EEG signatures of psychiatric and mental illness

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Signed: **Date:**

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Acknowledgments

I dedicate this study to my family, my daughter and my wife and I would like to thank them for the patient and faith on me during this year.

I’m very grateful to my supervisor Dr.Campbell Reid for his immense patient, share of knowledge, and for all of his time dedicated to this project.

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ABSTRACT

Schizophrenia is a mental disorder which is characterised by a combination of symptoms including paranoid delusions, visual and auditory hallucinations, disorganized thoughts and language, apathy and social dysfunction. There are many hypotheses about the factors that lead to this illness such as genetic predisposition, neurochemical deficiency and structural abnormalities of the brain. Currently there are no diagnostic tools that can categorically identify the disorder and the diagnosis is established mainly after the manifestation of the symptoms.

Many studies have been conducted in order to determine the criteria of biological markers that can be utilized to predict the onset of the illness. A possible endophenotype that is proving to be reliable is the Mismatch Negativity (MMN). The MMN is an acoustic event related potential (ERP) which is a memory based process generated automatically by the neurons as a response to the occurrence of changes in the auditory stimulus. This phenomenon occurs mainly in the primary auditory cortex, in the superior temporal gyrus and in the inferior frontal cortex.

The purpose of this study is to investigate further the time-frequency components present in each deviant generated by the MMN and to examine the suitability of a single channel dry-electrode device as a substitute for the normal laboratory based procedure of conducting electroencephalography (EEG). This approach is being considered due to the difficulty of performing lengthy and uncomfortable multi-channel EEG on psychiatric patients. For this purpose a commercially available single channel dry sensor system from NeuroSky will be compared with a 64 channel Neuroscan Synamp2 system, using a previously developed MMN protocol. Data will be collected from the same scalp location using both systems and output measures such as ERP amplitude and latency will be quantitatively compared to assess the accuracy and sensitivity of the device for use in clinical research.

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Chapter 1 Schizophrenia

1.1 Introduction

Schizophrenia is a severe mental disorder with an enormous socio-economic impact. It is currently estimated that the prevalence of the disorder is approximately 0.4% of the global population and is often associated with lifelong mental and physical incapacity that significantly influences the families of patients (World Health Organization, 2001). The direct costs for the treatment of the disorder and the indirect societal costs were approximately calculated to be 6.7 billion pounds in England for the year 2004/2005 (Mangalore & Knapp, 2007) and an estimated amount of 62.7 billion dollars in the United States for the fiscal year 2002 (Wu, et al., 2005).

The onset of the disorder is typically found during late adolescence or in the first years of adulthood; this is mainly attributed to a period of brain variations that may trigger different neuro-pathological mechanisms (Gogtay, et al., 2011). Schizophrenia has a higher incidence in young males compared to females while the prevalence shows that there is no statistical difference between the genders (Aleman & Selten, 2003; McGrath, 2007). With the term incidence is defined the amount of new cases of illness amongst persons at risk for being affected over a period of time. Prevalence measures the proportion of people inside a population who manifests a disease or have manifested it during their lifetime (Tandon, et al., 2008)

The course of the disorder disrupts the primary intellectual functions of the patient and distorts their emotional capabilities, affects the ability to reason rationally, to perceive and understand the mechanics of the world, and to express feelings and needs. In many patients the disorder persists for years and when there are more serious expressions of the disorder like hallucinations and delusions it often requires institutionalisation, with the inevitable loss of independence and complete social withdrawal. It is estimated that approximately 30% of the patients diagnosed

with schizophrenia will attempt suicide at some point during the progress of the disorder of which 10% will eventually succeed. Furthermore it is calculated that the life expectancy for a patient affected by schizophrenia is reduced on average by ten years (World Health Organization, 2001).

1.2 Symptoms

The term schizophrenia that describes the neuropsychiatric syndrome is relatively new; it was introduced back in 1908 by the Swiss psychiatrist Eugen Bleuler who is also famous for coining the term autism. The word schizophrenia was derived from the Greek words "σχίζειν" and "φρεν'' meaning split and mind respectively. However, regardless of the etymology, schizophrenia does not have symptoms characterised by multiple personalities. The German psychiatrist Emil Kraepelin in 1911, based on the clinical view of symptoms, came up with the concept of dementia praecox, where he considered schizophrenia as a single disorder based on etiologic criteria. By doing so he outlined for the first time the negative symptoms. Bleuler also set the fundaments for the identification and categorisation of symptoms by dividing them in two wide groups, that were later advanced to the two current categories of negative and positive symptoms with the later defined by the German psychiatrist Kurt Schneider (Andreasen, 2011).

The disorder comprises a wide variety of pathological mental processes that are divided into defined criteria in order to facilitate diagnosis, diminish heterogeneity, and facilitate research. A positive symptom or Type I, also referred to as a productive symptom, is considered any atypical mental state and neurological motor disorder that can be expressed as hallucinations, delusions, or thought and movement disorders. A negative symptom or Type II, denoted as a deficit, is described as a deficiency in normal function. Examples of deficiencies are anhedonia, lack of emotions, alogia, social withdrawal and cognitive deficits (Kay, 1991).

In more detail, the positive symptoms include: hallucinations, which are defined as a sensory experience perceived only by the patient. One of the most

frequent hallucinations present in almost half of the cases are auditory experiences, mainly in the form of voices that speak to the person: the voices are not related to any individual recognisable by the patient, are well-defined and the patient generally feels at ease with their presence. Other modalities of hallucinations are visual where only the patient is able to see objects or other people, olfactory where they smell non-existent odours and somatic sensations where they feel that they are being touched (Arango & Carpenter, 2011).

Delusions come in the form of false ideas and theories that cannot be linked to the patient's education or culture and are retained with a strong certainty that lack any rational justification. Based on their content, delusions can be divided in several types: such as delusions of control, where the patient believes that his mind and actions are being controlled by someone else; and thought insertion or broadcasting, where they imagine that their mind is transparent and everybody can introduce ideas or read their thoughts. Delusional ideas also include thoughts of grandeur, where the patient identifies himself with a famous or historical person, and delusions of persecution where they believe that other people are trying to harm them, spy on them or that they are victims of a conspiracy (National Institute of Mental Health, 2009).

Thought disorders are characterised by various degrees of intellectual deficiency and are more often found in the form of retardation, where the patients manifest continuous pauses during speech and cannot organise thoughts and language in a logical order. An additional form of thought disorder is thought blocking where the patient unexpectedly stops his flow of thinking without any plausible justification. Finally another form is represented by neologism, which is the creation of new words by the patient that haves no obvious meaning for his interlocutor.

Movement disorders can be expressed in the form of catatonia, where the patient performs little or no movements and presents an unjustified opposition to orders. The opposite of catatonia is an unrestrained motion with no apparent reason that is repeated constantly, following the same patterns (Arango & Carpenter, 2011).

Negative symptoms are an important tool in the diagnostic process: these are the symptoms that were first identified by the pioneer psychiatrists as the

fundamental indicators of the disorder and in the majority of the cases are prodromal to the onset of schizophrenia and the eventual expression of positive symptoms. Negative symptoms are defined as primary (or idiopathic) and secondary, and are divided in five global groups:

Alogia is a noticeable absence in the quantity and quality of speech, and can also occur as a total speech blockage or as a response delay.

Anhedonia is expressed as incapacity to feel enjoyable experiences, loss of sexual interest, inability to show affection and closeness that may undermine their will and capabilities for social interaction, leading to asociality.

Avolition is characterised by an absence of energy and lack of interest, non-attendance to personal care and hygiene, inability to keep up with the obligations in school or work and complete physical inactivity where the individual remains continuously passive.

Affective flattening is the symptom where the patient has lost the ability to express emotions and feelings in any circumstance: the patient lacks the capability to express their state of mind through facial expressions and gestures and fails to maintain prolonged eye contact.

Attention impairment is categorised mainly by the incapacity of the patient to remain focused during the assessment of their mental status and this can be seen also in his social life and working performance (Andreasen, 1982).

A third category called mixed schizophrenia has also been identified, based on the criteria defined by the positive and negative symptoms. All patients that suffer from symptoms in the two principal groups or that do not fulfil some of the criteria are included in this category (Andreasen & Olsen, 1982).

1.3 Diagnostic procedure

The extensiveness and heterogeneity of mental states and signs that contribute to the syndrome make the process of identification and diagnosis a very difficult one. In order to increase reliability and attain a precise diagnosis the World Health Organisation (WHO) and the American Psychiatric Association (APA) have

published well designed systems that are based on criteria and codes, improving considerably not only the assessment of symptoms but also research and international communication. The most recent versions of the two manuals are the 10th edition of the International Classification of Disease (ICD-10) published by WHO and the diagnostic and statistical manual of mental disorders 4th edition (DSM-IV-TR) published by APA. In both systems the concept of schizophrenia is outlined in the same context of an extensive symptomatology, including both positive and negative symptoms and at least two of the common symptoms must be present thus rejecting any similar mental disorders. Both systems require that the pathological signs endure for a sufficiently long period in order to be accepted as symptoms of mental disorder. The main difference between the two manuals is that, the ICD-10 specifies a required time of one month instead of six months in the DSM-IV-TR that also expects deterioration in the patient's overall performance (Andreasen, 1995).

Complementary to the above manuals, an extensive collection of psychiatric rating systems have been developed to offer a substantial and consistent calculation of the psychotic symptoms severity. One of the most significant and widely used rating scales is the Positive and Negative Syndrome Scale (PANSS), where the assessment is based on 30 parameters that offer an established association between the principal groups of symptoms, providing also a measurement in their relationship and proposes a description of the syndrome's severity (Kay, et al., 1987). Other important rating systems are the Scale for the Assessment of Negative Symptoms (SANS) that divides the negative symptoms into five global categories and each of the main groups are split into behavioural modules that are rated from 0 to 5 (Andreasen, 1982). Paired with the SANS, the Scale for the Assessment of Positive Symptoms (SAPS) was established, which provides a global disorder rating that is based on the two systems (Andreasen, 1990).

With the next revision for DSM-V being scheduled for 2013 and ICD-11 following soon after, many scientists are expressing concerns about the definitions and diagnostic modalities followed in the schizophrenia syndrome and have proposed several changes, that range from new terminology (Van Os, 2009) to reconceptualising the diagnostic process to a great extent by including more

advanced concepts like phenotypes, genomic and environmental factors (Keshavan, et al., 2011).

1.4 Biological markers and Endophenotypes

Although many worldwide efforts have already been made in order to understand the aetiology of the syndrome and establish a pathophysiological model for developing an appropriate diagnosis or treatment; at present there are no biomarkers or laboratory examinations robust enough to diagnose schizophrenia consistently.

A biomarker is described as a biological parameter that can be measured and quantified and is directly associated to a physiological process or related to the pathological manifestations of a disease. Consequently, a biomarker can be considered any macromolecule or protein that can be linked with a biological mechanism. There are several types of biomarkers and they are distinguished according to their application, such as antecedent, screening, diagnostic, prognostic and stratification markers. Of particular use in the identification of neuropsychiatric disorders is the diagnostic biomarker that must follow certain criteria: for instance it must be disorder specific, must not be related to the symptoms, and the measurement must be consistent, repeatable, reliable and efficient (Ritsner, 2009). Intermediate phenotypes, notably known as endophenotypes have been developed and have a similar purpose to biomarkers: they are a measurable biological or clinical variation hereditarily related to pathological conditions. Endophenotypes are disease specific biological defects that are inherited but can also be found in non-affected relatives: they exist in both conditions of sickness and wellbeing and hence are state independent and they occupy the space between genetic factors and clinical symptoms of the disease (Allen, et al., 2009). The conditions required for accepting a measure as an endophenotype are that it must be inheritable and that the variance from the related symptoms must be attributed to a smaller number of genes than the disease itself (Ritsner, 2009).Therefore, endophenotypes must be attributed to the causes of the disease and not be part of its effects or be affected directly by

pharmacological therapy. Subsequently, endophenotypes need to have a wide variability inside the overall population in order to provide a large sampling group; reducing the potential biasing and eliminating all possible correlations with other non-disease specific factors. Finally, endophenotypes must be capable of providing information on the contributing role of abnormalities in a multilevel investigation of the affected neural systems (Egan & Cannon, 2011).

A very promising endophenotype that belongs to the field of neurophysiology is mismatch negativity (MMN). It is currently under an extensive investigation by several research groups and its robustness as a diagnostic tool for various mental illnesses and it's specificity for early detection of the schizophrenia disorder makes it a perfect candidate for clinical applications.

1.5 Mismatch Negativity as an Endophenotype

Mismatch negativity is a negative event related potential (ERP) component, which is computed by subtracting the ERP produced by a repeated standard stimulus from an ERP generated by a rare deviant stimulus. The automatic generation of the MMN can be located to the auditory cortex and more specifically in the primary and secondary auditory cortices, with this pre-attentive operation assumed to be a primitive sensory level intelligence (Näätänen, et al., 2001), and other contributing areas have been found in the dorsolateral prefrontal cortex (Sato, et al., 2003). In schizophrenia it has been adequately documented that in the majority of cases there is a reduction in amplitude of the MMN waveform with an estimated mean heritability of around 0.68 (Hall, et al., 2006), suggesting that MMN is a specific quantifiable measurement of the disorder and that it can be utilised adequately to predict the onset of schizophrenia, making it a perfect candidate for an intermediate phenotype.

1.6 Study aim

Schizophrenia is widely studied using the majority of available research tools that range from understanding the genetic traits of the disorder to advanced imaging techniques such as functional magnetic resonance imaging and positron emission tomography that provide valuable neural structural information and functional interactions. With the advance of multimodal modalities and the improved definition of endophenotype markers, the electroencephalogram (EEG) again became a powerful tool for research of clinical diagnostic applications in schizophrenia. The EEG represents all the electrical activity that arrives at the scalp and is produced by the activation of large group of neural cells. This activation represents all neurophysiological processes and can be associated with normal activities like walking, hearing and seeing to more complicated activities such as thinking, remembering and feeling. An improvement to the standard EEG technique is the use of ERPs in order to isolate and study specific brain processes in the presence of certain stimuli.

In this study, measurements of MMN were performed on healthy individuals utilising the standard procedure of EEG testing. The data collected was analysed in the time domain and in the frequency domain for every set of data obtained, in order to validate further the testing protocol developed by the department of Biomedical Engineering of the University of Strathclyde, regarding the use of the MMN component as a potential diagnostic tool for schizophrenia. An additional study was carried out on the MMN components to understand the correlation and connectivity between brain areas during the detection of deviant stimuli and establish the hierarchy of axonal connections during the formation of the response to those stimuli.

Furthermore, because of the complexity in the preparation and completion of the laboratory based EEG testing on psychiatric patients, there was an investigation into the possibility of acquiring the required data for the protocol from a commercially available low-cost wireless EEG system, composed of one dry electrode. For this purpose a custom made program was developed with the aim of

testing on healthy participants and the collected data being compared against the data collected from the normal EEG for reliability and suitability.

Chapter 2 Literature review

2.1 Electroencephalography

The human brain is composed of neurons that constitute the majority of cells present in the central nervous system and neuroglia that surrounds the neurons supporting their functionality by providing nutrients, preserving homeostasis and removing pathogens. Neurons are responsible for the transmission of stimuli and information in the form of action potentials that can be conducted throughout the body without decay. Neural cells connect to each other through synapses that are divided in inhibitory and excitatory synaptic connections. Synapses are where the exchange of cations and anions permits the flow of the action potential between cells. When an action potential is propagated inside the cell and arrives at an excitatory synapse, an excitatory postsynaptic potential (EPSP) take place into the next cell. Following an EPSP is a flow of charged particles inward to and outward from the neuron; this movement produces a current at the postsynaptic end of the cell due to the entry of cations and a current flow in the extracellular space. This extracellular current flow generates a small field potential, which intensifies with the addition of more field potentials from adjacent cells. This aggregate of field potentials, with a frequency normally smaller than 100 Hz, is termed an electroencephalogram (EEG) (Sanei & Chambers, 2007). The action potential that runs through the cortical neurons is barely contributing to the creation of the EEG signal since its direction is away from the scalp surface and commonly occurs asynchronously.

