [53, 20, 28, 40];
type name = {'Neutral', 'Angry', 'Happy', 'Sad'};

resp_type = {'keypad1', 'keypad2', 'keypad4', 'keypad8'};
```

```
skipped_set = {};
skipped_split = {};

load stroop_patients.mat
type_total_trials = zeros(4, length(subjects));
type_clean_trials = zeros(4, length(subjects));  % Trials by type (1, :) cong; (2, :)
incong
type_correct_trials = zeros(4, length(subjects)); % Correct Trials by type (1, :)
cong; (2, :) incong

for i = 1:length(subjects)

    data_files = strcat(data_dir, subjects{i}, '*ER*.set');
    files = dir(char(data_files));
    if isempty(files)
        skipped_set = [skipped_set; subjects{i}];
        continue;
    end
    f_name = split(files(1).name, '_B');
    f_name = char(f_name(1));

    rej_files = strcat(data_dir, 'rej_mats\', subjects{i}, '*ER*.mat');
    rej_files = dir(char(rej_files));
    disp('Splitting:')
    disp(f_name)

    % Load and concatenate dataset
    try
        ALLEEG = [];
        for j = 1:length(files)
            % Print file names being concatenated to verify correct file
            % are being processed for the give subject. Delete any datasets
            % that are incorrect from folder
            disp(' ')
            disp('Loading')
            disp(['File: ', files(j).name])
            disp(['Rejected epochs: ', rej_files(j).name])

            load([rej_files(j).folder, '\', rej_files(j).name])
            tot_epochs = length(rej.rejmanual);
            disp(['Total epochs: ', num2str(tot_epochs)])
            num_rejected = sum(rej.rejmanual);
            disp(['Retianed epochs: ', num2str(tot_epochs-num_rejected)])

            EEG_block = pop_loadset(files(j).name, files(j).folder);

            % Droping EOG channels
            drop_chans = [38, 39];
            disp('Dropping EOG channels: VEOG, HEOG...')
            EEG_block = pop_select(EEG_block, 'nochannel', drop_chans);
            % Capitalizing channel labels to avoid conflicts between subjects
            disp('Capitalizing channel labels...')
            EEG_block = capitalize_chan_labels(EEG_block);

            type = extractfield(EEG_block.event, 'type');
            [C,ia,ic] = unique(type);
            a counts = accumarray(ic,1);
            for k = 1:length(event_type)
                type_total_trials(k, i) = type_total_trials(k, i) +
a_counts(contains(C, num2str(event_type(k))));
            end
            EEG_block.reject.rejmanual = rej.rejmanual;
            EEG_block = pop_rejepoch( EEG_block, EEG_block.reject.rejmanual ,0);
            [ALLEEG, EEG_block, index] = eeg_store(ALLEEG, EEG_block);
        end
        EEG = pop_mergeset(ALLEEG, 1:length(files), 0);
    catch
        disp('Skipping loading:')
        disp(f_name)
        disp(' ')
        disp(' ')
        skipped_set = [skipped_set; f_name];
```

```
        continue
    end

    % Create datasets by types

    for k = 1:length(event_type)

        % Name of the new dataset with event type and type name appended
        set_name = strcat(f_name, '_', num2str(event_type(k)), '_',
char(type_name(k)));

        % Selecting one event at a time
        try
            % Selecting all epochs
            [EEG_type evnt_ind_test] = pop_selectevent(EEG, 'type', event_type(k));
            type_clean_trials(k, i) = length(EEG_type.epoch);
            % Further keeping epochs with correct response and within max resp time
            [EEG_type evnt_ind_test] = pop_selectevent(EEG_type, 'type',
resp_type(k), 'latency', '0<=2500');
            type_correct_trials(k, i) = length(EEG_type.epoch);
            EEG_type.setname = set_name;
        catch
            disp('Skipping split:')
            disp(set_name)
            disp(' ')
            disp(' ')
            skipped_split = [skipped_split; set_name];
            continue
        end

        % Saving the new dataset
        EEG_type = pop_saveset(EEG_type, 'filename', set_name, 'filepath',
byType_dir);
        clear EEG_type
    end
    clear *EEG*
end

function EEG = capitalize_chan_labels(EEG)
    for i = 1:length(EEG.chanlocs)
        EEG.chanlocs(i).labels = upper(EEG.chanlocs(i).labels);
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Healthy Controls

```
data_dir = 'E:\EngD
Data\Sibani\Pilot\PILOT\datasets\ER\withICA_1Hz\withMarked\withRejectEpochs\byType\';
%Directory where ER datasets are saved
data_files = strcat(data_dir, '*ER*.set');
files = dir(data_files);

% Event types and their names to append to file name before saving
event_type = [53, 20, 28, 40];
type_name = {'Neutral', 'Angry', 'Happy', 'Sad'};

commands = {};

for i = 1:length(files)
    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_ER');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
```

```
end

std_dirpath = 'E:\EngD Data\Sibani\Studies\ER\controls wICA';
if ~exist(std_dirpath)
  mkdir(std_dirpath);
end

name = 'control ER wICA';
[STUDY ALLEEG] = std_editset([], [], 'name', name, ...
                             'task', 'ER', ...
                             'filename', name, ...
                             'filepath', 'E:\EngD Data\Sibani\Studies\ER\', ...
                             'commands', commands);

% All
CURRENTSTUDY = 4; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name', 'control_ER_All', ...
                       'variable1','condition', ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','on', ...
                             'erp','on',...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 400});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEGLAB STUDY creation: Patients

