Central Nervous System Organisation Following Traumatic Incomplete Spinal Cord Injury (*iSCI*):

A Longitudinal Clinical Study

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DEDICATION

To the Souls of My Late ***Parents*** Hajjah Amna Moh-Ahmed and Shaikh Mohamed Hassan Izzeldin,

*My **Wife** Hala Fadl I. Abdul-Gadir,*

*My lovely **Children** Noor, Sarah, Ahmed and Yasmin,*

My two lovely sisters and six supportive brothers,

*My extended **family** and many kind **friends**,*

… they all believed in me and my abilities at times when I briefly didn't'

Yours, Isam

To the ***love of my life*** from ***Western Sudan*** in the heart of Africa

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To All,

Sincerely and unequivocally,

Thank You.

ABSTRACT

Traumatic spinal cord injury (SCI) triggers pathophysiological consequences and secondary injuries that combine to determine the extent and final outcome of SCI. This study is aimed at examining a set of electrophysiological tests for their potential practicality and accuracy in assessing incomplete SCI and associated clinical presentation. These electrophysiological tests, which are less frequently used in clinical practice, included somatosensory evoked potential (SEP) methods improved with the addition of Dermatomal SEP (D-SEP) and analysis of event-related synchronisation (ERS) and desynchronisation (ERD), potentially providing more information about the ascending spinal tracts sub-serving examined sensory modalities. In a manner complementary to this sensory assessment, transcranial magnetic stimulation (TMS) of cerebral cortex was used to assess integrity and function of descending motor cortico-spinal tracts (CST) sub-serving signals from cortical pyramidal neurons to corresponding muscles above and below specified SCI levels. Coupled simultaneous electroencephalography (EEG) and surface electromyography (EMG) from corresponding muscles, Cortico-Muscular Coherence (CMC), was analysed to expose any EEG-EMG synchrony to highlight functional relationships of cerebral motor cortex and target muscles served. Information from sensory and motor spinal tract assessment of 9 SCI patients was charted alongside clinical assessment of neurological function using the American Spinal Injuries Association (ASIA) scale obtaining valid comparative electrophysiological clinical means of longitudinal follow up of any possible improvement or deterioration seen following SCI. Similar electrophysiological assessment was performed for 14 healthy volunteers (normal subjects used as control) obtaining normative data. The resulting data were collected for computational analysis and results obtained on the integrity and function of SCI lesions, as well as trends in electrophysiological measurements. These data also informed ways to predict possible recovery and outcome of SCI. The study faced technical challenges that stood out as limitations to the full potentials.? The electrophysiological tests carried out for SCI patients in acute hospital settings are extremely challenging, raising fundamental questions of how these tests could be brought into the acute clinical setting in the caring for SCI patients.

Individual electrophysiological tests included conventional SEP measurements. These were relatively straightforward as part of assessing SCI patients. These include improved SEP measures combined with electrophysiological means of assessing the integrity of peripheral nerves. D-SEPs are generally less reliable than standard mixed-nerve SEPs; however, with the improvements, D-SEP measurements brings useful anatomical detection of level information.

For both SEP and D-SEP measurements, reporting of abnormalities might have been enhanced by improving specificity of deciding abnormal results relating to amplitude and latency. Motor Evoked Potentials (MEP) parameters are a reliable electrophysiological measure of motor function, and are used in concordance with the clinical Asia Impairment Scale scores. MEP parameters have a potential relevance to functional outcomes such as hand function and walking following SCI. An area of improvement of MEP includes estimation of central conduction time (CCT) to allow detection of any peripheral nerve abnormality or degeneration affecting MEP measurements. However, the Cortico-Muscular Coherence (CMC) is not easy to obtain due to clinical factors and the use of medications in the context of SCI. CMC however has potential for future improved measures of muscle function in patients with recovering muscle power tested at time intervals. Overall, combining improved SEP and MEP measurements offer better information on sensory and motor function and pathways, respectively. This offers the best chance of obtaining reliable comprehensive information on injured spinal tracts and their recovery process. The study concluded that examined electrophysiological methods of assessing sensory and motor spinal tracts were sensitive, reproducible and accurate. They are reliable for use in assessing SCI patients in an acute hospital setting. This study focussed on the technical challenges facing these electrophysiological methods used in the clinical setting for accurately measurement of outcome or recovery following SCI.

CONTRIBUTION TO KNOWLEDGE

Dissemination of knowledge arising from work associated with this thesis:

(Published and presented with the permission and assistance of the supervisor):

It was a privilege for the author of this thesis to be able to disseminate the knowledge and experience gained from work directly related to this study to a wider audience in the years since the start of this research project in the following forms:

Abstracts published in Journals:

- **Izzeldin IM**, Allan DB & Conway BA. (2006). Use of somatosensory evoked potentials (SSEP) in assessing recovery of incomplete traumatic spinal cord injury (iSCI). Clinical Neurophysiology 117 (suppl. 1), S249.

Abstracts published in Conference Proceedings:

- Conway BA, **Izzeldin IM** & Allan DB. (2006). Somatosensory evoked potentials in spinal cord injury assessment. In Neuroscience Meeting Planner, Online edn, pp. 586.584/OO565. Society for Neurosciences, Annual Meeting, Atlanta, GA, USA.

- Lakany H, **Izzeldin, I**, Allan D, Conway B (2006). Optimal kernel time-frequency representation of EEG signals in patients with spinal cord injury. Society for Neuroscience, Annual Meeting, Atlanta, GA, USA.

- Lakany H, Conway B, **Izzeldin I** & Allan D. (2006). Sensorimotor Cortex Activation in Spinal Cord Injured Patients: Spatio-Temporal Evidence. In the Proceedings of the IEEE Medical Signal and Information Processing – MEDSIP 2006, CD-Rom MEDSIP2006_0036_paper.pdf. Glasgow, UK.

Reports published in Scientific Reports and Research Reviews:

- **Izzeldin IM**, Conway BA & Allan DB (2005). "Electrophysiological assessment of CNS recovery following incomplete spinal cord injury" - 1st Year Project Report, International Spinal Research Trust Research Network Meeting, Sept 2005, pp. 31. London.

- **Izzeldin IM**, Conway BA (2004). "Electrophysiological assessment of CNS organisation following incomplete spinal cord injury" - 2nd Year Project Report, International Spinal Research Trust. Research Network Meeting, 3-th Sept 2004, p45.

- **Izzeldin IM**, Conway BA (2003). "Electrophysiological assessment of CNS organisation following incomplete spinal cord injury". In The International Spinal

Research Trust Annual Research Review, ed. Cavanagh J, 2003, pp. 54-55. Spinal Research Trust, UK

Invited Lectures:

- '*Electrophysiological Assessment of CNS organisation following Traumatic Spinal Cord Injury*', International Spinal Research Trust (ISRT) Annual Scientific Network Meeting, London, UK – September 2003.

- *'Electrophysiology Assessment in Spinal Cord Injury'*, Specialist Registrars Annual Neurology Teaching Week-end, Coventry, UK – June 2005.

- '*Neuroregeneration and Neuroplasticity for Clinicians',* Nyala Teaching Hospital, Nyala, Southern Darfur, Sudan – December 2005.

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LIST OF ABBREVIATIONS

ADR	Autonomic Dys-reflexia
ANS	Autonomic nervous system
ASIA	American Spinal Injury Association
CMC	Cortico-muscular coherence
CMCT	Central Motor Conduction Time
CNS	Central nervous system
CST	Cortico-spinal tracts
D-SEP	Dermatomal SEP
DCSP	Dorsal column sensory pathways
EDC	Extensor Digitorum Cummunis
EEG	Electroencephalography & Electroencephalogram
EMG	Electromyography & Electromyogram
ERD	Event-related Desynchronisation
ERP	Event-related Potential
ERR	Event-related Response
ERS	Event-related Synchronisation
ERSP	Event-related Spectral Perturbations
IOM	Intra-operative monitoring
IPL	Inter-Peak Latecny
iSCI	Incomplete Spinal cord injury
ISRT	International Spinal Research Trust
MEP	Motor-evoked Potential
MRC	Medical Research Council
NCS	Nerve Conduction Studies
OEC	Olfactory Ensheathing Cells

PMCT	Peripheral Motor Conduction Time
PNS	Peripheral nervous system
PTN	Posterior tibial nerve
QENSIU	Queen Elizabeth National Spinal Injuries Unit, Glasgow, Scotland
RED	Russell Extrication Device
SCI	Spinal cord injury
SEP	Sensory Evoked Potentials
SSEP	Somato-Sensory evoked potentials
STT	Spino-thalamic tracts
TA	Tibilais Anterior
TMS	Trans-cranial magnetic stimulation

1. Introduction

1.1 Rationale of this Research Project

This electrophysiological prospective **longitudinal follow up study** with parallel clinical assessment is designed to investigate the potentials of electrophysiological methods in assessing the integrity and function of residual central nervous system following incomplete traumatic spinal cord injury (SCI). **Currently** available clinical therapeutic management options are aimed at preserving SCI lesions, initiating suitable rehabilitation programmes to facilitate any possible neurological improvement. However as early as onset of SCI, while efforts are directed towards resuscitation and maintenance of vital signs and organ functions, treating clinicians SCI patients, carers and families are all occupied by a much complex question of recovery.

The need for **prediction** of the possible outcome of SCI becomes increasingly vital as SCI patients are moving away from the acute phase. However, currently there is no known way of precisely predicting recovery potentials and outcome of SCI other than information gathered from clinical assessment, protocols, SCI centres and cumulative experience treating SCI patients. **Clinical methods** assessing physical neurological status and functional deficits following SCI are in wide use in hospitals and research purposes. However, these clinical methods are understandably subjective, inter-ratter dependent, lack robust and reliable reproducibility and do not suit SCI patients in acute clinical hospital settings such as altered levels of consciousness pain or use of immobilisation devices. There is a desperate need for improving methods of assessing central pathways of spinal cord in different types of SCI at various levels. In a sense, assessment methods need to go beyond the limited accuracy that is characteristic of current classification methods which are designed for clinical are purposes.

On the other hand, the **electrophysiological methods** are objective, accurate, reproducible and potentially suitable for use in acute hospital settings for SCI patients who otherwise might not tolerate and cooperate with detailed clinical examinations. Therefore, the electrophysiological assessment methods have the potential for detecting subtle changes in spinal cord function that are otherwise sub-clinical and are therefore **undetectable on clinical neurological examination methods alone**. Furthermore, electrophysiological methods are also potentially capable of addressing the fundamental question of predicting outcome of SCI and any possible neurological recovery and functional improvement gained from any given SCI lesion. Beside the massive benefit of adjusting expectations patients and their families for the modified future following

SCI, prediction of outcome enables clinicians planning the therapy any suitable rehabilitation programmes.

Therefore, this **study is designed to look** at (*assess and examine*) the potential of a few known though less frequently used electrophysiological methods for their potentials as accurate methods of assessing *integrity* and *function* of the residual spinal cord central nervous system tissues following SCI. This would eventually enable clinicians and researchers to **objectively measure** benefits SCI patients might be getting from existing therapy and rehabilitation programmes or any potential future interventions that might be available in future, respectively. The finding of an accurate outcome measure is vital as clinical trials are likely to be made available for SCI patients in the near future. These trials would be interested in assessing **recovery and outcome** of SCI both on the currently used conventional therapeutic and rehabilitation methods as well as any **novel therapeutic interventions** that might be made available in the near future.

1.2 Limitations

Several practical and theoretical difficulties were encountered in pursuing this study with the specified longitudinal follow-up design, the clinical assessment protocols and complex electrophysiological methods described. The difficulties and challenges, which are detailed under *Limitations* and in the *Methods chapter*, constantly stretched the abilities of the research team and the tested the patience of subjects volunteering for participation in this study both from healthy individuals and patients with SCI. These difficulties and challenges are therefore stood out as limitations that affected the realisation of the full potentials and ambitious vision of this research project at its outset and possibly affected its final outcome and drawn conclusions. These factors are outlined below in order of importance under specific areas encountered:

1.3 Study Design, Protocols and Clinical Setting:

- The electrophysiology tests used in this study were *not previously applied* in the same extensive manner in clinical settings, repeating the whole test protocols over a relatively long follow up period with reproducibility.

- This study was performed in *hospital setting for a complex group of patients with incomplete SCI*, most frequently in *acute high dependency or intensive care settings*.

- This study's *testing combination and protocols* performed in acute clinical settings in a hospital caring for complex group of SCI patients raised many technical and logistic challenges. SCI Patients were significantly diverse.

- The follow up period for purpose of *longitudinal nature of this study was relatively long* considering the average inpatient time spent in the spinal unit by SCI patients. For

instance, patients with incomplete SCI are usually discharged early to enable more independent life style. This meant that some patients with incomplete SCI were discharged home before the time for performing the 'retest' sets has come.

- *Busy time schedules for Clinical and Rehabilitation programmes* which made it very difficult and sometimes impossible to reserve or dedicate a time slot with the SCI patients for the purposes of undergoing various electrophysiological experiments.

- *Clinical management of SCI patients by all means has to continue unaltered* by this research project. When test sessions coincided with patients' clinical rehabilitation or social activities, tests were cancelled and rescheduled not to alter or affect any of the patients' therapy routines or recreation programmes.

1.4 Low Numbers of Participating SCI Patients:

Many of the above factors were frequently intermixed and co-worked in a combination contributing to having less numbers of SCI patients volunteering for participation in this study. The same factors affected the numbers of the SCI patients being successfully tested initially and retested when the follow up periods have elapsed. Similar factors also reduced the number of the healthy volunteers participating in this study largely to concept proof the validity of the tests as well as formation of the normative data.

1.5 Technical and Scientific Aspects:

The principles and related literature underpinning this ambitious research project, as well as its experimental work, result extraction, analysis and conclusions span three major subject areas of electrophysiological techniques including SEP and D-SEP, the related ERS and ERD measurements, TMS used for MEP calculations and finally the use of CMC from coupled EEG and EMG recordings. This widened the scope of the scientific and technical aspects of this research project into variable contrast areas.

1.6 Two Working Sites:

The Department of Bioengineering of the University of Strathclyde, where the work of this research project is housed and administered, is located in the city centre of Glasgow. Meanwhile the QENSIU, where recruitment of SCI patients and their subsequent clinical assessment, electrophysiological testing and further follow up, is housed within premises of the Southern General Hospital which is located around few miles off the centre. This necessitated extensive communication and frequent visits to augment presence and efficacy of the team at both sites, with challenges include:

- **Transport** between two sites of personnel, equipment and very rarely volunteers and patients.
- **Equipment shift** involved dismantling, packing, safe transfer and resetting the tests at the other site.
- **Personnel-involved** was mainly limited to the author of this study.
- **Time-involved** in transport and equipment shift between two sites.

1.7 Coordination and Communication:

The operation and progress of this research project involved extensive and continuous communication between all teams at the two sites involved in this research project. The role of the author of this thesis was vital in coordinating and communicating the university's research team and hospital's clinical team, in addition to frequent visits of the author to QENSIU for recruitment, clinical assessment, electrophysiological tests, follow up and communication with the SCI patients' population.

1.8 Information Technology and Technical Support Staff:

With no dedicated technical or support staff for this research project, the author of this thesis filled in performing every task needed at all times, occasionally supported by the university's technical and support personnel and facilities and teams at QENSIU.

1.9 Equipment:

Some purchases for firmware and software equipment were slowed down or hampered by limited funding. However, solutions were eventually found and put in place for this research project to continue moving forward as intended though with a slower pace.

1.10 Loss of Recorded Data:

In the process of mobilizing equipment and machines, an external hard drive containing recorded data dropped to the floor and consequently stopped working. Time and effort were invested to extract and restore a large amount of the data, however some data was 'corrupt' and not suitable for use and some was permanently lost in the process. This event had implications on the analysis of some data sets and subsequently for drawing conclusions for some of the SCI patients.

1.11 Time:

Time allocation given for this research project was to be completed in 36-months, and results to be reported back to the funding body, The International Spinal Research Trust (ISRT). This time allocation, given the described difficulties and challenges, was not long enough to enable more sufficient longitudinal follow up, observations and comments, results and conclusions gathered from this research project. The main constraint was related to the limited time and capacity to recruit many more healthy subjects to create a baseline of normative data. Similarly, it was not possible to recruit originally desired number of SCI patients especially for the 'retest' as the time window for effective longitudinal follow-up was closing.

1.12 Funding:

Money allocation did not allow expansion of time or capacity beyond the limits shown above. This limited the study to merely answering the questions raised at the time of securing the funding of this research project.

1.13 Conclusions:

This research project with study aims and design, protocols and methods as discussed in the appropriate sections, faced difficulties and challenges standing as limitations, which are described above. Nevertheless, this research project achieved the proof of original concepts, validated electrophysiological testing methods, answered some tough technical questions and therefore opened real windows of opportunities. The hope is that eventually this study's tested electrophysiological concepts, design, technical and clinical protocols and eventual results and findings would be extended much more widely carrying real chances of expanding this subject area of scientific research into assessing, monitoring and predicting outcome of SCI lesions.

2. Literature Review

2.1 Introduction

The clinical entity designated spinal cord injury (SCI) could potentially be caused by a multiplicity of processes ranging from trauma to other acquired or congenital diseases eventually leading to disruption of the fibres sub-serving spinal cord functions. For the purpose of this study, other causes of SCI of non-traumatic origin will not be discussed any further, and in the subsequent sections only traumatic SCI will be further discussed and detailed.

In the process of spinal cord injury (SCI), a previously healthy or relatively healthy spinal cord tissue is subjected to a direct or indirect injury leading to a primary spinal cord lesion. This is usually followed over time by multiplicity of secondary pathological consequences, many systemic and immunological changes that lead to secondary spinal cord injuries. Primary lesion is the direct result of trauma and secondary SCI results from consequences of primary SCI (Sekhon and Fehlings, 2001). The combined damage caused by primary spinal cord lesion and results of secondary injuries shape the neurological deficits resulting from any specific SCI. The loss of function largely depends on the severity of the primary lesion and the extent of the triggered secondary injures; however, is also determined by level of the SCI along the spine (Dumont et al., 2002). Spinal cord injury (SCI) can arise from developmental growth failure, congenital, vascular, aggressive malignant tumours and trauma. However, for the purposes of this study only traumatic SCI lesions will be discussed. The relatively less complicated model of traumatic SCI is related to the relatively simple nature of initial SCI lesion and subsequent secondary injuries, pathological consequences, immune and systemic changes that follows SCI. Traumatic SCI model enables linear observation of recovery outcome including prediction of recovery informed by knowledge of natural history of CNS healing processes. The model also enables documentation of any such neurological improvement using clinical assessment tools extracting lessons from the recovery processes being observed following traumatic SCI. It is essential to understand the structure and function of the healthy spinal cord to be able to capture the clinical and electrophysiological manifestation of SCI lesions governed by the location (level) and extent (severity) of each individual SCI lesion.

In this chapter, details of the ***Structure and Function of Healthy Spinal Cord*** will be presented followed by an overview of ***Traumatic SCI***. The chapter will then focus on

Recovery following Traumatic SCI and includes *Rehabilitation, Neuro-Plasticity and Neuro-Regeneration*, and the *Obstacles* facing the recovery process. Finally, this chapter concludes with a ***Clinical Assessment*** followed by the ***Electrophysiological Tests or Measurements***, giving the rationale for the work that this thesis will cover.

2.2 Anatomy and Function of Healthy Spinal Cord

Spinal Cord is a Caudal Structure of CNS (continuous):

Spinal cord is the *caudal most part* of the central nervous system (CNS) retaining vital neural connections and being anatomically *continuous* with the medulla oblongata and brainstem. The spinal cord *extends* from the level of the foramen magnum of the skull all the way downwards to the level of the first or second lumbar vertebra (Gray, 1981; Martini2001).

Vertebrae and Vertebral Column (containment & protection):

The *vertebrae* are the bony building blocks which form the vertebral column which contains and protects the delicately structured spinal cord. There are 33 vertebrae of which 24 are articulating presacral (7 Cervical, 12 Thoracic and 5 Lumbar) and 9 fused (5 Sacral and 4 Coccygeal) vertebrae.

The spinal cord extends within the vertebral column from the transition of the brainstem at the base of the skull, where the spinal cord leaves the foramen magnum, to its termination at the level of first or second lumbar vertebrae. The bony vertebral column protects the spinal cord contained within its cavity. However, this protection is variable resulting in some segments being much more vulnerable than others such as the mobile and highly flexible cervical region (Gray, 1981; Martini2001).

Cerebrospinal Fluid & Meninges *(anchor, immune, vascular function & nourish):*

The CNS part of spinal cord is *nourished* and *balanced* for vascular volume and pressure by the cerebrospinal fluid (CSF) surrounding the spinal cord which is *cushioned* by the CSF within the protective bony structure of the vertebral column. The spinal cord is sheathed in the same three meningeal layers that cover the brain and continuous with them. These layers are organised in sequence as an outer tough Dura, middle vascular Arachnoid and inner Pia which is closely adherent to the spinal cord surface. A series of Lateral Denticulate ligaments emanate from Pial folds anchoring the spinal cord to the Dura. With its membrane proliferation, vascular diffusion

barrier (blood brain barrier) and its bony protection, the CNS and its components represent a highly isolated and protected organ system with complex haemostatic control mechanisms.

Vascular Structure and Blood Supply:

The brain and spinal cord require approximately 20% of the resting circulation output due to high metabolic demands. The arterial blood supply of the spinal cord in the upper cervical region is derived from the *Anterior Spinal Artery* and *Posterior Spinal Artery*, which are branches of the *Vertebral Arteries*. The *paired anterior spinal arteries* join at the level of the medulla to form a *single artery*, which lies in the anterior median fissure of the spinal cord. While the *posterior spinal arteries remain paired* and form a chain of anastomosis over the posterior aspect of the spinal cord. The anterior and posterior spinal arteries are connected by *Arterial Vasocorona*, an anastomosis formed at the surface of the spinal cord. This guarantees an uninterrupted blood supply along the entire length of the spinal cord. Most of the lower levels of anterior and posterior aspects of the spinal cord are supplied by approximately 6 to 8 pairs of Radicular Arteries branching from Cervical, Trunk, Inter-costal and Iliac Arteries. These radicular arteries form an anastomotic network in connection with the anterior and posterior spinal arteries which become narrower below the cervical levels.

Segmental Structure (spinal cord regions or divisions of longitudinal organisation**):**

The spinal cord is divided into four regions these are Cervical, Thoracic, Lumbar and Sacral regions. Some spinal regions can be visually distinguished such as the Cervical Enlargement extending (between C3 and T1 spinal segments) and Lumbar Enlargement (extending between L1 and S2 spinal segments), both giving out multiple nerve to supply limb girdles. Example can be seen (https://sites.google.com/a/wisc.edu/neuroradiology/anatomy/spine/slide-1) with spinal regions or divisions, segments and spinal nerves, with complementary vertebrae giving spinal level. A section of the spinal cord that gives rise to one spinal nerve is called a segment. Therefore, spinal segments can be defined by bilateral dorsal roots entering and ventral roots exiting the spinal cord and forming a pair of spinal nerves one innervating structures on the left side, the other innervating structures on the right side of the body. Thus, in total there are 31 segments defined by 31 pairs of spinal nerves exiting the spinal cord including 8 Cervical (C1-8), 12 Thoracic (T1-12), 5 Lumbar (L1-5), 5 Sacral (S1-5) and 1 Coccygeal cord. Embryologically, each spinal nerve is composed of fibres which are related to the region of muscles (myotomes) and skin areas (dermatomes) developing from one somite or from the same embryological segment (Gray1981; Martini2001).

Structure of Individual Segments *(spinal cord segments & horizontal organisation)*:

On a transverse section, the structure of the spinal cord is characterised by peripheral white matter and inner grey matter with a CSF filled central canal surrounded by a single cell neurological epithelial layer called the Ependyma. The centrally located grey matter, shaped like the letter H or 'butterfly,' contains the nerve cell bodies. The grey matter varies in shape and density according to the level of the spinal cord which vary with the amount of ascending and descending tracts of nerve fibres and spinal segment reception field innervation zones. The right and left sides of the two wings of the butterfly are connected across the midline by a Posterior (Dorsal) Grey Commissure and Ventral (Anterior) White Commissure. The structure of individual spinal cord segment seen as transverse section can be seen in (www.apparalyzed.com). The neuronal cell bodies of the grey matter are divided into four main columns: Dorsal Horn, Intermediate Column, Lateral Horn and Ventral Column.

Dorsal Roots (*sensory****):***

Sensory signals from skin, skeletal muscles and joints are relayed to the spinal cord by nerve cells located in the dorsal root ganglia and defined as Primary Sensory dorsal root ganglion cells where axons give origin to dorsal root fibres transmitting the sensory information from peripherally located receptors (Gray1981; Martini2001). Each ascending dorsal nerve root axon bifurcates before reaching the spinal cord into ascending and descending branches which enter several segments below and above own segment. The dorsal root fibres input from innervation zones known as dermatomes that show *discrete body areas* relating to each spinal nerve.

The dorsal root fibres entering the cord are grouped into two divisions namely Lateral and Medial. The ***Lateral Division*** contains most of the unmyelinated and small myelinated axons carrying Pain and Temperature information and terminates in the Rexed Laminae I, II and IV of the grey matter. The ***Medial Division*** consists mainly of myelinated axons conducting sensory fibres mediating skin, muscles and joints sensations, entering posterior column and ascending to terminate in Ipsilateral nucleus gracilis and cuneatus levelled with the medulla oblongata. Axons of ***first order*** *sensory neurons*, within the dorsal root ganglion synapse at the medulla oblongata, and synapse with the medulla oblongata, and synapse with ***second order*** *sensory neurons*, within gracilis and cuneatus.

On entering the spinal cord, all root nerve fibres send collaterals to different Rexed Lamina. Axons entering the sacral region of the spinal cord are found in the dorsal column near the midline (close to central CSF canal) comprising *Fasciculus Gracilis*, also known as **Tract of Goll** and

carries information about fine touch, vibration and conscious proprioception to lower brainstem. The axons which enter the spinal cord at higher levels are added to lateral positions comprising the *Fasciulus Cuneatus*, also known as **Tract of Burdach** transmitting sensory information from the arms. The understanding of this orderly representation, termed ***Somatotopic Representation***, is vital in understanding the clinical presentation of spinal cord disorders. For instance, a *syringomyelia* exerting pressure *from within* affecting centre of the spinal cord and an *extrinsic tumour* pressing spinal fibres *at the periphery* tend to present neurological symptoms progressively ascending and descending, respectively (Gray, 1981; Martini, 2001).

Ventral Roots (*motor****):***

The ventral root nerve fibres are the axons of ***Motor and Visceral Efferent*** fibres and they emerge from poorly defined *Ventral Lateral Sulcus* as *Ventral Rootlets*. The Ventral Rootlets from discrete spinal cord segments unite to form the Ventral Root, which contain efferent motor nerve axons from ***Motor and Visceral*** Neurons. The visceral or autonomic neurons send pre-ganglionic fibres to innervate the visceral organs. The ***alpha*** *motor nerve axons* innervate the ***Extrafusal*** Muscle Fibres, while the smaller somatic ***gamma*** *motor neuron axons* innervate the ***Intrafusal*** Muscle Fibres located within muscle spindles. These fibre branches join the dorsal root fibres distal to dorsal root ganglion to form spinal nerve.

Spinal Nerves (*structural arrangement & distribution****):***

The 31 paired spinal nerves innervate discrete body areas and gives a segmental pattern to muscle and cutaneous innervation zones. The Dorsal (sensory) nerve roots enter the vertebral column through the Inter-vertebral foramen at vertebral bodies corresponding to the spinal segment, while the Ventral (motor) nerve roots leave the same way in the opposite direction.

All 31 emerging mixed (motor and sensory) spinal nerves, exit below their corresponding vertebrae except the first one. In the cervical region, there are 8 cervical nerves exiting above each of C1 down to C7 corresponding vertebra, whereas C8 spinal nerve exits below C7 vertebrae and above the first thoracic vertebrae, below this each subsequent spinal nerve leaves below corresponding vertebra. In the thoracic and upper lumbar regions, the difference between vertebrae and cord level are three segments, therefore root filaments of the spinal cord segments travel longer distance to reach corresponding inter-vertebral foramen from which spinal nerves eventually emerge. Lumbosacral roots are collectively known as the cauda equine as previously shown and discussed.

The individual spinal nerves contain fibres collecting sensory information from the distribution of the Dorsal Primary Ramus and supplying skin and muscle motor input supplied by Ventral Primary Ramus.

Dermatomes and Corresponding Nerve Supply of the Skin:

A dermatome is an area of the skin supplied by nerve fibre originating from a single dorsal nerve root. Dermatomes are named according to spinal nerve which supplies them. Dermatomes form bands around trunk but in limbs its organisation is complex because dermatomes were 'pulled-out' by limb budding during early embryological development. There are currently well-defined maps for the clinically most important dermatomes (Figure 2.01). Some charts demarcate these dermatomes have been identified by injection of local anaesthetics into single dorsal root ganglia which show bands of hypoalgesia (anaesthesia) continuous longitudinally from periphery up and back to spine.

Dermatomal maps derived from clinical observations of Herpes Zoster lesions distributions and surgical roots sections show discontinuous pattens (Lee et al., 2008). In clinical practice, this could be seen and used as an overall representation of the Key Sensory Points as depicted in the ASIA Impairment Scale, shown in (Figure 2.01).

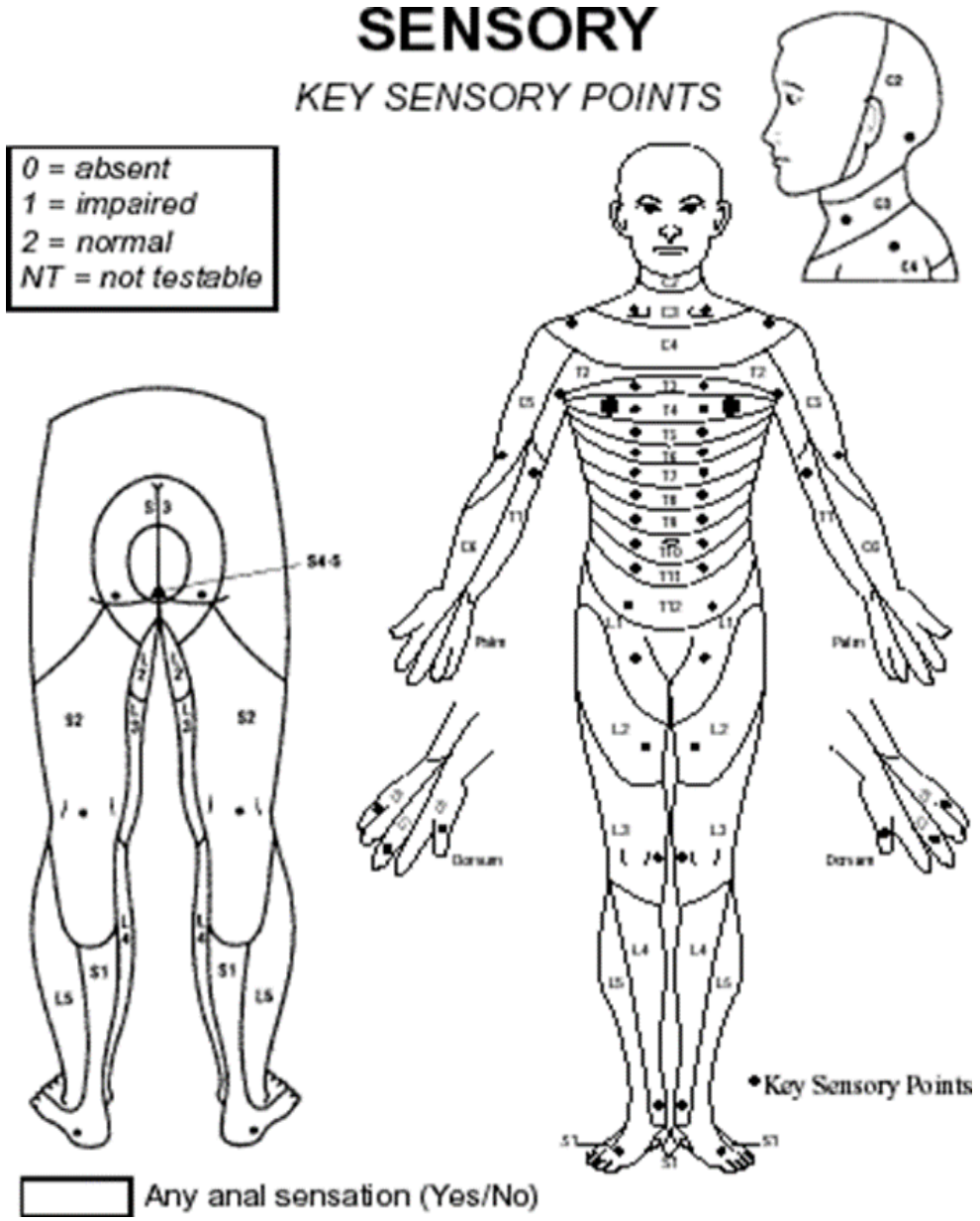


Figure 2.01: Shows the key segmental distribution of cutaneous nerves of the upper and lower extremities in anterior, and for the lower limb, the anterior and posterior views (this figure is used with permission from ASIA, the American Spinal Injury Association).

Innervation from one dermatomal segment to another, overlaps considerably especially for touch sensation much more than pain. Therefore, if there is a loss of afferent nerve function of one spinal nerve, the skin sensation from the dermatome it supplies is not completely lost due to overlap from the adjacent spinal nerves taking place however there will be a reduced sensitivity. It is observed that dermatomes travel from the back anteriorly to chest and abdomen and dip inferiorly, which can be seen clearly in the schematic representation by ASIA Impairment Scales, which are the main depictions used throughout this study.

Based on the figures described above, the clinically most important dermatomes in terms of SCI are also shown in the list below:

- **C2 and C3** - Posterior head and neck
- **C4 and T2** - Adjacent to each other in the upper thorax
- **T4 or T5** - Nipple
- **T10** – Umbilicus
- **Upper extremity:**
  - **C5** - Anterior shoulder
  - **C6** - Thumb
  - **C7** - Index and middle fingers
  - **C7 and C8** - Ring finger
  - **C8** - Little finger
  - **T1** - Inner forearm
  - **T2** - Upper inner arm
  - **T2 and T3** - Axilla

- **Lower extremity:**
  - **L1** - Anterior upper-inner thigh
  - **L2** - Anterior upper thigh
  - **L3** - Knee
  - **L4** - Medial malleolus
  - **L5** - Dorsum of foot
  - **L5** - Toes 1-3
  - **S1** - Toes 4 and 5; lateral malleolus
  -
- **S3 and Cx1** - Anus

Segmental Functional Structure ***(****horizontal & vertical neural connections****):***

At individual segments, the spinal cord *distributes* cortico-bulbar and cortico-spinal motor tracts to target organs or effectors (e.g. muscles and glands). Simultaneously, the spinal cord *collects* sensory information from somatic and visceral afferent fibres to be relayed to higher sensory neural centres in brainstem, diencephalic (thalamic) connections and eventually the sensory cortex (Gray, 1981; Martini, 2001). Also reflex output has segmental and propriospinal circuits.

Grey Matter:

At individual spinal cord segments, the neuronal cell-bodies of grey matte are divided into four main columns: Dorsal Horn, Intermediate Column, Lateral Horn and Ventral Horn Column. The ***Dorsal Horn*** is found at all spinal cord levels containing sensory nuclei which receive and process the incoming somatosensory information which are then relayed through the ascending projections to midbrain and diencephalon. The ***Intermediate Column*** and ***Lateral Horn*** comprise Autonomic neurons innervating visceral and pelvic organs. The ***Ventral Horn*** contains motor neurons that innervate the skeletal muscles. The nerve cells in the spinal cord grey matter

are multipolar with variable morphology and are mostly Golgi Type I and Golgi Type II cells. Golgi type I possess long axons that passes out of the grey matter into ventral spinal roots or white matter tracts, while axons and dendrites of the Golgi type II neuronal cells are largely confined to action in connecting the neighbouring grey matter neurons. Grey matter spinal neurons at each individual segment divided into: Root Cells, Column or Tract Cells and Propriospinal Cells.

The ***Root Cells*** of the Ventral and Lateral grey matter contribute axons to Ventral (anterior) roots of spinal nerves. Ventral roots are *Somatic Efferent Root Neurons* innervating skeletal muscles and *Visceral Efferent Root Neurons* (alternatively called pre-ganglionic autonomic axons) innervating various autonomic ganglia.

The ***Column or Tract Cells*** and their axonal processes are mainly located in the dorsal grey horn and are entirely confined to the CNS. The axons of the Column Cells form Longitudinal Ascending Tracts which travels proximally in the white columns and terminates on the neurons of the brainstem, cerebellum and diencephalon. The *Inter-segmental Association Column* Cells are a population of the column cells, which send their axons up and down to terminate in other grey matter neurons not far from their origin. Likewise, the *Intra- segmental Association Column Cells* are column cells with axons terminating within segment they are originating from. *The Commissure Association Column Cells* are column cells that send their axons across the midline to terminate in the grey matter close to their origin on the opposite side.

Interneurons from approximately 90% of spinal grey matter neurons have axons which do not leave the spinal cord. Some of the fibres are possibly associative and connective fibres and are found around the spinal cord grey matter collectively been named the Fasiculus Proprius or Propriospinal Tract or Archispinothalamic Tract.

White Matter:

At individual spinal cord segments, the white matter surrounds the grey matter, containing myelinated and unmyelinated nerve fibres, and conducting the neural signals (information) up (ascending) and down (descending) the spinal cord. At individual segment levels, the ascending and descending white mater (or tracts) are divided into dorsal (or posterior) column (or Funiculus), Lateral Column and Ventral (Anterior) Column. The Anterior White Commissure locates in the centre of the spinal cord and contains the crossing nerve fibres of *Spino-thalamic Tracts, Spino-cerebellar Tracts* and *Anterior Cortico-Spinal Tracts.*

Long Spinal Tracts *(fibre layout, organisational links & intricate function)**:***

Three general types of nerve fibres could be distinguished in the spinal cord white matter which are:

1. ***Long Ascending Nerve Fibres*** which are (sensory) originating as column cells that are found in all columns and makes synaptic connections to neurons in brainstem, cerebellum and dorsal thalamus.
2. ***Long Descending Nerve Fibres*** which are (motor) originating from the cerebral cortex and various brainstem nuclei, found only in the lateral and anterior columns, making synaptic connections within different Rexed Layers of the spinal grey matter.
3. ***Short Inter-connecting Nerve Fibres*** which interconnect various spinal cord levels exemplified by the fibres responsible for coordination of spinal flexor reflexes.

To identify the terms often used, bundles of axons found in white matter include: **funiculus** describing large nerve fibre group within posterior funiculus, **fasciculus** as described above, **tract** sharing same origin, destination and course having similar functions, and **pathway** referring to entire neuronal circuit responsible for a specific function, usually including all nuclei and tracts associated with that specific function.

Of tracts longitudinally coursing the spinal cord, these are relevant to clinical practice:

Lateral Cortico-Spinal Tract (*Lateral CST****):***

with axons from neurons in motor cortex projecting through interneurons directly to motor neurons at segmental levels.

Anterior Cortico-Spinal Tracts (*Anterior CST****):***

with direct pyramidal tract fibres varying in size inversely with lateral CST as the main CST

Spino-Thalamic Tracts:

Formed by sensory fibres sub-serving pain & temperature (and crude touch), joining after entering each segment through dorsal roots, synapse and the second order neuron cross to the opposite side.

Posterior (Dorsal) Column:

Formed by sensory fibres sub-serving position vibration and discriminative touch, joining after entering through dorsal roots directly without synapse nor crossing over (remains ipsi- lateral).

Ascending Spinal Tracts:

Ascending spinal tracts ***transmit sensory information*** from peripheral *Receptors* to higher centres within the CNS and ultimately support sensory processing in the brain. The nerve fibres that comprise the ascending spinal tracts start and emerge from ***First Order Neuron*** traversing through the dorsal roots. The ascending *Gracile Fasciculus* and *Cuneate Fasciculus* from the ***Dorsal Column*** sometimes termed the ***Dorsal Funiculus***. These fibres carry sensory information serving Tactile, Two-point Discrimination of simultaneously applied pressure, Vibration, Position, and Movement Sense and Conscious Proprioception. In the ***Lateral Column***, sometimes termed the ***Lateral Funiculus***, the Neospinothalamic Tract or Lateral Spinothalamic Tract (STT) is located more anteriorly and laterally. Lateral STT caries information mediating Pain, Temperature and Crude Touch sensations from Somatic and Visceral structures. Laterally to the STT, the dorsal and ventral Spino-Cerebellar Tracts carry unconscious proprioception information from muscles and joints to the cerebellum. In the ventral column (funiculus), four prominent tracts are found: 1. ***Paleo-Spino-Thalamic Tract*** (or Anterior Spino-Thalamic Tract) carrying pain, temperature and touch-associated information to brainstem nuclei and to the diencephalon. 2. The ***Spino- Olivary Tract***, carrying information on changes in muscle tension from Golgi Tendon Organs. The muscle spindles with muscle afferents carry information on changes in muscle length, both serving proprioception. 3. ***Spino-Reticular Tract*** and 4. ***Spino-Tectal Tract***. There are inter-segmental nerve fibres travelling several (2-4) segments, and located as a thin layer around grey matter, is known as ***Fasciculus Proprius***, Spino-Spinal or Archi-Spino- Thalamic Tract. It carries pain information to brainstem and diencephalon.

B. <u>Descending Spinal Tracts</u>: Descending spinal tracts carry neural information that is associated with ***maintenance of motor activities*** such as Posture, Balance, Muscle Tone and Reflex Activities including Visceral or Somatic reflexes. Descending spinal tracts originate from different cerebral cortical areas and from brainstem nuclei. The descending spinal tracts include Lateral Corticospinal Tracts (**Lateral CST**) and the Rubrospinal Tracts located in the lateral column (Lateral Funiculus) and these tracts carry information associated with ***Voluntary Movement***. Other Reticulospinal Tracts, Vestibulospinal Tracts and Anterior Cortico-spinal Tracts (**Anterior CST**) mediate ***Balance and Postural Movements***. Lissauer's Tract is wedged between the dorsal horn and the surface of the spinal cord and carry the descending fibres of the Dorsolateral Funiculus (DLF) regulating Incoming Pain Sensation at the spinal level and intersegmental fibres.

Lateral Cortico-Spinal Tracts – Lateral CST (major component of CST):

Lateral CST (also called Crossed Pyramidal Tract or Lateral Cerebro-Spinal Fasciculus) is the largest part of CST extending throughout the full length of spine. On a cross section, it appears an oval area anterior to the posterior column and medial to the posterior spino- cerebellar tract. Fibres forming lateral CST arise from neuronal cells of the motor cerebral cortex on the contralateral side, descend ipsi-laterally, cross-over at the level of the medulla oblongata and further descend part of the Lateral Funiculus of the spine. The fibres of the Lateral CST provide fine motor control of the limbs and digits.

Anterior Cortico-Spinal Tracts – Anterior CST:

Anterior CST (also called Direct Pyramidal Tract, Anterior Cerebro-Spinal Fasciculus Ventral CST or Medial CST), is small bundle and varies in size inversely with lateral CST as the main CST. On a cross section, it is seen lying close to the Anterior Median Fissure, only presentative of upper parts of spine, gradually diminishing in size till it ends at the middle of the thoracic region. Fibres forming anterior CST arise from neuronal cells of the motor cerebral cortex on **same** side. As running down the spine, anterior CST crosses in succession though Anterior White Commissure to opposite side and ends in the anterior column directly or indirectly forming branches around and with anterior horn cell motor neurons. Anterior CST conducts impulses from motor neuronal cells of the pre-central gyrus to motor centres of the spinal cord. A few of the anterior CST fibres pass to the lateral CST ipsilaterally and to the grey matter at the posterior column (Martini, 2001).

Autonomic Function of the Spinal Cord:

Autonomic Function is served by *Pre-ganglionic Sympathetic* (cholinergic) outflow fibres, which descend and synapse to cell bodies in the Lateral Cell Columns or **Inter-medio-lateral Columns** of segments T1 and T2 (possibly T3). From these columns, axons (mostly use norepinephrine) pass ventrally and contribute to the formation of the Ventral (Motor) Roots from which ***Sympathetic Fibres*** exit between T1 and T2 and reach end organ ganglia. The *Sacral Pre-ganglionic Para-Sympathetic* neurons are located in Inter-medio-lateral Cells or Nuclei along segments between S2 and S4. These cholinergic ***Para-Sympathetic Fibres*** exit and synapse at end-organ ganglia, with post-ganglionic cholinergic fibres controlling defecation, urine and erection.

Neural Control of the Urinary Bladder:

The urogenital tract is innervated by 3 groups of peripheral nerves: ***Sacral Parasympathetic***, with preganglionic neurons in the Intermedio-lateral grey matter, run through pelvic nerves and are excitatory to the urinary bladder. ***Lumbar Sympathetic*** have preganglionic neurons in the grey matter of the Rostral Lumbar Spine. The Thoraco-lumbar sympathetic pathways come from the lumbo-sacral sympathetic ganglia and inhibit the detrusor muscle (beta mediated) and excite base of the bladder and urethra (alpha mediated). Most importantly, these fibres modulate the function of the parasympathetic ganglia through inhibition (alpha-2) and facilitation (alpha-1). ***Sacral Somatic Efferent*** nerves originate from a circumscribed lateral ventral horn region called Onuf (or Onufrowicz) nucleus and innervate the striated muscles of the urethra. Alpha and C afferent pathways initiate micturition. Alpha fibres exhibit graded response to passive distension, while C fibres have a much higher threshold, being activated by inflammation and noxious stimuli. Fullness of the bladder is detected by receptors in the bladder wall, which send impulses through the sacral parasympathetic nerves. Impulses are relayed to cortex through spinothalamic tracts. Sensation that micturition is imminent arises from receptors at the trigone and ascends in dorsal column. Urine is stored when the external urethral sphincter muscle (somatic) and the internal urethral sphincter muscle (sympathetic) are contracted as well as the detrusor muscle and sacral para-sympathetic are inhibited through sympathetic mediation (Furness, 2006).

Innervation of Sexual Organs:

The ***Parasympathetic*** fibres arising from Sacral spine innervate erectile tissue of the penis and clitoris, smooth muscle and glandular tissue in the prostate, urethra, seminal vesicles, vagina and uterus, as well as blood vessels and secretory epithelia in various genital and pelvic structures.

Autonomy of the Spinal Cord *(a CNS auto-centre or generator)*:

The spinal cord possesses a degree of neural autonomy distinct from brain and crucial for its integrity and function. Autonomous spinal circuits offer the spinal cord an innate capability as a neuronal generator mediating robust spinal functions, largely including spinal reflexes that are vital in initiating and regulating posture and motion. Autonomy involves spinal control of autonomic functions including control of bowel and bladder sphincters, sexual functions and mediation and regulation of heart rate and blood pressure (Martini, 2001).

Conclusions:

The description of anatomy and function of healthy spinal cord, as depicted in above sections, shows the complexity of the integration properties of the spinal cord. It also begins to highlight the possible complexity and multiplicity of clinical manifestations which might be seen in situations associated with disease or injury sustained by the spinal cord. The subsequent sections will detail abnormalities of spinal cord function caused by traumatic SCI.

2.3 Traumatic Spinal Cord Injury

2.3.1 Introduction

Traumatic SCI is a chronic multi-system condition triggered by acute injury to a relatively localised area of the spinal cord. The location nature and characteristics of the initial trauma ultimately define the *severity* of SCI. The consequences of SCI lesion, range of possible secondary effects, including immunological and chemical processes that develop over time, all combine to contribute to the deleterious patho-physiological changes that eventually determine *extent* and *functional impact* of any specific SCI lesion (Sekhon and Fehlings, 2001). The combined factors described above collectively determine the residual integrity and function of the spinal neural tissue and eventually shape the possible final prognosis and patient's outcome. Acute traumatic SCI care is critically important in managing SCI patients. This includes much improved clinical approach suspecting, recognising and investigating acute and multiple-injured patients with potential SCI. Leading to efficient and safe management of individual patients with potentially variable SCI (Bernhard et al., 2005). An important factor in correctly planning the management of SCI patients is the sound understanding of various pathological processes taking place following a primary SCI lesion as well as changes thereafter. The combined effects of primary lesion added to the secondary injuries disrupt previously healthy (likely normal) spinal cord anatomy and physiology. The resulting pathological processes eventually define outcomes of SCI lesions and neurological consequences evident on clinical assessment (Jackson et al., 2004). It is vital to understand structure and function of the healthy spinal cord in order to manage patients with disordered spinal cord function in the context of SCI. Depending on extent (severity) and location (level) of each individual SCI lesion, the clinical presentation of each individual patient with SCI needs to be accurately determined. The presented motor, sensory or autonomic neurological symptoms or signs enable clinicians caring for SCI patients to obtain and read vital clues about the severity and level of the SCI lesion underlying the given clinical presentation. This clinical correlation is based on symptoms and signs which inform of the presence or absence of various aspects of normal spinal cord functions.

2.3.2 Epidemiology and Characteristics of Traumatic SCI

Incidence and Prevalence of Traumatic SCI:

Traumatic SCI has been part of the human experience for as long as humans existed. In the past, SCI would be considered a fatal condition and the victim would only have a short life course post injury (Jackson et al., 2004). However, in its current challenging multisystem clinical entity, prognosis of SCI has certainly evolved much over the years. This was possibly brought about by

increasing knowledge of nature of SCI, aetiology, clinical management, science and research. It was arguably perceived that developments in caring for SCI have been paralleled by growing prevalence of SCI especially in industrial and developed countries. It has been estimated that the annual incidence of SCI worldwide is 15-40 cases per million (WHO, 2011, 2013). In the United States of America (USA) alone, where the incidence and prevalence is higher than the rest of the developed world, there are approximately 10,000 new cases of SCI per year (National Spinal Cord Injury Statistical Center (NSCISC), 2010). However, it is much more likely that a process of better awareness, improved detection and recognition of SCI has taken place. There are also much better clinical classifications, care definitions, provision of rehabilitation, and access to assistive technology that aid in giving SCI patients the best possible outcomes post injuries and near normal life expectancy. It has been suggested that life expectancy of some SCI patients depends on ability to walk and the need for catheterisation (Shavelle et al., 2014). In the UK and Ireland, it is estimated that around 1,000 individuals sustain SCI each year, and around 50,000 people live with paralysis. The majority of patients are young adults and approximately 80% of those living with SCI are male. This picture has been changing recently because of emerging information that SCI is a problem for older people due to falls, as in (Golob et al., 2008). In the Physical Medicine and Rehabilitation Board Review, the chapter on SCI indicated that there are 30–60 new injuries per million populations per year in the USA. This review thus reports an ***incidence*** (new cases of SCI) of 10,000 per year, and the ***prevalence*** (total number of existing cases of SCI) to be 200,000–250,000. Based on this review, with 2012 mid-year population estimate for the UK of 63.7 million according to Office for National Statistics, it would be possible to calculate the UK incidence of SCI.

The calculated UK figures of SCI incidence would be approximately over 1,900 to 3,800 per year. For Scotland, with the 2012 mid-year population estimate of 5.3 million according to the Office for National Statistics, the incidence of SCI would be 159–318 cases per year. However, the National Health Service (NHS) for England in a publication from 2013 under Group D Trauma (D13 Spinal Cord Injury) of the Clinical Reference Group, highlighted that the incidence of SCI in the UK is estimated at between 12 and 16 per million of population. This would give an estimated incidence of around 764 to around 1,019 cases per year, with the majority of cases been caused by trauma. The NHS report has indicated that spinal cord injury services are provided by eight Spinal Cord Injury Centres (SCICs) in England.

Scotland is served by the Queen Elizabeth National Spinal Injuries Unit (QENSIU) based at the Southern General Hospital placed at the South-side of Glasgow city. An example of SCI load in Scotland is illustrated by the Annual Report from 2014-2015 showing 290 new outpatients and 164 new admissions, of which 120 with neurological deficits and 44 with non-neurological injuries. Older ages (70-79 years) feature higher involvement in SCI with falls causing 58% while RTA only 24% of total admissions with SCI. (Queen Elizabeth National Spinal Injuries Unit, 2015). It has been suggested by some researchers that numbers of SCI represent significant under reporting. Injuries which might not be recorded in statistics include SCI cases where patients recover promptly or soon after initial injury and remain with little or no neurological deficit. The category of less counted or missed SCI patients also includes individuals who sustained spinal category of neurological symptoms or problems secondary to trauma not classified as SCI (Winter and Knight, 2005).

Causes of Traumatic SCI:

SCI is caused by events that vary from one community to another and based on circumstances surrounding the involved people. The causes reported to have been associated with SCI depend on the study population. Motor vehicle accidents or road traffic accidents (RTA) came top in the causation with around 46% as in (Figure 2.02). However, there is reduction in mortality attributable to spinal injury and marked reduction in SCI due to motor vehicle accidents, which might be related to improvements in motor vehicle safety and traffic regulations. The elderly population is more likely to suffer SCI, especially by blunt injury at multiple levels influenced by anatomical, physiological and mechanism of injury (Oliver et al., 2-12).

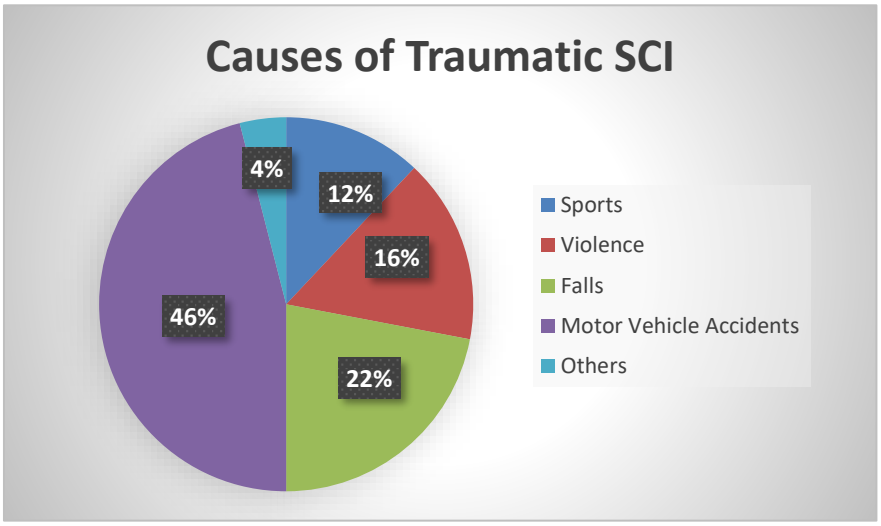
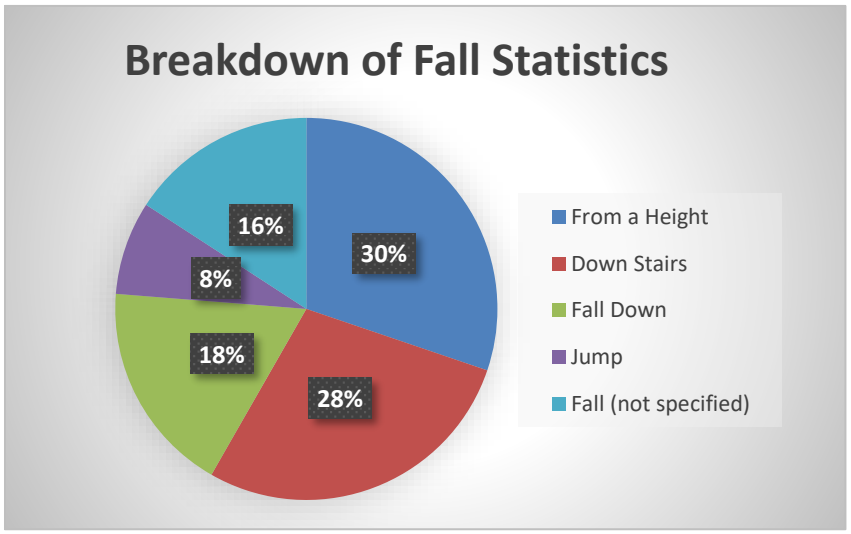


Figure 2:02: This bi-chart shows typical distribution of the Causes of Traumatic SCI, with the leading cause related to motor vehicle accidents. (Field work produced from data analysis for this thesis).

The use of seat belts reduces up to 60% of potential SCI in motor vehicle accidents and seat belt with airbag combined reduces up to 80% of potential SCI. Falls follow accounting to around 22%, violence around 16% and injuries related to various sports around 12%. It seems the majority of individuals involved in SCI are males who account for around 80% of all patients (Chen et al., 1997). Studies reinforce causes of SCI as motor vehicle collision, violence, falls and sport-related injuries, respectively. Other studies reiterate the same findings with motor vehicle accidents (40%), falls (over 25%), violence (15%), sports and recreational injuries (8%). It was highlighted that SCI after the age of 65-years is most likely caused by a fall, and a breakdown of reported falls and sports injuries that lead to SCI is shown in (Figures 2:03 **(A) & (B)**).

A.



B.

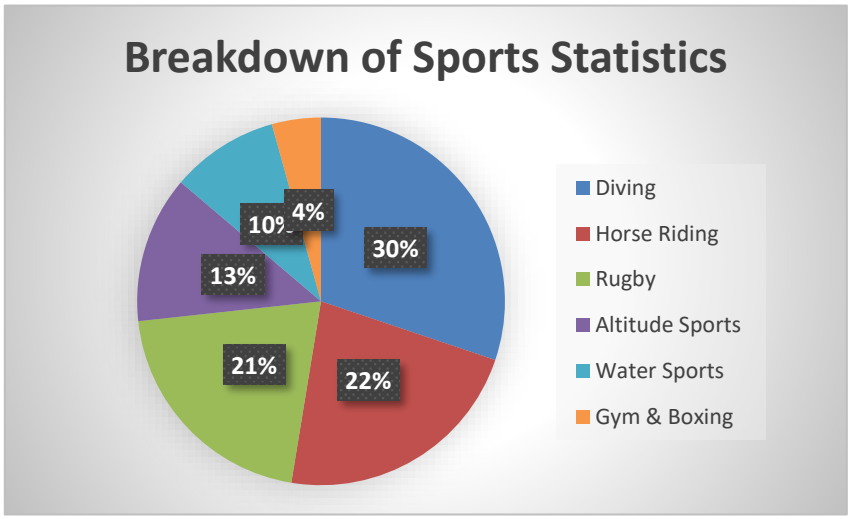


Figure 2:03: These two bi-charts show breakdown of the statistics of falls (A) and sports (B) causing SCI. (Field work produced from data analysis for this thesis).

Acts of violence causing SCI are gunshots and knife wounds. In common, gunshots and knife wounds caused by stabbing are deep penetrating injuries capable of reaching the spinal cord. However, in the UK, injuries of this form are less common. Sports that repeatedly present the risk of SCI include impact sports such as rugby and sports where falls and collisions are likely, skiing, diving in shallow water and horse riding. Furthermore, alcohol use has been highlighted as a factor in one out of every four spinal cord injuries. Industrial accidents or occupational injuries were reported to cause some SCI. Causes of SCI are similar in industrial countries. In the process of managing Traumatic SCI, the MRI plays an important diagnostic role in management. This includes the revealing any extrinsic compression on the spinal cord and any disruption of the discs and ligaments which might cause mechanical instability. Furthermore, the MRI points to any intramedullary (intrinsic) changes, weather primary from the initial trauma or secondary injury, as well as any long-term post-traumatic gliosis or cystic changes (Figure 2.04).

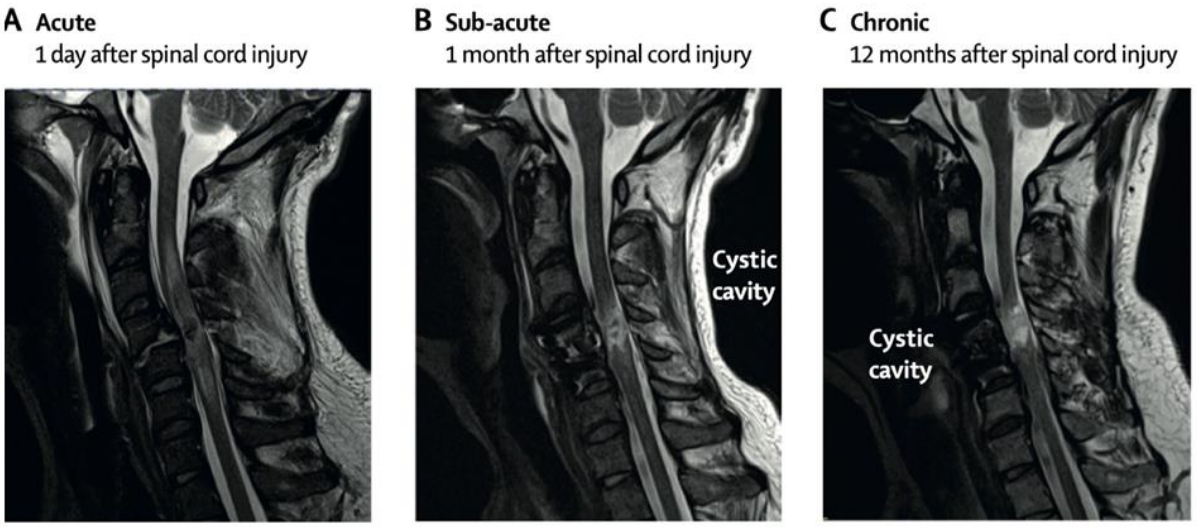


Figure 2:04: The importance of MRI in detailing all levels injury, to the musculoskeletal (disc, ligaments and bone) structures, and indication of further investigating any resulting instability. Assessed longitudinal, the MRI shows evolution of the spinal cord lesion, with fibrosis and cystic formation, in a patient with SCI with clinical presentation of ASIA-A tetraplegia. (*Source* – with permission from Freund, et al., 2019).

In high income countries legislations for safety has reduced the incidence of SCI by industrial accidents and RTA. Similarly, use of personal safety equipment in sports also reduced the potential risk of SCI. However, it seems that living circumstances and life style patterns shape the epidemiological aspects of SCI. In Taiwan, a large study of 1,586 new cases of SCI found out that the leading causes of SCI were traffic accidents and accidental falls not dissimilar to the West (Burns and O'Connell, 2012). However, the difference is that motorcycle collisions accounted for 62% of these traffic accidents. And because most of the motorcycle riders did not use helmet protections, head injury was the major associated injury of SCI in Taiwan (Chen et

al., 1997). In a study from Saudi Arabia, the frequency of traumatic SCI was found to be much higher in males in ages 16-30 years compared to females. In this study, out of 466 patients with traumatic SCI 80.1% were caused by motor vehicle accidents, possibly reflecting a specific local pattern (Al-Jadid, 2013). SCI carries a high morbidity and mortality in Zimbabwe, where it has been reported that in the past almost all SCI patients discharged from hospital die within one year. However, establishing a spinal unit close to 1998 had impact improving the quality of living and survival of individuals with SCI (Levy et al., 1998). A review of global studies of SCI epidemiology over two decades found out that the incidence rates vary greatly between the developed and developing countries, with 2-fold difference in the highest mortality in developing countries and that in the developed countries. Traffic accidents were leading cause of SCI in developed countries whereas falls were the leading cause in developing countries. However, it remained the same that male sex and ages 30-50 years are similar in being strong risk factors for having SCI. (Burns and O'Connell, 2012).

Age, Gender and Race influencing traumatic SC:

It is also noticeable that SCI is more prevalent in young individuals especially those younger than 30-years. Studies estimate that the majority of individuals with SCI are aged from mid to late teenage into the third and fourth decades of life. (Dincer et al., 1992). The frequency and distribution of SCI vary with age and gender, affecting younger males in the age group 15-39 years more than older females. Motor accidents affect younger patient while older patients are increasingly affected by falls. It had also been suggested that white individuals are more affected by SCI than the black in studied Western communities. The gender variation was 82% males and 18% females. The average age of individuals at the time of SCI was found to be 31.7 years, which has risen since 1990s to 34.8-years, while it has also been reported that 56% of SCI occur among persons in the age range of 16-30 years. The life expectancy of individuals suffering SCI has significantly improved with rehabilitation training and pharmacological interventions aimed at improving quality of living and maximising the potentials for clinical improvement (Houle and Tessler, 2003). Children aged 15-years and younger account for 4.5% while people older than 60-years account for 10% of SCI of which falls are by far the most common cause of SCI in the elderly followed by motor vehicle accidents. However, incidence of SCI in older people is steadily increasing over the years with the common cause being falls.

It has been suggested that clinical assessment of SCI in children in the context of ISCSCI may have poor utility under 4, poor precision of motor exam under 15 and poor sensory exams in under 5-year old children (Mulcahey et al., 2007).

Aging populations, Shifting Demographics and Current Ages of SCI Patients:

Falls overtake motor vehicles as a leading cause of SCI after age 45-years (NSCISC, 2013), indicating that causes of SCI may significantly vary in different age groups. The proportion of individuals with Tetraplegia increases markedly after the age of 45-years. Out of all injuries, Tetraplegia comprises two third of individuals above 60-year and 87% of those above 75 years. With aging populations, increasing in numbers of older age people at risk of falling, it is possibly inevitable that with time, there would be an eventual increase of age of SCI patients. A retrospective review of SCI patients treated in the USA in over a decade demonstrated a significant reduction in mortality due to SCI. There was a marked reduction in SCI due to motor vehicle accidents, due to improvements in road safety standards and traffic regulations. It was suggested that improved health care resources, possibly with improved longevity and aging, elderly individuals are more likely to suffer SCI, especially blunt injury and at multiple levels.

The types and seriousness of SCI in the elderly are possibly due to anatomical, physiological and mechanism-related reasons (Oliver et al., 2012). Life expectancy of persons with ASIA Impairment Scale D spinal cord injury depends strongly on the ability to walk and the need for catheterization (Shavelle et al., 2014). It is suggested that the characteristics and incidence of traumatic SCI might have been changing. With time, SCI might possibly be shifting from being a disease of young men injured in sports, vehicular accidents or as victims of violence to a disease of older men and women living with multiple medical problems having falls leading to traumatic SCI. It is also possible that the age shift of SCI individuals is boosted by increasing numbers of independently-living advancing-age individuals which increase risks of falls leading to much more serious injuries and potentially causing SCI. Age and co-morbidity were highlighted as the most important predictors of both psychological and physical functioning after more than one year post SCI, among other factors including type of injury especially associated traumatic brain injuries to the extremities (Khan et al., 2016). There is evidence suggesting that elderly populations have unfavourable outcome associated with certain types of spinal injuries (Golob et al., 2008). In this study, it has also been shown that isolated cervical spine fractures, with or without associated traumatic or spinal cord injuries, carries long term mortality. Nevertheless, some authors suggest that age was not predictor of motor functional outcome and therefore effective rehabilitation can be achieved in elderly patients with SCI and should be started as soon as possible. The same study however highlighted that admission motor FIM score, level and severity of injury, interval between onset of SCI and admission, psychological factors including anxiety/depression score and length of stay might predict functional outcomes of the

rehabilitation process (Abdul-Sattar, 2014).

Life-style, Socioeconomic Factors and Alcohol influencing Traumatic SCI:

In some reviews, the epidemiological data suggest that SCI has higher incidence in summer, which mostly take place in weekends and at night-time (Soopramanien, 1994). These additional aspects are explicable, at least partially by various social factors and lifestyle patterns that govern sports and recreational activities involved in the causation of SCI. The review goes on and shows close association between risk of SCI and number of indicators of social class which also have profound implications for rehabilitation. It has been observed that SCI patients have *fewer years of education* than their uninjured counterparts, are more likely to be *unemployed* than non-SCI patients and more likely to be single, separated, divorced or never been married. In addition, it has also been observed that post-injury marriages survive better than pre-injury marriages. As stated before, it has been highlighted that alcohol plays a role in almost 25% of SCI. In a USA report titled 'Facts and Figures at a Glance' by the National Spinal Cord Injury Statistical Center published in March 2013, it was seen that SCI due to sports decreased over time while SCI due to falls increased, partially might be due to increased elderly population especially in the West. SCI caused by violence peaked between 1990 and 1999 to 24.8% compared to only 13.3% prior to 1980 but eventually declined since 2010. In some instances, the age range of acute SCI patients averaged 14-89 years with a median age of 32. The male to female ratio of 4.5:1 indicated a lower number of the affected males compared to outcome other range of studies (Lenehan et al., 2012).

Industrial Accidents and Occupational Injuries causing Traumatic SCI:

In an analysis of the epidemiologic factors of acute SCI, it was found that accidents at work accounted for 29.3% of the patients presenting with acute SCI to hospitals in Canada (Ekong and Tator, 1985). In the remaining percentages, traffic accidents accounted for 34.4%, sports and recreational 15.4% and falls at home 9.8%. This study highlighted several important epidemiologic factors which could be used in developing programmes aimed at reducing the frequency of SCI. There was emphasis made on raising awareness among young persons of their risks as young automobile drivers and hazards of diving in shallow water. Similarly, awareness aimed at the middle-aged working in construction and elderly farmers exposed to working at height or on unstable vehicle could be improved.

Socio-economic Factors and Health Burden of Traumatic SCI:

As indicated in the above sections, traumatic SCI primarily affects individuals, particularly young males at peak of their productive and working lives. The WHO in its First Global Report on Disability, has indicated that the global proportion of people with disabilities is rising and now it stands at 1 billion which, account for 15% of the world's population. This has been complemented by a report from Access Economics in 2009, which has estimated the ***lifetime cost*** per incidence of paraplegia to be $5 million and the life time cost per incidence of tetraplegia to be $9.5 million. This is further explained and supported by facts obtained from a report on National Disability Services 2010, contained in the 2012-2020 National Disability Strategy of the Initiative by the Council of Australian Governments. In this report, it has been suggested that the return to work of just 10% of carers from families of people with disability would boost the country's economy by $3 billion. This would take place when appropriate personal support has been provided for the relatives with disabilities these carers have been helping. The report also suggested that if just 2% of people with disability come off pension (benefits) and refer to work following appropriate employment training, a $2.5 billion injection into the country's economy would result. The WHO reported in 2013 that 'people with a spinal cord injury are 2-5 times more likely to die prematurely than people without a spinal cord injury, quoting even worse survival rates in low and middle income countries. It has also been highlighted that SCI is associated with lower rates of school enrolment and economic participation, and stated that SCI carries substantial individual and societal costs.

These facts highlight the economic fallout caused by SCI to individuals, their families and carers as well as the immediate small communities and eventually the population at large. It has also been observed that five years post injury, 88% of single people with SCI remained single versus 65% of non-SCI counterparts, while 81% of married people with SCI remained married compared to 89% of non-SCI persons. It has also been observed that 58% of individuals with SCI were employed and 41% unemployed (including students and retirees).

Employment of individuals following SCI fell significantly for those with tetraplegia compared to individuals with paraplegia. The outcome of post-injury employment status can be predicted by secondary education and higher functional independence (Ferdiana et al., 2014). Most SCI individuals returning to work in the first year post-injury usually go to the same employer and possibly doing the same job. Understandably, the length of time needed to return to work might indicate a relatively milder SCI. However, some individuals getting SCI happened to be students going out for work unaffected by their injuries.

Mortality of Traumatic SCI:

The WHO (http://www.who.int/news-room/fact-sheets/detail/spinal-cord-injury) reports that the risk of mortality is highest in the first year after SCI and remains high compared to the general population. It transpires that people with SCI are 2 to 5 times more likely to die prematurely than people without SCI. Seemingly, the risk of mortality increases with injury level and severity of SCI, and is strongly influenced by the availability and quality medical care. Transfer method to hospital after sustaining SCI and time from injury to hospital admission have been highlighted as important factors that would affect morbidity and eventually impact on mortality rates. In another study, it has been reported that overall 85% of patients who survive the first 24-hours of SCI are still alive 10-years later, compared to 98% of their uninjured counterparts from the population matched for age and sex. Crucially, the overall mortality from SCI continues to decline following the first two years (Strauss et al., 2006). In the WHO report, preventable secondary conditions such as infections caused by untreated or poorly treated pressure ulcers no longer among the leading causes of death in individuals with SCI living in high-income countries. However, these very conditions frustratingly remain the main causes of death in individuals with SCI living in low-income countries. Studies report the most common cause of death as respiratory dysfunction while renal failure was the most likely cause of death previously. In a study of SCI ***mortality*** in the UK, the 834 patients examined were around 20 or more years following initial SCI injury, with a median survival time of 32 years. It has also been highlighted that the number of renal deaths is decreasing over time while the cause of death patterns in the aging groups of individuals with SCI began to match and approximate those of the general public. As expected, ***morbidity*** patterns were found to be associated with age or years spent with SCI or both based on the named medical complications in question. Medical examination of survivors of SCI with longer median survival time show a significant decline in functional abilities associated with the aging process. However, around 25% of the overall patients with SCI who were interviewed reported a self-rating of their ***quality of life*** as either good or excellent which necessarily includes a reasonably maintained health status.

As indicated in the previously discussed WHO report, mortality rates remain significantly higher during the first year after injury than subsequent years. This is possibly owing to much improved quality of health care coupled with better living standards for surviving individuals following SCI. There is increasing number of individuals with SCI dying of unrelated causes such as cancer or cardiovascular diseases in similarity to the general public. A Cochrane review found out that no controlled randomised trials have been conducted to answer whether immediate referral to a spinal injuries centre improves outcome. The review highlighted a need for future well-designed

prospective studies with appropriately matched controls to ascertain benefits of early referral to spinal cord injuries centres (Jones and Bagnall, 2004).

Prevention and Public Health Issues of Traumatic SCI:

Prevention programmes are understandably focussed on the risks associated with the leading causes of SCI which are centred on road traffic accidents and automobile crashes, falls and violence. In addition, it is observed that a significant proportion of traumatic SCI is due to work and sport related injury, and therefore effective legal and environmental interventions have been sought to prevent several of the main causes of SCI. These interventions included improvements of the roads and driving conditions and special attention to vehicles and people's behaviour on while the roads to avoid road accidents and reduce the severity of any possible crashes (Draulans et al., 2011). Programmes and guards to prevent falls from taking place especially in older age individuals (Chen et al., 2016). Reports suggest policies and procedures to prevent harmful use of alcohol and access to firearms in efforts to reduce related violence.

2.3.3 Pathological Changes Involved in Traumatic SCI:

Trauma received by the vertebral column might be severe enough to cause fractures and/or dislocations causing vertebral bones or resulting bony fragments to compress or bruise the delicate underlying tissues of the spinal cord (Figure 2:05).