Typically the amplitude of the EEG signal varies between a few microvolts (μV) to 100 μV and is associated with the synchronous interaction of the cortical neural cells; consequently simultaneous activation of a large group of neurons will generate a high amplitude waveform due to the combination of the signals from single neurons in a time coherent way, low amplitudes in the EEG signal occur when neurons are activated asynchronously. A repetitive synchronous activation over time will produce a rhythmic EEG that can arise from deep cortical regions that act as a

pacemaker such as the thalamus and subcortical areas (Sherman & Walterspacher, 2006). Furthermore, the pace making property of the thalamus is partially responsible for the frequency of the EEG signal; additionally the frequency is derived from synchronised neurons in a specific cortical region as part of a feedback mechanism. There are principal frequency bands in the human brain, which considered in conjunction with age and mental state contain useful clinical information.

The 5 different bands are described as follows: The δ (delta) band ranges from 0.5 to 4 Hz and typically is present in the course of deep sleep and may also be seen in a waking state caused by muscle activity near the scalp surface or from brain injuries. The θ (theta) band between 4 and 7 Hz is a common feature in an EEG signal of children and occurs during sleep or drowsiness in adults, large portions of theta waves are associated with several pathologies. The α (alpha) band varies from 8 to 13 Hz, and is more prominent in the occipital region of healthy individuals and is present during a relaxed awake state with the eyes closed. The β (beta) band is found mainly in the frontal and central areas of the brain. It is characterised by low amplitudes and frequencies between 14 and 30 Hz, and is linked to increased cortex activation. Finally the γ (gamma) band, also referred as fast beta waves, has frequencies that exceed 30 Hz and appears during intense cortical activity and sensorimotor areas stimulation (Sörnmo & Laguna, 2005).

The acquisition of EEG signals is done by using the arrangement defined by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology, which utilise the standard 10-20 system (Figure 1.1) for positioning the electrodes. For obtaining data from the electrodes it is possible to utilise a monopolar (referential) or bipolar (differential) derivation. In a monopolar derivation the signal is acquired from the variance between each electrode placed on the region of interest and one or two distant electrodes that act as a common reference. In the bipolar derivation each EEG signal is acquired from a channel that is derived from the difference of two neighbouring electrodes (Sherman & Walterspacher, 2006).

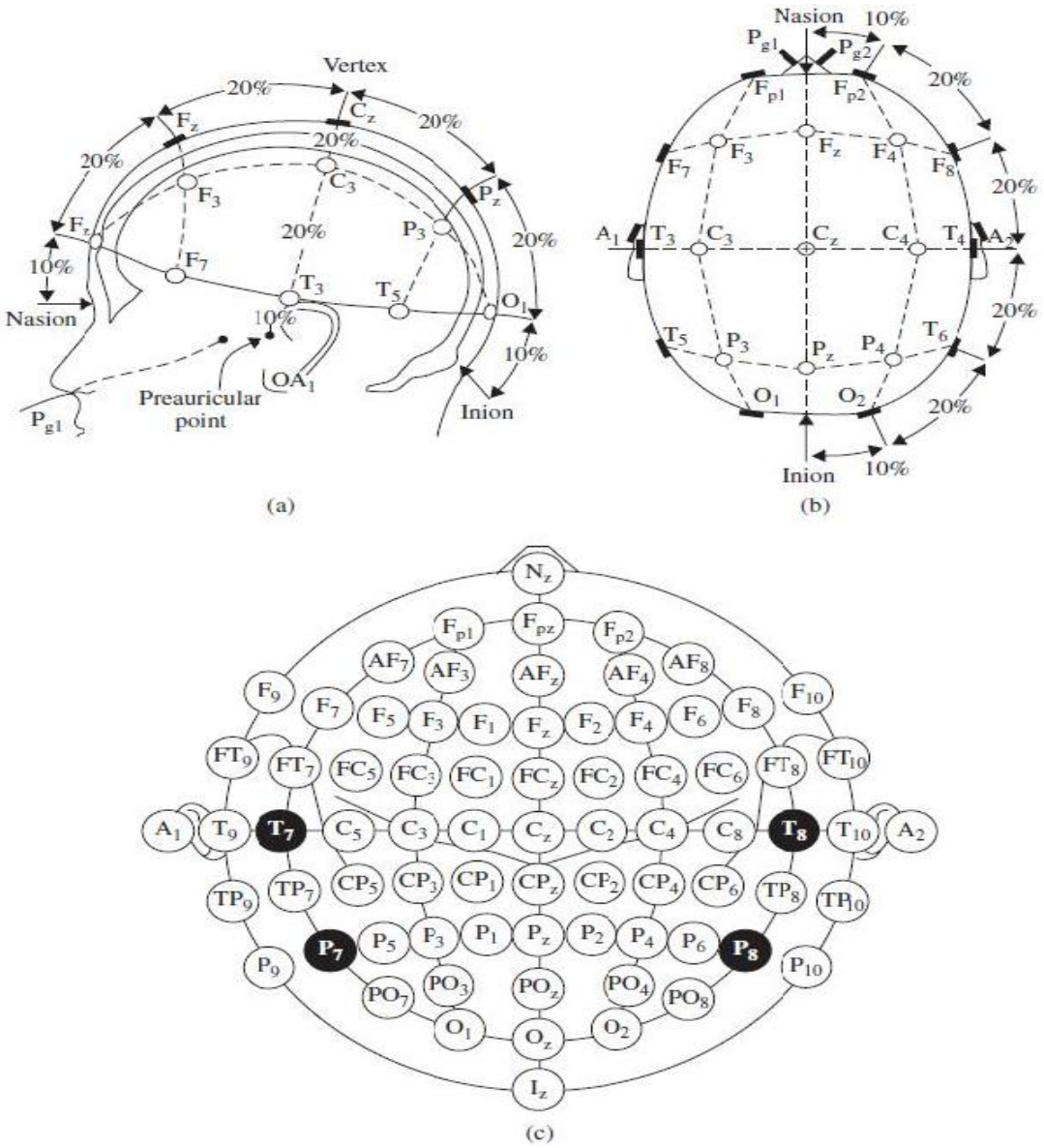

Figure 2-1 Standard 10-20 setup configuration diagram. (a) and (b) indicate how each electrode location is defined and (c) the setup configuration for 75 electrodes. (Sanei & Chambers, 2007)

The EEG signal is an important tool in the location of neurological and physiological variations in the brain, one of the major advantages of this technique is the very high temporal resolution that is in the order of milliseconds. However, the spatial resolution is very limited compared to the time resolution and is proportional to the number of recording electrodes. This is related to what is known as the inverse problem, where there is not a unique solution to identify precisely the location of the

source following the distribution of the voltage variations on the scalp (Winterer & McCarley, 2011).

2.2 Evoked potentials

A very useful diagnostic technique in neurology and psychiatry is the evoked potential that represents time locked activity of the cortex to various types of stimulating events such as somatosensory, auditory and visual stimulation. The recording of evoked potentials utilises the same setup configuration as a normal EEG with the EEG signal recorded as background, the evoked potentials appear as transient fluctuations in the recorded voltage and their amplitude and form are proportional to the stimulus that produced them. The amplitude of the evoked potentials is very small compared to the background EEG and varies from 0.1 to 10 μV, thus averaging over a large number of trials is necessary in order to remove the unrelated background EEG signal influence (Sörnmo & Laguna, 2005).

Three main characteristics can describe quantitatively the form of the evoked potential signal: amplitude, latency and source localisation. The amplitude represents the magnitude of the summated cortical activity in response to the stimulus, the latency measures the time that the peak of the waveform occurred at; additionally the latency can be decomposed providing further information on the time locked events. The source localisation represents an estimation of the underlying cortical structure that generated the spatial distribution of the signal on the scalp during every event.

The evoked potential waveform can have positive or negative amplitude, for convention any positive component of the waveform is designated with the letter P followed by a number that represents the latency of the peak from the time that a specific stimulus is presented, measured in milliseconds. For a negative component, the peak is denoted with the letter N. In many cases the number corresponds to the temporal sequence of components, up to a maximum of ten (Sanei & Chambers, 2007).

Evoked potentials are divided in three basic modalities based on the type of stimulation used to elicit the event. For that reason there are visual evoked potentials most frequently produced by alternating visual shapes and flashing lights, auditory

evoked potentials that are generated as a reaction to a sound in form of a tone or click and somatosensory evoked potentials that represents the response to a momentary electrical stimulation on peripheral nerves. Furthermore evoked potentials can be distinguished based on the characteristics of the stimulus, so a potential that is generated following the physical properties (strength, length and occurrence) of the external stimulation are termed an exogenous evoked potential. In contrast, the term endogenous is used when the potential is elicited according to an internal brain activity.

The term event related potential (ERP) classifies an extensive category of evoked potentials that are produced as reactions to the presence or not of specific stimuli. For the generation of ERPs the most frequently utilised technique is the oddball paradigm, where two or more stimuli are alternated in a sequence following a pseudorandom distribution. The stimulus that occurs more often is called standard, the test stimuli is called deviant, and occurs less frequently and without anticipation (Quiroga, 2006).

2.3 Auditory event related potentials

The auditory ERP is elicited in the presence of an auditory stimulus and represents the result of neural activation from the peripheral auditory regions to the primary auditory cortex. This activation is classified based on the latency of the ERP in three parts: the brainstem response; the middle latency response; and the late latency response. The brainstem response can be localised in the auditory neural nerves of the brain stem and forms the initial part of the evoked potential, with latencies less than 10 ms and very small amplitudes oscillating between 0.1 to 0.5 μV (denoted with green in Figure 2-2). The middle latency response is elicited in the thalamus and comprises a sequence of broader voltage variations compared to the brainstem response and the latency fluctuates between 10 to 50 ms after the beginning of the auditory stimulus, with amplitudes from 0.2 to 1 μV (designated red in Figure 2-2). The late latency response is generated in the cortex and begins from

50 to 100 ms and the amplitudes are significantly higher ranging from 1 to 20 μV (represented with blue in Figure 2-2) (Sörnmo & Laguna, 2005).

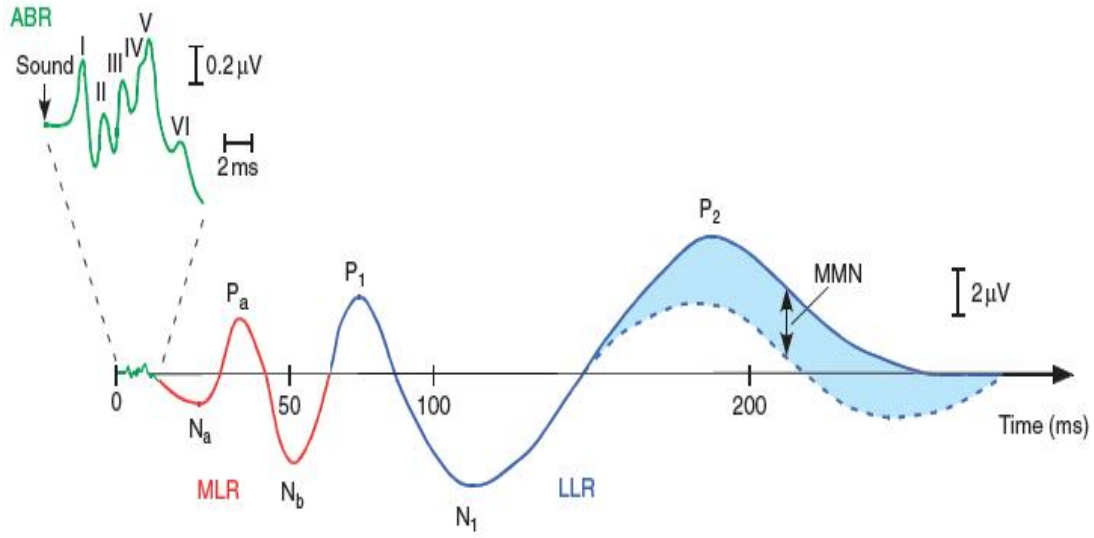

Figure 2-2 Illustration of the three auditory evoked potentials. ABR denotes the auditory brain stem response, MLR stands for middle latency response and LLR signifies late latency response. Illustrated as well is the mismatch negativity, obtained from difference between the dashed and solid waveforms. Figure adapted from (Melcher, 2009).

All the auditory evoked potentials are dependent on the physical properties of the auditory stimulus, therefore with an increased rate in the auditory stimulation there is an amplitude reduction and when the stimulus is increased in intensity the ERP also increases in amplitude but decreases in latency. These features are attributed to the physiognomic properties of the auditory nerve: the beginning of the primary wave in the brainstem response drives the activation of the remaining neurons by providing the input. Additionally to the dependent response on the physical properties of the auditory stimulus, auditory ERP are also affected by the composition of the stimulation. A well-documented pattern of this dependency is the mismatch negativity (MMN), which is elicited when the stimuli are present in the setting of the oddball paradigm. The response to the deviant sound is different when the sound is presented inside the paradigm and when the same sound is repeated numerous times independently (Melcher, 2009).

2.4 Mismatch Negativity

Mismatch negativity is the negative component of an event related potential which is generated as an automatic neural response to an auditory stimulation. It occurs when there is a violation in the pattern of the presented acoustic stimuli by a deviant sound that varies from the standard stimulus in one of the physical features such as duration, frequency, intensity and location. This response is elicited independently from the arousal status of the subject, and demonstrates the ability of the brain to execute laborious comparisons on continuous sounds without apparent conscious effort (Näätänen, 2000).

The waveform of the MMN is obtained by subtracting the ERP generated by the standard stimulus from the ERP elicited by the occurrence of the deviant stimulus. The negative component of the MMN normally peaks 100 to 250 ms following the deviant stimulus and the maximum amplitude of the component is reported in the frontocentral and central scalp areas. A very important requirement in order to elicit the MMN is that the central auditory system has to establish a description of the physical features for the standard stimulus before the deviant stimulus occurs and infringes this representation (Näätänen, et al., 2007).

This requirement clearly indicates the dependency of the MMN on the presence of a memory trace established by the previous stimuli. At the beginning of each train of stimuli the leading standard stimuli creates a memory trace that contains all the physical features of the stimulus and the occurrence of a rare stimulus during the activation of the memory trace triggers the automatic discrimination process that elicits an MMN. The memory trace has been estimated to have duration in the region of 10 seconds (Näätänen, 2000). From this perspective the MMN represents the first step in the process of biologically important cognitive procedures that are occupied in the alerting and redirecting of attention to the new auditory event that potentially may correspond to a noteworthy situation for the person (van der Stelt & Belger, 2007). When a deviant sound produces a switch in attention, a positive P3a peaks around 250ms from the deviant onset (Kujala & Näätänen, 2010).

Attention is not switched each time an auditory variation is presented, though it may not be consciously perceived. This can be explained by the fact that the

deviant stimulus is not different enough from the stimulus present inside the memory trace: either the difference is insufficient to activate the discrimination process, or the memory trace containing the previous stimulus has already decayed making the automatic comparison process impossible. Other possible explanations are that at the moment of change the attention is directed somewhere else causing a rise in the attention threshold switch, or the subject anticipates the arrival of the deviant stimulus that is noted by the absence of the P3a and even though the MMN is elicited no attention switch is noted (Näätänen, et al., 2007).

The MMN has characteristics that are comparable to those of other waveforms like the N1, which is elicited by changes in the energy or the physical properties of the stimulus, contrary to the MMN that represents a higher order memory process. The N1 amplitude normally peaks at 100ms subsequent to the changes in the stimulus and it has been noted that repetitive stimulation will reduce the amplitude of the N1 component (Kujala & Näätänen, 2010). The N1 generators are reported to be in the temporal lobes, where a neural population gave a different response to the rare stimulus and did not respond when it was stimulated by each rare tone presented individually inside a sequence, and did not respond to the presence of standard tones that were alternating in rate. This suggests that the locus of MMN generation is different from the location of N1 generators (Näätänen, et al., 2007).