```
data_dir = 'E:\EngD Data\Sibani\Patient
Data\datasets\ER\withICA_1Hz\withMarked\withRejectEpochs\byType\';   %Directory where
Stroop datasets are saved
data_files = strcat(data_dir, '*ER*.set');
files = dir(data_files);

% Event types and their names to append to file name before saving
event_type = [53, 20, 28, 40];
type_name = {'Neutral', 'Angry', 'Happy', 'Sad'};

commands = {};

for i = 1:length(files)

    f_loc = [files(i).folder, '\', files(i).name];

    subject = split(files(i).name, '_ER');
    subject = subject{1};

    condition = split(files(i).name, ["_","."]);
    condition = condition{end-1};

    commands = {commands{:} ...
        {'index' i 'load' f_loc 'subject' subject 'condition' condition}};
end

std_dirpath = 'E:\EngD Data\Sibani\Studies\ER\patients_wICA';
if ~exist(std_dirpath)
  mkdir(std_dirpath);
end

name = 'patient_ER_wICA';
[STUDY ALLEEG] = std_editset([], [], 'name', name, ...
                             'task', 'ER', ...
                             'filename', name, ...
                             'filepath', 'E:\EngD Data\Sibani\Studies\ER\', ...
                             'commands', commands);

% All
```

```
CURRENTSTUDY = 4; EEG = ALLEEG; CURRENTSET = [1:length(EEG)];
STUDY = std_makedesign(STUDY, ALLEEG, CURRENTSTUDY, ...
                       'name','patient ER All', ...
                       'variable1','condition', ...
                       'filepath', std_dirpath);
[STUDY EEG] = pop_savestudy( STUDY, ALLEEG, 'savemode','resave');
[STUDY ALLEEG] = std_precomp(STUDY, ALLEEG, 'channels', ...
                             'recompute','on', 'savetrials', 'on', ...
                             'erp','on',...
                             'ersp', 'on', 'itc', 'on', ...
                             'erspparams', {'cycles', [.5 0], 'freqs', [2 50],
'nfreqs', 100, 'ntimesout', 400});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

ERP Analysis and Plot grids for each Emotion Type

```
% Load previously formatted and saved data
load('E:\EngD Data\Sibani\Studies\ER\extracted data\control data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\schizOnly_data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\nonSchizOnly_data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\allPatients_data.mat')

[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\ER\patient_ER_wICA_SchizOnly.study');


stat_method = 'montecarlo';
stat_corr = 'cluster';
stat_cluster = '''clusterstatistic'','maxsum''';
STUDY = pop_statparams(STUDY, 'groupstats', 'on', ...
                       'mode', 'fieldtrip', ...
                       'fieldtripmethod', stat_method, ...
                       'fieldtripalpha', 0.05, ...
                       'fieldtripmcorrect', stat_corr, ...
                       'fieldtripclusterparam', stat_cluster);
stats = STUDY.etc.statistics;
stats.paired = {'off'  'off'};

emotion_types = {'Neutral', 'Happy', 'Angry', 'Sad'};

for e = emotion_types
    figure('Position', [1 41 800 748.8000]);

    for i = 1:length(control_er)

        erptimes =  control_er(i).erptimes;
        control_data = control_er(i).(lower(e{1}));
        patient_data = patient_er(i).(lower(e{1}));
        schiz_data = schiz_er(i).(lower(e{1}));
        nonSchiz_data = nonSchiz_er(i).(lower(e{1}));
        channel = control_er(i).channel;
        disp([e{1} ', Channel: ' channel])

        fig_title = channel;

        erpdata = {control_data patient_data}; % 2 groups, cond 1
        [pcond pgroup pinter] = std_stat(erpdata, stats);
        pgroup = pgroup{1};

        erpdata = {control_data schiz_data}; % 2 groups, cond 1
        [pcond pgroup_schiz pinter] = std_stat(erpdata, stats);
        pgroup_schiz = pgroup_schiz{1};

        erpdata = {control_data nonSchiz_data}; % 2 groups, cond 1
        [pcond pgroup_nonSchiz pinter] = std_stat(erpdata, stats);
        pgroup_nonSchiz = pgroup_nonSchiz{1};

        control_erp = mean(control_data, 2);
        patient_erp = mean(patient_data, 2);
        schiz_erp = mean(schiz_data, 2);
```

```
        nonSchiz_erp = mean(nonSchiz_data, 2);

        time ind = erptimes>-200 & erptimes<1300;
        erptimes = erptimes(time_ind);

        control_erp = control_erp(time_ind);
        patient_erp = patient_erp(time_ind);
        schiz erp = schiz erp(time ind);
        nonSchiz_erp = nonSchiz_erp(time_ind);
%
        pgroup = pgroup(time_ind);
        pgroup_schiz = pgroup_schiz(time_ind);
        pgroup_nonSchiz = pgroup_nonSchiz(time_ind);


        x = (control_er(i).chanx + 85)/200;
        y = (-control_er(i).chany + 85)/200;

        if i==1
            y = .2; x = .875;
        elseif i==2
            y = .6; x = .875;
        elseif i>2
            y = mod((i-3),5)*.2;
            x = 1 - (floor((i-3)/5)*.125 + .25);
        end
        if i>32
            y = y+.2;
        end

        subplot('Position', [y, x, .175, .1]);
        er_plot_3(control_erp, schiz_erp, nonSchiz_erp,...
                  erptimes, 0, fig_title, ...
                  pgroup_schiz, pgroup_nonSchiz, pgroup)
    end
    erp_file_name = [e{1} '_ERP_All'];

    suptitle(e{1});
    set_fig_props();
    print(erp_file_name, '-dpng', '-r300');
    close
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

ERP plotting function