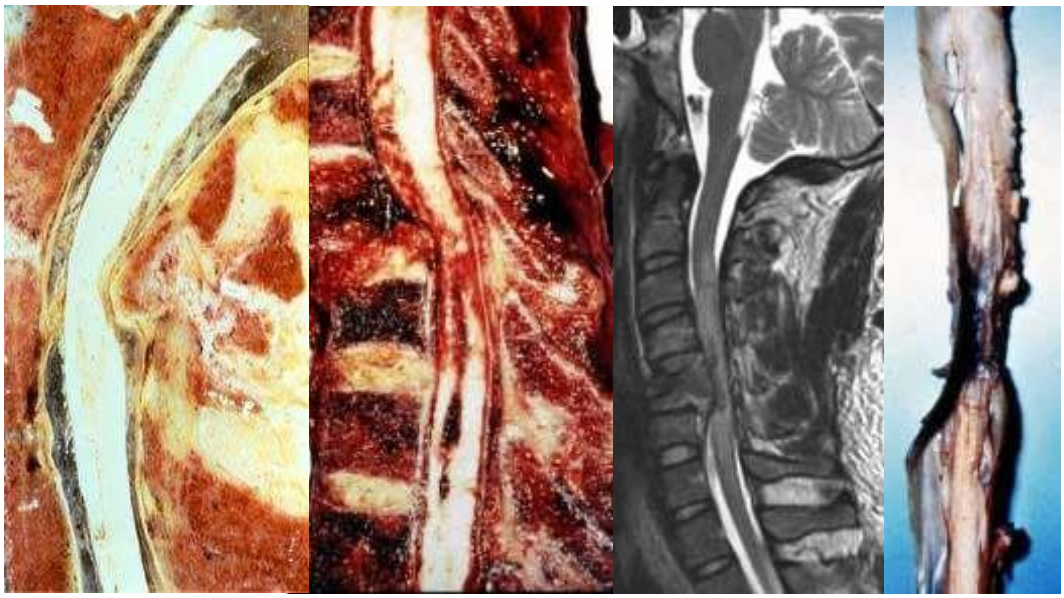


Figure 2:05: (Left): a post-mortem saggital section of spinal cord/vertebral column following acute SCI showing crushed spinal cord, contusion, haemorrhage and associated compression and fracture dislocation of adjacent bony vertebrae. (Right): post-mortem pathology specimen from a patient with chronic SCI showing fibrosis, tissue loss and possible changes with cavity formation. (Middle): a T2 sagittal MRI of the spinal cord showing cervical burst fracture with cord compression, contusion and Haemorrhage. (Field work, from imaged provided by the clinical and surgical team, spinal unit).

SCI is a pathological process that disrupts either partially or completely the structure and function of the spinal cord, leading to a disease process that immensely impacts on the lives of the affected individuals directly and through related consequences (Harkey III et al., 2003). The resulting trauma which is received by healthy spinal cord tissues causes a ***primary lesion*** in addition to ***secondary injuries*** as direct or indirect consequences of the initial SCI lesion (Tator and Fehlings, 1991). A wealth of knowledge on the pathophysiological changes that takes place following SCI has been established from animal studies based on animal models mainly in rodents which are designed to simulate various types of SCI. It has been indicated that animal models subjected to stretch injury suggest ***axonal injury*** with possible ***demyleination*** however with no definite underlying major cellular or vascular changes. These studies helped to further characterise molecular basis of ***neural cell death*** including Glutamate-induced Excitotoxicity, which is a very important pathological process that follows SCI with potential therapeutic insights (Dumont et al., 2002).

Alterations in ion-channel homeostasis have been demonstrated following SCI, including voltage-gated potassium channels (VGPC) which are important in axonal function as well as its potentials for future therapeutic interventions. It was demonstrated that several weeks following SCI (sub-acute and chronic) a subset of VGPC displayed ***up regulation of protein and gene expression in glial cells***, but not axons of spinal cord white matter. This up regulation of this VGPC subset is therefore an indirect marker for proliferating oligodendroglia (ODG) following SCI. It has been suggested that ***inadequate blood supply to injured spinal cord tissues*** contributes to paucity of regeneration following SCI. The cellular and molecular mechanisms of angiogenesis, characterising its temporal course and basal lamina deposition following SCI, has been investigated. IT has been demonstrated that a ***robust angiogenic response within the epicentre of the ventral grey matter*** develops seven days following SCI. This given the basis for the proposal that therapeutic strategies aimed at enhancing angiogenesis and improving blood supply to lesions following SCI should be implemented between 3-7 days post-injury. Eventually, as demonstrated in these studies, using a contusion injury model of SCI in rodents, new ***vascular tissue rapidly replaces neural parenchyma and vessels, which were damaged***. The ***newly formed vascular bridge*** might serve blood supply to the damaged tissue, as well as providing a basis for speeding axonal regeneration at the SCI site. However, much more severe forms of SCI would involve ***cellular*** and matrix changes with ***inflammatory cell proliferation***, while other SCI lesions would involve ***vascular insults*** resulting in ischemic or haemorrhagic consequences weather micro or macro depending on vessels involved (Dumont et al., 2002).

Studies characterised some ***changes in expression of number of genes*** following SCI and these also serve a starting point for identifying candidate genes to be singled out for further studies of pathological gene mechanisms and therapeutic potentials (Strong et al., 2007). It has been shown that SCI due to spinal cord transaction or contusion induces ***class 3 semaphorin expression in fibroblasts*** at the neural scar. It was felt that these semaphorin molecules contribute to the ***inhibitory nature of the neural scar*** and in this way, they attenuate any possible regeneration of the injured spinal cord. Further understanding of the role of molecules such as the semaphorins identify areas of possible therapeutic effect built on creating environments that are permissive of spinal cord regeneration. The ***localization and regulation of the extracellular chaperone molecule clustering two days following SCI*** has suggested its role and participation in sub-acute and late phases of SCI. The putative role of ***inhibitors of DNA, binding including Id1, Id2 and Id3*** from specific gene families, was investigated illustrating that Id genes are time-dependently up regulated in astrocytes, oligodendrocytes and neural progenitor subpopulations following SCI supporting their role in the cellular response to the injury. The ***expression of extracellular matrix***

(ECM) molecules, which are shown to be potent inhibitors of regeneration of the CNS following injury, have been demonstrated following SCI. Along these lines, it was reported that a member of the chondroitin sulphate proteoglycan class of the putatively ***inhibitory ECM molecules*** called ***NG2*** is expressed by macrophages and oligodendrocyte progenitors at SCI sites and possibly serve to hamper axonal regeneration. The expression of another class of ECM molecules known as ***keratan sulphate proteoglycan*** is induced following SCI in macrophages, reactive microglia and oligodendrocyte progenitors. Furthermore, it was demonstrated that ***type IV collagen, laminin-1 and a1 laminin may contribute to the formation of glial scar*** following SCI, similarly demonstrating that ***neurite-outgrowth may be inhibited*** following SCI. This provided an understanding of the dynamics of extracellular matrix and basement membrane formation and relevant remodelling following an event of SCI. The role of inflammation in the pathogenesis of SCI has been demonstrated by examining the ***cellular localization and temporal pattern of expression of growth factors***. This included the ***transforming growth factor-b***, which modulated inflammatory and neural responses, and ***transforming growth factor-b2*** which regulated glial and collagen scarring following SCI. The immediate ***release of cytokines*** from injured spinal cord tissue contributes to the subsequent ***induction of cytokine messenger RNA***. The inflammatory response to tumour necrosis factor *alpha* (TNF-
a) and nuclear factor-kB, at least in part, initiate or propagate the ***apoptosis cascades*** (including capase activation). The contribution of cytokines to the inflammatory response observed following spinal cord contusion in rats was further investigated illustrating that cytokine messenger RNA (interleukin-1a, interleukin-1b, TNF-a, and interleukin-6) increased
2 hours following compression injury. Furthermore, the pharmacological blockade of interleukin-1 and TNF-a receptors significantly reduced expression of TNF-a, interleukin-1a and interleukin-1b following SCI. Cytokines are thought to activate the ***inducible nitric oxide synthase enzyme in macrophages and glia*** among other cells leading to the production of nitric oxide following SCI. In another pathological aspect following SCI in transgenic mice, it has been shown that more than 95% of all ***CD4-positive T-lymphocytes were reactive with endogenous myelin basic protein*** which contribute to tissue injury and impair functional recovery. In previous work, it has already been suggested that lymphocytes which are responding to myelin proteins following SCI may contribute to post-traumatic secondary degeneration. Examination of the pro-inflammatory molecule platelet-activating factor (PAF) on cultured astrocytes and oligodendrocytes demonstrated that ***platelet activation factor induces cell death in cultured CNS glial cells***, at least partly being dependent on caspase-3 activation. Information from studies in rats demonstrated that allograft ***inflammatory factor-1 positive microglia/macrophages*** were among the first cells to respond to injury supporting their role in the initiation of the early micro-glial response leading to activation and proliferation essential

for mediating the acute response to SCI. The ***expression of brain-derived neurotrophic factor*** following experimental SCI in rat was characterised showing that this factor is acutely synthesized in both neurons and astrocytes during the immediate response to SCI. This brain-derived neuropathic factor acts as a ***neuroprotective agent*** and is obviously subsequently expressed in macrophages/microglia during a later phase with probable role in neurorestoration. It has been suggested that the various ***mechanisms of neuronal death following SCI*** remain incompletely understood at present in spite of the fact that they have been extensively investigated. When a model of peripheral nerve-SCI in both rats and mice was used, it was demonstrated that ***motor neuron apoptosis*** in this model was controlled by upstream and downstream mechanisms. The upstream mechanisms involved ***DNA damage and activation of p53*** and the downstream mechanisms involved ***up-regulated Bax and cytochrome c, and their translocation, accumulation of mitochondria and activation of caspase-3***. The data gained from several studies contributed significantly to the useful knowledge about the role of gene expression in the patho-physiological processes that follows SCI. This body of knowledge is important for the planning future studies and design of experiments examining novel therapy for SCI lesions. It is obvious that the advancements in understanding the pathophysiological mechanisms underlying SCI would prove critical in the development and implementation of future effective therapy for patients suffering SCI (Dumont et al., 2002).

Experimental SCI triggers a ***systemic neurogenic immune depression*** characterised by fluctuations of immune cell populations. In humans, there is a rapid and drastic decrease in immune cells within the first 24-hour period after SCI reaching a trough within the first week. It is suggested ***high dose methylprednisolone***, which is used for acute SCI, contributes to the decrement seen in immune cells. Cell populations seen to decrease in SCI include CD14 monocytes, CD3 T-lymphocytes, CD19 B-lymphocytes and MHC class II (HLA-DR) cells.

Traumatic SCI causes ***widespread glial activation and recruitment of immune cells*** of the CNS, weather innate including neutrophils and monocytes or adaptive including T and B lymphocytes. The exact functions of the astrocytes, microglia, neutrophils and monocytes seen the immediate post-traumatic phases of SCI are yet to be further studied and better understood. There is a significantly well observed yet much less understood ***lymphocyte activation*** following traumatic SCI. The T and B cells are however thought to be activated by traumatic SCI and goes on to play significant roles in shaping ***post-traumatic inflammation*** and downstream cascades of neurodegeneration and repair following SCI. Trauma sustained by the CNS in the events of SCI triggers ***intra-parenchymal inflammation*** and ***activation of systemic immunity*** that eventually exacerbates neuropathology processes and stimulates mechanisms of tissue repair. At

the time of initial SCI, some neurons are partially damaged while others are completely damaged; however, the majority of spinal neurons remain intact at least for a period of time following initial injury. It has been described that when some of the spinal or any other central nervous system neurons die, they release toxic chemicals that would eventually cause uninjured neighbouring neurons to also die (Dumont et al., 2002). This secondary process increases the neuronal loss and consequently the size of the affected area within the damaged neural tissue (Tator, 1995). Taking a timeline of injury sustained by the spinal cord neuronal tissue suggest that the initial ***minutes*** are characterised by mechanical injury, cell injury and/or cell death and accompanying process of local or cellular haemorrhages and ischemia The following ***hours and days*** then see changes resulting in excitotoxic cell death, the triggering of body's immune responses as well as cell proliferation. Following several ***days into weeks*** following the initial SCI, there is an astrocytic hypertrophy as well as glial scar formation marking the beginning of the chronic phase of SCI. At this stage, when healing over time lead to bony stabilisation of the initial SCI injury, the loss of neurons is accompanied by scar tissue formation in areas of the damaged neurons. After the passage of ***weeks and months*** following the time of the initial SCI, there are changes characterised by cyst formation, schwannosis, chronic demyelination and a process of adhesions formation and subsequent fibrosis. Data from several studies contributed significantly to the useful knowledge about the role of gene expression in patho-physiological processes that follows SCI. This body of knowledge is important for planning future studies and designing experiments that could examine novel therapy for SCI lesions.

2.3.4 Recovery Following SCI (regeneration and neuro-plasticity)

The changes primarily caused by SCI and the secondarily processes triggered by subsequent pathological and immunological changes largely determines clinical and functional recovery. Observed or measured clinical improvement might relate to underlying neuro-plasticity or some degree of neural regeneration or both. However, most of the observed clinical improvement might be a direct outcome of effective rehabilitation training, adequate medical management of SCI patients, with the appropriate pharmacological interventions needed based on clinical indications. It is hard to ascertain the input of each component into the final outcome of given SCI. Evidence from basic science demonstrates that the CNS is adaptable and can learn following sustaining injury, especially with regard to locomotion with rehabilitation programmes based on activity and therapy to improve recovery of walking ability (Behrman et al., 2006).

Many studied ***neuroplasticity*** trying to understand CNS repair strategies following injury such as SCI (Gulino et al., 2015). A feasible strategy that has been described involves activation of

neural precursor cells (NPCs), which is helpful for spinal cord repair, however with limited ability to generate neurons after SCI (Gulino and Gulisano, 2012). Synaptic plasticity is also described as useful in promoting functional recovery following SCI (Edgerton et al., 2004). Other mechanisms of spinal repair post injury involve brain-derived neurotrophic factor (BDNF) (Gulino and Gulisano, 2012). Sonic hedgehog (Shh) which is a molecular factor secreted glycoprotein and promoting the proliferation of NPCs and differentiation into neurons and oligodendrocytes (Gulino and Gulisano, 2012). Notch-1 as cell- surface receptor is a regulator of NPCs proliferation, cell fate, dendritic and axonal morphology (Androutsellis-Theotokis et al., 2006; Akai et al., 2005). Numb is a factor for signal transduction and involved in stem cell maintenance and differentiation, as well as in neuritogenesis by means of antagonizing Notch-1 signalling (McGill and McGlade, 2003). Noggin involved in embryonic morphogenesis and induces neural tissue by inhibiting bone morphogenetic proteins. Information on these plasticity factors and processes was established using mice models of motoneuron depletion induced by cholera toxin-B saporin (Krause et al., 2011). Furthermore, TDP-43 was identified inside cytoplasmic inclusions observed in amyotrophic lateral sclerosis, frontotemporal lobar degeneration and Alzheimer's disease, suggesting a toxic effect of TDP-43 that might be linked to loss of function of the normal TDP-43 (Arai et al., 2006). TDP-43, a transactive response DNA-binding protein of 43 kDa, is nuclear RNA/DNA binding protein involved in the regulation of transcription and RNA processing (Cohen et al., 2011). TDP-43 localizes at the synapse and affects synaptic strength and is therefore an important regulator of synaptic plasticity, probably in collaboration with proteins involved in the neurogenesis and synaptic plasticity. Overall, hope is great in the suggestion that stimulating intrinsic repair potentials of spinal cord might produce interesting results with the rapidly increasing knowledge about spinal cord plasticity. In the context of CNS repair, ***therapeutic agents*** are being looked at with interest to improve overall clinical recovery following SCI. High dose methylprednisolone, given in the first eight hours after acute SCI improves the overall neurological recovery with sustained improved at further chronic stages. This has been explained by the fact that methylprednisolone supresses the breakdown of membrane by inhibiting lipid peroxidation and hydrolysis at the site of injury (Bracken et al., 1990). There is still a long way towards establishing meaningful ways of improving clinical recovery by improving the processes linked to and supporting neuroplasticity to eventually impact on the overall functional outcome.

Efforts are being made in promoting ***regeneration*** of the injured spinal cord bridging the gap of the SCI lesion. With the background of modest success of current therapies using biologically active agents to promote neuronal survival and/or growth, there is yet to be an adequate answer

to the devastating consequences of the disruption of axonal continuity resulting from SCI. An engineering approach proposed a design of cell-free graft to build a bridge across the injured area for axons to regenerate through. Difficulties therein have been uncovered highlighting the importance of the bridge being soluble given the recently increasing understanding of factors controlling axon regeneration. Furthermore, the use of such a soluble bridge has to be part of complex series of treatments involving trophic factors to neutralise inhibitory molecules allowing axon regeneration (Geller and Fawcett, 2002). There are ***challenges and obstacles*** facing approaches that aim at developing and establishing ways of promoting repair of the spinal cord. This is tried by translation of scientific work done in animal models to humans while considering the complex clinical contexts. Several approaches aimed at developing and establishing ways of promoting repair of the spinal cord, however not without technical difficulties. One basic obstacle is that animal models rely on transection of the spinal cord while in human SCI mainly caused by contusion. As representative of the typical injury mechanism, contusion typically leads to injury in two or three segments. Additional factors that translate into additional difficulties include the quadrupedal organisation of locomotion in animals compared to humans. Furthermore, damage of motor neurons and roots associated with contusion spinal injury is not adequately addressed though has implications for rehabilitation and functional outcome. There is evidence for degradation of neuronal function below the lesion especially in chronic complete patterns of SCI. Finally, the acute settings caring for SCI limit intervention aimed at reconnecting the injured spinal cord (Dietz and Curt, 2006). Advances in medical and rehabilitation allow individuals living with SCI to lead productive lives of nearly normal life expectancy. This fact signals the need for novel treatments that promotes repair and improves recovery after SCI. It seems that a therapeutic strategy combining rehabilitation and pharmacological modulation might be promising in increasing recovery after longstanding injury. In chronically injured spinal cord, transplants applied in the first 2 weeks after experimental SCI in combination with neurotrophic factors produced limited long-distance axon regeneration. When transplants were applied to SCI older than 4 weeks the treatments almost failed to overcome the neurons' diminished capacity to for regeneration and increasing hostility to growth at and beyond the injury site. These obstacles might need to be overcome in order to make progress of these therapies, in addition to the challenge of trials to elicit regeneration in the setting of the acutely injured spinal cord (Houle and Tessler, 2002). The work done towards this thesis is aimed at improving assessment methods of the state of SCI as well as monitoring any potential recovery. Electrophysiological methods examined by this study might be sensitive, reliable and objective methods to determine the magnitude of any observed recovery weather

bought by natural processes or developed by novel therapy.

2.3.5 Clinical Aspects & Management of Traumatic SCI

The clinical presentation of patients sustaining traumatic SCI may be incomplete or complete loss of motor function leading to muscle weakness or complete paralysis, and loss of sensory function leading to reduced sensations or complete anaesthesia, respectively. As shown in previous sections, traumatic SCI results from an insult to the spinal cord causing a temporary or permanent change(s) of motor, sensory or autonomic function. The symptoms and signs caused by the SCI depend on the extent or severity of the lesion, level of injury and the involvement of white matter and grey damage affecting spinal tracts or segmental connections. It is likely that combined motor and sensory dysfunctions coexist in the same patient with varying degrees depending on the extent and pattern of SCI lesion. In some patients, there is loss or dysfunction of autonomic fibres leading to autonomic dysfunction affecting bladder, bowel, sexual functions or control of blood pressure and heart rate when high cervical cord segments are involved (Kewalramani, 1980).

The following terminology is used in defining SCI:

- **Tetraplegia** (replacing the former term quadriplegia) refers to complete loss of muscle strength in all four limbs, while **Tetrapareis** (replacing the former term quadriparesis) refers to partial loss of muscle strength in all four limbs.

- **Paraplegia** refers to complete loss of muscle strength in the lower limbs, while **Paraparesis** refers to partial loss of muscle strength in the lower limbs.

A survey of the neurological categories of SCI observed since 2005 showed the most frequent SCI subtypes to be Incomplete Tetraplegia (30.1%), Complete Paraplegia (25.6%), Complete Tetraplegia (20.4%), Incomplete Paraplegia (18.4%) and less than 1% of surveyed patients reported to have experienced complete neurological recovery by the time of discharge from hospital. However, in over a decade and a half it seems that the percentage of individuals with incomplete Tetraplegia increased while those with complete paraplegia and complete tetraplegia decreased slightly. It was observed that 53% of patients with existing SCI reported complete loss of voluntary muscle power and sensation, 44% reported some degree of neurological function below level of injury and 3% of SCI patients provided no information on severity of their injury remaining with unclassified severity. The method of description of the preservation of function below the injury level was also appraised (Barcelos et al., 2009). In studies of SCI patients, Tetraplegia remains the major clinical pattern followed by Paraplegia. Tetraplegia was the main

clinical presentation of SCI with (51.9%) of which Incomplete Tetraplegia was (29.6%) and complete Tetraplegia was (18.5%). Meanwhile, patients with Paraplegia account for 46.27% of which 28.1% of the injuries were complete and 21.5% were incomplete Paraplegia. There were few (0.7%) of the patients who had complete or substantial recovery by the time of hospital discharge and (0.7%) with no information been made available. The most common level of injury in Tetraplegia is C5, while the most common level of injury in Paraplegia is T12. Similar frequencies of level of SCI involvement can be seen from data screening patients with existing SCI. This shows the most segments or levels involved to be Thoracic (from T10 to L1 – 33%) and Cervical (from C4 to C6 – 32%), as surveyed by the Spinal Injury Association, UK.

An obvious rationale for classifying SCI into clinical entities sharing similar characteristics is to ease the processes of identification, care provision, monitoring, rehabilitation and outcome prediction. Nevertheless, clinical subtypes of SCI are not entirely distinct or clearly separable of one another in clinical practice. A British neurologist, Dr Frankel, developed a more detailed system of classification of neurological function following SCI (Frankel et al., 1969). This was used in further assessments of the neurological deficits caused by SCI in further studies (Maynard et al., 1997). The Frankel Scale was further refined and finalised as the American Spinal Injury Association (ASIA) grading injuries from A (a complete injury) to E (recovery). The International Standards for Neurological and Functional Classification of Spinal Cord Injury (ISNCSCI) which could be found in this link (http://asia- spinalinjury.org/wp-content/uploads/2016/02/International_Stds_Diagram_Worksheet.pdf), was published by the American Spinal Injury Association (ASIA) and are currently widely used guide in clinical evaluation, classification of neurological impairment and functional abilities of SCI patients. The standard ASIA Classification is also known as **ASIA Impairment Scale (AIS)** and is defined as follows (Figure 2:07 - left):

A = Complete (no motor or sensory function is preserved in sacral segments S4-S5).
B = Incomplete (sensory but not motor function is preserved below the neurological level, including the sacral segments S4-S5 – sparing of sacral sensations).
C = Incomplete (motor function is preserved below the neurological level, with more than half of key muscles below the neurological level have muscle grades less than 3).
D = Incomplete (motor function is preserved below the neurological level, with at least half of key muscles below the neurological level have muscle grade ≥ 3).
E = Normal (motor and sensory functions are normal).

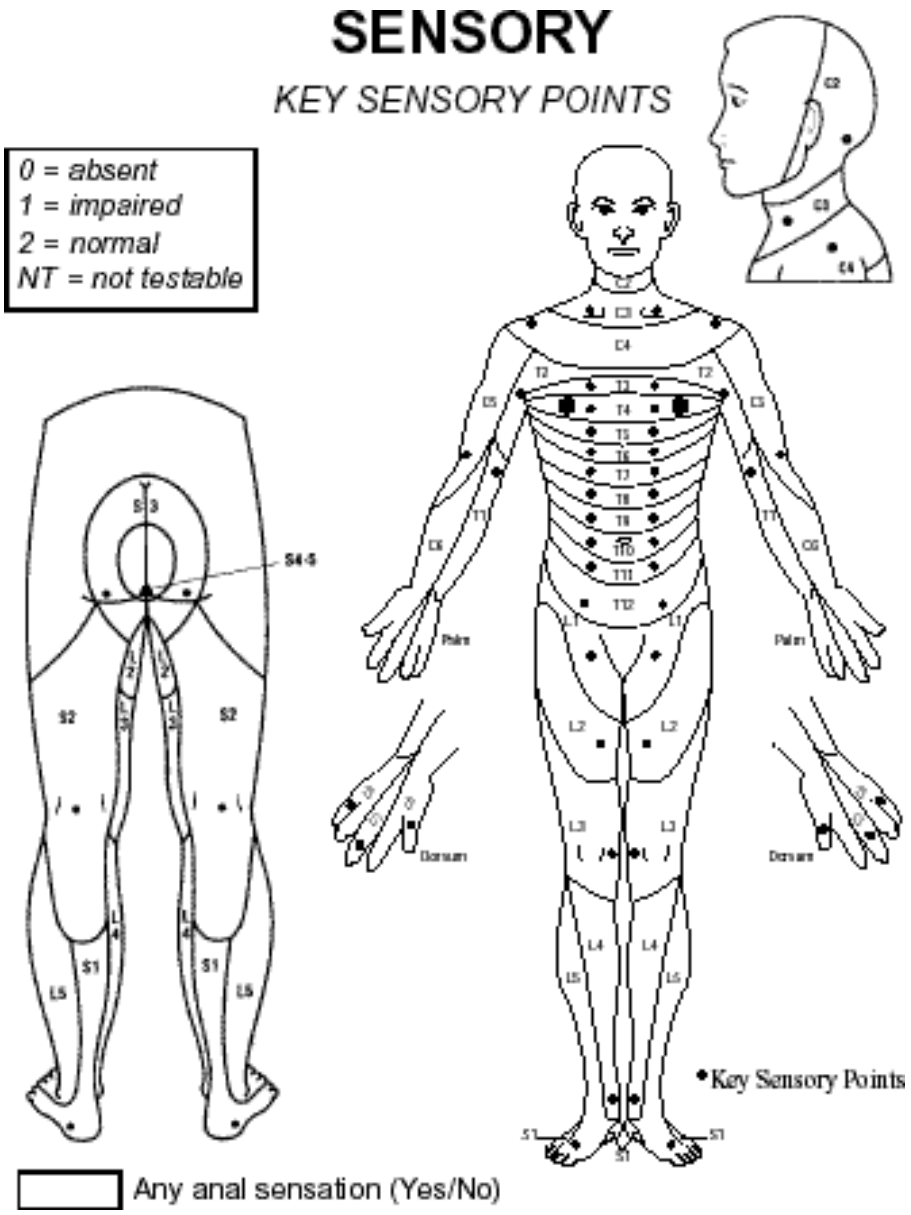


Figure 2:06: Key Sensory Points for ASIA Impairment Scale (AIS).
(Used with permission from the American Spinal Injury Association).

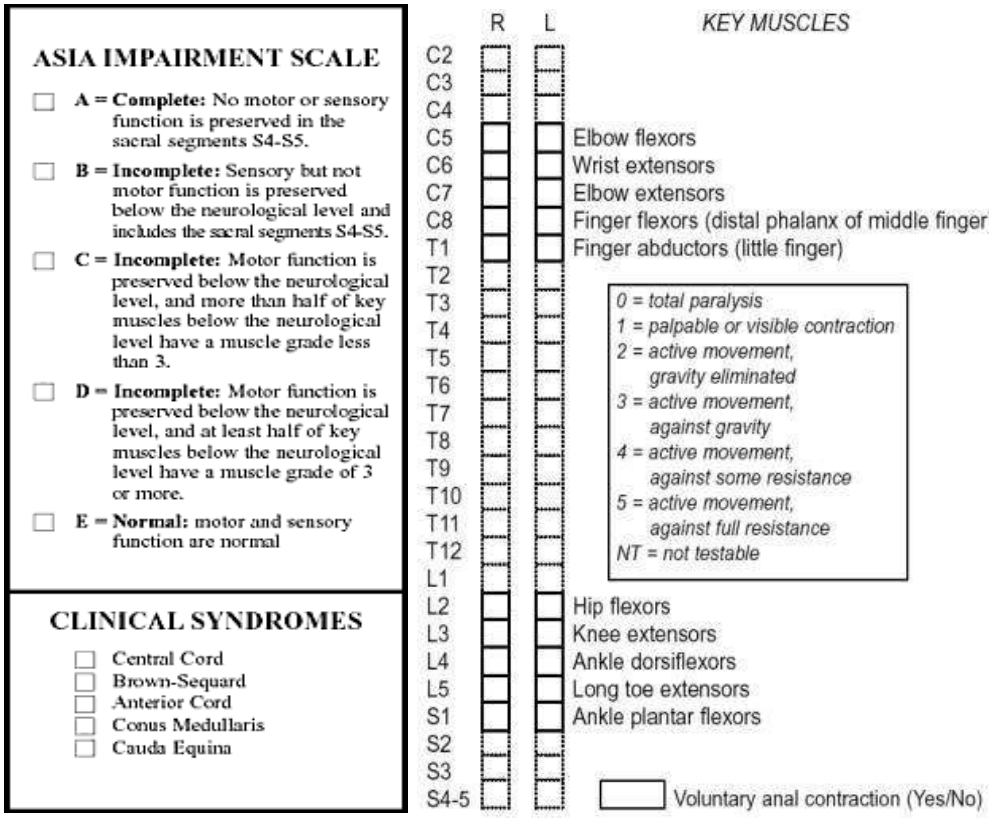


Figure 2:07: Extent of SCI according to AIS (left) and Key Muscles (right).
(Used with permission from the American Spinal Injury Association).

The **ASIA Impairment Scale (AIS),** which is (**modified from Frankel**), is vital in the aid of clinical definition, categorisation, assessment, monitoring and outcome prediction of different SCI clinical subtypes affecting various patients with traumatic SCI (Kirshblum et al., 2011). Several ***SCI Definitions*** which are used in clinical assessment, health care definitions, management and rehabilitation of SCI patients are detailed below as follows:

- **Sensory level** is the caudal most level at which both pin prick and light touch sensations are normal and determined by examination of the key sensory points (Figure 2:06).
- **Motor level** is defined by the caudal most level with muscle power being ≥ grade 3 on MRC Scale determined by examination of key muscles shown to the right (Figure 2:07), with patients assessed in the supine position.
- **Neurological level** (of injury) is the most caudal (lowest) spinal segment with normal sensory and motor function (muscle power ≥ grade 3 on the MRC Scale) on both right and left sides of the human body.
- **Skeletal level** is the level at which the greatest vertebral damage is found by the use of radiographic examination. Skeletal level is not currently part of the ISNCSCI because not all SCI are associated with bony injuries, and bony injuries do not correlate well with the neurological injuries sustained by the spinal cord.

- **Sensory score** is a numerical summary score of sensory function at key sensory points, with a maximum total of 56 points for each of light touch and pin prick modalities totalling 112 points for each side of the human body. Sensory score reflects degree of neurological sensory impairment associated with the SCI being assessed.
- **Motor score** is a numerical summary score of motor function, with a maximum total score of 25 for each extremity, totalling 50 for both upper limbs and 50 for both lower limbs. The motor score reflects the degree of neurological impairment associated with the SCI being assessed.
- **Zone of partial preservation (ZPP)** is a term which is only used with complete SCI and refers to dermatomes and myotomes rostral to sensory and motor levels that remain partially innervated.

Obviously, nerves above the level of injury continue to work normally following SCI, while nerves below the SCI level are impaired due to loss of descending from lesioned tracts. Therefore, motor and sensory structures innervated by nerves below the level of injury suffer a dysfunction caused by lack of descending drive or modulation. Some structures and body parts may no longer function or operate. As the spinal cord is part of central nervous system and connected with nerves serving the whole human body, damage to the spinal cord or part of it eventually affects every system in the whole body. For instance, SCI affect the injured individual's ability to move (muscle weakness or paralysis) and feel (reduced sensations or anaesthesia). However, SCI also affect skin, breathing, bladder, bowel, sexual functions and subconscious control of blood pressure, sweating and heart rate. Injury of upper motor neurons (UMNs) disrupt higher control signals at the level of SCI, and lower motor neurons (LMNs) consequently lose inhibitory modulation. This causes uncontrolled muscle contractions (or spasticity) with the resulting weakness described as spastic paresis or paralysis. In contrast, injury to lower motor neurons (LMNs) causes flaccid weakness or paralysis due to interruption of nerve supply to the related muscles.

Clinical presentation of SCI varies greatly depending on ***level*** and ***extent*** (severity) of SCI, essentially meaning that each single SCI lesion is different. This fact has led to the clinical entities of SCI displaying very variable characteristics and significantly distinct presentations. These variations have also been influenced by considerations that individuals affected by SCI always have different circumstances surrounding their general health, co-morbidity and bodies' ability to cope with SCI and their potential for recovery. All these factors are combined provides resulting clinical patterns of SCI that are variable in clinical course all the way from onset, progress, recovery potentials and final outcome.

Clinical Features of Traumatic SCI

Some of the common clinical patterns seen in the context of SCI are defined and described in details below:

Complete SCI (Complete Transection Syndrome)

In the acute phase, complete spinal cord transaction at high cervical levels is considered serious enough to cause death in most patients with SCI above C3 (Gould and Smith, 1984). Patients with these high cervical SCI who survive or those with less serious SCI lesions present to medical attention in a state of spinal shock. This gives a constellation of symptoms and signs including respiratory insufficiency, tetraplegia, areflexia of upper and lower limbs, anesthesia below the affected level, neurogenic shock (causing hypotension without compensatory tachycardia), loss of sphincter tone of rectum and urinary bladder sphincter, urinary and bowel retention (which might lead to abdominal distention), ileus and delayed gastric emptying. High thoracic SCI lesions might lead to paraparesis instead of tetra-paresis but with marked autonomic symptoms. Patients might also present clinically with (Horner's syndrome) constituting ipsilateral ptosis, miosis, and anhydrosis due to interruption of descending hypothalamic sympathetic pathways. Patients might also experience problems with temperature regulation because of the above-mentioned sympathetic impairment leading to hypothermia. Obviously, in lower cervical injuries, the respiratory muscles are spared. In lower thoracic and lumbar lesions, hypotension does not take place; however, urinary and bowel retention does. With time, the flaccid weakness of the spinal shock is gradually replaced by the return of intrinsic activity of the spinal neurons including the return of reflexes and development of spasticity. These developments mark the end of spinal shock usually taking three weeks from onset of SCI. However, in some instances spinal shock might be prolonged by other medical complications such as infections. Following gradual phasing off the spinal shock, hyper-reflexia, increased tone and extensor plantar responses develop due to loss of sustained inhibition or modulation from supra-spinal neural centres. At any given level of SCI, there is more loss of anterior horn cells, leading to flaccidity with loss of reflexes and atrophy in a LMN pattern. The atrophy here is denervation atrophy and not the disease atrophy seen in other muscles that remain innervated below the level of lesion.

Incomplete Spinal Cord Injury Syndromes

The clinical patterns of syndromes caused by incomplete variable patterns of involvement of spinal cord fibres might be defined and described as the following:

1. Anterior Cord Syndrome is caused by damage to the front portions of spinal cord and, typically observed with infarction in the territory of the anterior spinal artery. This incomplete SCI syndrome leads to paralysis below the injury level in association with loss or impairment of pain and temperature sensations, and relative preservation or sparing of fine touch, pressure, vibration and joint sensations. The relatively intact posterior (sensory) columns receive primary and most blood supply from posterior spinal arteries.

2. Central Cord Syndrome is more common in cervical segments being caused by damage to the central parts of the spinal cord. This incomplete SCI syndrome displays loss of motor function (weakness) of the arms while preserved muscle strength in the legs, characteristically giving 'man-in-a-barrel' clinical pattern or syndrome. Variable degrees of sensory and reflex deficits are observed, with the most affected being pain and temperature sensations compared to other sensory modalities. The sensory pattern might sometime being referred to as dissociated sensory loss which is often present in 'cape-like' distribution. The pattern of sensory involvement is due to the fact that fibres of lateral spino-thalamic tracts cross closely ventral to the central canal where might be affected. It is common for patients with central spinal cord syndrome to gain considerable recovery. Lateral extension of injury might result in ipsi-lateral Horner's syndrome due to involvement of cilio-spinal center, while dorsal extension of injury might result in ipsi-lateral loss of vibration and position senses due to involvement of dorsal column. Similarly, involvement of dorso-median and ventro-median motor nuclei supplying the paraspinal muscles might lead to kyphoscoliosis and involvement of the corticospinal tracts (CST) can lead to spastic paralysis. Variable dysfunctions of bowel and bladder control are seen as part of this syndrome. Lesions above the lumbo-sacral spinal bladder control centres cause an initial urinary retention which is later replaced by the development of spastic (automatic) bladder. Much lower lesions causing lower motor neuron (LMN) pattern of injury can lead to the development of a permanently lax (atonic) bladder.

3. Posterior Cord Syndrome (PCS) is caused by damage to the back of the spinal cord leading to preservation of good muscle power (anterior spinothalamic) pain and temperature sensations, but with difficulty in coordination of limb movements. The clinical features of PCS could be complemented by MRI findings of T2-weighted high signals characteristic appearances for PCS.

4. Brown-Séquard syndrome (BSS) is caused by damage to one side of the spinal cord and might be considered an equivalent of a hemi-cordectomy (section of the cord). BSS is most commonly seen after traumatic SCI; however, it remains that the full spectrum of BSS is rare. BSS leads to impairment or loss of muscle movement (paralysis) in the injured (same) side with hyperreflexia

and extensor plantar response. There is also ipsilateral loss of vibration and position sensations, as well as ipsilateral segmental anesthesia at the level of the SCI lesion. However, there is preserved pain and temperature sensations on the side of the SCI lesion. Contralateral to the SCI hemi-section, there are preserved or normal muscle movement (motor power), but with loss or impairment of pain and temperature sensations observed below SCI level at 2-3 segments below owing to the organisation of segmental spinal nerves. Patients with BSS usually undergo reasonable recovery and obtain substantial improvement with time. More specifically, this has been shown in a retrospective review of 412 patients with traumatic incomplete cervical SCI with an average follow-up period of 2 years. This has shown that incomplete injury, young age and clinical patterns compatible with central cord and Brown-Sequard syndrome have a more favourable prognosis for recovery. (Pollard and Apple, 2003).

Cauda Equina Syndrome (CES) is caused by lesions affecting the cauda equina. Although this syndrome is not a central nervous system disorder, it is discussed because it occasionally presents clinical similarities to involvement or injury of the lower spinal cord, but mostly it is difficult to distinguish CES from plexus or nerve involvement. Patients with lesions affecting only the cauda equina might present with lumbosacral polyradiculopathy characterised by pain sensory, radicular changes, lower motor neuron (LMN) type asymmetric leg weakness and sphincter dysfunction. It is emphasised that in lesions affecting only the cauda equina, early disturbance of bowel and bladder functions is seen.

A. **Radiculopathy Syndromes** develop in SCI patients who suffer involvement of spinal roots. These patients present with dermatomal sensory changes when dorsal roots are involved and myotomal (muscle) weakness when ventral roots are involved. In general, radicular pain is characterised by root distribution and shooting character. It increases with increased intra-spinal pressure which is observed with coughing, sneezing or any other activity that involves Valsalva manoeuvre.

Autonomic Dysreflexia (AD) is a serious medical condition that might take place in individuals with SCI at or above T6 (Colachis, 1992). AD is an example of uncontrolled reflexes due to lack of descending control over the autonomic nervous system caused by loss of connections from the brainstem sympathetic outflow. AD is therefore characterized by abnormal firing of the sympathetic neurons in response to certain stimuli perceived below the SCI level. Interruption of descending projections to spinal cord, prevent inhibition of the sympathetic centres of the spinal cord leading to continuous and inappropriate firing which is only terminated by removal of the offending stimuli (e.g. pain or bladder distention). In response to this process, a vagal inhibitory

reflex might be triggered generating signals to the heart eventually leading to bradycardia worsening the symptoms of AD much further. Stimuli which might trigger AD include those signalling pain or discomfort including painful stimuli, sunburn or laboured muscle contractions. Any cutaneous stimuli which are painful or cold might also lead to AD through triggering massive sympathetic neuronal firing. In relation to the urinary bladder, AD might be triggered by full bladder or bladder distension, stimulation or manipulation of the bowel or urinary bladder (including the process of urinary catheterisation). As part of the clinical presentation of AD, there is usually an initial hypotension seen in high cervical SCI lesions. The initial low blood pressure might later resolve however at times it persists as orthostatic hypotension. These postural hypotension symptoms might be made worse by ensuing bradycardia taking place secondary to vagal reflexes in response to initial sympathetic firing (Sugarman, 1985). AD is potentially life- threatening condition because escalating blood pressure can peak as high as 300 mm Hg. An increase in systolic blood pressure by at least 20% is seen plus one of the other manifestations including sweating, chills, cutis anserine (goose skin), headache or flushing. Other common symptoms include nasal congestion (secondary to vasodilatation) malaise and nausea (secondary to parasympathetic/vagal effect), blurred vision and increased spasms. Headache is one of the commonest symptoms that might be seen in AD and it might be the result of vasodilatation and complicated hypertension. Cardiovascular responses associated with AD are complex and variable. Although it has been suggested that bradycardia is common during episodes of AD, this has been observed with much variable responses among SCI individuals. For instance, the physiological response of baroreceptors, when triggered by abnormally high blood pressure (hypertension seen in AD), is the increase of parasympathetic activity to reduce the heart rate eventually causing bradycardia. However, this is not always been the case in patients who developed AD, because tachycardia is not an uncommon finding and some patients might display some forms of cardiac tachyrhythmia (Colachis, 1992).

As indicated above, if AD is not appropriately managed with symptoms and signs promptly treated, it can lead to serious medical complications including cerebral end organ damage, cardiac dysfunction and possibly death.

Initial Rescue, Recovery from Injury Site and Transport to Hospital:

Initial rescue, onsite treatment, prompt recovery and quality transport to hospital are all important in overall care for SCI patients. Much effort is directed towards highlighting procedures to be followed by rescue workers towards recognising injury circumstances with potential SCI as well as raising public awareness to timely alerting emergency services. More knowledge and techniques involved are meant to uphold the principles of prompt and early recognition of SCI.

Followed by safe recovery from scene of injury, effective resuscitation, initiation or request of emergency treatment and safe transfer for expert medical attention (Fleming et al., 2016). However, there are still much areas of work to improve rescue and clinical management towards improving the final outcome of SCI. It has been suggested that emergency services in the USA, including fire and police, out-performed medical teams involved in the rescue of individuals sustaining SCI. It established that the arrival of SCI patients to the specialty treatment centres was achieved within 7 hours. Further sub-set analysis revealed that patients with SCI had long transit times of all other patients. Focus on the improvement of transportation triage system and reduction of time loss for traumatic SCI patients is crucial. This is especially true that the information from clinical trials of potential therapeutic strategies suggesting that earlier intervention might lead to improved recovery outcomes. Nevertheless, the Cochrane review previously discussed found no controlled randomised trials that answer if immediate referral to a spinal injuries centre improves final outcome. The Cochrane review highlighted need for future well-designed prospective studies, with appropriately matched controls, to ascertain if there are definite benefits for early referral to SCI. More work is obviously needed to improve crucial stages of care for individuals with SCI. Nevertheless, SCI remains one of the most devastating clinical conditions known to man typically the young with male preponderance are affected. Most individuals with neurologically complete lesions above C3 level die before receiving medical treatment, 50% have other system injuries and survivors of this category usually remain dependent on mechanical ventilators (Huber et al., 2015).

Cardiac and Respiratory Resuscitation:

Immediately following an acute traumatic SCI, hypotension and hypoventilation might be encountered which might by life threatening and increase the extent of neurological impairment. Cardiac and respiratory resuscitation, recovery and stabilisation of any other life- threatening or potentially disabling injuries are crucial as initial steps in the correct medical care and treatment of acute SCI. The standard resuscitation techniques might need to be modified to ensure stability of any potential spinal fractures and therefore prevent further neurological damage to the spinal cord. SCI patients should be transported in supine eye-up position, with NGT on continuous drainage and ready suction facility.

Spinal Splinting:

A key principle in rescue and resuscitation is recognising the likelihood of an unstable spine. Extra care should be taken protecting further mobility which might inflict further damage as well

as preventing inadvertent neck movements during resuscitation. A preferred means of rapidly and safely immobilising the neck to prevent further flexion and extension is the application of one of the semi-rigid cervical collars (e.g. Ambu or Stifneck). However, some additional effort should be sought to maintain lateral cervical immobilisation (e.g. using blanket roll, a blanket halo, Extrication Device or other types of immobilisation boards); (Figure 2:08 (**A**) and (**B**).

Figure 2:08 (**A**): Miami J rigid cervical collar (**left**) used for neck immobilisation in SCI patients, and an example of an Extrication Device (**right**) used for immobilisation of individuals with serious high cervical or spinal injuries with circumstances suspicious for instability of spinal cord structure. (left from www.mayfieldclinic.com – and right from www.medtree.co.uk).

The standard version of the Extrication Devices is Russell Extrication Device (RED) used for stabilising patients with acute SCI and vertebral fractures. RED lead to no deterioration of the patients' neurological status during the entire transfer process (including application/removal of the RED) of 64 patients over one year study period (Cohen et al., 1990)

Figure 2.08 (**B**): Ambu rigid adjustable cervical collar used for immobilisation and transport of SCI patients, with unstable neck and bony injuries. (from www.ambu.com).

Much more recent modifications have been made and incorporated into the standard Russell Extrication Device. These feature improvements added quality and reliability to the intended functions of the initial RED including effective immobilisation achieved by the device.

Detection of Obscured Internal Injuries: *Loss of sensation* over thorax, abdomen or limbs caused by SCI is often associated with altered sensation from abdominal viscera or skeletal structures. SCI might abolish spontaneous pain, tenderness to palpitation, local guarding and generalised rigidity which are signs that are often present with other intra-abdominal injuries. SCI alone might produce *signs of ileus* within a period of 30 minutes to 48 hours of injury, causing disruption of the normal propulsive ability of gastro-intestinal tract giving evident signs on auscultation and radiographs. Circumstances with evident *hypotension* combined with *tachycardia* in the absence of other overt sources of haemorrhage, should prompt investigation for potential abdominal sources of haemorrhage as well as secondary survey of other systems for missed sources. Search for alternative explanation should be undertaken using various diagnostic methods because the combination of hypotension and tachycardia is seldom attributable solely to SCI.

Maintaining Body Temperature:

It has been observed that patients with cervical SCI, might develop an inability to maintain body temperature. Poikilothermia is medical condition in which patients' body temperature tends towards that of immediate environment. This clinical challenge necessitates prompt and adequate temperature correction and further monitoring besides the usual search for possible secondary infective causes (Otis, 1995).

In most instances of acute SCI, patients should be kept covered and warm with the use of space blankets at times proves to be of great value. Body temperature of patients should be determined regularly by oral thermometers; but, if hypothermia is evident, it might be clinically necessary to check core temperature using rectal thermometers.

Air Transport of SCI Patients:

The current understanding is that whenever possible patients should go directly from injury scene to the spinal unit, likewise speedy dispatches are made from peripheral hospitals to the tertiary care centres. To achieve speedy, effective and safe transfer of SCI patients, it has now become common practice in industrial countries to use helicopter transfer. It has been advocated that helicopter transfer is best for distances over 10 and under 200 kilometres.

Advantages included achieving uninterrupted transfer speed of 150km per hour minimising number of times patients are handled and mobilised. There is also the chance of providing highly trained medical escorts especially for multiple injured patients, the low vibration during air transfer minimises further tissue trauma and finally the valuable time saved is critical in establishing re-perfusion of injured spinal cord. It has been estimated that emergency responses to the primary scene accounted for just under half of all medical evacuation transports and cervical SCI represented 30% of requests for helicopter transfer. There is a room for improvements aimed at cutting total transport time eventually improving chances for prompt access to expert management (Fleming et al., 2016).

Pre-transport Check List:

Before each transfer, the healthcare teams involved usually work towards securing safety and quality of SCI patients transfer. This includes securing airway, breathing, oxygen supply, circulation, stable blood pressure measurements, vascular access, NGT insertion ensuring stomach is decompressed, urinary bladder drainage and establishing monitor of urine output. In addition to this, the entire spine is immobilised before transport using appropriate devices (e.g. Russel Extrication Device, Ambu or Stifneck Collar) and pressure over bony prominences has been relieved and cushioned. At times, it might be necessary to establish endo-tracheal intubation and ventilation of patients with high cervical and serious injuries or have associated reduced level of consciousness. In some instances, a chest X-ray might be necessary for this initial assessment, however all SCI patients should have pre-transport baseline full neurological assessment of SCI level and extent of injury.

Admission to Hospital, Initial Resuscitation and Clinical Management:

Sub-group of SCI patients, especially those with minor clinical neurological deficits, might be admitted to non-SCI hospital settings. Most of the SCI patients comprising this sub-group, generally suffering minor and minimal neurological deficits possibly displaying ongoing or eminent recovery, are likely to be discharged from hospital with no formal diagnostic tag of SCI attached. This very sub-group of individuals with minimal neurological deficits and prompt recovery, escaping recognition and inclusion in the records as SCI, leads to substantiated impression that SCI is globally under-reported clinical entity.

Acute and Critical Care of SCI: Caring for the acute phase of traumatic SCI requires robust quality management of acute injuries using modern evidence-based therapeutic interventions.

The steps of management include resuscitation and restoration of deranged cardiovascular or respiratory functions as priorities, alongside resuscitating and preserving the spinal cord and functions especially in high cervical injury which frequently requires ventilator support.

Pharmacological Therapeutic Interventions:

A systemic review for Cochrane database was performed in the USA (Bracken, 2012) looking at the randomised trials of pharmacological. It assessed therapies used for acute SCI to limit extent of secondary injuries to eventually reduce permanent paralysis and loss of function. It was reported that high dose methyl-prednisolone (MEP) steroid therapy is the only pharmacological therapy that is shown to have efficacy. High dose MEP has been shown to improve neurological outcome, indicated by significant recovery in motor function, up to one year post injury. The MEP need to be administered in a dose regimen comprising an initial bolus dose of 30mg/kg of body weight over 15 minutes, followed by a maintenance dose in the form of an infusion drip of 5.4 mg/kg of body weight per hour for the subsequent 23 hours. The high dose MEP need to be administered immediately, as soon as possible or at the very latest within 8 hours of the onset of SCI as it was found in phase-3 randomized trial. It has also been indicated in another trial that additional benefit on the recovery outcome might be gained by extending the maintenance dose from 24 to 48 hours. This would be especially true if the start of the high dose MEP treatment was initially delayed for 3-8 hours post injury. High dose MEP is accepted as a standard drug therapy in many countries now but there is still need for more trials to study other potential therapeutic agents.

Surgical Decompression & Stabilisation

In management of acute SCI, surgical intervention might be necessary to alleviate pressure of injured spinal cord, treat associated tissue injuries and stabilise fractures. A prospective Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) pilot study (Ng et al., 1999) examined the difficulties and barriers precluding the performance of acute surgical decompressive procedures within the critical 8-hour time window to improve the final neurological outcome. The study examined feasibility of obtaining radiological diagnoses of spinal canal compromise of 25% or more and performing spinal cord (C3-T1) decompressive procedures within the 8 hours post injury time period. Significant difficulties were encountered performing immediate MRI for patients with acute SCI, and fewer than 10% of acute cervical SCI patients were managed through the surgical protocol. Patients received one of three decompressive methods including traction alone, traction and surgery and surgery alone. Total time delay exceeded the 8-hour ‘injury to decompressive surgery’ window, because of combined

time required for rescue, resuscitation, transport, imaging study and surgical preparation. It was highlighted that several major changes were still required to be embraced to enhance early interventional and decompressive therapy including surgery.

Continuing Hospital (inpatient) Care and Clinical Management:

The hospital care management of SCI patients include other medical and nursing measures. These include observation, monitoring and correction of vital organ and system functions using conventional evidence-based medications and procedures to eventually improve overall healthcare. The inpatient care provided in hospital or SCI centre also include promoting early physical and functional rehabilitation besides caring for their psychological wellbeing, emotions and socioeconomic issues assisting in management and recovery outcome of affected individuals. Anti-emetic medications might be used especially prior to transfer to combat nausea, and sometimes in combination with narcotic analgesia, which might be used in small amounts orally or intravenously for the management of pain experienced in SCI or other associated injuries while monitoring consciousness for any signs of drowsiness. In some clinical instances, delivery of oxygen under pressure in hyperbaric chamber used to alleviate tissue hypoxia within 8-hours from initial injury. Periods of hypoxia might hamper recovery of SCI function post injury.

Prevention of Skin Pressure Ulcers:

Pressure ulcer prevention remains one of the most important aspects of caring for SCI patients and other medical conditions with various forms of physical disability leading to potential prolonged periods of recompense. Attention is paid to relief of pressure off the skin over bony prominences especially skin over the sacrum and heels. SCI patients are usually lifted briefly every two hours and supported using devices such as the Jordan Frame. However, these forms of patients' transfer should be used for the shortest practicable periods of time with no lumps or straps left to pressurise the skin. Patients' lifting and turning used to be done manually by at least 4 trained personnel plus one supporting the neck. However, modern occupational health guidelines are increasingly promoting minimal manual handling, putting in place policies, procedures and making available devices to make it possible. Heel protection including foam or sheepskin padding is also routinely used in modern clinical practices (Rajpaul and Acton, 2016). Similar sheepskin, foam pad or special mattress might be inserted under the sacrum following careful lift of the patient's pelvis. No potential lumps should be left to possibly create pressure on skin, including the removal or keys and money from pockets and possibly removing of all hindering clothes might be necessary.

Some of the devices used in the prevention of pressure ulcers that might affect SCI patient's skin are sown in (Figure 2:09).

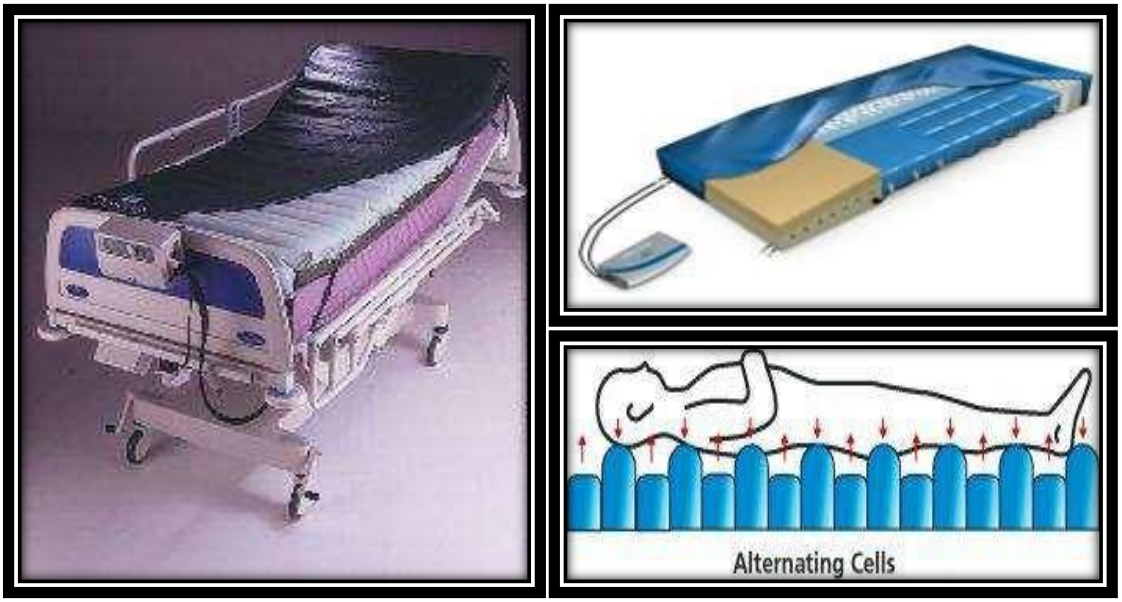


Figure 2:09: shows pictures for pressure alternating and dynamic system bed (left), air mattress with attached electric pump attached (right-top) and schematic illustrating the distribution of weight of a patient using pressure alternating dynamic systems (right-bottom) – from www.arjo.com).

Spinal Injuries Units Caring for SCI Patients:

There is evidence showing that the clinical management of SCI patients by dedicated comprehensive teams produces the best outcomes for SCI patients. Involvement of specialist teams close to onset of traumatic SCI for restoration of mobility, functionality and reintegration into the community is crucial in achieving good outcomes. There is an obvious rationale for including services directed at managing patients with SCI into frames of national service definitions and management guidelines. In the United Kingdom, this model was exemplified by the Specialised Services National Definitions Set (SSNDS) initiated by the health authorities to define priorities, guide health care professionals, direct resources and drive towards a positive change in the management of SCI patients (SSNDS, 2010). Hence, SCI patients and experts looking after them are concentrated in relatively few specialist centres considering population catchment. In total, there are 11[1] spinal injuries centres in the whole of the UK, of which 8 are in England and one centre in each of Wales (Cardiff),

[1] SIA Spinal Cord Injuries Centres. Updated July 2014 Spinal Injuries Association Registered Charity Number: 1054097.

Northern Ireland (Belfast) and Scotland (Glasgow) each operating to serve the corresponding population.

Obviously, centralisation of services was made necessary by the fact that, care for SCI was a naturally low volume, high cost service. In addition, SCI usually results in multi-system physiological dysfunction and multi-system pathological involvement both with significant potentials for developing complications. Therefore, the management of SCI patients is obviously a multi- specialist task each forming part of the total effort delivered by the multi-disciplinary team caring for SCI patients.

Provision of Hospital Care, Health Burden and Economics of SCI:

As indicated in above sections, caring for the acute phase of SCI remains challenging, often demanding of the highest standards of modern medical practice. It frequently requires the full engagement of highly trained personnel, clinical expertise, well-rehearsed clinical guidelines and practice protocols, policies and procedures running spinal injury centres and certainly ample of resources including equipment, procedures, medications and prolonged bed occupancy. This level of demand for instant and high-quality care serving SCI patients mounted excessive cost and high economic burden on healthcare provision for nations.

This lead to innovative ways of enhancing the care of individuals with SCI and fund the specialty centres caring for patients with SCI. ***The National Institute on Disability and Rehabilitation Research (NIDRR) of the USA*** is a component of federal agency that supports applied research, training and development aimed at improving the lives of individuals with disabilities. NIDRR is therefore committed to generating new knowledge and promoting its effective use in improving abilities of persons with disabilities. This enables these individuals to perform activities of their choice in community including improvement of activities of daily living (ADL). NIDRR is also expanding society's capacity to provide full opportunities and accommodations for citizens with disabilities. NIDRR accomplishes this mission improving SCI outcomes through funding, monitoring and promoting Model Spinal Cord Injury Systems (MSCIS) Program. This MSCIS programme involves covering cost of treatment of SCI patients in return for excellence in practice and research standards, of which collaborative research been one successful aspect.

It was shown that collaborative research is advantageous and superior to single centre studies, especially in areas around generating larger numbers, turning out quick results, producing broad-based samples and more generalised results and facilitating the use of more expertise than possible for a single research centre.

2.3.6 Rehabilitation and Monitoring of Clinical Recovery of SCI:

Introduction

Rehabilitation is an important concept and vital aspect of managing individuals who suffer SCI. It assists patients achieving their optimum recovery potentials, implement modifications necessary for them to cope with loss of motor and sensory functions, and eventually improve and possibly shape the final outcome of SCI. Increasing knowledge and experience in the treatment and rehabilitation of SCI patient brought a considerable wave of optimism which highlighted ever improving recovery prospects of SCI towards much better outcomes (Morawietz and Moffat, 2013). Full knowledge of the exact prognosis of individual SCI is lacking, and prediction of any possible neurological recovery is very challenging and frequently unavailable. It has been suggested that SCI patients who sustain mild to moderate disability scored well in the recovery of physical and psychosocial functions, with the most important predictors of recovery being age and co-morbidity. Most functional problems were experienced in categories relating to work, ambulation, home management and recreation. As previously indicated, type of injury was a good predictor of recovery of both psychosocial and physical functions after more than one year post injury. This is especially true of injuries that involved trauma to brain, spinal cord and extremities.

Independent of characteristics and extent of SCI and patients affected by them, it seems that rehabilitation works. The emphasis is that timely and quality rehabilitation received following traumatic SCI offers affected individuals the best chances they might have for neurological recovery and betterment of future outcomes. It is common knowledge that early introduction of rehabilitation is vital for SCI patients. Timing matters in rehabilitation of SCI patients because early introduction of processes involving mobility and retraining of muscles and nerves captures the potentials for neurological recovery. Rehabilitation offers SCI individuals' chance of the normalising posture, regaining and retaining physiology and mobility which are essentially limiting further damage such as pressure sores and vascular stagnation.

The longer SCI patients stay in acute hospital settings with limited rehabilitation potentials, the more complications and less recovery potentials they develop. Besides length of stay, incidence of deep vein thrombosis among SCI patients also increased in high body weight, males, complete motor paralysis, longer hospital stay, associated pelvic or lower limb fracture and delayed admission to specialised spinal (Clements et al., 2017).

It has been established that ***deep vein thrombosis*** (DVT) might be seen due to the increased length

of stay of patients with SCI in acute hospital settings, which effectively delays the start of early rehabilitation (DiGiorgio et al., 2017). In acute settings, the cumulative incidence of venous thromboembolism (VTE) including DVT cases recorded in patients with traumatic SCI is 4.1%, mainly been related to extended length of stay in hospital, recumbence and delayed access to rehabilitation. Patients with traumatic SCI developing VTE are nearly 4- times likely to have stayed around 12 or more days in acute care settings compared to non-DVT groups adjusted for other variables. Average length of stay in acute care was found to be 32 days, largely affected by quality of care provided in acute settings and funding issues. These included weather patients were in possession of suitable insurance funding that provide adequate cover that comfortably shoulder the relatively very high cost of treatment and rehabilitation.

Principles of Rehabilitation designed for SCI Individuals:

The principles of rehabilitation combine ***physical therapies*** with ***skill-building occupational*** activities. There is an early attention to psychological and emotional aspects with the appropriate ***counselling*** providing ***social and emotional support***. It has been established that most SCI patients at some stage feel frightened, anxious, or confused about the SCI experience however with significantly great variation. It is common for SCI individuals to have mixed feelings of relief that they are still alive and disbelief at nature and extent of their new disabilities. Therefore, ***education***, ***motivation*** and early ***active involvement*** of SCI individuals, their ***carers, families*** and ***friends*** are vital in boosting recovery potentials. It is becoming increasingly important to educate newly injured individuals to enable them manage consequences of their neurological impairment and disability. For long-term coping, empowerment and self-efficacy seem crucial for independence and self-management. As rehabilitation progresses ongoing education incorporates teaching strategies to develop key skills for successful rehabilitation outcomes from different methods (Morawietz and Moffat, 2013). Rehabilitation of SCI patients is usually lead by medical doctors who specialise in the field of rehabilitation medicine. The rehabilitation team contains other clinicians including Specialist Nurses, Physiotherapists, Occupational Therapists, Psychologists, Social Workers, Recreational Therapists, Nutritionists, Vocational counsellors, Case Workers and possibly other specialists depending on individual needs, as follows:

- **Communication skills:** writing, typing, using telephone or computer keyboard need to be boosted to match pre-injury skill levels. Therefore, these might require adaptive or assistive devices especially for some SCI individuals with tetraplegia.
- **Physical Therapy:** exercises meant to re-establish mobility and regain leg and arm strength.

This, for some SCI-injured individuals, might only be possible with devices such leg bracers, walkers or wheelchairs. These adaptive devices help SCI individuals to increase mobility, regain independence and improve quality of life. Other assistive technology which might be used includes electronic stimulators, assisted gait training (*with neural prostheses or without as in manually-assisted),* including body-weight support (BWS) and treadmill training, computer-assisted technology and many other computer-based adaptations. BWS

- **Occupational Therapy:** includes assistance to redevelop fine motor skills needed for activities of daily living such as getting in and out of bed, self-grooming and self-feeding as well as bladder and bowel management programs teaching basic toileting routines. SCI individuals acquire coping strategies for recurring episodes of spasticity, autonomic dysreflexia and neuropathic pain episodes.
- **Vocational Rehabilitation:** identifies basic work skills, physical and cognitive capabilities of SCI individuals for purpose of employment. It identifies potential work places and any assistive equipment needed and arranging user-friendly workplace. If necessary, it arranges educational training to develop skills for new lines of work that are less dependent upon physical abilities, but utilise computer or communication skills. Individuals with SCI that is incompatible with re-joining the workforce are equally encouraged to maintain productivity. Sense of satisfaction and boosted self-esteem was achieved by participation in activities including suitable educational classes, hobbies, membership of special interest groups, family and community events and functions.
- **Recreational Therapy:** encourages SCI individuals to participate in recreational activities and sports suitable to their physical abilities and level of mobility aiming at balanced lifestyle providing opportunities for socialization and self-expression.
- **Other Therapy and Specialist Rehabilitation:** there are many other specialists working in the rehabilitation group towards reinstating skills and functions lost to SCI building confidence and independence in individuals recovering from SCI.

Methods and Procedures in Common Use in Rehabilitation of SCI:

Over time, many methods and procedures were developed to cater for varying types and extents of SCI as part of other CNS impairments. Some methods and procedures were specifically designed for SCI individuals to assist better mobility and promote independence by regain much more effective functionality. There seem to be little evidence of effectiveness of locomotor therapy over other methods, as all approaches show potential for improvement of ambulatory function without superiority of single approach over another (Morawietz and Moffat, 2013). Some

methods and procedures used in current SCI rehabilitation centres include:

Treadmill Training:

Principles of treadmill training (TT) with body weight support (BWS) commonly abbreviated as (BWSTT) or even without BWS has been described as beneficial to improving functional ambulation following SCI (Hicks and Ginis, 2008). However, it is a demanding training method and labour intensive for SCI patients and therapists, yet with reports suggesting lack of superiority of BWSTT as locomotion training over other conventional methods on improvement of ambulatory function (Morawietz and Moffat, 2013). Nevertheless, there are other functional values for BWSTT extending towards improving the functional ambulation of SCI. These include cardiovascular effects and fitness, muscle composition and metabolism, fat and bone mass, in addition to clear psychological benefits associated with body-upright exercise benefits to patients with acute and chronic SCI (Hicks and Ginis, 2008). Treadmill training is increasingly used in rehabilitation after incomplete spinal cord injury. It has been studied in spinal cats, where treadmill accelerates locomotor recovery and improves weight bearing during treadmill walking. However, there were no additional benefits of or changes observed when systematic treadmill training was used in search for any additional improvement (Fouad et al., 2000). Treadmill training combined with electrical stimulation improved muscle movements in SCI even with complete lesions, with possible metabolic, cardio respiratory responses and bone mineral density. These changes were reported to be associated with better coordination of voluntary and autonomic muscle and nerve functions with no clear causal links established (D'Ancona et al., 2010). ***Over-ground Walking*** has largely been assessed in relation or combined with treadmill training which improves over- ground walking ability in SCI patients. For instance, overground locomotor training programme was tried with two 90-minute sessions per week for 12-15 weeks also involving joint mobility, volitional activation, task isolation, task integration and activity rehearsal. It was found that this overground locomotor training is feasible and improved the speed and economy of overground walking in chronic cervical SCI (Gollie et al., 2016).

Partial Body Weight Support Walking:

This has been tried alone but largely in combination with other locomotor training including treadmill training and assessing over-ground walking with or without electrical stimulation. Body weight support (BWS) and treadmill training (TT) rely on spinal cord neurons' capacity for learning independent of the brain improving walking ability in patients with paralysis from SCI (Behrman and Harkema, 2000). Locomotor training with bodyweight support is shows up benefits rehabilitation of patients with SCI. It was found that irrespective of the training protocol used, patients with SCI benefit with increase of muscle strength, maintaining or increasing bone

density, decreasing heart rate and physical conditioning (Dutra et al., 2013). It seems that body weight support (BWS) locomotor training, although it proved effective in promoting recovery of load-bearing stepping in lower mammals, it scored limited efficacy in patients with SCI where outcomes largely depend on severity of SCI (Cote et al., 2016). However, the combination of partial body weight-supported treadmill training improves gross motor skills in patients with CNS disorders (Su et al., 2013).

Functional Electrical Stimulation (FES)/Use & Benefits:

Functional electrical stimulation is used in neurological rehabilitation with well-established efficacy in knee osteoarthritis and stroke. There are reports indicating the potential benefits from FES in context of activity-dependent neuroplasticity promoting functional recovery following SCI. It has been shown that the systematic application of FES in patients with SCI optimizes neural activity below level of injury. It also reduces complications and improves the overall health of SCI patients (Martin et al., 2012). There are many studies that look at variable aspects of FES and its benefits in rehabilitation when used alone or in combination with other methods mainly treadmill training (TT) and partial body weight support (BWS). There is increasing evidence that the combination of these locomotion methods works better in improving the functional outcome of patient with SCI. It has been suggested that FES cycling can provide functional improvements as measured by total motor score, FIM scores and spasticity levels. All these improvement measures are seen in later periods of recovery following SCI as patients could ambulate independently or with the assistance of a cane or walker (Yasar et al., 2015).

Combined Methods in Current Rehabilitation Settings and Programmes: It has been shown in a small group of SCI patients that combining partial weight-bearing (PWB) supported treadmill training augmented with functional electrical stimulation (FES) gave a positive effect on over-ground gait parameters. There was an increased over-ground walking endurance and walking speed, which would potentially accelerate gait training of individuals with incomplete SCI (Postans et al., 2004). This result was achieved by walking the tested subjects for 25-minutes a day, five days a week for four weeks compared to the control subjects receiving standard physiotherapy. The assessed variables included over- ground walking endurance and speed, cadence, stride length, observational gait analysis, walking speed, distance and percentage PWB support on the treadmill.

A Cochrane review of five randomised control trials found inconclusive results. There is no statistically significant superiority of locomotor training on walking function after SCI compared

to other forms of physical rehabilitation. Furthermore, there were no differences in adverse events or dropouts between different study groups. The use of bodyweight supported (BWS) treadmill training as locomotor training for SCI individuals did not significantly increase walking velocity or walking capacity.

A study of stroke patients receiving robotic-assisted locomotor training combined with regular physiotherapy positively affected functional and motor outcomes (Schwartz et al., 2009). However, the effects on patients with SCI exhibited reduced walking capacity compared with individuals receiving other forms of intervention. The sense of uncertainty of the specific types of locomotor training which might effectively improve the walking function in patients following traumatic SCI highlighted the need for further studies. Some studies compared body-weight-supported treadmill training (BWSTT) or robotic-assisted BWSTT with conventional gait training in acute and sub-acute subjects. Other studies assessed different locomotor training interventions in chronic participants. Only minor differences in outcomes measures were seen between groups albeit small sample sizes were used. Gait parameters improved slightly more after BWSTT and robotic gait training for acute participants. However, improvements were greater for chronic SCI after BWSTT with functional electrical stimulation and over-ground training with BWS and functional electrical stimulation. These were superior to BWSTT with manual assistance, robotic gait training, or conventional physiotherapy. It seems that all approaches show some potential for improvement of ambulatory function without obvious superiority of one approach over another, however combining BWS with Treadmill Training with FES offer better results in chronic SCI (Field-Fote, 2001). Nevertheless, some studies offered a different impression suggesting the need for further studies. Two randomised controlled trials showed that subjects with ASIA C or D SCI of less than one year duration reached higher scores of Functional Independence Measure (FIM) undergoing over-ground training compared with control undergoing BWSTT (Lam et al., 2007). However, no differences were seen regarding walking velocity, activities of daily living or quality of life.

Most of the currently known training procedures and rehabilitation methods are used in standard programmes embraced by many SCI centres around the UK and other industrial countries. An example of over-ground walking training is shown, assisted manually and with minimal instrumentation is shown in (Figure 2:10). This illustration shows improvement of an incomplete SCI patient over weeks of walking therapy. Follow-up picture shows an improved posture and ability towards much more skilled and independent over-ground walking.

This pattern of neurorehabilitation is clearly demonstrated in Figure 2:10 as shown (below).

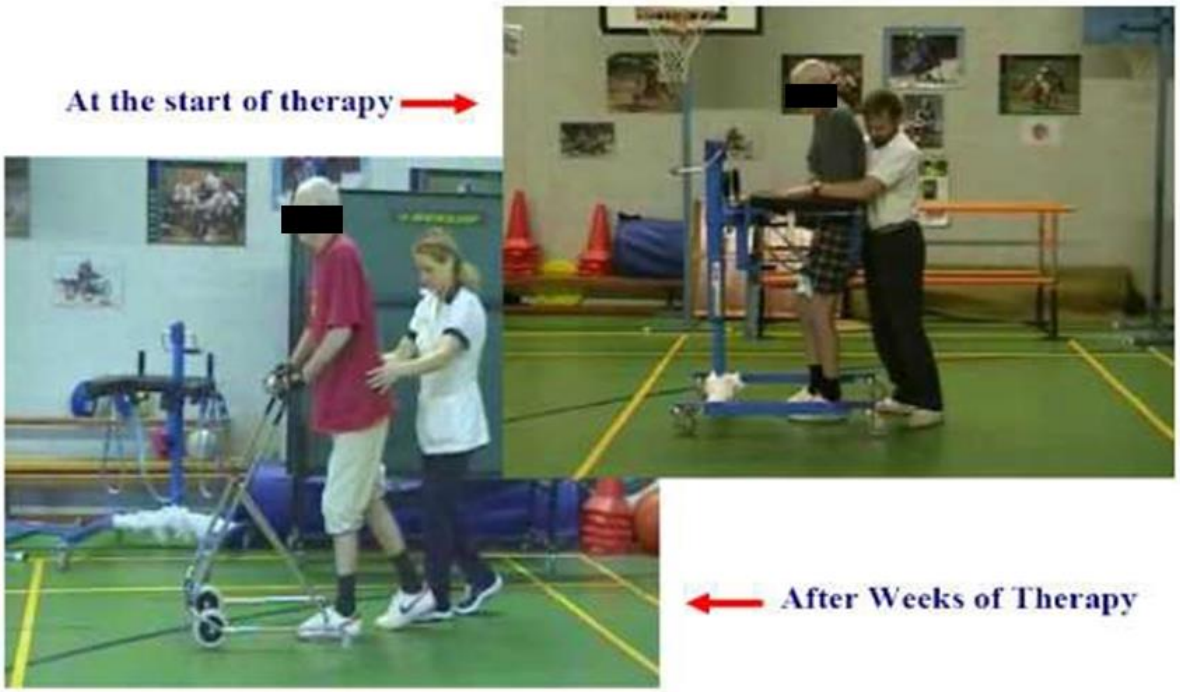


Figure 2:10: Consecutive pictures (weeks apart) of recovery SCI patient undergoing assisted walking training supervised by physiotherapists working on SCI rehabilitation. (*Source*: Field work: courtesy Jon Hasler, Physiotherapy Superintendent, Queen Elizabeth National Spinal Injuries Unit, Glasgow).

Conclusions:

There is ongoing clinical and laboratory research aimed at exploring potentials for SCI recovery. Similarly, there is accumulating work on experience gained from SCI centres, improving methods of regaining mobility and training procedures, tailored to the specific physical and psychological needs of individuals SCI patients. There is a growing optimism towards the field of rehabilitation medicine, with special reference to programs designed to care for SCI patients. An increase in sophistication and efficacy of therapy and retraining methods is evident. This is used to improve mobility and function of SCI patients with better understanding of psychology.

2.3.7 Following Hospital Discharge:

Looking at destinations of patient after discharge from hospital, it has been shown that 92% went to private residence, 4% nursing home, 2% transfer to other hospital and 2% group home. There was no obvious relationship between severity of SCI and nursing home admission however it was more common among elderly individuals. However, it is obvious that specialized rehabilitation potentially reduce discharge to nursing homes Cheng et al., 2017). Nursing home

admission is also influenced by other factors such as the presence of medical complications and the family's inability to care individuals with SCI. It has also been suggested that older individuals with SCI experienced a different clinical pathway from younger patients suggesting a need for rehabilitation programs tailored to older individuals (Hsieh et al., 2013). Each year, it has been estimated that around one third to half of all individuals with SCI get re-admitted to hospital, with skin and urinary complications being the most frequent causes for readmission (Savic et al., 2000). There is an obvious difference between complete and incomplete injuries; however, there was no difference in re-admission rates between individuals with paraplegia and tetraplegia.