The generator sources of the MMN have been reported from the amplitude peaks to be in frontocentral areas that can be explained by the sum of the activity bilaterally in the supratemporal cortices, these findings were also supported by magnetoencephalographic source localisation which also showed maximum signal peaks in both supratemporal peaks. Animal studies presented the existence of a relationship between the appearance of the MMN and responses in the thalamus and hippocampus, but this evidence is not clear (Näätänen, et al., 2007).

The MMN is elicited by performing a passive (no task is executed during the testing) oddball paradigm. That is composed of frequent standard stimuli that are mixed with rare-deviant stimuli that are different in the physical features such as location, volume, frequency and duration. In order to have enough rare stimuli proportional to the standard, the duration of the paradigm was beyond 60 minutes. In order to overcome this problem Näätänen et al proposed an optimal paradigm that

could accommodate 5 different types of deviants in the same time as a traditional oddball protocol composed of only one deviant. The deviants are different from the standard in duration, frequency, location, intensity and by presenting a silent gap in the middle. Since the deviant stimuli are presented alternately with standard stimuli the duration of the test is reduced to 18 min (Näätänen, et al., 2004).

2.5 Mismatch Negativity and schizophrenia

In the literature there are frequent reports about the reduction in amplitude of the mismatch negativity in schizophrenia. The reduced MMN component has been reported in untreated patients as well as in patients medicated with antipsychotics and remained reduced even when the patients changed the treatment or when administrated with sedative medication (Todd, et al., 2012).

The alterations presented in the MMN are specific to schizophrenia when compared to other mental disorders such as major depression or bipolar disorder. In a study that included 26 patients diagnosed with schizophrenia, 16 patients affected from bipolar disorder, 22 patients with major depression and 25 healthy control subjects, they found significantly reductions on the amplitudes of the schizophrenic patients compared to the other subjects. Evidence was also presented of the direct connection in the dependency of the generation of MMN with the functioning of the receptor N-methyl-D-aspartate (NMDA) (Umbricht, et al., 2003).

Another study performed on 25 patients diagnosed with schizophrenia based on the DSM-IV criteria suggested that the reductions in the MMN were highly associated with a comprehensive deterioration in the quotidian activities of the patients, suggesting also those patients with lower MMN amplitudes reported a greater impairment in everyday functioning (Light & Braff, 2005).

The majority of the studies on MMN in schizophrenia have used frequency or duration alterations as the deviant stimulus. It was reported that the reduction of the MMN when elicited by a duration deviant was more significant than the MMN reduction elicited by the frequency deviant (Michie, 2001). This finding that was also confirmed by a meta-analysis, which also suggested that the differences between the

two tested deviants (duration, frequency) may be the result of a hidden bias, proposing that significant variations on the MMN elicited by the duration deviant are more noticeable in first episode patients than in chronic patients (Umbricht & Krljes, 2005).

With respect to the influence of the characteristics of the deviant and the first episode patients, a study conducted on 25 chronic patients compared to 26 patients with the first symptoms of schizophrenia, 25 patients with a recent onset (from 1.5 to 5 years after first hospitalisation) and 39 healthy control subjects, found that the both groups of chronic and recent onset patients had lower MMN amplitudes compared to the first episode patients. They also confirmed that there was not any difference between the MMN reduction elicited by a frequency deviant and the reduction produced by the duration deviant. Furthermore, they observed that first episode patients who had received higher education showed a normal MMN, and they suggested that MMN deficits may be an indicator of cognitive alterations associated with the progress of the disorder (Umbricht, et al., 2006).

This assumption was later confirmed by the study done on two patient groups composed of recently diagnosed subjects and chronic subjects and for the first time they studied the response when the MMN was elicited by differences in duration, frequency and intensity. They found that the MMNs generated by deviants in the duration and intensity were lower in the patients who were in the initial stage of schizophrenia, while the chronically affected group had significantly lower amplitudes of the MMN for the frequency deviant with a smaller reduction due to the duration deviant (Figure 2-3).

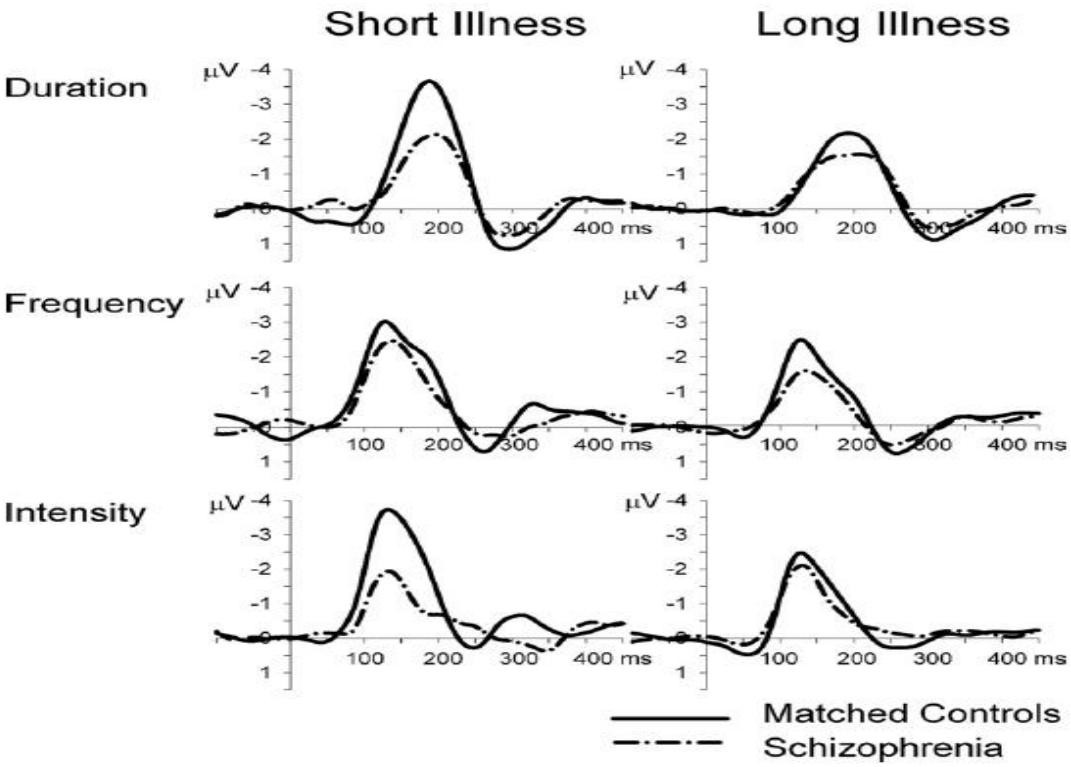

Figure 2-3 The MMN as seen at the Fz electrode in patients with schizophrenia and healthy control subjects. Figure taken from (Todd, et al., 2008).

This proposes that during the progression of schizophrenia there is a variation in the MMN pattern according to the stimulus features (Todd, et al., 2008).

Although it is widely accepted that the duration and frequency deviants are indicators of neuropathological changes in the progress of schizophrenia, there is no clear consensus among the studies on whether the variations in the MMN represent structural brain alterations that precede the onset of schizophrenia or whether the reduction of the MMN reflects brain modifications that are secondary to the disorder (Todd, et al., 2012).

2.6 Event Related Potentials Analysis

When the signal encompasses frequency components that appear and disappear in restricted intervals like the EEG signals, the localisation of the active components in the time-frequency domain provides valuable estimates about the

amount of activity at each frequency over time. One of the methods that is widely used for this purpose is the wavelet transform that provides an optimal representation in the time and frequency domain because of the logarithmic sampling that permits the observation of high frequencies in short time intervals and low frequencies in long time intervals (Sanei & Chambers, 2007). The correlation between the original signal and the two wavelet transforms, one for the high frequency components and one for the low ones, provide the details of the original signal in different scales. This permits the observation of the neural activity oscillations in response to the stimulus that elicit an ERP inside the noisy background of the EEG (Quiroga, 2006).

An additional aspect in the analysis of ERPs is the spatial localisation of the signal on the scalp to the underlying cortical structures, which can be used in order to detect neuropathological variations. The spatial representation is usually done by the use of equivalent current dipoles that are assumed to be the generating sources of the signal, the estimation of the dipole is done via spherical head models and each dipole is assigned with six parameters, three for the location and three for the magnitude. Due to the complexity in the calculations of all parameters no more than three dipoles can be computed at a time. Currently a number of different algorithms are being employed for the purpose of spatial localisation such as the low resolution electromagnetic tomography algorithm (LORETA), that is also used jointly with independent component analysis (ICA) and the multiple signal classification (MUSIC) (Quiroga, 2006; Sanei & Chambers, 2007).

As discussed previously, mismatch negativity is a specific ERP that is elicited when there is a violation in the continuity of auditory. The alterations found in this ERP have been consistently documented between healthy individuals and patients affected by schizophrenia. This emphasizes the need for a deeper understanding of the neuro pathophysiologic interactions and the requirement for reliable detection techniques.

2.7 NeuroSky EEG system

NeuroSky has developed a non-invasive, dry electrode system for consumer applications in order to register the brain's electrical activity and translate it into states of attention and meditation. The system consists of three dry electrodes, with the main electrode positioned on the forehead while the reference and ground electrodes are attached to the ear. The raw data recorder from the system is implemented using suitable algorithms and is transmitted via Bluetooth to a personal computer. Benchmarks tests conducted to compare the EEG signals measured from the NeuroSky system against the data collected with a system used in medical and research applications showed a close agreement between the results, with the NeuroSky system found to be less noisy in low frequency bands (NeuroSky, 2009).

Chapter 3 Methodology

3.1 Optimal Paradigm for mismatch negativity

For the generation of the mismatch negativity the stimuli were presented to each subject binaurally using foam insert earphones. During the execution of the test the participant's attention was distracted by attending a mute video. The arrangement of the auditory stimuli was done following the protocol developed by the Department of Biomedical Engineering in the University of Strathclyde, that it was also based on the optimal paradigm proposed by Näätänen, et al., 2004.

According to the optimal paradigm, the standard stimuli are harmonic tones consisting of 3 sinusoidal partials of 500, 1000, and 1500 Hz. The duration of the standard tone is 75 ms, including a 5ms rise and fall time at the start and end of the tone. The intensity of the second partial was lowered by 3dB compared to the first partial, while the intensity of the third partial was reduced by 6 dB, all the tones were generated with equal phase and are presented at a level of 80 dB sound pressure level (SPL). The time interval between each successive stimulus was set to 1000ms.

The deviant tones interspersed with the standard tones were different in duration, frequency, volume, source location, and with a silent gap in the middle of the tone. All deviant stimuli had a pseudo-random distribution with one standard between two deviants. The standard tones had a probability of 0.5 and each of the five deviants had a probability of 0.1 (Figure 3-1).

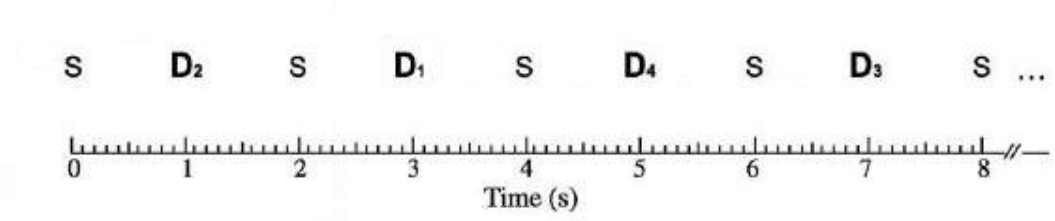

Figure 3-1 Illustration of the stimulus temporal distribution. The letter S denotes the standard tone and D the 5 different deviant tones. Adapted from (Näätänen, et al., 2004)

The total number of tones presented was 1510, composed of 760 standard stimuli interspaced with 150 deviants from each different category.

For the deviants of frequency, volume and location there are two variations: the frequency deviants are divided equally in to 10% higher partials and 10% lower partials. The volume deviants are split equally in to -10dB and +10dB relative to the standard. The location deviants were equally divided into left and right locations by advancing either the left or right channel by 800μs, equivalent to locations ±90° relative to the standard tone.

The duration deviant was shorter than the standard with a time of 25ms and has the same rise and fall as the standard stimulus of 5ms. The gap deviant was created by the addition of a silent interval of 7 ms duration in the middle of the standard tone (Näätänen, et al., 2004).

The presentation of the stimuli began with a sequence of 11 standard tones in order to establish the memory trace. The total duration of the experiment for the presentation of the 1510 tones was approximately 25 min.

3.2 EEG data acquisition

The electroencephalographic data was acquired from 32 electrodes that were position on the scalp using a 64 channel quick cap provided by Compumedics. The channels are positioned on the cap according to the International Standard 10-20, and half of them were prepared on each subject in accordance to the requirements of the experiment. The electrodes used in the cap are made of silver/silver chloride and are placed firmly inside a neoprene gel reservoir.

The channels required for the testing were FP1, FPZ, FP2, AF3, AF4, 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, O1, OZ, O2. M1 was placed on the left earlobe and M2 situated on the right earlobe. The ground channel that functions as a common reference locus for the voltage is positioned by default in the quick cap between the channels FZ and FPZ. The reference was taken from the averaged signal acquired

from the electrodes placed on the mastoids bones; details of the channel configuration are seen in Figure 3-2.

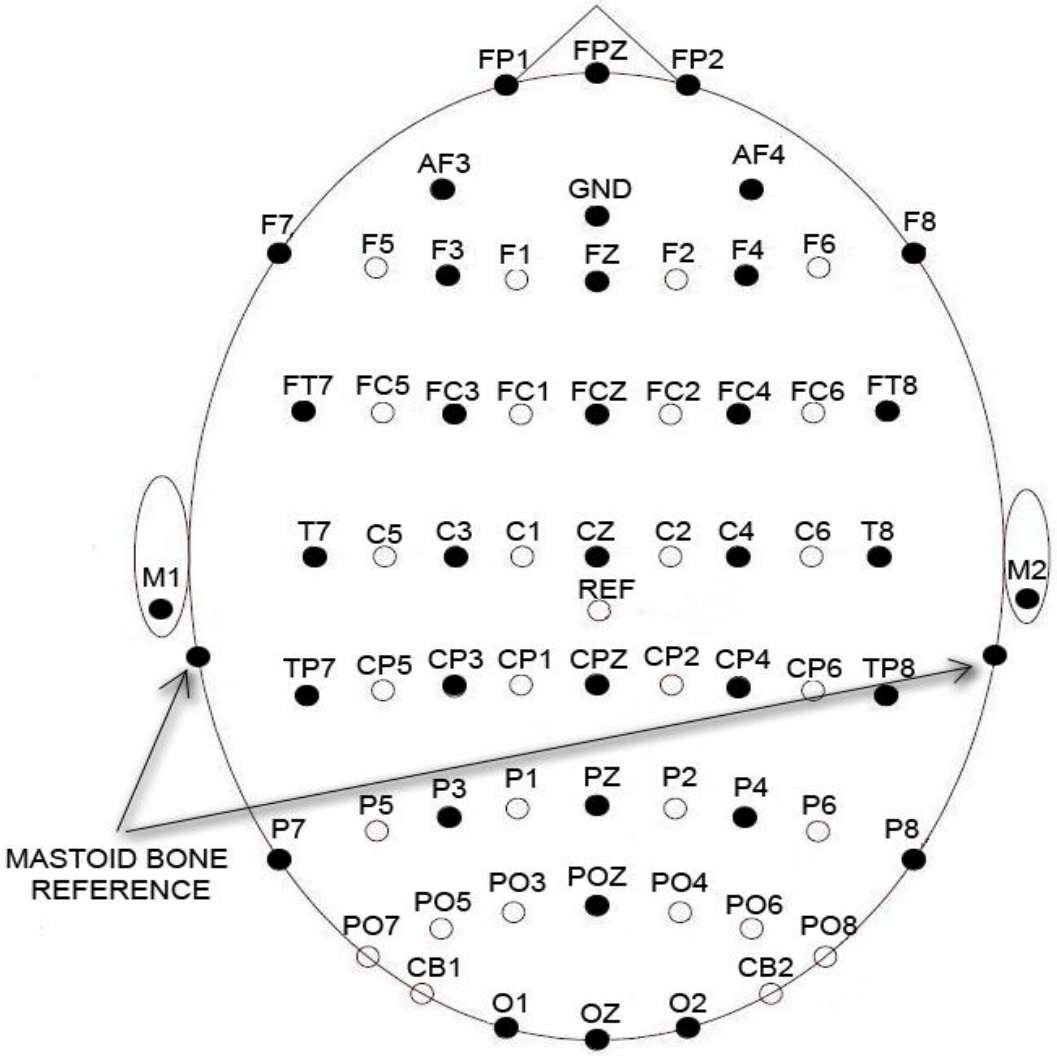

Figure 3-2 Electrode configuration on the Compumedics quick cap, black circles indicate the electrodes used in the experiment. (Adapted from http://63.134.192.29/UserFiles/File/SynAmps2_64_Channel.pdf)

Furthermore, two additional bipolar channels were positioned close to the eyes: the vertical electro-oculographic electrode (VEOG) monitors vertical movements (blinks) of the eyes, positioned above and below the left eye; and the horizontal electro-oculographic electrode (HEOG) monitors horizontal eye movements, positioned to the side of left and right eye.