```
function er_plot_3(control_erp, schiz_erp, nonSchiz_erp,...
                   erptimes, reverse, fig_title, ...
                   pgroup_schiz, pgroup_nonSchiz, pgroup)  %, p_thresh)

    colors = brewermap(5, 'Dark2');

    min_y = -10;
    max_y = 10;

    plot(erptimes, control_erp, 'linewidth', 1., 'color', colors(1, :))
    hold on;
    plot(erptimes, schiz_erp, 'linewidth', 1., 'color', colors(2, :))
    plot(erptimes, nonSchiz_erp, 'linewidth', 1., 'color', colors(3, :))
    plot(erptimes, zeros(length(erptimes), 1), 'k', 'linewidth', .5)

    patch_schiz_y = [min_y+.4 min_y+.7];
    patch_nonSchiz_y = [min_y+.9 min_y+1.2];

    patch_c = [0.3 0.3 0.3];
    patch_schiz_c = colors(2, :);
    patch_nonSchiz_c = colors(3, :);
    times = erptimes;
    regions = pgroup;
    patch_y = [min_y+2 max_y];
```

```
    if sum(regions)>0
        r_ind = find(regions==1);
        r_ind_change = find(diff(r_ind)>1);
        r_ind_change = sort([r_ind_change' r_ind_change'+1]);
        r_ind_change = [1 r_ind_change length(r_ind)];

        for i = 1:2:length(r_ind_change)-1
            tmp_t = [times(r_ind(r_ind_change(i))) ...
                     times(r_ind(r_ind_change(i+1)))];
            tmp_p = patch([tmp_t(1) tmp_t(2) tmp_t(2) tmp_t(1)], ...
                          [patch_y(1) patch_y(1) patch_y(2) patch_y(2)], ...
                          patch_c);
            set(tmp_p, 'edgecolor', 'none', 'FaceAlpha', .25);
        end
    end

    regions = pgroup_schiz;
    patch_y = [min_y+.8 min_y+1.1];
    if sum(regions)>0
        r_ind = find(regions==1);
        r_ind_change = find(diff(r_ind)>1);
        r_ind_change = sort([r_ind_change' r_ind_change'+1]);
        r_ind_change = [1 r_ind_change length(r_ind)];

        for i = 1:2:length(r_ind_change)-1
            tmp_t = [times(r_ind(r_ind_change(i))) ...
                     times(r_ind(r_ind_change(i+1)))];
            tmp_p = patch([tmp_t(1) tmp_t(2) tmp_t(2) tmp_t(1)], ...
                          [patch_y(1) patch_y(1) patch_y(2) patch_y(2)], ...
                          patch_schiz_c);
            set(tmp_p, 'edgecolor', patch_schiz_c);
        end
    end

    regions = pgroup_nonSchiz;
    patch_y = [min_y+1.2 min_y+1.5];
    if sum(regions)>0
        r_ind = find(regions==1);
        r_ind_change = find(diff(r_ind)>1);
        r_ind_change = sort([r_ind_change' r_ind_change'+1]);
        r_ind_change = [1 r_ind_change length(r_ind)];

        for i = 1:2:length(r_ind_change)-1
            tmp_t = [times(r_ind(r_ind_change(i))) ...
                     times(r_ind(r_ind_change(i+1)))];
            tmp_p = patch([tmp_t(1) tmp_t(2) tmp_t(2) tmp_t(1)], ...
                          [patch_y(1) patch_y(1) patch_y(2) patch_y(2)], ...
                          patch_nonSchiz_c);
            set(tmp_p, 'edgecolor', patch_nonSchiz_c);
        end
    end

    box off
    set(gca,'FontSize',14, 'fontname','Garamond')
    yticks(min_y+1:2:max_y-1);
    plot([0, 0], [min_y max_y], 'k', 'linewidth', 0.5)
    ylim([min_y, max_y]);
    xlim([min x, max x]);

    set(gca,'visible','off')
    t = title(fig_title);
    set(t,'position',get(t,'position')-[0 1.4 0])
    set(findall(gca, 'type', 'text'), 'visible', 'on')
    if reverse
        ax = gca;
        ax.YDir = 'reverse';
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