Conclusions:

It should be emphasised that post-hospital discharge, rehabilitation effort should continue to improve the quality of life of individuals with SCI in tandem with any possible residual score expected in the recovery curve of their individual SCI lesions. Healthcare professionals, carers, family, family and community are in great call for assisting this transitional process, improve understanding and remove as much possible of misconceptions and barriers to progress.

2.3.8 Natural History and Outcome of Traumatic SCI (Prognosis)

The natural history following SCI and the prediction of outcome of patients treated for SCI remains challenging and it remains difficult to assign prognosis to patients with given SCI lesions in hospital settings. SCI patients battle with the initial injures and challenging acute phases, endure prolonged hospital stay and treatment, overcoming massive psychological and emotional difficulties. Patients then go through demanding rehabilitation programmes, get discharged out of hospital or spinal unit and eventually phase into a different stage of living with chronic SCI in the community. This chronic phase of SCI in the community is a complete and potentially permanent overturn of the living circumstances known to these individuals prior to the SCI. The terms of this new living style, health circumstance and perceived quality of life (QoL) all depend on level and extent of initial SCI, clinical neurological improvement achieved going through earlier phases of treatment and rehabilitation and support and resources (e.g. assistive technology, finance, home care and transport) made available to individuals affected by the SCI.

Phasing into Chronic SCI

After initial care, hospital treatment and rehabilitation, individuals with SCI phase into a chronic phase of SCI, reality of living with residual effects of SCI, possible physical disability and dents on psychology, emotions and socioeconomic status. The care of SCI patients requires attention to

multiple bodily systems, sensitivity to the effects of interventions on function and lifestyle, and a special vigilance because of the tendency of spinal cord injuries to mask problems. Improved clinical care, however, has increased the life expectancy of people with spinal cord injuries and therefore the prevalence of such injuries. The Americans with Disabilities Act in the USA and similar legislations elsewhere (e.g. Disability Discrimination Act 1995 in the UK) should make people with spinal injuries more visible, as they participate in and contribute to society in greater numbers with legal powers not to be denied access to services. Maintenance of health brings greater opportunities for self-care and mobility through rehabilitation and may allow people with SCI to take advantage of future opportunities for neurologic improvement or cure.

Complications of Sub-Acute and Chronic SCI

SCI predispose affected patients to numerous complications, and associated risks of developing secondary conditions that adds to the individuals' co-morbidity, health burden, mortality and overall outcome. These conditions include deep vein thrombosis (DVT), urinary tract infections (UTI), muscle spasms, osteoporosis, pressure ulcers, chronic pain and respiratory complications. It has been emphasised that these common medical complications have impact on rehabilitation, long-term follow-up for individuals with SCI and possible final outcome. There is an ongoing care demands on addressing complications of SCI that might constitute barriers to early and effective rehabilitation. These include pressure skin ulcers, unilateral lower-extremity swelling usually as a result of DVT, hetero-topic ossifications and fractures. It is also vital to understanding the pathophysiology causing some of the medical complications and other related phenomena which frequently encountered in most patients with SCI lesions. Besides the sound baseline knowledge of these conditions, which include spasticity, autonomic dysreflexia, orthostatic hypotension and pain, it is also extremely vital to gear the healthcare systems to promptly recognise, properly assess and adequately treat these conditions to improve safety, reduce co-morbidity and improve outcome. Patients in the sub-acute and chronic phases of SCI develop a range of medical complications and health care issues that require long term care from general practice care to specialists. Individuals surviving SCI and living with SCI-related comorbidities, exhibit multiple and diverse health issues. These require ongoing medical attention with visits to outpatient clinics for advice. The ongoing care includes services linked to prescribing medications, procedures, assistive devices, pain clinic management protocols, reviewed admissions and treatment of any relevant complications to existing SCI.

Psychological and Emotional Impact of SCI:

The early stages of SCI, the process of phasing into chronic SCI and the potential long-term residual physical deficits for previously healthy individuals, all put obvious and significant strain on the emotions and psychology of these SCI sufferers. It has been estimated that up to one third of individuals suffering SCI show significant clinical signs of depression. This has a negative impact on potential rehabilitation improvement, recovery, physical functionality, mental strength and overall health. It should also be noted that SCI have a negative impact on mental health with significant psychosocial distress in immediate post-injury period all the way to post-discharge from hospital (Craig et al., 2015). Studies found that the rate of suicide is high among individuals with SCI as part of spectrum of person with disabilities including multiple sclerosis and learning disabilities (Giannini et al., 2010). Another study lasting close to four decades in Denmark assessed the relationship of the functional status following SCI and risk of suicide. In the 888 patients with SCI included in the study, 236 (26.6%) died out of whom 23 (9.7%) committed suicide making a third of all recorded mortalities following SCI. It was highlighted that this SCI-related suicide rate was nearly five times higher than the expected general population, and the rate was lower for men than for women involved. Unexpectedly, the suicide rate in individuals with marginal disability was nearly twice as high compared to the group suffering functionally complete tetraplegia. Furthermore, it has been shown that the suicide rate has doubled over the later period of 1970s to the 1990s compared to the 1950s through to the 1970s (Hartkopp et al., 1998). It was highlighted that there is a need for raising awareness among general practitioners (GPs), hospital clinicians and rehabilitation staff regarding depression, psychological adjustments and emotional difficulties. Special attention to the early symptoms and signs of mental health disorders during initial phases of hospitalisation and rehabilitation might eventually assist in reducing the high suicide rates attached to sufferers of SCI.

Baseline Mortality:

As it was indicated by the WHO, risk of mortality is highest in the first year after SCI and remains high compared to the rest of the population. It has been highlighted that 85% of patients who survive the first 24-hours of SCI are still alive 10-years afterwards, compared to 98% of uninjured age and sex matched controls from the general population. Individuals with SCI are 2–3 times more likely to die prematurely than people without SCI. The risk of mortality increases with severity of SCI and injury level and is strongly influenced by access to quality health care and medical facilities. The most common causes of death are related to respiratory disorders followed by renal failure, with no significant recent changes. Secondary conditions such as

infections from untreated pressure ulcers are no longer among the leading causes of death in individuals with SCI in high income countries. These health conditions frustratingly remain the main causes of death of SCI individuals in low-income countries.

Overcoming Barriers and Improving Care of SCI Patients:

Many of the consequences associated with SCI do not result from the condition itself but from secondary changes and complications brought about by inadequate medical care and rehabilitation services as well as barriers inherit in physical, social and policy environments. There are many misconceptions, negative attitudes, physical and conceptual barriers to basic mobility leading to exclusion of SCI individuals from full and active participation in local communities and society at large. It has been observed that children with SCI were less likely to start school and when at schools are less likely to advance compared to their peers with no SCI. Adults with SCI face similar barriers to economic participation, partly contributing to low unemployment rates globally estimated to be over 60% among individuals suffering SCI (Ferdiana et al., 2014). As potentially disabling medical condition, SCI affects socioeconomic status of individuals similar to the effects on their baseline health and physical abilities. SCI might render individuals who were otherwise healthy prior to injury, dependent on caregivers. At the stage of non-recovering residual disabilities, the use of assistive technology might often be necessary to facilitate mobility, communication, self-care and performing domestic and activities of daily living (ADL) (Platts and Fraser, 1993). In the same line of thoughts modifications of motor vehicles enabled SCI individuals to benefit from this means of mobility (Tsai et al., 2014). The same approach is true for children and adolescents with increasing potentials for use of these technology for improving functional outcome and independence (Bryden et al., 2012). In the past, SCI carried a tough sentence characterised by confinement to wheelchair, bed or home and lifetime impaired health and medical complications. Treatment and readjustments available for clinicians, nurses and rehabilitation staff to offer to individuals with SCI was very limited as far back as the 1990s causing lots of frustration and mental distress. The modern advances in neurosciences enhanced research into SCI with beneficial effects on healthcare as well as extended hope for novel advanced therapeutic interventions that might realise the hopes for regeneration and significant functional recovery. These scientific advances reduced level of scepticism and gave way to firm understanding believing that SCI lesions would eventually be repairable and therapeutic strategies would aim at full restoration of spinal cord function.

Effect of Improving Health Care Standards:

It is indicated by WHO that mortality rates remain significantly higher during the first year after

injury than during subsequent years. However, it has been observed that an increasing number of individuals with SCI dying of totally unrelated causes such as cancer or cardiovascular diseases very similar to the general public. This has been seen as possibly owing to much improved access and quality of health care in association with better living standards made available to individuals affected by SCI. Furthermore, WHO made further reports and recommendations aimed at enhancing reintegration in the community and support of individuals with SCI as they are coming out of hospitals and health institutions and starting long journeys living with SCI (WHO, 2013). Measures include legislations, policy and programmes intended to promote the following:

1. Improving access of physically disabled SCI patients to homes, schools, workplaces, hospitals and transportation.
2. Inclusive education, with efforts to eliminate discrimination in employment and education and work settings.
3. Vocational rehabilitation to optimise employment opportunities.
4. Financial measures and self-employment benefits to boost individuals seeking and achieving alternative forms of financial self-sufficiency.
5. Access of SCI patients to social support and benefits that is not discouraging SCI individuals returning to work.
6. Correct understanding of SCI and positive attitude towards living with it.

In contrast with these efforts and measures aimed at improving care of individuals with SCI and overcoming barriers to their full functionality and integration into their communities, the situation remains far from accomplished for less advantaged populations and well-funded health and social programmes. Only fraction percentage (5-15%) of people in low and middle income countries have access to the assistive devices they need.

Physical Fitness of SCI and Competitive Sports:

The improving approach to the physical disabilities and mental health of individuals with SCI along with better understanding, available support and resources, eventually lead to success in improving the quality of lives of these individuals. An example of a major breakthrough in the improvement of physical health and mental strength of individuals with SCI has been the increasing fitness and participation in sport. SCI individuals with improving physical performance took part in sports at personal levels as well as national, regional and international competitive levels achieving records of significantly improved physical performance given the initial SCI lesion. The positive motive is that there is no evidence that intense training and competition is harmful for individuals with SCI and health benefits from exercise are not just restricted to the non-disabled person. However, there are special areas of risk that need observation and monitoring. These include effects of sensory impairment, temperature

regulation, cardiovascular and autonomic functions, any risk of autonomic dysreflexia as areas of heightened health considerations and require close monitoring. Endurance training improves exercise performance and exercise tolerance for individuals with paraplegia and tetraplegia. Sport and exercise activities included wheelchair pushing, arm crank ergometer, aerobic swimming, ambulation training, canoeing and wheelchair basketball. It was also found out that endurance training improves cardiovascular health and eventually long-term effects such as reducing cardiovascular survival morbidity and reduce mortality. This is because ordinary daily activities of SCI individuals are usually not adequate for maintaining cardiovascular fitness. An excellent and inspiring example is a wheelchair modification for racing undertaken by SCI individuals with paraplegia (Madorsky and Madorsky, 1983). Further more in-depth understanding from better structured studies is needed to establish more information on the potentials and benefits lying ahead for physically disabled SCI individuals. This might give some clues or insights into the possible underlying adaptation of muscles and nerves and possible neuro-plasticity. The process of extensive training eventually lead to significant improvement of the final physical performance, which has taken place with apparently the same existing and potentially unchanged baseline neurological deficits.

Prevention of SCI:

Several epidemiologic factors were identified which are important for developing programs to reduce the frequency of cord injury. SCI prevention programmes vary in understanding and contents to suit different communities dealing with SCI (Draulans et al., 2011). However, overall message and targets remains similar aiming at young age groups protecting them at this productive age. Young persons should be made aware of their risks as automobile drivers and hazards of diving in shallow water. In addition, middle-aged workers in the construction industry are at risk of spinal cord injury from falls. Elderly farmers are also at risk of falling or accidents as being crushed by overturned tractors.

2.4 Clinical (Neurological) Improvement and Recovery of SCI

2.4.1 Introduction

Clinical (neurological) improvement is said to have taken place if conventional clinical neurological examination methods demonstrate a measurable difference in various functions attributable to the spinal cord, irrespective of possible underlying reasons underpinning such an improvement. Clinical (neurological) recovery is again defined by measurable difference in clinical (neurological) status following SCI. However, the possible causes underlying these clinical (neurological) observations are perceived to be secondary to variable degrees of actual recovery of fibres mediating spinal cord functions examined. Clinical improvement or outcome of any possible neurological recovery following SCI seems to vary greatly depending on multiple factors however largely remains unpredictable. Many studies tried to find answers to important questions including weather a particular clinical (neurological) deficit caused by SCI would eventually *improve* and the *extent* of any possible clinical (neurological) improvement seen, and weather it is due to recovery fibres of the spinal cord weather partial or complete. These questions have been continuously burning the minds of SCI patients, their families and carers, as well as clinicians and health care professionals caring for them. The scientific and research community working in the field of SCI is most certainly interested in finding answers to these above questions, in addition to a most obvious though highly intuitive question of *why* changes related to clinical (neurological) improvement or recovery are taking place. In this study, the author of this thesis and co- researchers are using electrophysiological measurements trying to address a longstanding and staggering question whether neuro-plasticity or even neuro-regeneration are the fundamental processes which underlie any possible significant clinical (neurological) improvement seen following traumatic SCI.

Clinical (neurological) improvement seems to be more consistent and almost certain to take place in certain subgroups of SCI patients who sustained certain subtypes of traumatic SCI. The resulting patterns of clinical (neurological) improvement following these types of traumatic SCI might be outlined and further studied to draw answers for questions wondering about prognosis and final outcome of traumatic SCI lesions. To be able to fulfil requirements for 'potentially' answering the main question of this study, there was a desperate need to precisely identify patients with traumatic SCI who are likely to improve clinically (neurologically) from other patients who are not likely to improve. This process of identification of patients with traumatic SCI and a good potential for clinical (neurological) improvement is particularly important. It is hoped to provide basis for enabling comparison of electrophysiological measurements made at

baseline (time of enrolment into this study) with recordings made following any chosen length of a follow up period. The second recording after a period of follow up, under standard medical management and rehabilitation, is obtained once there is evidence that significant clinical (neurological) improvement measurable on the American Spinal Injury Association (ASIA) Scale ensued. Any such measurable clinical (neurological) improvement might reflect on spinal cord functions and usually reported by SCI patients as perceived favourable outcome. Once two measurements are obtained at two different occasions over follow up period of time, based on the similarities or otherwise differences seen on the resulting electrophysiological tests, this longitudinal comparison would probably give indications of the possible nature of the processes which might be underlying any improvement or recovery. Therefore, SCI patients with tendency for clinical improvement, gaining points on the ASIA Scale on clinical assessment, would most probably provide potential means for answering the main question of this study. Clinical guidelines for enrolling patients with incomplete traumatic SCI into this study were drawn and used in this study. This has been possible because there is evidence which identify subgroups of incomplete traumatic SCI lesions who possess a tendency to improve clinically (neurologically), most probably with potentials for clinical (neurological) recovery whether that is partial or complete.

2.4.2 Clinical Predictors of Recovery

The most important pre-morbid factors for survival after acute SCI are ***age***, ***level*** of injury, and neurological grade (Claxton et al., 1998:144-49).

The diagnosis of incomplete motor and/or sensory SCI lesion in patients with acute SCI, such as identifying *sacral sparing* in motor complete patients, provides good prognosis for recovery of spinal cord function (Foo et al., 1981:201-05; Schrader et al., 1987:533-35). ***Sacral sparing*** includes the identification of 'pin prick' and/or 'light touch' sensations at the mucocutaneous junction and 'deep anal sensation' on digital per rectal (PR) examination. Meanwhile, the motor component is indicated by the presence of 'voluntary contraction' of the external anal sphincter on digital (PR) examination (Waters et al., 1991:573-81). The use of sacral skin scratching (SSS) and more recently cough and sneezing reflexes, instead of the digital PR examination, to elicit an anal motor response has been advocated. Although the reproducibility of SSS, cough and sneezing reflexes in obtaining reliable test results might need to be further verified, these tests currently stand as potentially better methods being more comfortable, sensible and less intrusive examining the perineum of this delicate and sensitive group of patients. There are obviously different prognostic values for 'light touch' and 'pin prick' sensations when documented below

the level of incomplete SCI lesion. It has been documented that 70% of patients with acute motor SCI, with preserved 'pin prick' sensation below the level of the lesion, gained functional recovery of muscle strength. This is compared to less than 20% in patients with only preserved 'light touch' but lack the 'pin prick' sensation in the corresponding dermatomes (Foo et al., 1981:201-05; Crozier et al., 1991:119-21).

Based on the '***72-hour post injury ASIA score***', none (0%) of traumatic SCI patients with complete paralysis and tetraplegia (ASIA Grade A), achieved ambulatory capacity in one year. This is in contrast to 50% of Grade B (ASIA) and 87% of Grade C (ASIA) patients with incomplete traumatic SCI lesions (Maynard et al., 1979:611-16). In addition, there is a significantly reduced possibility of recovery of motor function in the lower extremities if SCI patients remain motor and sensory complete for more than ***one month post injury*** (Waters et al., 1993:242-47).

Furthermore, the successful diagnosis of specific post-traumatic SCI syndromes allows clinicians in the estimation of degrees of possible neurological improvement or recovery following acute SCI (Dietz and Young, 1996:641-52). A very favourable outcome due to very good recovery in up to 90% of patients is observed in traumatic SCI presenting as Brown-Sequard syndrome. Less recovery of around 50% is seen in patients with central cord syndrome, while the least recovery of around 16% is seen in patients presenting with anterior cord syndrome (Stauffer, 1984:532-34; Roth et al., 1990:18-23). The limitation in this approach is however related to the fact that clinical differentiation of these syndromes is rather gross. This clinical differentiation based on classification into clinical subtypes is therefore not sensitive enough to allow excellent prediction. Therefore, it would not allow accurate information on possible clinical improvement or recovery of specific neurological abilities such as locomotion, hand function and bladder function, which are all crucial in determining the overall outcome, level of performance of activities of daily living (ADL) enabling functional independence.

When traumatic SCI is complete, the greatest neurological recovery is seen in lesions which are much more rostral (cranial). Conversely, patients with more caudal spinal injuries show the least rates of neurological recovery (Tator, 1983:479-94). This fact boosts clinical observations from experience that cervical spinal cord injuries have better recovery potentials following an injury that proved to be incomplete on initial clinical assessments. This fact also brings home and enforces the information discussed above ensuring that a much more reliable clinical assessment is the 72-hour post-SCI ASIA score rather than the initial assessments at the time of SCI (Maynard et al., 1979:611-16). The excellent recovery of the cervical segments is followed by thoracic and

finally thoraco-lumbar injuries (Curt and Dietz, 1999:157-65). It is therefore perceived that the prognosis is worse in paraplegia. It has been documented that 73% of patients diagnosed with complete paraplegia at one month post SCI, experienced no clinical change in the neurological level one year afterwards. None of the patients who suffered a SCI with an initial level above T9 regained any motor function in the lower extremity (Waters et al., 1992:784-89).

An additional important factor is severity of injury in patients with incomplete SCI. It has been observed that regardless of the level involved, neurological recovery is hampered by the severity of traumatic SCI manifested clinically in the initial neurological deficit. It has been stated that SCI patients with greater neurological deficit at the time of injury, suggesting more severe injuries, show much less favourable neurological recovery in future (Tator, 1983:479-94).

In certain clinical circumstances, neurological recovery might be predicted by the likelihood of descent of motor level observed on initial clinical assessment. It has been observed that motor strength of Grade 2–5 on Medical Research Council (MRC) muscle strength grading system at a given level (*exemplified by C5 Biceps*) on one week post injury, would result in patients gaining functional muscle strength ≥ Grade 3 at the motor level immediately below (caudal) to it (*exemplified by C6 Extensor Carpi Radialis*) (Ditunno et al., 1987:287-90). For instance, in complete tetraplegia, 90% of muscles strength Graded 1 or 2 at one week to one month post-injury, eventually recover some strength Graded ≥ 3 on MRC. Meanwhile, muscles with Grade 0 at one month post injury and are located below the most caudal functioning motor level still recover however at variable rates. Muscles which are only one level below the functioning motor level recover by a rate of 27%, however if muscles are located two levels below, they tend to recover by a much lower rate of 1% (Ditunno et al., 1982:431-36; Waters et al., 1993:242-47).

Correlation between osseous injuries (fractures) and neurological improvement or recovery shows that ‘anterior dislocations’ and ‘fracture dislocations’ are much more likely to result in complete SCI than ‘burst fractures’ or ‘compression fractures’ (Tator and Benzel, 2000:15- 19). However, the impact of this fact on future potentials for neurological improvement or recovery has not been certain. It has also been observed that the less intensity (severity) of the SCI lesion (being incomplete) and less documented vertebral displacement (being under 30%), are associated with statistically better neurological improvement or recovery outcomes. There were no correlations between neurological improvement or recovery and other variables including the degree of vertebral wedging, type of fracture (compression or flexion- rotation), method of fracture management weather conservative or surgical intervention (Bravo et al., 1996:164-66).

It has been emphasised that the degree of motor recovery following SCI sustained by stabs to the spine is no greater than other aetiologies previously reported when controlled for level and extent (completeness or not) of SCI (Waters et al., 1995:98-101). The prediction of a worsened neurological status in six weeks post injury was weakly associated with the presence of spinal cord oedema seen on MRI. On the other hand, findings of spinal cord haemorrhage, contusion and oedema were not associated with the diagnosis of complete SCI (Shepard and Bracken, 1999:833-37).

Treatment with high dose corticosteroids or surgical intervention had no significant effect on the outcome of traumatic SCI, but only the pattern of injury in relation to level and severity was found to be the main determinant of any possible recovery (Poynton et al., 1997:545-48). It has been expectantly pointed out that patients treated in Acute Spinal Cord Injury Units (ASCIU) were clinically better. This was seen in the facts that patients treated in ASCIUs showed significant increase in rates of neurological improvement or recovery (doubling the neurological scale used), reduction of the length of stay (LOS) in hospitals and eventual reduction of the overall mortality (Tator et al., 1995:254-62).

2.4.3 Timing of Clinical Assessment

An ***initial clinical examination soon following acute traumatic SCI*** is important for documentation purposes. This is usually performed at the Accident and Emergency (A&E) department however it is usually difficult to perform and might lead to errors. On the other hand, the '72-hours post injury examination' is superior to the initial A&E examination and much more reliable in judging long term prognosis (Maynard et al., 1979:611-16; Brown et al., 1991:546-48). Therefore, this later '***72-hour post injury clinical examination***' has been used to decide post-SCI neurological status and relate it to any possible prediction of recovery of SCI lesions. This later assessment might be used to predict outcome of SCI in the first week as imperative to rehabilitation assisting in justifying and readjusting planning of further clinical management, therapeutic interventions and rehabilitation programmes (Crozier et al., 1992:762-67; Ditunno, 1999:361-64; Ditunno et al., 2000:389-93; Marino et al., 1995:510-13).

Another commonly used timed assessment (or examination interval) in ascertaining neurological deficits and predicting any possible improvement or recovery on clinical grounds is '***one month post injury***' examination (Waters et al., 1991:573-81). This timing or elapsed interval is important in clinical assessment because it is closely corresponding to the time when SCI patients are admitted to the rehabilitation facilities or shortly following it. However, in recent times and considerations of reforms guiding health care and medical services, SCI patients are

being admitted to the rehabilitation facilities much earlier (Kirshblum and O'Conner, 2000:1-27). At this 'one month post injury' examination, if a SCI patient remains motor and sensory complete then it is generally perceived that there a little chance of sound functional motor recovery (Waters et al., 1993:242-47). Whichever timing of examination the clinicians choose to assess SCI patients, the perceived or calculated prognoses should be based on medical literature or studies which used the same intervals or timing of the clinical assessments (Kirshblum and O'Conner, 2000:1-27).

It was observed that most of the neurological recovery expected in complete SCI takes place during the first 6-9 months. Afterwards, the rate of improvement rapidly declines to reach a plateau at 12-18 months post injury, with little or no improvement seen beyond this (Waters and Donald, 1998:195-99). This timely recovery pattern is clearly demonstrated in (Figure 2:11). This graph also shows variable extents of neurological improvement or recovery seen in SCI patients based on initial neurological deficits as measured by ASIA impairment scale (Waters and Donald, 1998:195-99; reprinted in Burns and Ditunno, 2002).

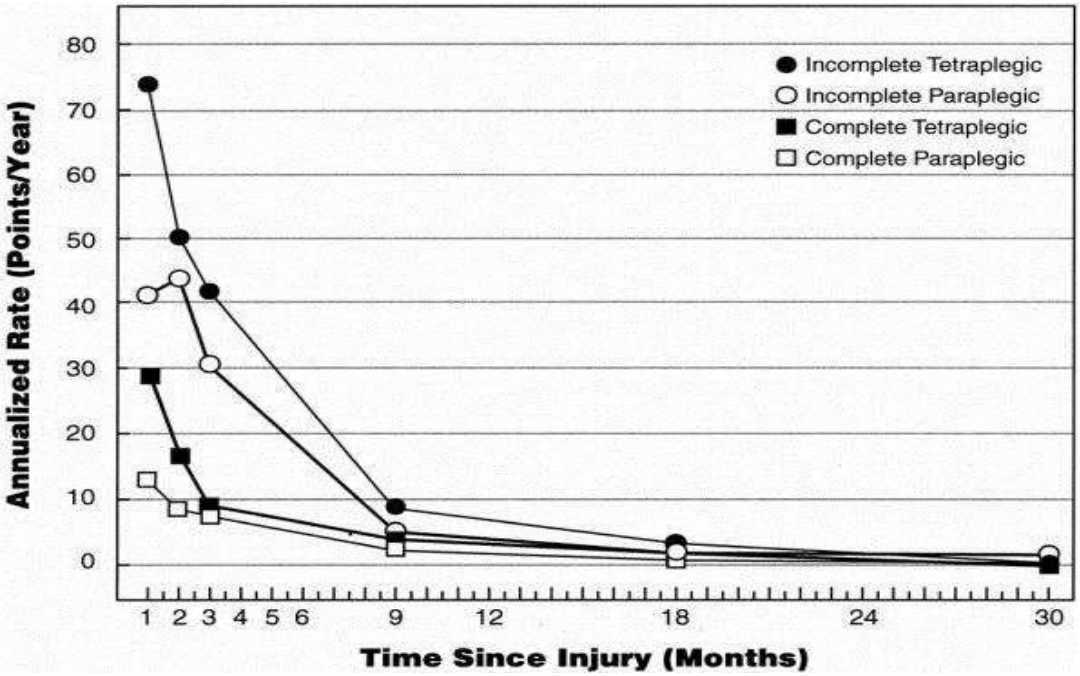


Figure 2:11: Recovery rates of ASIA motor scores for individuals with incomplete and complete paraplegia and tetraplegia based on neurological classification obtained at 1-month post traumatic SCI. (reprinting permission in Burns and Ditunno; 2002 from Waters RL. Donald Munro; 1998; 21:195-9).

2.4.4 Co-morbidity Effects on Rate and Extent of Recovery

Co-morbidity with a presence of pre-SCI disease or existence of injuries sustained other than and beside SCI, usually leads to a worse outcome. This, referred to as 'combined outcome', reflects the final outcome of traumatic SCI added to the outcome or effects of other coexisting disease or injury. For instance, the proportion of patients who gain

ambulatory function following incomplete tetraplegia caused by SCI taking place on top of pre-existing cervical spondylosis is less than that of the control group. However, the recovery of motor strength remained the same and comparable to that of the controls (Waters et al., 1996:711-15). Furthermore, it has been observed that the presence of co-morbidity or associated organ injury eventually alter the overall outcome of the SCI. These co- morbid factors are found to reduce mobility, delay the start of the rehabilitation process and effectively impair potential neurological improvement or recovery. From comparative studies on *spinal animals*, immobilization has been shown to impair recovery following SCI in rats (Little et al., 1991:408-12). Another group documented, that diabetic rats are more susceptible to compressive SCI lesions and demonstrate poor recovery following neural trauma compared to non-diabetic animals (Tariq et al., 1998:239-51). It is suggested that human individuals with Diabetic Mellitus who sustain traumatic SCI might behave similarly with regard to potential for neurological improvement or recovery following SCI. This concept might prove to be true for other neurological disorders of central nervous system (e.g. Multiple Sclerosis) as well as others that affect the Peripheral Nervous System (PNS).

2.4.5 Conclusion

It has been obvious that prediction of the outcome of SCI in particularly for each patient involved remains of utmost importance for clinicians providing health care management of SCI patients as well as planning future rehabilitation programmes. The knowledge of the predicted outcome assists in readjusting the patients' expectations and outline the specific care needs as these are widely variable for each individual patient with traumatic SCI. With forward information, the patients, their carers families and friends might be able to plan ahead and purposely modify future care and lives of these individuals in the aftermath of trauma incidents they suffered which leads to SCI. Although it is clearly useful and advantageous to be able to predict outcome of traumatic SCI, it is yet remaining difficult to achieve on clinical grounds alone. That is to say that the currently available evidence from clinical methods is very useful for outlining post injury care of SCI patients including guiding clinical management, directing therapeutic interventions and delivering suitable rehabilitation programmes. However, these clinical assessment methods can not accurately predict prognosis of SCI or precisely outline the overall outcome. It has therefore been indicated that the clinical methods need to be interpreted and used in conjunction with other non-clinical parameters such as electrophysiological tests (Curt and Dietz, 1999:157-65). In this study, it is postulated that the combined utilisation of newly introduced and other old improved electrophysiological methods can assist bringing the task of predicting the outcome of traumatic SCI much closer to realisation.

2.5 Clinical Assessment of SCI: (Diagnosing Level & Extent of SCI):

2.5.1 Introduction:

As illustrated in Chapter 1, traumatic spinal cord injury (SCI) is a disease condition which results from fairly uniform aetiology manifested by physical trauma directed at spinal cord. Nevertheless, SCI fans out displaying multi-faceted clinical, pathological, immunological, therapeutic and rehabilitation entities mostly with variable prognosis and final outcome. This is adds to the clinical heterogeneity of traumatic SCI, but it is also owing to complex healing, adaptive as well as deleterious pathological processes triggered by either the initial trauma or further secondary injuries endured by spinal cord. Therefore, significant difficulties are encountered by clinicians and scientists who are attempting to design unified protocols for assessment, therapy and rehabilitation to suit most if not all SCI patients. Patients with traumatic SCI are frequently observed to be generally diverse in many clinical, pathological or rehabilitation aspects and at times some patients are different in all of these aspects. In particular, emphasis is laid on the clinical heterogeneity because clinical assessment constitutes the means and source of very important and useful clinical information. In addition, clinical assessment might give clues of the possible underlying pathological changes and ongoing healing and adaptive processes. Therefore, accurate assessment of patients with traumatic SCI is the gateway to eventually obtaining accurate and quality clinical management needed by these patients. Complete and thorough clinical assessment of SCI patients include clinically judging level and extent of injury coupled with radiological evaluation of any possible associated structural abnormalities such as bony fractures or fracture dislocations. Initial clinical assessment phase secures sound further management of patients and increases chances of realising full therapeutic and rehabilitation potentials hoped for by SCI patients their carer and families.

2.5.2 Classification of SCI

Classification of SCI into clinical entities of similar symptoms and signs is found to ease clinical identification and management including monitoring and rehabilitation as well as hinting the possible recovery outcomes. The earliest effort of assessing, staging and classifying SCI was pioneered by a British Neurologist called H L Frankel (Frankel, 1971). Frankel introduced the first systematic classification of SCI based on the degree of residual neurological function below the level of the SCI lesion (Frankel et al., 1969). **Frankel Grades** were further refined, incorporated or integrated into the American Spinal Injury Association

(ASIA) grading injuries from A to E (American Spinal Injury Association, 2003). The **American Spinal Injury Association** (ASIA) went on to publish the **International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)** which are currently widely used. The ISNCSCI guide clinical evaluation, classification of neurological impairment and functional abilities of SCI patients.

The standard ASIA Classification, also known as **ASIA Impairment Scale (AIS)**, is defined and detailed as follows:

A = Complete (no motor or sensory function is preserved in sacral segments S4-S5).

B = Incomplete (sensory but not motor function is preserved below the neurological level, including the sacral segments S4-S5 – sparing of sacral sensations).
C = Incomplete (motor function is preserved below the neurological level with more than half of key muscles below the neurological level have muscle grades less than 3).
D = Incomplete (motor function is preserved below the neurological level with at least half of key muscles below the neurological level have muscle grade $\geq$ 3).
E = Normal (motor and sensory functions are normal).

Irrespective of the names describing SCI grading systems which are used to determine the level and extent of SCI, the key muscles in upper and lower limbs are examined neurologically and graded from 0 to 5. These 6-grades constitute the main grades of muscle strength according to the internationally agreed and most widely used system called the Medical Research Council (MRC) Scale for Muscle Strength. However, the MRC scale was criticised because it has been observed that it lacks of sensitivity, as well as claims that it being non-linear. The lack of linearity has been explained that a change of one unit on the scale (e.g. from grade 5 to 4) might represent a much greater loss of muscle force than that seen in change of from grade 1 to 0 (Mills, 1997). For these reasons, the MRC Scale was subject to scrutiny which has led to subsequent modifications and addition of sub-grades in the scale which are frequently seen in literature. An example of this is seen in the work of Bhardwaj and Bhardwaj (2009) and Jackson (2008), displaying clinically reasonable arguments for the use of sub-grades with MRC scale. Eventually, some modification attempts lead to successfully improving the sensitivity of MRC Scale middle grades (2, 3 and 4). These additions are meant to enable these middle grades of the MRC Scale, which were previously less sensitive moderate changes in muscle strength, to detect and project in the clinical assessment any minor variations in muscle strength tested. These changes to the

MRC Scale therefore might have enabled essential upgrade in the sensitivity and differential capability of the MRC Scale. A typical example of these modifications to the MRC Scale is shown below in (table 2:01):

Table 2:01: shows an example of a modification for MRC* scale used for grading muscle strength, with details of sub-grades A, B and C, which are used to separate, detect and record subtle variations of muscle strength which are otherwise not picked-up by MRC grades 2, 3 and 4. (*Source* – modified from MRC; used with the Permission of the Medical Research Council, MRC).

Grade	Subdivision	Description
0	-	No contraction
1	-	Perceptible contraction in the muscle but no movement
2		**Gravity Eliminated**
	A	Motion less than or equal to half range
	B	Motion more than half range
	C	Full range of motion
3		**Against Gravity**
	A	Motion less than or equal to half range
	B	Motion more than half range
	C	Full range of motion
4		**Motion Against Resistance**
	A	Able to lift less than 30% weight of the normal side through full range
	B	Able to lift 30–60% weight of the normal side through full range
	C	Able to lift more than 60% weight of the normal side through full range
5		Normal strength

These subtle yet detectable clinical changes of muscle strength observed during examination of SCI patients might possibly assist clinicians determine whether small neurological improvement or otherwise deterioration has taken place. Intuitively, the work of introducing sub-grades to further sub-classifying grades 2, 3 and 4 of the MRC scale, would indicate that these MRC grades are too broad. These MRC grades are incapable of separating small variations in muscle strength, detect and record them. Therefore, the MSC scale grades are insensitive to minor changes such as subtle clinical neurological recovery patterns taking place over time. Efforts continued to sub-divide middle grades 2, 3 and 4 of the MRC Scale into detailed and more sensitive sub-grades. This reflected the necessity encountered in clinical circumstances on daily basis including dealing with recovering SCI patients. From experience and clinical practice, the importance of improving the sensitivity and capability of the grades of the MRC Scale could not be over emphasised. This is partly because the fine changes of muscle strength grading measurements

obtained on clinical neurological examination are frequently observed to be taking place in the middle grades of the MRC scale, loosely fitting these rather loose grades of the scale. The work of refining the middle grades of the MRC Scale and reshaping them into definitive sub-grades aim to complement clinical neurological examination. This would be hoped to eventually address an inherent question of increasing the sensitivity and subjectivity of the MRC scale.

Incomplete injury: It is emphasised that the term Incomplete SCI (iSCI) is used when there is preservation of any sensory and/or motor function below the neurological level that includes preservation of sensation in the lowest sacral segments S4-S5 denoting presence of sacral sparing. Sensory sacral sparing includes sensation preservation weather intact or impaired (partially preserved). This would be ascertained by examination of light touch, pin prick, or deep anal pressure (DAP) tested at the muco-cutaneous junction of the anus (S4 and S5 dermatomes) either on one or both sides. Sacral sparing of motor function includes the presence of voluntary contraction of the external anal sphincter observed upon digital rectal examination (Kirshblum et al., 2011).

Complete injury: It is emphasised that the term Complete SCI (cSCI) is used when there is a complete absence of sensory and motor functions in the lowest sacral segments (S4 and S5) denoting no sacral sparing.

AIS Sensory Scoring Chart:

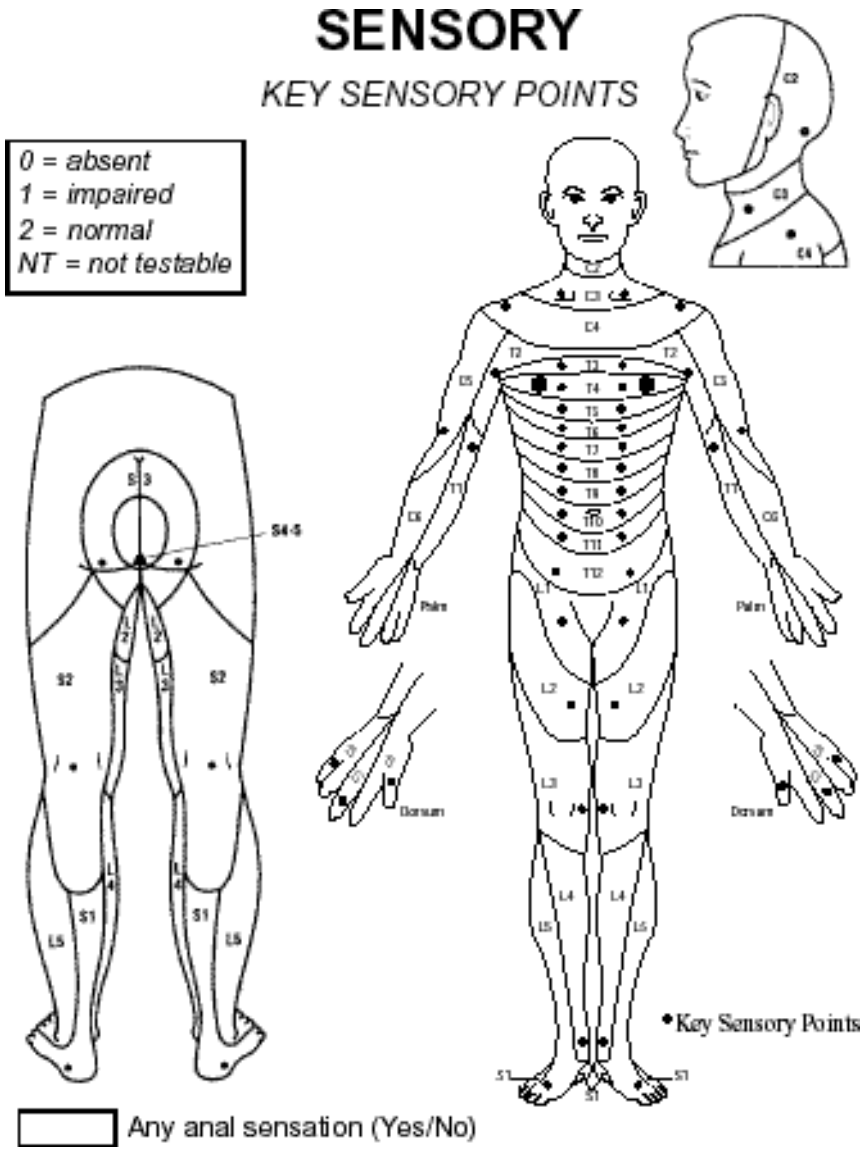


Figure 2:12 : shows Sensory Scoring Chart as defined by AIS based on Key Sensory Points.

Source: American Spinal Injury Association; Manual of the International Standards for Neurological Classification of Spinal Cord Injury. Chicago, IL: American Spinal Injury Association; 2003

AIS Motor Examination Chart:

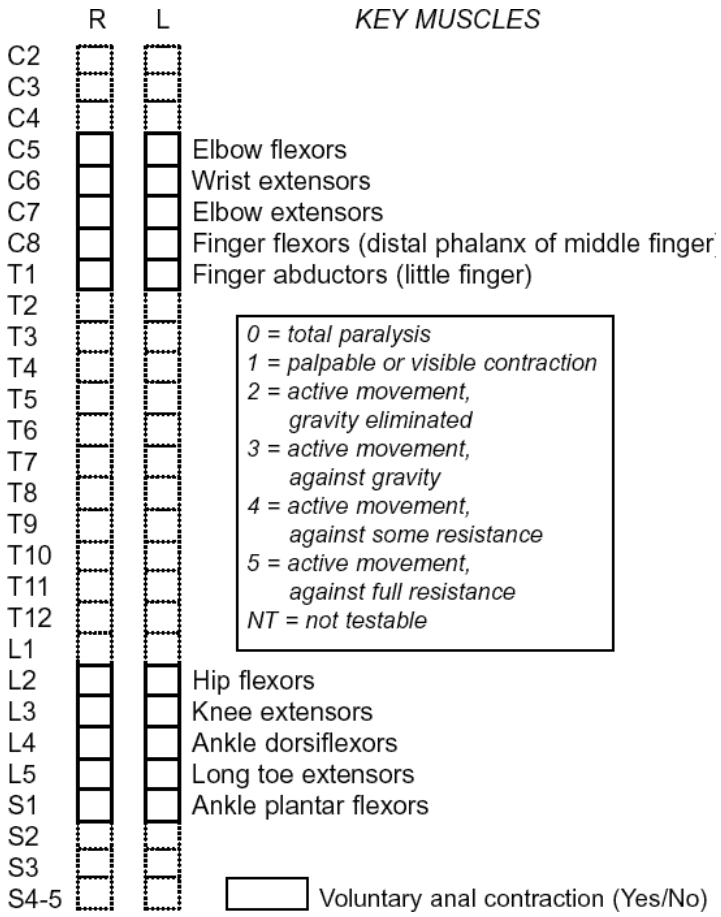


Figure 2:13: shows the Motor Examination Chart as defined by AIS based on Key Muscles

Source: American Spinal Injury Association. Manual of the International Standards for Neurological Classification of Spinal Cord Injury. Chicago, IL: American Spinal Injury Association; 2003

The **ASIA Impairment Scale (AIS)**, **modified from Frankel scale**, aid clinical definition, categorisation, assessment, monitoring and outcome prediction of different SCI clinical subtypes affecting various patients with traumatic SCI (Kirshblum et al., 2011). There are several definitions which used in clinical assessment, monitoring, defining care, clinical management and rehabilitation:

Sensory level is the caudal most level at which both pin prick and light touch sensations are normal as determined by examination of key sensory points.

Motor level is the caudal most level with muscle power being ≥ grade 3 on MRC Scale determined by examination of key muscles in the supine position.

Neurological level (of injury) is the most caudal (lowest) spinal segment with normal sensory and motor function (muscle power ≥ grade 3 on the MRC Scale) on both right and left sides of the human body.

Sensory score is a numerical summary score of sensory function at key sensory points, with a maximum total of 56 points each for light touch and pin prick sensory modalities, totalling 112 points for each side of the human body. The sensory score reflects the degree of neurological impairment associated with the SCI being assessed.

Motor score is a numerical summary score of motor function, with a maximum total score of 25 for each extremity, totalling 50 for both upper limbs and 50 for both lower limbs. The motor score reflects the degree of neurological impairment associated with the SCI being assessed.

Zone of partial preservation (ZPP) is a term which is only used with complete SCI and refers to dermatomes and myotomes rostral to sensory and motor levels that remain partially innervated.

Skeletal level is the level at which the greatest vertebral damage is found on radiographic examination. Skeletal level is not currently part of the ISNCSCI because:

1. Not all SCI lesions are associated with bony injuries.
2. Bony injuries do not correlate well with the neurological presentations due to injuries sustained by the spinal cord.

Radiological Assessment

Assessment of integrity or otherwise any possible damage of the Bony Skeleton is an important part of the clinical assessment of patients and SCI lesions. This is obtained by the use of multiple imaging techniques using different modalities to assess the different tissue characteristics. Simple X-rays used when there is a clinical need to assess structural alignment of vertebral bones; shown in (Figure 2:14). However, by far the most efficient and sensitive commonly used modality is magnetic resonance imaging (MRI) (Takemura et al., 2006). MRI offers much more details of the anatomy of the spinal cord and the layers of the neighbouring tissues as well as good description characteristics of the structural damage sustained by tissues in relation to the SCI lesions.

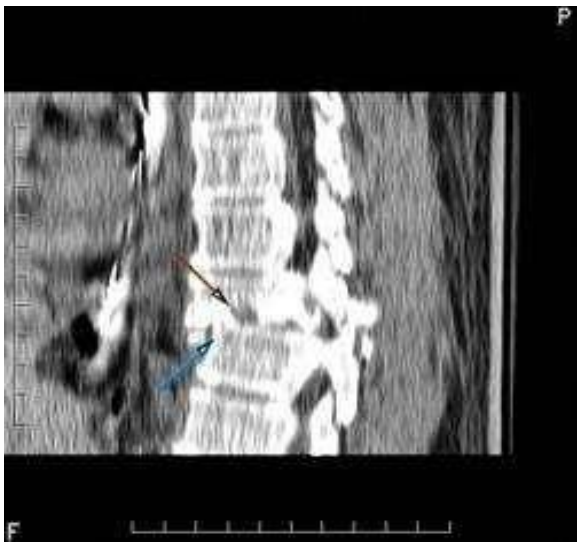


Figure 2:14: Saggital CT scan of the Thoraco-Lumbar spinal cord segments for SCI patient with paraplegia showing fracture dislocation of lower vertebra (blue arrow) and burst fracture of upper vertebra (brown arrow), significant dislocation of lower vertebra, compression and displacement of adjacent spinal cord (from field work: provided and used with permission of Spinal Surgery, Queen Elizabeth National Spinal Injuries Unit, 2002).

2.5.3 Difficulties Facing Clinical Assessment & Deficiencies of the Methods used in Clinical Assessment

Clinical methods assess the physical and functional neurological deficits following SCI and they are in wide use in clinical practice as well as research purposes. Clinical assessment methods as they exist possess multiple difficulties in the process of recognising, defining, diagnosing and monitoring the SCI lesions and patients being affected by those spinal injuries. Obviously, these clinical methods are highly ***subjective***, ***not accurately reproducible*** and ***inter-ratter? dependant***. It has also been observed that clinical methods ***might not suit acute clinical settings*** with patients suffering altered ***levels of consciousness*** (e.g. drowsiness and confusion), ***pain*** or patients being managed with ***immobilisation devices*** (e.g. Halo Brace). Furthermore, clinical information gained from neurological assessment of SCI patients, aided by the cumulative ***experience*** of specialist clinicians looking after SCI patients, all combined and used to ***predict prognosis***, future clinical course and possible final outcome of the given SCI lesions and patients suffering them. However, the clinical methods used to date assessing SCI lesions and their neurological deficits and monitoring progress are deficient. This is because of the subjectivity attached to these clinical methods, lack of accuracy and reliability in addition to these methods being unsatisfactory in predicting outcome of patients suffering specific SCI lesions.

During routine clinical assessment, muscle strength is neurologically examined and graded using the ***Medical Research Council*** (MRC) Scale, which involve assessing and measuring muscle strength by the clinical examiner manually rating the muscular effort of key muscles of the patient

being examined. This is obviously ***highly operator dependent*** and would vary with different clinical examiner especially with different ***level of experience*** and event different personal body built and muscle strength, as shown in work Mills (1997), Bhardwaj and Bhardwaj (2009), and Jackson (2008).

Clinicians caring for SCI patients have long used clinical scales grading the severity of neurological deficits along with the level of SCI lesion. The initial clinical assessment scales were first devised before World War II in the United Kingdom at the spinal unit based at Stokes Manville. The clinical assessment scales were developed and made popular by the British neurologist **H.L. Frankel** in the years leading to the 1970s. The original clinical scoring segregated SCI patients into five categories including (A = no function), (B = sensory only), (C = some sensory and motor preservation), (D = useful motor function) and (E = normal). **The ASIA Impairment Scale** followed Frankel scale but is differed from the older scale in several important respects detailed below:

It therefore critical to note that the developed ASIA A and B classifications depend entirely on a ***single observation***, which is the loss or otherwise preservation of motor and sensory functions of the sacral segments (S4 and S5) known as Sacral Sparing.

- **ASIA A** – instead of (no function below the injury level), it is defined as SCI lesion (with no motor or sensory function preserved in the sacral segments S4-S5), which is a clear and unambiguous definition.

- **ASIA B** – is essentially identical to Frankel B but added is the (requirement of preserved function in the sacral segments S4 and S5).

The ASIA Impairment Scale also ***added quantitative criteria*** for C and D because the original Frankel scale asked clinicians to evaluate usefulness of lower limb function. This feature in Frankel scale had introduced a ***subjective element*** to Frankel Scale in addition it had ***ignored arm and hand function*** in patients with cervical SCI. ASIA Impairment Scale got around this problem, of improving the assessment of arm and hand functions, by stipulating that a patient would be an ASIA C if more than half of the muscles examined have power grades less than 3 out of 5 on the MRC scale. If this is not the case, then the SCI lesion would be assigned as ASIA D severity:

- ASIA E is a very interesting category of the ASIA Impairment Scale because it implies that an individual might have ***SCI without any neurological deficits***. Meaning that, at least ***no clinical changes in dermatomes or muscles that are detectable*** on routine clinical neurological examination of this type performed for the purpose of SCI.

- The motor and sensory scoring system used in ASIA Impairment Scale might not be sensitive to ***subtle weakness***, presence of ***spasticity*** and ***pain***. Several other forms of certain ***sensory changes*** (such as ***dysethesia*** displaying disturbed, altered or burning sensations), which are forms of abnormal sensations that are all possible results of SCI lesions and subsequent progress. An individual with these annoying and occasionally disabling, yet fairly common manifestations of SCI would be placed in AIS category and assigned as ASIA E equivalent to normal.

From a **rehabilitation** point of view, there is a pressing need for valid and reliable outcome measures to be used in assessing the functionality of recovering SCI patients as well as future clinical trials of any novel treatment interventions. It is conceivable that many future clinical trials might be geared towards the use of walking capacity and ambulation abilities as powerful and valid outcome measures. A few of these assessment methods and outcome measures are related to walking function and include measures of walking capacity. These include Short-distance Timed Walk, Long Distance (6-min) Walk and the Walking Index for SCI (WISCI) and its modified version II (WISCI-II). The use of version II of the walking index for SCI (WISCI) II is recommended for assessing SCI patients' walking capacity. It has been shown that WISCI II used in the assessment of patients with acute and sub-acute, it seems to have high intra-rater reliability (IRR) and good reproducibility when administered by trained raters (Scivoletto et al., 2014).

Above sections offered some examples of **difficulties and limitations** facing currently used clinical methods of assessing neurological deficits in patients with SCI lesions. It all shows that clinicians and health care experts are searching for firm and consistent clinical methods that well correlate and complement motor and sensory findings in the accurate and final assessment of SCI lesions and patients suffering them. To date, the search is still on while clinicians are obviously reaching out for alternative reliable assessment methods such what might be offered by electrophysiological tools.

2.6 Electrophysiological Assessment of SCI

2.6.1 Introduction

As highlighted in the above section under clinical assessment, patients with traumatic SCI are clinically diverse and their underlying SCI lesions are heterogeneous. This indeed adds to the many difficulties and challenges faced in obtaining accurate clinical assessment. Some of these difficulties include the fact that clinical methods are highly subjective, largely depends on experience and accuracy of the clinical examiner and lack reliable reproducibility. Furthermore, clinical methods might not suit some acute clinical settings with patients suffering altered levels of consciousness (e.g. drowsiness and confusion), being managed with immobilisation devices (e.g. Halo Brace) and finally patients who are in pain.

The electrophysiological methods are naturally and potentially objective, accurate and reproducible. In addition, these methods are largely suitable for use in settings with patients suffering acute SCI and those who might not be able to cooperate with clinical examination (drowsy or confused) or tolerate some detailed clinical examinations. The electrophysiological methods search for evidence of connectivity and functionality of the long tracts of the spinal cord. In addition, electrophysiological assessment methods carry the potential of predicting outcome of SCI lesions through assessment of existing function and connectivity of surviving spinal cord fibres following a traumatic SCI. This might assist in the prediction of possible subsequent clinical (neurological) improvement or recovery that might take place with time.

Electrophysiological measurements include a group of tests capable of examining the electrophysiological function of the ascending (sensory) and descending (motor) long tracts of the spinal cord. The outcomes of the assessments of sensory and motor spinal cord systems and tract functions are complementary owing to the intricate nature of the spinal long tract fibres being examined. Therefore, the information from sensory and motor electrophysiological assessments might best be jointly interpreted to obtain a better overall picture of the underlying spinal cord tracts and fibres.

In the coming sections, sensory and motor electrophysiological assessment methods are discussed separately for the purpose illustrating these two test categories, starting with methods of examining the sensory spinal tracts then those of the motor tracts.

2.6.2 Assessment of Sensory Tracts in SCI (Sensory Assessment):

There is evidence on the subjectivity of clinical examinations as well as the practical difficulties faced, especially in settings dealing with acutely ill patients with SCI. This is particularly true for the clinical examination of the functions of the sensory tracts of the spinal cord. With this provision, a design of sets of electrophysiological methods is made to assess sensory spinal tracts complementing to the information obtained by the clinical examination. The design of sensory electrophysiological tests is in conformity with the Acute Spinal Injury Assessment (ASIA) scale as the main and most widely used clinical assessment (impairment) scale.

The electrophysiological tests assessing sensory tracts are potentially capable of providing information on ***connectivity*** and ***function*** of the ascending (sensory) spinal tracts in patients with traumatic SCI. This is done by means of examining upper and lower limb sensory or mixed nerves corresponding to levels above and below the level of the SCI exploring and piling information about the residual function of the spinal tracts and fibres at the level of the SCI lesion.

Two electrophysiological sensory assessment methods are currently available for scientists, as well as limited number of clinicians working in research fields, would be discussed in the subsequent sections below. These include Somato-sensory Evoked Potentials (SEP) and its related function the Event-related Synchronisation and Event-related De-synchronisation (ERS and ERD).

Somatosensory Evoked Potentials (SEP)

It is usually relatively easy to conduct clinical sensory examination, including touch and pin prick sensations, for conscious patients who are able to follow instructions and comply with the clinical tests. The resulting sensory information is then incorporated in the neurological assessment. The relative ease of the sensory clinical examinations meant that the much more difficult and rather complicated electrophysiological measurements of somatosensory evoked potentials are rarely used in clinical practice. This is standing as true even for complex clinical situations such as acute SCI where SEP and related tests are shown to provide substantial and helpful diagnostic and prognostic information. The useful use of SEP is even much more needed in circumstances when accurate and complete clinical assessments are not feasible due to impaired consciousness (e.g. drowsiness, sedation or confusion) or when patients are not able to follow instructions or comply with the clinical examination techniques due to SCI or other related injuries (Date et al., 1998; Snowden et al., 1992). There is emerging evidence that retention of SEP responses very early following acute SCI correlates well with neurological recovery of hand function and

walking ability. Therefore, the SEP measurements among other electrophysiological tests are increasingly being incorporated in spinal units as part of routine assessment and management of SCI patients.

Principles of SEP

This section explores the underpinning principles of SEP including discussion of the ***Basic Technology, Sensory Stimulation*** *and* ***Spinal Pathways***. These are involved in the generation and maintenance of the SEP and the underlying sensory modalities being tested by SEP methods. The closest practical measurement of a moving electrical charge in an organism is that of the near-field potential. This recording is obtained via electrodes applied on surfaces where neural impulses pass immediately beneath these surfaces (Misulis and Fakhouri, 2001). For instance, in electroencephalography (EEG) near-filed action potentials are generated by cerebral cortex and attenuated by intervening skull and scalp tissues. Visual evoked potentials (VEP) which are commonly used in clinical practice is another example of near-field action potentials. However, most evoked potentials (EP) are far-field potentials generated by movement of electrical charges in nerve tracts to and from relay nuclei. The near-synchronous volley of action potentials in the nerve tracts produces the far-field potentials which are recorded at scalp electrodes as cortical EPs. Mixed near- and far-field potential components are combined in the formation of some EP, this includes the examples of SEP and dermatomal SEP which are obtained from mixed (nerve) field potentials (Misulis and Fakhouri, 2001).

An example of near-field potentials is what might be seen in clinical settings using spinal SEP in intra-operative monitoring (IOM). In some clinical circumstances both cortical and far-field SEPs may be absent when obtaining surface recordings due to the combined effects of dysfunction of spinal signals by disease, effects of anaesthesia and temporal dispersion of the sensory afferent volley. Electrodes positioned close to spinal cord may pick reproducible near-field SEPs allowing IOM. SEPs picked up by electrodes placed on dorsal surface of spinal cord are often complex and polyphasic, at times precluding simple measurements of latency and amplitude. This is because the spinal cord volley is desynchronized or due to the fact that near-field electrodes pick up activity in several different fibre populations (Legatt, 1991). Some of the principles discussed are illustrated in (Figure 2:15), with intra-operative recordings of cervical SEPs.

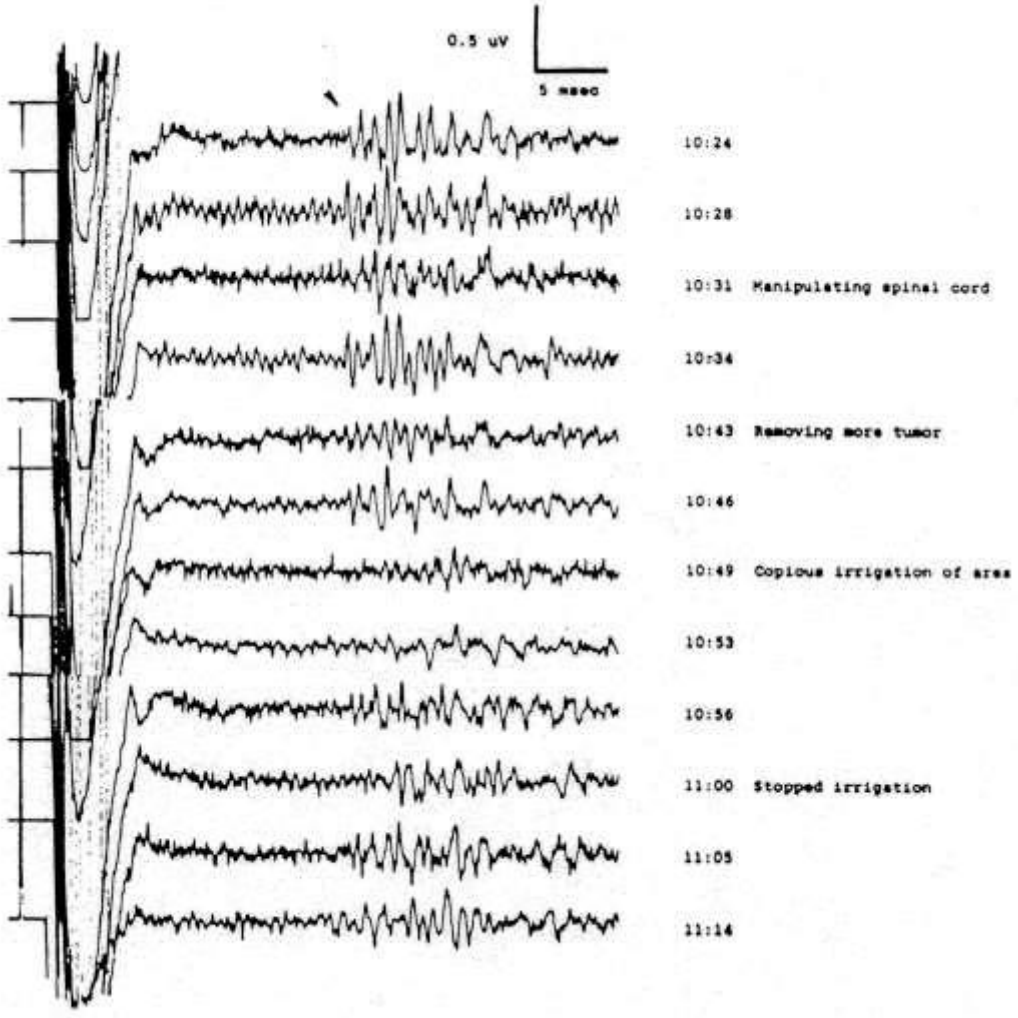


Figure 2:15: Desynchronized, polyphasic SEPs to posterior tibial nerve stimulation recorded during surgery for the removal of tumour compressing the spinal cord. The bipolar recording electrodes were placed on dorsal surface of the spinal cord rostral to the lesion. Cervical SEPs were highly inconsistent not suitable for monitoring and cortical SEPs were absent. (*Source* Legatt, 1991, used with permission).

Stimulus intensities used for generating SEPs only excite the large myelinated somaesthetic A-fibres contained in the peripheral nerves. These *large fibre myelinated* nerve fibres might be cutaneous (light touch), subcutaneous (pressure), proprioceptive (position and joint movement sensations) and muscle afferent nerve fibres (Bremner-Smith et al., 1999). Contrary to this, the *smallest pain-mediating non-myelinated C-fibres* are not usually excited by the relatively low intensity cutaneous stimuli which are routinely used in obtaining SEP recordings in clinical research or hospital settings (Chiappa, 1997). The cell bodes of the large myelinated fibres, which form the caudal parts of the posterior column sensory pathway, lie in the dorsal root ganglia. Meanwhile, the central processes of these unipolar ***first-order neurons*** travel rostrally

in the ipsi-lateral ascending sensory spinal tracts. They eventually synapse in the nuclei of the Gracilis fasciculus and Cuneatus fasciculus situated at the caudal parts of the medulla oblongata at the cervico-medullary junction. The fasciculus Gracilis lies medially to the Cuneatus in the posterior column and subserves sensations from the legs. The fasciculus Cuneatus lies laterally and sub-serves sensations from the arms. Fibres from the ***second-order neurons***, shortly after originating and emerging from the nuclei of the dorsal medulla, cross to the opposite side. The decussating sensory fibres then travel cranially within the medial longitudinal lemniscus (MLF) towards the primary sensory receiving nucleus of the ventroposterolateral (VPL) thalamus. Fibres from the ***third-order neurons*** travel further upwards in the thalamo-cortical projections of the sensory pathway. These third-order neuronal fibres terminate in the fronto-pariental somatosensory cerebral cortex (Chiappa 1997) eventually getting connected primary and secondary cortical sensory relay areas of the post-central gyrus and Brodmann areas 1-3.

Overall nerve fibres of the spinal long tracts comprise specific fibre types, functioning in mediating signals of sensory modalities conveying sensory information obtained caudally to most cranially located centres. The fibre types involved in the structure and function of (ascending) sensory spinal tracts, as shown in (**table 2:02**), include: fibres **Ia** (***primary*** receptors of muscle spindles), some **Ib** (Golgi tendon organ), **II** (***secondary*** receptors of muscle spindles and all cutaneous mechanoreceptors), **III** (free nerve endings of touch and pressure, nociceptors of neo-spinothalamic tract, cold thermoreceptors), **IV** (nociceptors of paleo-spinothalamic tract and warmth receptors).

Table 2:02: shows the various sensory nerve fibre types contributing to the ascending long spinal tracts sub-serving sensory modalities described.

Fibre *Type*	***Myelin*** *Sheath & Diameter* ***µm***	***Conduction*** *Velocity (**m/s**)*	***Receptors*** *or Sensory Organs*	***Sensory Modality*** *Served*
Ia *(Aα)*	*Myelinated* ***Large*** *13-20*	*Fast:* ***80-120***	*- 1º R M-Spindles*	*-* ***Muscle Stretch*** *(Onset & Progress)*
Ib *(Aα)*	*Myelinated* ***Large*** *13-20*	*Fast:* ***80-120***	*- Golgi Tendon Org*	*-* ***Tendon Stretch***
II *(Aβ)*	*Myelinated* ***Medium*** *6 -12*	*Medium:* ***33-75***	*- 2º R M-Spindles* *- All Cutaneous mechanoreceptors*	*-* ***Touch*** */Hair Move (**Discriminative**)* *-* ***Pressure*** *Superficial + Deep* *-* ***Vibration*** *- Skin Press/Stretch*
III *(Aδ)*	*Thin Myelinated* ***Small*** *1-5*	*Slow:* ***3-30***	*- Free N-endings of Touch & Pressure,* *- Nociceptors of Neo Spino-thalamic Tract* *- Cold Thermo-Recept*	*-* ***Crude Touch*** *-* ***Severe Pressure*** *-* ***Pain*** *(?? type)* *-* ***Temp*** *(?? Cold)*
IV *(C)*	*Un-myelinated* ***V-Small*** *0.2-1.5*	*V-Slow:* ***0.5-2***	*- Nociceptors of Paleo Spino-thalamic Tract* *- Warmth Thermo-R*	*- Touch ?Crude* *- Pressure* *- Pain (?? type)* *- Temp (??Warmth)*

N-endings = nerve endings, **1º R M-Spindles** = primary receptors of muscle spindles, 2 **2º R M-Spindles** = secondary receptors of muscle spindles,

(*Source*: tabulated information is modified from (Patestas and Gartner, 2016).

Sensory Modalities involved in the Generation of SEPs

SEPs are averaged recordings of the proximal propagation of electrical volleys generated by distal (caudal) stimulation of mixed peripheral nerves (SEPs) or specific dermatomes yielding dermatomal SEP (D-SEP). The exact locations of the proximally located recording sites are dictated by two factors. Firstly, the layout of the sensory pathways along which the cranially propagated electrical volleys are travelling towards cerebral cortex. Secondly, the locations of certain anatomical landmarks which possess best recording capabilities. The pathways which facilitate this hierarchy propagation of sensory electrical impulses are mainly, but not exclusively, the nerve tracts contained in the posterior column. Therefore, SEP measurements are essentially a test of function of the posterior column sensory system (Chiappa, 1997).

SEPs and D-SEPs are therefore expected to inform the examiner about the functional performance of the tested tracts. Nevertheless, allowance is given for the technical difficulties which might be encountered during SEP recording sessions as well as the surrounding clinical circumstances. These are either physiological as seen in healthy volunteers or pathological changes seen in patients participating in each SEP tests. However, there is another less evidence based and less popular theory about SEP physiological pathways. It suggests that SEP propagating components are not transmitted via a single definitive pathway but are mediated through independent routes probably involving different first-order neuron fibres (Yamada et al., 1981).

The popular and well documented theory, however, remains that conventional SEP recording methods examine the integrity and function of the posterior column sensory system (Chiappa, 1997; Giblin, 1964). The posterior column normally mediate sensory functions related to passive joint movement (and sense of joint position), vibration and light touch sensations (Anziska and Cracco, 1980). In particular, two sensory modalities including position sense and passive joint movements are particularly mediated by posterior column (Giblin, 1964; Halliday and Wakefield, 1963). SEPs and D-SEPs have potentials of informing the examiner of the functions of sensory tracts tested, and therefore SEP recordings are expected to be impaired, in some way, if sensory function of the tested tracts is clinically abnormal. Furthermore, the extent of SEP abnormalities is shown to correlate with the degree of loss of passive joint position sense as one modality of the posterior column sensory pathway (Williamson et al., 1970). It might be extrapolated that when clinical examination detects neurological deficits involving posterior column sensory modalities, it is likely that an abnormality is observed in SEP recordings. It is therefore widely accepted that performing SEP recordings for the sole purpose of confirming predetermined clinical sensory deficits is generally not recommended. This is because no further gain of information, but with the disadvantage of additional cost and possible inconvenience to individual patients. Current SEPs tests inform of the integrity and function of posterior column sensory system which serve the following sensory modalities:

- Joint sensations (joint position sense (JPS) and sense of joint movement),
- Vibration,
- Light touch.

As indicated in (Giblin, 1964), SEP recordings are rarely affected in patients with loss of sensory function involving:

- stereognosis,
- two-point discrimination sense,

Similarly, from (Noel and Desmedt, 1975), SEP waveforms are not affected in patients with sensory loss involving lateral spinothalamic tracts which mediate:

- Pain and crude touch (also stimulating nociceptive receptors, which consequently activates slow-conducting pain C-fibres),
- Temperature,

However, it seems that SEPs and D-SEPs are sensitive enough to detect abnormalities of ascending sensory pathways, but with variable sensitivity and specificity to certain spinal cord lesions than others.

Diagnostic Potentials of SEPs

A large volume of research work has been done covering many pathophysiological aspects and technological principles of SEPs and investigating their potential uses for clinical and research purposes. Nevertheless, a range of SEP aspects remained out of the scope of many of previous studies and SEPs remained under scrutinized. These aspects include technicalities, reproducibility, reliability, sensitivity and specificity of SEPs. This is especially true when SEP tests are used in clinical context, whether hospital-based settings or research laboratories investigating human health or disease. Therefore, lots remain unravelled in the process of establishing SEPs full potentials, maximising their use as investigative tools in clinics and research units and steadfast methods establishing normality or otherwise diagnosing diseases of posterior column. While the progress is being made towards realising and establishing this, great expectations were built upon the potential ability of SEPs and D- SEPs in assessment. Traumatic spinal cord injury (SCI) is a particularly important pathological condition. In SCI, it is absolutely crucial to assess integrity and connectivity of residual tracts across lesions of the spinal cord, and obtain this once, patients are clinically stable following the initial phases of trauma. Assessment following SCI could partly be achieved by SEPs informing the examiner of ascending posterior column (sensory) pathways. This is done alongside other electrophysiological testing modalities

which are all directed functions of the tracts weather spared or injured as part of lesion sustained by the injured spinal cord. SCI is recognised as a separate clinical and pathological entity in the affected individuals, and is ever gaining attention and paramount importance in clinical practice and research. This is due to considerations of therapeutic and rehabilitation potentials, and understandable patient's expectations. An example of diagnostic SEP and D- SEP is shown in (Figure 2:16), with an example of electrophysiological changes used to assess level of SCI and assisting diagnosis.

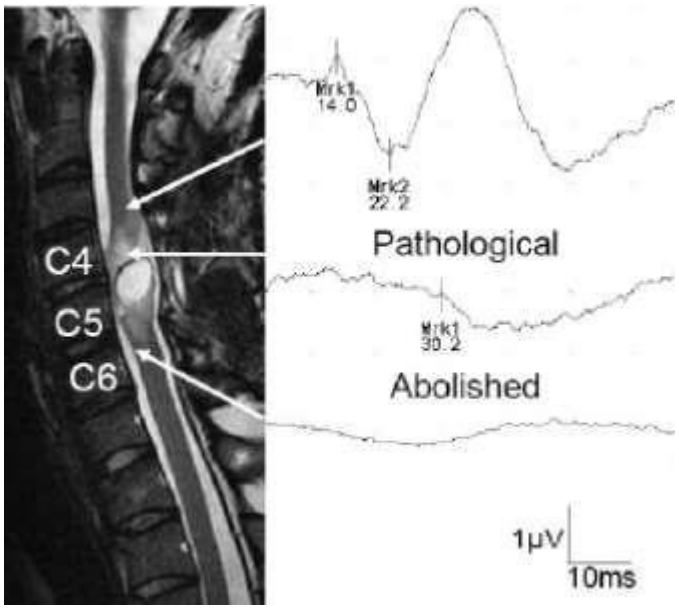


Figure 2:16: Shows SEP waveforms obtained from upper limb nerve stimulation with normal findings (top) from above the SCI lesion, while abnormal waveforms are obtained from the impaired level (site of lesion) as well, recording below the SCI lesion. (*Source* Kramer et al., 2008, used with permission).

Spinal Cord and Brainstem Lesions

There is compelling evidence that large-fibre sensory system (spinal cord posterior columns and higher lemniscal system) carries impulses responsible for the generation of SEPs (Chiappa). Therefore, a good correlation was found between type of sensory loss in patients with lesions of the spinal cord and brainstem and the recoded SEP changes (Giblin, 1964) and (Halliday and Wakefield, 1963). However, best correlation observed was expectedly in relation to deficits of position sense and passive joint movement. It has been observed that if these named posterior column sensations were anything worse than minimally impaired, the SEPs were found to be abnormal. On the other hand, SEPs were found to be normal if the affected sensations were only related to pain and temperature mediated by the lateral spinothalamic pathways. In a group of patients with some brainstem vascular lesions causing loss of pain and temperature sensations, the SEP waveforms were normal (Noel and Desmedt, 1975).

Thalamocortical and Cerebral Lesions

The correlation between SEP findings and extent of clinical sensory loss is however less precise in patients with cerebral lesions (Giblin, 1964). In one study, in over 80% of patients who had SEP amplitude abnormalities, 16.5% with lesions sparing the primary somatosensory receiving area had normal SEPs in the presence of sensory deficits comprising definite loss of two-point discrimination, stereognosis and joint position sense. Meanwhile, 2.4% had absent cortical SEP responses with no apparent clinical deficits. In a different group of patients with unilateral cerebral lesions, a good correlation existed between the extent of joint sensory loss and SEP abnormalities. It was shown that no patient with mild clinical sensory loss ever showed significant or marked changes in SEP waveforms (Williamson et al., 1970). Similarly, patients with thalamocortical pathway lesions and no clinical sensory losses, the SEP responses were normal (Mauguiere et al., 1982).

SEP and D-SEP Measurement Parameters

Upper Limbs (Median SEP, C5 and C6 D-SEP):

Amplitude:

Stimulation of cutaneous nerves through the skin surface comprises dermatomal SEPs (D- SEPs) with wave configurations similar to SEPs obtained through stimulation of the mixed nerves. However, D-SEPs stimulation setup and subsequent propagation of the electrical volley yields smaller amplitudes (Chiappa et al., 1983). For instance, responses which are normally recorded at sites on cervical and lumbar spine might not be registered even from healthy subjects when cutaneous nerves are simulated including digital, musculo-cutaneous, saphenous or sural nerves. Therefore, strong electrical stimuli of up to about three times the sensory threshold (3xST) might be required. The relatively high stimulation intensity is required to tap on cutaneous nerves in order to elicit scalp recorded responses (D-SEPs). The amplitudes of these D-SEPs are generally half the size of those of the SEPs obtained from mixed nerve stimulation at intensities equal to their sensory threshold (1xST).

Latency:

All SEP components show appropriate latency shifts when stimulating proximal (musculo-cutaneous) compared to sites distal to the wrist (in digital or dermatomal). Responses from distal stimulation sites show significant delay when compared to the proximal setting of stimulation and resulting waveforms. This is because cutaneous and muscle afferents are additive to the amplitude

response in proximal recording, as they too travel together in the posterior column sensory pathway. When conduction distances are adjusted, there are equal conduction times in cutaneous (superficial radial and digital) nerves as well as mixed (Median) nerves.