The quick cap channels were connected through an adapter to the SynAmps^2 amplifiers, and the continuous EEG signal was recorded with dedicated software (Neuroscan Acquire 4.5, Compumedics, Aus). Neuroscan Stim^2 Gentask software was used for the presentation of the auditory stimuli. The Stim^2 hardware was integrated with the acquire module of the SynAmps^2 system in order to synchronise the auditory stimuli triggers with the recorded raw EEG data. Electrode impedance was kept below 5kΩ in order to improve the connection between the scalp and electrode and to avoid data contamination from external sources of noise. The sampling rate was 2000Hz, and a 50Hz notch filter was applied to the raw data for the rejection of electrical noise produced by the power lines and computers. The data was filtered from DC to 500 Hz.

3.3 MMN data acquisition

Following the acquisition of the continuous EEG data, Edit 4.5 software from Compumedics was used for the offline analysis of the recordings. The raw data was epoched between -100 ms and 900 ms relative to stimulus onset, in accordance to the type of stimulus (standard, duration, frequency, etc.). The acquired epochs were baseline corrected to remove any DC offset, and artefact rejection was performed to remove noisy epochs. The channels chosen for this operation were the HEOG and VEOG, which monitor the eye movements, and the FP1, FP2, AF3, AF4, F7 and F8 electrodes, close to the frontal recording area above the eyes. Every epoch that surpassed the threshold values of ±50μV in any of those electrodes was rejected automatically. After the artefact rejection all the rejected sweeps were deleted and the remaining epochs were averaged, forming the event related potential (ERP) response to each stimuli.

Finally after the generation of each ERP response, the MMN waveform was calculated by subtracting the ERP elicited in response to the standard stimulus from the ERP elicited by the rare stimulus.

3.4 Experimental protocol

For the purpose of this study 14 healthy participants (11 males and 3 females) were recruited, ranging in age between 22 and 32 years. The data from 12 participants was accepted for further analysis, and the results from 2 participants were discarded, one for excessive artefacts and the other because of a high amplitude time locked event, peaking to early to be considered as a physiological stimulus response.

The experiments were carried out in the neurophysiology laboratory of the Department of Biomedical Engineering in the University of Strathclyde. After the arrival of the participant in the laboratory, the purpose of the study and the experimental process was explained to the volunteer. Next, informed consent was obtained: the study was approved by the University of Strathclyde ethics committee, and by the Biomedical Engineering Unit Departmental Ethics Committee. The preparation of the participant started with the selection of the correct quick cap size based on head circumference. To position the electrodes correctly, the intersection of the midpoint between the nasion and inion and from the left preauricular to right preauricular point was found and the CZ electrode was placed on that point. The skin was prepared with cotton swabs and abrasive gel on the locations of the additional electrodes, including the VEOG, HEOG, M1, M2, and the reference electrodes. The impedance between the skin and EEG electrode was reduced by the injection of electro conductive gel with a blunt tipped syringe into the apposite gel reservoir. The impedance value was constantly monitored through the Neuroscan Acquire 4.5 software and an effort was made to keep the values of the impedance lower than 5kΩ.

Once the values were brought to an acceptable level and the electrode activity did not show any flat or noisy channels, the participants were instructed to avoid as much as possible eye blinks, jaw clenching, and unnecessary head movements. For this purpose, the participants were asked to watch the EEG monitor in order to understand the effects of any movement on EEG signal and how these effects can negatively influence the outcome of the experiment, as seen in Figure 3-3.

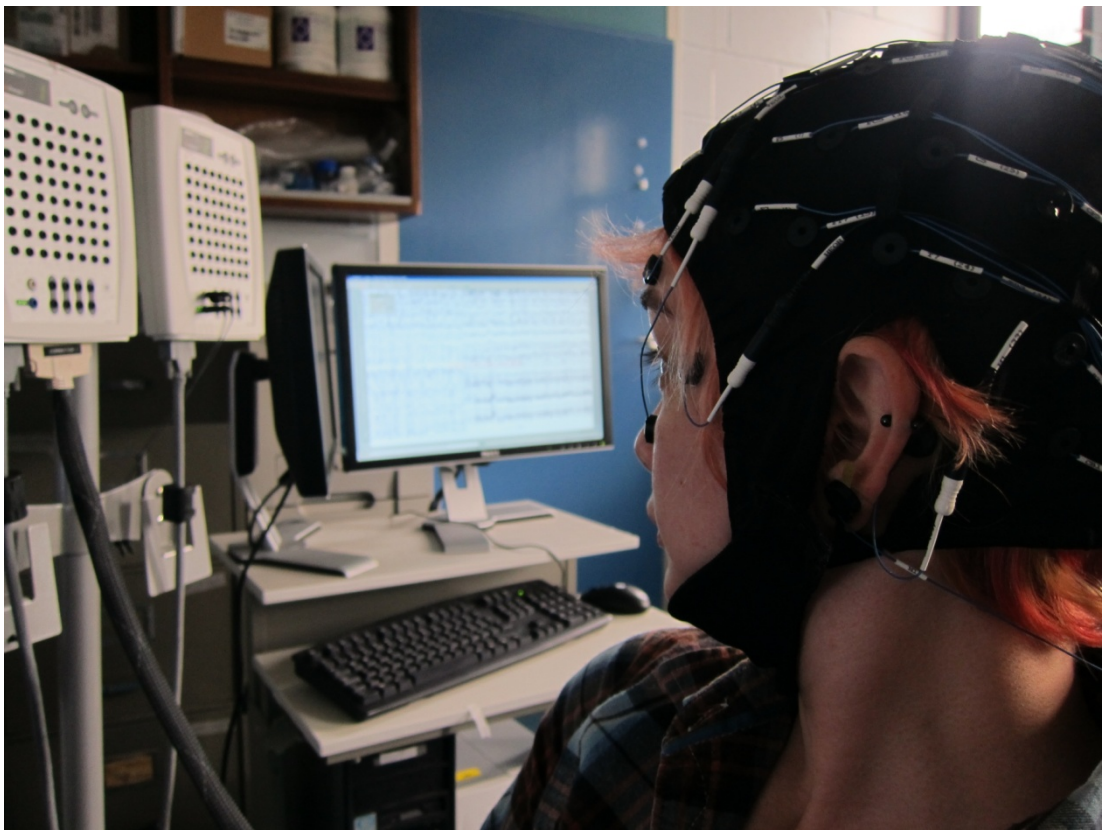

Figure 3-3 EEG instrumentation and quick cap view. Participant is watching the EEG waveforms, observing the effects of movements on the signal.

The participants were advised to stay awake and alert while the auditory stimuli were presented and to concentrate on the task, on this occasion watching a muted video with no subtitles, without paying any attention to the incoming tones.

Afterwards the participants placed into the ear canal special foam insert earphones that expanded, adequately blocking any external noise. Finally, special attention was paid to ensure that the sound stimulus triggers were sent in synchronisation to the EEG recording software.

The overall length of the experiment was approximately 90 minutes including the time for the preparation of the participant and the duration of the paradigm, that as mentioned before was 25 minutes.

3.5 ERP study

Offline analysis of the data generated by Neuroscan Edit 4.5 was performed using the freely available software EEGLAB running under the MATLAB environment. The epoched data files were imported into the EEGLAB software suite and ERP averages were created for each subject and each stimulus, as well as the grand average across all participants for every response. Additionally the event related spectral perturbation (ERSP) was obtained for each condition.

The ERSP provides an image of the averaged variations in spectral power as a function of time over a wide frequency range, relative to a baseline period. For the calculation of the ERSP, the power spectrum over the time interval of the time locked event is calculated, and after that the value is averaged over the data trials. In this graphical representation of ERSP each pixel is designated with a colour that indicates the power measured in dB associated to the time and frequency of a time locked event (Delorme & Makeig, 2004).

Another index that was investigated is the inter trial coherence (ITC) which is a measurement in the frequency domain that provides an estimation of the synchronisation of neural activity during time locked experiments. The value of ITC ranges from 0 to 1, where 0 indicates the complete lack of synchronisation in that particular latency and with 1 the complete EEG phase repeatability through the time locked events. For the computation of the ITC only the phase of each trial is measured which is obtained through the estimation of the frequency and time complex vectors at a given latency (Delorme & Makeig, 2004).

Another aim of the project was to investigate the possibility of applying an experimental toolbox for the EEGLAB, called SIFT to the data. This purpose of this application purpose is to detect, model and visualise the flow of activity between generators of EEG data, and gives the opportunity to explore the transient changes in the interactions between these different brain source processes. An important feature of the SIFT analysis is that it provides an estimate of the multivariate connectivity in the source domain rather than between scalp electrode signals, thus achieving an improved spatial localisation of the neural activity while reducing signal components

from other cortical sources that are registered by the scalp electrodes (Delorme, et al., 2011).

Chapter 4 Experimental Outcomes

4.1 Time domain outcomes

The calculation of amplitudes and latencies of the event related potentials attained during the experiments was performed offline with the software EEGLAB. For a sufficient data analysis an adequate number of accepted epochs were required, as seen in table 1. An artefact rejected algorithm was applied to the data with a strict amplitude criteria of ±50μV, reducing considerably the number of the accepted sweeps, contrary to the majority of studies into mismatch negativity where the rejection criteria values have been between ±75μV and ±100μV (Umbricht, et al., 2003; Näätänen, et al., 2004; Todd, et al., 2008). As discussed previously in section 3.4 the datasets from subject 7 and subject 14 were discarded from further analysis.

Table 1 Total number of accepted epochs for each ERP.

Accepted Epochs						
SUBJECTS	**Standard**	**Duration**	**Frequency**	**Volume**	**Location**	**Gap**
1	108	28	21	24	23	20
2	114	22	20	28	26	24
3	224	53	43	50	63	46
4	97	21	24	19	25	20
5	294	55	59	55	67	48
6	82	18	15	15	21	16
8	258	46	50	43	66	30
9	430	91	66	73	102	71
10	236	45	44	54	47	41
11	358	64	68	76	70	56
12	342	79	67	62	75	55
13	298	53	56	51	71	54
Mean	236.80	47.92	44.42	45.83	54.67	40.08
Standard Deviation	115.20	23.13	19.86	20.40	25.94	17.76

The grand average of the ERP elicited from the standard stimulus can be seen in the following figure 4-1. The N100 is a preattentive auditory mechanism and is elicited by the presentation of an unexpected auditory stimulus while the subject is focused elsewhere. The elevated amplitude of the N100 component is associated with higher intellectual capabilities and is not affected by age and gender. A decrease in amplitude of the N100 has been reported in schizophrenic patients. The P200 is associated to an initial designation of attention and early consciousness, the amplitude of the P200 component is influenced by the level of education as well as by age (Lijffijt, et al., 2009). Figure 4-1 shows the grand average from the standard tone, the N100 component has an amplitude around of approximately -5.81μV and the P200 component has an amplitude of 2.51 μV.

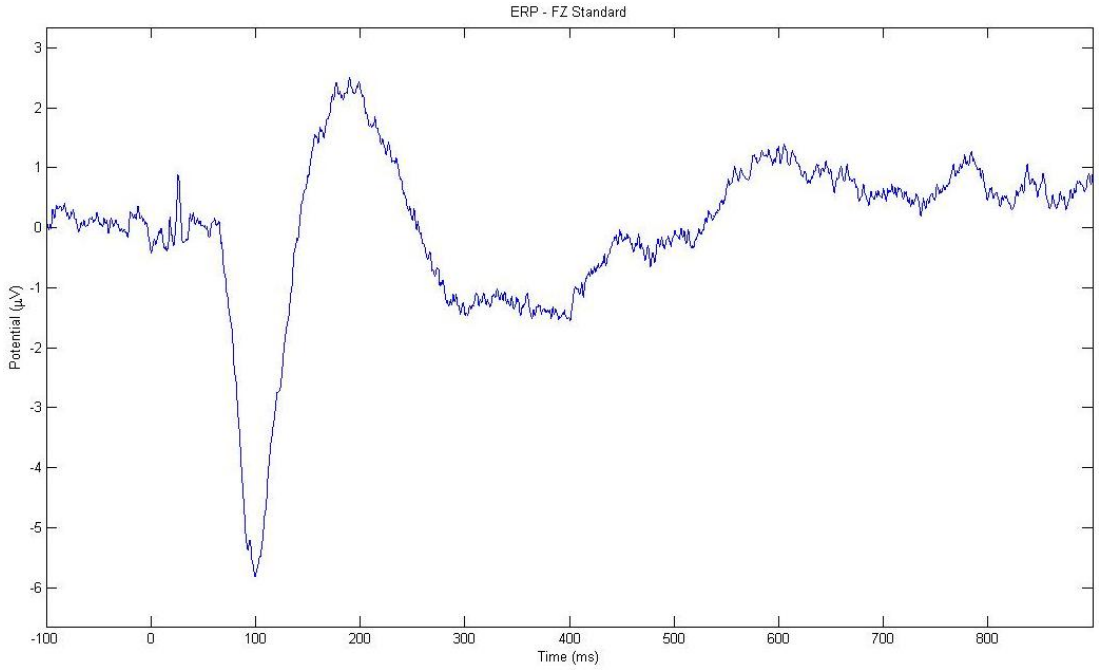

Figure 4-1 Grand average of ERPs elicited by standard deviant, acquired from channel FZ.

The graphical representations of the deviant stimuli ERP are now presented; both the N100 and P200 can be identified in the successive graphs, with higher amplitudes found for the duration, frequency and gap deviants.

Figure 4-2 shows a representation of the ERP evoked by the duration deviant: the N100 component has an amplitude of approximately -7.38μV and the P200 component has an amplitude of 3.62 μV.

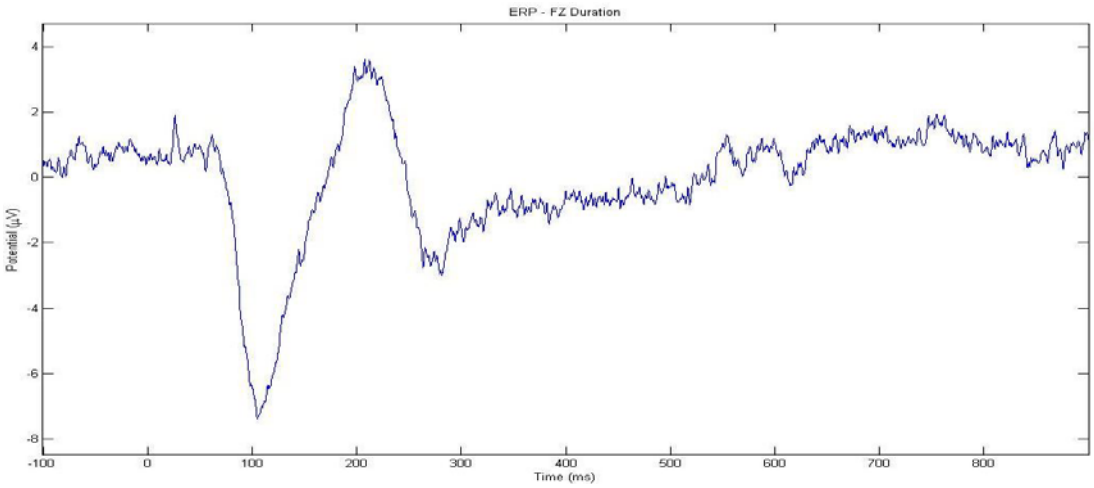

Figure 4-2 Grand average of ERPs elicited by duration deviant, acquired from channel FZ.