ERSP Analysis and Plots for each Emotion Type

```
% Load previously formatted and saved data
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\control_data_ersp.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\schizOnly_data_ersp.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\nonSchizOnly_data_ersp.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\allPatients_data_ersp.mat')

[STUDY, ALLEEG] = pop_loadstudy('E:\EngD
Data\Sibani\Studies\ER\patient_ER_wICA_SchizOnly.study');


stat_method = 'montecarlo';
stat_corr = 'cluster';
stat_cluster = '''clusterstatistic'','maxsum'''';
STUDY = pop_statparams(STUDY, 'groupstats', 'on', ...
                       'mode', 'fieldtrip', ...
                       'fieldtripmethod', stat_method, ...
                       'fieldtripalpha', 0.05, ...
                       'fieldtripmcorrect', stat_corr, ...
                       'fieldtripclusterparam', stat_cluster);
stats = STUDY.etc.statistics;
stats.paired = {'on'  'on'};


emotion types = {'Neutral', 'Happy', 'Angry', 'Sad'};

for e = emotion_types

    for i = [1, 27]

        ersptimes =  control er(i).ersptimes;
        erspfreqs =  control_er(i).erspfreqs;
        control_data = control_er(i).(lower(e{1}));
        patient_data = patient_er(i).(lower(e{1}));
        schiz_data = schiz_er(i).(lower(e{1}));
        nonSchiz_data = nonSchiz_er(i).(lower(e{1}));
        channel = control_er(i).channel;
        disp([e{1} ', Channel: ' channel])

        fig_title = [e{1}, ': ', channel];

        time_ind = ersptimes>-200 & ersptimes<1300;
        ersptimes = ersptimes(time_ind);
        control_data = control_data(:, time_ind, :, :);
        patient_data = patient_data(:, time_ind, :, :);

        erspdata = {control_data patient_data}; % 2 groups, cond 1
        [pcond pgroup pinter] = std_stat(erspdata, stats);
        pgroup = pgroup{1};

        control_ersp = mean(control_data, 4);
        patient_ersp = mean(patient_data, 4);
        schiz_ersp = mean(schiz_data, 4);
        nonSchiz_ersp = mean(nonSchiz_data, 4);

        er_ersp_plot(control_ersp, patient_ersp, ...
                     ersptimes, erspfreqs, pgroup, e{1}, channel)
        erp_file_name = [e{1} '_ERSP_' channel];
        set_fig_props();
        print(erp_file_name, '-dpng', '-r300');
        close
    end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

ERSP Plotting function

```
function er_ersp_plot(control_ersp, patient_ersp, ...
```

```
                        ersptimes, erspfreqs, pgroup, emotion_type, channels)

    figure('Position', [1 41 1536 650]);
    rdbu_map = brewermap(200,'RdBu');
    c_val_esrp = [max(max(abs(control_ersp))), ...
                  max(max(abs(patient_ersp)))];
    c_val_esrp = max(c_val_esrp);

    erspfreqs = log(erspfreqs);

    fticks = [2 4 8 16 24 32 40, 48];

    p1 = subplot('Position', [.075, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, control_ersp);
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal');
    set( get(p1,'XLabel'), 'String', 'Latency (ms)');
    set( get(p1,'YLabel'), 'String', 'Frequency (Hz)');
    set(gca,'ytick',log(fticks));
    set(gca,'yticklabel', string(fticks))
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title('')

    p2 = subplot('Position', [.375, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, patient_ersp);
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p2,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks));
    colormap(rdbu_map);
    hcb = colorbar;
    title(hcb, 'dB')
    caxis([-c_val_esrp, c_val_esrp])
    title('')

    p3 = subplot('Position', [.675, .125, .275 .8]);
    imagesc(ersptimes, erspfreqs, patient_ersp - control_ersp);
    hold on;
    plot([0 0], [erspfreqs(1) erspfreqs(end)], 'k:', 'linewidth', 1.5);
    set(gca, 'YDir', 'normal', 'yticklabels', []);
    set( get(p3,'XLabel'), 'String', 'Latency (ms)');
    set(gca,'ytick',log(fticks)); %(inds(1:2:end)));
    colormap(brewermap(200,'RdBu'));
    hcb = colorbar;
    title(hcb, 'dB')
    c_val = max(max(abs(patient_ersp - control_ersp)));
    caxis([-c_val, c_val])
    hold on;
    x = linspace(ersptimes(1), ersptimes(end), length(ersptimes));
    y = linspace(erspfreqs(1), erspfreqs(end), length(erspfreqs));
    contour(x, y, pgroup~=1, 'k')
    title('')