Lower Limbs (PTN SEP and L2, L3 D-SEP):

Amplitude:

The same factors described for upper limb SEPs and D-SEPs (section 1.1) applies to lower limbs giving low amplitudes in response to cutaneous stimulation (D-SEPs) in comparison to responses obtained by mixed nerve stimulation (SEPs). Furthermore, SEP and D-SEP waveforms from the lower limb stimulation are hard to obtain. This is because of dispersion of the propagating electrical volleys travelling relatively longer distance proximally compared to responses from upper limb stimulation. Dispersion of lower limb SEP and D- SEP responses might well affect the amplitudes as well as latencies rendering waveforms difficult to capture and record.

Latency:

Stimulation of a lower limb cutaneous nerve (e.g. sural) produces scalp-recorded dermatomal evoked potentials (D-SEPs) with prolonged latencies. Mean difference in latencies of 2-3 seconds are seen relative to cortical SEPs produced by stimulation of a mixed nerve at the ankle such as Posterior Tibial Nerve (PTN). Prolonged latencies seen in cutaneous (dermatomal) stimulation in D-SEPs are observed even though the distance between stimulation site (ankle) and spinal cord is approximately the same in comparative SEP and D- SEP stimulation settings (Chiappa et al., 1983). These factors explain attenuation and delay of scalp-recorded cortical SEP responses obtained by dermatomal stimulation (D-SEP) from lower as well as upper limbs. The distinction between D-SEP and SEP latencies is possibly related to the contribution of fast-conducting muscle afferents in generating evoked potentials from stimulation of mixed nerves (e.g. PTN). It is believed that muscle afferents from lower limbs travel in the dorso-lateral (spinocerebellar) pathways rather than the posterior column. Meanwhile, cutaneous afferents mediating dermatomal stimulation (e.g. sural nerve) travel predominantly in slow-conducting posterior columns. The average diameter of posterior column axons is less than spinocerebellar axons. Hence, conduction velocity of muscle afferents contributing to PTN is faster than cutaneous pathways which contribute in Sural nerve conduction. D-SEPs in the upper limbs however benefit from the fact that propagating electrical volleys travel shorter distances. This means less dispersion and more reproducibility of the scalp-recorded cortical waveforms compared to the lower limb. Norma values for ***SEP amplitude and latency parameters*** for

Median and PTN, as well as upper and lower limb D-SEPs, are established using a conventional scale graded from 1 to 4 on the basis of description of the resulting waveforms:

1. Presence or ***Absence*** of responses,
2. ***Amplitude*** measurement ***values*** for **N20-N27** (for the upper limbs), and **N30-P40** (for the lower limbs),
3. Peak ***Latency Measurements***,
4. ***Inter-peak Latency*** (IPL) ***Measurements*** of **N9-N20** (Erb's point to cortex for the arm) and **N9-P37 or P40** (Popliteal fossa to cortex for the leg).

SEP and D-SEP Interpretation

Based on the above, the SEP and D-SEP waveforms are considered to be abnormal if:

- Amplitude is abnormal (***absent*** or ***significantly reduced***) or
- Latency is abnormal (***significantly delayed***) or
- Abnormal ***Inter-side Asymmetry*** (if inter-side comparison shows significantly asymmetrical waveform components (i.e. abnormal inter-side disparity).

Amplitude

Amplitude abnormalities might fall under one of the following categories:

- ***Response or 'waveform' is absent***;

It has been suggested that absence of SEP responses might predict 'no recovery' is seen following SCI (York et al., 1983). This suggests that SEPs have a prognostic value and might predicts potential recovery of the spinal cord as documented in patients with acute SCI (Rowed et al., 1978). It has been reported that presence of SEP responses shortly after injury indicates an incomplete spinal cord lesion with possible subsequent recovery of sensory or motor functions. Similarly, absence of SEPs suggests a complete spinal cord lesion with no significant recovery of spinal cord functions. It is worth mentioning that the presence of SEP responses is not always associated with recovery of motor function.

This is because the retention of normal SEP responses understandably requires connectivity and function of the posterior column sensory pathways. Meanwhile, motor activity and connectivity depend on anterior and anterolateral descending motor spinal tracts, which are structures with different source of blood supply and vulnerability to mechanisms causing SCI (Katz et al., 1991).

- ***Amplitude value is significantly small*** (**N20-P27 is <1µV**).

This means significantly low amplitude or small value measurement, provided that the inter-trial variability is low or absent (no inter-trial variability):

A. SD < the minimum amplitude in a group of normal series.

B. 3SD < the mean (transformed data or nonparametric statistical measure).

The cortical responses of SEP and D-SEP responses for upper limb stimulation are conventionally designated N20. This consists of an early negative (N20) and later positive (P27) or (P30) components. These components are important establishing normal or otherwise abnormal values of these measured responses. For instance, amplitude of the cortical response is considered to be abnormal if N20-P27 amplitude is less than 1 microvolt (Cheliout-Heraut et al., 1998).

Latency

Two practical types of latency measurements are generally considered:

- ***Absolute latency*** (onset or peak latency of response waveform),
- ***Inter-peak latency*** (famously used in upper limbs for N9-N20),

The latency is considered to be abnormal if:

- Latency of **N20** response waveform for **Median SEP** is significantly delayed (Latency is more than **32 ms**), or
- Latency of **N20** response waveform for **C5 or C6 dermatomes** of upper limb D-SEP is significantly delayed (Latency is more than **34 ms**).

Delayed absolute latency (AL) measurement render SEPs or D-SEP responses as abnormal even with apparently normal-looking waveforms and amplitudes values (Cheliout-Heraut et al., 1998). Therefore, AL is a measure weather SEPs are normal or abnormal, is relatively easy to calculate and been widely used in clinical practice. It however been criticised because of multiple factors that might influence its value and hence accuracy. Examples of these factors have been individual tested subject's height or variable limb temperature. These factors would affect impulses generated at the peripheral stimulation sites and its propagation cranially to reach scalp recording electrodes (Chiappa, 1997).

- Latency of **P37 or P40** response waveform for **PTN** or L2 and L3 lower limb SEP and D-SEP, respectively is significantly delayed (i.e. Latency is recorded to be more than **43 ms**),
- Latency of **P20** response waveform for **Median SEP** is significantly delayed (Latency is more than **32 ms**), or

Inter-side Comparison

The inter-side comparison is considered to be abnormal:

- When the absolute ***amplitude is near the limits of normal***, and
- The ***amplitude difference between two sides is more than 2.5 times***, and
- ***No significant difference in the amplitude of Erb's point potential***, and
- ***Applying a conservative interpretation*** when it is the only abnormality.

Summary of SEP and D-SEP Measurements & Interpretations

Applying above-discussed methods which utilize data from standard normative tests obtained from various electrophysiological laboratories and collating previous studies, the SEP and D-SEP responses might be judged as normal or abnormal as follows:

For upper limb – N20 (for Median SEP, C5 and C6 D-SEP)

1 - **N20** waveform or response is absent, or

2 - **N20** amplitude is less than **0.19 μ volts** for Median SEP, and **0.07 μ volts** for C5 and C6 D-SEP, or

3 - **N20** latency is more than **27.5 ms** for Median SEP, and **32.25ms** for C5 and C6 D-SEP.

For lower limb – P37 (for PTN SEP, L2 and L3 D-SEP)

1 - **P37** (or P40) waveform or response is absent, or

2 - **P37** (or P40) amplitude is less than **0.1 μ volts** for PTN SEP and **0.24 μ volts** for L2 and L3 D-SEP, or

3 - **P37** latency is more than **43.06 ms** for PTN SEP, and **41.34 ms** for L2 and L3 D-SEP.

SEP and D-SEP Measurements in Clinical Practice & Spinal Injury

The SEP and D-SEP measurements are being increasingly employed in assessing patients with SCI outlining prognosis and predicting recovery outcomes. From work done by Curt and Dietz (1996), it was highlighted that SEP measurements performed beside the ASIA scores are related to the outcome of ambulatory capacity including walking following traumatic SCI provided the participating patients comprehend and able to cooperate with these testing protocols (Curt and Dietz, 1997) Similar use of SEP has also been shown in relation to hand function (Curt and Dietz, 1996), , with Median and Ulnar SEP predicting the outcome of hand function beside indicating

level of injury and degree of sensory impairment in patients with SCI. These are obtained by graded electrical stimulation of peripheral nerves (in some instances dermatomes) generating SEP responses from bipolar EEG montages derived from multichannel monopolar recordings. Averaged 1000 stimuli delivered at 2.8Hz were averaged to SEP measurements characterised by latency and amplitude.

2.6.3 Event-Related Synchronisation and De synchronisation:

Introduction

SEP and D-SEP methods enable the assessment of ascending sensory systems with predilection for the posterior column sensory pathways. These conventional EEG time averaged evoked responses used in SEP and D-SEP highlight components of EEG which are phase-locked to the triggering stimulus. This SEP and D-SEP analysis and subsequent assessment of ascending sensory pathways could be supplemented by examination of evoked responses in the frequency domain. This could particularly be achieved by examining the spectral perturbations of EEG in response the triggering stimuli. The event-related spectral perturbation (ERSP) is similar to the event-related synchronization and desynchronisation (ERS and ERD). However, the difference is that ERSP shows the relative changes in EEG spectral power over the entire spectral range of EEG bands as induced by the stimulus triggering them, rather than looking at single bands of EEG power as in ERS and ERD. Therefore, ERSP and related ERS and ERD are calculations which might be used in sensory assessment methods to enable higher and much more detailed scrutiny of cortical responses generated by the stimulation of the peripheral somatosensory system. ERSP sensory assessment have the ability of providing more information on the sensory cortical responses in healthy and individuals with SCI; hence detecting minor changes which might accompany neurological recovery or otherwise clinical deterioration. It is therefore perceived that ERSP provide a sensitive measure for investigating sensory function and allow greater insight into processing the sensory cortical recordings.

Spectral Analysis

Traditionally, most EEG researchers interpret data by measuring peaks in event-locked ERP averages. The use of ***response averaging*** is justified by the fact that single-trial EEG data time locked to triggering events consists of averaged event-related potentials (ERP) with fixed time course and polarity across the trials, and other EEG processes with time courses which are completely unaffected by the triggering events. The cortical sources of ERP are likely to be spatially distinct from sources of spontaneous EEG activities. It has also been demonstrated that

focussing data analysis on response averaging alone ignores event-related dynamics that do not appear in or are poorly represented in response averaging. Furthermore, it ignores ongoing EEG processes which might be partially time and phase-locked by experimental events. Increasingly, more comprehensive methods are being used. The availability of free and easy to use signal processing software applications for EEG data, has encouraged more comprehensive analytical methods. As described by (Acar and Makeig, 2010), EEG with summed scalp projections of partial EEG sources expressing simulated 9-10 alpha band activities, are shown with scalp dynamics.

To achieve more ***advanced and comprehensive computational analysis***, EEGLAB computer function is used as part of matlab (The Mathworks, Inc). EEGLAB is an interactive Matlab toolbox which is used for processing continuous and event-related electrophysiological data including EEG. EEGLAB incorporates Independent Component Analysis (ICA), ***time/frequency analysis***, artefact rejection, event-related statistics, and several other useful modes of visualisation of the averaged and single-trial data as well as *runica* (a function of automated information ICA decomposition). Basic functions of EEGLAB includes Independent Component Analysis (ICA)/EEG toolbox of Mekeig and colleagues (1997). A primary tool of EEGLAB is used to facilitate the process of applying and evaluating the results of ICA. ICA algorithms are capable of isolating artefacts and neural-generated EEG sources whose EEG contributions are independent from one another. EEGLAB is therefore a collection of Matlab functions used for signal processing and visualisation of EEG data, including one important application processing time-frequency analysis used in the formation of event-related spectral perturbation (ERSP) maps (Delmore and Makeig, 2004).

Time-frequency analysis aims to assess event-related spectral amplitude changes of phase and coherence perturbations through EEGLAB employing spectral decomposition techniques. Event-related Spectral Perturbations (ERSP) is one of the three event-related time/frequency measures. ERSP measuring mean event-related changes in the power spectrum at a data channel or component (Makeig, 1993). ERSP plots the baseline- normalised spectrogram or event-related spectral perturbation. These plots are increasingly used in EEG data to visualise mean event-related changes in spectral power over time in a broad frequency range. These plots generalise narrow-band event-related desynchronisation (ERD) and synchronisation (ERS) measures which were introduced by Pfurtscheller and colleagues (Pfurtscheller and Aranibar, 1997). The process of calculating ERSP requires computing the power spectrum over a sliding latency window then averaging across data trials. It is observed that the colour at each image pixel indicates power (in dB) at a given frequency and latency relative to the time locking event. A typical formula for

calculating ERSP (where ***n*** trials, ***f*** frequency and ***t*** time) is the following equation:

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

This is obtained using the EEGLAB Version 4.0 toolbox of MATLAB versions 6 and 7, it was possible to create event-related spectral perturbation (ERSP), using visual maps as illustrated in (Delorme and Makeig, 2004). This is done by Offline Analysis and Data Processing of Epochs (-1000ms to +2000) extracted from raw EEG recordings obtained on Scan 4.2 to prepare for frequency domain analysis.

ERSP is a method used to provide visualisation of the mean stimulus-induced changes (of cortical somatosensory evoked responses) within EEG's power spectrum (of various frequency bands) over time. ERSP visual maps were obtained for averaged and single-trial data. Both phase locked and non-phase locked activity changes of the frequency domain measurements were obtained in line with principles of event-related synchronisation and desynchronisation (ERS & D) discussed in previous work (Pfurtscheller and Lopes da Silva, 999; Neuper and Pfurtscheller, 2001). Statistical analysis of the visual ERSP frequency analysis maps was performed using MATLAB scripts. This used in order to verify the statistical significance of the visual changes observed on the spectral maps over time, by applying analysis of variance ANOVA for ERSP. Serial ERSP visual maps were compared to extract any detectable visual or statistical changes in the SEP & D-SEP patterns over time. The ERSP changes were also compared to the SEP & D-SEP data sets on time domain analysis to check for any concordance or disparity of findings using these two different acquisition and analytical methods.

Therefore, the use of spectral analysis of SEP through application of ERS/ERD measurements provides visualisation of mean stimulus-induced changes in EEG spectral power over time, with plots of ERSP calculated using computational analysis.

2.6.4 Assessment of Motor Tracts in SCI (Motor Assessment):

Introduction

In this section, methods used in the assessment of spinal motor tracts are reviewed and detailed along with successes and challenges faced in obtaining sensitive accurate and reproducible measurements relevant to patients with traumatic SCI. These methods examining motor cortico-

spinal tracts (CST) are mostly but not exclusively used with previously discussed methods of sensory assessment. The complementary motor and sensory methods are aimed collectively at obtaining information on integrity and function of descending and ascending spinal tracts, respectively determining deficits caused by the given SCI lesions.

Electrophysiological methods are generally used to overcome subjectivity attached to assessments obtained using clinical methods. In addition, they overcome other practical difficulties and limitations facing current clinical methods when used in settings caring for acute or ill patients with SCI. However, the outcomes of motor assessment methods are used largely to complement information obtained from conventional clinical examination methods. Therefore, most of electrophysiological techniques or methods used in assessing motor spinal tracts are designed in reasonable conformity with ASIA Impairment Scale (AIS). This is meant to allow translation of information obtained using electrophysiological methods into meaningful and useful clinical information and vice versa. This possibly allows comparison of outcomes of baseline clinical examination and further objective electrophysiological assessment undertaken afterwards during longitudinal follow-up.

The Motor Assessment Methods include ***Trans-cranial Magnetic Stimulation*** (TMS) of motor cortex while recording ***motor evoked potentials*** (MEP) through surface EMG electrodes placed on key upper and lower limb muscles. Transcranial magnetic stimulation (TMS) is a painless, safe and non-invasive method used for evaluating the integrity and conductivity of cortico-spinal tracts (CST), as previously discussed and shown in schematic representations. TMS is getting increasingly popular, used in clinical settings and research labs for the evaluation of health as well as diagnosing or monitoring neurological disorder (Matamala et al., 2013).

TMS is obtained by applying a calculated magnetic stimulus delivered to the cerebral cortex using purpose-designed magnetic coils. These stimulating coils are applied to the scalp overlying specified cortical areas and getting through to the motor cortex corresponding to the target muscles in the contra-lateral upper or lower limbs. Surface electrodes are placed on corresponding limb muscles to record EMG activity in response to the trans-cranial magnetic stimulation to be used in calculating the MEP latency and amplitude parameters. The settings for the TMS recording are standard and mirroring those in clinical and research units.

In response to TMS, EMG activity is recorded using surface electrodes placed over corresponding muscles in upper and lower limb locations contra-lateral to the motor cortex responsible for their motor supply and further higher control via the descending motor pathways

included in the cortico-spinal tracts (CST). Stimuli used during TMS trigger responses that are recorded from contra-lateral limb muscles in the lower limb, namely Tibialis Anterior (TA). In upper limb contra-lateral to the cortical site of the TMS, surface EMG is used to record the triggered MEP responses from the Abductor Pollicis Brevis (APB) or Extensor Digitorum (ED) muscles. The recording from these peripheral muscles is done at rest and during sustained tonic contraction for facilitation. Central motor conduction time (CMCT) was derived from MEP latency and peripheral motor conduction time (PMCT).

2.6.5 Motor Evoked Potential (MEP) Measurements

TMS methods are used to obtain information on the motor evoked potentials (MEPs) as calculated and characterised by latency and amplitude measurements.

Latency and amplitude of motor evoked potentials (MEPs) vary among healthy subjects and no specified normal reference values for MEPs in healthy older adults are available (Matamala et al., 2013). Studies obtained some reference values for MEP measurements using TMS for healthy adults older than 70-years. The average values for upper extremity MEP latency were 23.3 ± 1.9 ms at rest and 19.9 ± 1.9 ms during tonic contraction, while lower limb MEP latencies were 30.6 ± 2.5 ms at rest and 27.2 ± 2.3 ms during tonic contraction. There was a significant correlation between MEP latency and standing height, greater in the lower extremities, while female gender appeared as an independent factor determining lower extremity MEP latency, but not CMCT, in upper and lower extremities. It has been highlighted that the difference between genders might be due to the lower height of women (Matamala et al., 2013). Some researchers advocated application of additional measures assessing ***facilitation of lower limbs motor evoked potentials*** (MEP) to improve the diagnosis of damaged motor tracts and monitor motor function in patients with incomplete SCI. These measures included task-dependent modulation of MEP obtained from TA and would be used complementary to MEP delay measurements to allow estimation of severity of damage to spinal motor tracts. These measures involve assessment of the different effects on TA MEP facilitation from static and dynamic motor tasks including isometric foot dorsi- flexions while recording EMG from tibialis anterior (TA) muscle. Static and dynamic muscle activation performed at comparable levels of maximal voluntary contraction (MVC) was obtained. The influence of these motor tasks on excitability and facilitation of MEP was compared between healthy controls and patients with incomplete SCI. There was an increased facilitation of TA MEP at lower levels of dynamic activation compared to static activation with the level MEP responses were increased. However, at comparable levels of TA activation, the MEP responses were significantly reduced in patients with incomplete SCI (Diehl

et al., 2006). It is worth mentioning that beside EMG recordings in response to TMS yielding MEP latency and amplitude measurements, motor assessment of CST employing TMC included the calculation of MEP Silent Period, Torque Performance and TMS Triggers (Diehl et al., 2006). The EMG silent period following magnetic motor evoked potential (MEP) is seen when the target muscle contract tonically (post-MEP silent period). In upper limb muscle (first dorsal interosseus muscle – FDI) the post-MEP silent period duration increased proportionately with the stimulus intensity, but not to the size of MEP preceding it. The post- MEP silent period was longer in hand and forearm muscles than in upper arm muscles. Meanwhile, some weak magnetic stimuli evoked silent periods preceded by no MEP in several subjects (Cantello et al., 1992). It was highlighted that MEP measurements are superior to SEP measurements as well as clinical sensory scores based on the ASIA Scale in detecting long spinal tract dysfunction. MEP show some similarities to ASIA motor scores in relation to the outcome of ambulatory capacity (lower limb muscles) and hand function (upper limb muscles) in patients with SCI, however the MEP measurements are particularly valuable to clinical examination in uncooperative or incomprehensive individuals (Curt et al., 1998). TMS is useful and applicable in ICU setting, with less optimal conditions as well as trauma centres where it could be performed in unconscious patients with advantage that the procedure is painless compared to trans-cranial stimulation. TMS is capable of assessing conductivity of spinal cord following acute stage of SCI or later-on during long-term follow- up of patients, with MEPs readily obtainable from upper limbs while of lesser value when obtained from lower limbs.

Studies analysing correlation of electrophysiological tests for the functional assessment pointed to the superior sensitivity of MEP measurements over SEP. MEP found to detect early stages of spinal tract dysfunction in patients with slight, unspecific and non- confirmative symptoms without pyramidal signs yielding abnormal MEP but normal SEP findings. The case for complementing SEP responses and MEP measurements is argued to obtain fuller electrophysiological assessments of the spinal tracts being tested (Simo et al., 2004). Largely, the MEP measurements seem to correspond well with physical motor ability as obtained by the ASIA motor scores and reflected in motor function. In correlating MEP to functional outcome and physical ability, it seems that amplitude is more robust than latency measurements in demonstrating this, with MEPs improve with SCI recovery while latencies not (Xiel and Boakye, 2008). Contrasting MEP to H-reflex modulation, which reflect the changes in spinal excitability; however, do not surpassed clinical evaluation methods in predicting outcomes. Considering safety, the subjects undergoing TMS are screened for medical risk factors or co- morbidities constituting relative or absolute contraindication to TMS exposure. Screening includes history

or clinical evidence of electronic implants such as cardiac pacemakers while other less ferromagnetic metallic objects like stainless steel aneurysmal clips are generally not considered to be much affected by trans-cranial magnetic stimulating coils. Nevertheless, checks extend to include subjects with metal implants such as brain, eye, ear, dental devices and old shrapnel or metals. Precautions also include checking history of epilepsy (especially poorly controlled), brain tumour, previous stroke or head injury. Mostly, the described risks are related to repetitive trans-cranial magnetic stimulation (rTMS) weather low or high frequency, while these factors do not pose a significant risk for single pulse trans-cranial magnetic stimulation. Additional history of migraine is also searched for fear that TMS might precipitate or aggravate migraine attacks.

2.6.6 Cortico-Muscular Coherence (CMC) Calculations:

Motor assessment methods also include ***cortico-muscular coherence*** (CMC) calculated from analysis of coupled recordings of electroencephalography (EEG) and simultaneous electromyography (EMG) from key upper and lower limb muscles during sustained contractions. These motor assessment methods, are designed to provide information complementary to the AIS about the integrity and any possible residual motor function below the level of given SCI lesion. It has however been noted that TMS, the resulting MEP components and measurements of latency and amplitude parameters are the mainstay and reliable methods of assessing the motor spinal tracts. Therefore, the standard TMS assessment methods of motor function following SCI involve measurements of MEP delay or latency and amplitude parameters and used routinely beside clinical examinations. CMS reviewed along with the potential successes and challenges ahead.

3. METHODS

This chapter discusses the overall aims of this research project, ethical considerations, study design, protocols and details of experimental methods and techniques used.

3.1 Aim of Project

This electrophysiological follow up assessment study was designed with the aim of addressing the continued need and real challenge of establishing reliable diagnostic tools for spinal cord injury. The clinical initiative (Ellaway et al., 2004) aimed at enhancing the translation of basic science to clinical trials to establish tools that are objective, quantitative, sensitive, reproducible, non-invasive and clinically applicable to the complex nature of SCI and the related clinical set ups. This project aimed to explore the use of a range of non- invasive electrophysiological methods for assessing the integrity and connectivity of key ascending (mainly the sensory posterior column) and descending (mainly the motor corticospinal) tracts in patients with spinal cord injury (SCI). The main objectives were to provide a battery of diagnostic tests for use in assessing the severity of SCI that are quantitative and sensitive enough to detect small changes in lesion status. Hence, these tests would be suitable for use in monitoring changes in spinal tract function in response to any natural recovery of function or recovery promoted by novel therapeutic interventions which might be available in the future.

The aims of this study therefore included investigation of the use of somatosensory evoked potentials (SEPs) and the related event-related synchronisation and desynchronisation (ERS&D) measurements in the assessment of the sensory (ascending) spinal tracts, mainly the posterior (dorsal) column medial lemniscal system. Similarly, the study aimed at the investigation of the use of motor evoked potential (MEP) measurements, obtained by the means of trans-cranial magnetic stimulation (TMS), in assessing the motor (descending) corticospinal tracts (CST). In addition, the study aimed at investigating the use of coherence measurements of simultaneously recorded electroencephalography (EEG) and surface electromyography (EMG) during low level sustained muscle contraction. Theses coherence measurements aimed at obtaining more information about the connectivity and conductivity of the motor (descending) spinal tracts. The aims of the study included comparing the measurements obtained by these electrophysiological methods to the conventional clinical examination findings obtained in accordance with the American Spinal

Injury Assessment (ASIA) Impairment Scale (AIS) (Maynard et al., 1997). As illustrated under 'clinical assessment protocol' and the associated figures, clinical examination of SCI consists of AIS Sensory Scoring Chart and AIS Key Muscle Motor Examination Chart. Based on the clinical examination obtained by means of AIS, the severity or extent of SCI could be divided into grades from A (equivalent to complete injury), through B, C and D (being decrementing severity grades of incomplete SCI) and finally E (which is equivalent to normal levels of motor and sensory spinal cord functions). The specifics of the ASIA measurements and illustrations are shown below in Figures 3.02, 3.03 and 3.04. Clinical examination according to AIS alongside electrophysiological tests were used to provide useful combination of complementary assessment methods, which could assist in obtaining additive and more accurate information about given spinal cord lesions with regard to level and extent of injuries. Finally, another aim of this study was to plan a longitudinal follow-up, using the same combination of electrophysiological and clinical methods, to assess patients with incomplete SCI (iSCI) over set periods of time long enough to allow the possible detection and therefore charting any measurable patterns over time (this may amount to neurological recovery or otherwise deterioration due to secondary injury).

3.2 Ethical Approval

The study was conducted with the assistance of normal subjects (healthy volunteers) and SCI patients from the Queen Elizabeth National Spinal Injuries Unit (QENSIU) based at the Southern General Hospital in Glasgow, for longitudinal testing. The study design, protocol and experimental methods were therefore approved by the ethical bodies of the University of Strathclyde and the National Health Services (NHS). The information sheet used and consent form used are shown in the appendix. All participants either from healthy individuals or patients with SCI, who volunteered for the study, provided a prior informed written consent.

3.3 Design of Study

The study was designed to allow longitudinal clinical and experimental measures to be repeated after a period of time. Figure 3.01 is a schematic showing the progress of the study through three measurement points over around 50.1 weeks. This shows the time line and progress of the clinical and electrophysiological assessments, with SCI onset marked as the starting point or zero time:

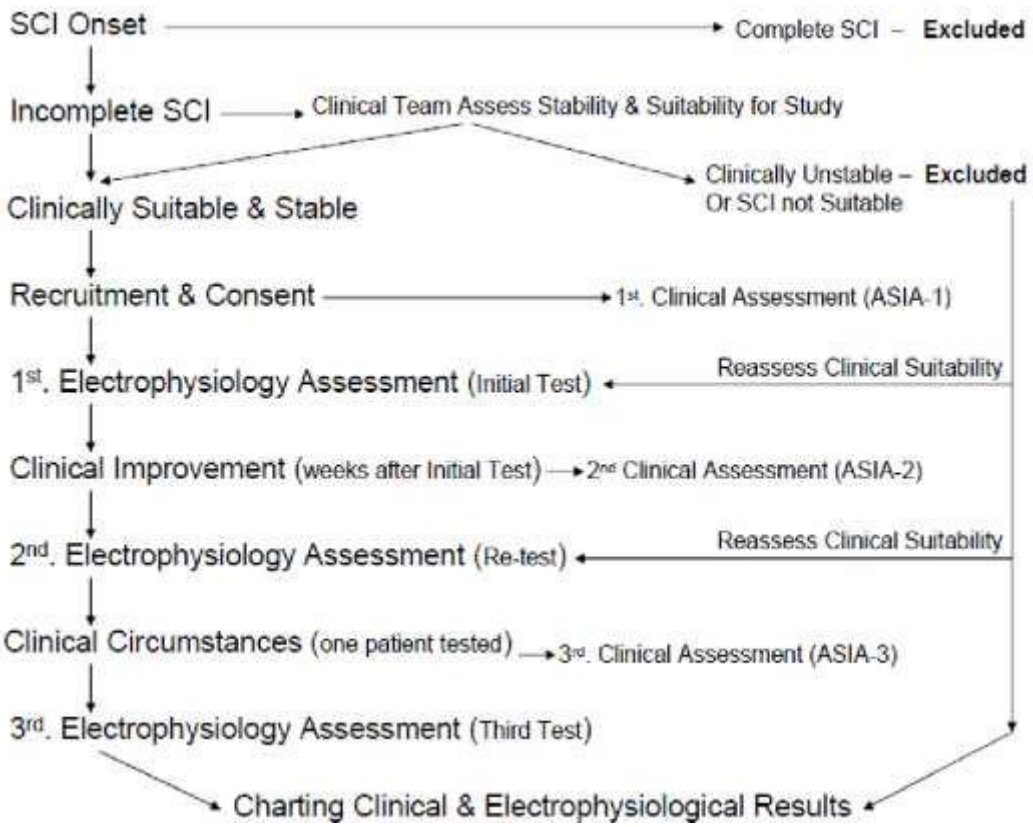


Figure 3.01: Schematic of the overall clinical and electrophysiological assessment and follow-up plan followed in the study. *Source*: Field work.

Before applying the study design to the clinical settings, it was useful to establish an appropriate protocol translating the laboratory tests to clinical (bedside) procedures that are suitable for acute and sub-acute SCI settings. Furthermore, to obtain data sets that allow comparison with data gathered through the longitudinal follow up testing the same group of SCI patients. This meant that the study contained two study groups:

HEALTHY INDIVIDUALS

A group of healthy volunteers were recruited to the study to establish normative data prior to the start of testing SCI patients. The participants of this group were 14 healthy individuals mainly university students and staff with no relevant health problems to preclude the validity of electrophysiological tests. They were appropriately informed about tests and consented in accordance with 'The Code of Practice on Investigation on Human Beings' outlined by the University of Strathclyde and requirements of the NHS Central Office for Research Ethics Committee (COREC).

PATIENTSwith SCI

Recruitment, Inclusion and Exclusion Criteria:

Patients who participated in this study were recruited from inpatients admitted with SCI to the Queen Elizabeth National Spinal Injuries Unit (QENSIU), at the Southern General Hospital, in Glasgow in the years 2004 and 2005. The recruitment specified conditions for acute or subacute traumatic SCI with means and opportunity for study examinations early enough to monitor any possible neurological recovery. As well, the patients included in the study were clinically stable and therefore it was considered safe to be examined clinically and electrophysiologically for the research purposes, given the clinical safety precautions (see Table 3.01, detailing the combined inclusion and exclusion criteria and guidelines).

Table 3.01: **The clinical criteria and guidelines used for deciding on suitability of patients with acute and sub-acute traumatic SCI for the longitudinal assessment and follow-up study (**the list shows the combined inclusion and exclusion criteria used for the process of recruiting SCI patients**):** *Source:* Field work.

- *Adult* age (preferably < 45-years) any gender – exclude children.
    - Full *comprehension* (exclude confusion, learning difficulties and dementia (ethics, informed consent, cooperation and follow up).
- Tetraplegia (next best category is Thoracic Paraplegia).
- Tetraplegics *should* have spared respiratory function (below C4).
- Motor *Incomplete* (residual muscle strength 1 – 2 on MRC*).
    - Sensory *Incomplete* (*sensation below motor level* +/- *sacral sparing*).
    - Intact sensory modality of *pin prick* is superior to *light touch*.
    - Pathologically/Aetiologically (preferably *not ischemic lesions*) other types of lesions or mechanisms of injury to be excluded.
    - Exclude *other causes of SCI* e.g. Abscess, Tumour, Vasculitis (the progress and recovery usually altered by the primary pathology).
    - Radiology [no restrictions based on radiological findings except for spinal cord oedema (worse 6 weeks outcome then rapid recovery) – preferably avoid anterior dislocation and/or fracture dislocation].
    - *Additional, dual or multiple injuries* – which may confuse the AIS clinical findings and electrophysiological test results.
    - Absence of skin sores, organ function impairment/failure and/or complications which could delay/prevent mobilization, exercises, etc.

- Lack of neurological or systemic *co-morbidity* which directly affect nervous system e.g. Diabetes, Multiple Sclerosis, Neuropathy, etc.

- Psychologically stable (insight, *informed consent*, cooperation and likelihood of retaining state of consent for the length of the study).

- Circumstantial and socio-economic [(proximity of home, possible travel, availability for future tests, access to treatment which might alter prognosis (treadmill training and FES**), transfer equipment, need for carer (outdoor activities), travel expenses].

* MRC = medical research council.
** FES = functional electrical stimulation.

Longitudinal Follow-up Plan of SCI Patients:

Patients with incomplete SCI, who matched the inclusion criteria and were considered to be clinically stable, were recruited for an '***initial***' test (see Table 3.02, for time from ***Injury to Test 1***). The second test '***retest***' was generally performed after several weeks' interval ranging 10-17.5 weeks (see table 3.02, for time from ***Injury to Test 2***, which averaged 7 weeks depending on any changes on the clinical examination status). On two occasions, circumstances were suitable to allow a recall of patients from home to QENSIU outpatient clinic or the electrophysiology laboratory at the bioengineering department of the University of Strathclyde. A '***third test***' was performed for one patient in whom the circumstances allowed this delayed retest to take place. Largely the 'third test' was possible because the patients stayed longer in the QENSIU as an inpatient for pure clinical therapeutic indications.

Table 3.02: Brief details of patients recruited to longitudinal phase of study (Subjects 1 & 2 shown in table 3.07, as patients with chronic stable SCI not suitable for retesting). *Source:* Field work.

Subject number	*SCI Level (Neurological)*	*ASIA impairment At Test 1*	*Interval between **Injury & Test 1***	*Interval between **Injury & Test 2***
3	*C5*	*B*	***270** days 33.*	*No Re-test*
4	*C6*	*C*	***34** days*	***175** days*
5	*C5*	*C*	***60** days*	***147** days*
6	*C5*	*B*	***90** days*	*No re-test*
7	*C5*	*C*	***56** days*	***154** days*
8	*T10*	*A*	***5** days*	*No Re-test*
9	*C6*	*B*	***50** days*	***147** days*
10	*T10*	*A*	***30** days*	***175** days*
11	*T12*	*C*	***42** days*	***147** days*
12	*C4*	*D*	***70** days*	***140** days*

Study Protocols:

The study protocols were designed to cover all procedural steps and guide the clinical assessment and the electrophysiological methods through the testing programme. These protocols could be divided into three major areas of within the study:

Recruitment Protocol:

As shown in Table 3.01, the recruitment process was to make available for the '*initial test*' patients with recent (acute and sub-acute) incomplete SCI (iSCI) and to ensure their availability for '*retest*' after an interval of time during which some change in their clinical (neurological) status is likely to have taken place. This part of the recruitment process, and clinical assessment conducted by the investigator Dr. Izzeldin, included careful consideration and review of the individual patient's clinical presentation, underlying pathology, AIS on admission, initial clinical progress, likely recovery pattern, psychological and social factors, carers and family, depth of patient's understanding of the terms of consent for this study and likelihood that the patient remains committed to lengthy and sometimes tiring testing protocols. This process meant that the default rate from the study was significantly lowered, and in actual fact only one patient voluntarily withdrawn the consent due to change of mind, with no underlying clinical influence of the decision. The general features of the process followed in the process of recruitment of SCI patients is outlines below:

1. ***Regular visits*** to QENSIU acute admission ward to identify new patients.
2. ***Clinical appraisal*** (by the investigator) on the suitability of patients identified for the study, in discussion with the treating physician and other therapists.
3. ***Approaching the suitable patients*** for obtaining interest in participation.
4. Supplying the study's potential candidates with ***information leaflet*** (in appendix).
5. Formal face-to-face ***review*** of the potential candidates, which included a detailed explanation of the experimental protocols and electrophysiological tests, the possible effects on participants, the expected plan of follow up, discussion of any arising issues answering the questions of patients. This review session was the basis for an ***Informed Consent*** process.
6. A formal consent obtained, a written ***consent form*** (in appendix) signed and filed in the study records, and paper copy is also kept in patients' notes along with their clinical records.

7. Liaison with the treating consultant and the clinical therapy team (CTT) for the ***ideal testing timetable***, duration of individual tests and any modifications of the tests required due to limitation imposed by the clinical status of patients.
8. ***Initial clinical examination*** by the (investigator) for baseline AIS.
9. The ***tests*** were then ***started***, always in agreement with all parties and all views.
10. As will be shown under '*Electrophysiology Testing Protocols'*, tests were split into ***short interval testing sessions*** to reduce the time demand and fatigue resulting from effort required by attending each testing session, maintain higher levels of patient's interest in the tests and most importantly to avoid and/or minimise interruption of normal daily clinical care. For instance, some patients with acute SCI undergoing the 'initial' tests had set limits on the periods of time they could sit upright, lie on their backs or on one side, and other patients experienced dizziness and/or exhaustion after substantial periods of sitting upright, as a consequence of autonomic insufficiency or orthostatic dizziness. Some patients required regular clinical care (e.g. bladder emptying by intermittent self-catheterisation at set time periods to allow bladder training), and others needed regular therapy sessions (e.g. frequent muscle lengthening and massage sessions or urgent physiotherapy for sudden, painful or disabling spasms). Some patients were frequently interrupted by unexpected visitors including care related personnel, carers or family members that the patients felt obliged to attend to. Guided by the patients' welfare and preferences, these clinical human and social considerations were given priority over the testing protocol, practically invalidating lengthy testing sessions. Therefore, the length of the testing sessions was always kept to the minimum required for obtaining data sets adequate for the necessary for analysis.
11. **Infection Control Policy**: Implementation of the universal standards used for infection and UK clinical protocol for infection control in hospitals were followed. These guidelines were enforced to prevent patient-investigator cross infection and the equipment acting as a media for transferring infection between patients in the setting of the spinal unit. It is acknowledged that SCI patients are generally vulnerable for inter-current infections and some are possibly immuno-compromised. In addition, patients who were confirmed to be infected with the so called super bugs (Methicillin Resistant Staph Aureus, MRSA and Clostridium Difficile, C.diff) were not recruited to the study, and ones with prolonged course of infective episodes were also excluded from the study.

During the recruitment process and for the length of time period in which the SCI patients remained consented and participating in the study, several issues, difficult questions and challenges were encountered and appropriately managed. The issues relating to recruitment and ethical dimensions of the study are outlined here:

- Initial and further access to patients was controlled by the medical staff of the (QENSIU), represented by the treating consultant.
- Tests were performed at times which did not interfere with the clinical protocols of usual patient's care, therapy or rehabilitation programme.
- Ensuring that SCI patients are not disadvantaged in any way, shape or form if they decided not to consent for participating in the study.
- Ensuring that the clinically indicated treatment offered routinely to SCI patients is not affected by deciding to opt in or out of the study.
- Ensuring that treatment received by SCI patients is a standard evidence based clinical management plan, which is not enhanced in any way by the fact that the receiving patients are participating in this study.
- Emphasising that any patients' questions were adequately answered at the outset and ensuring that patients, treating physicians and therapists were involved in answering any questions or issues. This helped avoiding any confusion or potential conflict of interest, and greatly aided the clinical care team in maintaining an integrated care plan for individual patients. For the full length of this study, the responsibility of care for the SCI patients who participated in the study rested solely with the treating consultants based at the QENSIU. This ensured an excellent continuity of care and palpable convenience to the great satisfaction of patients, all members of the clinical therapy team and the study investigator.
- As adjunct to the above 'clinical care agreement', any results obtained by the study's electrophysiological tests are therefore handed over to the treating consultants, who were able to discuss the results with individual patients in the light of other investigation results, clinical information and clinically oriented integrated care plan.
- Through this channel, patients participating in the study were kept informed of progress of tests, information extracted from analysed results and any practical implications for the status of their SCI.
- No financial benefits, gifts or incentives were offered or handed out to patients to induce participation in the study. When patients were called from home for the 'retest', travel expenses at standard rates for a return journey were paid by the University of Strathclyde

directly to patients through the routine channels.

As shown in Table 3.03; During the study period, 22 patients with acute or sub-acute SCI fulfilled the inclusion criteria and were approached for consent to take part in the study. 12 of them provided informed written consents and therefore participated in the study with a good compliance rate (only one patient withdrew consent due to unprovoked change of mind).

Table 3.03: Summary of the recruitment and retention of patients in this study: *Source:* Field work.

Category	Numbers	Comments
Suitable SCI	> **22**	Suitable patients identified by medical staff at spinal injuries unit (QENSIU).
Approached for Consent	**22**	Patients approached and briefed on nature of study by research team (investigator).
Consented & forwarded for testing protocol and procedures (tested).	**12**	22 – 12 = **10 Patients** did not provide unconditional written consent.
Withdrawals & Exclusion	**3**	2 Voluntary withdrawal 1 Developed symptom of autonomic dysreflexia (excluded).
Completed all components of 1st set of assessments – 'initial test'.	**9**	
Partially completed batches of assessments in 1st set of tests.	**2**	1 completed SEP & DSEP measurements 1 completed SEP & DSEP and coherence measurements.
Patients proceeding to 2nd set of assessments – 'retest'.	**7**	
Number of patients who partially Completed 2 sets of assessments.	**2**	These patients completed all SEP, ERD.S & Coherence measurements but not TMS.
Number of patients who completed full 1st and 2nd set of assessments – 'initial' and 'retest'.	**5**	The total time needed for each patient to complete full data collection for all test modalities = 4 hours (recording time).

Clinical Assessment Protocol:

SCI patients who were considered to be suitable for electrophysiological longitudinal follow up were assessed by medically qualified practitioner documenting the systemic and full neurological examination findings. The initial clinical examination took place prior to 'initial' test and before future 'retest' performed by the same clinician. This helped minimising inter- rater variability of clinical assessments which is subjective and depending on experience. The advantage being comments gathered on elements of emotional, psychological and mental factors associated to acute SCI.

Clinical assessments of the ***American Spinal Injury Assessment (ASIA) Impairment Scale (AIS)*** as in Maynard et al. (1997), shows AIS Sensory Scoring Chart (Figure 3.02) and Key Muscle Motor Examination Chart (Figure 3.03).

Modified from the AIS, the sensory assessment paradigm is shown below:

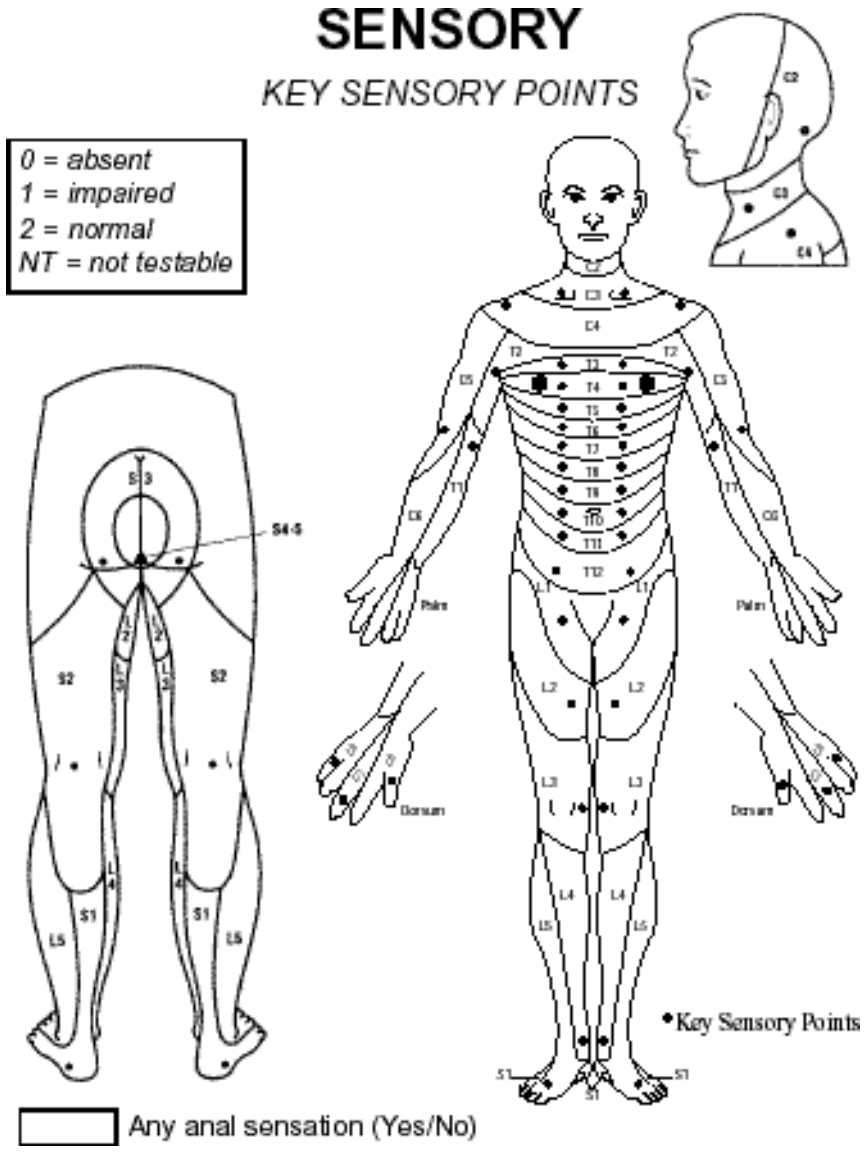


Figure 3.02: **AIS Sensory Scoring Chart:** This is used during clinical (neurological) examination to test and chart the ***pin prick*** and ***touch*** sensations.

Source: American Spinal Injury Assessment Impairment Scale (Maynard et al. (1997).

Similarly, from AIS, the motor assessment paradigm is shown below:

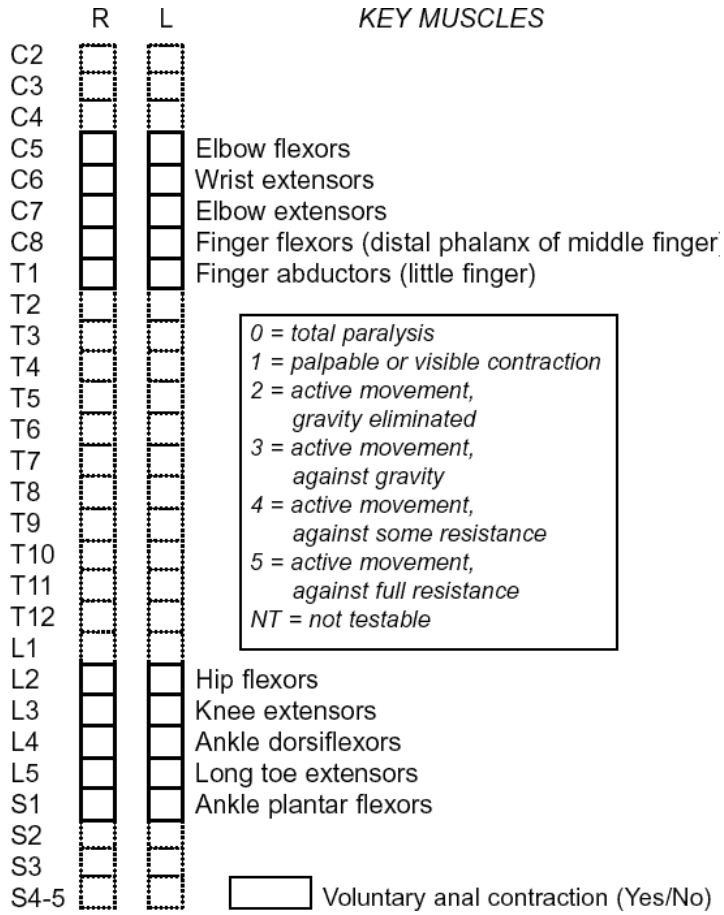


Figure 3.03: **AIS Key Muscle Motor Examination Chart:** This is used for grading the strength of key muscles in the upper and lower limbs according to the Medical Research Council (MRC) Scale of Muscle Strength.

Source: American Spinal Injury Assessment Impairment Scale (Maynard et al. (1997).

Based on the clinical examination obtained by means of AIS, the extent of SCI can be divided into grades from A (equivalent to complete injury), through B, C and D (being decrementing severity grades of incomplete SCI) and finally E (which is equivalent to normal levels of motor and sensory spinal cord functions). Details of the various grades of SCI according to the AIS are shown in Figure 3.04.

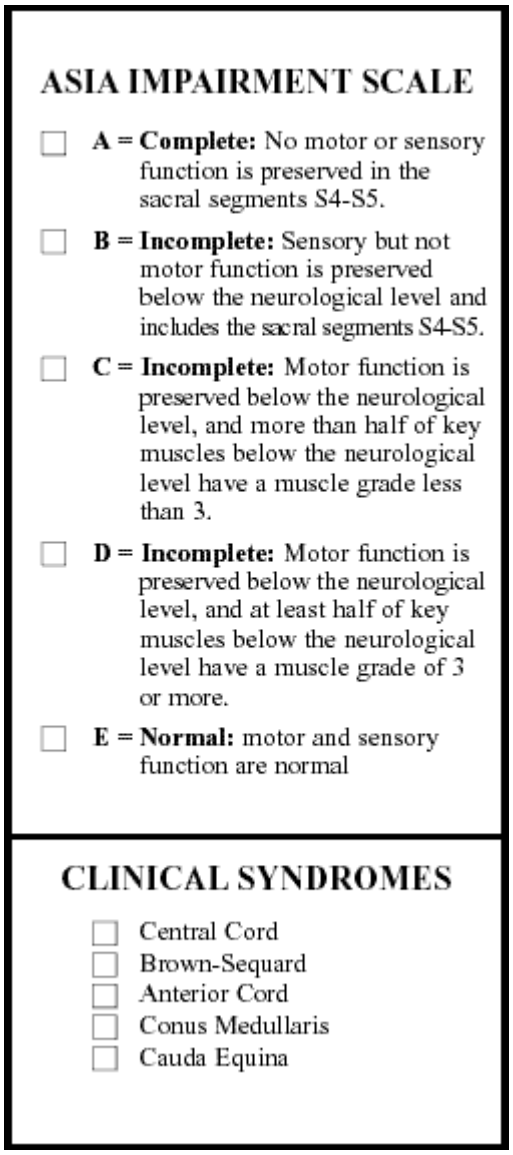


Figure 3.04: **Grades of AISA Impairment Scale (AIS) –** used to establish the level and extent (severity) of spinal cord injury.

Source: American Spinal Injury Assessment Impairment Scale (Maynard et al. (1997).

Classification of SCI into known AIS levels is established by Frankel (1970), which resolved some ambiguity in defining categories A and B by preservation of motor or sensory sacral sparing in segments S4-S5 for ASIA B, and none for ASIA A.

The other area of distinction is that AIS added quantitative criteria to differentiate categories C and D, by stipulating that in ASIA C more than half of the examined muscles are graded less than 3/5 on MRC Scale, and if not then categorised ASIA D. Obviously, the remaining C and E categories are identical in Frankel and AIS.

Irrespective of the name used for describing this SCI grading system, as part of determining the extent of SCI, the key muscles in the upper and lower limbs (shown previously in Figure 3.03), are neurologically tested and graded 0–5, which are the main grades of muscle strength according to the internationally agreed and most widely used Medical Research Council (MRC) Scale for Muscle Strength. The MRC Scale has been criticised as being non-linear, in a way that a change of one unit in the scale, say from 5 to 4, represents a much greater loss of muscle force than from 1 to 0 (Mills, 1997). Due to this and other observed lack of sensitivity, the MRC Scale has been subjected a substantial criticism leading to subsequent sub-grade modifications which are frequently seen in the literature. Nevertheless, it is quick to do and remains very popular component of clinical motor function. One of the examples is seen in the work of (Bhardwaj and Bhardwaj, 2009) and (Jackson, 2008), which display many clinically reasonable arguments. These eventually lead to successful attempts at improving the sensitivity of the middle (2, 3 and 4) grades of the MRC Scale, in order to these grades could detect and subsequently project the minor variations in muscle strength tested (see tables 3.04, for one of the typical examples listing modifications discussed above).

Grade	Subdivision	Description
0	-	No contraction
1	-	Perceptible contraction in the muscle but no movement
2		**Gravity Eliminated**
	A	Motion less than or equal to half range
	B	Motion more than half range
	C	Full range of motion
3		**Against Gravity**
	A	Motion less than or equal to half range
	B	Motion more than half range
	C	Full range of motion
4		**Motion Against Resistance**
	A	Able to lift less than 30% weight of the normal side through full range
	B	Able to lift 30–60% weight of the normal side through full range
	C	Able to lift more than 60% weight of the normal side through full range
5		Normal strength

Table 3.04: This modified MRC Scale for Muscle Strength shows details of sub-grades A, B and C used to further separate subtle variations in muscle strength seen on MRC grades 2, 3 and 4. These subtle but detectable changes in the neurological examination finding could determine whether minor clinical improvement or otherwise deterioration is taking place. This intuitively suggests that the MRC grades 2, 3 and 4 are too broad and therefore insensitive to mild clinical recovery patterns seen over time. *Source* is modified and used with the permission from the Medical Research Council, MRC).

Guided by clinical experience, the importance of the additional sensitivity and capability of the MRC Scale could not be over emphasised. This is because, frequently, the fine measurements of muscle strength grading obtained on clinical neurological examination are observed to be fitting

loosely in a rather loose nature of the middle grades of the MRC Scale. Refining MRC Scale three middle grades and reshaping them into definitive sub-grades would complement clinical examination and address inherent question of sensitivity and subjectivity (see Table 3.05, for another sub-grade modification, MRC Muscle Strength Scale).

Table 3.05: Modified MRC Scale for Muscle Strength, with 11 sub-grades described (on the left) meant to give more specific measurement of muscle strength as close to the reality of clinical examination as possible, in comparison to the classical 6 grades of MRC Scale. *Source* is modified and used with the permission from the Medical Research Council, MRC).

Modified MRC* Grade	Degree of Strength
5	Normal Power.
5 –	Equivocal, barely detectable weakness.
4 +	Definite but slight weakness.
4	Able to move the joint against combination of gravity and some resistance.
4 –	Capable of minimal resistance.
3 +	Capable of transient resistance but collapses abruptly.
3	Active movement against gravity.
3 –	Able to move against gravity but not through full range.
2	Able to move with gravity eliminated.
1	Trace contraction.
0	No contraction.

* MRC = Medical Research Council of Great Britain

Using the clinical scales and grading systems described, study patients were assessed initially at the time of enrolment to the study, then assessed prior to each 'initial' and 'retest' using electrophysiological methods. Longitudinal follow-up chart was created for each patient, and therefore possible clinical recovery patterns could be identified. Any detectable recovery by clinical measurements could then be compared with the electrophysiological counterpart tests, looking for any emerging pattern of coinciding clinical and electrophysiological improvement during the follow up period.

3.4 Electrophysiological Testing Protocols

The electrophysiological assessment methods which were used in this study could be divided into three categories as follows:

Sensory Tests:

- **SEPs** in response to electrical stimulation of mixed nerves.
- **D-SEP** (dermatomal SEP) in response to direct skin region electrical stimulation.
- **ERS/ERD event-related Measurements**: event-related changes in EEG power as a result of electrical stimulation of mixed nerves.

Motor Tests:

- **TMS** obtaining the MEP Latency and Amplitude measurements.
- Cortico-muscular (EEG-EMG) **coherence** measurements.

Experimental methods used in each of these test categories are described below.

i) SEP and ERS & D Experimental Protocols:

1. The subjects were advised to wear ***clothing*** to allow access to arm and legs.
2. The subjects were tested while being ***seated*** in a comfortable arm chair, while the SCI patients were tested in a modified setting to suit clinical needs. In Figure 3.11, an example set-up created for SCI patients unable to sit upright because cervical SCI patients frequently develop exhaustion and dizziness with prolonged unsupported upright sitting. For them, most tests performed in ***supine*** position or considered for ***shortened time length*** when seated upright.
3. Healthy volunteers participated in at least ***two electrophysiological testing sessions*** set to be completed at two separate timing, which was found to be more comfortable arrangement preferable for participants. However, for SCI patients it was essential requirement to cater for the clinical needs described. It also shortened the time needed for testing sessions eventually reducing interference with the ordinary clinical activities and rehabilitation of SCI patients.
4. SEP and D-SEP measurements were made in response to graded electrical stimulation of ***sites identified*** to best anatomical correlates of key dermatomes, described in (Foerster, 1933), and tested clinically by pin prick and light touch sensory neurological examination in AIS (see Figure 3.05 and Table 3.06).

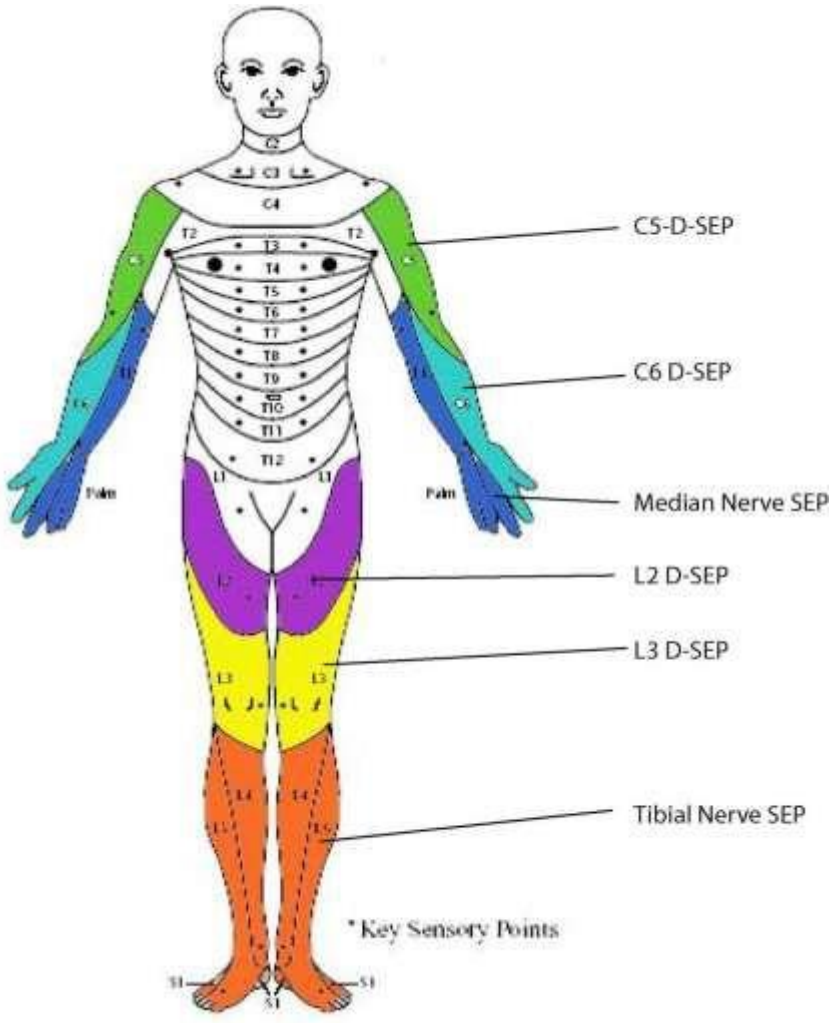


Figure 3.05: Schematic modified from ASIA Impairment Scale (AIS). *Source* (modified from American Spinal Injury Assessment Impairment Scale (*Source* – field work of thesis, with modified information in line with the ASIA Impairment Scale).

Table 3.06: Summarize the main innervation zones (represented by dermatomes or peripheral mixed nerves) which were tested by the SEP or D-SEP measurements. *Source:* Field work.

Innervation zone associated with Evoked Potentials	*ASIA Key Sensory Points*
C5 D-SEP	***C5***
C6-D-SEP	***C6***
Median Nerve SEP	*C6*, ***C7***, ***C8***, ***T1***
L2 D-SEP	***L2***
L3 D-SEP	***L3***
Tibial Nerve SEP	***L4***, ***L5***, ***S1***, *S2*

5. The actual testing sites, as described above, for SEP and D-SEP measurements were decided following careful consideration of each of the studies within a clinical setting and to allow easy comparison with ASIA chart measurements.

6. Chosen in a way that the resulting series of SEP & D-SEP readings would effectively provide an electrophysiological chart (as shown in Figure 3.06), which mirrors the sensory scoring chart obtained by clinical examination performed in accordance with the ASIA Impairment Scale.

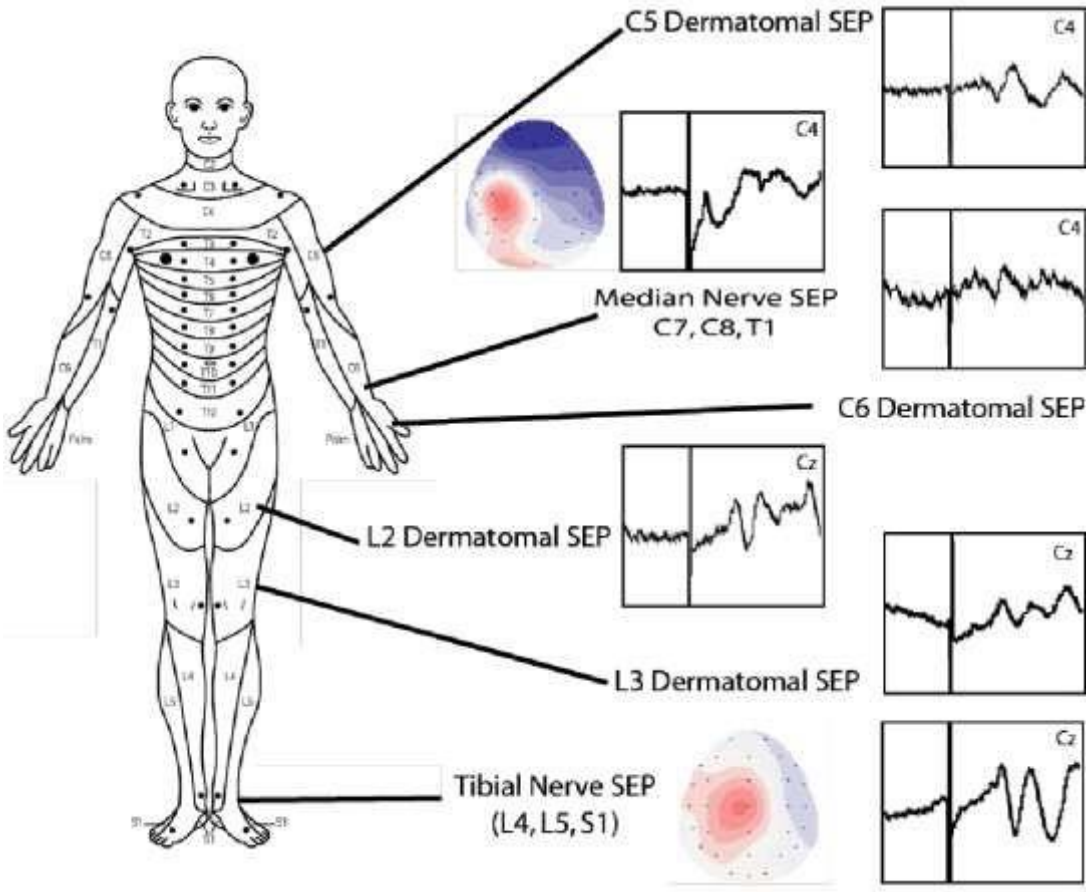


Figure 3.06: Shows the design of electrophysiological sensory testing chart for the SEP and D-SEP intended to mirror key dermatomes assessed clinically using the ASIA Scale. The SEP and D-SEP sites tested on healthy subjects shown in this diagram include left C5, C6, L2 and L3 D-SEPs and SEPs for left Median and Tibial nerve stimulation, depicted as averages of C4 and Cz electrode recordings for upper and lower limbs, respectively. (*Source*: Field work of thesis, in line with ASIA Scale).

7. SEP and D-SEP measurements were obtained in response to graded electrical stimulation of set testing criteria using standard lab equipment approved for patient use and having passed all appropriate electrical safety tests.
8. SEP and *D-SEP* Testing Specifications and Equipment Used:

Stimulator and Stimulus Specifications:

- **Stimulator**: Model DS7 (Digitimer, UK).
- **Stimulus**: **1000** shocks, pulse width = **0.2ms** square wave (variable electrical current in mA), delivered at 1 pulse every 350ms (frequency = **2.857Hz**).
- **Stimulus Intensity for SEP**: was adjusted to = 2 x **Motor Threshold** (MT), judged by appearance of visible muscle twitching in corresponding muscles innervated by the stimulated nerve, as well guided by tolerance for the stimulus by the subjects being tested (in 2 x MT was found to be well tolerated by most subjects in the healthy and patients' groups).
- **Stimulus Intensity for D-SEP**: was adjusted to = sub-motor threshold, which was often more than 2 x **Sensory Threshold** (ST). This was adjusted by keeping the stimulus intensities just under levels which produced visible muscle twitching, and adjustments of stimulus was also guided by tolerance of the subjects being tested for the stimulus, whichever reached first.
- **Mixed Nerve** (SEP) **Stimulation**: was delivered using an electrical bar comprising 2x6mm pad separated by 25mm. The electrical bar is fixed over the upper and lower limb nerve by adjustable Velcro straps (by VIASYS Healthcare, UK). Pads were moistened in Saline. SEPs were evoked by stimulation of the Median and Tibial nerves of left and right side. The stimulation sites conformed to standard clinical neurophysiology practices and protocols.

Median Nerve Stimulation Site: The bipolar bar electrode was placed over the wrist longitudinally along the course of the median nerve: the ***proximal pad*** over the wrist's 2nd skin crease immediately medial to *Flexor Carpi Radialis* tendon and lateral to *Palmaris Longus* tendon, if palpable, and the ***distal pad*** placed 20mm distal to the proximal pad.

Tibial Nerve Stimulation Site: The bipolar electrode was placed vertically on the medial aspect of the ankle joint, 2–3cm posterior to and slight superior to the medial malleolus of the tibial bone.

Dermatomal SEPs were evoked from 2 cervical and 2 lumbar sites as described below:

- **Dermatomal** (D-SEP) **Stimulus** was delivered using adhesive skin surface 32x25mm discs for dermatomes C5, L2 and L3 and 106x8mm ring disposable stimulating electrodes (by **TECA** Accessories, Oxford Instruments Medical, USA) for C6 tests. Electrodes were secured on skin surface using 25mm hypoallergenic Micropore tape (by 3M Health Care, Germany).
- **Dermatomal (D-SEP) Stimulation Site**: surface electrodes used for dermatomal stimulation located within the areas of C5, C6, L2 and L3 dermatomes illustrated in (Foerster, 1933).

Recording Equipment and Recording Specifications

- **Acquisition**: A Syn-Amps-1 EEG amplifier was used for signal acquisition running '**Scan 4.3**' software, which is a digital EEG acquisition and analysis system (by Compumedics Ltd, NEUROSCAN, USA).

- **32** channel monopolar digital recording with **the following electrode set-up**:

- **28** Scalp channels layout placed according to **International 10-20 System for EEG Electrode Placement** (Steinmetz et al., 1989), as illustrated in the schematic representation, shown in figure 3.08.

- **EEG Electrode Positioning Systems**: Two commercial electrical cap systems '**Quick-Cap**' (NEURO MEDICAL SUPPLIES, Neurosoft, Inc, USA) were used to place scalp electrodes on subject heads. The Quick-Cap's fabric lost elasticity due to frequent use and wash. This was replaced by **'EASYCAP**' (EASYCAP GmbH, Germany), using **Ag/AgCl** sintered ring electrodes snapped into electrode adaptors shown in Figure 3.07.

Figure 3.07: An electrode adaptor (left) and AgAgCl sintered ring electrode snapped into the adaptor (right) ready to be fixed to button-whole of Electrode Positioning EasyCap (Field work). *Source:* Field Work

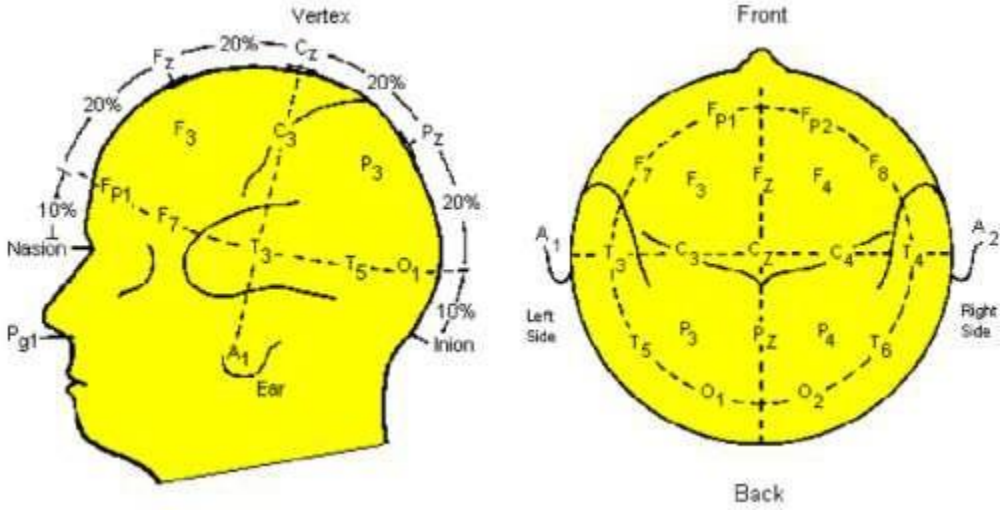


Figure 3.08: A schematic of the layout of scalp on coronal (left) and axial (right) views with key anatomical landmarks used to determine electrode locations in accordance with the International 10- 20 System of EEG Electrode Placement. (from the Standard 10-20 EEG Recording System).

Electrode Cap Positioning: The subjects' head circumferences were measured and matched to individual cap sizes (designated 52, 54, 56, 58 centimetres of head circumferences). On mounting EEG caps, attention was particularly given to positioning key electrodes in relation to the actual measured points on the subject's head (e.g. Cz was ensured right-left centred half-way between Nasion and Inion, lateral electrodes were symmetrical and frontal-polar and occipital electrodes were correctly positioned). Once these electrode sites were adjusted, the caps were secured by chin straps. The EEG caps utilize the 10-20 International System, with 32 electrodes.

A consistent approach to cap placement was taken in order to ensure:

i. accurate electrode placement on consequent testing days, and
ii. a minimal time for testing up.

4 additional non-cephalic electrodes with variable sites were used. The SEP connection identifies the need for these electrodes in order to analyse the waveforms fully. Additional electrodes as follows:

For upper limbs:
- **Erb-1** (Left anatomical Erb's point).
- **Erb-2** (Right anatomical Erb's point).

- **Cerv-6** (6th Cervical Vertebral Spine).
- **Cerv-2** (2nd Cervical Vertebral Spine).

For lower limbs:
- **Pop-1** (Left Popliteal Fossa.
- **Pop-2** (Right Popliteal Fossa).
- **L-1** (1st Lumbar Vertebral Spine).
- **Cerv-6** (6th Cervical Vertebral Spine).

Wraparound patient **ground** electrode (by **TECA** Accessories, Oxford Instruments Medical, USA), saline moistened felt pad, was applied to bony limb surfaces.

The process of preparing the electrode positioning caps and the layout of experiments during SEP and D-SEP recording sessions are illustrated in figures 3.09 and 3.11, with other features including an indication of the location of the non-cephalic electrodes.

Figure 3.09: SEP and D-SEP recording session, with a healthy subject fitted with a 32-channel electrode '**Quick-Cap**', which aid positioning the scalp electrodes according to the International 10– 20 System of EEG Electrode Placement. In addition, electrodes are positioned on both Erb's points (**Erb-1** and **Erb-2**), over two key cervical vertebral spines C2 and C6 (**Cerv. 2** and **Cerv. 6**), for upper limb recording and over first lumbar vertebral spine (**L1**) for lower limb recording, respectively. Electrode contact points with scalp were gently abraded using an abrasive gel 'NuPrep', and lubricated using an electro-conductive 'ELECTRO-GEL' to lower the electrical impedance below 5kΩ, monitored on the computer screen 'vertical arrows' appearing on the far left-hand side of this photograph. A white wrist strap (Velcro) holding a 'blue bar' electrical stimulating electrode 'tilted arrows' – appearing at the bottom left-hand corner of this photographs – placed in position for a left median mixed nerve stimulation test. *Source*: Field work.

- **Reference (Non-cephalic)**: Ag/AgCl reusable ear-linked clip electrodes were placed one on each earlobe, satisfying condition for non-cephalic referencing.
- **Ground (Cephalic)**: A ground electrode was placed on the 10-20 AFz location, satisfying the requirement for cephalic grounding.
- **Data sampling rate** = 10000, **Gain** set to 500.
- **Band-pass filter settings**: 5 – 2000Hz.
- **Sweeps**: 1000 acquired: Start: 0ms, End: +100ms relative to stimulus onset.
- **Automated Artefact Rejection**: disabled; **Notch Filter**: off.

Electrode Application & Recording Preparation:

- **Scalp Electrodes**: Abrasive skin prepping gel 'NuPrep' (by D.O. Weaver & Co, USA), passed through the electrode cavities on cotton-tipped applicators was used to separate the hair and gently abrade scalp to reduce impedance. The electrode cavities were filled by 'ELECTRO-GEL' (by Electro-Cap Intl, Inc, USA), using 10-20mls disposable syringes and sterile 14G blunt square grind metal needle, sterilised using standardised unit and sterilising techniques. Gentle skin abrasion assists in reducing electrical impedance.
- **Ear References**: Sites on both ear lobes were gently abraded using NuPrep.
- **Skin Surface Electrodes**: Electrodes which were applied to non-hairy skin surfaces (e.g. earlobe references and prefrontal Fp1 and Fp2 electrodes) were attached using thick Ten20 Conductive Paste (by D.O. Weaver & Co, USA).
- **Non-cephalic Electrodes**: Skin was gently abraded using NuPrep and **1**-meter lead 'Neuroline' surface recording electrodes (by Ambu A/S, Denmark) were applied to the abraded skin recording sites and secured by Micropore tape.