Figure 4-3 corresponds to the evoked potential due to the presence of the frequency deviant, and the N100 component has an amplitude of approximately -6.73μV and the P200 component has an amplitude of 3.89 μV.

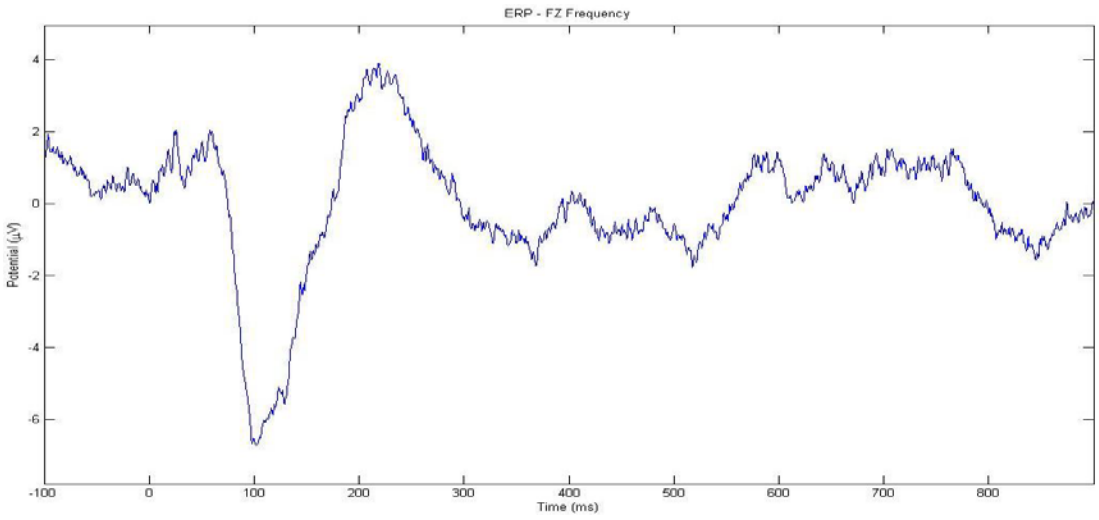

Figure 4-3 Grand average of ERPs elicited by frequency deviant, acquired from channel FZ.

The ERP evoked by the volume deviant can be seen in figure 4-4, where the N100 component has an amplitude of approximately -5.61μV and the P200 component has a low amplitude of 0.77 μV.

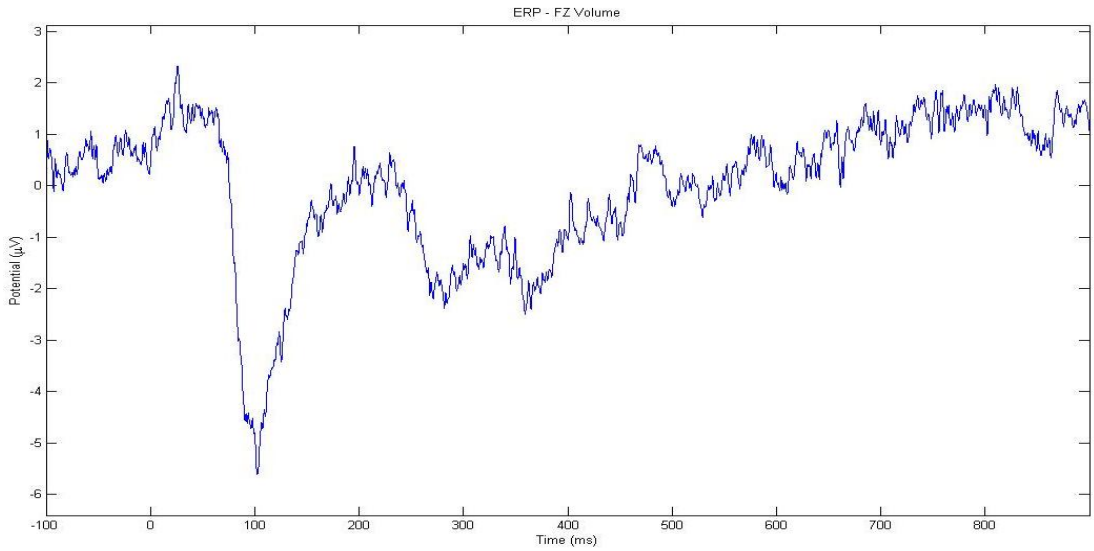

Figure 4-4 Grand average of ERPs elicited by volume deviant, acquired from channel FZ.

Figure 4-5 represents the evoked potential induced by the location deviant, from the graph it is noticeable that the N100 component has an amplitude of approximately -6.96μV and the P200 component, similar to the volume deviant, has a low amplitude of 1.98 μV.

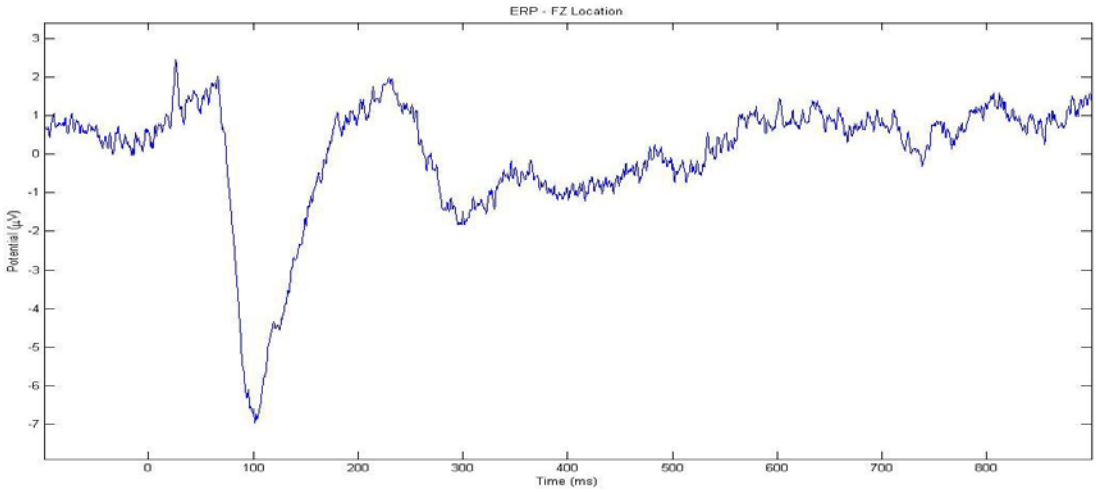

Figure 4-5 Grand average of ERPs elicited by location deviant, acquired from channel FZ.

Finally figure 4-6 denotes the ERP produced by the presence of a silent gap inside the standard deviant. From the graph the N100 component has an amplitude of approximately -7.28μV and the P200 component has the highest amplitude of 4.25 μV compared to the other deviants.

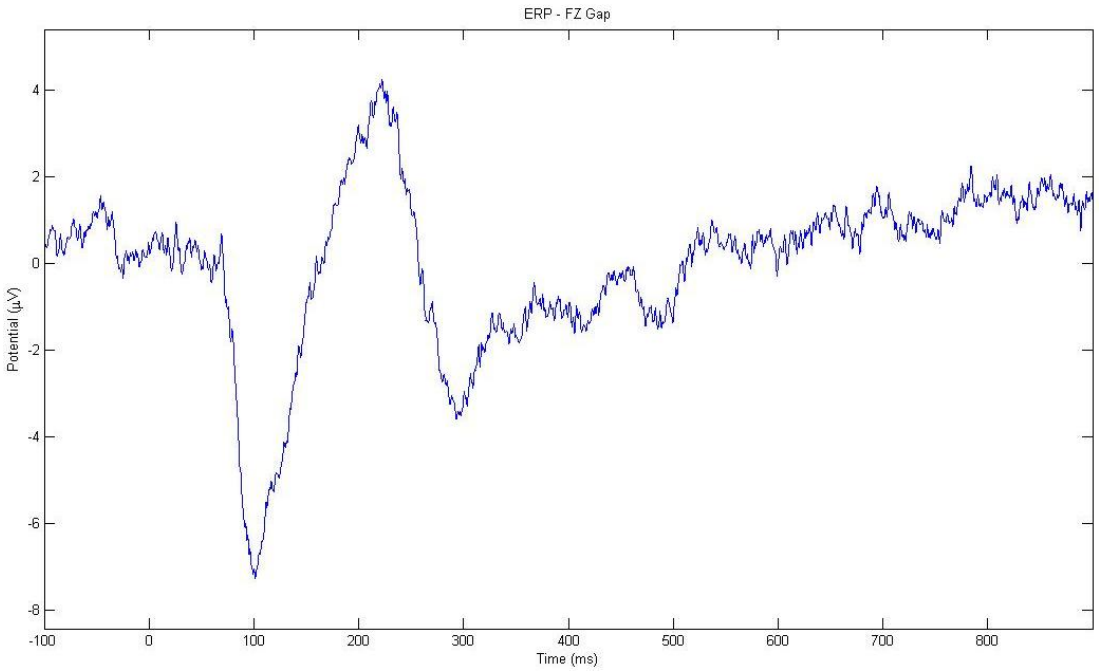

Figure 4-6 Grand average of ERPs elicited by silent gap deviant, acquired from channel FZ.

In Table 2 are included the values for the peaks latency and amplitude generated as a response to the standard stimulus. The data obtained from the experiments is compared with the values determined after filtering the epochs with EEGLAB employing a two way least squares FIR bandpass filter of 30Hz. This is done in order to improve the signal to noise ratio by removing the higher frequency components, enhancing the discrimination of the latency and amplitude peaks, the use of non-causal filtering is considered safe for low frequencies with a trade-off of introducing side lobes before signal onset (Rousselet, 2012). The effect of this procedure is an overall decrease in the values of the amplitude peaks for all ERPs of approximately 1 μV, contrary to the latency peaks where only the silent gap MMN latency was altered considerably.

Table 2 Peak latency and amplitude for standard tone ERP. Acquired from channel FZ.

Standard tone				
SUBJECTS	Raw data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	98.50	-9.14	100.50	-8.91
2	106.50	-4.62	102.50	-3.57
3	99.50	-3.55	102.50	-2.99
4	105.50	-7.62	101.00	-7.35
5	99.00	-3.77	96.50	-3.61
6	90.50	-8.45	97.00	-7.81
8	99.00	-7.67	99.00	-7.34
9	107.00	-5.17	104.50	-4.76
10	97.50	-7.07	96.50	-6.78
11	100.50	-1.30	95.00	-0.83
12	97.00	-13.22	95.00	-12.79
13	105.50	-2.62	100.50	-2.19
Mean	100.50	-6.18	99.21	-5.74
Standard	4.85	3.32	3.18	3.37

The peak values for the mismatch negativity elicited by duration deviant are included in table 3; again the raw data for each subject is compared to the filtered. The MMN usually peaks at its maximum during a time interval from 100 to 240ms following the presentation of the rare tone (Umbricht & Krljes, 2005). In accordance to previous experiments, in this study the latencies of the MMN reach their peak during the same expected time interval.

Table 3 Peak latency and amplitude for MMN from duration deviant compared to filtered values for the same response from channel FZ.

MMN Duration				
SUBJECTS	Raw Data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	121.50	-5.16	123.00	-4.50
2	146.00	-6.01	145.00	-4.55
3	95.00	-2.77	97.00	-2.06
4	167.00	-5.83	165.00	-4.71
5	118.00	-6.22	115.50	-5.54
6	119.50	-5.99	116.50	-4.17
8	146.00	-5.20	148.50	-4.36
9	110.50	-5.29	117.50	-4.67
10	102.50	-2.54	109.00	-1.80
11	100.50	-4.15	105.50	-3.76
12	118.50	-5.95	115.50	-5.22
13	123.00	-5.31	132.00	-4.30
Mean	122.33	-5.03	124.17	-4.137
Standard	21.14	1.24	19.83	1.13

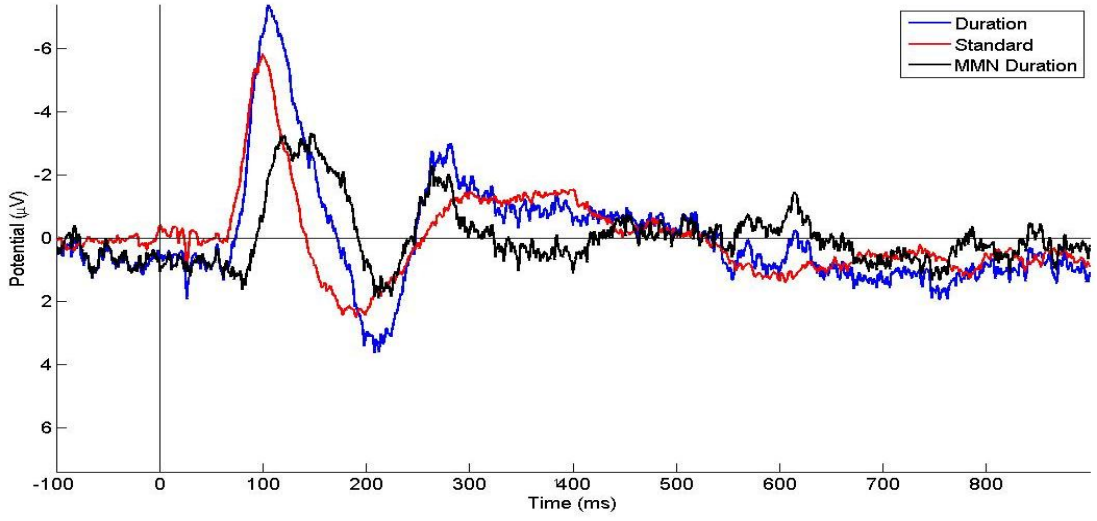

Figure 4-7 Grand averages of duration ERP with standard ERP and their difference MMN generated by duration deviant. Peak amplitude is -3.25μV and at a latency of 120.50ms.

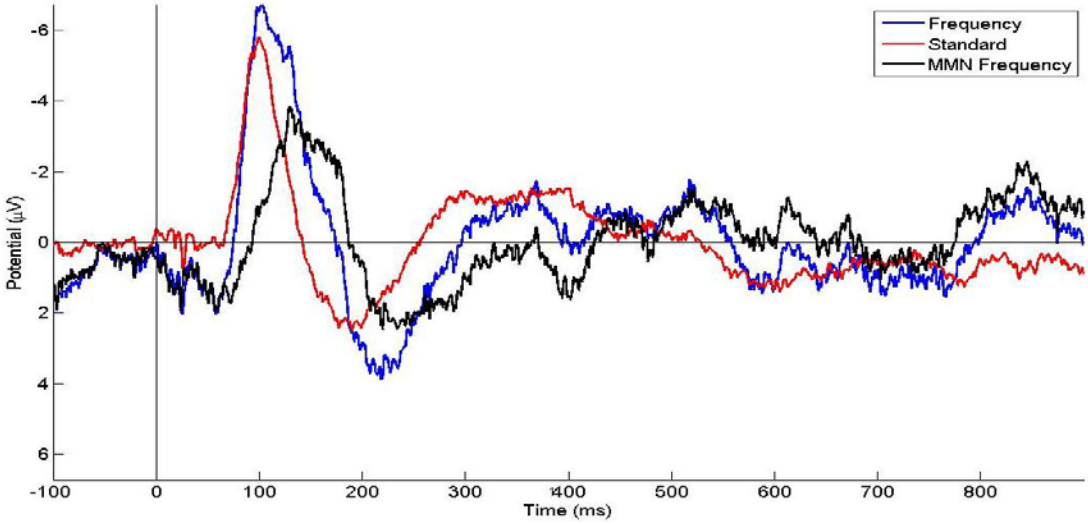

Figure 4-8 Grand averages of frequency ERP with standard ERP and their difference MMN generated by frequency deviant. Peak amplitude is -3.83μV and at a latency of 130.50ms.