    suptitle(emotion_type)
    set(findall(gcf,'-property','FontSize'),'FontSize',24)
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Facial Emotion Response EEG Response ANOVA Analysis

```
% Load previously formatted and saved data
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\control_data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\schizOnly_data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\nonSchizOnly_data.mat')
load('E:\EngD Data\Sibani\Studies\ER\extracted_data\allPatients_data.mat')
```

```
% ANOVA for P100 at electrode P8
emotion types = {'Neutral', 'Happy', 'Angry', 'Sad'};

p100_peak = [];
p100_lat = [];

group var = [];
type_var = [];

for e = emotion_types

    for i = 27   % electrode P8

        erptimes =  control_er(i).erptimes;
        control_data = control_er(i).(lower(e{1}));
        patient_data = patient_er(i).(lower(e{1}));
        schiz_data = schiz_er(i).(lower(e{1}));
        nonSchiz_data = nonSchiz_er(i).(lower(e{1}));
        channel = control_er(i).channel;
        disp([e{1} ', Channel: ' channel])

        time_ind = find(erptimes>50 & erptimes<200);
        erptimes_sub = erptimes(time_ind);

        control_erp = control_data(time_ind, :);
        patient_erp = patient_data(time_ind, :);
        schiz_erp = schiz_data(time_ind, :);
        nonSchiz_erp = nonSchiz_data(time_ind, :);

        [control_p100_peak, ind] = max(control_erp);
        p100_peak = [p100_peak, control_p100_peak];
        control_p100_lat = erptimes_sub(ind);
        p100_lat = [p100_lat, control_p100_lat];
        group_var = [group_var, repmat({'Control'}, 1, length(control_p100_peak))];

        % Uncomment for for 2x4 ANOVA design
%         [patient_p100_peak, ind] = max(patient_erp);
%         p100_peak = [p100_peak, patient_p100_peak];
%         patient_p100_lat = erptimes_sub(ind);
%         p100_lat = [p100_lat, patient_p100_lat];
%         group_var = [group_var, repmat({'Patient'}, 1, length(patient_p100_peak))];
%
        % Uncomment next 2 code chunks for 3x4 ANOVA design
        [schiz_p100_peak, ind] = max(schiz_erp);
        p100_peak = [p100_peak, schiz_p100_peak];
        schiz_p100_lat = erptimes_sub(ind);
        p100_lat = [p100_lat, schiz_p100_lat];
        group_var = [group_var, repmat({'Schizophrenia'}, 1,
length(schiz_p100_peak))];

        [nonSchiz_p100_peak, ind] = max(nonSchiz_erp);
        p100_peak = [p100_peak, nonSchiz_p100_peak];
        nonSchiz_p100_lat = erptimes_sub(ind);
        p100_lat = [p100_lat, nonSchiz_p100_lat];
        group_var = [group_var, repmat({'Schizoaffective'}, 1,
length(nonSchiz_p100_peak))];
    end
    type_var = [type_var, repmat(e, 1, 24)];
end

[p,tbl,stats,terms] = anovan(p100_lat, {type_var, group_var}, ...
                             'model', 'interaction', ...
                             'varnames', {'Type','Group'});

% ANOVA for N170 at electrode P8
emotion_types = {'Neutral', 'Happy', 'Angry', 'Sad'};

n170_peak = [];
n170_lat = [];

group_var = [];
type_var = [];
```

```
for e = emotion_types

    for i = 27   % electrode P8

        erptimes =  control_er(i).erptimes;
        control_data = control_er(i).(lower(e{1}));
        patient data = patient er(i).(lower(e{1}));
        schiz_data = schiz_er(i).(lower(e{1}));
        nonSchiz_data = nonSchiz_er(i).(lower(e{1}));
        channel = control_er(i).channel;
        disp([e{1} ', Channel: ' channel])

        time_ind = find(erptimes>50 & erptimes<250);
        erptimes_sub = erptimes(time_ind);

        control_erp = control_data(time_ind, :);
        patient_erp = patient_data(time_ind, :);
        schiz_erp = schiz_data(time_ind, :);
        nonSchiz_erp = nonSchiz_data(time_ind, :);

        [control_n170_peak, ind] = min(control_erp);
        n170_peak = [n170_peak, control_n170_peak];
        control_n170_lat = erptimes_sub(ind);
        n170_lat = [n170_lat, control_n170_lat];
        group_var = [group_var, repmat({'Control'}, 1, length(control_n170_peak))];

        % Uncomment for for 2x4 ANOVA design
%         [patient_n170_peak, ind] = min(patient_erp);
%         n170_peak = [n170_peak, patient_n170_peak];
%         patient_n170_lat = erptimes_sub(ind);
%         n170_lat = [n170_lat, patient_n170_lat];
%         group_var = [group_var, repmat({'Patient'}, 1, length(patient_n170_peak))];

        % Uncomment next 2 code chunks for 3x4 ANOVA design
        [schiz_n170_peak, ind] = min(schiz_erp);
        n170_peak = [n170_peak, schiz_n170_peak];
        schiz_n170_lat = erptimes_sub(ind);
        n170_lat = [n170_lat, schiz_n170_lat];
        group_var = [group_var, repmat({'Schizophrenia'}, 1,
length(schiz_n170_peak))];

        [nonSchiz_n170_peak, ind] = min(nonSchiz_erp);
        n170_peak = [n170_peak, nonSchiz_n170_peak];
        nonSchiz_n170_lat = erptimes_sub(ind);
        n170_lat = [n170_lat, nonSchiz_n170_lat];
        group_var = [group_var, repmat({'Schizoaffective'}, 1,
length(nonSchiz_n170_peak))];
    end
    type_var = [type_var, repmat(e, 1, 24)];
end

[p,tbl,stats,terms] = anovan(n170_lat, {type_var, group_var}, ...
                             'model', 'interaction', ...
                             'varnames', {'Type','Group'});


% ANOVA for P300 mean at electrode FP1
emotion_types = {'Neutral', 'Happy', 'Angry', 'Sad'};

p300_mean = [];

group_var = [];
type_var = [];

for e = emotion_types

    for i = 1  % electrode FP1

        erptimes =  control_er(i).erptimes;
        control_data = control_er(i).(lower(e{1}));
        patient_data = patient_er(i).(lower(e{1}));
        schiz_data = schiz_er(i).(lower(e{1}));
```

```
        nonSchiz_data = nonSchiz_er(i).(lower(e{1}));
        channel = control_er(i).channel;
        disp([e{1} ', Channel: ' channel])

        time_ind = find(erptimes>=400 & erptimes<=600);
        erptimes_sub = erptimes(time_ind);

        control erp = control data(time ind, :);
        patient_erp = patient_data(time_ind, :);
        schiz_erp = schiz_data(time_ind, :);
        nonSchiz_erp = nonSchiz_data(time_ind, :);

        control_p300_mean = mean(control_erp, 1);
        p300_mean = [p300_mean, control_p300_mean];
        group_var = [group_var, repmat({'Control'}, 1, length(control_p300_mean))];

        % Uncomment for for 2x4 ANOVA design
%         patient_p300_mean = mean(patient_erp, 1);
%         p300_mean = [p300_mean, patient_p300_mean];
%         group_var = [group_var, repmat({'Patient'}, 1, length(patient_p300_mean))];

        % Uncomment next 2 code chunks for 3x4 ANOVA design
        schiz_p300_mean = mean(schiz_erp, 1);
        p300_mean = [p300_mean, schiz_p300_mean];
        group_var = [group_var, repmat({'Schizophrenia'}, 1,
length(schiz_p300_mean))];

        nonSchiz_p300_mean = mean(nonSchiz_erp, 1);
        p300_mean = [p300_mean, nonSchiz_p300_mean];
        group_var = [group_var, repmat({'Schizoaffective'}, 1,
length(nonSchiz_p300_mean))];

    end
    type_var = [type_var, repmat(e, 1, 24)];
end

[p,tbl,stats,terms] = anovan(p300_mean, {type_var, group_var}, ...
                             'model', 'interaction', ...
                             'varnames', {'Type','Group'});

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

EEG Measures Correlations with Patient Demographic data