Linear Derivation for Creation of Bipolar Channel:

- From the monopolar acquisition of SEP & D-SEP cortical components, a simple **Linear Derivation (LDR)** was performed, referenced to Fz, to enable the creation of **6 Bipolar Channels**. The LDR montage was used to characterise short latency (early components) SEP and D-SEP in the measurement terms of latency and amplitude parameters. See figure 3.10 for an illustration of the process of offline creation of a '6 Channel Bipolar Montage' from originally acquired 'monopolar' EEG recordings.
- The channels created are **Fz-C3, Fz-C4, Fz-Cerv-2, Fz-Cerv-6, Fz-Erb1 and Fz-Erb2.**

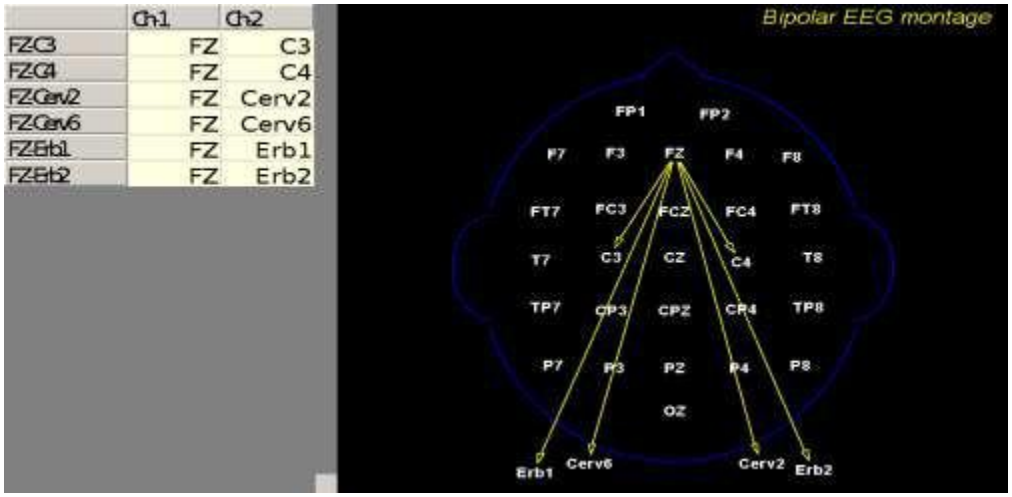


Figure 3.10: A schematic bipolar representation of the cortical SEP responses derived, from the original monopolar SEP set-up, by simple linear derivation (Initial 'raw' SEP recording obtained on a monopolar montage referenced by ear linked electrodes and a cephalic ground). This illustration shows creation of 6 bipolar montage (used to characterise SEPs in terms of amplitude & latency) in which bipolar channels are created between **Fz** and EEG electrodes **C3**, **C4**, in addition to electrodes placed over left and right Erb's points (**Erb1** & **Erb2**) and electrodes placed over key cervical vertebral spines (**Cerv2** & **Cerv6**). *Source*: Field work.

- LDR bipolar channel for upper and lower limbs were set as follows:

  i. For the upper limbs, bipolar channels were created and referenced to **Fz** and EEG electrodes **C3**, **C4**, in addition to electrodes placed over the left and right Erb's points (**Erb-**

1 and **Erb-2**, respectively) and electrodes placed over two key cervical vertebral spines (**Cerv-2** was read over C2 and **Cerv-6** was read over C6).

ii. For the lower limbs, bipolar channels were created and referenced to **Fz** and EEG electrodes **Cz, CPz, Pz, C3** and **C4**. In addition, electrodes placed over two key vertebral spines (**Cerv-6** over C6 and **L-1** over L1). Similar to upper limbs, electrodes were placed over left (**Pop-1**) and right (**Pop-2**) Popliteal Fossa, to ensure adequate stimulus intensity.

- From the **6-Channel Bipolar LDR Montages**, created for upper and lower limb recordings, short latency SEP measurement parameters were extracted using bipolar scalp referenced SEP recording in response to limb stimulation.

Other Aspects of the Experimental Protocol:

- **Testing time**: The SEP and D-SEP testing duration was around **90 minutes**, inclusive of one or two short breaks accommodated according to subjects' preferences or dictated by SCI patients' comfort and clinical needs.
- **Post-Examination**: On completion, **electrodes** were **removed**, **skin cleaned**, and subjects assisted to resume their activities of daily living, with subjects getting convenient breaks.
- **Cleaning & Disinfection**: Following each test, the reusable equipment (EEG Cap, EEG and Ear Clip electrodes), were thoroughly washed with water and disinfected according to manufacturer's instructions, soaked in mild dilution of Milton Sterilising Fluid (by Proctor & Gamble, UK) and left to dry. The remaining firmware equipment was wiped clean using antimicrobial impregnated wet wipes or alcohol gel and gauze. Reusable metal needles, used to deliver electrolyte gel into specific electrode locations on the scalp, were sent for cleaning and sterilisation unit at the Bioengineering, University of Strathclyde).

Offline Analysis and Data Processing:

- SEP & D-SEP analysis was performed (see under section Signal Processing).

9. ERS & D Measurement Specifications and Equipment Used:

It should be emphasised that the protocol as in SEP and D-SEP, including equipment, recording specifications, electrode sites and application, was used to record ERS and ERD sensory assessment data. This was obtained in the same way done for SEP and D-SEP however with the following items applied differently as specified below as follows:

Stimulus Specifications:

- **Stimulus**: **70** shocks, pulse width = **0.2ms** square wave (variable electrical current in mA), was applied to the sites used for mixed nerve and dermatomal stimulation, delivered at 1 pulse every 10 seconds (frequency = **0.1Hz**) at stimulus intensity = 2 x **Motor Threshold** (MT).

Recording Specifications:

- **Acquisition:** SynAmps-1, running '**Scan 4.2**' Digital EEG Acquisition and Analysis **Software** (by Compumedics Ltd, NEUROSCAN, USA).
- **Data sampling rate** = 1000, **Gain** set to 500.
- **Band-pass filter settings**: 1 – 100 Hz.
- **Seeps**: 70 acquired: Start: -1000ms, End: +2000ms relative to stimulus onset.
- **Automated Artefact Rejection**: disabled; **Notch Filter**: off.

Offline Analysis and Data Processing:

- ERSP analysis was performed (see under section Signal Processing).

10. After the experimental methods were validated and normative data obtained from health volunteers, pilot trials of the assessment protocols were performed on two patients with long standing (chronic) complete (clinically stable) spinal cord injuries (see Table 3.07). These trials, performed at an early stage of this study, allowed further refinement of electrophysiological tests, outlining the clinical assessment routines and longitudinal follow plan (discussed above), and fine tuning of testing protocols to suit clinical settings of acute and sub-acute SCI patients with variable clinical, social and psychological needs.

Table 3.07: Details of Patients with Chronic Stable Clinically Complete SCI. *Source:* Field Work

Subject ID	*SCI Level*	*ASIA at injury date*	*Date of testing post0injury*	*ASIA at date of test*
1	*T6*	*A*	*8 months*	*A*
2	*T4*	*A*	*6 months*	*A*

11. The study progressed to study patients with incomplete SCI (iSCI) as per main targets of this research project. Figure 3.11 shows SCI patient being tested for SEP and D- SEP giving an insight about testing in acute clinical settings. This figure illustrates validity of SEP & D-SEP testing being conducted in supine position when electrophysiological tests could not be managed, which means otherwise performing them while sitting.

Figure 3.11: Testing SCI in a hospital set up at the QENSIU in Glasgow, for one of the study patients with cervical SCI, illustrating the possibility of testing while patients are comfortably resting in supine position. The photograph shows the EEG Easy Cap applied to the head (vertical arrows) with the EEG electrode leads connected to the preamplifier box (horizontal arrows) and connected to the acquisition equipment trolley and controlled by the computer appearing at top right- hand corner of this photograph. *Source*: Field work.

ii) MEP (TMS) Experimental Protocols:

1. Trans-cranial magnetic stimulation (TMS) was performed obtaining the ***motor evoked potentials*** (MEPs) defined by latency and amplitude measurements assessing integrity and function of corticospinal tracts (CST) motor systems.
2. The testing of healthy subject volunteers assisted in validating the testing protocol, creating normative data and fine tuning of the experimental routines (the data on healthy subject volunteers is presented in the results section).
3. The subjects were advised to wear ***clothing*** that allows access to peripheral parts of upper and lower limbs, dorsal forearm and upper shin, respectively.
4. The subjects were usually tested while being ***seated*** comfortably in an arm chair. In the case of a motor study of SCI patients, the setting was frequently modified to suit their clinical needs, comfort and preferences (as discussed in sections on protocols).
5. Performing TMS while patients were supine in hospital beds carried extra magnetic safety precautions and measures. However, it gave an unintended added value having stable stimulation sites (coils delivered TMS pulses which precisely targeted cortical locations corresponding to contra-lateral limb muscles), while head was supported.

6. The volunteering subjects participated in a ***single testing session*** lasting from 30 to 45 minutes, which was well received and well tolerated by SCI patients.
7. The study subjects were tested in accordance with the standard safety requirements for single shock TMS. Safety requirements for TMS resemble magnetic resonance imaging (MRI) guidelines used for clinical and research purposes. Safety procedure for TMS discussed in (Jalinous, 1998) and (Hovey et al., 2003) followed included:
   - To ***screen subjects for any medical risk factors*** or co-morbidities constituting an absolute contraindication of TMS (e.g. electronic implants or cardiac pacemakers) or relative (e.g. metal implants in brain, eyes, ears, dental devices and old shrapnel or fragments). Precautions include checks for epilepsy, brain tumour, stroke, significant head injury, and migraine as TMS precipitate or aggravate attacks.
   - Prior to tests, subjects ***removed metal objects*** (e.g. hair clips, glasses, ear rings). Subjects were required to locate recording devices, discs or credit cards at least 1-meter ***safe distance*** from stimulating coil to avoid damage by magnetic fields.
   - The safety features of actual TMS testing parameters were set as much as possible to comply with the following features set for repetitive TMS:
     - to keep stimulus ***threshold*** $\leq$ ***90%***.
     - to ***reduce rate of stimulus*** as much as possible (for clinical safety reasons).
     - to use as ***brief periods of stimulation*** as possible.
     - to allow ***sufficient recovery time*** after each stimulation.
   - Total number of stimuli per one subject was always under 600 stimuli, which is well under maximum allowed by safety guidelines, stating a maximum of 4000 stimuli per day in order to protect subjects' ears against the possible dangers of magnetic coil discharge click noise.

8. TMS testing procedures were used to obtain motor evoked potentials (MEPs) from upper and lower limb muscles which were chosen to correspond to ***cervical*** and ***lumbosacral*** myotomes. Hence, the chosen myotomes and their resulting MEP measurements technically represent electrophysiological assessments carried out on muscles above and below given spinal cord lesions.
9. Muscles used to record MEP measurements using TMS were **Extensor Digitorum Communis** (**EDC**) and **Tibialis Anterior** (**TA**) and are considered to correspond to key muscles on motor assessment chart of ASIA Impairment Scale (AIS) relating to wrist extension and foot dorsiflexion, respectively.

10. The muscles and anatomical sites used for recording MEPs from the upper and lower limbs during TMS procedure are shown in Figure 3.12.

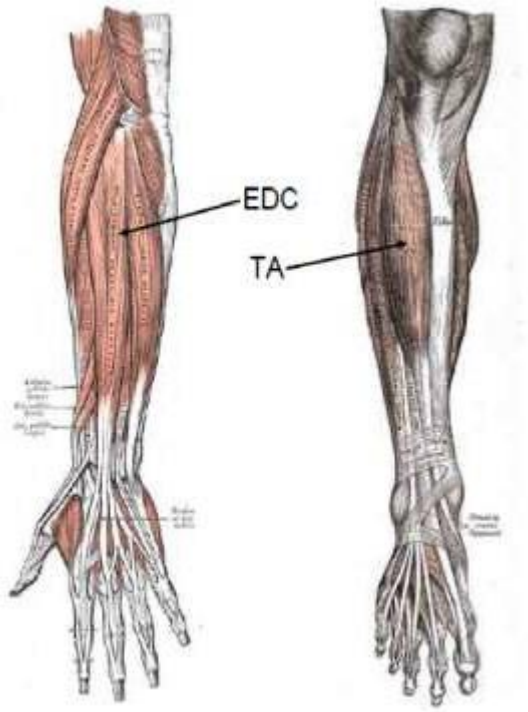


Figure 3.12 shows the anatomical locations of Extensor Digitorum Communis (**EDC**) and Tibialis Anterior (**TA**) muscles in upper & lower limbs, respectively. Tips of the tilted arrows indicate skin sites corresponding to surface points for motor recording using EMG electrodes to obtain MEPs in response to TMS. (*Source*: illustrations are modified from Gray's Anatomy, online electronic book).

11. TMS tests were planned to assess corticospinal tracts obtaining MEP measurements from anatomical sites corresponding to AIS motor charts. Figure 3.13 shows a schematic representation of the testing set-up and typical TMS equipment used to obtain motor evoked potentials (MEP) in healthy subjects and SCI patients.

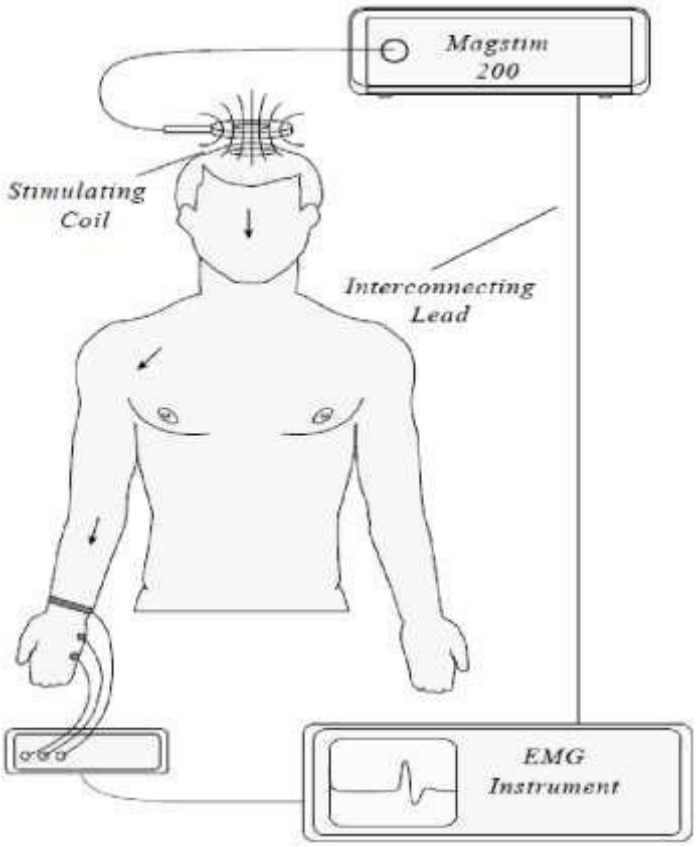


Figure 3.13: Experimental set-up which allows trans-cranial magnetic stimulation and peripheral recording of motor evoked potentials picked up by surface EMG electrodes placed over selected limb muscles. *Source*: modified schematic representation from 'Magstim Manual, 2003'.

12. MEP (TMS) Testing Specification & Equipment Used:

TMS Equipment & Stimulus Specifications:

- **Magstim Model 200**, a magnetic stimulator with a monophasic output pulse (by The Magstim Company Ltd, UK).

- **Magnetic Stimulating Coils**: The magnetic pulses were delivered to cortical stimulation sites by means of applying stimulating coils (by Magstim, UK) to specific anatomical locations on subjects' heads. For upper limb (ED) muscle stimulation, a Double 70mm Coil was used, while a Double Cone Coil was used for lower limb (TA) muscles. Careful manoeuvring of these coils over selected scalp locations overlying motor cortex helped locate 'hot spots' that yield the maximum MEP response amplitudes. The 'hot spots' (scalp locations overlying the cortical motor areas controlling muscles on contra-lateral upper and lower limbs) were stimulated while evoked motor responses on corresponding muscles were recorded using an EMG acquiring device (see figure 3.14). The physical characteristics and calculated energy outputs for the coils used in the TMS experiments are shown in table 3.08.

Table 3.08: Shows the physical characteristics and maximum calculated magnetic (*and electrical*) outputs of the two coils used (with Magstim 200 Magnetic Stimulator) in the study for obtaining upper (**EDC**) and lower (**TA**) limb MEP responses as indicated. *Source*: Field work.

Coil Type & Name	***Double 70mm Coil***	***Double Cone Coil***
Inside Diameter	*56 (x2) mm*	*96 (x2) mm*
Outside Diameter	*87 (x2) mm*	*125 (x2) mm*
Number of Turns	*9 (x2)*	*7 (x2)*
Peak Magnetic Field Strength	***2.2 Tesla***	***1.4 Tesla***
Muscle Stimulated by the Coil	*Upper Limb (**EDC**)*	*Lower Limb (**TA**)*

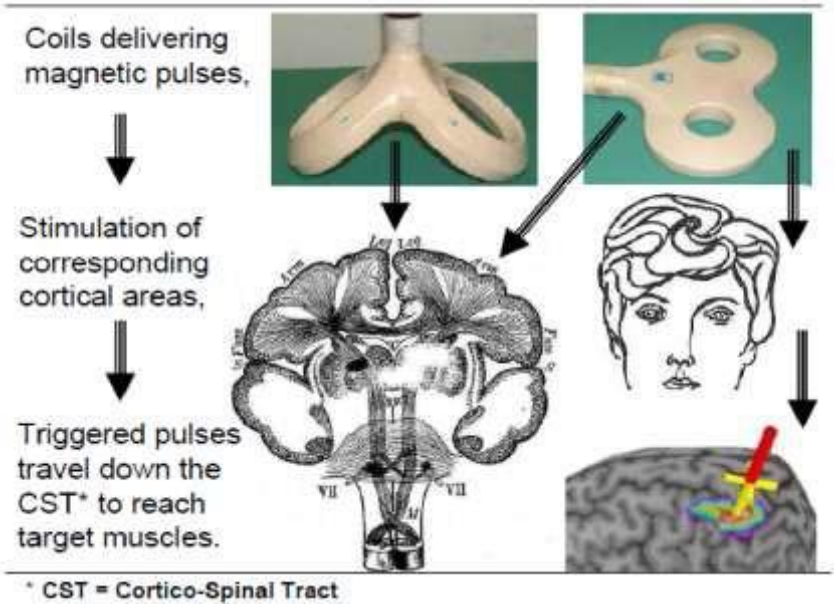


Figure 3.14: shows approximate cortical locations 'hot spots' targeted during trans-cranial magnetic stimulation used to obtain MEPs from contra-lateral limb muscles, with curvilinear reconstructions of brain anatomy displaying a hot spot of a coil induced magnetic pulse for right upper limb stimulation. *Source*: schematic of the filed work representation and modifications from 'Magstim Manual, 2003'.

- **Coil Stand**: A compatible coil stand capable of holding a double cone coil appearing in **Figure 3.15** was used to locate the stimulating coil precisely over targeted cortical locations or 'hot spots' with subjects kept still and their head supported.
- **Stimulus**: **10–15** magnetic pulses, of peak magnetic field strength = 2.0 Tesla for 'Circular 90mm Coil', and = 1.4 Tesla for 'Double Cone Coil'. Magnetic pulses were delivered at a rate of 1 pulse every 5 seconds (Inter-Stimulus Interval 'ISI' = 5s), a **Frequency** = 0.2Hz).
- **Trigger**: An input trigger for discharging the magnetic stimulator was obtained by using (Digitimer Stimulator Model DS7, Digitimer, UK), which was set to simultaneously trigger the onset of EMG recording sweep for the motor evoked potentials (MEP) from corresponding muscles (the set-up and necessary connections for the TMS experiment are shown in Figure 3.15).

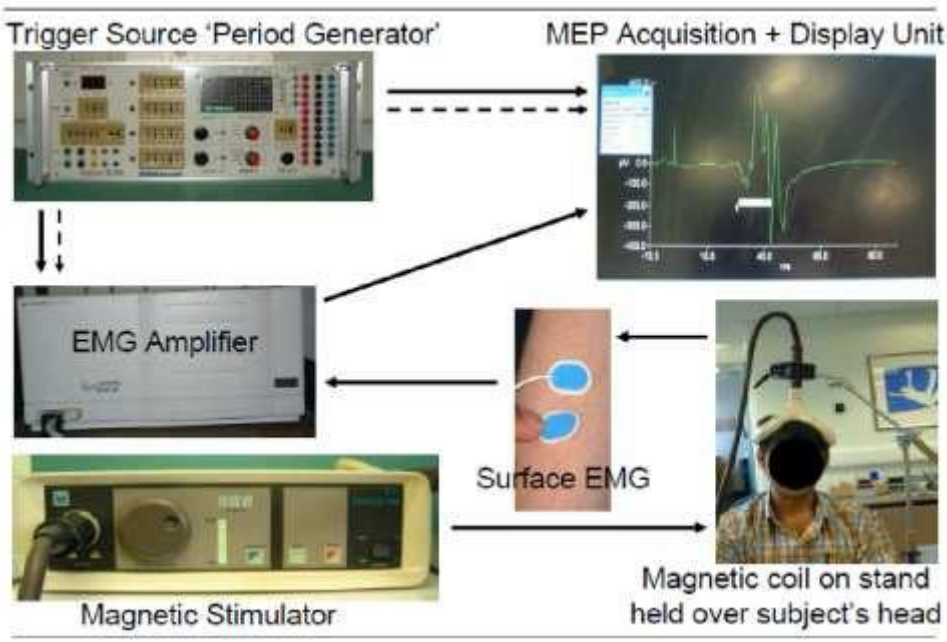


Figure 3.15: Schematic representation of TMS test showing layout of experiment, equipment used and necessary connections. Dashed lines indicate the triggering received from period generator to simultaneously discharge magnetic stimulator and trigger sweep onset for MEP recording as displayed on computer screen (the recorded MEPs represent amplified surface EMG signals from corresponding limb muscles in response to contra-lateral TMS). The displayed double cone coil activates lower limb cortical areas of both hemispheres simultaneously enabling simultaneous recording of EMG activity from right and left tibialis anterior muscles. *Source*: Field work.

- **Stimulus Intensity**: Incremental stimulation intensities were used starting at 40% (of Magstim output) up to 95%, increasing by 5% at a time targeting the maximum threshold intensity tolerated by participating subjects, yielding 12 sets of stimulation intensities as follows: 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% and 95%. In TMS recording sessions, these set intensities were used to produce approximately 12 sets of MEP recordings for each EDC and TA muscles, on both right and left sides. For each patient, approximately (12 sets x 2 muscles x 2 sides) 48 sets of the MEPs were obtained. The approximation is due to the fact that some subjects did not tolerate higher stimulation intensities hence giving fewer than planned MEP set recordings. The gradual increments enabled identification of motor threshold intensity, which is the minimum intensity that is capable of producing measurable motor evoked potential, obtained for each tested muscle.

Recording Equipment and Recording Specifications:

- **MEP (EMG) Recording**: AgAgCl skin surface 25x15mm 'Blue Sensor' electrodes (by Ambu A/S, Medicotest, Denmark) were placed near to the motor points of (**EDC**) and (**TA**), as shown in **Figure 3.12.** Electrodes were applied on right and left sides to obtain bilateral MEP readings from corresponding cortical TMS. Recording electrodes and cables were secured in place by Micropore tape, especially during induced muscle jerks.
- **Skin Preparation**: Sites of application of surface electrodes were prepared using standard alcohol swaps for cleaning, and gently abraded using NuPrep to reduce skin impedance.
- **Acquisition**: A computer running **Scan 4.3** (specified in SEP & D-SEP tests) was used. Sweep onset of the EMG acquisition computer was triggered by same stimulus which triggered discharge of the magnetic stimulus (described under trigger), and shown in Figure 3.14, which outline layout of experiment, equipment used and necessary connections for acquisition of MEPs.

- **Skin Preparation**: Sites of application of surface electrodes were prepared using standard alcohol swaps for cleaning, and were gently abraded using NuPrep to reduce the skin impedance.
- **Ground**: A wraparound patient ground electrode (by **TECA**Access, Oxford Instruments Medical, USA), saline moistened felt pad, was applied, as much as possible, to bony surfaces on tested limbs.
- **Data sampling rate** = 5000, **Gain** set to 500.
- **Band-pass filter settings**: 5–1000Hz.
- **Seeps**: 10–15 acquired: Start: -10ms, End: +100ms relative to stimulus onset.
- **Automated Artefact Rejection**: disabled; **Notch Filter**: off.

Other Aspects of the Experimental Protocol:

- **Testing time**: The TMS testing duration was around **70 minutes** in total.
- **Post-Examination**: On completion, **electrodes** were **removed**, **skin cleaned**, and subjects assisted to resume the activity of daily living interrupted for test.
- **Cleaning & Disinfection**: Similar measures as for SEP & D-SEP.
- **Infection Control Policy**: Similar to the measures applied for SEP & D-SEP.

Offline Analysis and Data Processing:

- MEP analysis was performed (see under section Signal Processing).

iii) Cortico-muscular Coherence (CMC) Experimental Protocols:

Analysis of coherence between simultaneously recorded electroencephalographic (EEG) rhythms and electromyographic (EMG) signals during sustained (for health subjects) and attempted (for SCI patients) low level muscle contraction, was obtained for upper and lower limb muscles to measure corticospinal tract function in SCI patients. The experimental process followed and testing protocols implemented are discussed below, where the coherence analysis is referred to as cortico-muscular coherence (CMC). Analysis of CMC on healthy volunteers was performed and with validated results shown on results section.

13. EEG recordings for the purpose analysing and measuring CMC, were obtained in same way described for SEP & D-SEP, with the following **exceptions**:

- **EEG Recording Electrodes**: 32 Cephalic (EEG) channels applied to the scalp according to the International 10-20 System.
- **Acquisition Settings**: Sampling rate: 2000Hz, Band Pass Filter: 1.0–500Hz.
- **Recording Protocol**: Simultaneous recording of EEG (acquisition as specified above and in sections describing SEP & D-SEP and TM experiments) and EMG (as described below and in the section describing EMG for TMS experiment) were obtained for 4 x 30 seconds periods.
- **Duration of Recordings**: Simultaneous EEG and EMG recordings were made for 4 repeated periods of 30 seconds recordings (see under EMG for CMC analysis the 'Duration of Recordings'.

- **External Factors (**Medications**)**: SCI patients undergoing 'retest' were almost always on a variety of medications required by their clinical condition (e.g. Baclofen and Benzodiazepines for spasticity and spasms). These medications were also noted at the time running the EEG & EMG tests for CMC analysis, as it was possible that these medications may affect the EEG rhythms and power spectrum leading to influence of the CMC analysis.

14. EMG recordings for the purpose analysing and measuring CMC, were obtained in same way described for TMS, with the following **exceptions**:

    - **The Acquisition Settings**: As described in EEG for CMC analysis.
    - **Recording Protocol**: As described in EEG for CMC analysis.
    - **Duration of Recordings**: As described in EEG for CMC analysis, simultaneous EEG and EMG recordings were made for 4 repeated periods of 30 seconds recordings. This was designed to break the total period of recording into smaller sections which were achievable by SCI patients, who tend to gradually fatigue and therefore drop the force of contraction with time. The target recording time of 2 minutes, which was necessary for the purpose of CMC analysis, was then achieved offline by connecting the 4 '30 seconds' segments of EEM-EMG recordings. In many circumstances of testing SCI patients, subjects with weakness involving tested limbs even 30 seconds low level sustained contraction was not achievable. Apparently, the obtained level of contraction was variable (interrupted) weak and incomplete, and in some instances, it was aborted before the test was complete. This was observed and noted as it was perceived by the (investigator) as a possible influence on the resulting CMC analysis. Occasionally, the tested muscles were so weak to react, and in such circumstances, SCI patients were asked to imagine the intended movements for 30 seconds while the EEG was being recorded. Analysis of the EEG and EMG during 'intended' muscle contraction was observed and noted.
    - **External Factors (**Medications**)**: Medications are less likely to affect the power of the EMG signals, but the overall CMC analysis might be affected due to the effect of the EEG as described under EEG for CMC analysis.
    - **Muscles**: As indicated previously, the surface EMG recordings were obtained from the exact locations described for the TMS experiments (EDC for upper limbs and TA for lower limbs). The obtained CMC is therefore informing on the same levels tested by TMS in the context of SCI, and therefore the information is additive on assessing the motor corticospinal tracts (CST).

Other Aspects of the Experimental Protocol:

- **Testing time**: Time taken by CMC set of tests 'approximately' 60–70 minutes in total.
- **Post-Examination**: On completion, **electrodes** were **removed**, **skin cleaned**, and subjects assisted to resume the activity of daily living interrupted for test.
- **Cleaning & Disinfection**: Similar measures as for SEP & D-SEP.
- **Infection Control Policy**: Similar to the measures applied for SEP & D-SEP.

Offline Analysis and Data Processing:

- CMC analysis was performed (see under section Signal Processing).

15. The above accounts conclude all test methods performed in this study.
16. The data obtained from (SEP, D-SEP, ERSP, TMS and CMC) experiments was pooled for offline analysis and extraction of results (see signal processing)

17. The analysed data giving results of the sensory and motor electrophysiological tests for each patient charted with AIS neurological examination as well as clinical information obtained on patients and their SCI lesions.
18. This was repeated twice: first at the start of the study 'initial test', and then at the end of the follow up period 'retest', forming basis for comparing clinical and electrophysiological information obtained over time.
19. In the section dealing with results, the findings of all the electrophysiological tests as well as the clinical findings are listed and compared.

3.5 Signal Processing, Data Analysis and Statistical Protocols

Following the described experimental settings and clinical protocols, the acquired data was collected in master computer and analysed offline using various computer programmes, software and computational statistical methods. These will be described each under the relevant process and tests producing the data:

3.5.1 SEP and D-SEP (Offline Analysis and Data Processing)

Recording sessions were analysed offline based on the raw experimental data digitisation and file at the time of the experiment. The resulting data files were initially inspected to establish data quality and artefact contamination.

- Eye blink artefact rejection was performed, setting automated parameters to (-50ms, +100ms, -50µV, +50µV).
- SEP & D-SEP data was acquired on Scan 4.3 and stored as CNT files.
- For Mixed Nerve SEP or Dermatomal D-SEP, 1000 trials were obtained and made available for offline processing (this is in comparison to 250-500 in hospital settings).
- Simple Linear Derivation (LDR) is performed from monopolar acquisition of SEP and D-SEP, referenced to Fz to enable the creation of 6 Bipolar Channels. The LDR montage was used to characterise the early components of the short latency SEP and D-SEP measuring the latency and amplitude parameters. The channels created are as follows: Fz-C3, Fz-C4, Fz-Cerv-2, Fz-Cerv-6, Fz-Erb1 and Fz-Erb2.
- Using Scan 4.3 software functions, simple averaging was performed to obtain short latency SEP and D-SEP measurements. Through offline analysis, using this software, it was possible to obtain other form of result representations including 2 and 3 spatio-temporal cortical maps which were useful in detecting subtle changes in SEP and D- SEP response topography and time course.

- For SEP & D-SEP measurements, they were characterised by means of amplitude and latency, calculated directly from the averaged Scan files.
- SEP and D-SEP waveforms, characterised by latency and amplitude were assessed in terms of normality or abnormality guided by ranges of standard deviations obtained from healthy subjects. Measurement criteria (Chiappa, 1997) for each of the SEP and D-SEP parameters were followed to enable conclusions on the correlation of results with the clinical details of SCI patients at the time of corresponding tests.
- SEP & D-SEP averaged waveforms from the 'initial' and 'retest' sessions were compared (overly 'initial' and 'retest' waveforms) for any signs of change in signal that might match clinical improvements.

3.5.2 Event-related Spectral Perturbation – ERSP (Offline Analysis and Data Processing):

- Epochs (-1000ms to +2000) were extracted from raw EEG recordings obtained on Scan 4.2 to prepare for frequency domain analysis.
- Using the EEGLAB Version 4.0 toolbox of MATLAB versions 6 and 7, it was possible to create event-related spectral perturbation (ERSP), representative of the event response as visual maps (Delorme and Makeig, 2004), ERSP were calculated by the following equation and implemented in Matlab by the EEGlab software:

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

- ERSP were used as a method of providing visualisation of the mean stimulus-induced changes (of cortical somatosensory evoked responses) within EEG's power spectrum (of various frequency bands) over time. ERSP visual maps were obtained for graded averaged and single-trial data. Both phase locked and non-phase locked activity changes of the frequency domain measurements were obtained in line with principles of event-related synchronisation and desynchronisation (ERS & D) discussed in previous work (Pfurtscheller and Lopes da Silva, 1999; Neuper and Pfurtscheller, 2001).
- Statistical analysis of the visual ERSP frequency analysis maps were performed using MATLAB scripts that applied analysis of variance (ANOVA) for ERSP maps.

- Serial ERSP visual maps were compared to extract any detectable visual or statistical changes in the SEP & D-SEP patterns over time.
- The ERSP changes were also compared to the SEP & D-SEP data sets in time domain analysis to check for any concordance or disparity of findings using these two different acquisition and analytical methods.

3.5.3 TMS (Offline Analysis and Data Processing)

- MEPs obtained using TMS were acquired and analysed via use of Scan 4.3 software.
- For each TMS intensity obtained (10-12 intensities for each tested muscle), average MEPs were calculated.
- The MEP files were extracted into Spike2 version 4.16 software (by Cambridge Electronic Design, Ltd, UK) to enable further quantificational analysis.
- MEPs were rectified to enable further analysis and characterisation of waveforms.
- Latency and area amplitude parameters of MEP were measured, using a MATLAB script, to characterise the averaged MEP waveforms.
- The motor thresholds (magnetic stimulation intensities that are capable of evoking measurable motor evoked potentials) were noted for each muscle for possible comparison with similar readings over follow-up period.
- Graphs charting latency and amplitude changes over time were drawn to illustrate possible measurable MEP changes over time.

3.5.4 Coherence (Offline Analysis and Data Processing)

- The EEG and EMG were obtained in Scan 4.3 software.
- The combined EEG and EMG raw files were extracted into MATLAB version 6 and 7 and further analysed.
- Coherence measurements were calculated between EEG and EMG recorded from corresponding muscles during 'sustained' or 'attempted' low level contraction – to detect any synchrony of signals that might indicate a level of CST function.
- Coherence maps for the tested muscles were obtained: significant coherence was plotted against cortical area of which EEG signals were observed to be synchronised to EMG, with an illustration of cortical topographic maps of most coherent cortical areas with EMG signals.

- The CMC analysis findings were compared with findings of TMS tests, to inform on the status of the motor tracts (namely CSTs).
- The CMC measurements from the 'initial' and 'retest' were compared to be able to comment on changes over time.

3.6 CONCLUSIONS

The described study protocol was pursed to accomplish the clinical examination and mirror electrophysiological tests aligned with them. These were conducted in line with the ethics of clinical research and encountered several practical and theoretical difficulties.

4. RESULTS

This chapter will describe the results obtained using the methods outlined in chapter 3. This chapter opens with information on the recruited healthy and SCI volunteers. Results of each electrophysiological measurement modality when tested in normal subjects will be presented first as it sets the normative data for comparison with patient based tests. When presenting information on patients, clinical information will be presented followed by the results of electrophysiological tests. This is done in order to facilitate clinical interpretation of the data generated for every tested patient. The SCI patients' tests will be illustrated through use of examples but all individual results are packaged for the record in the appendix.

4.1 Healthy Subjects

1. Population: A total of **14** healthy subjects volunteered to participate in this study. Subject details are provided in table 4.01, with breakdown of their demographic information. Ethical approval for all procedures and recruitment were provided by the local NREC ethics committee and the University of Strathclyde's ethics committee. Tests on healthy subjects were performed in the neurophysiology lab at University of Strathclyde. All healthy volunteers were recruited through personal approach from Dr Izzeldin and handed '*invitation letters*' that explained the aims and methods of the study. *Written informed consent* was obtained from subjects who volunteered to participate in the study. Protocols, procedures, safety policy and administrative instructions, as detailed in Chapter 3, were followed in assessing healthy subjects and SCI patients. Resulting normative data obtained from healthy volunteers is shown at the beginning of each section discussing results of the correspondent electrophysiological testing modality.

2. Observation & Subject Specific Information:

3. Table 4.01 provides the age, gender and health status of the recruited normal subjects. The table also lists via the use check-marks (x) which protocols each subject participated in. Of the 14 recruits, 9 were male, 5 completed all required tests, 7 completed 2 of the set and 4 completed one protocol each.

Table 4.01: Shows the demography of Healthy Volunteers taking part in this study. Healthy subjects overlapped three parts of electrophysiological tests which included SEP (+ERS&ERD), MEP obtained through TMS and finally CMC of simultaneously recorded EEG and EMG. Ages ranged 24- 45 years with high male gender compared to females participating in the study over the whole length of the follow up period. *Source:* Field work.

Subjects	***Age***	***Gender***	***Health***	***Tests***	***SEP***	***MEP***	***CMC***
1	*45*	*Male*	*Clear*	*CMC*			***x***
2	*36*	*Female*	*Clear*	*MEP*		***x***	
3	*34*	*Male*	*Clear*	*SEP ERS&D*	***Xx***		
4	*29*	*Female*	*Clear*	*SEP ERS&D*	***x***		
5	*30*	*Female*	*Clear*	*All*	***x***	***x***	***x***
6	*26*	*Male*	*Clear*	*All*	***x***	***x***	***x***
7	*27*	*Male*	*Clear*	*All*	***x***	***x***	***x***
8	*28*	*Female*	*Clear*	*SEP& MEP*	***x***	***x***	
9	*24*	*Female*	*Clear*	*SEP& MEP*	***x***	***x***	
10	*26*	*Male*	*Clear*	*All*	***x***	***x***	***x***
11	*28*	*Male*	*Clear*	*SEP ERS&D*	***x***		
12	*30*	*Male*	*Clear*	*SEP ERS&D*	***x***		
13	*30*	*Male*	*Clear*	*SEP & ERS&D*	***x***		
14	*26*	*Male*	*Clear*	*All*	***x***	***x***	***x***
	Average **29.9 years**				***12***	***8***	***6***

4.1.1 Normative Data

SEP & D-SEP

Measurements of SEPs and D-SEPs provide the cortical responses of short latency somato-sensory waveform parameters characterised by latency and amplitude. To illustrate normal SEP and D-SEP cortical responses, this section illustrates example normal '***waveform***' data and gives estimated '***latency and amplitude parameters***' obtained from the tested individuals (**N = 12**). A 32-channel, mono-polar electrode set-up using the 10-20 International System of electrode placement is used. In healthy subjects the most prominent averaged SEP or D-SEP signals are detectable at electrode sites overlying areas of cerebral cortex contra-lateral to peripheral stimulation sites for the upper limb and over the vertex for both lower limbs.

Figure 4.01 gives an illustration of the anatomical sites used for stimulation. These are the Median and Posterior Tibial nerves of upper and lower limbs, respectively for SEP measurements and dermatomes C5, C6 and L2, L3 of the upper and lower limbs, respectively for the D-SEPs. Figure 4.01 also shows a representative averaged evoked response resulting from stimulation of these sites. In this example, the C4 and Cz electrode recordings were used to observe the evoked responses elicited from peripheral stimulation to the left targets. There are minor variations observed in the cortical responses of individual D-SEP waveforms from dermatome C5 stimulation compared to C6. However, more obviously are the variations seen between the D-SEP and SEP waveforms. These variations are apparent as sharper and more distinctive and larger peaks in the SEP waveforms. These differences are likely due to factors related to the site of stimulation, its distance from spinal entry points and the level of synchrony in the afferent volley.

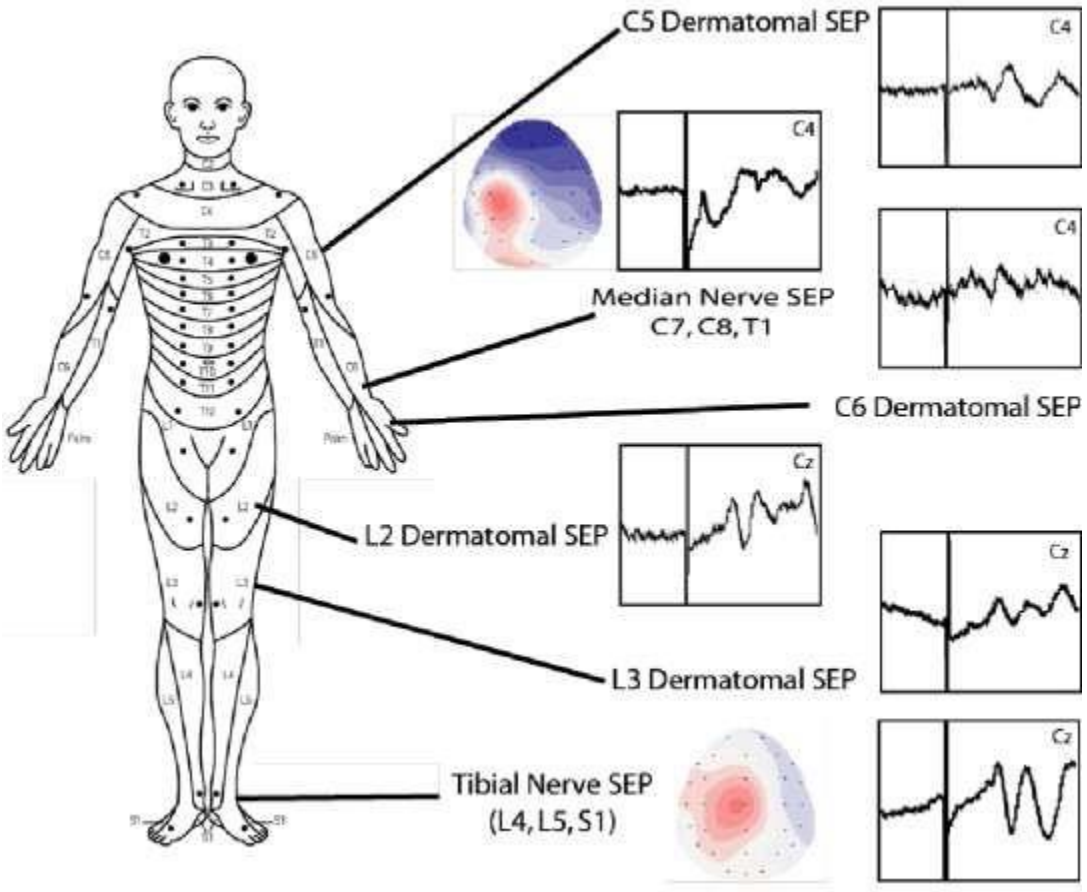


Figure 4.01 Illustrates testing sites of mixed nerves and dermatomal areas above and below given SCI lesions in order to reflect the integrity and function of nerve fibres across the given SCI lesions. These tests were repeated in the same way for the 'initial' test and after a period of longitudinal follow up as 'retest'. *Source*: Field work – modified from ASIA Impairment Scale (AIS).

In Figure 4.02, cortical D-SEPs are seen in response to left C5 dermatome stimulation in a monopolar scalp map where each electrode site is represented by the averaged evoked response at that site and graphed in a way to illustrate the way the evoked response varies with recording site. As expected, the main features of the C5 D-SEPs are most easily observed from electrodes contralateral to the stimulation and clustered over sensorimotor areas of cortex.

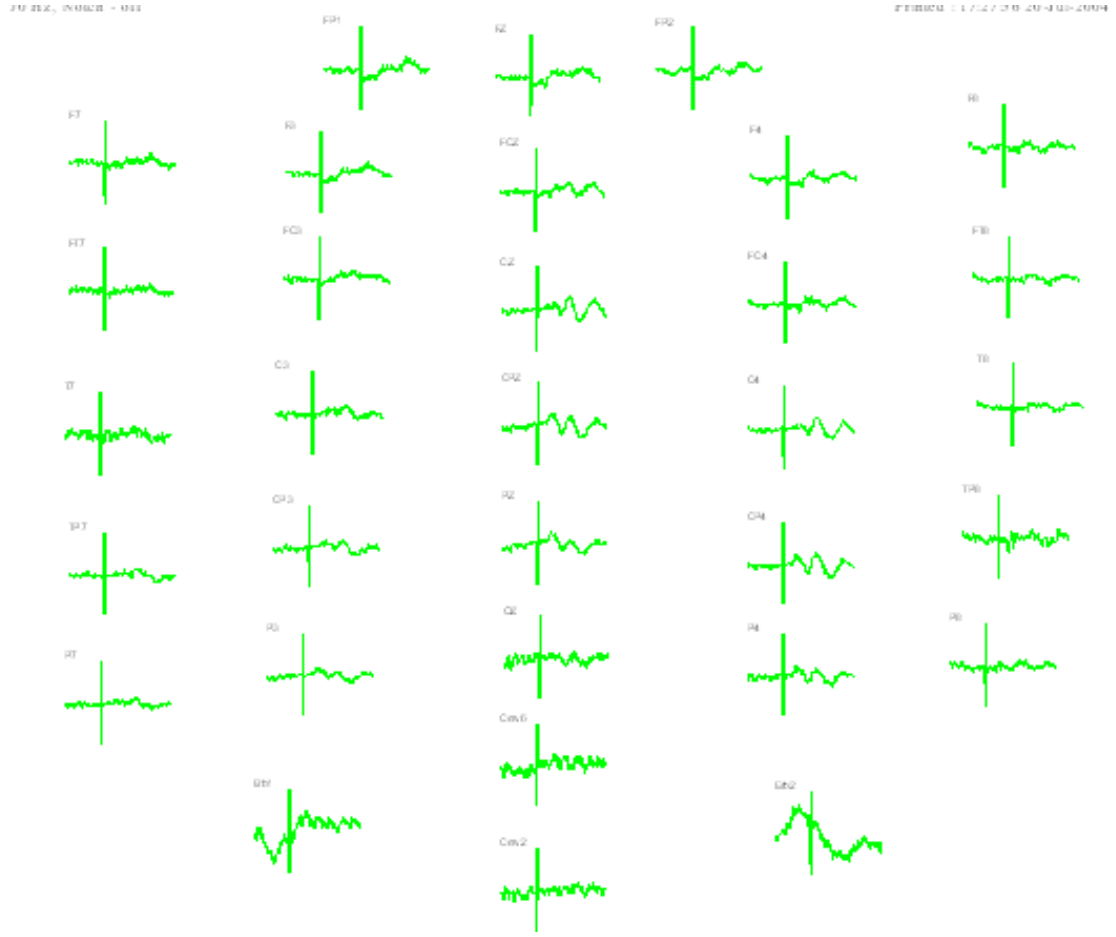


Figure 4.02: shows example from healthy volunteer with averaged **left C5** dermatomal SEP (D-SEP) recorded via 32-channel mono-polar electrode set-up in accordance with the 10-20 International System. Most prominent averaged SEP signals are seen arising at the electrode sites overlying areas of cerebral cortex contra-lateral to the peripheral stimulation sites. *Source:* Field work.

To evoke the cortical D-SEP responses in this study the stimulus strength was set to a level that was just below the strength which evoked a visible twitch of muscle below the electrode. In example shown, the stimulus intensity was equivalent to seven times the sensory perceptual threshold.

Figure 4.02 can be further explored by creating an iso-potential map representation of the key features of the waveform at a particular latency. An example of this approach is shown in figure 4.03 which shows the data from figure 4.02 in this format. The 2-D cartoon of figure 4.03 illustrates the spatial distribution of the cortical D-SEP response arriving at a latency of 34.10ms, a slower D-SEP cortical response than the standard representation N20 component of SEP cortical responses from the upper limb peripheral nerve stimulation. As can be seen from the cartoon the potential is most clearly localised to right side of the skull overlying the sensory cortex.

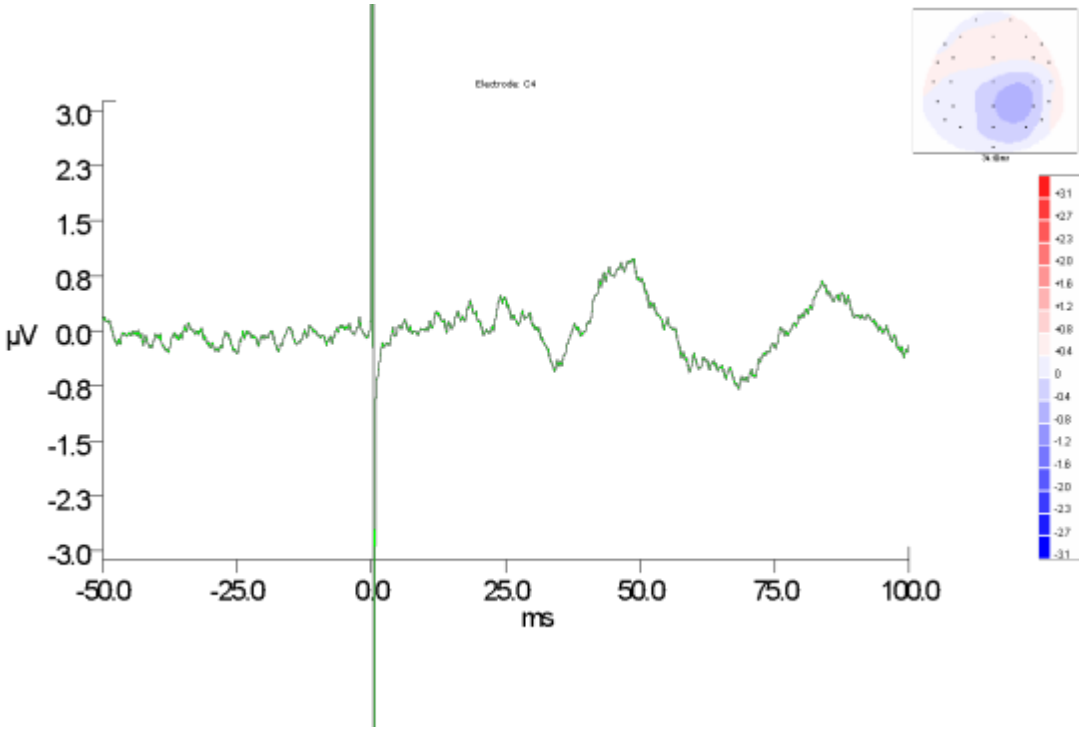


Figure 4.03: shows averaged mono-polar recording from a single channel extract from the initial 32-channel mono-polar EEG recording obtained during peripheral stimulation of the **left C5** dermatome. C4 cortical electrode overlying the right cerebral cortex corresponds to the stimulation site at the contral-lateral C5 dermatome. In addition, a 2-D iso-potential contour map is shown in the top right- hand corner illustrating the spatial distribution of the D-SEP at the latency of cortical N20 component of the average. *Source:* Field work.

Similarly, Figures 4.04 and 4.05 show the normal D-SEP responses obtained from mono- polar recordings during stimulation of left C6 dermatome. In this instance the evoked responses were generated at 5x ST as greater stimulation strengths induced muscle twitching. It is noted that, the cortical D-SEP response from C6 stimulation appears less synchronised and prominent compared to that from C5 stimulation. This is probably due to factors related to the innervation of the stimulation sites and highlights difficulties in achieving a standard stimulation paradigm that is applicable to different dermatomes and sites within a single dermatome.

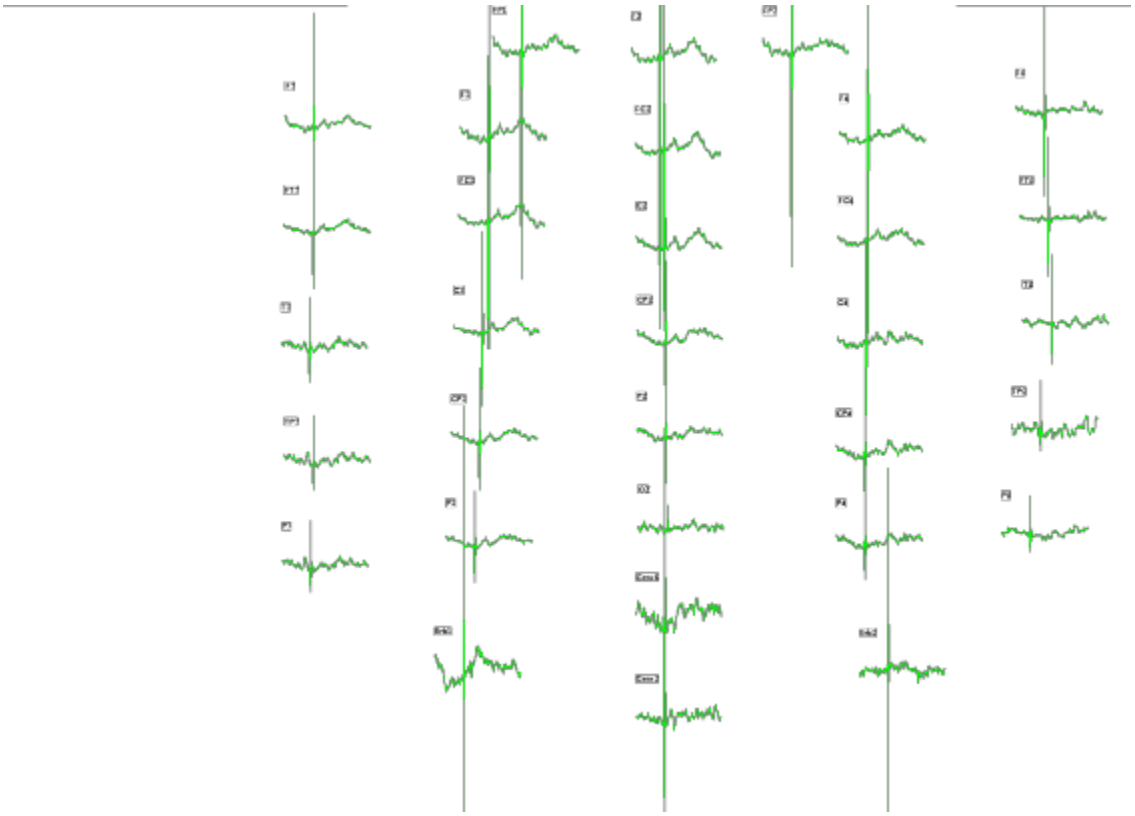


Figure 4.04: shows example from healthy volunteer with averaged **left C6** dermatomal SEP (D-SEP) recorded via 32-channel mono-polar electrode set-up in accordance with the 10-20 International System. Most prominent averaged SEP signals are seen arising at electrode sites overlying areas of cerebral cortex contra-lateral to the stimulation site. *Source*: Field work.

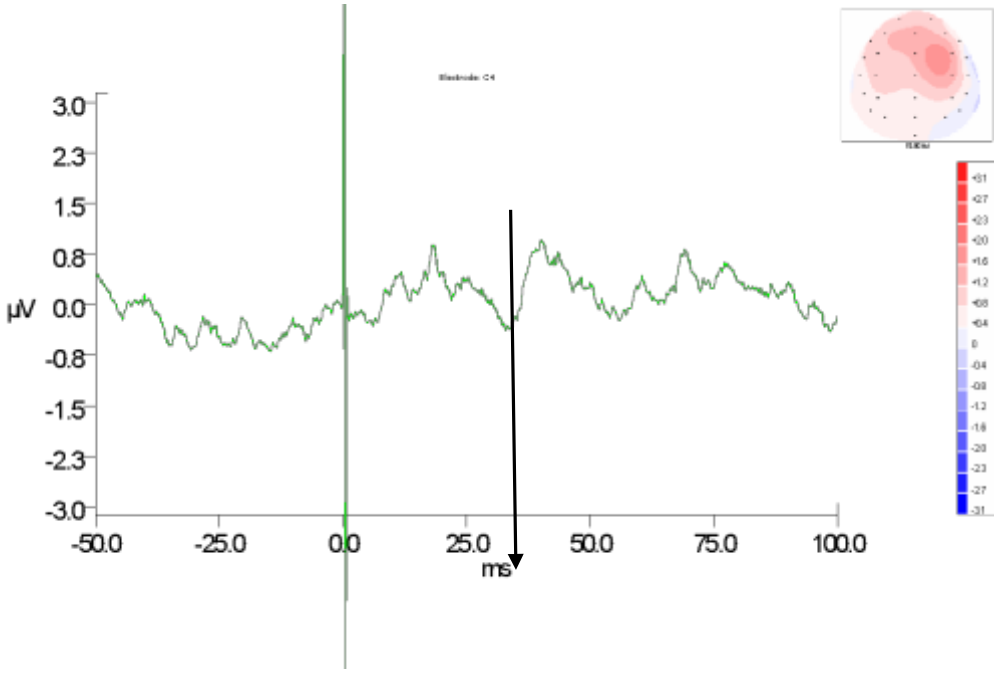


Figure 4.05: shows averaged mono-polar recording of **left C6** D-SEP from C4 electrode which overlies right cerebral cortex contra-lateral to the left C6. N20 is seen arriving at latency longer than usual SEP possibly related to nature of D-SEPs and length of recording site on the dorsum of digit-1 to cervical signal entry point. A 2-D iso-potential contour map is also showing the spatial distribution of D-SEP at latency of averaged N20 component. *Source:* Field work.

Similar In contrast to D-SEPs the SEP responses obtained for the Median and Posterior Tibial (PTN) nerves are more easily standardised to a set stimulation intensity relative to motor thresholds or perceptual sensory thresholds. Figure 4.06 shows an example of left Median SEP and figure 4.07 an example of left PTN SEP recorded in electrophysiological parameters similar to that described for D-SEP responses. In contrast to D-SEPs the SEPs are clearer and have sharper appearance. Figures 4.08 and 4.09 show the single electrode illustrations of cortical SEP responses at sites contra-lateral to the peripheral recording site for median nerve stimulation (Figure 4.08) and from the vertex for PTN stimulation.

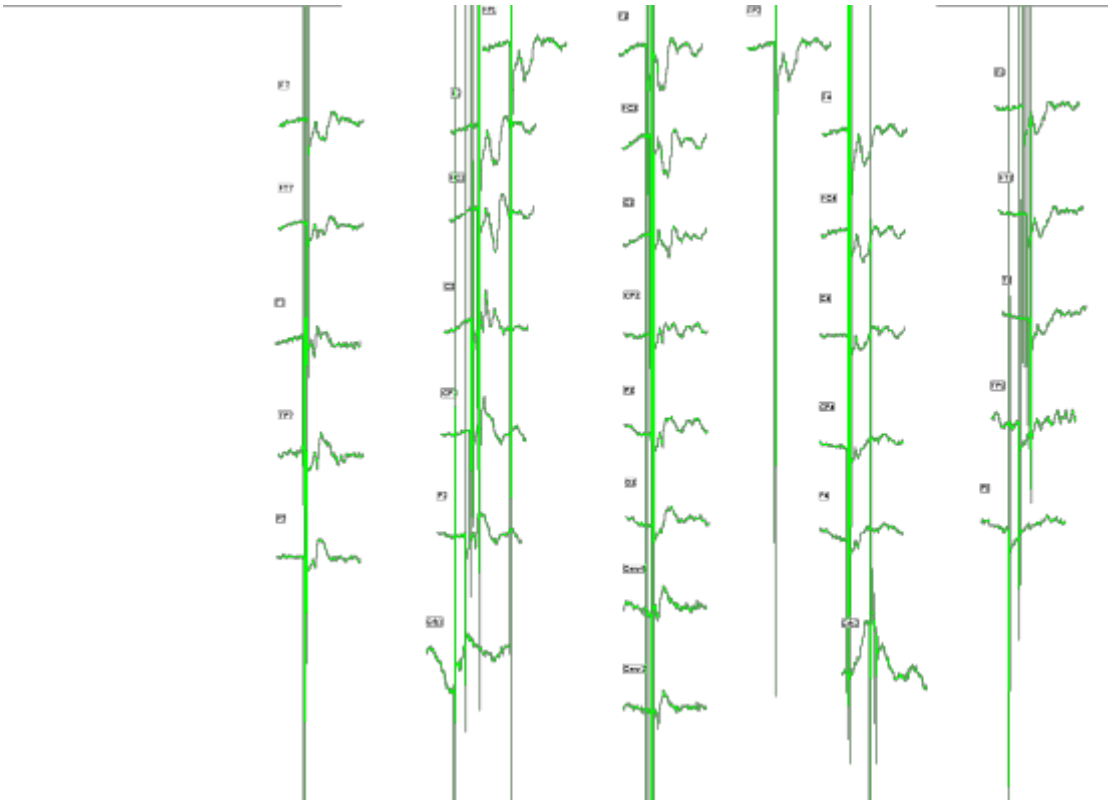


Figure 4.06: shows example from healthy volunteer with averaged **left Median** SEP recorded using 32-channel mono-polar electrode set-up according to the 10-20 International System. Most prominent averaged SEP signals are seen arising at electrode sites overlying areas of cerebral cortex contra- lateral to the peripheral stimulation site. *Source*: Field work.

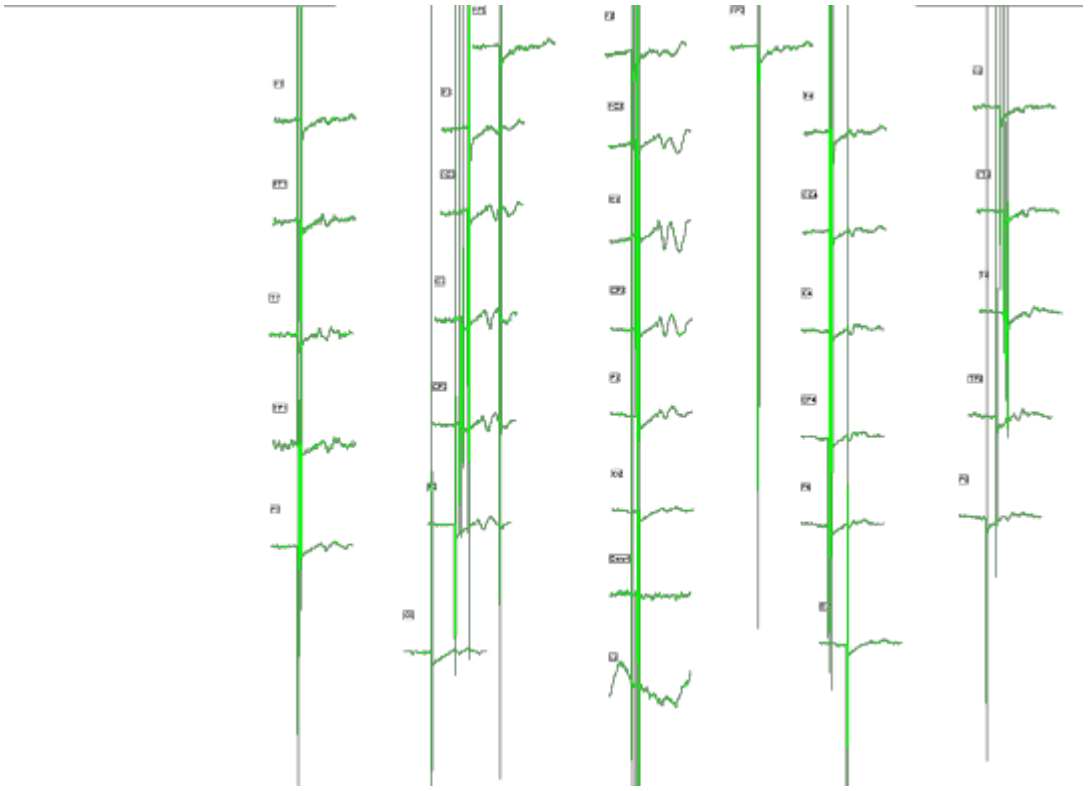


Figure 4.07: shows example from healthy volunteer with averaged **left Posterior Tibial Nerve (PTN)** SEP recorded using 32-channel mono-polar electrode set-up according to the 10-20 International System. Most prominent averaged SEP signals are seen arising at the central electrode sites overlying areas of cerebral cortex corresponding to the peripheral sites of mixed nerve stimulation. *Source*: Field work.

Similarly, the figures below show single electrode illustrations and iso-potential cartoon maps of the cortical SEP responses for Median and PTN, respectively. These are shown in figure 4.08, with left Median SEP's most prominent cortical responses seen on sites contra-lateral to the peripheral stimulation sites represented by C4 electrode. Meanwhile, Figure 4.09, shows left PTN SEP with the most prominent cortical responses seen on the sites correspondent to the stimulation sites represented by Cz electrode.

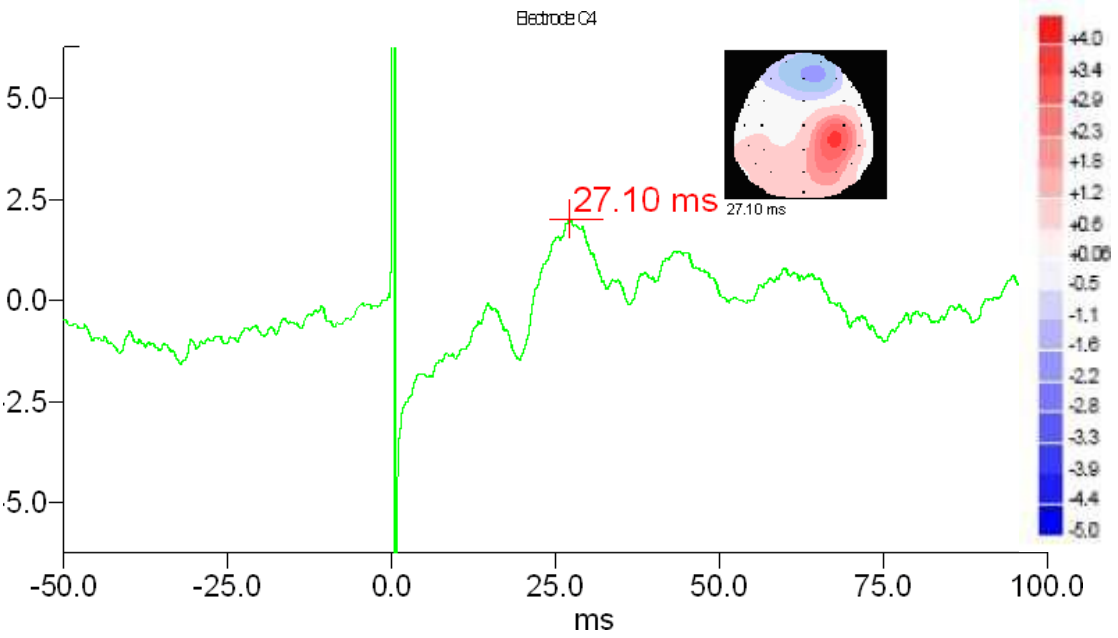


Figure 4.08: averaged cortical responses of early components of Short-Latency SEPs obtained by graded electrical stimulation of the left Median nerve at 1.5 times motor threshold (1000 stimuli, 2.8Hz). SEP latency measurement is arriving at 27.1 ms of the stimulus onset, recorded at the contra- lateral cortical electrode C4 (10-20 International System), represented in the head cartoon at the hottest (red) cortical spot. *Source*: Field work.

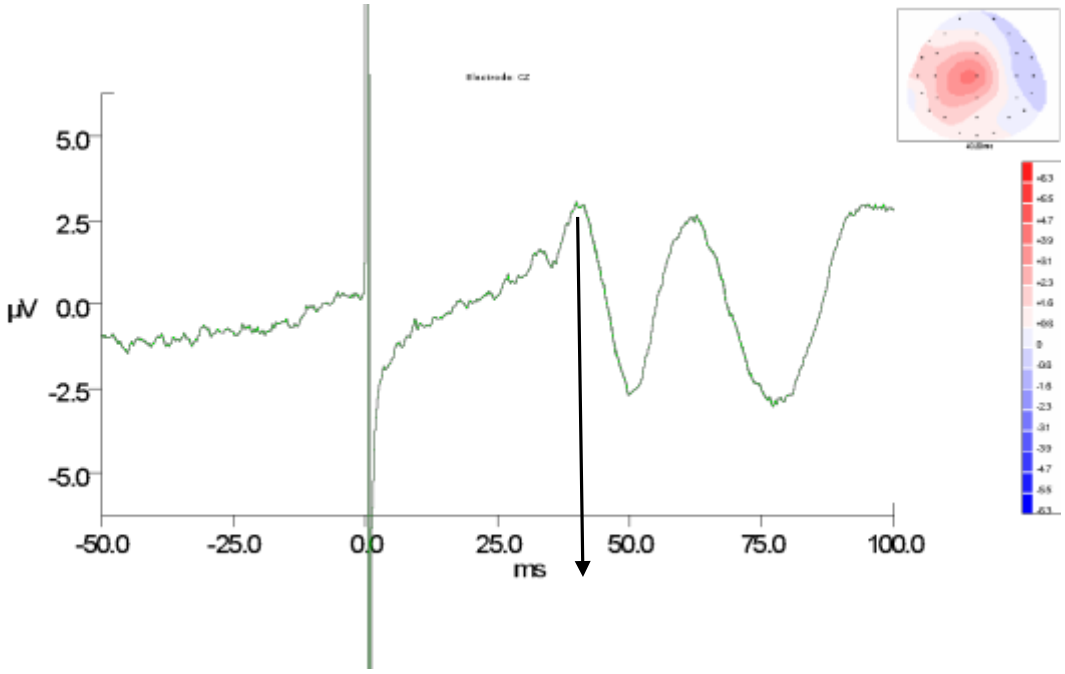


Figure 4.09: shows Normal Short-Latency Cortical SEPs recorded at the central Cz electrode (10-20 International System), in response to electrical stimulation of the left PTN at 1.5-2.0 times of motor threshold (MT). The cortical response to peripheral stimulation is seen arriving at latency of around 42ms. In the top right-hand corner, there is a 2-D iso-potential contour map illustrating the spatial distribution of averaged cortical response (P37) of early components short-latency SEPs seen here as the hottest (red) cortical spot. *Source*: Field work.

As the monopolar recordings contain near and far field components it is desirable to create a bipolar representation of the signals in order to reject the common far fields and observe only the local differences between potentials recorded between pairs of electrodes. To do this, bipolar formats corresponding to pairings being between Fz, C3, C4, electrodes at both Erb's and key cervical spine points are often reported. These bipolar representations can be derived by the simple arithmetic subtraction of the monopolar data epochs from the appropriate electrode sites. This process of linear derivation of bipolar evoked responses referenced to Fz enable precise characterisation of short-latency (early component) SEP, D-SEP and give basis for consequent amplitude and latency measurements. Example of LDR bi-polar montage is Figure 4.10.

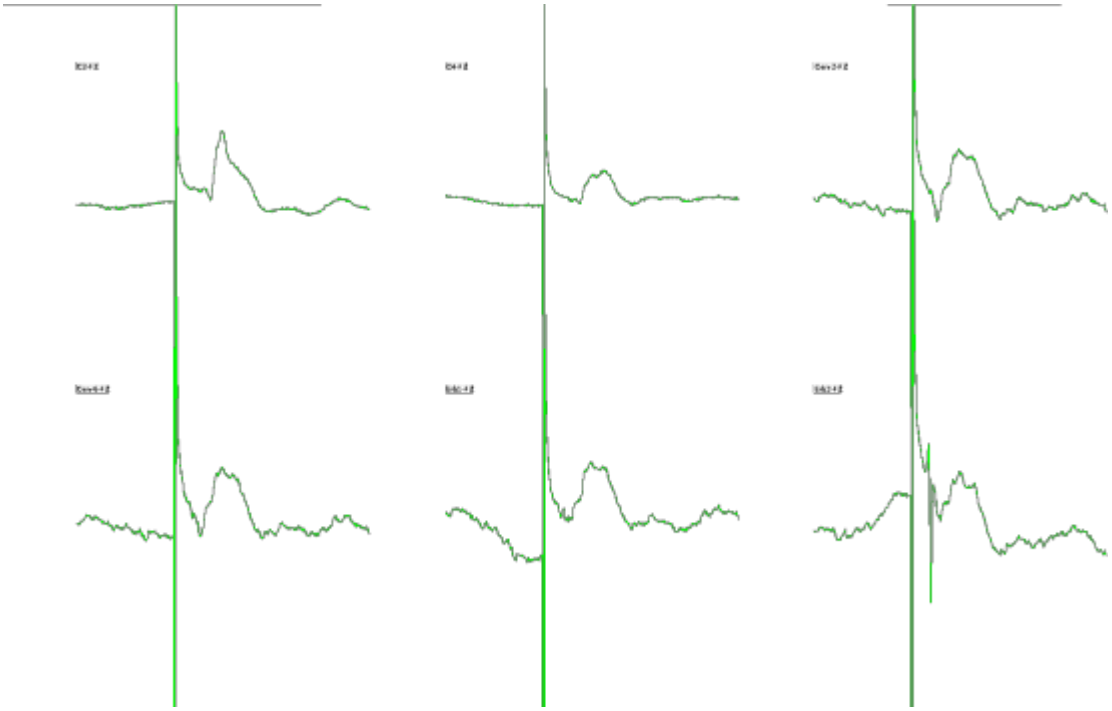


Figure 4.10: shows LDR bi-polar montage obtained by initial mono-polar recording as previously described of cortical SEPs in response to stimulation of left PTN at an intensity of 1.5-2.0 times motor threshold (MT). The cortical response to peripheral stimulation is seen illustrated in the middle on the top row at C4Fz bi-polar electrode. *Source*: Field work.

Similarly, the electrophysiological process of linear derivation (LDR) is used to transform the initial mono-polar cortical acquisition into LDR bi-polar montages for each individual D-SEP and SEP in the upper and lower limbs. The resulting waveforms and subsequent amplitude and latency measurements are shown in examples below, with upper limb SEP and D-SEP represented by C4Fz LDR bi-polar electrode subtraction, and lower limb SEP and D-SEP by CzFz LDR bi-polar electrode subtraction. These are shown for upper limb in Figure 4.11 (**A**) & (**B**), and lower limb in Figure 4.12, SEP and D-SEP counterparts.

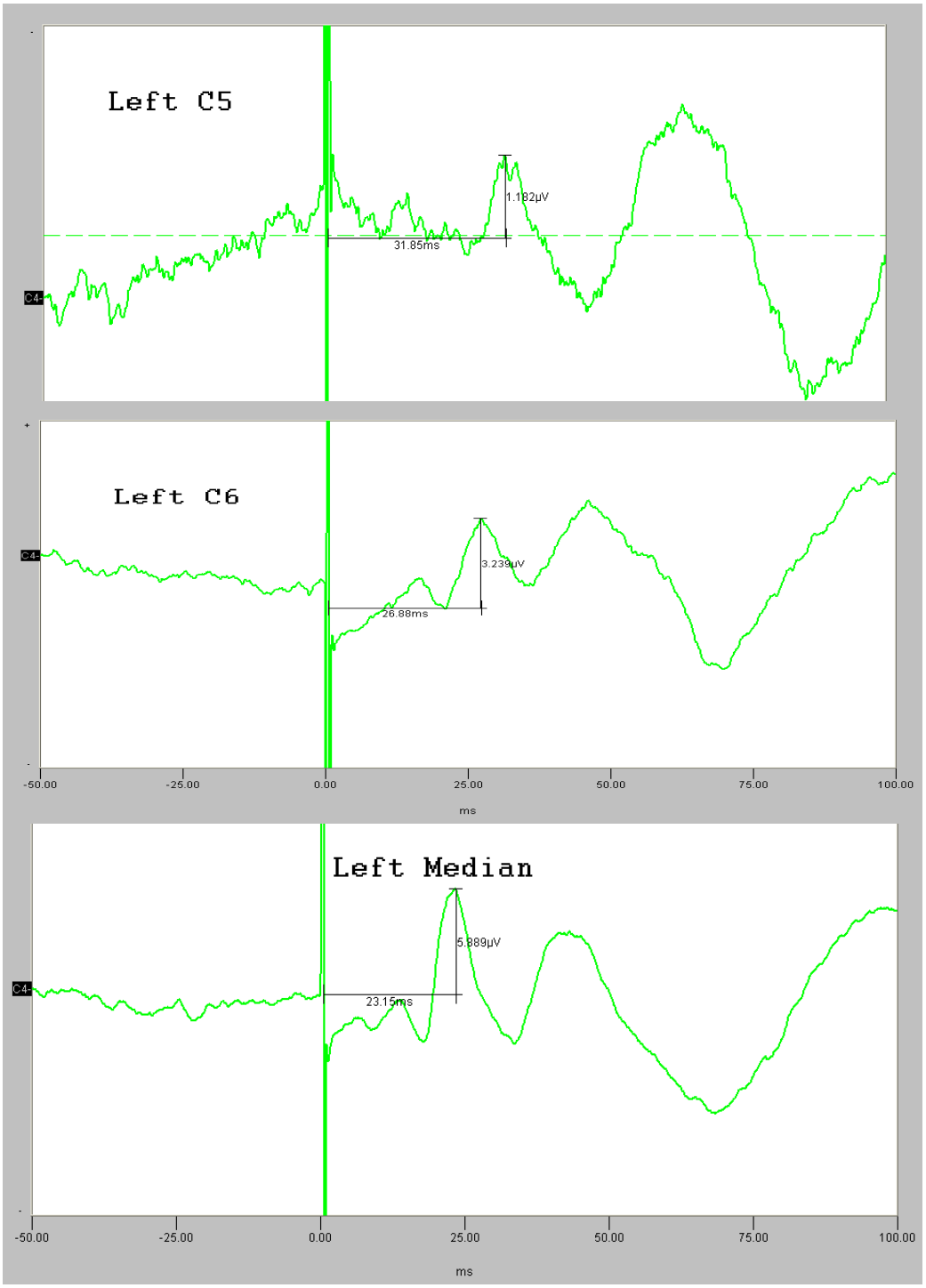


Figure 4.11 (A): shows bipolar representations obtained by LDR of initial mono-polar recordings obtained for upper limb D-SEP and SEP, with cortical components at C4Fz electrode in response to stimulation of the left C5, C6 dermatomes and left Median nerve, with waveforms displayed in this figure from top down, respectively. *Source*: Field work.