The values of the amplitude response to the frequency deviant has higher amplitude compared to the other MMN deviants as can be noticed from the values in the table 4 and from the values obtained from the figure 4-5.

Table 4 Peak latency and amplitude for MMN from frequency deviant compared to filtered values for the same response from channel FZ.

MMN Frequency				
SUBJECTS	Raw Data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	136.00	-5.83	136.00	-4.98
2	172.00	-6.53	168.00	-5.24
3	139.00	-3.94	113.00	-3.23
4	157.50	-1.87	158.50	0.32
5	122.50	-5.54	124.00	-5.06
6	130.00	-12.69	130.50	-9.65
8	141.00	-6.68	139.50	-6.07
9	116.50	-3.93	112.00	-3.58
10	167.00	-4.89	173.50	-4.22
11	118.00	-2.95	84.50	-1.93
12	148.50	-3.39	139.00	-3.16
13	136.00	-3.38	130.00	-3.00
Mean	140.33	-5.13	134.04	-4.15
SD	18.11	2.80	25.01	2.43

Table 5 Peak latency and amplitude for MMN from volume deviant compared to filtered values for the same response from channel FZ.

MMN Volume				
SUBJECTS	Raw Data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	165.50	-6.57	165.50	-6.06
2	201.00	-8.41	202.00	-5.51
3	175.50	-2.26	183.00	-1.03
4	126.50	-1.09	170.00	0.09
5	182.00	-4.84	179.00	-4.01
6	146.50	-6.44	152.00	-3.23
8	161.50	-1.71	217.50	-1.57
9	179.50	-4.51	178.50	-4.16
10	182.00	-5.31	179.50	-4.50
11	77.50	-3.29	84.50	-2.51
12	210.00	-12.15	209.00	-12.17
13	157.00	-3.56	154.00	-2.70
Mean	163.70	-5.01	172.88	-3.95
SD	35.40	3.11	34.41	3.15

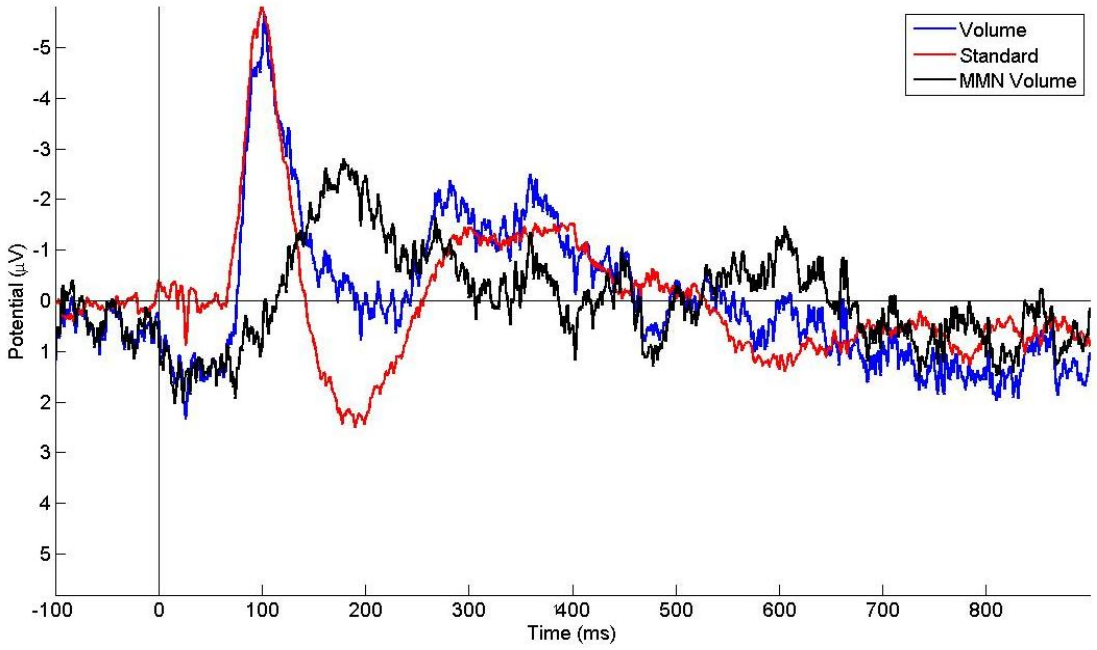

Figure 4-9 Grand averages of volume ERP with standard ERP and their difference MMN generated by volume deviant. Peak amplitude is -2.81μV and at a latency of 179ms. The volume MMN has a higher latency compared to the rest of deviants.

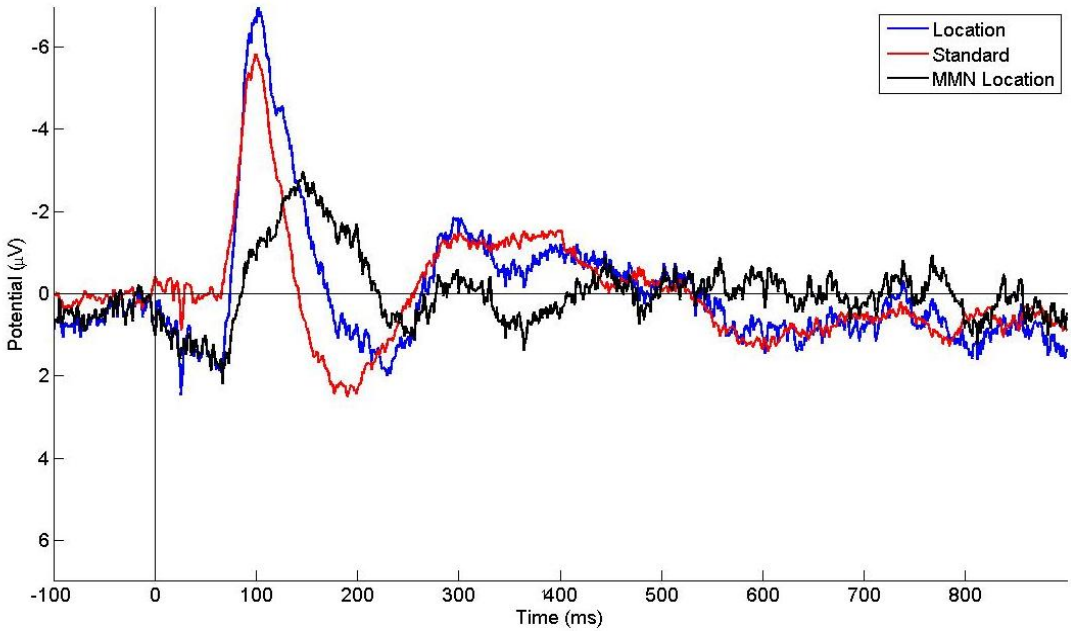

Figure 4-10 Grand averages of location ERP with standard ERP and their difference MMN generated by location deviant. Peak amplitude is -2.94μV and at a latency of 146ms.

Table 6 Peak latency and amplitude for MMN from location deviant compared to filtered values for the same response from channel FZ.

MMN Location				
SUBJECTS	Raw Data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	172.00	-6.06	164.50	-5.50
2	134.50	-7.36	137.00	-5.22
3	177.50	-2.80	136.50	-2.09
4	141.50	-5.39	149.00	-4.29
5	125.50	-4.48	130.00	-3.11
6	134.00	-2.30	131.50	-0.12
8	146.00	-4.07	144.00	-3.39
9	117.00	-3.19	111.50	-2.48
10	170.50	-5.12	170.00	-4.03
11	83.00	-4.20	88.00	-2.97
12	135.50	-5.77	141.50	-5.94
13	101.50	-4.36	101.50	-3.98
Mean	136.54	-4.59	133.75	-3.59
Standard Deviation	28.30	1.45	23.97	1.62

Table 7 Peak latency and amplitude for MMN from gap deviant compared to filtered values for the same response from channel FZ.

MMN Gap				
SUBJECTS	Raw Data		Filtered	
	Latency	Amplitude	Latency	Amplitude
1	117.50	-2.46	126.50	-1.06
2	201.50	-8.35	205.20	-5.87
3	133.50	-4.21	133.00	-3.59
4	123.50	-3.55	154.50	-2.32
5	121.50	-3.04	121.00	-2.35
6	105.00	-8.35	100.00	-5.51
8	141.50	-5.26	141.50	-4.67
9	143.50	-5.33	142.50	-5.02
10	133.50	-3.80	133.50	-2.55
11	111.00	-5.73	115.50	-5.04
12	105.50	-4.03	103.50	-4.12
13	124.00	-3.95	124.50	-3.33
Mean	130.13	-4.84	156.20	-3.79
SD	25.84	1.89	27.57	1.50

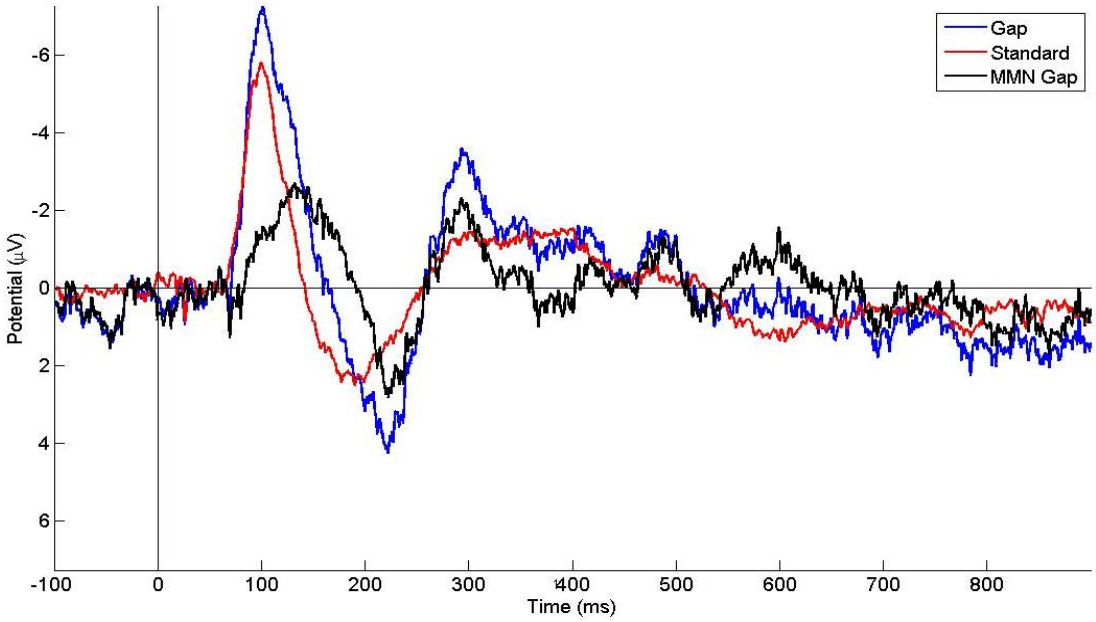

Figure 4-11 Grand averages of silent gap ERP with standard ERP and their difference MMN generated by gap deviant. Peak amplitude is -2.71μV and at a latency of 132ms.

Table 8 Mismatch negativity peak latency obtained from standard tone and the five deviants.

Comparison data for standard tone and five deviants						
SUBJECTS	MMN Latency in ms					
	Standard	Duration	Frequency	Volume	Location	Gap
1	98.50	121.50	136.00	165.50	172.00	117.50
2	106.50	146.00	172.00	201.00	134.50	201.50
3	99.50	95.00	139.00	175.50	177.50	133.50
4	105.50	167.00	157.50	126.50	141.50	123.50
5	99.00	118.00	122.50	182.00	125.50	121.50
6	90.50	119.50	130.00	146.50	134.00	105.00
8	99.00	146.00	141.00	161.50	146.00	141.50
9	107.00	110.50	116.50	179.50	117.00	143.50
10	97.50	102.50	167.00	182.00	170.50	133.50
11	100.50	100.50	118.00	77.50	83.00	111.00
12	97.00	118.50	148.50	210.00	135.50	105.50
13	105.50	123.00	136.00	157.00	101.50	124.00
Mean	100.50	122.33	140.33	163.70	136.54	130.13
SD	4.85	21.14	18.11	35.40	28.30	25.84

Table 9 N100 peak amplitudes obtained from standard tone and the five deviants.

Comparison data for standard tone and five deviants						
SUBJECTS	MMN Amplitude in µV					
	Standard	Duration	Frequency	Volume	Location	Gap
1	-9.14	-5.16	-5.83	-6.57	-6.06	-2.46
2	-4.62	-6.01	-6.53	-8.41	-7.36	-8.35
3	-3.55	-2.77	-3.94	-2.26	-2.80	-4.21
4	-7.62	-5.83	-1.87	-1.09	-5.39	-3.55
5	-3.77	-6.22	-5.54	-4.84	-4.48	-3.04
6	-8.45	-5.99	-12.69	-6.44	-2.30	-8.35
8	-7.67	-5.20	-6.68	-1.71	-4.07	-5.26
9	-5.17	-5.29	-3.93	-4.51	-3.19	-5.33
10	-7.07	-2.54	-4.89	-5.31	-5.12	-3.80
11	-1.30	-4.15	-2.95	-3.29	-4.20	-5.73
12	-13.22	-5.95	-3.39	-12.15	-5.77	-4.03
13	-2.62	-5.31	-3.38	-3.56	-4.36	-3.95
Mean	-6.18	-5.03	-5.13	-5.01	-4.59	-4.84
SD	3.32	1.24	2.80	3.11	1.45	1.89

4.2 Frequency domain analysis

The analysis performed in the time frequency domain has the potential to discriminate the peak amplitude of an ERP attributed to an increase in the spectral power of a phase locked event between trials. When taken together the measurements of the ERSP and ITC can provide a model of neural activity as a response to an event occurring through several trials. ERSP measures the induced response of the event and the ITC gives a quantification of the evoked event related dynamics (Makeig, et al., 2004)

The graphs for ERSP and ITC were computed using EEGLAB and the analysis was performed on the total amount of accepted data attained from the all participants. The ERSP and ITC are compared based on the difference between the response in the standard stimulus and the response in the five deviants. The colour in the ERSP plots indicates the power measured in decibels at a given latency and frequency that is related to the time locked event. In the ITC plots the measures are given a value that range between 0 and 1, where a value near 1 indicates a perfect EEG phase reproducibility across trials at a given latency, and values near 0 represents lack of synchronisation between EEG data and time locking events (Delorme & Makeig, 2004).

The ERSP of the standard tone is represent in figure 4-12; the power spectrum is considerably increased in the lower frequencies approximately 95ms after the onset of the stimulus and in the higher frequencies peaks earlier. After 110ms that matches with the peak of the N100 there is a significant decrease in the power across all frequencies.

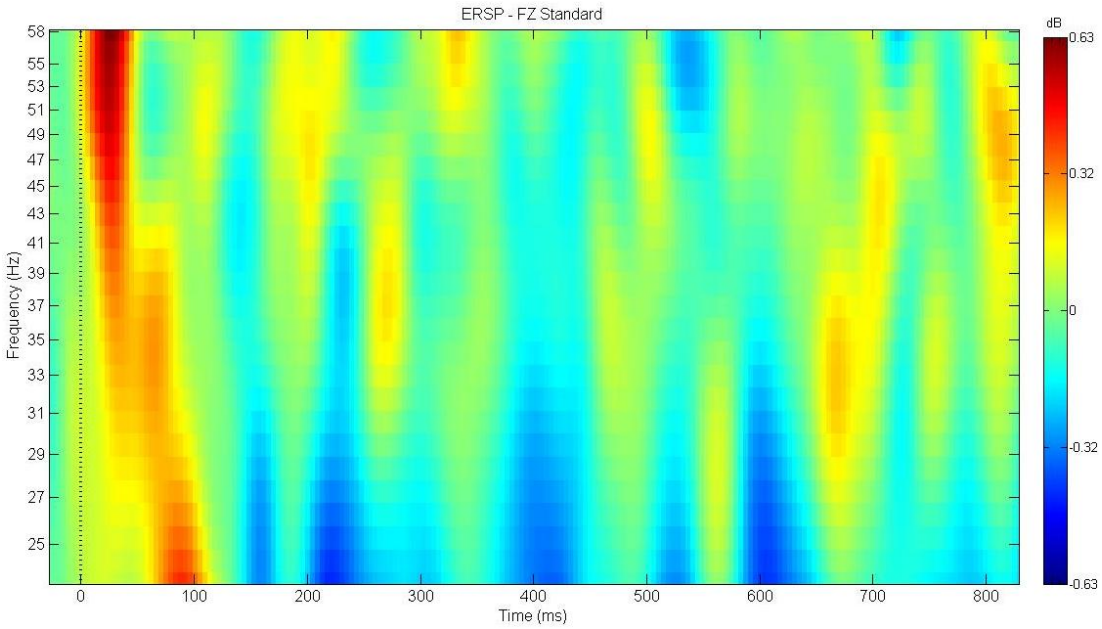

Figure 4-12 ERSP graph of Standard tone. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

The ITC graph for the standard stimulus is seen in figure 4-13, the higher values are distributed around the 100ms that is approximately the time of the peak for the N100 component.