```
% Loading Patient demographic data
clc
load_patient_demo_data
patient_scores = patient_demo_data(:, {'PatientCode', 'Age', ...
                                       'PANSSP_session2', 'PANSSN_session2', ...
                                       'PANSSG_session2', ...
                                       'MADRS_session2'});


patient_scores_schiz = patient_scores(4:end, :);
% Sorting the rows alphabetically as thats how the data is stored in STUDY
patient_scores_schiz = sortrows(patient_scores_schiz, 'PatientCode');
patient_scores_schiz = patient_scores_schiz{:, 2:end};
patient_scores_nonSchiz = patient_scores(1:3, :);
patient_scores_nonSchiz = sortrows(patient_scores_nonSchiz, 'PatientCode');
patient_scores_nonSchiz = patient_scores_nonSchiz{:, 2:end};

% Plotting for Schizophrenia Patients
fig_title = 'P100 Peak: Schizophrenia';
f_name = 'p100_peak_corrs_schiz';
schiz_inds = ismember(group_var, {'Schizophrenia'});
disp('Doing P100 peak Schizophrenia')
disp(reshape(type_var(schiz_inds), [], 4))
plot_ER_demo_corrs(p100_peak(schiz_inds), patient_scores_schiz, fig_title, f_name)

fig_title = 'P100 Latency: Schizophrenia';
f_name = 'p100_latency_corrs_schiz';
```

```
schiz_inds = ismember(group_var, {'Schizophrenia'});
disp('Doing P100 latency Schizophrenia')
disp(reshape(type var(schiz inds), [], 4))
plot_ER_demo_corrs(p100_lat(schiz_inds), patient_scores_schiz, fig_title, f_name)

fig_title = 'N170 Peak: Schizophrenia';
f_name = 'n170_peak_corrs_schiz';
schiz inds = ismember(group var, {'Schizophrenia'});
disp('Doing N100 peak Schizophrenia')
disp(reshape(type_var(schiz_inds), [], 4))
plot_ER_demo_corrs(abs(n170_peak(schiz_inds)), patient_scores_schiz, fig_title,
f_name)

fig_title = 'N170 Latency: Schizophrenia';
f_name = 'n170_latency_corrs_schiz';
schiz_inds = ismember(group_var, {'Schizophrenia'});
disp('Doing N170 latency Schizophrenia')
disp(reshape(type_var(schiz_inds), [], 4))
plot_ER_demo_corrs(n170_lat(schiz_inds), patient_scores_schiz, fig_title, f_name)

fig_title = 'P300 Mean: Schizophrenia';
f_name = 'p300_mean_corrs_schiz';
schiz_inds = ismember(group_var, {'Schizophrenia'});
disp('Doing P300 mean Schizophrenia')
disp(reshape(type_var(schiz_inds), [], 4))
plot_ER_demo_corrs(p300_mean(schiz_inds), patient_scores_schiz, fig_title, f_name)


% Plotting for Schizoaffective disorder Patients
fig_title = 'P100 Peak: Schizoaffective';
f_name = 'p100_peak_corrs_nonSchiz';
nonSchiz_inds = ismember(group_var, {'Schizoaffective'});
disp('Doing P100 peak Schizoaffective')
disp(reshape(type_var(nonSchiz_inds), [], 4))
plot_ER_demo_corrs(p100_peak(nonSchiz_inds), patient_scores_nonSchiz, fig_title,
f_name)

fig_title = 'P100 Latency: Schizoaffective';
f_name = 'p100_latency_corrs_nonSchiz';
nonSchiz_inds = ismember(group_var, {'Schizoaffective'});
disp('Doing P100 latency Schizoaffective')
disp(reshape(type_var(nonSchiz_inds), [], 4))
plot_ER_demo_corrs(p100_lat(nonSchiz_inds), patient_scores_nonSchiz, fig_title,
f_name)