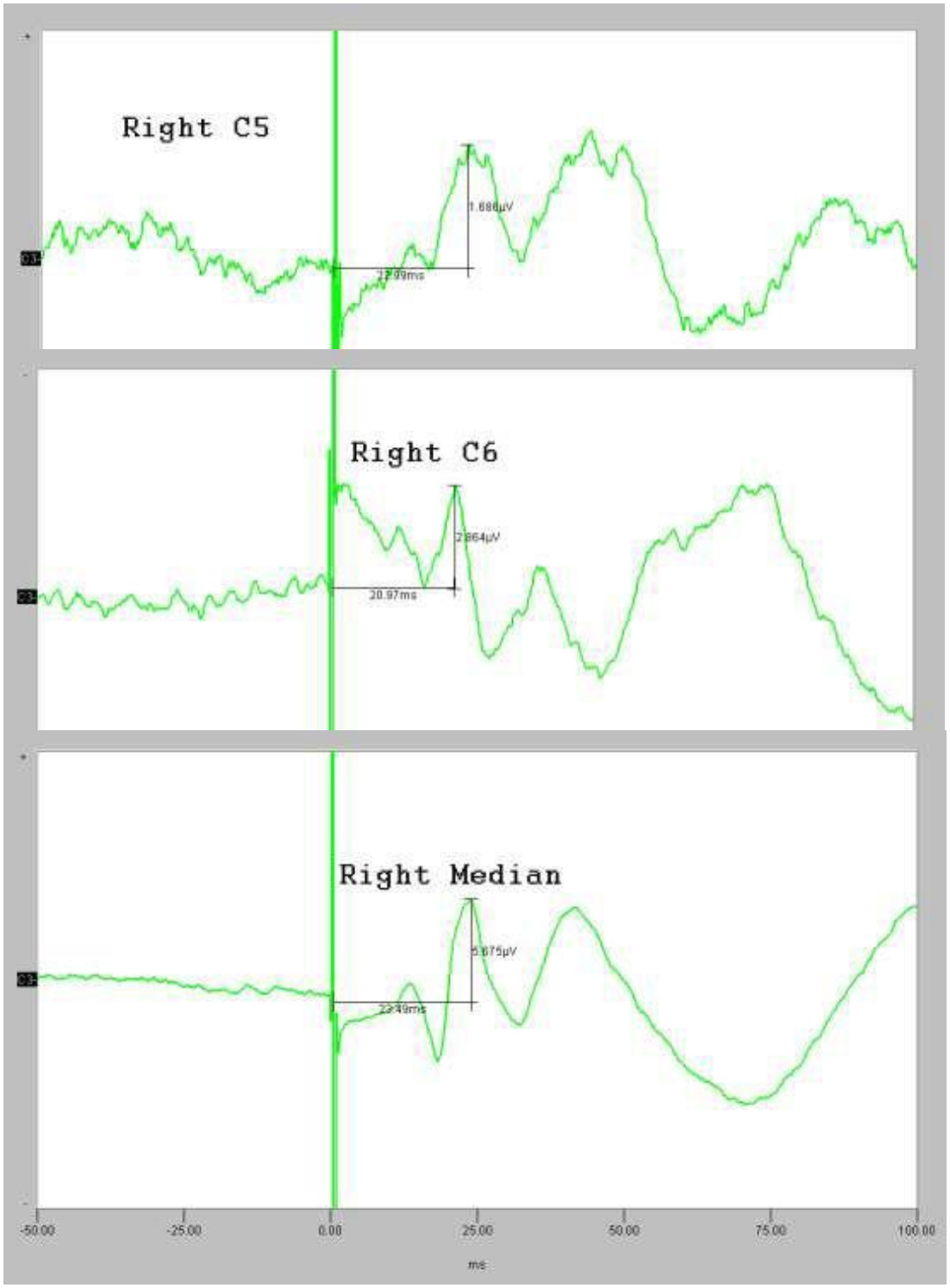


Figure 4.11 (B): shows bipolar representations obtained by LDR of initial monopolar recordings obtained for upper limb D-SEP and SEP, with cortical components at C3Fz electrode in response to stimulation of the right C5, C6 dermatomes and right Median nerve, with waveforms displayed in this figure from top down, respectively. *Source*: Field work.

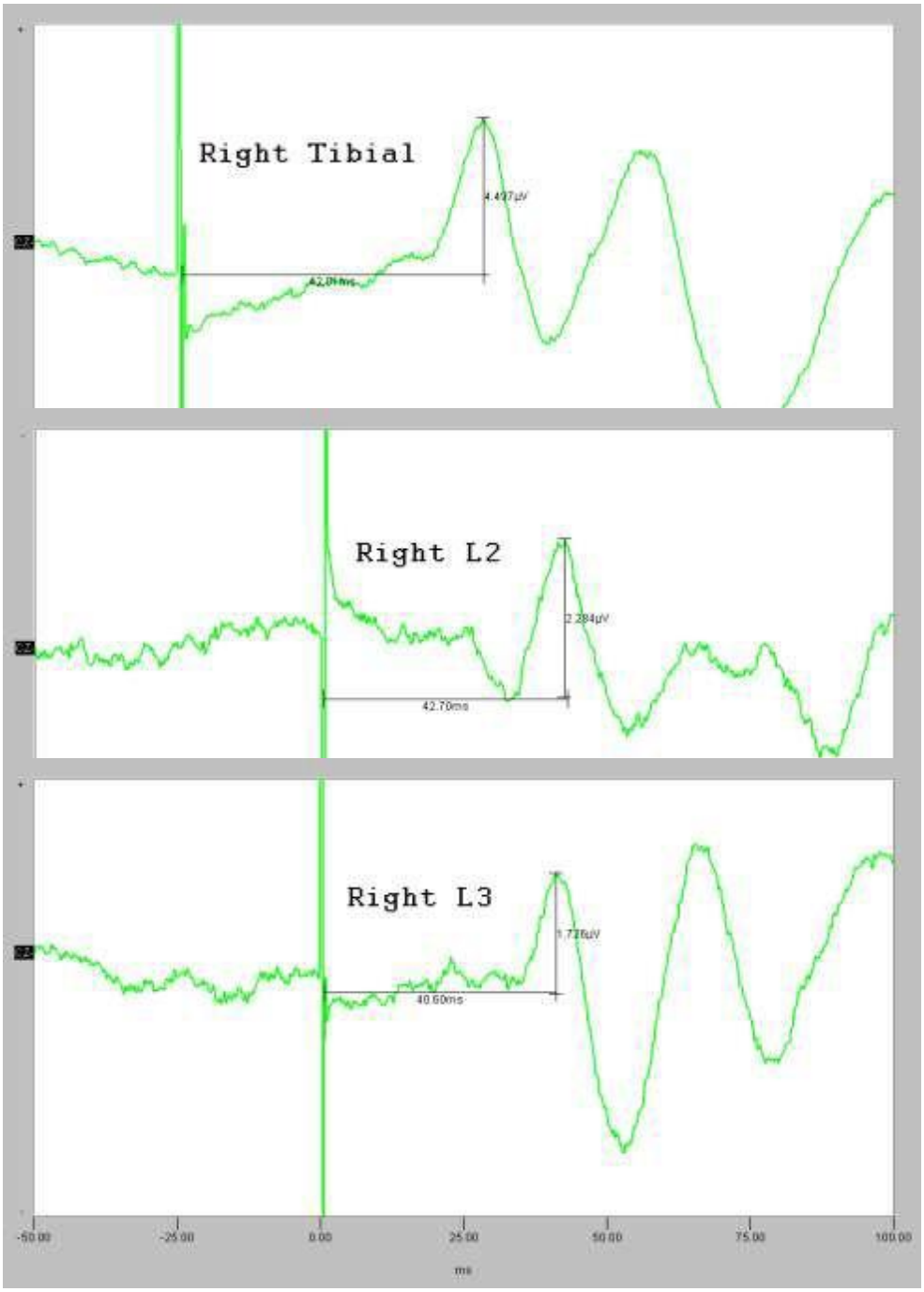


Figure 4.12: shows bipolar representations obtained by LDR of the initial mono-polar recordings obtained for lower limb D-SEP and SEP, with cortical components at CzFz electrode in response to stimulation of the left L2, L3 dermatomes and left PTN nerve, with waveforms displayed in this figure from top down, respectively. *Source*: Field work.

Based on these LDR bi-polar waveforms, measurements of latency and amplitude parameters of short latency SEPs and D-SEPs were estimated for the upper and lower limbs of the healthy volunteers and summarised in Table 4.02. Values of the amplitude and latency measurements for normal SEP and D-SEP of the upper and lower limbs are successively obtained. These Measurements of latency and amplitude parameters of short latency SEP and D-SEP responses

were obtained from healthy volunteers. Normal values constitute a normative data range for waveform measurements of latency and amplitudes, in addition to calculated values of standard deviations (SD) for each SEP or D-SEP responses.

Table 4.02: shows a summary of normal measurements of latency and amplitude parameters of short latency SEP and D-SEP cortical responses. Early components of short latency SEP and D-SEP derived from bipolar linear-derivation montages (using Fz–C3/C4 for upper limbs and Fz–Cz for lower limbs). From this method, the N20 and P37 cortical responses were identified. Latency and amplitude mean values from healthy subjects (**N = 12**) +/- standard deviation are shown. Values of 2SD were used to mark range of normal parameters calculated from SEP/D-SEP components of each individual dermatome or nerve stimulation (these include C5 and C6 dermatomes, and Median nerve in upper limbs, and L2 and L3 dermatomes, and Posterior Tibial nerve (PTN) in the lower limbs. Source: Field work.

	C5 - N20	C6 - N20	Med.N20	L2 - P37	L3 - P37	P.Tib - P37
Latency						
Mean (ms)	22.01	27.4	23.49	35.16	37.83	38.65
SD	2.05	2.43	1.99	3.09	1.64	2.21
– 2SD	17.92	22.55	19.5	28.98	34.54	34.24
+ 2SD	26.1	32.25	27.47	41.34	41.12	43.06
Amplitude						
Mean (μV)	1.06	0.94	2.2	0.61	0.29	1.85
SD	0.49	0.69	1.19	0.53	0.27	0.88
– 2SD	0.07	-0.44	-0.19	-0.45	-0.24	0.1
+ 2SD	2.05	2.32	4.59	1.68	0.82	3.6

Extraction of the values of normal latency measurements for SEP and D-SEP are shown in figure 4.13, with the standard deviation (SD) of the normal mean values.

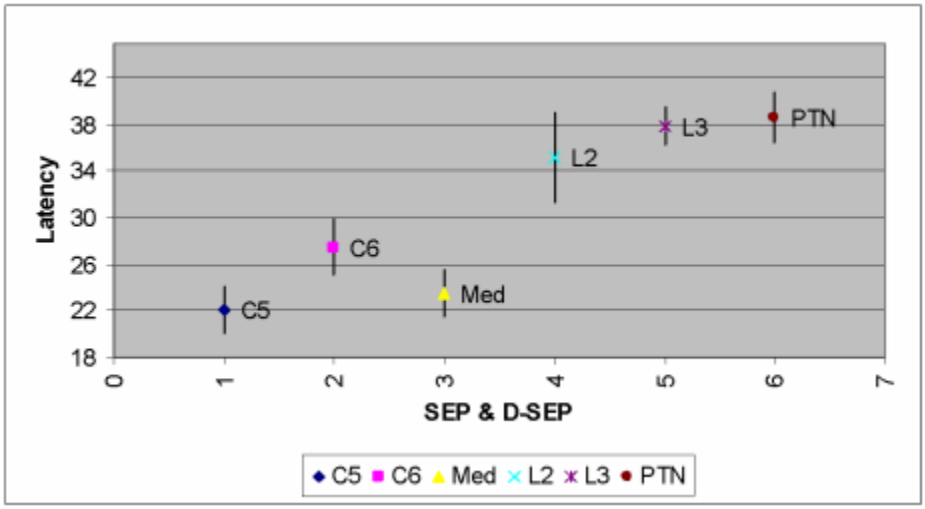


Figure 4.13: shows summary of normal values of averaged latency measurements for short latency components of upper and lower limb SEP and D-SEP cortical responses: recorded for C5 and C6 D-SEP, Median (Med) SEP, L2 and L3 D-SEP and Posterior Tibial (PTN) – with standard deviations been calculated and shown. Source: field work, from the analysis of data for this thesis.

4.2 Event-related Spectral Perturbations (ERSP):

Event-related spectral perturbations (ERSP) are used to visualise mean stimulus-induced changes of the cortical responses of SEP and D-SEP within the power spectrum of EEG's different frequency bands over time. The ERSP maps are a means of charting both phase locked and non-phase locked frequency domain changes of activity as demonstrable and reproducible measurements. This is considered a useful alternative approach to visualisation of the standard SEP time varying signal in patients with sensory tract damage as it may have the capacity to capture alterations in EEG activity that result from a less synchronised afferent volley. ERSP data was gained from 12 of the healthy volunteers who participated in the study. The normal form of ERPS maps and characteristic appearances, are shown in Figures 4.14, 4.15, 4.16, 4.17 and 4.18, which provide examples of right and left upper and lower limb ERSPs from median and posterior tibial nerves, respectively**.** The recordings illustrated are obtained from cortical sites where the responses to stimulation should be most evident (C3 or C4 for right and left upper limb nerves and Cz for both the lower limb). The common characteristic of a response to stimulation of a peripheral mixed nerves are prolonged periods of event related desynchronisation (ERD) evident at latencies of around 100ms and terminating approximately 400ms after stimulus onset when based on monopolar recordings (see Figure 4.14). The ERD band is seen as blue colours across a range of EEG frequencies but is most prevalent in alpha and beta EEG frequency bands. The ERD at 10Hz generally outlasts ERD seen at higher frequencies. This is the case in Figures 4.14 (right median nerve stimulation) and 4.15 (right posterior tibial nerve). In addition to ERD features, ERS features may become evident at short latencies and probably reflect the early components of the SEP. This is seen when comparing the time domain SEP representations shown immediately below the ERSP plots in both Figures 4.14 and 4.15.

In these illustrations (shown in the mentioned figures), there are examples of ERSP in response to Median nerve stimulation, with ERSP figures from healthy individuals showing the normal ERSP pattern. These ERSP shows pattern of EEG synchronisation and desynchronisation, illustrated with colour codes.

These ERSP patterns provide a sensitive measure of investigating sensory function and allow greater insight into the sensory processing when compared to conventional EEG time averages alone. Normal ERSP maps follow characteristic pattern for peripheral nerve stimulation.

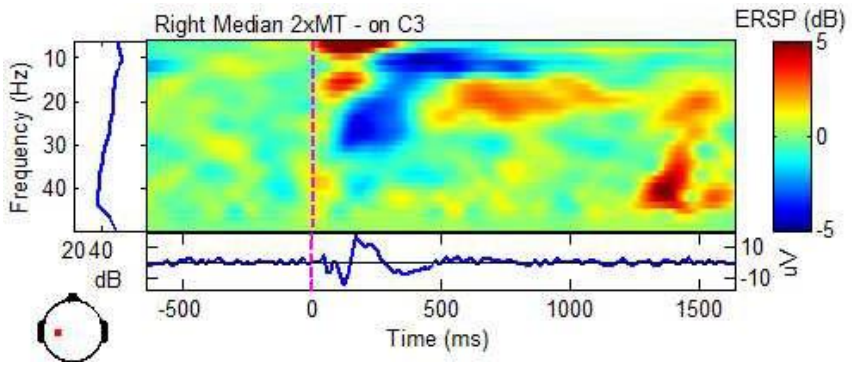


Figure 4.14: shows normal pattern event-related spectral perturbation (ERSP) map obtained from a healthy subject. Using bipolar montage, cortical responses recorded at **C3** electrode (10-20 International System), are seen in response to graded electrical stimulation of the contra-lateral **right Median** nerve at intensity twice the motor threshold. Power spectral changes are observed across a range of EEG frequencies but maximum in alpha and beta EEG bands. At approximately 200-300ms from the onset of stimulus (marked with vertical red dashed line), there are time-locked frequency changes representing areas of event-related desynchronisation (ERD) appearing in the graph as dark blue. Source: Field work.

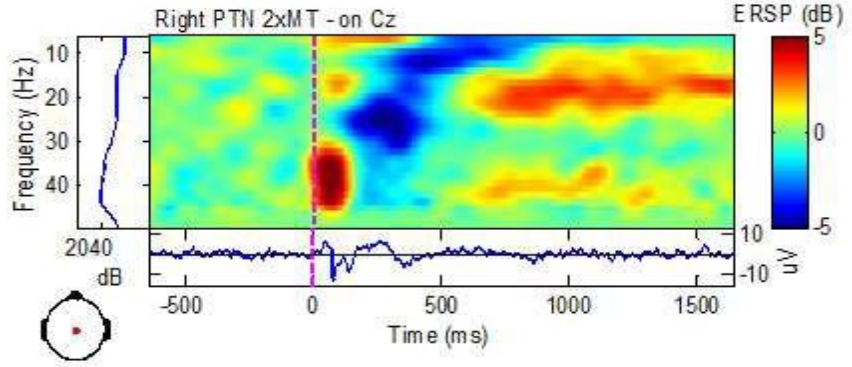


Figure 4.15: shows normal pattern event-related spectral perturbation (ERSP) map obtained from a healthy subject. Using bipolar montage, cortical responses recorded at **Cz** electrode (10-20 International System), are seen in response to graded electrical stimulation of the contra-lateral **right Posterior Tibial** nerve at a stimulus intensity twice the motor threshold. Power spectral changes observed across a range of EEG frequencies but most prominent in alpha and beta EEG bands. At approximately 200-300 ms from onset of stimulus (which is marked with the dashed red vertical line), there are time-locked frequency changes that represent areas of event-related desynchronisation (ERD) depicted in the graph as the dark blue (cold) colour ranges. Source: Field work.

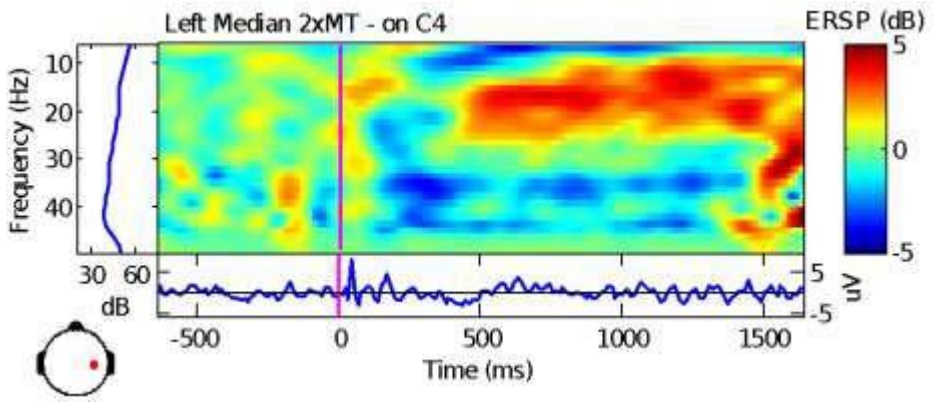


Figure 4.16: shows normal pattern event-related spectral perturbation (ERSP) map obtained from a healthy subject. Using bipolar montage, cortical responses recorded at **C4** electrode (10-20 International System), are seen in response to graded electrical stimulation of the contra-lateral **left Median** nerve at intensity twice the motor threshold. Power spectral changes are observed across a range of EEG frequencies but maximum in alpha and beta EEG bands. At approximately 200-300 ms from the onset of stimulus (marked with vertical red dashed line), there are time-locked frequency changes representing areas of event-related desynchronisation (ERD) appearing in the graph as dark blue. Source: Field work.

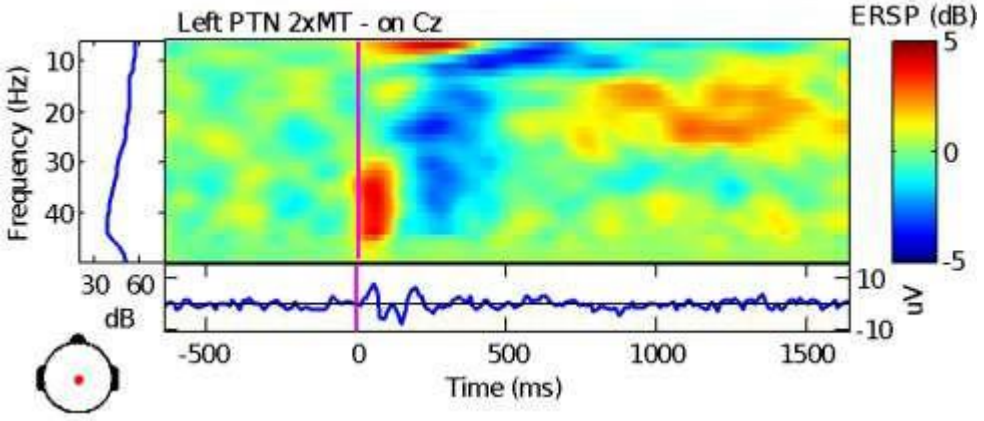


Figure 4.17: shows normal patterns event-related spectral perturbation (ERSP) of EEG map obtained from a healthy subject. Using bipolar montages, cortical responses are recorded at the central **Cz** electrode (10-20 International System), with the patterns of the ERSP of EEG seen in response to graded electrical stimulation of **left Posterior Tibial** nerve at intensity 2x motor threshold. Power spectral changes are observed across a range of EEG frequencies maximum at alpha and beta EEG bands. At approximately 200-300ms from onset of stimulus (marked with dashed red vertical line), changes of ERSP pattern are observed with areas of time-locked event-related de-synchronisation and synchronisation. Source: Field work.

The form of ERSP maps from right and left upper and lower limb stimulation is generally similar to those illustrated here and as shown for in (Figure 4.18) where both left and right Median ERSPs, with comparison of the patterns obtained from each side .

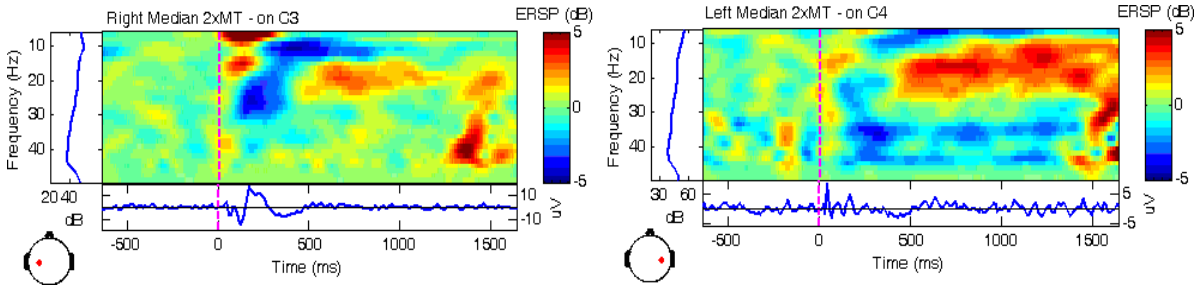


Figure 4.18: shows the overall picture of the ERSP maps for left and right upper and lower limb peripheral mixed nerve stimulation in the same manner for obtaining SEP, with the resulting ERSP EEG patterns as described above shown in a single map below. Source: Field work.

ERSP patterns were produced using computational analysis described in the chapter describing methods. Running a statistical analysis of variance (ANOVA) applied to power spectral analysis maps confirmed visually observed changes as reproducible as shown in Figures 4.14, 4.15, 4.16, 4.17 and 4.18. Typical patterns of ERSP maps show blue 'cold' spots indicating areas of desynchronisation and red or light colour 'hot' spots indicating synchronisation in response to peripheral electrical stimuli of corresponding nerves or dermatomes. The ERSP hot and cold map areas of event-related synchronization and de- synchronization respectively were confirmed genuine EEG power spectral changes in response to peripheral sensory stimulation.

4.3 MEP (through Trans-cranial Magnetic Stimulation (TMS)

Trans-cranial magnetic stimulation (TMS) over specific scalp areas was used to obtain motor evoked potentials (MEP) from contra-lateral limb muscles in a small group of healthy volunteers (**N = 6**) in order to become proficient in the techniques and to show that results obtained were in keeping with the data sets by Rothwell those generated within the laboratory by Proudlock et al. (1992).

A typical example of MEP waveforms obtained from TMS on healthy subjects is shown in Figure 4.19. These recordings are made in relaxed muscles with no background EMG. Accordingly, the EMG waveform is characterised by an early latency evoked EMG wave and because there is no background EMG the silent period associated with intra-cortical inhibition cannot be visualised. In non-facilitated TMS the key parameters to note are latency, stimulation threshold and measures of MEP size. Onset latency data are shown in figure 4.20, and area measurements in Figure 4.21 for ED muscle and Figure 4.22 for TA muscle, respectively.

Systematic increases in stimulation intensities were used to generate recruitment curves and how that that increments in amplitude (measured by MEP area amplitude) and reduction in latency (measured as onset latency) accompany the MEP response as the stimulation increases.

In healthy volunteers MEP amplitudes are not linearly related to stimulus intensity (Figure 4.20), and recruitment curve normally plateaus before 100% stimulus intensity (reference?). Furthermore, latency reductions are greatest at stimulation intensities that are just above threshold and thereafter the latency remains relatively constant even as the stimulator output approaches its maximum. This is shown in Figure 4.20 with a histogram depicting nature of stimulating threshold.

4.3.1 MEP Waveform Response

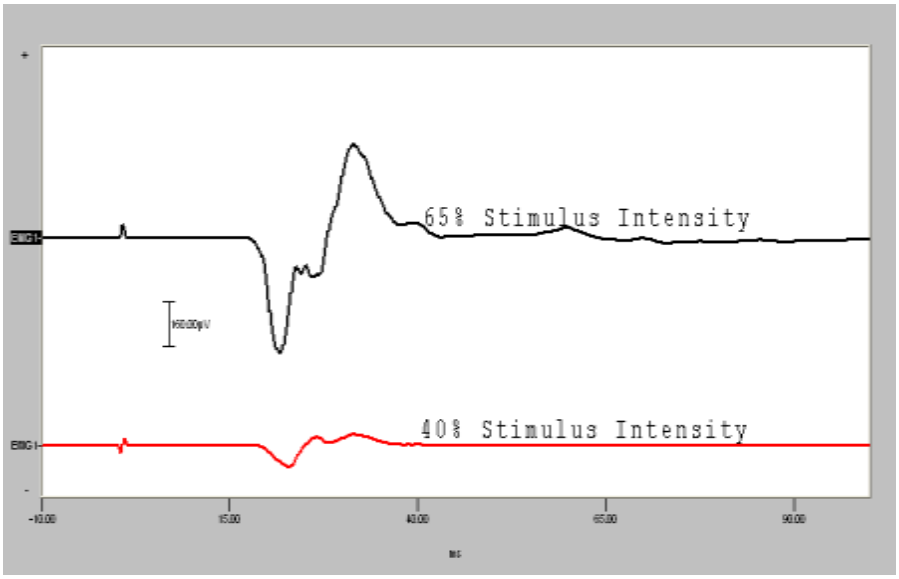


Figure 4.19: MEP waveforms from a healthy volunteer subjected to TMS of the motor cortex on the right cerebral hemisphere with simultaneous surface EMG recording from contra-lateral (left) *Extensor Digitorum* (ED) muscle. When baseline intensity of 40% (red trace) was increased to 65% (black trace), the resulting MEP amplitude increased significantly with minimal latency changes. It has been observed that MEP amplitude responses are proportionate to the intensity of the stimulus used. Source: Field work.

4.3.2 MEP Latency Curve

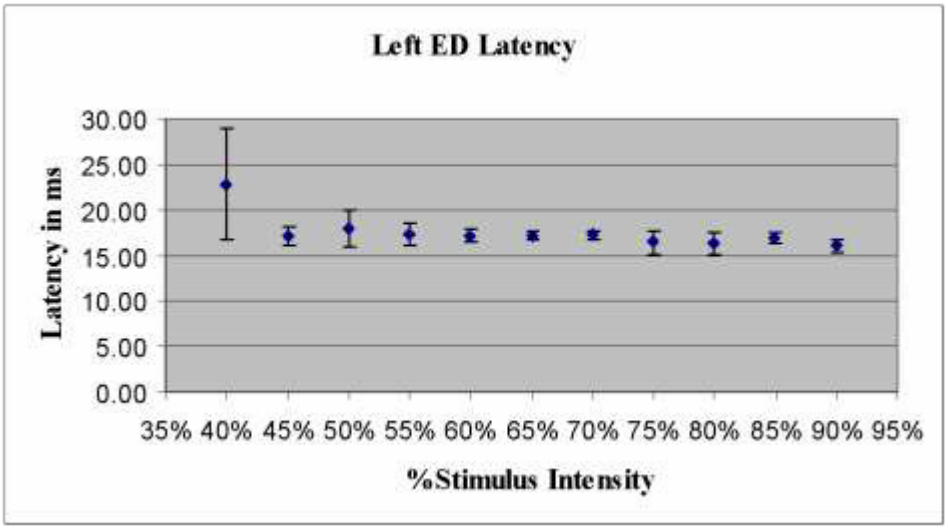


Figure 4.20: MEP waveforms obtained by surface EMG recording from left *extensor digitorum* (ED) muscle of a healthy volunteer subjected to TMS of the contra-lateral motor cortex. Measured MEP latencies are plotted in Y-axis and corresponding TMS intensities used in X-axis. There seems to be no significant latency shift (or shortening) when higher stimulation intensities were incrementally applied to cerebral cortex. Source: Field work. Why is the latency later at 40% stimulation? There is also a huge error bar.

4.3.3 MEP Amplitude Curve:

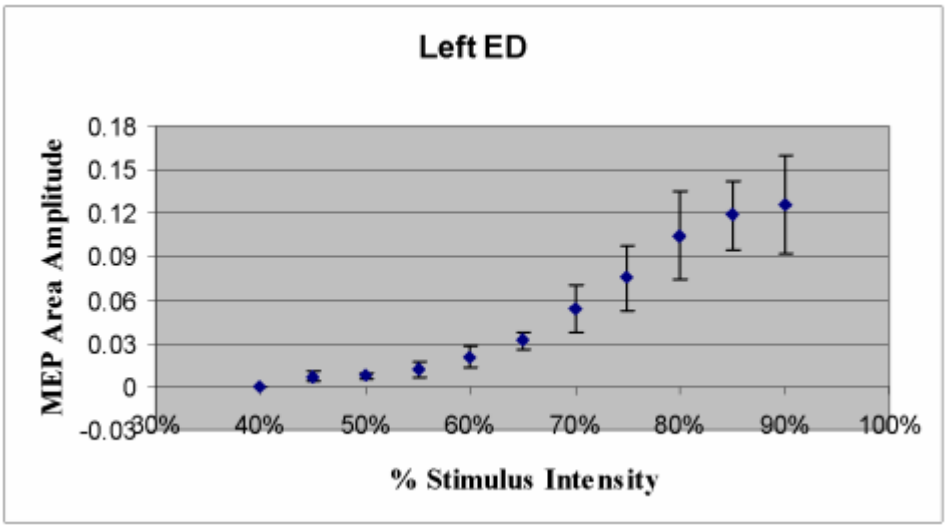
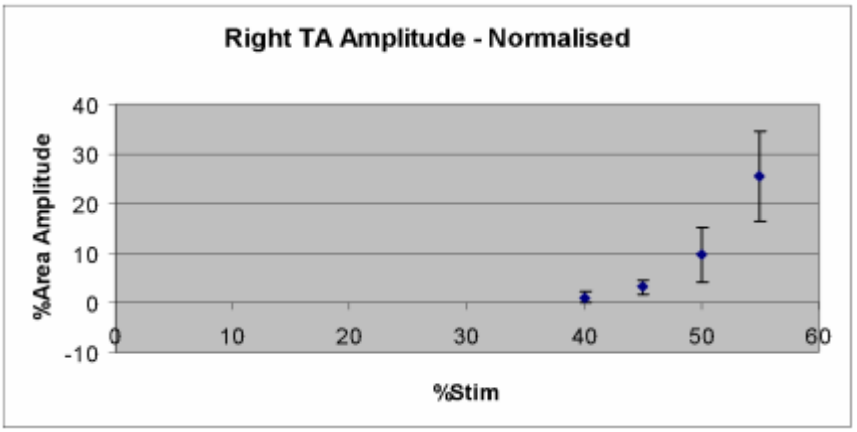


Figure 4.21: MEP waveforms obtained by surface EMG recording from left *extensor digitorum* (ED) muscle of a healthy volunteer subjected to TMS of the contra-lateral motor cortex. Measured MEP amplitudes plotted on Y-axis (with corresponding TMS intensities on X-axis), show proportionate and significant increase when higher stimulation intensities were incrementally used at the same site and other settings. Source: Field work.

(**A**)



(**B**)

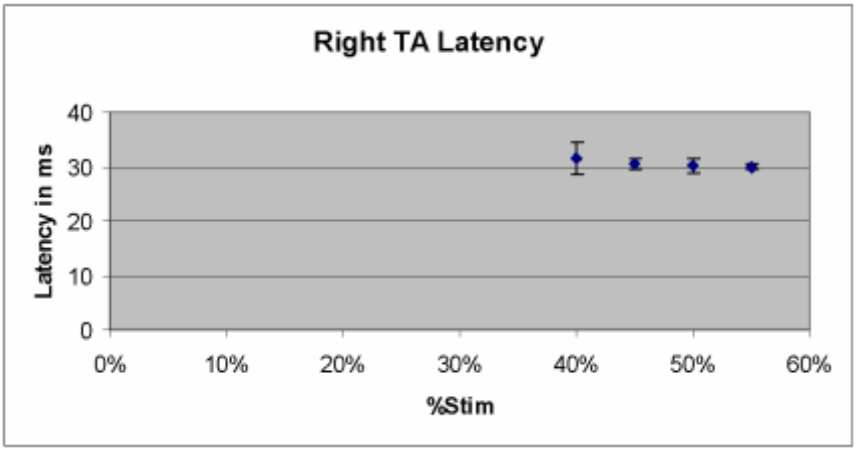


Figure 4.22: shows normal lower limb MEP waveforms from recordings of right TA muscle. Amplitudes are normalised to baseline 40% stimulation intensity or threshold (**A**), and MEP latencies show no changes with increasing stimulation intensity (**B**). *Source:* Field work.

4.3.4 Normal Latency Values

Eight healthy volunteers in order to provide normative data ranges for of the MEP latency for comparison with volunteers with SCI. Onset latencies were obtained for 10 TMS stimuli delivered at intensities of 40% upwards, with increments of 5% of maximum stimulus strength; which the maximum stimulus strength tolerated by individual subjects (normally between 75 and 95%). The mean latency values and standard deviations are presented in Table 4.03 for extensor digitorum and tibialis anterior.

Table 4.03 shows a summary of normal measurements of MEP onset latency obtained from trans-cranial magnetic stimulation (TMS). Tabulated are means of latencies obtained for ED and TA muscles in upper and lower limbs, respectively. *Source:* Field work.

Upper Limb ***Extensor Digitorum*** *(ED)*		
	Mean	***14.41031***
	SD	***0.72374*** ***+2SD = 15.86***
Lower Limb ***Tibialis Anterior*** *(TA)*		
	Mean	***29.08965***
	SD	***1.880409*** ***+2SD = 32.85***

4.3.5 Cortico-Muscular Coherence (CMC)

Calculation of Coherence

Coherence function is considered a useful parameter providing a measure of linear association between two recorded signals as described in chapter discussing 'methods' and may have utility in determining the functional status of corticospinal pathways. CMC was calculated from recordings obtained from healthy volunteers (**N = 6**) with results shown in graphs plotted below. Figure 4.23, illustrates the main four areas or components of the CMC calculations. Figure 4.23 (**fa**) shows estimated EEG spectrum and figure 4.23 (**fb**) illustrates the estimated spectrum of the rectified EMG obtained from the tibialis anterior of contra-lateral limb when measured simultaneously with the EEG (**fb**). The figure also shows the coherence between these signals and shows that it is significant over the range 22-30Hz (Figure 4.23 **coh**). The time domain equivalent measure is the cumulant and this is shown in (Figure 4.23 **q**) together with the phase (Figure 4.23 **ph**). As phase plots are only valid at frequencies where the coherence is significant it is a measure that is difficult to use in order to extract meaningful timing information. The cumulant on the other hand provides a much more interpretable measure. What is seen is an organised waveform composed of a number of peaks and troughs centred around 00ms and indicative of oscillatory coupling between the signals. The intervals between the peaks are being closely related to the range of coherent frequencies.

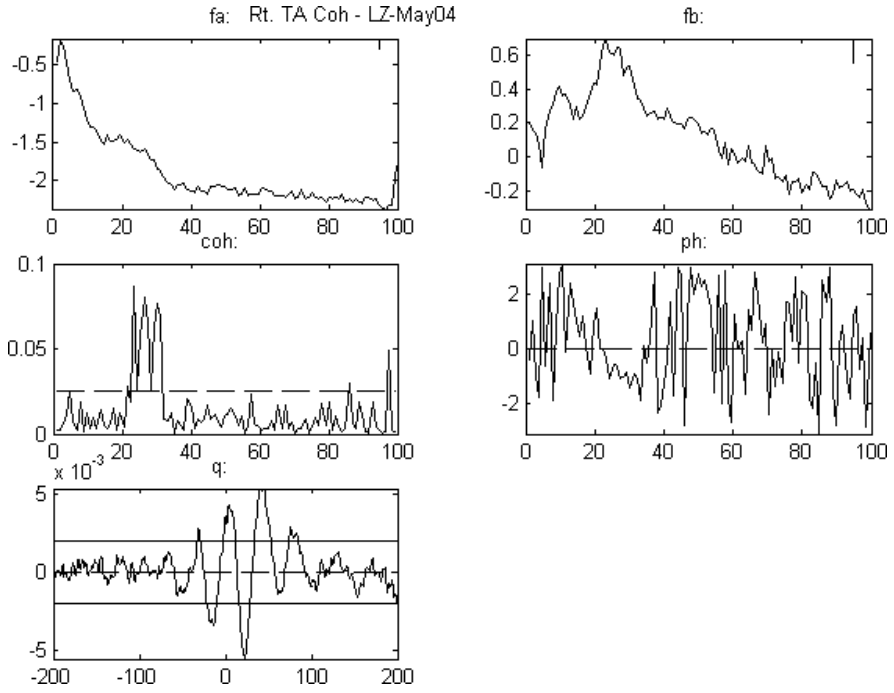


Figure 4:23: shows CMC during sustained low level muscle contraction of right Tibialis Anterior (TA) in a healthy subject. Sub-figure (**fa**) indicates EEG power spectrum, (**fb**) EMG power spectrum and (**coh**) is the calculated CMC where the horizontal dashed line indicates statistically significant coherence seen in the range 22-30Hz. Sub-figure (**q**) shows the cumulant of EEG and EMG signals. *Source:* Field work.

Coherence maps

As described in the chapter discussing 'methods', cortico-muscular coherence (CMC) was performed using simultaneously recorded mono-polar 32-channel EEG and surface EMG from Extensor Digitorum (ED) muscles (in upper limbs) and Tibialis Anterior (TA) muscle (in lower limbs). A computational analysis software (Matlab) was used with an analytical script written to calculate coherence between the acquired EMG signals and cortical areas represented by each individual cortical signals picked-up by scalp electrodes placed according to 10-20 International System. This resulting information created cortical coherence map for each ED or TA muscle recording during sustained low-level contractions. CMC topographic cortical maps for healthy subjects are shown in areas related to specific EEG scalp electrode placements according to the 10-20 International Electrode Placement (reference) System (Figures 4.24 and 4.25 **(A)** and **(B)**).

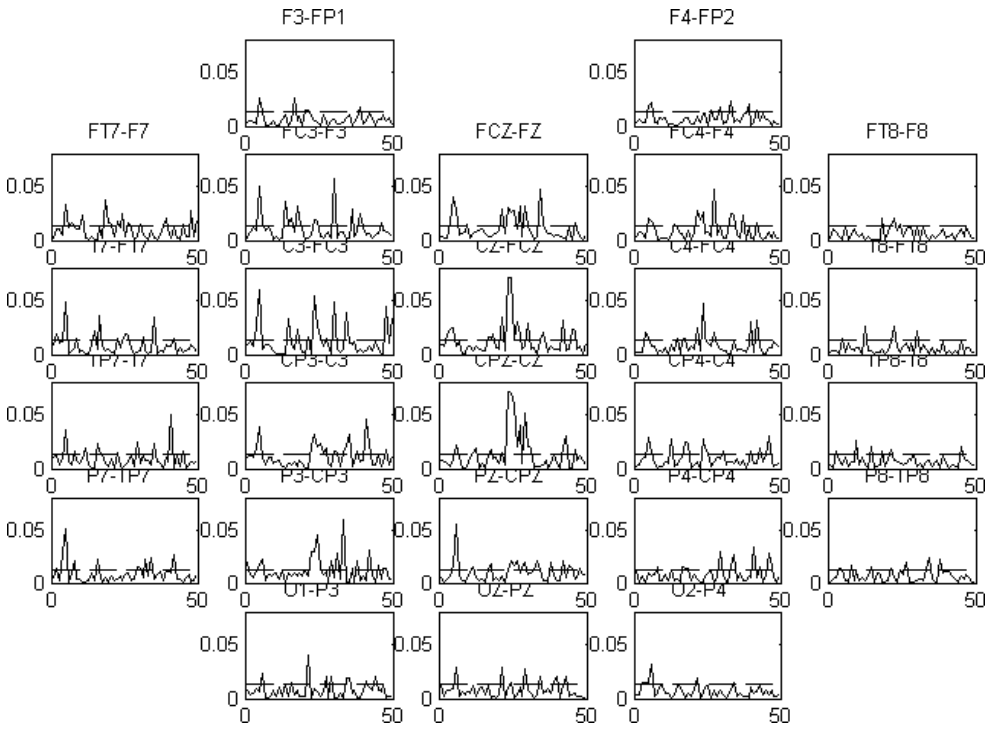


Figure 4:24: shows CMC map for a healthy subject obtained by calculating the coherence between EMG signals obtained from **right ED** muscle during sustained low level contraction, and EEG signals. The mono-polar EEG recording is obtained for each individual electrode at specific locations shown below in accordance with 10-20 International System. At each small square representing cortical recording site of underlying electrode, the horizontal dashed lines indicate the threshold for significant coherence calculated at the specific site. This map shows significant coherence, at varying EEG frequencies ranging 22-35Hz, distributed in midline and much more to the left cortical hemisphere. *Source:* Field work.

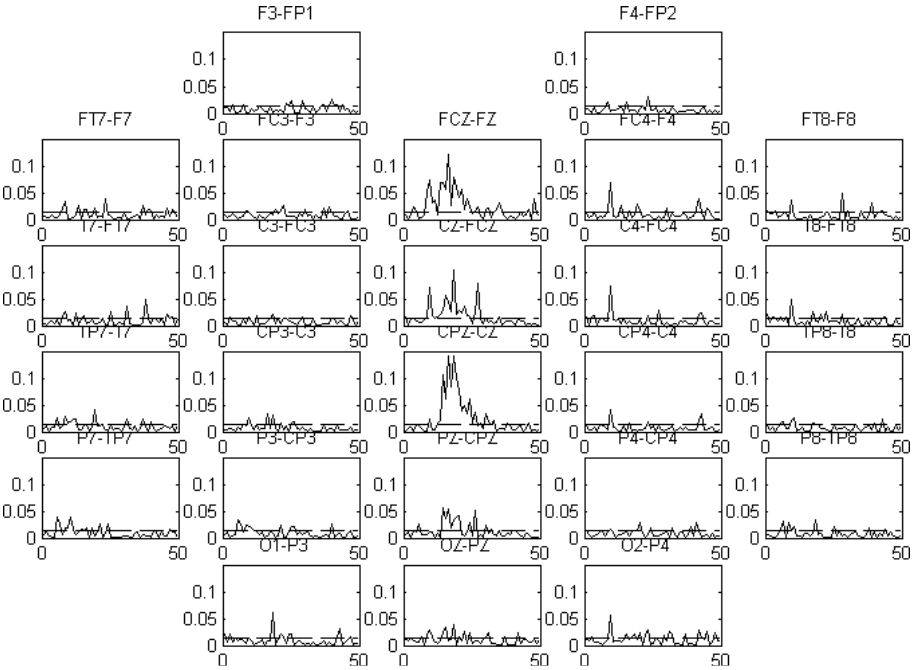


Figure 2:25 (**A**) shows another example of topographic cortical map for CMC coherence calculated from signals of mono-polar EEG and EMG from the right Tibialis Anterior (TA) muscle during low level sustained contraction. The calculated CMC coherence at specific EEG recording electrodes is shown below at the specific locations overlying corresponding EEG electrodes placed according to the 10-20 International System. At each site, dashed lines indicate threshold for significant CMC calculated, with the map showing significant coherence at varying EEG frequencies ranging around 18-30Hz displayed in the midline. *Source:* Field work.

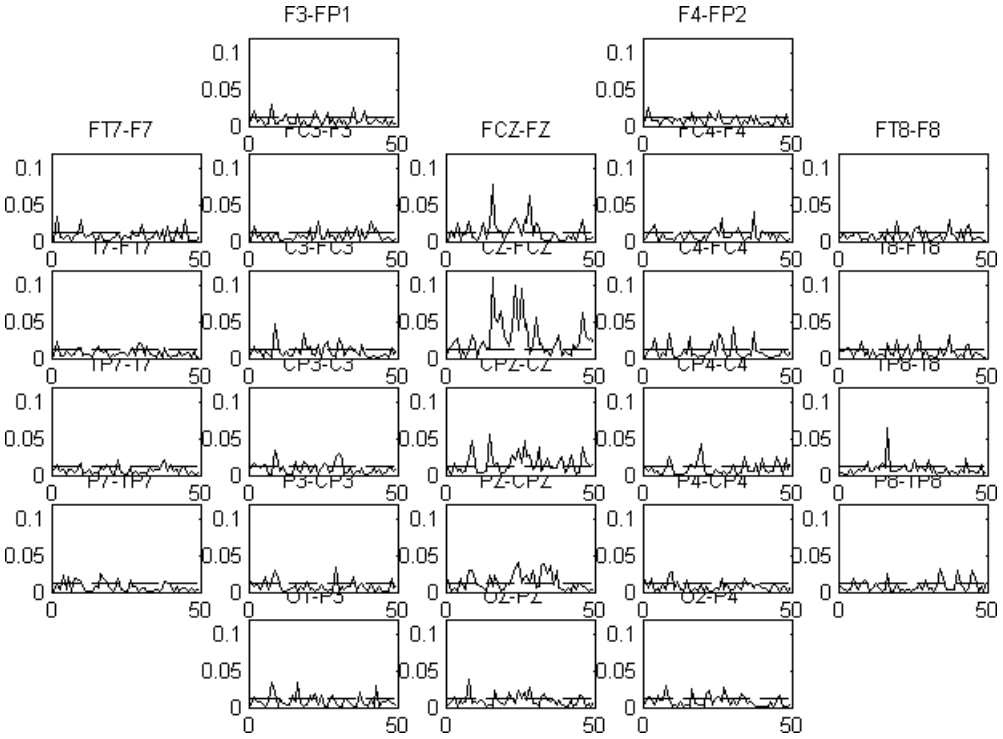


Figure 2:25 (**B**) shows similar example of CMC map for the left TA muscle. *Source:* Field work.

It was observed that some of the healthy subjects tested using simultaneous EEG and EMG recording during sustained low level muscle contraction showed signals that subsequent calculations do not show significant CMC. This is probably in line with what was previously described on the variability of CMC in perfectly healthy individuals indicating presence or absence of significant EEG-EMG coherence. The number of healthy volunteers tested for EEG-EMG coherence (CMC) are 6 in total, out of whom CMC was seen in two or three of them (this possibly conforms with the known variability reported on coherence of these bio- signals) suggesting that is cannot be a reliable biomarker until more is known on why some people show it and others do not.

4.4 SCI Subjects

4.4.1 Studied SCI Patients and Clinical Context

SCI patient volunteers with acute/sub-acute traumatic SCI and free from other medical conditions that might affect recovery profiles or the result/interpretation of electrophysiological tests were recruited to this study. The selection criteria were informed through consultation with clinical staff and the likelihood of an individual being compliant to longitudinal follow-up and repeat clinical assessments including electrophysiological testing. Table 4.04 illustrates the recruitment process that resulted in the final number of SCI patients who consented and completed the study. From an initial consideration of more than 22 cases admitted to the Queen Elizabeth National Spinal Injuries Unit a group of 12 patients provided informed consent.

Table 4.04: Summarises the progress of the recruitment process and numbers of the SCI patients who were approached and numbers through the study. *Source:* Field work.

Category	Numbers	Comments
Suitable SCI cases	**> 22**	Suitable patients identified by medical staff at spinal injuries unit (QENSIU).
Approached for Consent	**22**	Patients approached and briefed on nature of study by research team (investigator) as specified in ethical approval.
Consented & scheduled for testing protocol and procedures (tested).	**12**	22 – 12 = **10 Patients** did not provide unconditional written consent.
Withdrawals & Exclusion	**3**	2 Voluntary withdrawal 1 Developed symptoms of autonomic dysreflexia (excluded).
Completed all components of 1st set of assessments – 'initial test'.	**9**	

Partially completed batches of assessments in 1st set of tests.	**2**	1 completed SEP & DSEP measurements 1 completed SEP & DSEP and coherence measurements.
Patients proceeding to 2nd set of assessments – 'retest'.	**7**	
Number of patients who partially Completed 2 sets of assessments.	**2**	These patients completed all SEP, ERD.S & Coherence measurements but not TMS.
Number of patients who completed full 1st and 2nd set of assessments – 'initial' and 'retest'.	**5**	The total time needed for each patient to complete full data collection for all test modalities was 4 hours (recording time).

4.4.2 Protection of Patients' Identity and Data Should this not be in the Methods?

Compliance with ethical and data protection requirements, a coding system accessible only to the study investigators was designed and used to anonymise individual patients. Coding helped protect patients' identities and maintain privacy of participants in study.

In the process of detailing clinical information and electrophysiological results, SCI patients were referred to using these codes with no mention of any personal or identifying details.

SCI Patients' Group Results

The collective clinical profiles of the group of recruited patients are presented in order to provide the reader with a single site in the thesis summarising the key clinical features of the patients. As this is a heterogeneous group of patients the main experimental findings are presented through individual case presentations in the following sections.

Clinical Examination Findings: (Group Results)

These findings Clinical reporting follows the use of the International Standards for Neurological Classification of Spinal Cord Injury scoresheet (ISNCSCI) that incorporates the ASIA Impairment Scale (AIS), detailed review of patient's case notes and applying the principles of good clinical assessment. Table 4.05 provides a summary of the key clinical information for the SCI patients who completed the longitudinal follow-up involving clinical assessment and electrophysiological testing.

Table 4.05: Summarises clinical details of SCI patients, including AIS grade who completed all testing modalities performed at time of test 1 'initial' and test 2 'retest'. In each case, test and retests were performed at time intervals over which changes in a patient's status would be likely. This period ranged from 10 to 17.5 weeks. *Source:* Field work.

Subject Number	***Age at DOI***	***Clinical Diagnosis***	***ASIA At test-1 & Retest-2***	*Level* & ***Neurol** Level*	*Time Interval* ***Injury to 1st. Test*** & ***Injury to 2nd. Test***
S1	***49***	***Acute** Incomplete Tetraplegia* ***No MagStim***	***C*** ***D***	***C5 Injury*** ***Neurol Level*** ***C5 (**early C4**)***	*50 days* ***(7 weeks)*** ***(21 weeks)*** ***14 weeks** interval*
S2	***56***	***Acute** Incomplete Tetraplegia* ***No MagStim***	***C*** ***C***	***C5 Injury*** ***Neurol Level*** ***C5***	*52 days* ***(7 weeks)*** ***(22 weeks)*** ***15 weeks** interval*
S3	***44***	*Acute Complete Paraplegia* ***Complete x 2***	***A*** ***A***	***T9 Injury*** ***Neurol Level*** ***T10***	*23 days* ***(3 weeks)*** ***(19.5 weeks)*** ***16.5 weeks** interval*
S4	***45***	*Acute Complete Paraplegia* ***Complete x 2***	***A*** ***A***	***T7 Injury*** ***Neurol Level*** ***T4***	*60 days* ***(8.5 weeks)*** *26 weeks* ***17.5 weeks** interval*
S5	***24***	*Acute / Chr. Incomplete Tetraplegia* ***Complete x 2***	***C*** ***C***	***C6 Injury*** ***Neurol Level*** ***C5***	*21 days (lost) Redone 79 d* ***(11 w)*** *182 d* ***(26 w)*** ***15 weeks** interval*
S6	***67***	*Acute Incomplete Paraplegia* ***Complete x 2***	***C*** ***D***	***L1 Injury*** *Neurol Level* ***T12 or D12***	*42 days* ***(6 weeks)*** ***(21 weeks)*** ***15 weeks** interval*
S7	***55***	*Acute Incomplete Tetraplegia* ***Complete x 2***	***D*** ***D***	***C5 Injury*** ***Neurol Level*** ***C5 (**early C4**)***	*70 days* ***(10 weeks)*** ***(20 weeks)*** ***10 weeks** interval*

Table 4.06 further details the clinical information for each subject by reporting on the AIS sensory examination obtained for SCI patients who completed the longitudinal follow-up. The sensory scores obtained through AIS for 'initial' and 're-test' are shown with changes in AIS grades of severity and extent of SCI at given spinal levels. These scores illustrate clinical changes observed over time since injury and across the longitudinal follow-up period and give an

indication of either recovery or worsening of status since the initial clinical examination.

AIS motor scores are similarly presented in Table 4.07.

Table 4.06: Sensory scores of SCI patients obtained at time of test-1 and test-2 are shown alongside changes observed in ASIA grades. Together, these are in effect charting changes (progress) observed on clinical examination over time, indicating either clinical improvement or otherwise deterioration while in some instances no detectable changes were observed. *Source:* Field work.

Subject	Level	AIS at Test-1	AIS at Test-2	Injury to Test-1	Injury to Test-2
S1	C5	C Touch R=56 – L=56 Pin Prick R=52 – L=52	D Touch R=56 – L=56 Pin Prick R=56 – L=56	50 days 7 weeks	147 days 21 weeks
S2	C5	C Touch R=56 – L=56 Pin Prick R=43 – L=56	C Touch R=56 – L=56 Pin Prick R=56 – L=56	52 days 7 weeks	154 days 22 weeks (test-3) (
S3	T10	A Touch R=34 – L=34 Pin Prick R=36 – L=34	A Touch R=38 – L=34 Pin Prick R=39 – L=34	23 days 3 weeks	137 days 19.5 weeks
S4	T4	A Touch R=24 – L=24 Pin Prick R=24 – L=24	A Touch R=24 – L=24 Pin Prick R=24 – L=24	60 days 8.5 weeks	182 days 26 weeks
S5	C5	C Touch R=56 – L=56 Pin Prick R=39 – L=39	C Touch R=56 – L=56 Pin Prick R=41 – L=41	79 days 11 weeks	182 days 26 weeks
S6	T12	C Touch R=56 – L=56 Pin Prick R=45 – L=47	D Touch R=56 – L=56 Pin Prick R=53 – L=53	42 days 6 weeks	147 days 21 weeks
S7	C5	D Touch R=56 – L=56 Pin Prick R=36 – L=36	D Touch R=56 – L=56 Pin Prick R=39 – L=39	70 days 10 weeks	140 days 20 weeks

Table 4.07: Motor scores of SCI patients obtained at time of test-1 and test-2 are shown alongside changes observed in ASIA grades. Together, these are in effect charting changes (progress) observed on clinical examination over time, indicating either clinical improvement or otherwise deterioration, while in some instances no detectable changes were observed. *Source:* Field work.

Subject	Level	AIS at Test-1	AIS at Test-2	Injury to Test-1	Injury to Test-2
S1	C5	C Upper Limbs R=9 – L= 10 Lower Limbs R=14 – L= 15 Total R=23,, L=25	D Upper Limbs R=22 – L= 24 Lower Limbs R=23– L= 23 Total R=45,, L=47	50 days 7 weeks	147 days 21 weeks
S2	C5	C Upper Limbs R=15 – L= 7 Lower Limbs R=15 – L= 7 Total R=30,, L=14	C Upper Limbs R=13 – L= 12 Lower Limbs R=14 – L= 12 Total R=27,, L=24	52 days 7 weeks	154 days 22 weeks (test-3) 52.5 weeks
S3	T10	A Upper Limbs R=25 – L=25 Lower Limbs R=0 – L= 0 Total R=25,, L=25	A Upper Limbs R=25 – L=25 Lower Limbs R=0 – L= 0 Total R=25 ,, L=25	23 days 3 weeks	137 days 19.5 weeks
S4	T4	A Upper Limbs R=25 – L=25 Lower Limbs R=0 – L= 0 Total R=25,, L=25	A Upper Limbs R=25 – L=25 Lower Limbs R=0 – L= 0 Total R=25,, L=25	60 days 8.5 weeks	182 days 26 weeks
S5	C5	C Upper Limbs R=10 – L=11 Lower Limbs R=0 – L= 0 Total R=10,, L=11	C Upper Limbs R=13 – L=14 Lower Limbs R=0 – L= 0 Total R=13,, L=14	79 days 11 weeks	182 days 26 weeks
S6	T12	C Upper Limbs R=25 – L=25 Lower Limbs R=12 – L= 12 Total R=37,, L=37	D Upper Limbs R=25 – L=25 Lower Limbs R=18 – L= 18 Total R=43,, L=43	42 days 6 weeks	147 days 21 weeks
S7	C5	D Upper Limbs R=14 – L=11 Lower Limbs R=21 – L= 21 Total R=35,, L=32	D Upper Limbs R=18 – L=16 Lower Limbs R=24 – L= 23 Total R=42,, L=39	70 days 10 weeks	140 days 20 weeks

Clinical Information on SCI Patients

Information obtained from SCI patients who were assessed twice using clinical and electrophysiological methods are listed below. For ease of tracking the subject identification numbers used in tables 4.06 and 4.07 apply throughout the sections that follow.

Information on patient recruitment and retention was given previously (Table 4.04) and information on the testing intervals for individual patients was given in table 4.05. Of the 12 patients who gave written consent and were tested electro-physiologically only 7 patients were able to complete all test modalities on both testing sessions.

The mean time interval separating 'initial' and 'retest' was 14.7 weeks (range 10-17.5 weeks). Logistically, it was not possible to implement a standard testing interval due to difficulties in scheduling access to patients on dates and times that did not interrupt or interfere with a patient's treatment, visiting times for family and friends or rehabilitation. However, the intervals over which testing occurred were considered sufficient to allow for comparisons to be drawn between any recovery that occurred and that which could be captured by clinical or electrophysiological tests.

It is worth emphasising that identification of SCI level is in accord with ASIA Impairment Scale methods and refers to the **neurological level** (*defined by AIS as the most caudal spinal segment with normal neurological examination*) and completeness (A-D) and not the vertebral injury level.

In each subsequent case that will be presented reference between AIS grade and scores will be made with the experimental test data obtained from the electrophysiological responses. The results are therefore presented for the 7 SCI patients listed in Table 4.06 and Table 4.07.

The order of presentation of the individual patient cases will be based on grouping in accordance with AIS grade and recovery profile. Thus the results for the 2 AIS-A patients are presented first, these results are then followed by results for the SCI incomplete patients who did not show a change in AIS grade over the testing period and finally data is presented for the 2 AIS C patients who demonstrated a clinically measurable improvement in function and converted from AIS C to D. Table 4.08 shows the stratification and overall flow-charts listing patients in the order of their results as presented in the thesis, with the data obtained from examined SCI patients.

Table 4.08: shows a summary of the clinical information of all SCI patients, as an overall flow chart for the clinical progress of SCI patients who were tested along the longitudinal follow-up period documenting variable clinical changes seen with some changes indicating neurological recovery observed over this time period. *Source:* Field work.

Group A:
Patient S3: *ASIA-**A** **T10** – **remained ASIA-A*** ***– 16.5 weeks***
Patient S4: *ASAIA-**A** **T4** – **remained ASIA-A*** ***– 17.5 weeks***
Group B:
Patient S5: *ASIA-**C** **C5** – **remained ASIA-C*** ***– 15 weeks***
Patient S7: *ASIA-**D** **C5** – **remained ASIA-D*** ***– 10 weeks***
Group B'':
No MEP Data (one refused & one contra-indicated) ***Patient S2:*** *ASIA-**C** **C5*** ***– remained ASIA-C at Test-2*** *(lost some data)* ***– 15 weeks*** ***– recovered to ASIA-D at Test-3*** *(some displayed)* ***– 52.5 weeks***
Group C:
Patient S6: *ASIA-**C** **T12** – **recovered to ASIA-D*** ***– 15 weeks***
No MEP Data (one refused & one contra-indicated) ***Patient S1:*** *ASIA-**C** **C5** – **recovered to ASIA-D*** ***– 14-weeks***

Figure 4.26 also provides a schematic illustration of the changes seen in AIS measured over the time course of the study relative to the time post-injury. Over the time intervals between test-1 and test-2 clinical findings show that neither of the 2 AIS A patients converted from A. Similarly, 3 incomplete patients (2 AIS C and 1 AIS D) failed to show any change in AIS grade. However, as mentioned previously two AIS C patients converted to AIS D over the period between test 1 and test 2. Of the five patients whose AIS remained unchanged between test 1 and 2 only S3 (AIS A) was tested within a month of the date of injury. The remaining 3 clinically stable incomplete patients (S2, S5, S7) were initially studied between 8 and 12 weeks, post injury and again between 10 and 17.5 weeks later, a time period that should have coincided with periods where any recovery likely to occur would be evident and measurable by ASIA. This is evident from the ASIA data for S1 and S6 whose AIS classification showed a conversion from AIS D to C, over a time course similar to that for the patients who did not convert from a higher to lower category of lesion completeness.

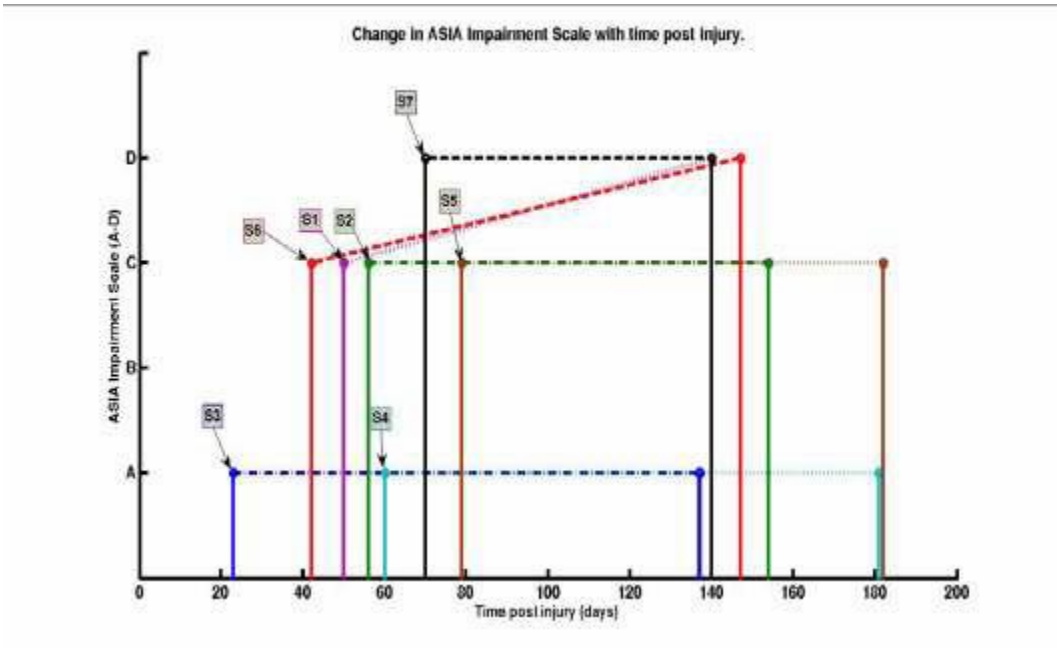


Figure 4:26 summarises clinical details of SCI patients who completed all testing modalities. Clinical assessment details are defined by AIS grading measured at test-1 and test-2 for each patient (S1 – S6), performed several weeks apart in the course of longitudinally assessment of this study. Based on clinical AIS, only 2 SCI patients in the study show one grade measure improvement over time elapsing between tests, which are patients S1 and S6 who went from ASIA C grade to ASIA D. The remaining patients (S2, S3, S4, S5 and S7) did not show changes measurable on the clinical AIS. *Source:* Field work.

This figure follows the longitudinal progress of the SCI patients, based the clinical improvement or deterioration measured by the AIS classification. Each of the SCI patients is shown on starting point and again at a point on the clinical course, after a period of clinical follow-up.

Detailed Results for Individual Patients:

These results are presented where possible using a standard sequence of presentation for each subject. Each case opens with the patient's Clinical Information (detailing patients' information, clinical circumstances, AIS grading with level and extent of SCI lesions, treatment, hospital course and any clinical improvement or deterioration). This is followed by the results from sensory electrophysiological testing (SEP, D-SEP results and ERSP maps) before consideration of motor testing results (MEPs and CMC calculations where available). Consideration between the results from clinical and electrophysiological testing is sought on a comparative basis to highlight common interpretations or the presence of undetected changes revealed by the different testing methodologies.

Results obtained from all patients are found in the appendix.

4.5 GROUP A – Patients with Complete SCI and No Measurable Recovery:

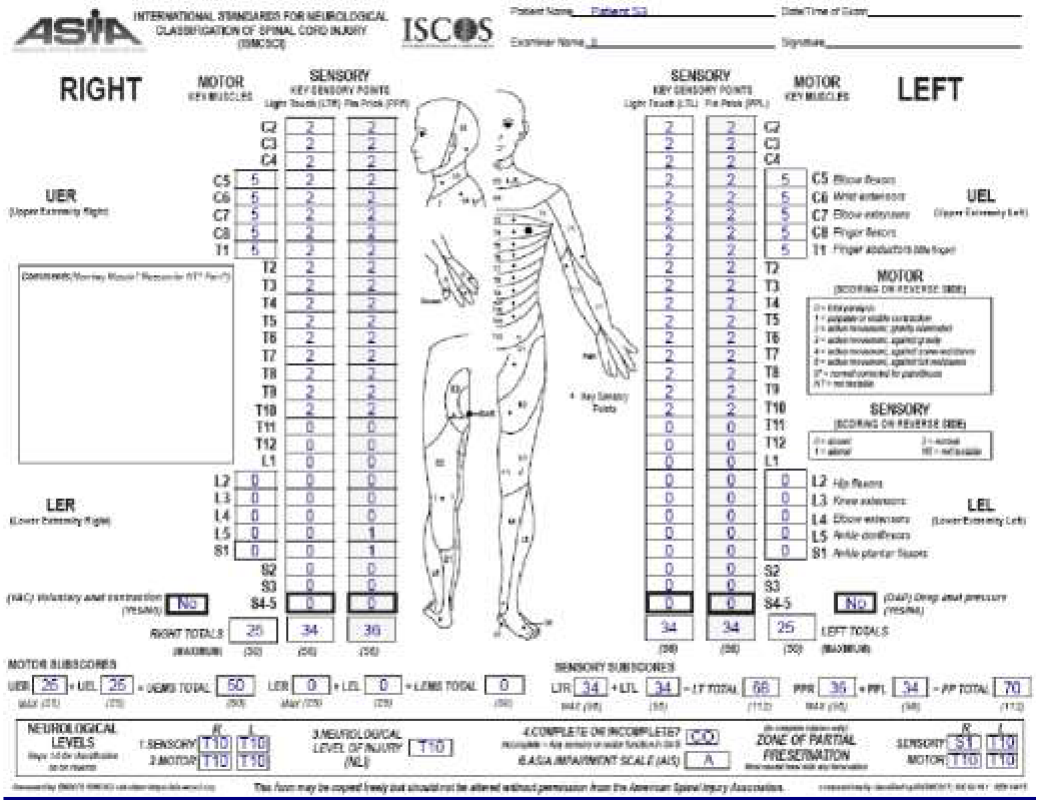
4.5.1 Patient S3 (ASIA-A Complete T10 Paraplegia)

Clinical Information

- Patient: 44-years-old male.
- **Injury level**ASIA-A **Injury level** T9
- Complications: ***severe*** and ***frequent*** reflex spasms and clonus (greatest in left lower limb, spreading to shake whole body including face and head. Frequency approx. 5 spasms per minute and present during test 2 recording session).
- Time Interval to test 1– **Injury to Test 1 'initial test'**: 23 days (3 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **T10 ASIA A**.
- Time Interval to test 2– **Injury to Test 2**: 137 days (19.5 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **T10 ASIA A**.
- Test - Retest Interval **–16.5 weeks**.
- Medications at time of Test 2: Tramadol 50mg x 4. Temazepam 10mg x 1.
- On Discharge: No significant difference in clinical assessment.
- Other information or comments: None.

Copies of the ASIA charts for S3 are provided for the initial and second test points in Figures 4.27 (**A**)and (**B**) respectively, together with cartoons which illustrate the sensory and motor scoring dermatomal maps (using EMSCI scoring illustrations shown at https://ais.emsci.org) using a colour chart related to the scoring values. While this patient was reported as AIS A on both test dates (no sensory or motor function in S4-S5) there was a change in the extent of the sensory zone of partial preservation associated with light touch and pin prick testing on the right side. This is most easily seen when comparing the colour maps of the results of the sensory examination at test-1 and test-2 as shown in Figures 4.28 (**C**) and (**D**).

(A) :



(B) :

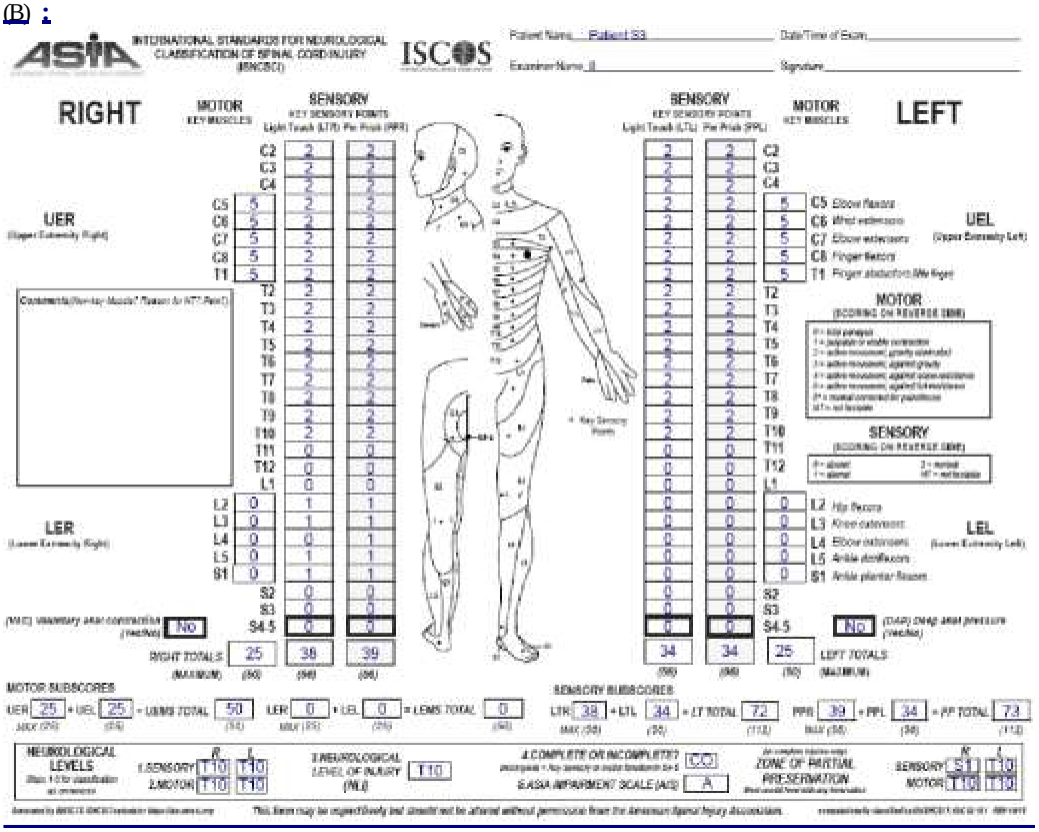
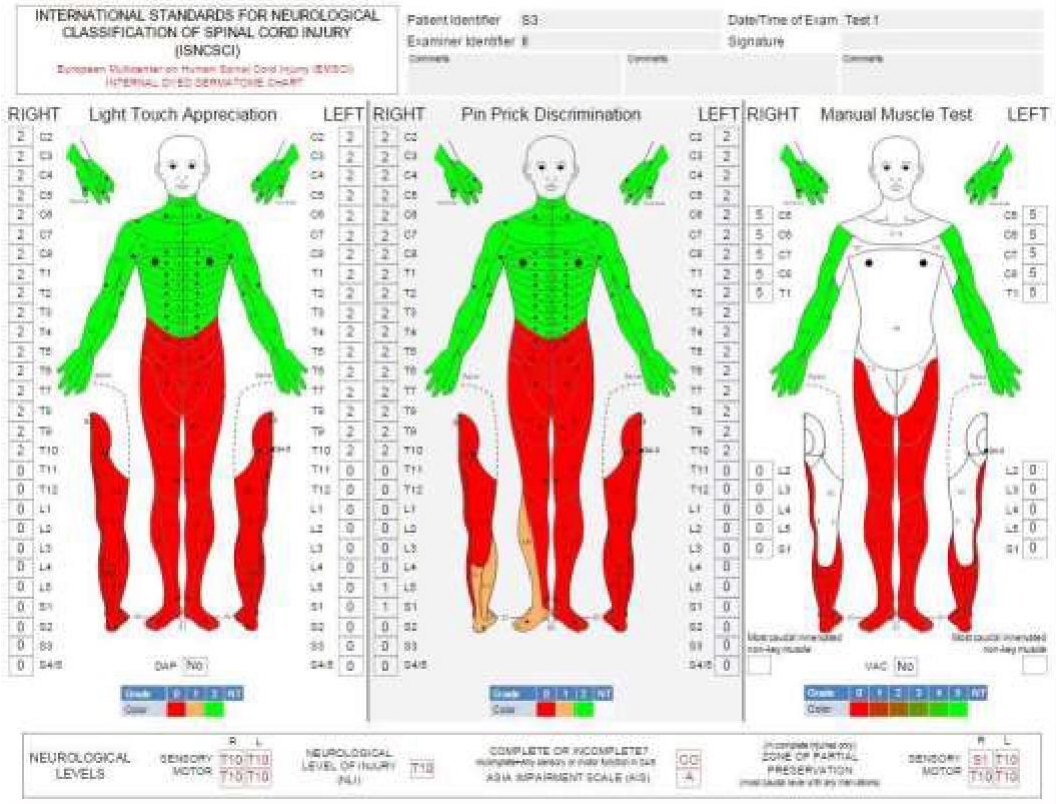


Figure 4:27 (**A**) and (**B**): shows ASIA Impairment Scale (AIS) for patients S3 at test-1 (A) and test-2 (B) examined 16.5 weeks apart. *Source:* Field work.