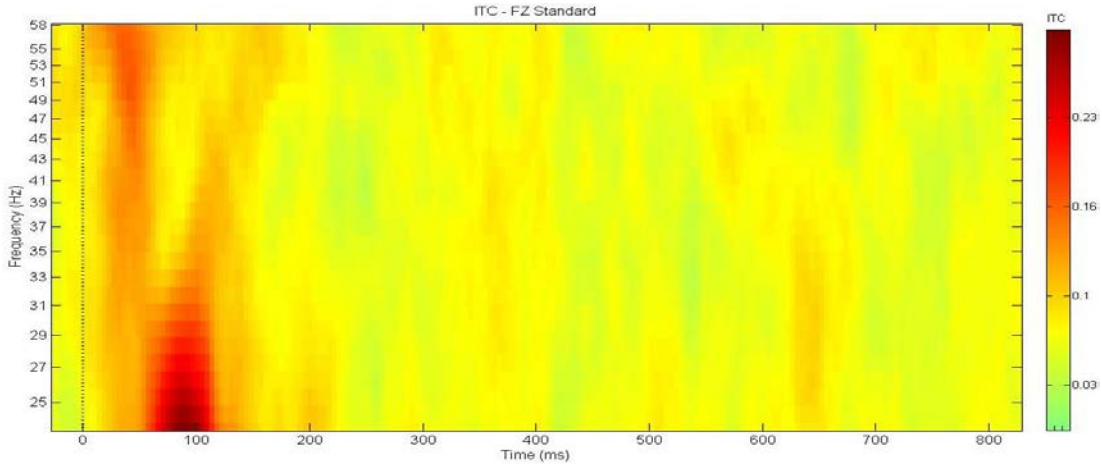

Figure 4-13 ITC graph of Standard tone. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

As seen in figure 4-14 the ERSP of the response to the duration deviant has a power peak in synchronisation with the N100 component and an increase in the power spectrum when the P200 arrives at its maximum. There is also an evident

decrease in power starting at approximately 115ms with a peak at 150ms and this diminution continues for 100ms.

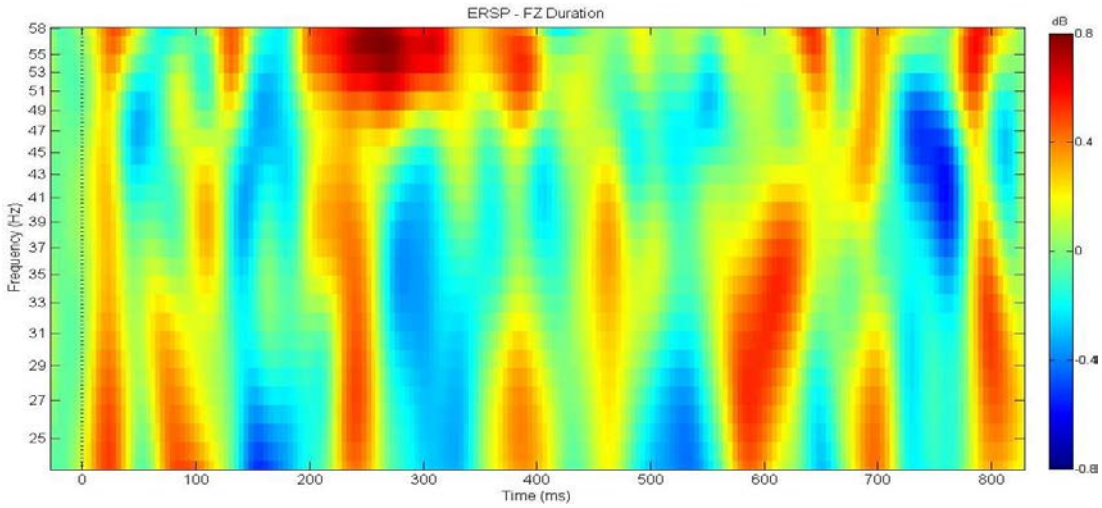

Figure 4-14 ERSP graph of duration deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

The ITC plot for the duration deviant in figure 4-15 demonstrates an increase in the evoked activity when the N100 arrives at its maximum.

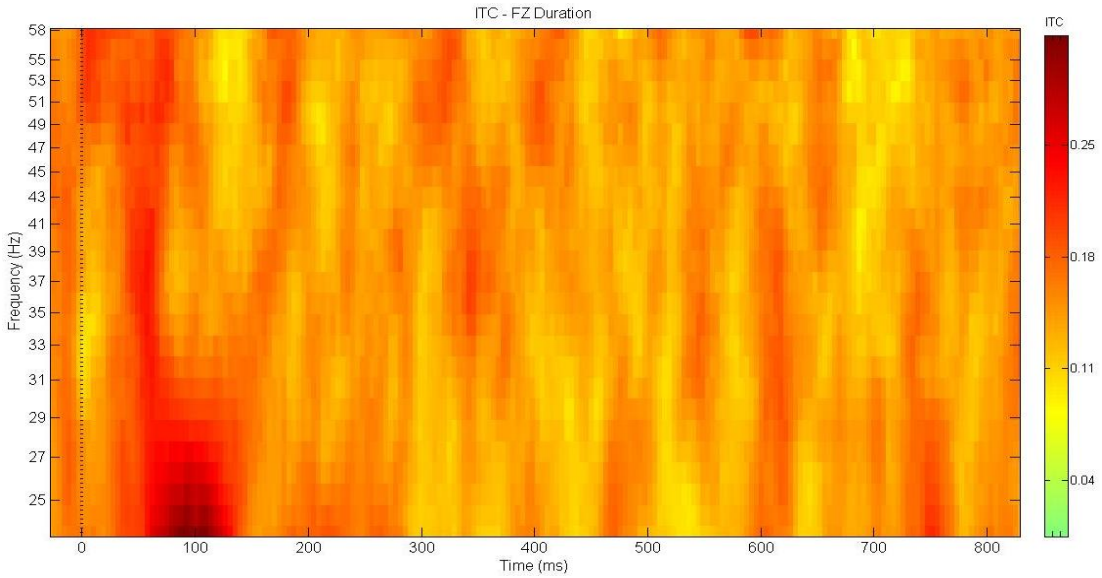

Figure 4-15 ITC graph of duration deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

In the ERSP plot of the frequency deviant although the power spectrum has large positive components at higher frequencies across the time interval, an increase around 100ms is noticeable.

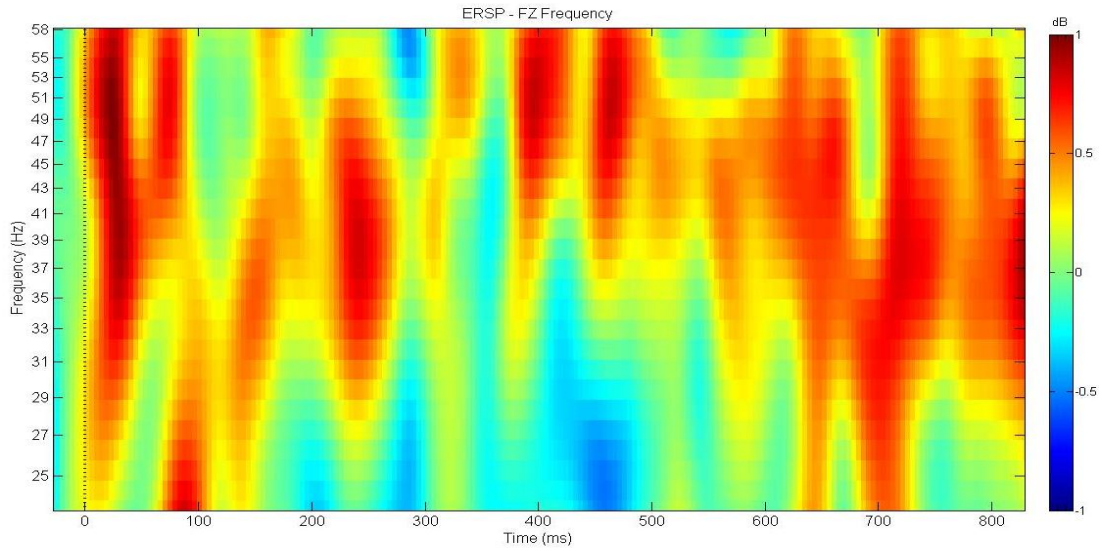

Figure 4-16 ERSP graph of frequency deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

Contrary to the ERSP in figure 4-26 the graph of the ITC from frequency deviant provides a stronger index of the activity 100ms after the onset of the stimulus.

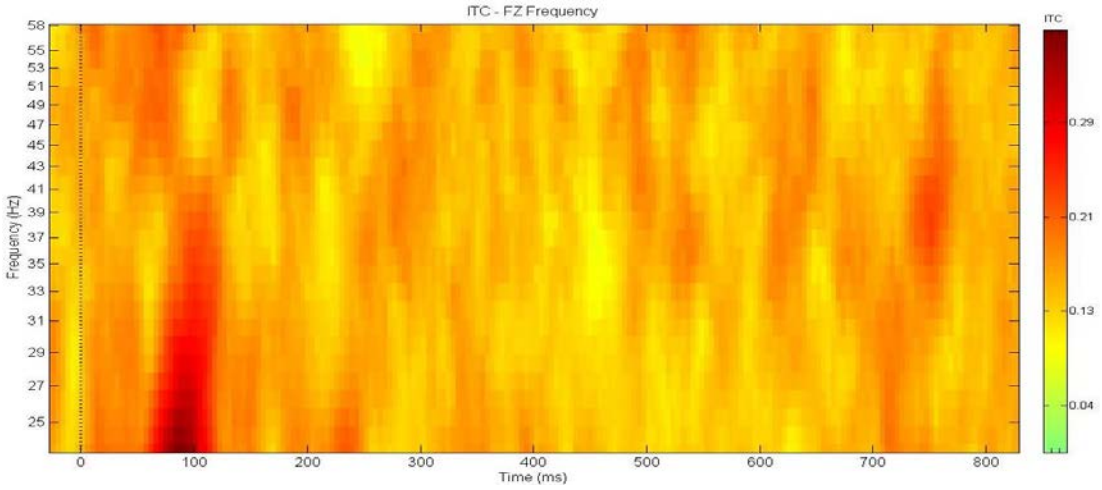

Figure 4-17 ITC graph of frequency deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

Similar to the ERSP from the frequency deviant, the volume deviant presents an equal distribution across time with an exception of a very high power value around 90ms.

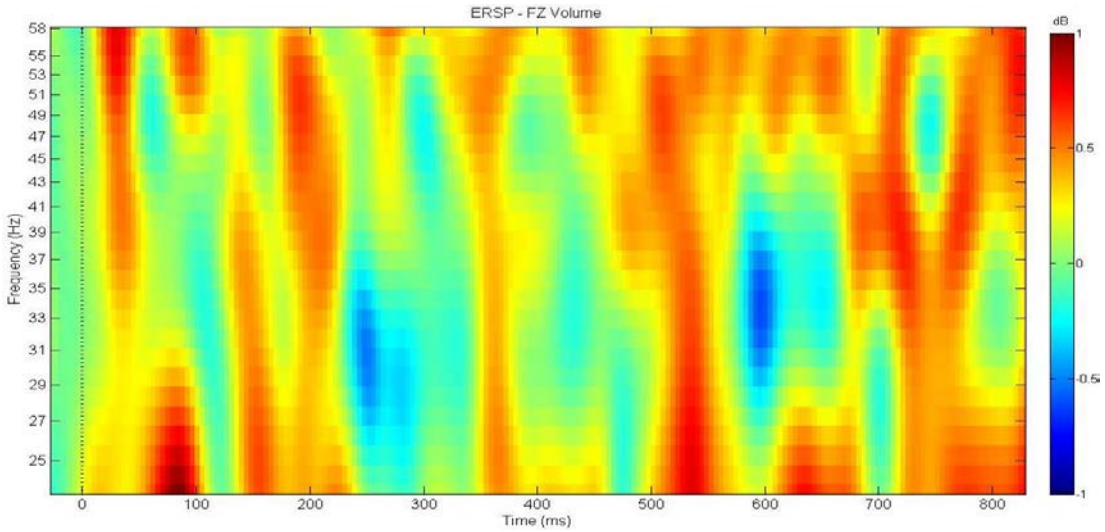

Figure 4-18 ERSP graph of volume deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

In contrast again to the volume ERSP, the ITC variation in accordance to the onset of the stimulus is very strong around 100ms.

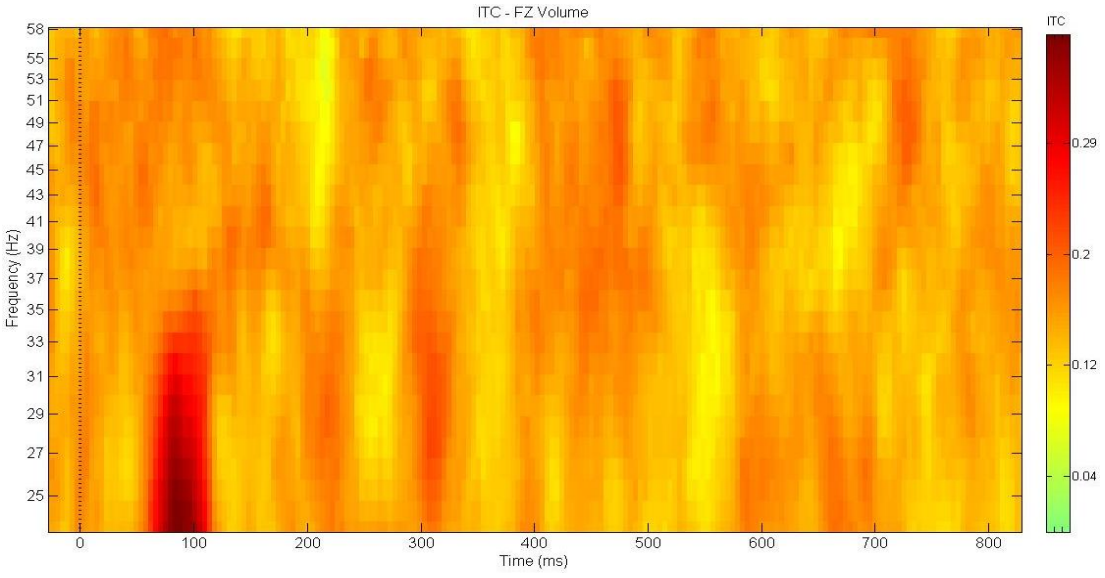

Figure 4-19 ITC graph of volume deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

The graph of the ERSP from the location deviant has an increased power spectrum from 50ms to 100ms and another increase is noticed from 180ms to 200ms that corresponds with the P200 peak.