fig_title = 'N170 Peak: Schizoaffective';
f_name = 'n170_peak_corrs_nonSchiz';
nonSchiz_inds = ismember(group_var, {'Schizoaffective'});
disp('Doing N100 peak Schizoaffective')
disp(reshape(type_var(nonSchiz_inds), [], 4))
plot_ER_demo_corrs(abs(n170_peak(nonSchiz_inds)), patient_scores_nonSchiz, fig_title,
f_name)

fig_title = 'N170 Latency: Schizoaffective';
f_name = 'n170_latency_corrs_nonSchiz';
nonSchiz_inds = ismember(group_var, {'Schizoaffective'});
disp('Doing N170 latency Schizoaffective')
disp(reshape(type var(nonSchiz inds), [], 4))
plot_ER_demo_corrs(n170_lat(nonSchiz_inds), patient_scores_nonSchiz, fig_title,
f_name)

fig_title = 'P300 Mean: Schizoaffective';
f_name = 'p300_mean_corrs_nonSchiz';
nonSchiz_inds = ismember(group_var, {'Schizoaffective'});
disp('Doing P300 mean Schizoaffective')
disp(reshape(type_var(nonSchiz_inds), [], 4))
plot_ER_demo_corrs(p300_mean(nonSchiz_inds), patient_scores_nonSchiz, fig_title,
f_name)

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Correlation plotting function

```
function plot_ER_demo_corrs(mat1, mat2, fig_title, f_name)

mat1 = reshape(mat1, [], 4);

[task_score_corr, p] = corr(mat1, mat2);
c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
emotions = {'Neutral', 'Happy', 'Angry', 'Sad'};
figure('Position', [1 41 1000 750]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:5)
set(gca, 'YTickLabel', emotions)
% axis square
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig i, sig j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title(fig_title)
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
print(f_name, '-dpng', '-r300', '-painters');
close;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

Behavioural data Correlations with Patient Demographic data

```
% Load previously formatted and saved data
load('ER_control_data.mat')
load('ER_patient_data.mat')

schiz inds = [3, 5, 6];
non_schiz_inds = [2, 1, 4];
schiz_patients = ERpatient(schiz_inds, :);
non_schiz_patients = ERpatient(non_schiz_inds, :);

schiz patients = dataset2table(schiz patients);
non_schiz_patients = dataset2table(non_schiz_patients);
emotion_types = {'Neutral', 'Happy', 'Angry', 'Sad'};

% Load Patient Demographic data
load_patient_demo_data
patient_scores = patient_demo_data(:, {'PatientCode', 'Age', ...
                                       'PANSSP_session2', 'PANSSN_session2', ...
                                       'PANSSG_session2', ...
                                       'MADRS_session2'});

patient_scores_schiz = patient_scores(4:end, :);
% Sorting the rows alphabetically as thats how the data is stored in STUDY
patient_scores_schiz = sortrows(patient_scores_schiz, 'PatientCode');
patient_scores_schiz = patient_scores_schiz{:, 2:end};
patient_scores_nonSchiz = patient_scores(1:3, :);
patient_scores_nonSchiz = sortrows(patient_scores_nonSchiz, 'PatientCode');
patient_scores_nonSchiz = patient_scores_nonSchiz{:, 2:end};

% Correlation Plots for Percent Correct
% Schizophrenia Patients
[task_score_corr, p] = corr(schiz_patients{:,2:5}, patient_scores_schiz);
```

```
c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task score corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
set(gca, 'YTickLabel', emotion_types)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Percent Correct: Schizophrenia')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'percCorr_demo_corrs_schiz.png';
print(f_name, '-dpng', '-r300', '-painters');

% Schizoaffective disorder Patients
[task_score_corr, p] = corr(non_schiz_patients{:,2:5}, patient_scores_nonSchiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
set(gca, 'YTickLabel', emotion_types)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Percent Correct: Schizoaffective')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'percCorr_demo_corrs_nonSchiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

% Correlation Plots for Latency
% Schizophrenia Patients
[task_score_corr, p] = corr(schiz_patients{:,6:end-1}, patient_scores_schiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
set(gca, 'YTickLabel', emotion_types)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
```

```
title('Trial Latency: Schizophrenia')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'latency_demo_corrs_schiz.png';
print(f_name, '-dpng', '-r300', '-painters');

% Schizoaffective disorder Patients
[task_score_corr, p] = corr(non_schiz_patients{:,6:end-1}, patient_scores_nonSchiz);

c_data = brewermap(100, 'RdBu');
c_inv = flipud(c_data);
score_type = {'Age'; 'PANSSP';...
              'PANSSN';...
              'PANSSG'; ...
              'MADRS'};
figure('Position', [1 41 1000 720]);
imagesc(task_score_corr, [-1 1])
colormap(c_inv)
set(gca,'TickLabelInterpreter','none')
set(gca, 'XTick', 1:5)
set(gca, 'XTickLabel', score_type, 'XTickLabelRotation', 45)
set(gca, 'YTick', 1:4)
set(gca, 'YTickLabel', emotion_types)
hold on;
[sig_j, sig_i] = find(p<0.05);
plot(sig_i, sig_j, '*', 'MarkerSize', 10, 'color', [.9, .9, .9]);
title('Trial Latency: Schizoaffective')
colorbar
set(gca, 'FontSize', 24, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 1)
f_name = 'latency_demo_corrs_nonSchiz.png';
print(f_name, '-dpng', '-r300', '-painters');
close;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