(C) **:**



(D) **:**

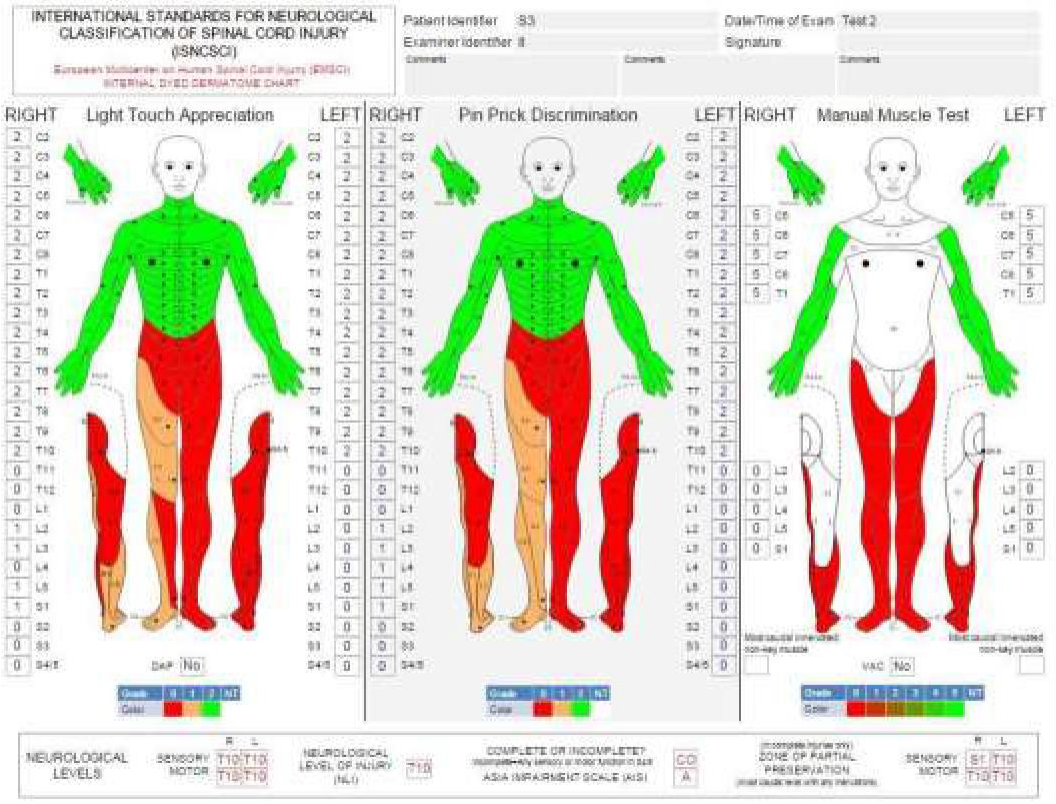


Figure 4.28 (**C**) & (**D**) shows cartoons illustrations of colour charts of the dermatomal maps related to sensory scoring values at test-1 (C) and test-2 (D) for patient S3. *Source:* Field work.

4.5.2 Evoked Responses (Amplitude and Latency Measurements): Averaged SEP and D-SEP waveform were measured and amplitude and latency parameters estimated from averages. The evoked responses in this patient were obtained by electrical stimulation of C5 and stimulation of C5 and C6 dermatomes and the Median nerve at the wrist on both sides for the upper limbs (ULs) and for L2 and L3 dermatomes together with the Posterior Tibial nerve (PTN) from both sides for the lower limbs (LLs). All tests were performed on two separate occasions separated by a time interval of 16.5 weeks commencing 3 weeks post injury. On both recording dates SEP and D-SEP responses from below the level of the lesion at T10 were absent at the stimulation intensities used. The lack of evoked brain responses in below lesion stimulation testing is in keeping with the ASIA-A clinical assessment and the lack of any change in clinical and functional status over time. However, it might have been expected that a detectable evoked response from the 2nd set of tests that were conducted on the right limb would be evident given the change in scoring apparent for light touch and pain over the time interval between tests. Table 4.09 shows the findings for SEP and D-SEP measurements from both LLs plotted at two separate occasions. The upper limb SEPs and D-SEPs were not affected by the T10 lesion and therefore were considered to be normal and not illustrated here or reported in Table 4.09.

Table 4.09: Shows details of values of measured actual amplitude and inter-peak latency parameters obtained from short latency SEP and D-SEP cortical waveforms. These were recorded on test-1 (initial) and test-2 (retest) performed at two occasions separated by 16.5 weeks interval in the longitudinal follow-up period. No cortical sensory responses were recorded in response to stimulation at any dermatome or mixed nerve sites on either side in the lower limbs (completely absent responses to maximum electrical stimulation). Responses obtained from upper limb (UL) stimulation were not included in the graph. *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 =* ***23 days (3 weeks).***	***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 =* ***137 days (19.5 weeks).***
S3	**Acute**	***A***	***A***
Patient S3	**T10**	***Rt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***	***Rt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***
44-yrs	Complete Paraplegia	***Am:*** -- -- -- *Absent* *Absent* *Absent*	***Am:*** -- -- -- *Absent* *Absent* *Absent*
	***UL** not tested	***Lat:*** -- -- -- *N/A* *N/A* *N/A*	***Lat:*** -- -- -- *N/A* *N/A* *N/A*
		Lt: ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***	***Lt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***
	Complete Test x 2	***Am:*** -- -- -- *Absent* *Absent* *Absnet*	***Am:*** -- -- -- *Absent* *Absent* *Absent*
		Lat: -- -- -- *N/A* *N/A* *N/A*	***Lat:*** -- -- -- *N/A* *N/A* *N/A*

Examples of averaged SEP waveforms obtained by stimulation of right and left posterior tibial nerves as well as D-SEP waveforms from L2 dermatomes of this ASIA-A T10 SCI patient are shown in Figures 4.29 (**A**) for right PTN, (**B**) left PTN and (**C**) L2 right D-SEP. The figures show the initial test result (red trace) aligned above the equivalent waveform (black trace) obtained during the retest session 16.5 weeks apart. As is clear, there are no measurable features in SEP or D-SEP responses. The absence of responses to electrical stimulation at the intensities used correlates with the results of sensory tests for light touch and pin prick on the left side which all indicated a sensory complete injury (AIS A), and no recovery in sensation below the lesion (Figure 4.29). However, this is not the case for the right side as mentioned previously (Figure 4.28 C and D), where visible recovery of pin prick sensation is reflected on the shown coloured sensory charts.

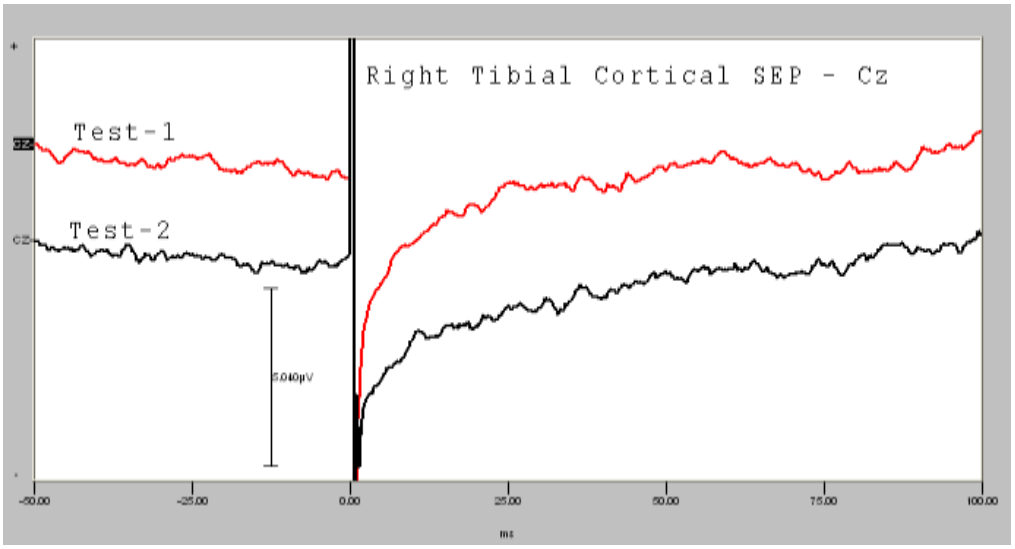


Figure 4.29 (**A**): Shows averaged SEP waveform recordings of the right Posterior Tibial nerve (PTN) from ASIA-A (complete) SCI patient. **Red** trace represents test-1 and **black** trace represents test-2 performed **16.5 weeks** apart, recording no measurable SEP responses on either test. *Source:* Field work.

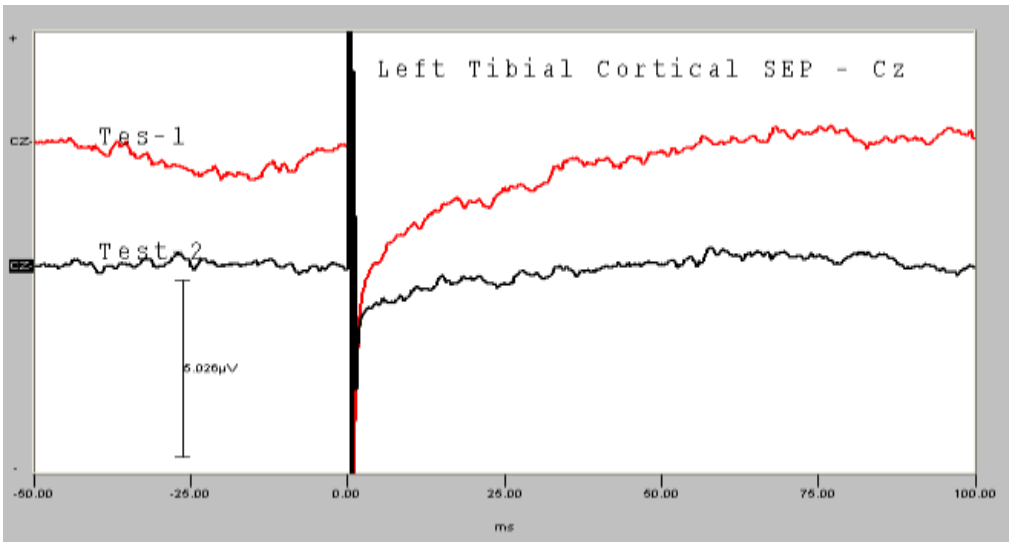


Figure 4.29 (**B**): Shows averaged SEP waveform recordings of the left Posterior Tibial nerve (PTN) from ASIA-A (complete) SCI patient. **Red** trace represents test-1 and **black** trace represents test-2 performed **16.5 weeks** apart, recording no measurable SEP responses on either test. Source: Field work.

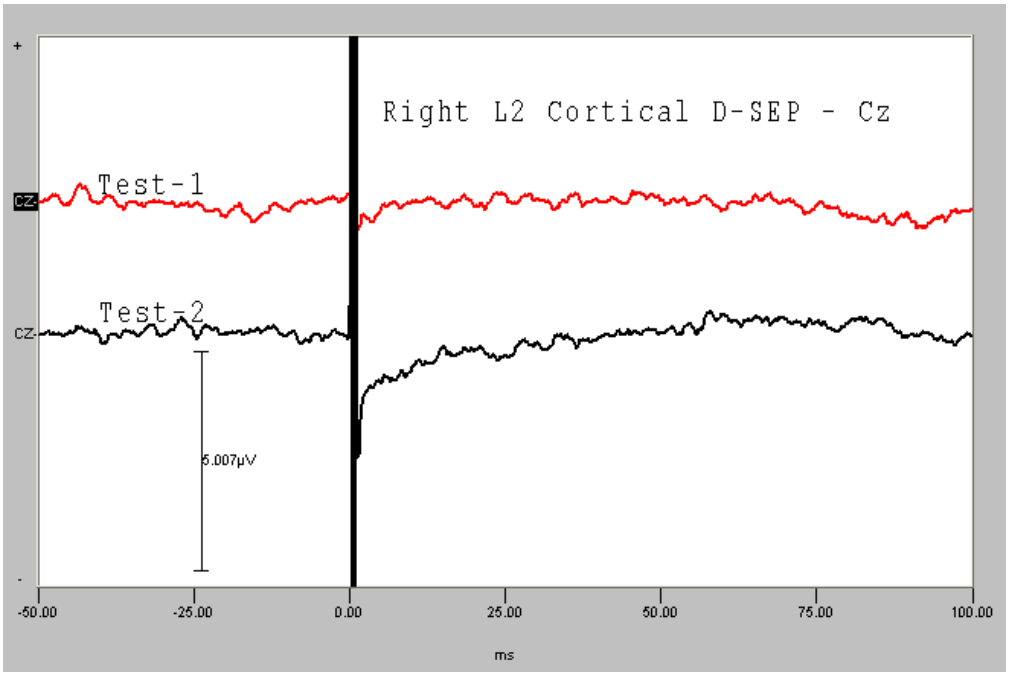


Figure 4.29 (**C**): Shows averaged D-SEP waveform recordings of the right L2 dermatome from ASIA-A Complete T10 Paraplegia. The **red** trace represents test-1 and **black** trace represents test-2 performed **16.5 weeks** apart, recording no measurable D-SEP responses on either test. *Source:* Field work.

This discrepancy between the result of a perceptual test and a neurophysiological test is surprising and will be considered more fully in the discussion in subsequent sections.

4.5.3 ERSP (Spectral Maps for low-rate Sensory Stimulation)

To further explore the sensitivity of SEP measurements ERSP maps were obtained for lower limb SEP and D-SEP stimulation sites, as described in the methods section. Figure 4.30 and Figure 4.31 shows initial and retest ERSP patterns respectively for illustrative purposes. In patient S3 the ERSP maps obtained for initial and retest (as shown in the figures below), do not show strong features or changes in the spectral composition of the EEG post stimulation and are in keeping with results from SEP tests. In the example shown for right limb PTN stimulation, a red hot-spot is evident at time zero in the data obtained on each test date, but these spectral changes most likely reflect the stimulation artefact and not physiological activity. Comparison with ERSP maps obtained from healthy individuals (Figures 4.15 and 4.17), shows that for this patient there is an event related period of desynchronisation or synchronisation in response to the stimulation. However, in the 2nd test conducted on the right limb there is a small and late period of desynchronisation occurring between 20 and 30Hz at latencies greater than 200ms. The general lack of clearly defined periods of synchronisation further highlight that the sensory neurophysiology supports the AIS A grading remaining unchanged over time. But the SEP and ERSP methods when applied to the right limb do not correlate with the changes reported by light touch and pin print in the zone of partial preservation evident as changes occurring between tests 1 and 2. Whether the weak desynchronisation seen in the 2nd ESRP result is significant and real is uncertain at present but could reflect processes associated with the change in sensation reported by this patient in the right lower limb as seen in the AIS coloured sensory charts.

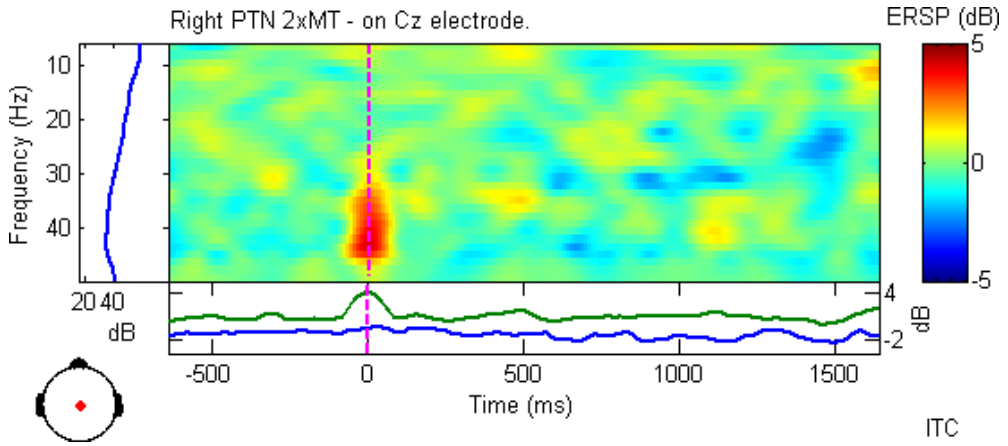


Figure 4.30: shows (**initial**) pattern of ERSP map obtained from SCI patient with ASIA-A Complete T10 Paraplegia, using bi-polar montage recording of cortical responses at Cz electrode in response to slow stimulation of right PTN. There were no observed patterns of ERD bands described in relation to the normal ERSP patterns. Absence of the normal pattern of ERSP map was consistent for 'initial' and 'retest' performed 16.5 weeks apart down the longitudinal follow-up period. The patient had no residual motor or sensory clinical function as measured on ASIA Impairment Scale. *Source:* Field work.

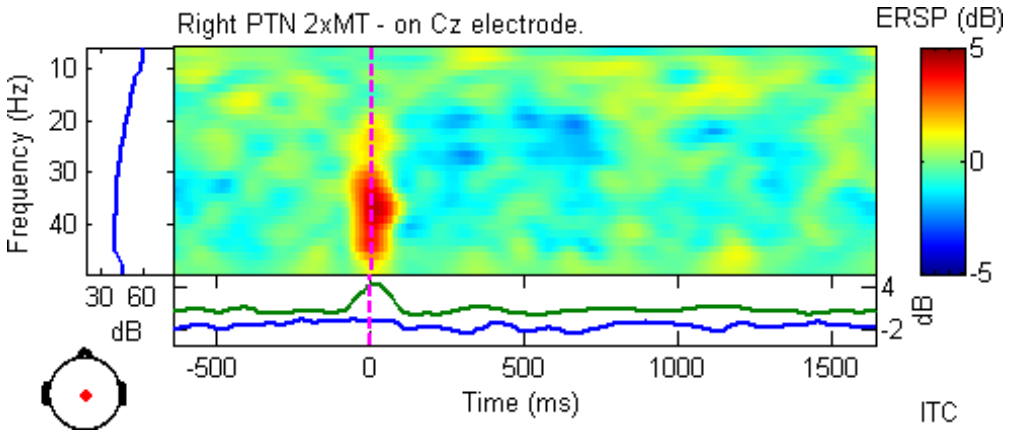


Figure 4.31: shows (**follow-up**) pattern of ERSP map obtained from SCI patient with ASIA-A Complete T10 Paraplegia, using bi-polar cortical recording at Cz electrode in response to slow stimulation of the right PTN. There were no observed patterns of ERD bands described in relation to the normal ERSP patterns. Absence of the normal pattern of responses shaping ERSP maps was consistent for 'initial' and 'retest' performed 16.5 weeks apart during the longitudinal follow-up period. The patient had no residual motor or sensory clinical function as measured on ASIA Impairment Scale. *Source:* Field work.

4.5.4 Transcranial Magnetic Stimulation – Motor Evoked Potentials:

Patient S3, TMS of the cerebral cortex over C_Z (vertex) did not provoke any noticeable motor response (muscle twitch or jerk) below the level of the lesion and resulted in no measurable EMG activity from either right or left TA muscles. The lack of MEP responses is observed on both testing dates. This is consistent with the clinical and electrical findings of complete ASAI - A SCI.

4.5.5 Cortico-Muscular (EEG-EMG) Coherence – CMC:

CMC measures were attempted, but as no voluntary EMG activity could be initiated it failed to reveal any results for either left or right sides. This lack of ability to generate voluntary EMG activity also helps to confirm the lesion as motor and complete and unchanged over time.

4.6 Interpretation of Electrophysiological Results (in light of clinical info)

The findings from all electrophysiological tests performed for (Patient S3), (**ASIA-A Complete T10 Paraplegia**) are concordant. **Clinically**, the patient showed no significant difference in the clinical assessment as measured by the ASIA Impairment Scale (AIS) at any time following admission through to their subsequent discharge from hospital. However, there was a change in the extent of the sensory zone of partial preservation associated with light touch and pin prick testing on the right side. Figures 4.28 (**C**) and (**D**) shows cartoon illustrations of the dermatomal maps using colour charts relating the values of sensory and motor scoring at test-1 and test-2.

Results of the **electrophysiological tests** performed **16.5 weeks** apart indicated no residual or evoked ascending (sensory) or descending (motor) pathways response. This offers reasonable evidence to suggest that at the times of these tests that the status as' an AIS A patient is confirmed as functionally and physiologically complete. In this instance, some gain in sensory perception of tough and pin prick which was not adequately picked-up by accompanying electrical tests is apparent.

The patient experienced frequent and severe **reflex spasms** (greatest in the left lower limb) that spread to shake the whole-body including head and face with five episodes occurring per minute. At times, these spasms were interfering with various functions and activities of daily living. **Medications** were used to calm these abnormal movements and at the time of 'retest' the patient was taking Tramadol 50mg four times per day and Temazepam 10mg once. The named **medications** could have **affected electrophysiological tests**, through changes that alter the EEG spectrum and through depression of cortical and spinal cord excitability. However, these medications (taken in these clinically-appropriate doses) would be unlikely to abolish synchronised SEP or D-SEP responses or block powerful MEP responses if those connections existed and were capable of function. Accordingly, in this patient there is a mismatch between the results of the sensory testing modalities that is largely unexplained.

4.6.1 Patient S4 (ASIA-A Complete T4 Paraplegia):

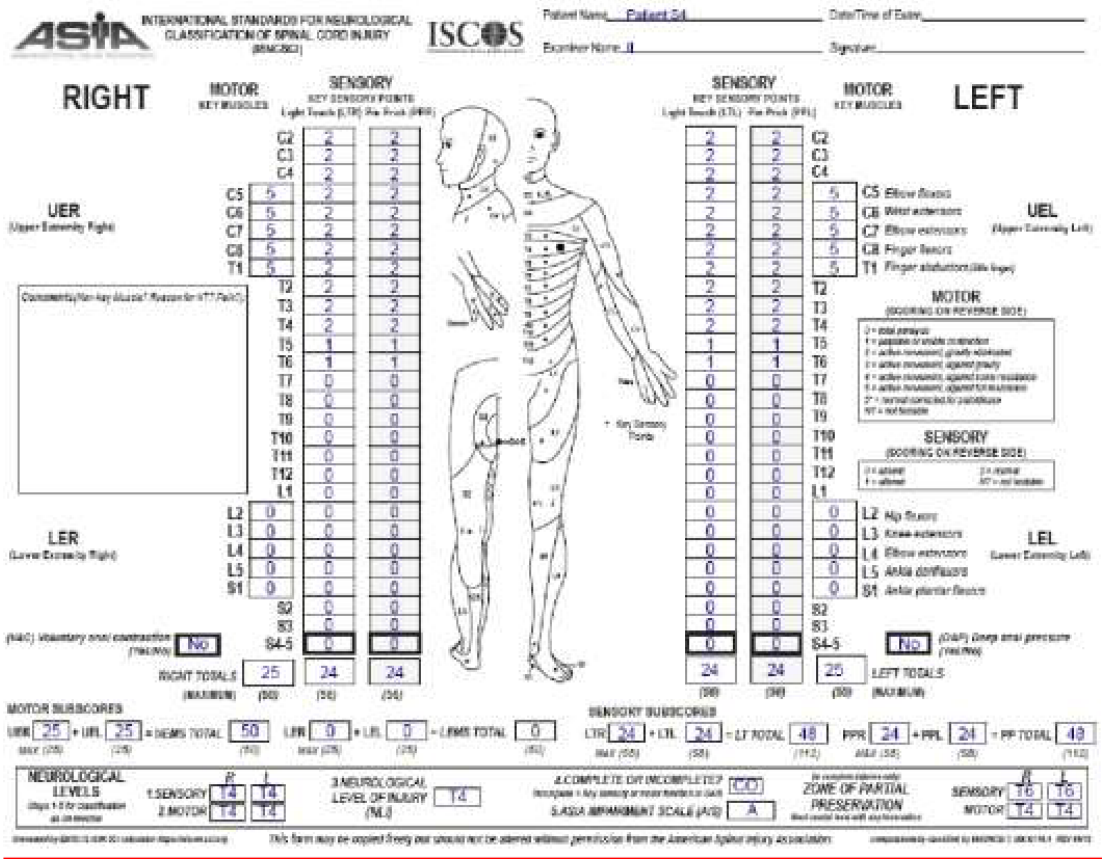
Clinical Information:

- Patient: 45-years-old male.
- Acute SCI Circumstances: Road traffic accident but **Retrograde and Post-Traumatic amnesia:** no recall of crash events or period of time immediately post event.
- **I**ASIA A –T4. **Injury level** T7
- Time Interval – **Injury to Test 1 'initial test'**: 60 days (8.5 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **T4 ASIA A**.

- Time Interval – **Injury to Test 2 'initial test'**: 182 days (26 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **T4 ASIA A**.
- Time Interval **– Test 1 to Test 2: 17.5 weeks**.
- Medications at time of Test 2: Diazepam 10mg x 1. Baclofen 25mg x 4.
- On Discharge: No significant difference in clinical assessment.
- Other information or comments: None.

In this patient the clinical testing illustrated by the charts in Figures 4.32 (**A**) and (**B**) show a person with stable AIS-A injury. In this individual all manual motor and perceptual sensory test results were consistent over the testing period.

(A) :



(**B**):

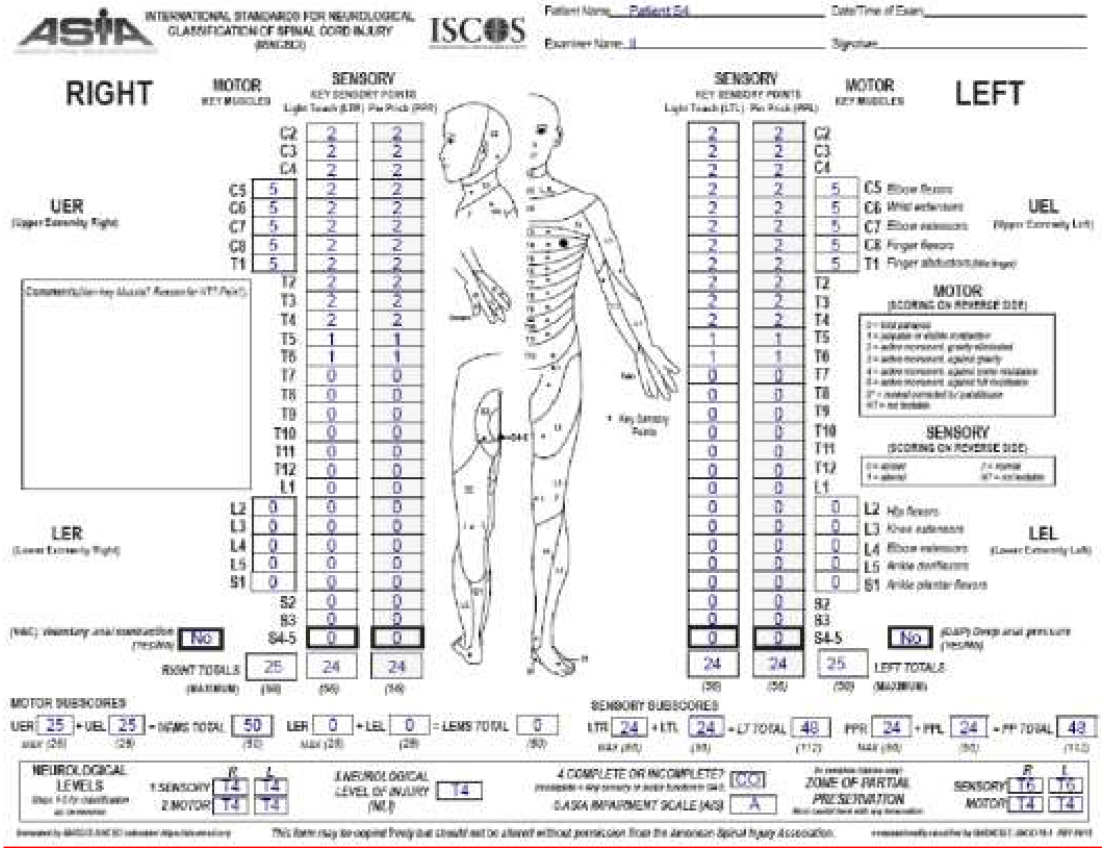
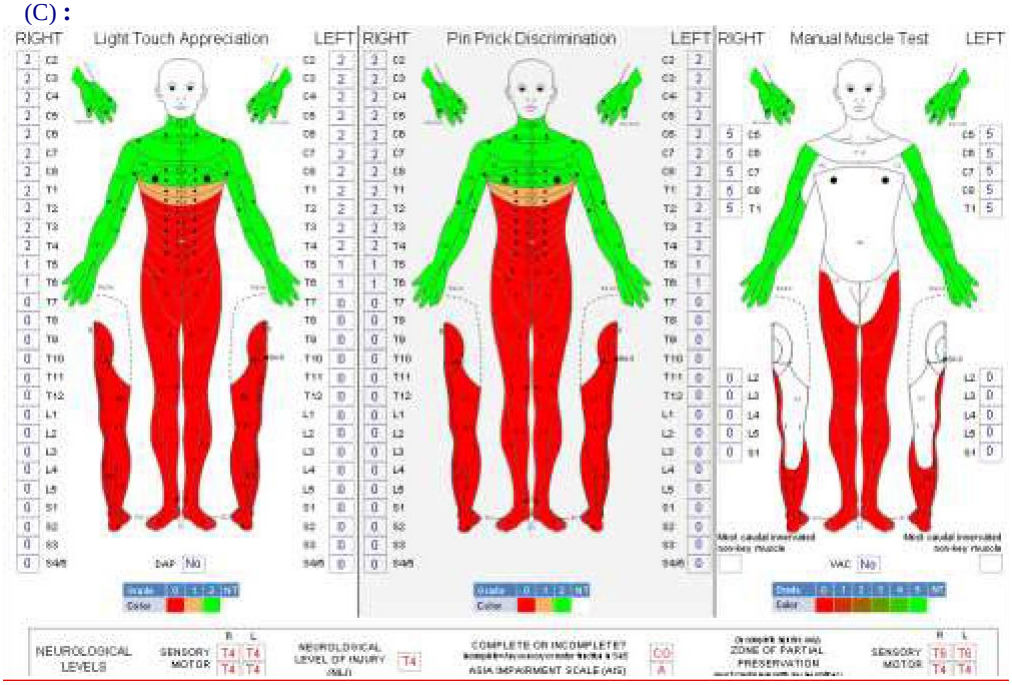


Figure 4.32 (**A**) and (**B**): shows ASIA Impairment Scale (AIS) for patients S4 at test-1 (A) and test-2 (B) examined 17.5 weeks apart. *Source:* Field work.

(C) :



(D) :

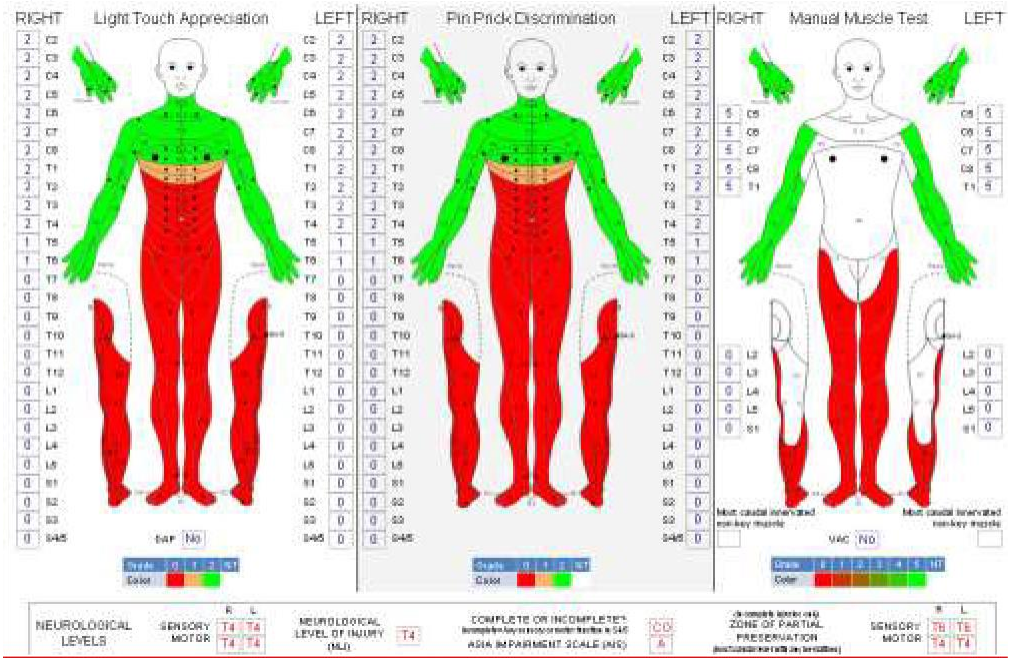


Figure 4.32 (**C**) and (**D**): shows cartoon illustrations of colour charts of the dermatomal maps related to sensory scoring values at test-1 (C) and test-2 (D) for patient S4. *Source:* Field work.

4.6.2 SEP & D-SEP (Waveforms & Lat-Amp Measurements):

Parameters of SEP and D-SEP sensory responses are shown in Table 4.10. In all cases electrical stimulation at sites below the level of the lesion failed to evoke detectable signals in the average SEPs or D-SEPS.

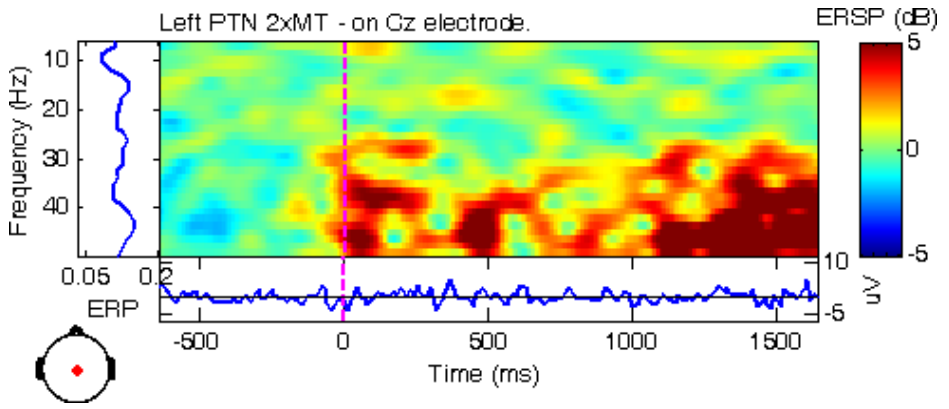
Table 4.10: Shows details of values of measured actual amplitude and inter-peak latency parameters obtained from short latency SEP and D-SEP cortical waveforms. These were recorded on test-1 (initial) and test-2 (retest) performed at two occasions separated by 17.5 weeks interval in the longitudinal follow-up period. No cortical sensory responses were recorded in response to stimulation at any lower limb dermatomes or mixed nerve sites on either side (completely absent responses to maximum electrical stimulation). *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 =* ***60 days (8.5 weeks).***							***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 =* ***182 days (26 weeks).***						
S4	**Acute**	***A***							***A***						
	T4	***Rt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***	***Rt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***
	Complete Paraplegia	***Am:***	--	--	--	*Absent*	*Absent*	*Absent*	***Am:***	--	--	--	*Absent*	*Absent*	*Absent*
45-yrs		***Lat:***	--	--	--	*N/A*	*N/A*	*N/A*	***Lat:***	--	--	--	*N/A*	*N/A*	*N/A*
	UL not Included here	***Lt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***	***Lt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***
Patient S4	**Complete Test x 2**	***Am:***	--	--	--	*Absent*	*Absent*	*Absent*	***Am:***	--	--	--	*Absent*	*Absent*	*Absent*
		Lat:	--	--	--	*N/A*	*N/A*	*N/A*	***Lat:***	--	--	--	*N/A*	*N/A*	*N/A*

Similar to the ERSP data obtained for Patient S3 shown in Figures 4.30 and 4.31, data from Patient S4 also demonstrated no evoked changes in EEG power identified on either test session, as in Figure 4.33 (**A**) and (**B**). This again is consistent with AIS sensory scoring of ASIA-A grade status with no indication of post injury recovery.

Nevertheless, there are widespread areas of hot spots (synchronisation) seen in ranges of high frequency in the power spectrum. It does not appear to be physiological or related response to the low-level electrical stimulation used here. In the same areas and frequency bands, there seem to be corresponding cold spots (desynchronisation) seen in the re-test performed after 175 weeks down the longitudinal follow-up period. These appearances on the ERSP maps are difficult to explain but it does not seem to be a physiological response and might be an artefact of some sort.

(A) :



(B) :

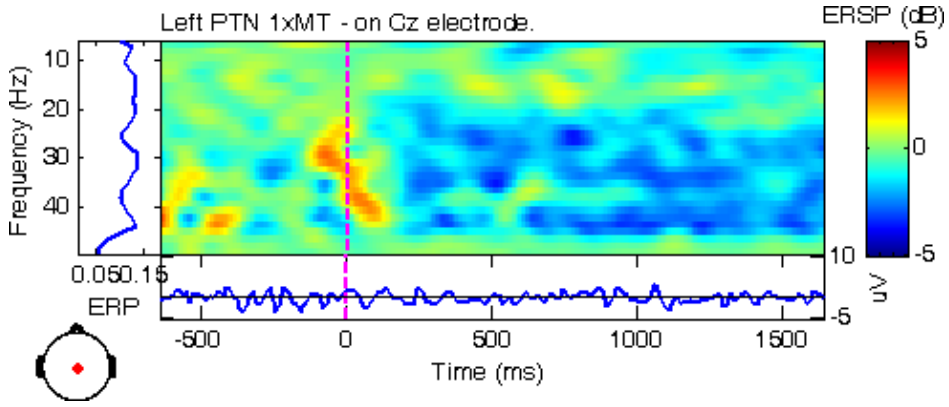
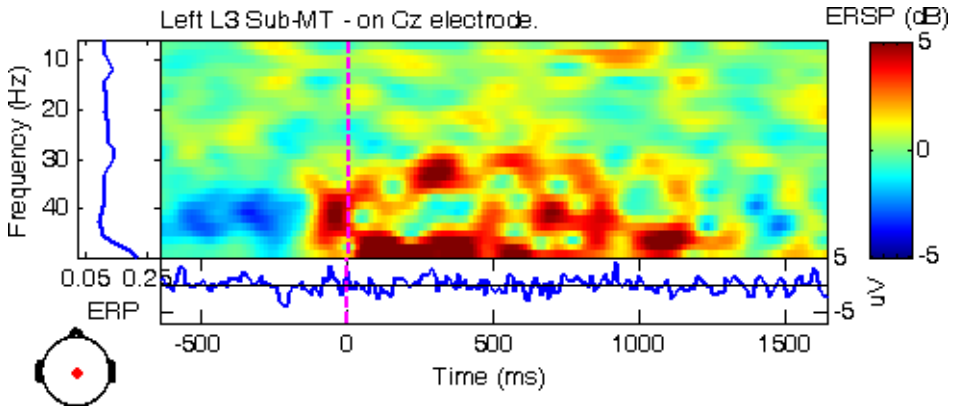


Figure 4.33 (A) and (B): shows ***initial*** and ***follow-up*** patterns of ERSP maps obtained from Patient S4, with SCI presenting with ASIA-A Complete T10 Paraplegia, using bi-polar montage recording of cortical responses at Cz electrode in response to slow graded electrical stimulation of the left PTN. There were no observed patterns of ERD bands described in relation to the normal ERSP patterns. Absence of the normal pattern of responses shaping ERSP maps was consistent for 'initial' test (A) and follow up 'retest' (B) performed 17.5 weeks apart down the longitudinal follow-up period. Patient S4 had no residual motor or sensory clinical function as measured on AIS. *Source:* Field work.

Similarly, ERSP from Patient S4 obtained from dermatomal stimulation of left L3 also demonstrated no evoked changes in EEG power on either initial test or follow up after 17.5 weeks, as shown in Figure 4.34 (**A**) and (**B**), consistent with AIS sensory scoring of ASIA-A grade status with no indication of recovery occurring post injury. The same pattern of hot spots (synchronisation) on initial ERSP map and blue cold spots (desynchronisation) on follow up ERSP are seen, with no obvious physiological explanation and are likely to be an artefact.

(A):



(B):

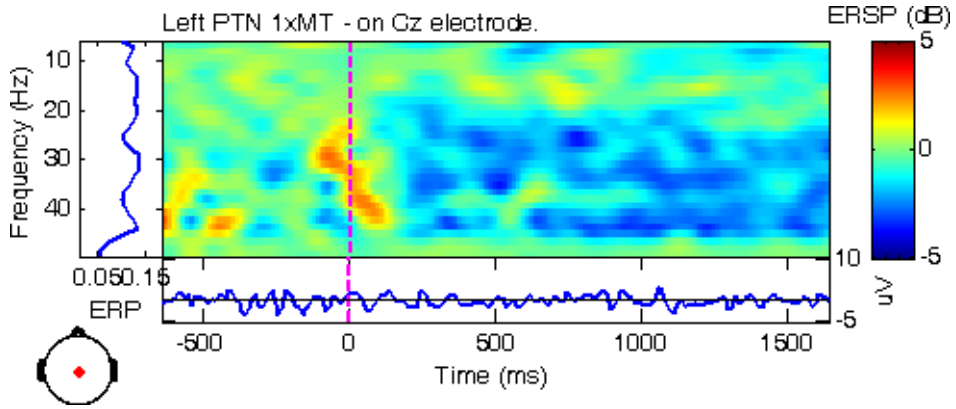


Figure 4.34 (**A**) and (**B**): shows patterns of ERSP maps from Patient S4 using bi-polar montage recording of Cz cortical responses to slow stimulation of left L3 dermatome. No observed ERD patterns as described in normal ERSP patterns, which is consistent for 'initial' (A) and follow-up (B) tests performed 17.5 weeks apart. *Source:* Field work.

4.7 Trans-cranial Magnetic Stimulation – Motor Evoked Potentials:

TMS of cerebral cortex at CZ (central) provoked no observable muscle response or measurable electrophysiological change (EMG activity) from lower limbs as monitored by right and left TA muscle EMG despite stimulation intensity reaching 90% of the maximum output. Again, this finding is consistent with complete ASAI-A SCI classification at test-1 and test-2 dates (see Figures 4.35 and 4.36).

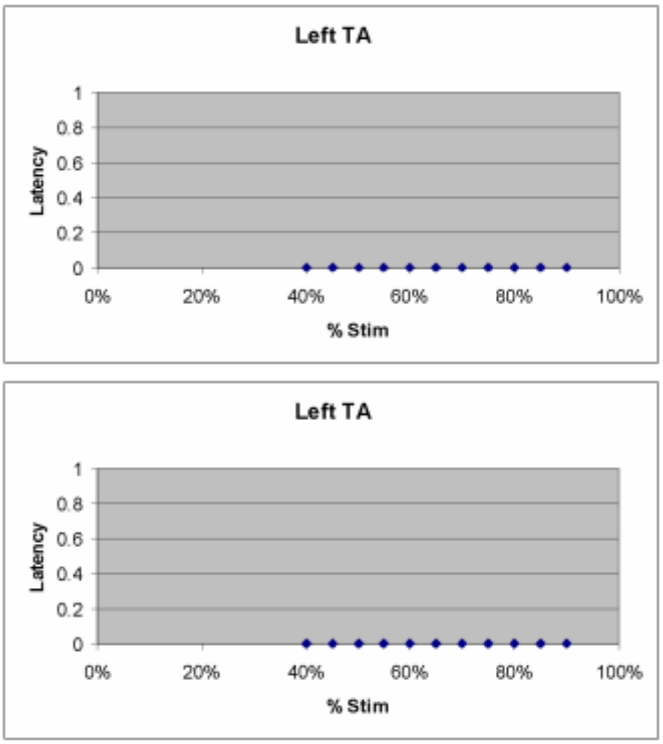


Figure 4.35: TMS at Cz cortical location showing no EMG responses from left TA muscle with no difference over 17.5 weeks from test-1 graph (**top**) to test-2 (**bottom**). *Source:* Field work.

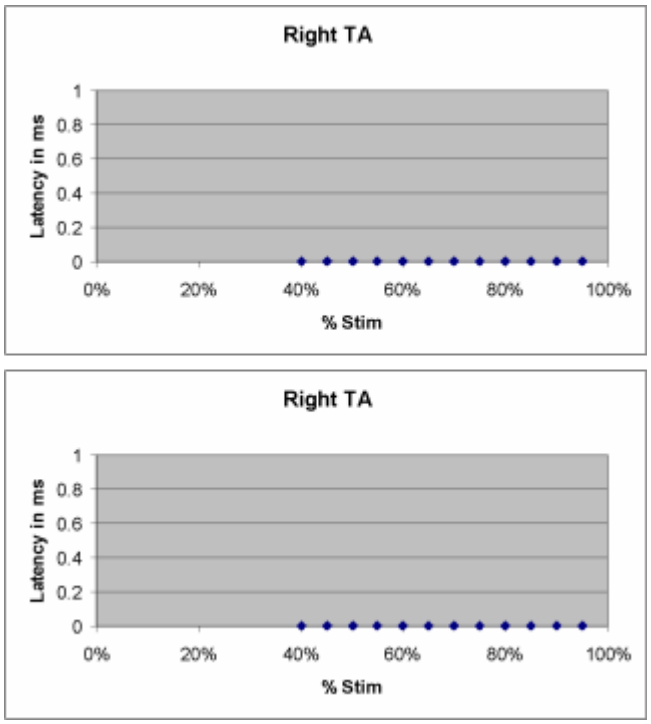


Figure 4.36: TMS at Cz cortical location shows no EMG responses from right TA muscle, not different after 17.5 weeks from test-1 graph (**top**) and test-2 (**bottom**). *Source:* Field work.

In this patient TMS induced MEP recordings made from left and right ED (ie above lesion level) muscles. The results showed normal latency characteristics with initial latency decreasing with increasing stimulation intensity (see Figures **4.37 A** and **B**).

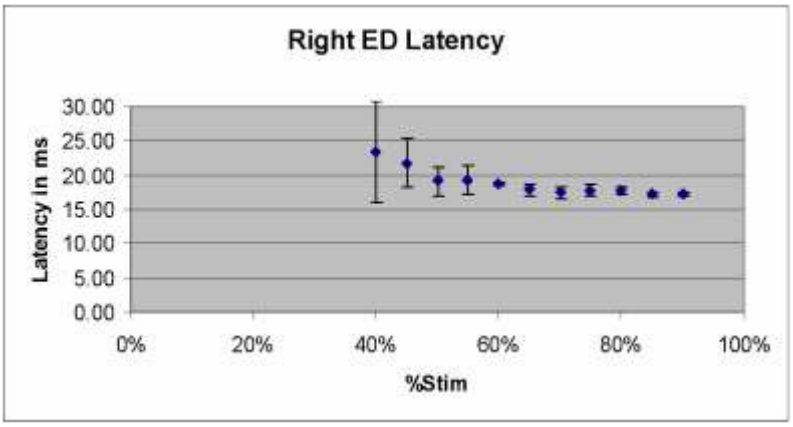


Figure 4.37 (**A**): shows MEP latency measurements for right ED muscle at test-1 (initial), displaying some mild decrement (shortening) of latency as stimulation intensity increases. *Source:* Field work.

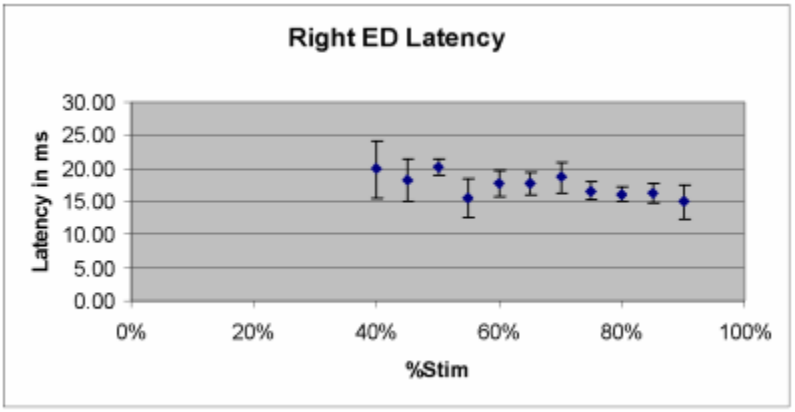


Figure 4.37 (**B**): shows MEP latency measurements for right ED muscle at test-2 (retest), displaying some mild decrement (shortening) of latency as stimulation intensity increases. *Source:* Field work.

However, the amplitude of the ED MEP at test-1 and test-2 did differ. In test-2, the rate of MEP amplitude increase with stimulation intensity is less than that observed in test-1 (see Figures 4.38), and the evoked response amplitude only reached a quarter of the size of the largest MEPs observed in test-1. This change in MEP recruitment/responsiveness was unexpected but most likely was the result of anti-spasticity medications depressing general CNS excitability.

A plausible explanation might be effects of medications (Both Diazepam and Baclofen were being prescribed and used at time of retesting). The muscle relaxant and excitability depressing effects of these drugs may therefore have produced a reduction in the responsiveness of the cortex and spinal cord to increasing levels of TMS stimulation.

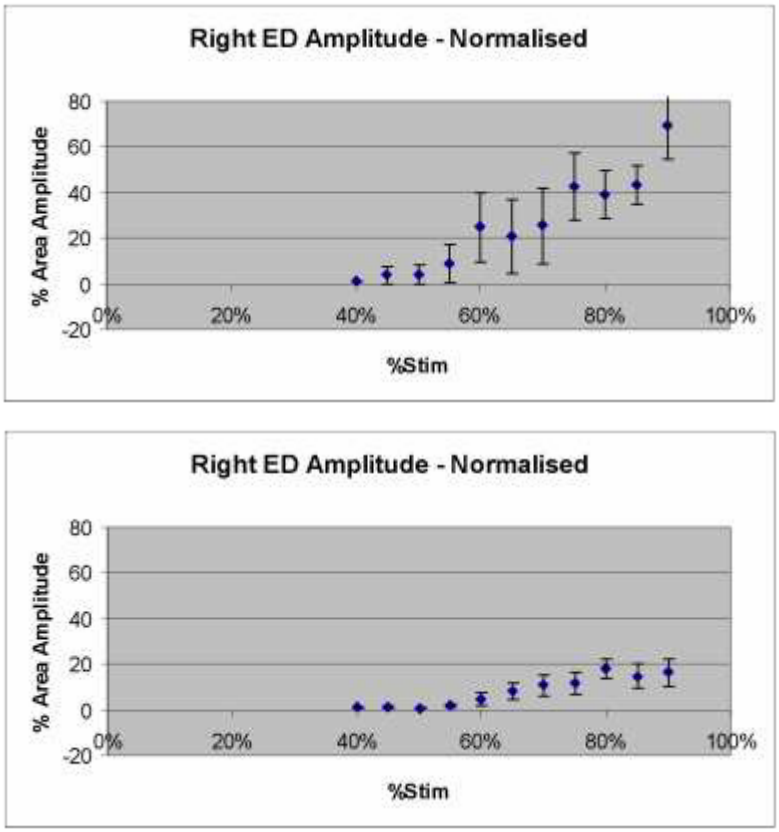


Figure 4.38 (**A**): shows MEP Amplitude measurements for right ED muscle at test-1 (**top** graph) and test-2 (**bottom** graph) displaying amplitude decreasing possibly due to drugs. *Source:* Field work.

4.7.1 Cortico-Muscular (EEG-EMG) Coherence – CMC:

As in patient S3 CMC tests could not be performed because no voluntary EMG signals could be recorded from either right or left TA muscles. This is consistent with the motor complete diagnosis, the lack of recovery and the negative MEP findings below the level of the injury. ASIA-A motor complete appears to be an accurate assessment of this patient's SCI clinical condition.

4.8 Interpretation of Electrophysiological Results (in light of clinical info)

The collective findings from all tests performed for Patient S4 an **ASIA-A Complete T4 Paraplegia** are concordant. **Clinically**, the patient showed no significant difference in the clinical assessment up to the time of discharge from hospital. The results of the **electrophysiological tests** performed **17.5 weeks** apart, show no residual/detectable or **measurable electrophysiological signals** in ascending (sensory) or descending (motor) pathways. This offers reasonable evidence to suggest that there is no factional **connectivity** in the spinal tracts examined by these electrical tests.

The patient sustained initial post-traumatic retrograde amnesia which might be related to an initial degree of intermittent cerebral dysfunction in relation to the known T7 mid-dorsal injury resulting in a neurological SCI level at T4. At the time of 'retest', medications were used to address various symptoms related to the initial SCI, secondary changes or neuro- modulation subsequent to the SCI. **Medications** including Diazepam (10mg once daily) and Baclofen (25mg four times daily) are recorded. The named medications potentially would affect any residual capacity to produce weak motor activation below the level of the injury but at no point did voluntary EMG activity become apparent during tests of coherence. MEP measures at above the level of the injury regressed over time. This observation is consistent with a drug action reducing the recruitment curve steepness but not the initial threshold. While this suggests care is needed in interpreting MEP data in cases where anti-spasticity drugs are used, there is no indication that similar actions on the sensitivity of EEG responses to sensory stimulation exist and that the lack of SEP and D-SEP waveforms is influenced by these medications. All sensory scoring below the level of the lesion remained zero for pain and light touch.

4.8.1 Group B – Patients with Incomplete SCI and No Measurable Recovery:

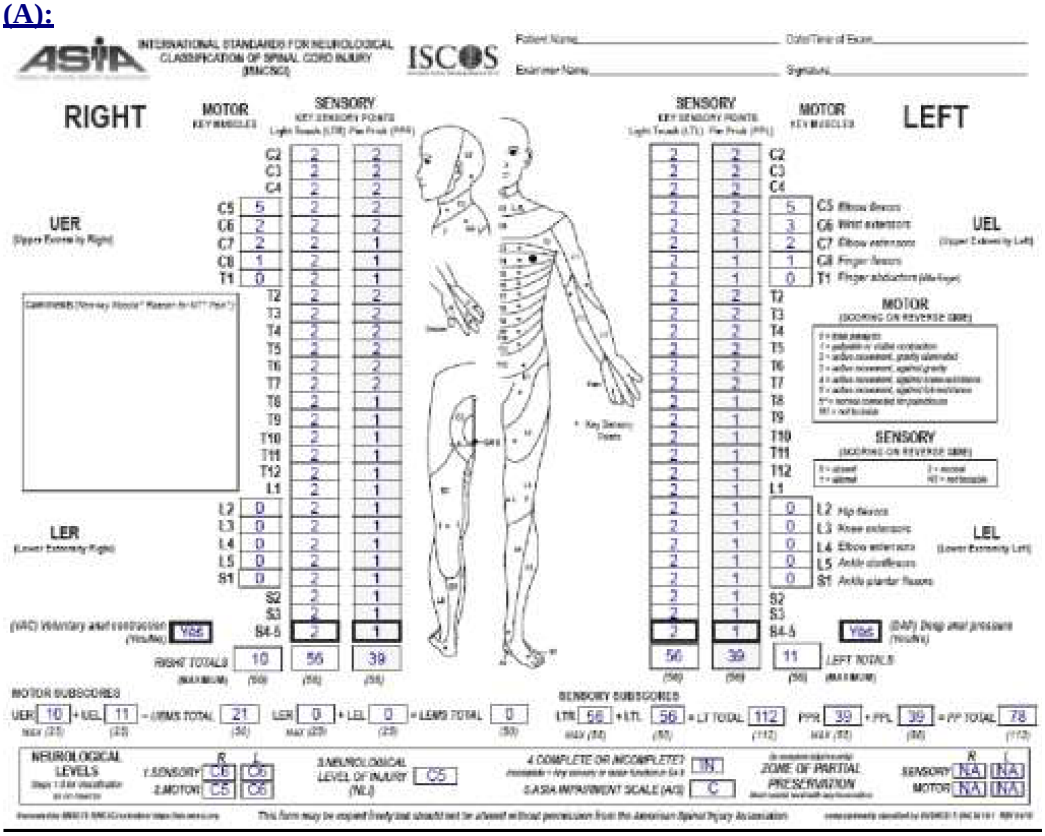
Patient S5 (ASIA-C Incomplete C5 Tetra-paresis):

Clinical Information:

- Patient: 24-years-old male.
- **Injury level** ASIA B –**Neurological** level was **C5**, **Injury level** C6
- Time Interval – **Injury to Test 1 'initial test'**: 79 days (11 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **C5 ASIA C**.
- Time Interval – **Injury to Test 2 'initial test'**: 182 days (26 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **C5 ASIA C**.
- Time Interval **– Test 1 to Test 2: 15 weeks**.
- Medications at time of Test 2:
  Distigmine 5mg x 3. Baclofen 25mg x 3.
- On Discharge: No significant difference in clinical assessment.
- Other information or comments: None.

Over the time interval of the 2 test dates, patient S5's AIS status remained as ASIA-C grade, as shown in figure 4.39 (**A**) and (**B**). Nevertheless, there are small grading improvements in motor scores and pin prick tests obtained from the upper limb musculature of the forearm, wrist and hand and dermatome bilaterally, as illustrated in colour charts shown in figures 4.39 **(C)** and **(D).**

(A):



(B):

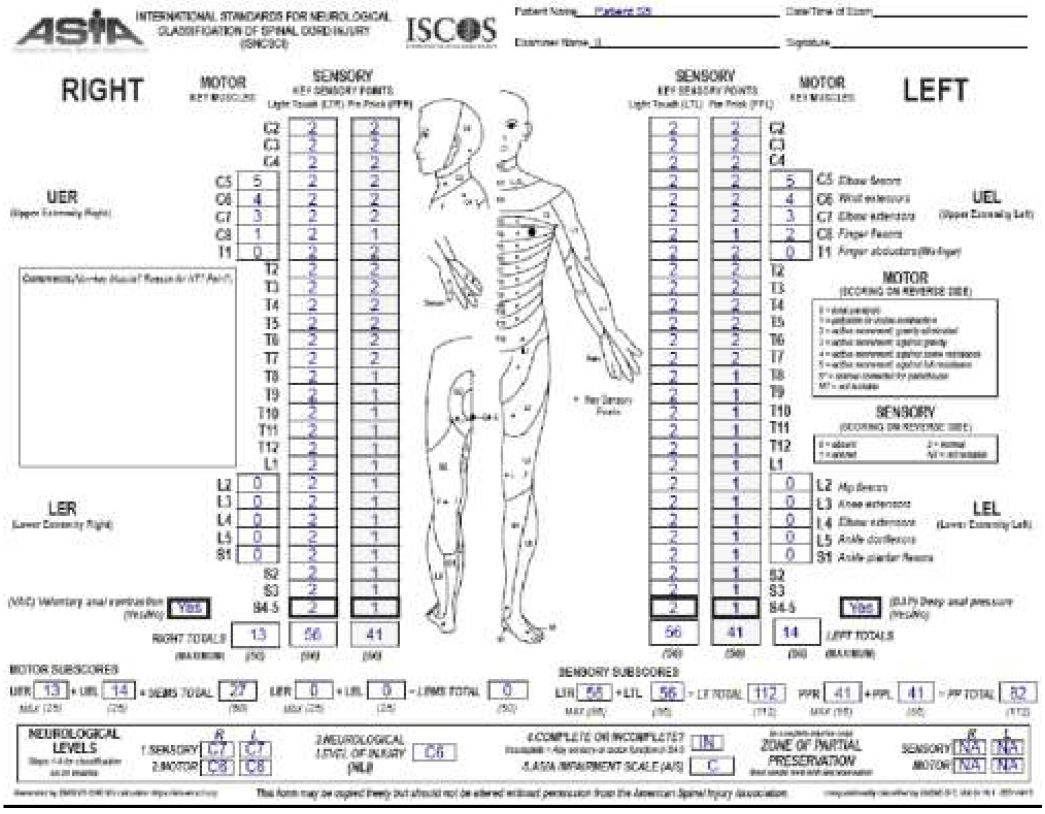
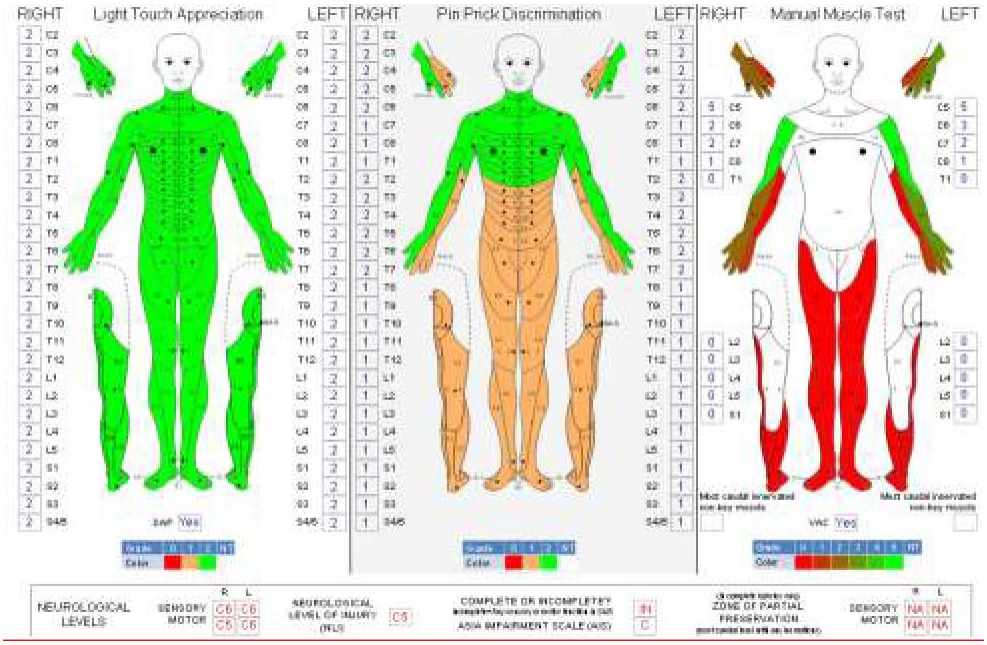


Figure 4.39 (**A**) and (**B**): shows ASIA Impairment Scale (AIS) for patients S5 at test-1 (**A**) and test-2 (B) examined 15 weeks apart. *Source:* Field work.

(C) **:**



(D):

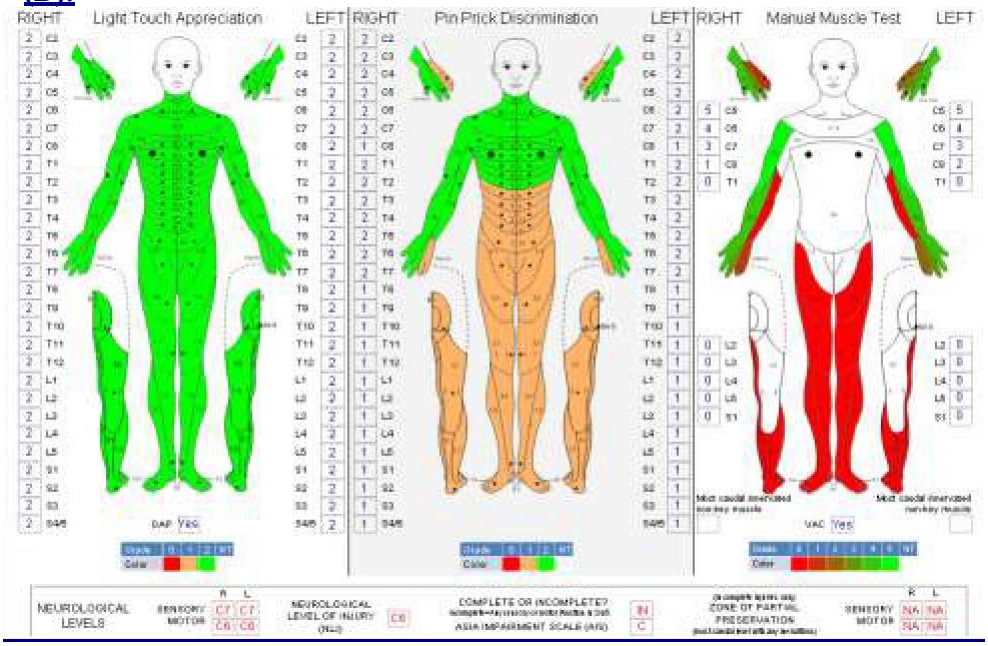


Figure 4.39 (**C**) and (**D**): shows cartoon illustrations of colour charts of the dermatomal maps related to sensory scoring values at test-1 (C) and test-2 (D) for patient S5. *Source:* Field work.

4.8.2 SEP & D-SEP (Waveforms & Lat-Amp Measurements):

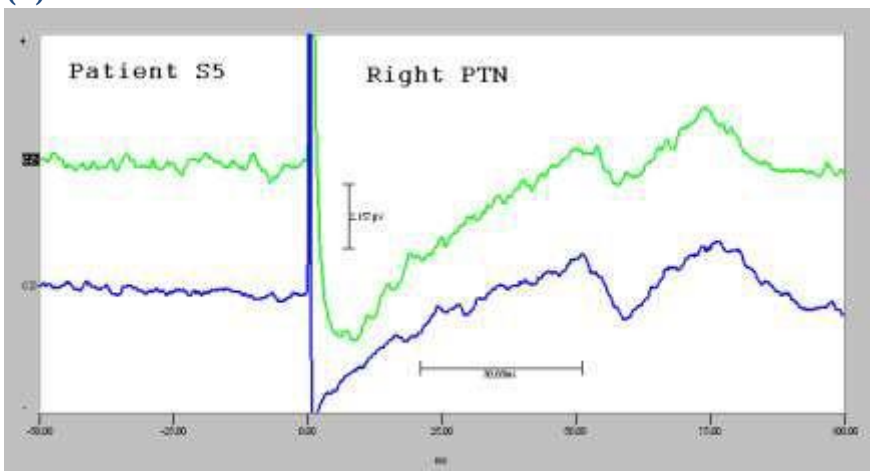
The patient and their SCI lesion showed no significant difference based on clinical assessment and no major variation on the functional outcomes. The sensory electrophysiological test results for this SCI patient (**ASIA-C Incomplete C5 Tetra-paresis**) are presented here. It is worth noting that at the time of retesting the patient was medicated with Diazepam and Baclofen. Parameters of SEP and D-SEP waveforms from upper and lower limb stimulation sites are shown and detailed in Table 4.11. These data show that upper limb SEP and D-SEP averages were observable for all test sites apart from left and right L2 and L3 D-SEPs on the test-1 and absent only from left L2, L3 D-SEPs sites at the time of test-2. In general, amplitudes of SEP responses were reduced when comparing the 2^{nd} test to the 1^{st} test. However, SEP latencies were largely unchanged. For upper limb D-SEPs there is also no consistent pattern of change. In the main, signals appear to become larger on the patients' right side but the opposite appears to be the case on the left-hand side of the body. This would suggest differential changes in conduction through sensory pathways on left and right sides but there is no evidence of this linking to any perceptual differences for light touch based on ASIA scores (see cartoons and charts on Figures 4.39 (**A**) and (**B**), then (**C**) and (**D**), respectively).

Table 4.11: shows details of values of measured actual amplitude and inter-peak latency parameters obtained from short latency SEP and D-SEP cortical waveforms. These were recorded on test-1 (initial) and test-2 (retest) performed at two occasions separated by 15 weeks interval down the longitudinal follow-up period. Cortical sensory responses were recorded in response to stimulation at upper and lower limb dermatomes or mixed nerve sites on either side, with obtained measurements are tabulated and detailed. *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 =* ***79 days (11 weeks).***	***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 =* ***182 days (26 weeks).***
S5	**Acute / Sub-acute**	***C***	***C***
		Rt: C5 C6 Med L2 L3 PTN	***Rt: C5 C6 Med L2 L3 PTN***
	C5	***Am:*** *0.36 1.03 3.19 Absent Absent 0.59*	***Am:*** *0.74 1.06 0.52 0.11 0.12 1.02*
24-yrs	Incomplete Tetraplegia	***Lat:*** *25.40 23.70 20.60 qN/A N/A 47.40*	***Lat:*** *29.60 23.10 23.10 41.70 36.40 42.50*
		Lt: C5 C6 Med L2 L3 PTN	***Lt: C5 C6 Med L2 L3 PTN***
Patient-5	**Complete Test x 2**	***Am:*** *0.31 0.97 2.62 Absent Absent 0.64*	***Am:****. 0.50 0.63 02.30 Absent Absent 0.52*
		Lat: *31.10 23.30 19.70 N/A N/A 40.80*	***Lat:*** *42.10 24.20 21.80 N/A N/A 41.30*

Figures 4.40 (**A**) and (**B**) show waveforms from which values of actual amplitude and inter- peak latency parameters were measured and shown in table 4.11. Waveforms were recorded in response to stimulation of lower limb dermatomes or mixed nerve sites on right and left sides at time of initial test-1 (**A**) and follow-up test-2 (**B**) performed 15 weeks apart during the longitudinal follow-up. The resulting cortical sensory responses were recorded from contra-lateral scalp electrodes, with small dispersed and delayed SEP for the right PTN stimulation, but this is completely absent for the right L3 D-SEP. The findings on this SEP and D-SEP studies are in keeping with the lack of any significant clinical recovery seen on sensory or motor scoring using AIS assessment parameters.

(A) :



(A):

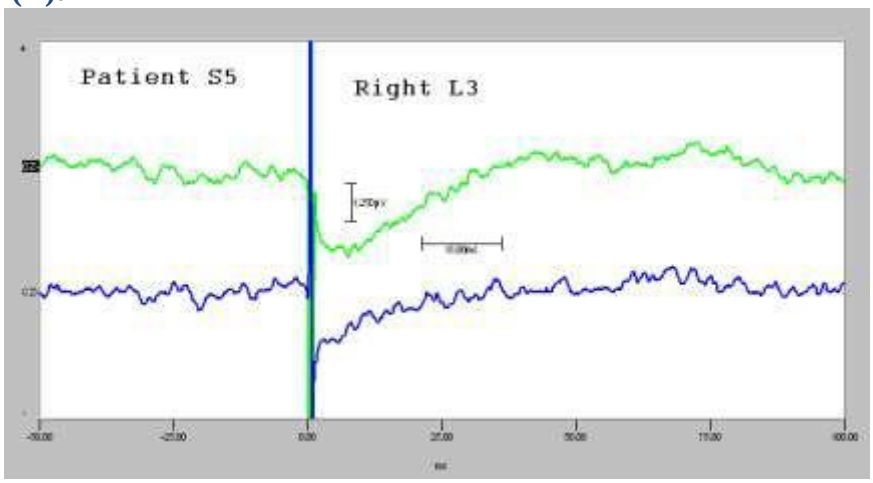


Figure 4.40 (**A**) & (**B**): shows averaged SEP and D-SEP waveform recordings of right PTN and right L3 dermatome, respectively, obtained from Patient S5. The **green** traces represent test-1 and **blue** represents test-2 performed **15 weeks** apart. Small dispersed & delayed SEP of right PTN is shown but with no measurable D-SEP response seen from the right L3 dermatome. *Source:* Field work.

Similar findings are seen on the left side nerves and dermatomes, as well as upper limb nerve and dermatomal stimulation, with no measurable electrophysiological changes in keeping with ASAI-A complete SCI with no observable functional recovery (figures not shown).

4.8.3 ERSP (Spectral Maps for Slow Sensory Stimulation):

ERSP maps for this patient at test-1 and test-2 reflect a 15-week interval but largely remained unchanged. For instance, Figure 4.41 shows C5 D-SEP responses at test-1 and test-2 with no significant visible changes in the EEG spectrum. The baseline D-SEP waveform measurements showed minimal recovery of amplitude (from 0.31 to 0.5mV) but a delayed latency (from 31.1 to 42.1ms) but the ESRP approach in this case provided no valuable information on changes occurring over the testing interval. As mentioned previously it is worth nothing than the C5

results for light touch were considered as normal on first and second test dates.

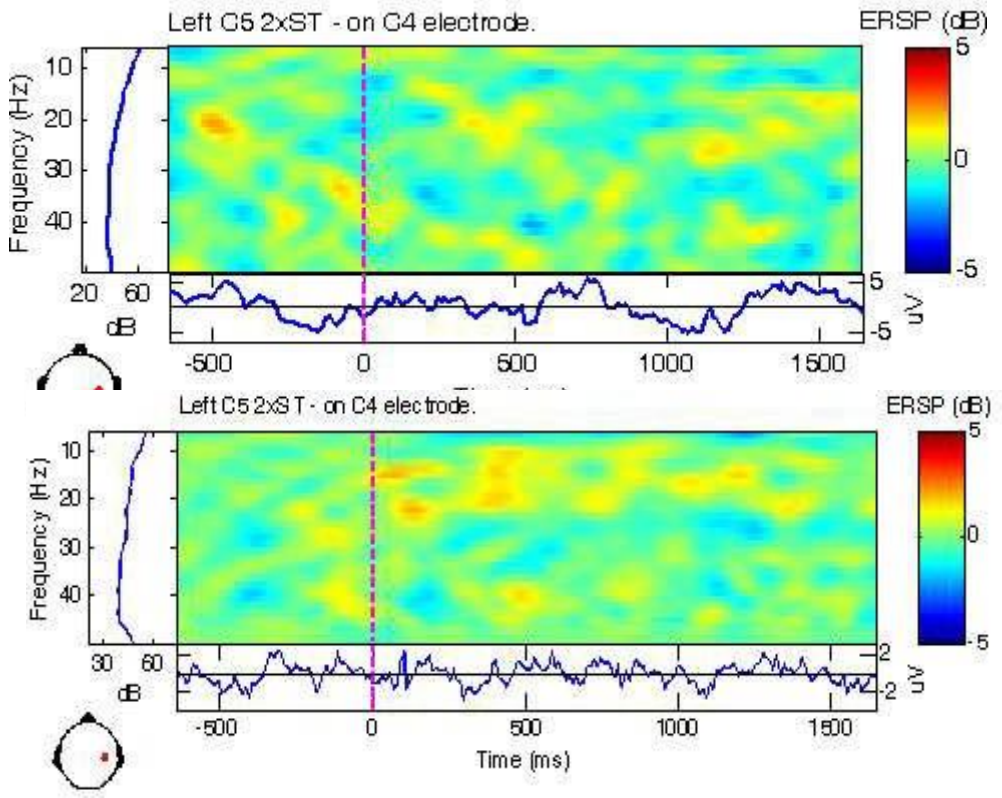


Figure 4.41: Shows an example of upper limb D-SEP (C5) at test-1 (**top** ERSP map) and test-2 result (**bottom** ERSP map) repeated after 15-weeks along the longitudinal follow-up time period, with no demonstrable EEG spectral changes seen in the ERSP map. *Source:* Field work.