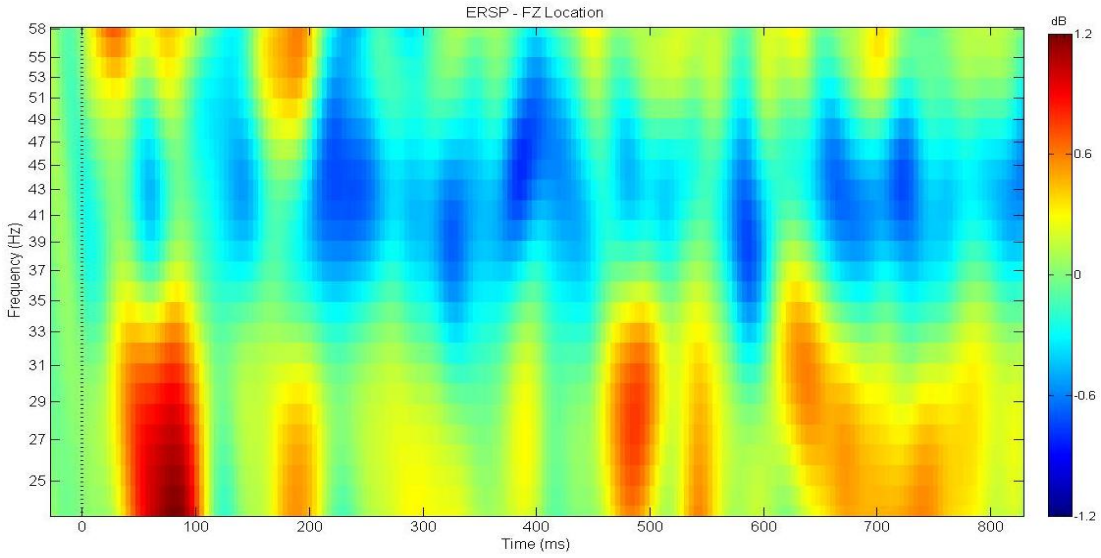

Figure 4-20 ERSP graph of location deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

The ITC graph for the location deviant can be viewed in the figure 4-21; the peak values are concentrated around 100ms, at roughly the peak of the N100 component.

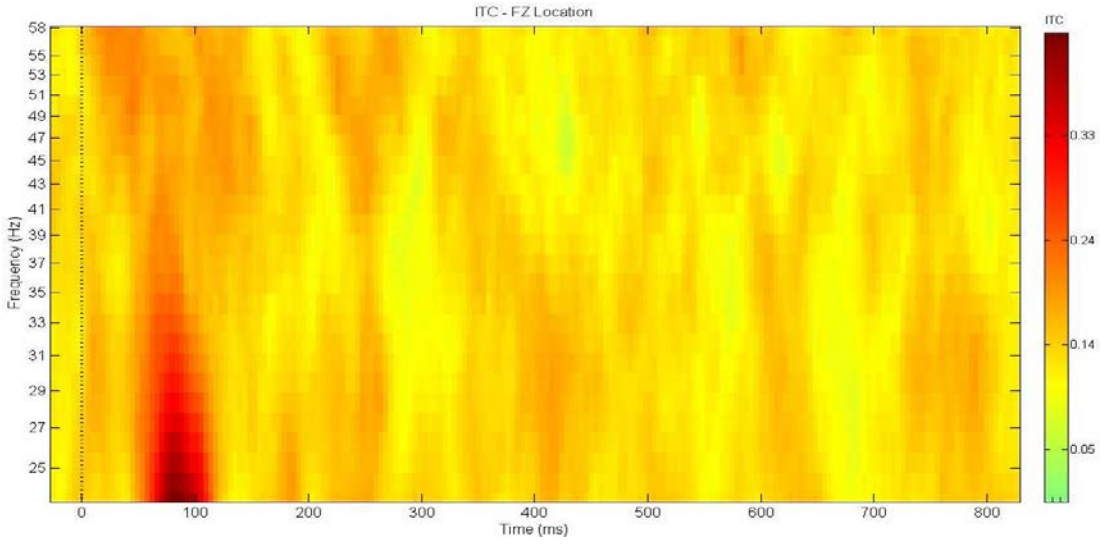

Figure 4-21 ITC graph of location deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

The silent gap deviant ERSP, presents an increased spectral distribution associated with the N100 component and spreads from low to higher frequencies evenly. After 100ms the power spectrum is considerably diminished over the rest of the time interval.

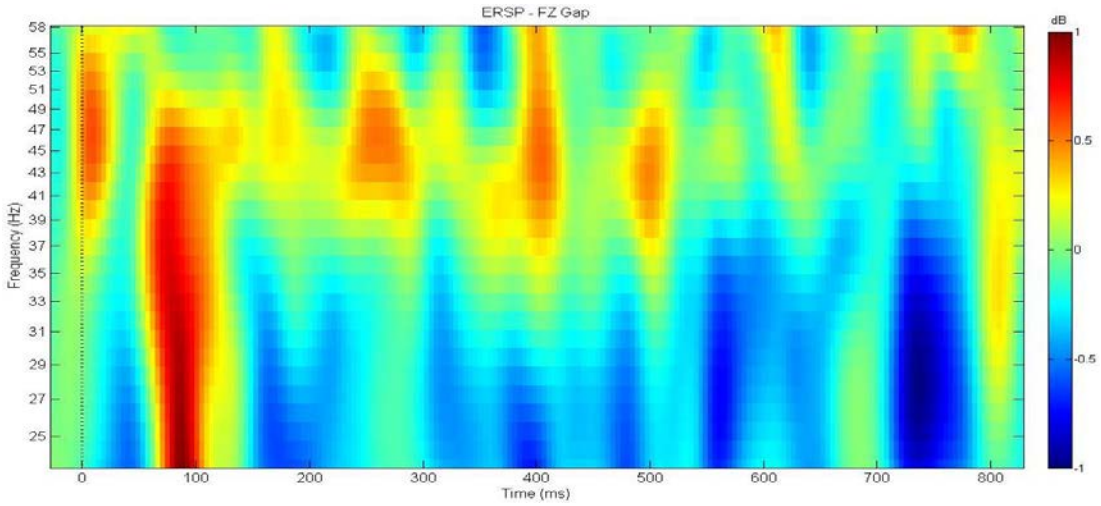

Figure 4-22 ERSP graph of silent gap deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates high neuronal activity and dark blue low neural activity.

The ITC of the silent gap indicates again a synchronisation in the activity that is time locked right before the peak of the N100 component in the time domain.

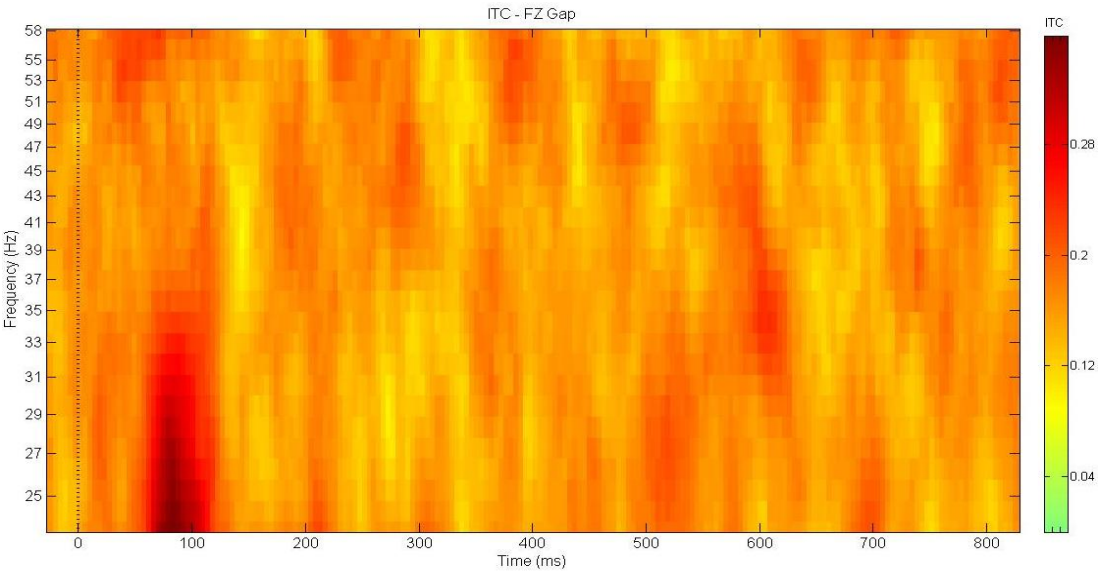

Figure 4-23 ITC graph of silent gap deviant grand average ERP. Raw data averaged at channel FZ, dark red indicates increased trial coherency and light green lower coherency.

As seen from the time-frequency plots there is a significant increase in neuronal activity around the peak value of the N100 component and this is also observed for the peak of the P200 component for the volume and location deviants. The activity is mainly concentrated between the frequency ranges of 24 Hz to 35 Hz for the deviant tones while the standard tone is distributed in an overall area comprised between 24 Hz to 60 Hz.

Chapter 5 Discussion

A great effort is carried out in the investigation of those factors that can identify and predict the onset of schizophrenia. A wide variety of methods and tools are being employed, new techniques are being developed to assess the cognitive, structural, and neurophysiological alterations during the first stages of the disorder. The ability to predict the prodromal phase will open up new routes in the treatment and prevention of the disorder.

Electrophysiology has a dominant role in the research and understanding of neural activities and their interactions. A very important technique engaged in neurophysiology involves event-related potentials, which provide a very precise exploration into the temporal distribution of the neural response when adequately stimulated. Several event-related potentials have been proposed as potential biomarkers in schizophrenia, and one of the most documented ERPs is the amplitude decrease in mismatch negativity. The mismatch negativity is a negative amplitude ERP component, elicited as a response to the violation of an established auditory pattern. Nevertheless there are indications proposing that MMN may not be specific to schizophrenia but an overlapping pathological feature of other psychiatric disorders that share common symptomatology (Kaur, et al., 2012; Todd, et al., 2012).

Mismatch negativity originates in the brain area that detects first the context variation in the auditory stimulus and this region has been located into the posterior superior temporal gyrus and Heschl's gyrus. Reduction of grey matter in Heschl's gyrus has been correlated to a reduction in MMN amplitude elicited by a frequency deviant in schizophrenic patients (Bodatsch, et al., 2011). The decreased amplitude of MMN in schizophrenia has been linked to poor verbal skills and reduced level of overall functioning (Light & Braff, 2005).

It has been noted that there is a significant reduction of the MMN amplitude on patients when the rare deviant differs in duration and frequency, with evidence suggesting that the duration MMN compared to the frequency MMN could predict the changeover from at-risk to fully developed schizophrenia in 2 years (Bodatsch, et al., 2011).

During this experimental study a protocol previously developed and tested by the same department was evaluated, based on the optimal oddball paradigm by Näätänen, et al., 2004, with the aim of developing a reliable procedure that can aid in the detection of the MMN in first stage patients. The need to carry the established protocol to the patients has imposed the requirement of a quicker, easier and more comfortable experimental setting. It has been observed in the current study that the participants fail to maintain an adequate level of concentration to their tasks at some point during the trial. Therefore there is an increased generation of artefacts as a result of excessive eye blinking, muscle tension, and deep breathing. This problem imposes a great limitation when schizophrenic patients are included in the experiment or individuals at risk of developing the disorder, because of their well-known susceptibility to irrational behaviour, their undistracted collaboration for the entire duration of a 90 minutes process may prove a challenging task. The proposed solution to this problem is the adoption of a portable wireless dry electrode EEG apparatus that can replace the bulky laboratory instrumentation.

For this purpose an EEG sensor acquired from NeuroSky that consists from an active electrode and a reference electrode that is placed on the earlobe was investigated. The acquired data is processed by the integrated ThinkGear chipset before being transmitted via Bluetooth to the computer. The data is stored in the computer for offline processing and analysis. Although the system is provided with EEG acquisition software, the characteristics of the protocol requires the synchronisation of the EEG data with the onset of the presented auditory stimulus in order to define the event related potentials. Based on this, custom made software was developed that operates under the MATLAB environment; the software interfaced successfully with the portable EEG system however there was a drawback concerning the parsing of the data payload, that will be addressed in the future.

The position of the referencing electrode of the portable EEG sensor imposed the only remarkable modification between the previous tested protocol by the Biomedical Engineering Department and the experimental setting of this study. Hence the data was acquired referenced to the average of the linked mastoids as an alternative to the nose reference that is chosen by the majority of the studies conducted on MMN.

The disadvantage of this selection is that in mastoids the MMN component reverses in polarity, while another ERP component the N2b that is generated in the same conditions as the MMN remains negative. Consequently the data from the mastoids could serve as a comparison in order to confirm that we actually measure the MMN component and not the N2b (Light, et al., 2010).

The advantage of this selection is that on the FZ electrode the ERP components of the N100 and P200 display very pronounced peaks with large amplitudes for the duration deviant (figure 4-2) and frequency deviant (figure 4-3). It was found that the N100 amplitude is a robust inherited characteristic and that a decrease in the N100 amplitude is present in patients affected of schizophrenia and is present in their unaffected relatives. Based on those findings the N100 amplitude is another candidate endophenotype for schizophrenia (Turetsky, et al., 2008).

A time frequency analysis was conducted on the grand averages for both the standard tone and the deviants. This analysis confirmed the previous experimental findings of the protocol, according to the results there is increased power spectrum in the gamma band 25 to 40Hz for all ERSP and the elevated power is also extended to higher range frequencies, which were removed during acquisition by the notch filter. In lower frequencies, in the range of 1 to 24 Hz, there are some interesting features present in the ERSP, however due to the use of wavelets in this study everything below 24 Hz is not observed. This activity is attributed to higher cognitive processes and is related to the status of awareness (Rieder, et al., 2011).

The EEG has a great advantage in obtaining neural activity with elevated temporal resolution, in the range of milliseconds. In contrast the spatial resolution is very restricted; to address this disadvantage techniques have been developed for source localisation. To understand better the structural and pathophysiological processes of the brain and to estimate the spatiotemporal progression of the MMN in order to identify variations between individuals, and between healthy and affected populations, a model of the underlying process must be developed. In this study an attempt was made to recognise the transient changes during the event related potentials by making use of the software EEGLAB and the plugin source information flow toolbox (SIFT). The SIFT models and visualises the information flow between the identified EEG sources that are obtained from an independent component

analysis (ICA). This SIFT process is based on multivariate autoregressive models that are extended to a collection of brain sources through the concept of Granger Causality, and with the use of a Fourier transform on the models, the transfer and spectral density is obtained, and the amount of phase coherence between two electrodes. The key aspect of SIFT is that it provides an estimate of connectivity between sources, offering a greater spatial localisation of the components (Delorme, et al., 2011). The primary goal in the SIFT analysis is to recognise which brain structures in a neuronal network are influencing other structures in some stage of their activity of information processing, this can give an estimate of the effective connectivity between brain areas. Analysis found that one area of the temporal cortex responds differently to frequency deviants among standards but did not respond in a different way when the sequence of the presentation was varied or the rate changed from slow to fast. There is also evidence that different parts of neural population are activated in the auditory cortex by different types of auditory stimulation (Näätänen, et al., 2007).

The limitation of this analysis, encountered also in this study, is that the ICA requires a large amount of data in order to adequately separate the sources, this requirement creates an insurmountable obstacle when the data is handled in conventional computers due to the great amount of processing power and physical memory requested. This restricted severely the amount of raw data given to the ICA, resulting in an inadequate source localisation, that penalised successively the SIFT analysis. Another limitation found in this study, is that for the generation of an accurate source localisation model is essential the acquisition of a high density scalp EEG data. As discussed earlier in this section a large number of electrodes form a substantial problem when the experiment involves psychotic individuals.

Conclusion

The combination of the single dry electrode together with the MMN protocol presents an exciting opportunity in the research of several pathologies. In this study a first attempt has been made in examining the potentials of the electrode for use as a diagnostic tool for schizophrenia onset. The mismatch negativity demonstrates an enormous potential as a candidate biomarker not only for schizophrenia but could also be applied to related disorders such as dipolar disorder and autism, or as a biomarker of cognition in infants.

The designated protocol for the MMN presents consistent findings in the time frequency domain as well as in the time domain even when in the data was referenced to the averaged mastoids. The evident appearance of the N100/P200 sensory gating mechanism in the present experiment and its possible application as a schizophrenia endophenotype is a noteworthy prospect that may requires further investigation.

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