APPENDIX I - MATLAB CODES: PCA ANALYSIS

```
% Controls
% CANTAB
load('cantab_data_thesis')
[cantab_subjects, sort_ind] = sort(control_subjects(1, :)');
control_data = control_data(:,sort_ind);
to_remove = [7, 12];
disp('Removing from CANTAB')
disp(cantab_subjects(to_remove))
control_data(:, to_remove) = [];
cantab_subjects(to_remove) = [];

task_inds = [3, 5, 12, 6, 13, 9, 16, 19, 20, 21, 22, 23, 25];
cantab_control_age = control_data(1,:);
cantab_data = control_data(task_inds, :)';

% MMN
load('MMN Figs\mmn_controls_metrics.mat')
load('mmn_controls_ages.mat')
mmn_control_age = control_age;
to_remove = [7, 8];
disp('Removing from MMN')
disp(mmn_subjects(to_remove))
mmn_subjects(to_remove) = [];
mmn_control_age(to_remove) = [];
mmn_mean_control(to_remove, :) = [];
mmn_latencies_control(to_remove, :) = [];
cond_var_control(to_remove, :) = [];
age_var_control(to_remove, :) = [];
```

```
% ER
load('er_control_pca_eeg_data.mat')
to_remove = [1,8,13];
disp('Removing from ER')
disp(er_control_subjects(to_remove))
er_control_subjects(to_remove) = [];
er_control_age(to_remove) = [];
control_er_data(to_remove, :) = [];

control_data_all = [cantab_data, ...
                    mmn_mean_control, mmn_latencies_control, ...
                    control_er_data];

% Patients
% CANTAB
load('cantab_data_thesis')
task_inds = [3, 5, 12, 6, 13, 9, 16, 19, 20, 21, 22, 23, 25];
cantab_data_patient = patient_data(task_inds, :)';
cantab_patient_age = patient_data(1,:);

% MMN
load('MMN Figs\mmn_patient_metrics.mat')
[sorted_mmn_ages, sort_ind] = sort(age_var_patient(:, 1));
age_var_patient = age_var_patient(sort_ind, :);
cond_var_patient = cond_var_patient(sort_ind, :);
group_var_patient = group_var_patient(sort_ind, :);
mmn_mean_patient = mmn_mean_patient(sort_ind, :);
mmn_latencies_patient = mmn_latencies_patient(sort_ind, :);

% ER
load('er_patient_pca_eeg_data.mat')

% Patient codes
patient_codes = {'P2', 'P1', 'P6', 'P3', 'P5', 'P4'};
patient_diag = {'Schizoaffective'; 'Schizoaffective'; 'Schizophrenia';
'Schizoaffective'; 'Schizophrenia'; 'Schizophrenia'};
patient_data_all = [cantab_data_patient, ...
                    mmn_mean_patient, mmn_latencies_patient, ...
                    patient_er_data];
%
all_data = [control_data_all; patient_data_all];
all_data_mean = mean(all_data, 1);
all_data_std = std(all_data, 1);
all_data_zscore = (all_data - all_data_mean)./all_data_std;

% do pca
[coeff, score, latent] = pca(all_data_zscore, ...
                             'Centered', 'off');
relative_latent = latent/sum(latent);

%
figure('Units' , 'normalized', ...
       'Position', [0., 0., .9, .9]);
plot(cumsum(relative_latent), 'o', 'MarkerSize', 15, ...
     'MarkerEdgeColor', [.3, .3, .3], ...
     'MarkerFaceColor', [.7, .7, .7], 'LineWidth', 2)
xlabel('Principal Components')
ylabel('Cumulative Variance')
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)
box 'off'
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
```

```
axis('square')
ylim([0, 1.05])
xlim([-1, 21])
xticks(0:2:20)
yticks(0:.1:1)
grid on

%
c_data = brewermap(20, 'RdYlGn');
color_data = brewermap(8, 'Dark2');
color_data = color_data([1,2,3,4,6,8], :);
figure('Units' , 'normalized', ...
       'Position', [0., 0., .9, .9]);

plot(score(1:end-6, 1), score(1:end-6, 2), 'o', 'MarkerSize', 15, ...
     'MarkerEdgeColor', c_data(15, :), ...
     'MarkerFaceColor', 'none', 'LineWidth', 4)
hold on
labels = {};
for i=[2,1,4,6,5,3]
    plot(score(end-6+i, 1), score(end-6+i, 2), 'o', ...
         'MarkerSize', 15,'MarkerEdgeColor', color_data(i, :), ...
         'MarkerFaceColor', color_data(i, :), 'LineWidth', 1)
    curr_label = [char(patient_codes(i)), ': ', char(patient_diag(i))];
    labels = [labels, curr_label];
end

xlabel('Prinicipal Component 1')
ylabel('Prinicipal Component 2')
xticks([])
yticks([])
labels = ['Healthy Controls', labels];
legend(labels, 'Location', 'northeastoutside')
legend boxoff
set(gca, 'FontSize', 32, 'FontName', 'Garamond', ...
    'FontWeight', 'Bold', 'LineWidth', 2)
box 'off'
txt = findobj(gca,'Type','text');
set(txt,'VerticalAlignment', 'Middle', ...
    'FontSize', 32, 'FontName', 'Garamond', 'FontWeight', 'Bold');
axis('square')

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```