In other instances, minor EEG spectral changes were observable ERSP maps performed for this patient **15 weeks** apart. For instance, Figure 4.42 (**A**) shows left Median ERSP at test-1 with no defining features, while at test-2 EEG spectral changes take a pattern with mild de-synchronisation at alpha and beta bands of EEG at 200-600ms of stimulation onset. Similarly, in Figure 4.42 (**B**), it seems the left PTN ERSP map began to display features of normal ERSP pattern (compare with normal PTN ERSP pattern in figure 4.17). These observations of a more normal ERSP pattern emerging on the left side are suggestive of adaptation occurring over time but while consistent with the patient's sensory scoring are not easy to reconcile with the amplitude and latency data from SEP and D-SEP analysis. The remaining ERSP maps are in the appendix, but these show no significant features changing over time.

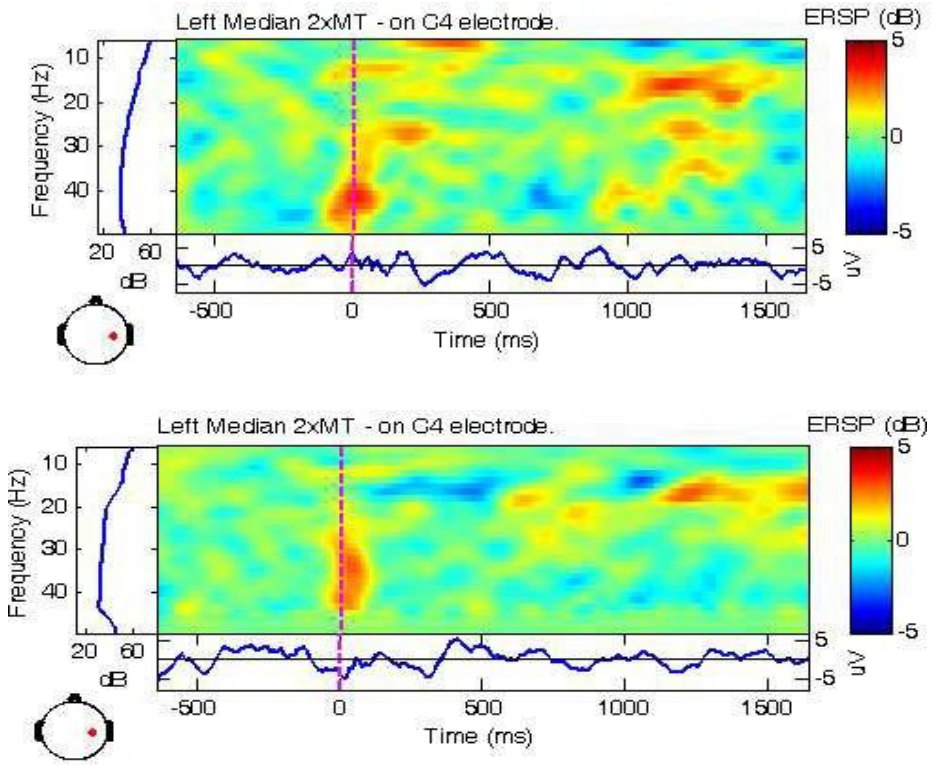


Figure 4.42 (**A**): Shows left Median SEP at test-1 (top map) with no specific features and test-2 (bottom map) performed 15-weeks later showing early organisation of pattern of de-synchronisation in alpha and beta bands at 200-600ms starting to simulate the normal. *Source:* Field work.

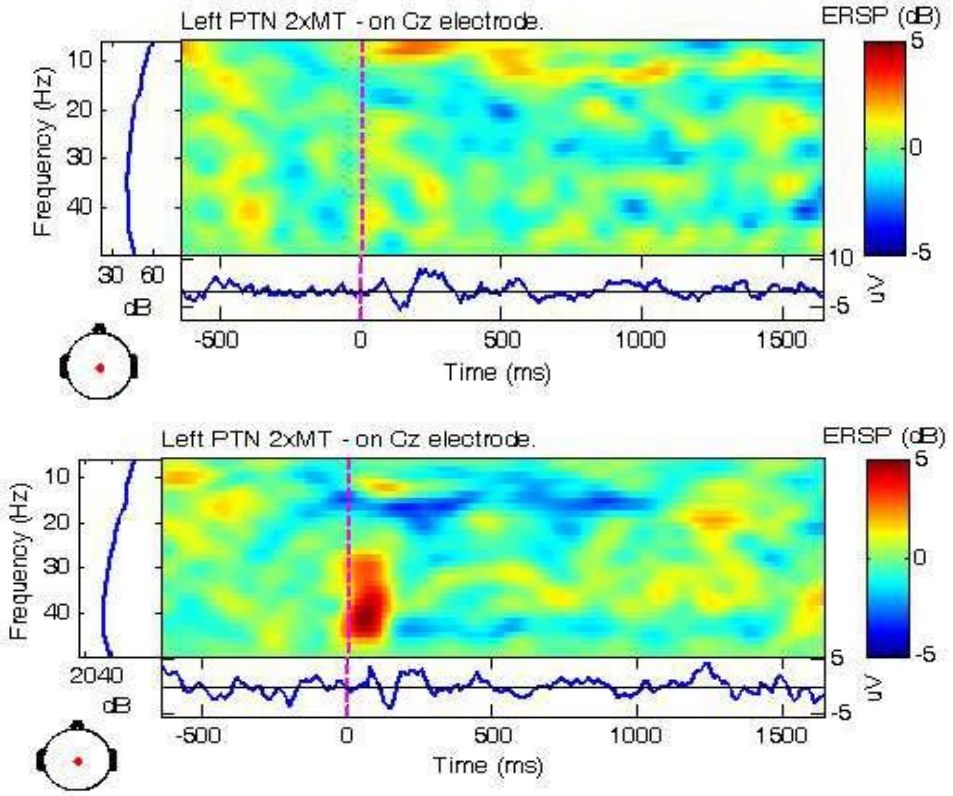


Figure 4.42 (**B**): Shows left PTN SEP at test-1 (top map) and test-2 (bottom map):

Source: Field work.

4.9 Trans-cranial Magnetic Stimulation – Motor Evoked Potentials: In this subject TMS of cerebral cortex was applied at sites over cortical areas normally activating the target limb muscles. In Figures 4.43 (**A**) and 4.43 (**B**), MEPs from ED recordings are shown for test-1 and test-2 recording sessions, respectively (interval = 15 weeks). Figure 4.43 shows MEP latency measurements, for left ED muscle in response to TMS, with recordings from test-1 (blue) and test-2 (purple). The recordings were overlapped to show changes in latency, with shortening of latency (coming quicker), which is statistically significant.

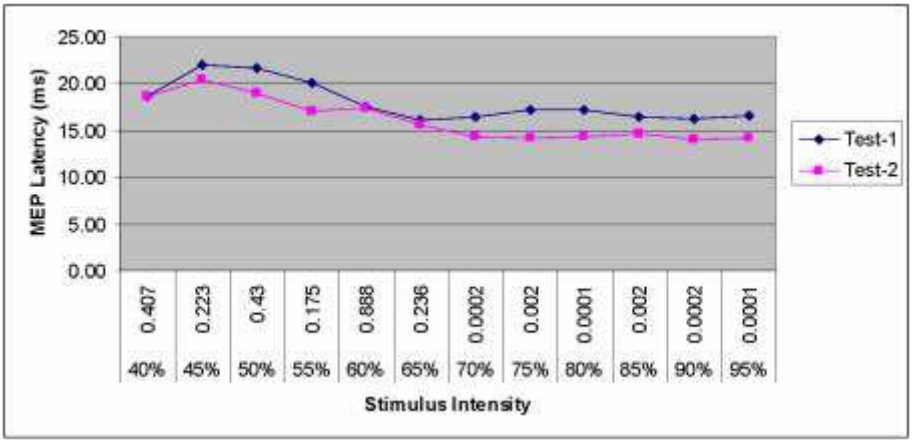


Figure 4.43 (**A**): MEP responses from EMG recording of left *Extensor Digitorum* (ED) muscle in response to TMS at C4 electrode on contra-lateral motor cortex. Two tests were performed separated by 15 weeks follow-up interval. MEP Latencies calculated at stimulation intensities for test-1 and test-2 from 40% to maximum tolerated. It is seen that over 65%, shortening of onset latency reached statistical significance with shift and early (quicker) arrival of the MEP responses at 'retest' for the same testing parameters. *Source:* Field work.

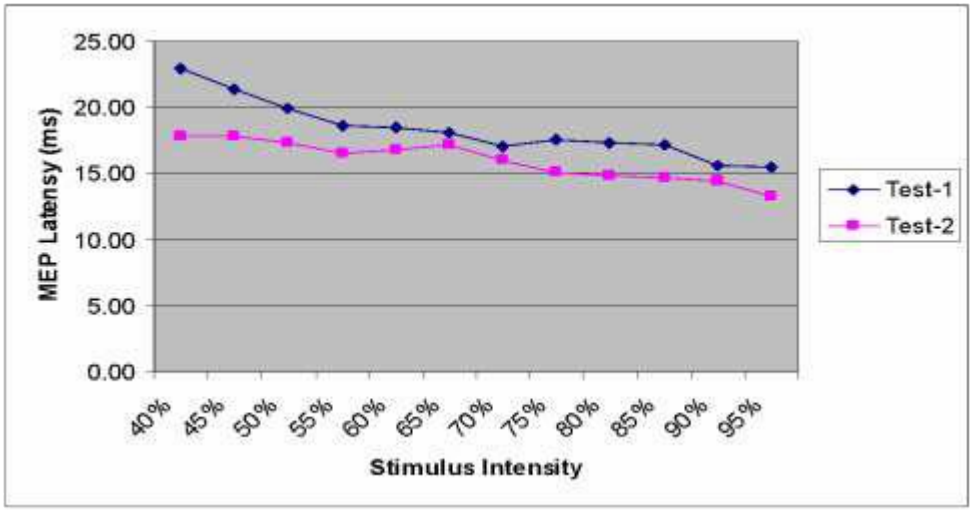


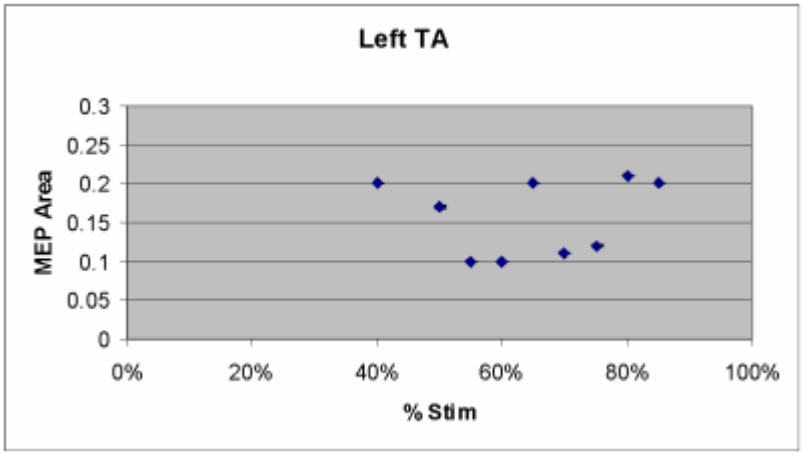
Figure 4.43 (**B**): MEP responses obtained from right ED muscle in response to TMS at C3 electrode at test-2 performed 15 weeks after test-1. Shortening of latency at test-2 is seen reaching statistical significance at most stimulation intensities, as indicated by 'P' values. *Source:* Field work.

During both test sessions, left and right MEPs show a reducing latency with increasing strength of TMS stimulation. Values of the MEP latency measurements for ED muscle obtained from this patient's upper limbs were in the range (22.0-18.6ms) using TMS at low stimulation intensities and (16.6-14.1ms) using high stimulation intensities. These values are slightly longer than normal ED MEP (15.86ms) latencies from health volunteers.

TMS also was used to evoke MEPs in right and left *Tibialis Anterior* (TA) muscles by placing the coil over the vertex (Cz). Figures 4.44 (**A**) and Figure 4.44 (**B)** show recordings made at initial test-1 and test-2 15 weeks later. It is worth noting that for S5 the motor score for left and right ankle dorsiflexion was zero (0) on both test dates.

For left and right EMG recordings, the MEPs demonstrate measurement findings, which are similar to the ED latency. These latencies tend to shorten with increasing stimulation intensities above motor threshold. However, the area data show inconsistent recruitment characteristics, suggesting abnormal behaviour in the corticospinal pathways. For the left TA there is no amplitude growth in area of MEP with increasing stimulation intensity despite the reduction in latency measurements. This abnormal recruitment curve pattern was not seen in the initial right TA where the MEP area increased with increasing stimulation intensity during test 1. However, this recruitment curve flattened when the retest was performed at 15 weeks later.

Test-1



Test-1

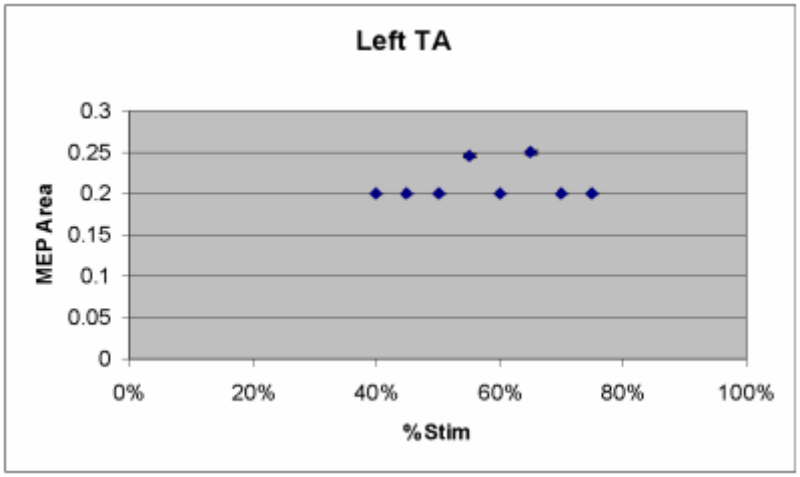
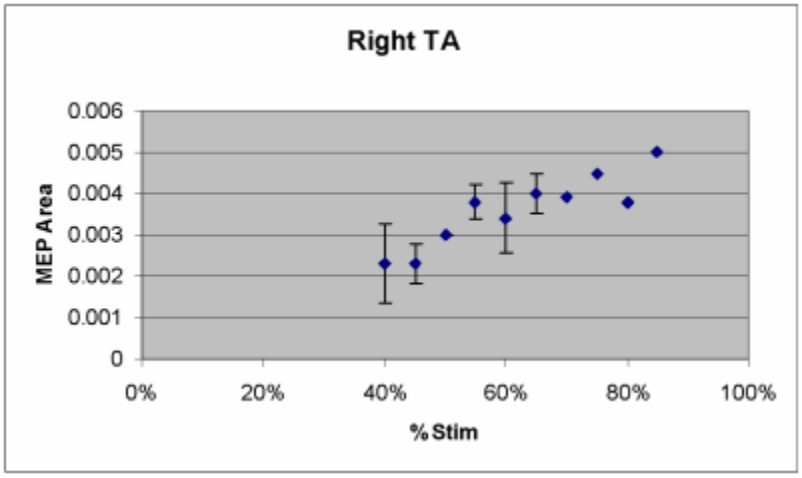


Figure 4.44 (**A**): MEP amplitude responses from EMG recording of left TA muscle in response to TMS at Cz electrode on motor cortex. Two tests were performed 15 weeks apart during follow-up. MEP Amplitudes calculated at stimulation intensities for test-1 (top) and test-2 (bottom) from 40% to maximum tolerated. Left TA amplitude shows no growth in the area amplitude of the MEP with increasing stimulation intensity despite reduction in latency. *Source:* Field work.

Test-1



Test-2

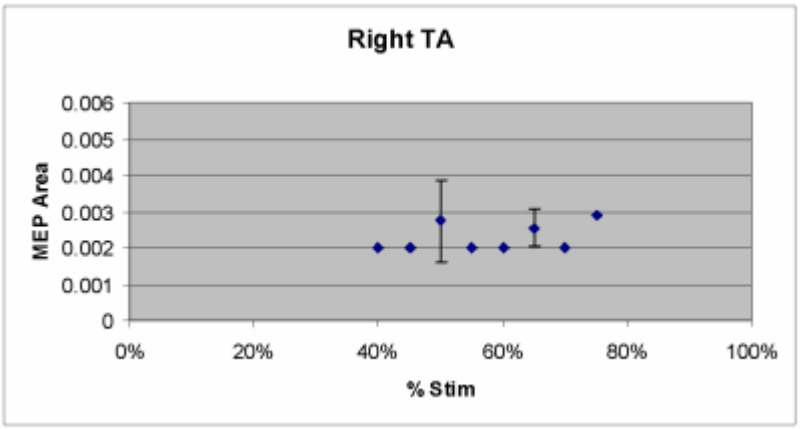


Figure 4.44 (**B**): MEP amplitude responses from EMG recording of right TA muscle in response to TMS at Cz electrode on motor cortex. Two tests performed 15 weeks apart during the follow-up, with MEP Amplitudes calculated at stimulation intensities for test-1 (top) and test-2 (bottom) from 40% to maximum tolerated. MEP area increases with increasing stimulation intensity at **test-1** however recruitment curve flattened at **test-2** 15 weeks later. *Source:* Field work.

MEP measurements were obtained from EMG recordings of the left Tibialis Anterior (TA) muscle in response to TMS at Cz cortical electrode at two testing occasions separated by 15 weeks along the follow-up interval. MEP Latencies were calculated at different stimulation intensities for the initial test-1 and test-2 from 40% to maximum tolerated. Onset latencies reached statistical significance with shift (early arrival) of the MEP responses at some stimulation intensities on test-2 as shown in Figure 4.45 (**A**) using the same standard testing parameters. On the other hand, MEP responses obtained from right TA muscle in response to TMS at Cz electrode at test-2 performed 15 weeks after test-1. None of the visually apparent shortening of MEP latencies at test-2 reached statistical significance as in Figure 4.45 (**B**).

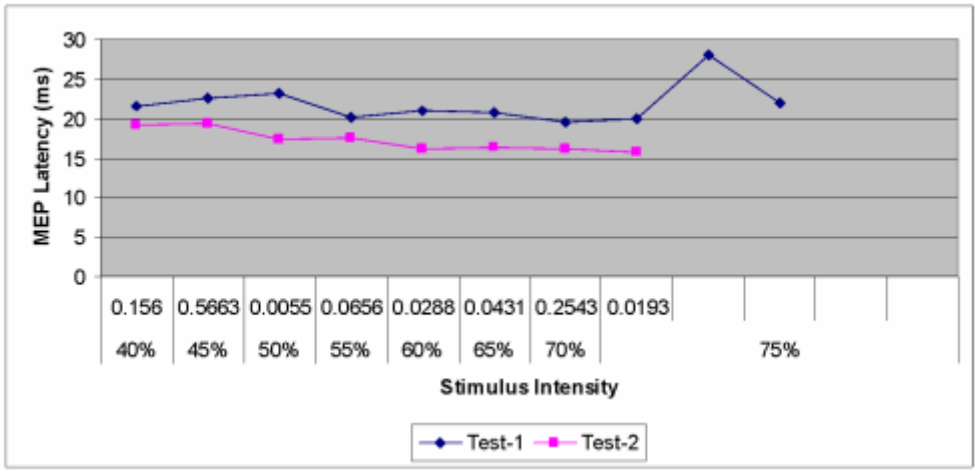


Figure 4.45 (**A**): MEP measurements from EMG recordings obtained from the left Tibialis Anterior (TA) muscle in response to TMS at Cz cortical electrode at two testing occasions separated by 15 weeks follow-up interval. MEP Latencies were calculated at different stimulation intensities for test-1 and test-2 from 40% to maximum tolerated. Onset latencies reached statistical significance with early shift (quicker arrival) of MEP responses at some stimulation intensities on test-2 (same standard testing parameters). *Source:* Field work.

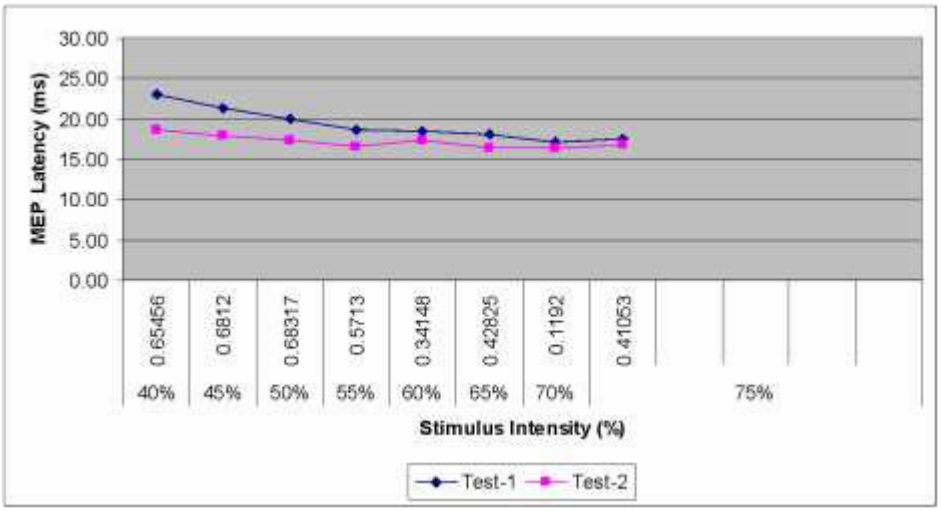


Figure 4.45 (**B**): Similarly, MEP responses obtained from right TA muscle in response to TMS at Cz electrode at test-2 performed 15 weeks after test-1. None of the visually apparent shortening of MEP latencies at test-2 reaches statistical significance. *Source:* Field work.

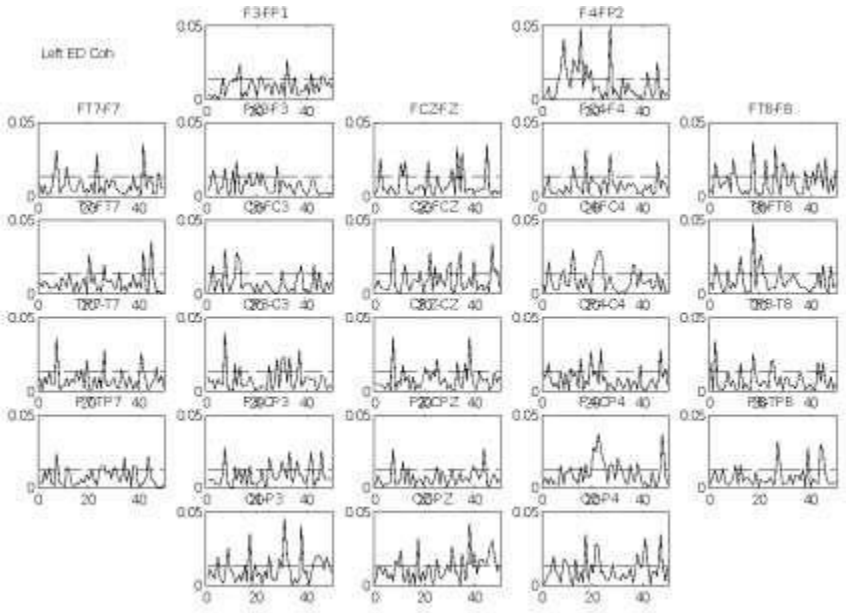
At test-1, the MEP latency was zero (0) in the right and left TA, and remained the same when tested 15-weeks later. The patient remained unable to generate voluntary EMG however TMS generated an EMG response. It would seem likely that the positive MEP demonstrated residual corticospinal connectivity. However, functionally (from clinical point of view), this has not been utilised to generate voluntary actions measured by motor scores (manual and visual) remaining zero (0). Furthermore, the lack of a well-defined recruitment curve for upper and lower limb MEPs would be in keeping with abnormal function of the corticospinal tracts.

4.10 Cortico-Muscular (EEG-EMG) Coherence – CMC:

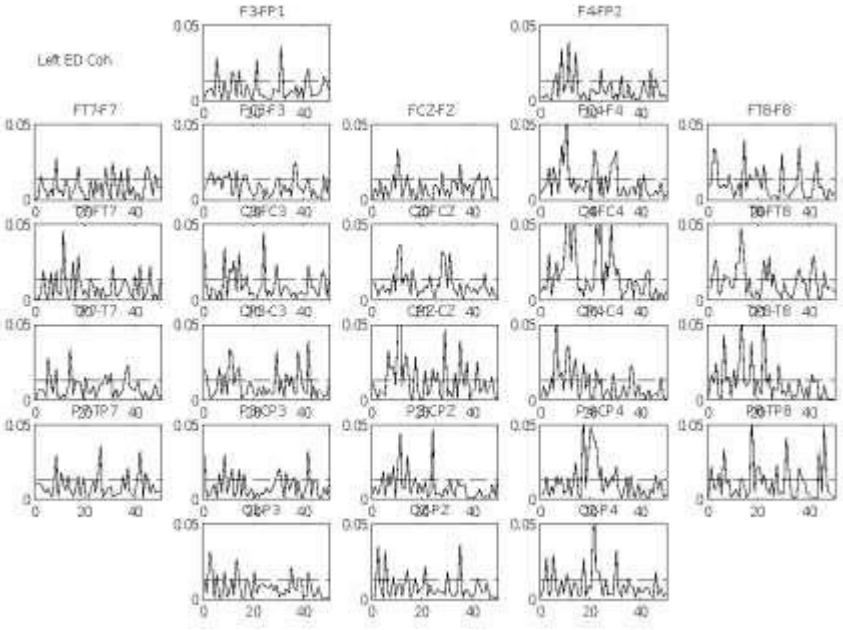
CMC estimates were obtained from simultaneous EEG and EMG (from left and right ED wrist muscle) recordings made during test-1 and test-2 sessions, only shown in Figure 4.46 (**A**) and (**B**) for ED muscles, as no voluntary EMG activity could be generated in TA muscles.

While interpretation of this data is difficult there appear to be some gross changes that can be commented upon in relation to left and right ED data sets. In test 1 data, very little significant coherence can be identified between EMG signals and the EEG electrodes placed over the contralateral scalp area. When repeated 15 week later a new pattern of coherence has emerged and shows stronger coupling occurring between the left ED and right cortical recordings.

When looking at the equivalent data for the right ED the change is not so apparent but contralateral EEG/EMG coherence can be observed in both test datasets.

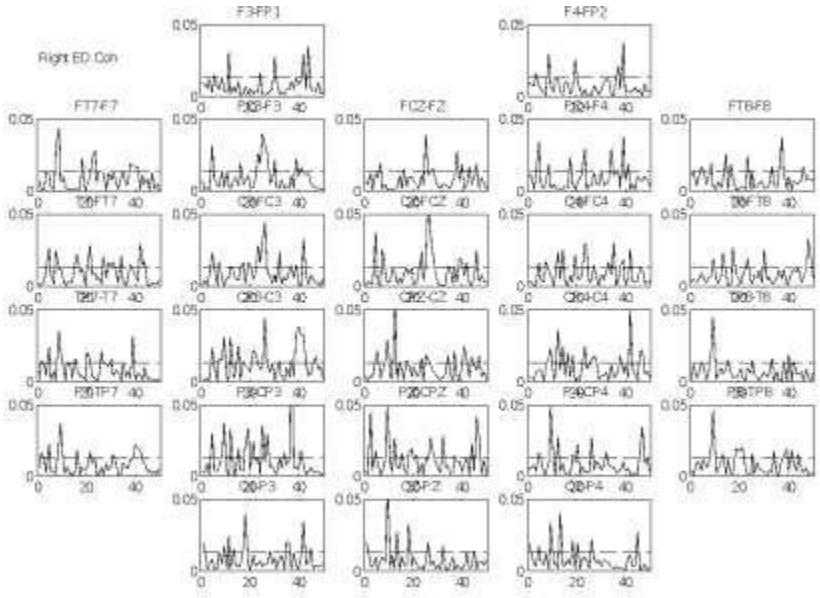


Test-1

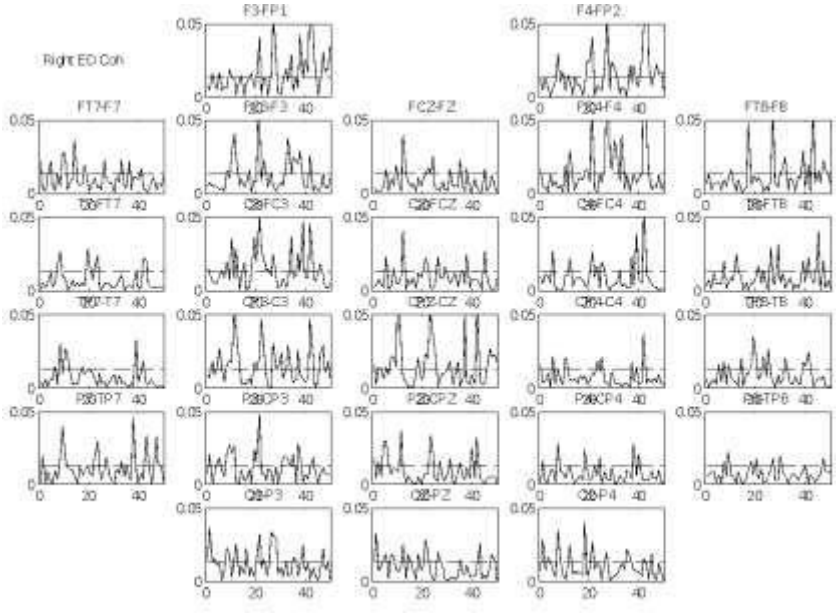


Test-2

Figure 4.46 (**A**) shows CMC maps performed for EEG and EMG from left ED muscle during voluntary contraction. The initial test-1 (**top**) shows variable areas coherence inconsistent with the usual pattern, however this becomes more organised over right cortical areas at test-2 (**bottom**). *Source:* Field work.



Test-1



Test-2

Figure 4.46 (**B**) shows CMC maps performed for right ED muscle during voluntary contraction, showing initial test-1 (top) and test-2 (bottom), however with no apparent coupling changes to be observed apart from usual accompanying EMG activity. *Source:* Field work.

4.11 Comments/Interpretation of Electrophysiological Results (in light of clinical info):

Clinically, patient S5 (AIS - C Incomplete C5 Tetraparesis) showed no significant change in clinical assessment up to the time of discharge from hospital, scoring no difference in AIS grading. Pin prick and light touch scores on left and right remained largely unchanged.

Motor scores showed minimal change in the upper limbs increasing from 10 to 13 for the right arm and 11 to 14 for the left arm. Scores of zero (0) were reported for all lower limb tests on both testing dates.

Results of objective tests despite no change in light touch scores for upper and lower limb dermatones L2 and L3 DSPs remained absent on the left side but emerged over the interval between tests on the right side. There was no consistent pattern to changes in sensory evoked responses and no clear relation between these observations and the lack of qualitative reports of changes in light touch perception (quality or location) by the patient.

On the results of motor examination, the MEP latency measurements show latency reductions with increasing stimulation strength but show abnormal recruitment curves. While this is indicative of a disruption to the corticospinal pathway, the identification of measurable MEPs is strongly suggestive that a pathway exists, but could not be utilised in a way that could support

voluntary voluntary EMG generation in this patient.

Patient S5 was taking Distigmine (5mg x 3) and Baclofen (25mg x 3) at the time of test-2. This needs to be considered when interpreting test results especially in relation to SEP and D- SEP proximal propagation, cortical processing, CMC calculation and MEP changes.

4.11.1 Patient S7 (ASIA-D Incomplete C5 Tetra-paresis)

Clinical Information:

- Patient: 55-years-old male.
- **Injury level**: C5 ASIA C
- Time Interval – **Injury to Test 1 'initial test'**: 70 days (10 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **C5 ASIA D**.
- Time Interval – **Injury to Test 2 'initial test'**: 140 days (20 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **C5 ASIA D**.
- Time Interval **– Test 1 to Test 2: 10 weeks**.
- Medications at time of Test 2:

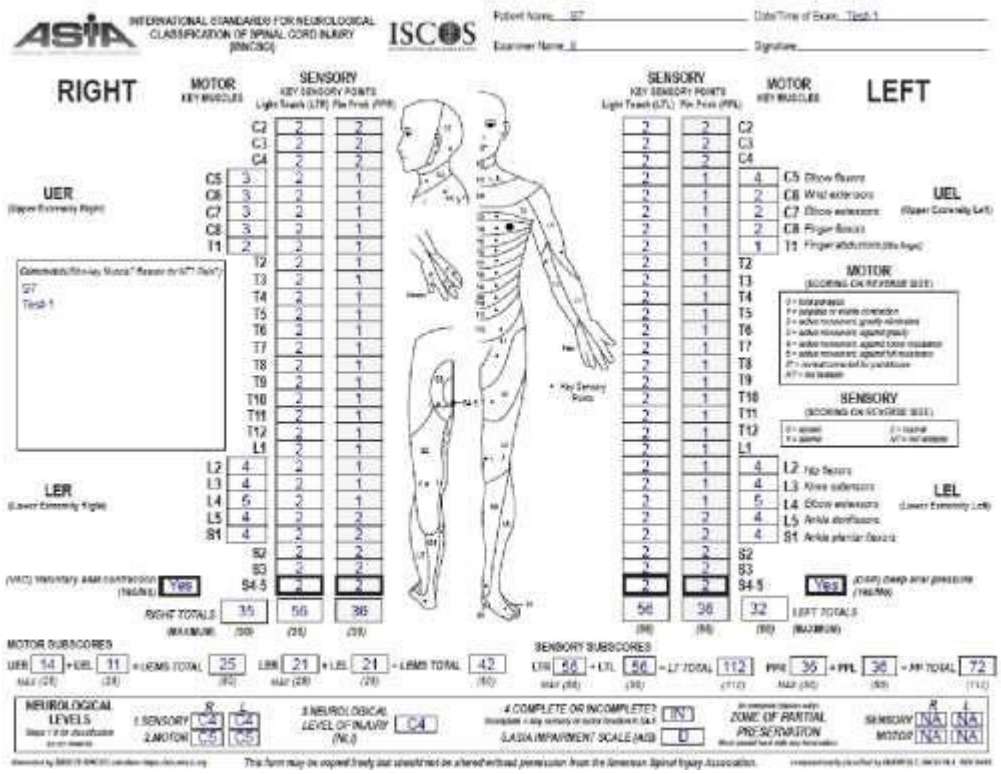
  Gabapentine 400mg 3 times a day. Tramadol 100mg at night.

  Baclofen 20mg three times a day. Imipramine 20mg at night.
- On Discharge: Marked improvement in functional abilities including: sitting and standing balance, walking and increased sensory perception.
- Other information or comments: None.

For this subject the ASIA charting tools reveal changes in scoring over the time between the first and second testing dates (interval 10 weeks) in sensory and manual muscle power tests in parallel there are observational improvement in motor behaviour. Yet the charting tool changes are not sufficient to change AIS status from D seen in Figure **4.47** (**A**) and (**B**), and sensory charts seen in Figure **4.47** (**C**) and (**D**).

The clinical presentation of the patient and the consequences of the SCI lesion **showed that improvement occurred over 10-week time course of the testing intervals.** From a functional perspective the patient experienced marked **improvement in balance** and gait (sitting, standing and walking) and **improved sensory level**. At the time of test-2, this patient was taking Gabapentine 400mg x 3, Tramadol 100mg x 1, Baclofen 20mg x 3 and Imipramine 20mg x1. These are drugs which are known to cause suppression of afferent signalling, reduced cortical responses including EEG; and this may be a factor that influences the neurophysiology data.

(A):



(A) :

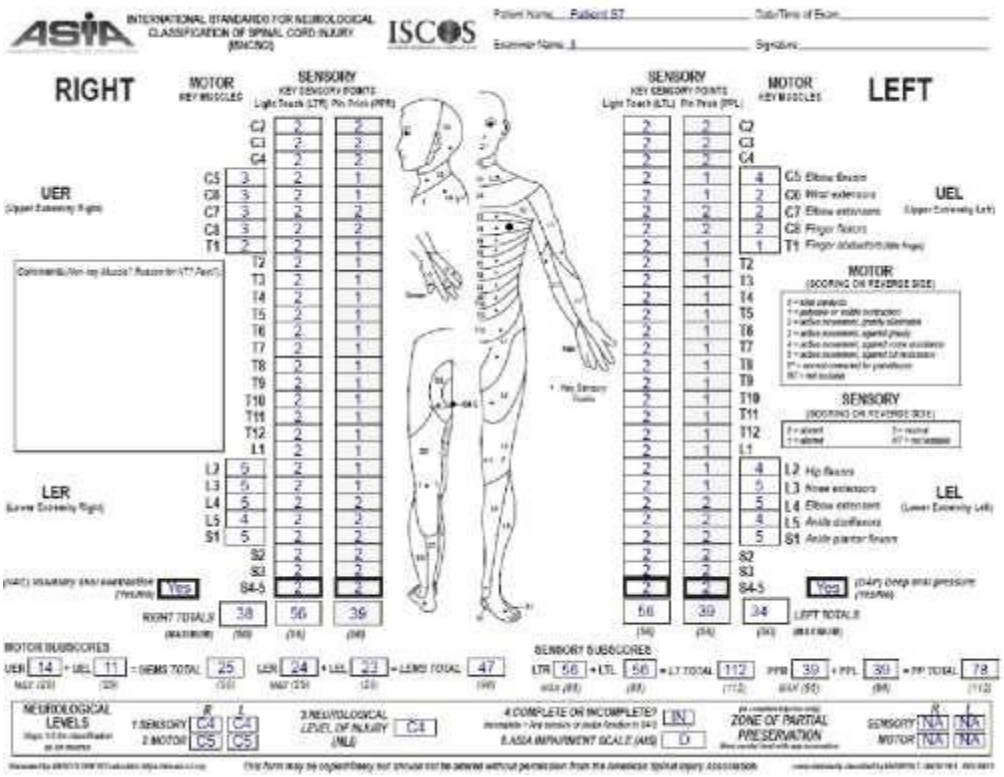
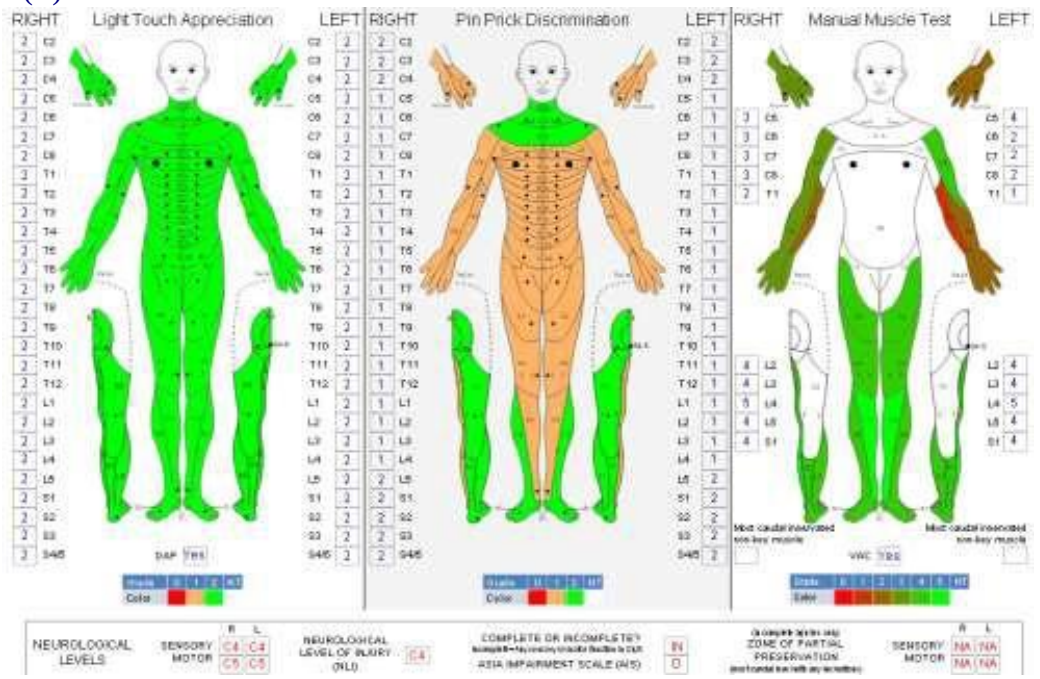


Figure 4.47 (**A**) and (**B**): shows ASIA Impairment Scale (AIS) for patients S7 at test-1 (**A**) and test-2 (B) examined 10 weeks apart. *Source:* Field work.

(C) :



(D) :

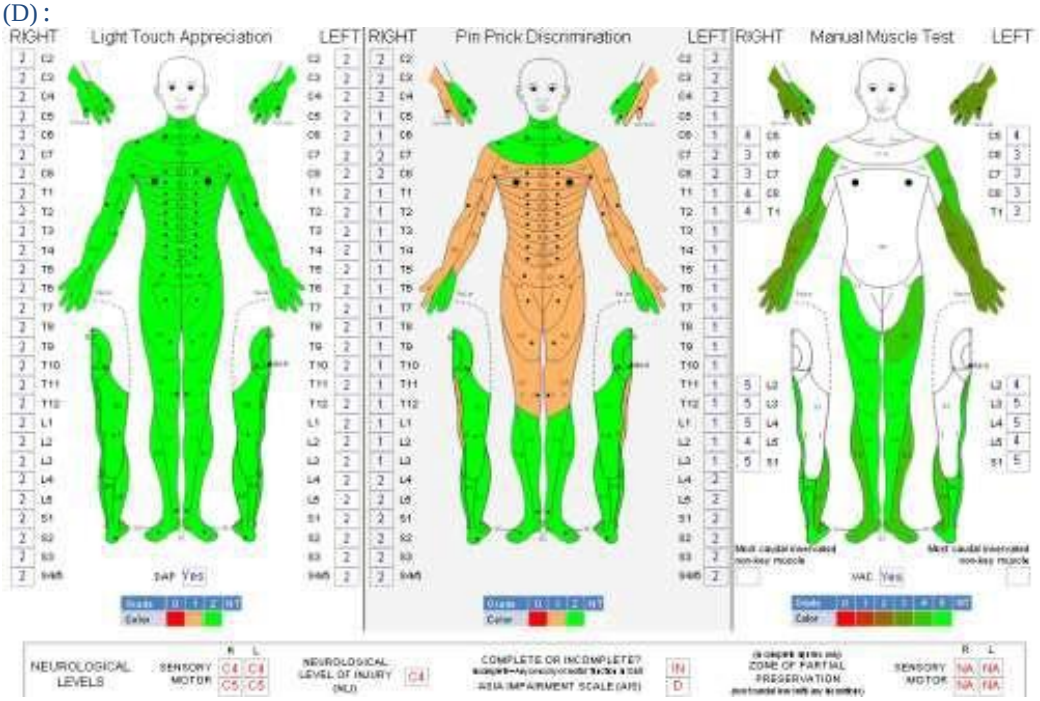


Figure 4.47 (**C**) and (**D**): shows AIS colour charts for sensory dermatomal and motor scoring maps for patient S7 at test-1 (**C**) and test-2 (**D**) examined 10 weeks apart down the longitudinal follow-up period. *Source:* Field work.

4.12 SEP and D-SEP (Waveforms and Lat-Amp Measurements):

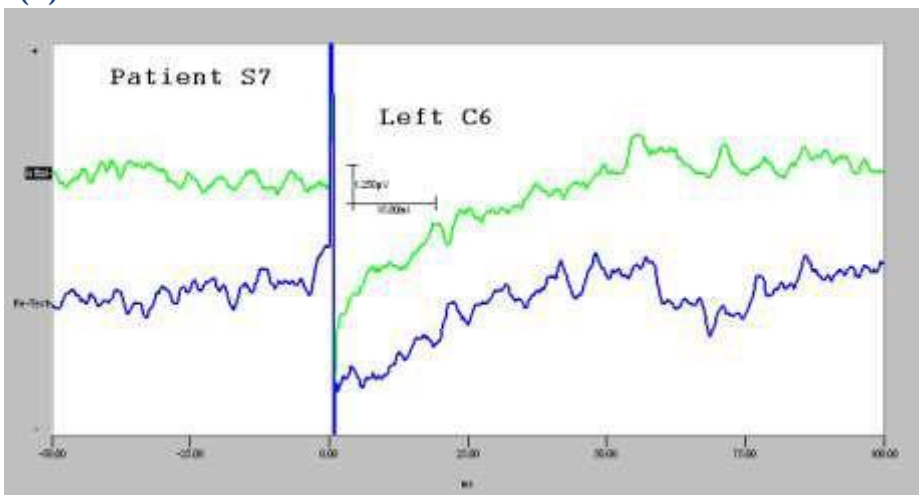
SEP and D-SEP waveform parameters from upper and lower limb stimulation sites are shown and detailed in Table 4.12. Right PTN SEP responses were absent in test-1 but became present in test-2 with reasonable latency and amplitude parameters within a normal range. Left PTN SEP amplitude also increased and latency decreased. SEP and D-SEP waveforms from C5, C6, Median, L2 and L3 were largely similar between tests but there were marginal gains in amplitudes towards normal for left Median and PTN SEP responses.

Table 4.12: details of measured values for amplitude and inter-peak latency parameters from upper and lower limb SEP and D-SEP waveforms recorded on test-1 and test-2 which were performed **10 weeks** apart. Cortical SEP and D-SEP recorded in response to stimulation of dermatomes and nerve sites on left and right sides. *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 = **70 days**.*	***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 = **140 days**.*
S7	**Acute**	***D***	***D***
	C4	***Rt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***	***Rt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***
55-yrs	Incomplete Tetraplegia	***Am:*** *0.11* *0.25* *0.13* *0.29* *0.48* *Absent*	***Am:*** *0.11* *0.37* *0.42* *0.16* *0.34* *0.53*
		Lat: *29.60* *38.70* *27.70* *49.50* *40.00* *N/A*	***Lat:*** *27.70* *28.20* *24.20* *50.40* *41.30* *36.20*
Patient S7	**Complete Test x 2**	***Lt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***	***Lt:*** ***C5*** ***C6*** ***Med*** ***L2*** ***L3*** ***PTN***
		Am: *0.51* *0.62* *0.64* *0.27* *0.27* *0.14*	***Am:*** *0.89* *0.60* *1.02* *0.38* *0.44* *0.96*
		Lat: *30.50* *40.40* *29.60* *35.10* *38.30* *40.00*	***Lat:*** *30.70* *32.80* *26.50* *31.50* *33.70* *36.60*

Figures 4.48 (**A**) and (**B**) show waveforms from which values of actual amplitude and inter- peak latency parameters were measured and shown in table 4.12. Waveforms were recorded in response to stimulation of upper and lower limb dermatomes or mixed nerve sites on right and left sides at time of initial test-1 (**A**) and follow-up test-2 (**B**) performed 10 weeks apart during the longitudinal follow-up. The resulting cortical sensory responses were recorded from contra-lateral scalp electrodes, showing no measurable responses from left C6 dermatomal D-SEP, see Figure 4.48 (**A**), while these, show dispersed and delayed response from the left Median SEP, see Figures 4.48 (**B**). Findings are consistent with lack of significant clinical recovery as assessed by AIS sensory or motor scoring parameters. Similar findings are seen on left side nerve or dermatomal stimulation (and upper limbs). No measurable electrophysiological changes seen, in keeping with ASAI-A complete SCI (no observed or measurable functional recovery).

(A) :



(B) :

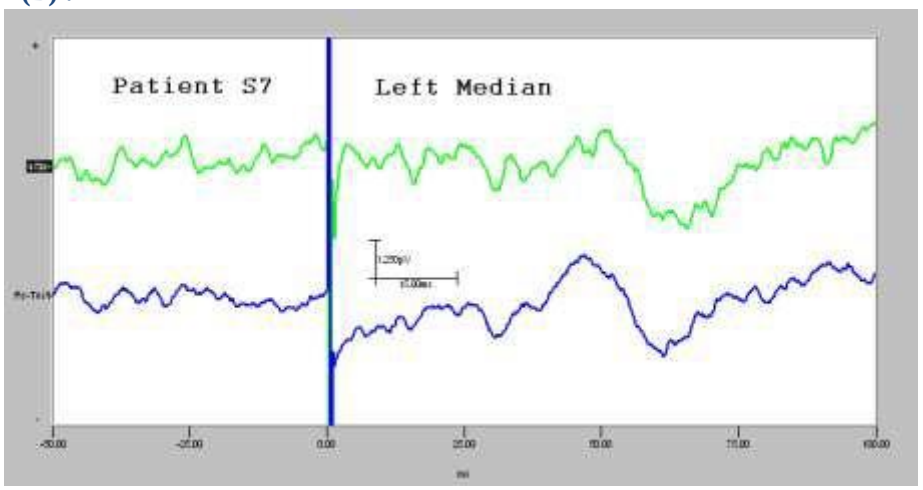


Figure 4.48 (**A**) & (**B**): shows averaged SEP and D-SEP waveform recordings of right PTN and right L3 dermatome, respectively, obtained from Patient S5. The **green** traces represent test-1 and **blue** represents test-2 performed **15 weeks** apart. No measurable D-SEP responses seen on either test on left C6 dermatome; but the left Median SEP show a dispersed and delayed response. *Source:* Field work.

4.13 ERSP (Spectral Maps for Slow Sensory Stimulation):

ERSP maps obtained from this patient at initial (test-1) and retest (test-2) were performed **10-weeks** apart but no major change in spectral components could be identified that suggest the presence of normal patterns of event related synchronisation or desynchronization. ERSP appearances obtained from right C5 and right Median are shown in Figure 4.49 (**A**) and (**B**), respectively.

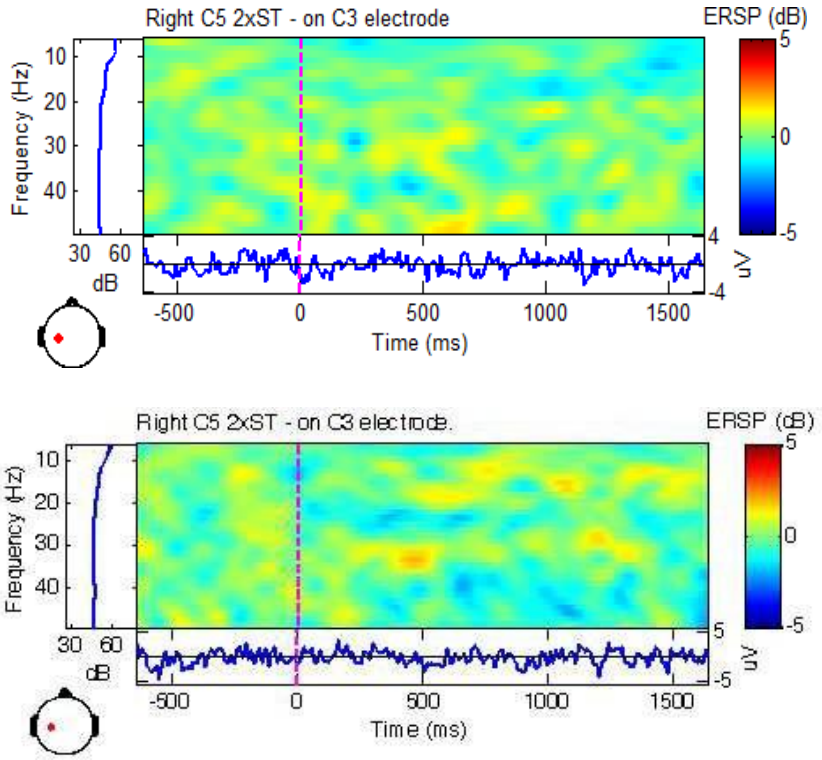


Figure 4.49 (**A**): shows right C5 D-SEP at test-1 (**top map**) with no specific features and test-2 (bottom map) performed 10-weeks later, with no spectral ERSP changes. *Source:* Field work.

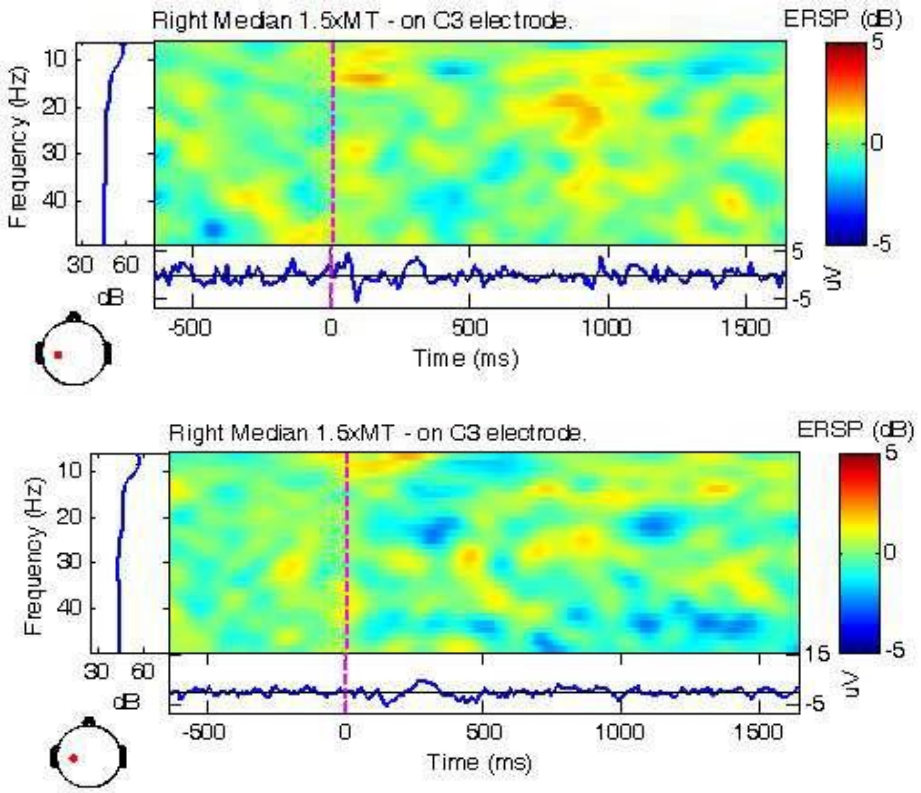


Figure 4.49 (**B**): shows right Median SEP at test-1 (**top map**) with no specific features and test-2 (bottom map) performed 10-weeks later, with no ERSP pattern changes observed. *Source:* Field work.

4.14 Trans-cranial Magnetic Stimulation – Motor Evoked Potentials: In Figures **4.50** (**A**) and **4.50** (**B**) the left and right upper limb MEP latency measurements for S7 in response to increasing levels of stimulation at test-1 and test-2 are plotted. For both left and right upper limbs there is little difference between the latency measurements made on test-1 and test 2. ED is largely innervated by C6 and C7 spinal segments and on motor testing the patient achieved an initial motor score of 3 for segments on the right side, 2 for segments of left side rising to 3 at the time of the 2nd test on the left side.

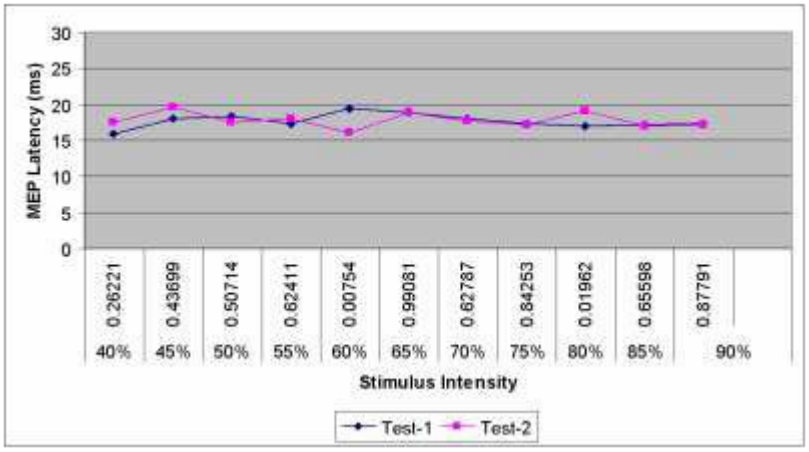


Figure 4.50 (**A**): MEP responses from EMG recording of left *Extensor Digitorum* (ED) muscle in response to TMS at C4 electrode on contra-lateral motor cortex. Two tests were performed after **10 weeks** interval. MEP responses were significantly shorter at 60% and 80% stimulation intensities in test-2 compared to test-1, with no significant difference obtained at the remaining stimulation intensities during follow-up. *Source:* Field work.

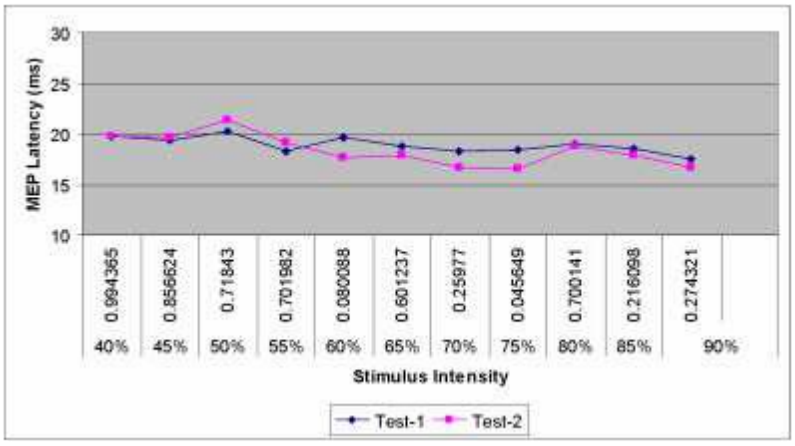


Figure 4.50 (**B**): Similarly, MEP responses were obtained from right ED in response to TMS at C3 electrode for test-2 performed 10 weeks following test-1. No shortening of latency at test-2 is seen reaching statistical significance apart from once seen at 75%. *Source:* Field work.

MEP latency and amplitude measurements obtained during TMS directed to the vertex (Cz) and recorded by EMG from right and left *Tibialis Anterior* (TA) are illustrated in Figures 4.51 **(A)** and 4.51 (**B**). For this subject manual muscle testing of ankle dorsiflexors were recorded as 4 bilaterally and remained at 4 on both test dates. The pattern of latency measurement changes associated with increasing stimulation strength differed on left and right sides over the testing interval. On the left side the MEP latency began to show a more normal behaviour by decreasing with increases in stimulation strength whilst for the right side the latency appeared to increase with stimulus strength and time (compare test 1 and test 2 curves, Figure 4.51 **(B**).

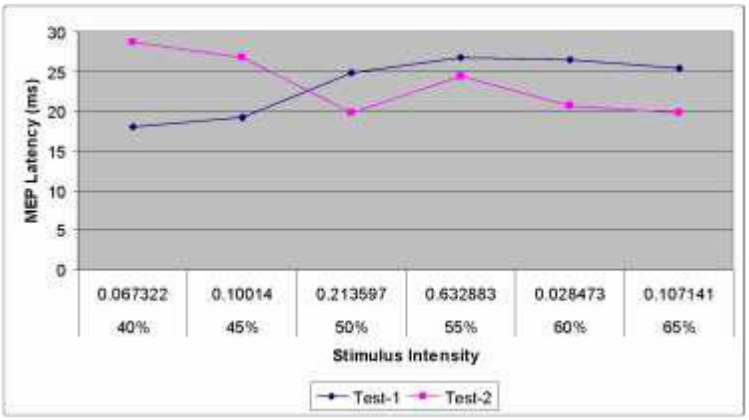


Figure 4.51 (**A**): MEP measurements obtained from left *Tibialis Anterior* (TA) muscle in response to TMS at Cz electrode performed at two occasions 10 weeks apart between test-1 and test-2. Shortening of onset latencies did not reach statistical significance at any of the stimulation intensities apart from MEP recording at 60%. *Source:* Field work.

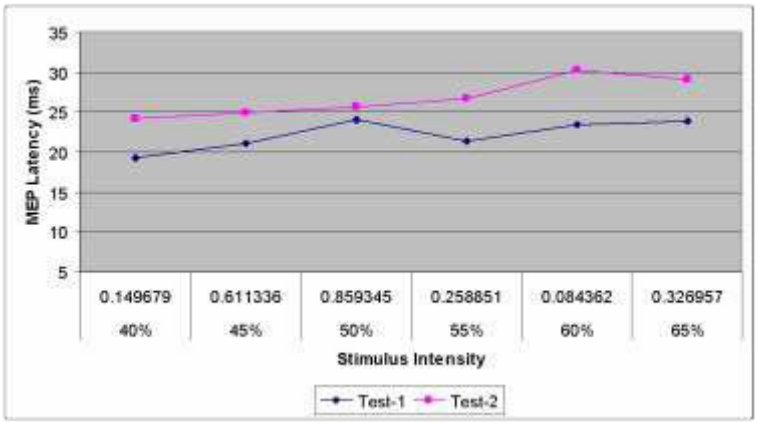
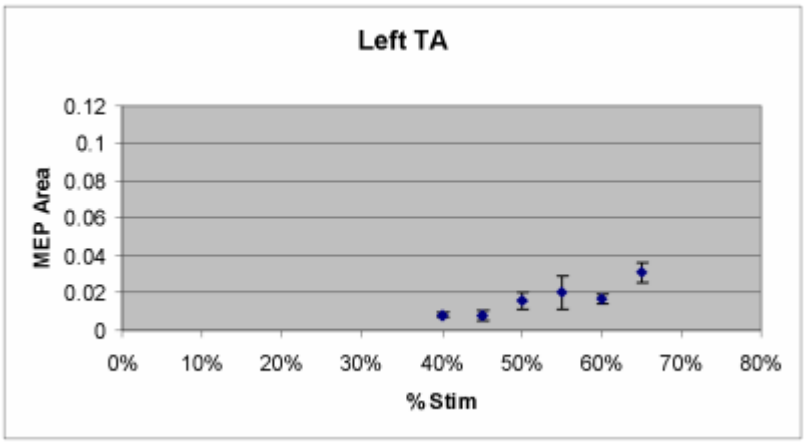


Figure 4.51 (**B**): Similarly, MEP responses were obtained from right TA in response to TMS at Cz electrode for test-2 performed 10 weeks following test-1. No shortening of latency at test-2 is seen reaching statistical significance at any stimulation intensity. *Source:* Field work.

MEP amplitude in TA on both sides tended to increase with increasing stimulation strength with gains in amplitude also being evident for the left TA at the time of the second test session as seen in Figures 4.52 (**A**). The changes in MEP responsiveness were not reflected in changes in manual muscle testing results which remained at 4 on each testing date.

Test-1



Test-2

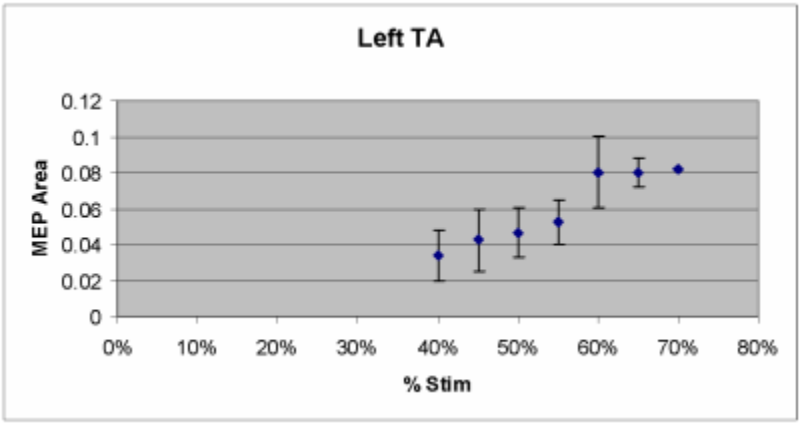
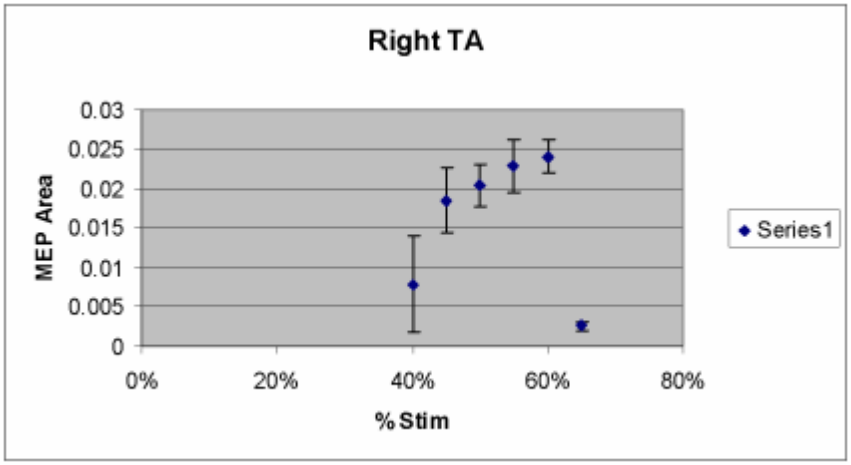


Figure 4.52 (**A**) shows MEP measurements from left Tibialis Anterior (TA) muscle in response to TMS at Cz electrode performed at two occasions 10 weeks apart between test-1 (top) and test-2 (bottom). There is obvious increase of the MEP amplitude with increasing stimulation strength. *Source:* Field work.

Similarly, in Figure 4.52 (**B**), increase in MEP amplitude of TA muscle is seen with increasing stimulation strength on the right side, as seen at the time of the second test session with no changes in manual muscle examination on AIS.

Test-1



Test-2

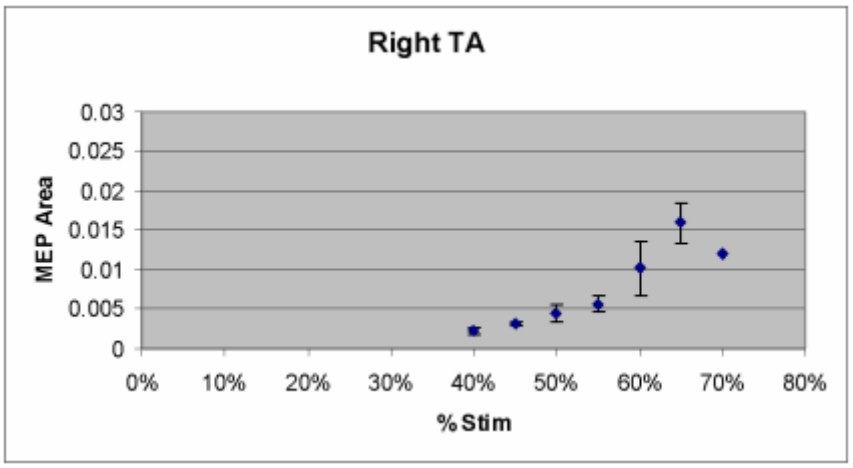
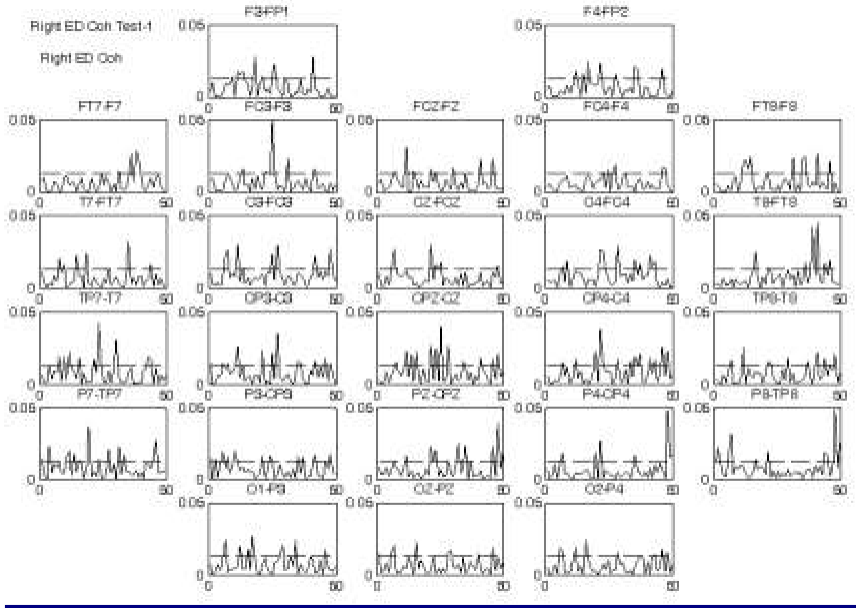


Figure 4.52 (**B**) shows MEP measurements from right Tibialis Anterior (TA) muscle in response to TMS at Cz electrode performed at two occasions 10 weeks apart between test-1 (top) and test-2 (bottom). MEP amplitude increases with stimulation intensity. *Source:* Field work.

4.15 Cortico-Muscular (EEG-EMG) Coherence – CMC:

CMC estimated from simultaneous EEG and EMG recordings at test-1 and test-2 were obtained from upper and lower limb recordings. For upper and lower limbs, S7 was able to generate sustained EMG voluntary activity as expected from the results of manual motor tests. However, there does not appear to be any clear pattern to the coherence measurements either in terms of frequency bands at which coherence is evident or at EEG electrode sites overlying the hand (seen in Figure 4.53) or leg (seen in Figure 4.54) areas of the contralateral or ipsilateral cortex.

Test-1



Test-1

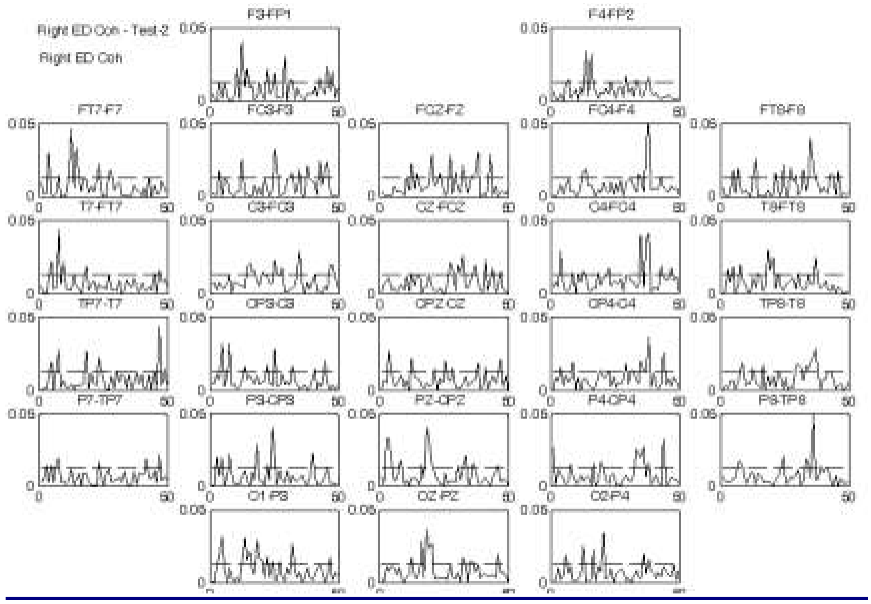
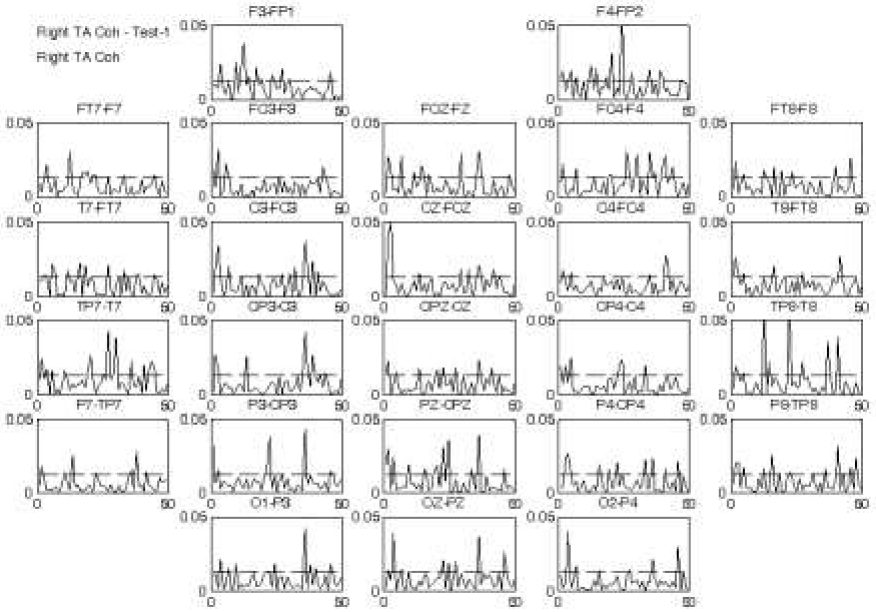


Figure 4.53 shows CMC maps performed for EEG and EMG from right ED muscle during voluntary contraction at two occasions 10 weeks apart between test-1 (**top**) and test-2 (**bottom**). No clear pattern of coherence measurements is seen either in terms of frequency bands or at EEG electrode sites overlying corresponding cortical areas. *Source:* Field work.

From a consideration of the CMC plots made on test 1 and test 2 the most interesting feature is the appearance of a high coherence at 8-10Hz during sustained contractions of the right TA muscle, as shown in Figure 4.54. This low frequency coherence is seen at several electrode sites and would normally not be a feature of normal CMC measures. However, 10Hz coherence can be seen in cases of tremor disorders and may reflect activity that is organised into coherent low frequency bursts.

Test-1



Test-2

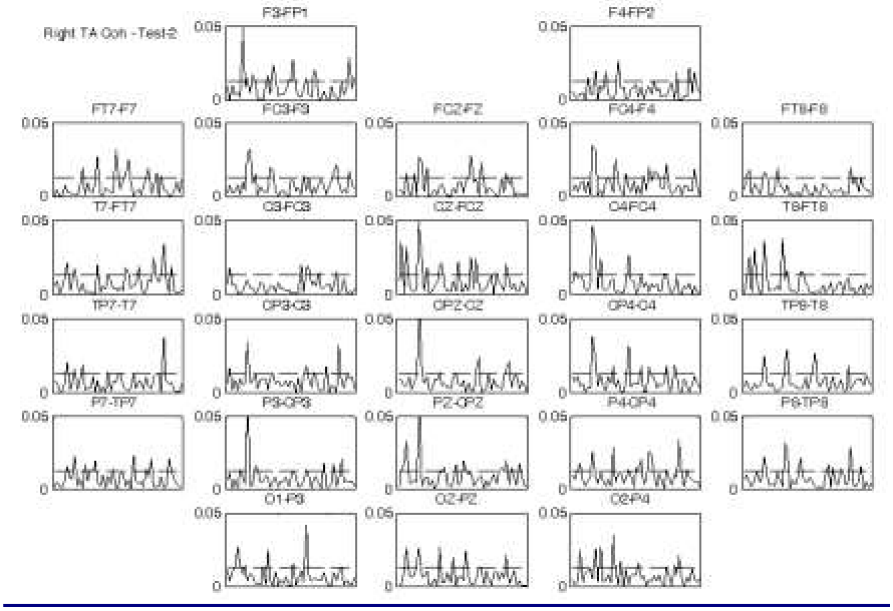
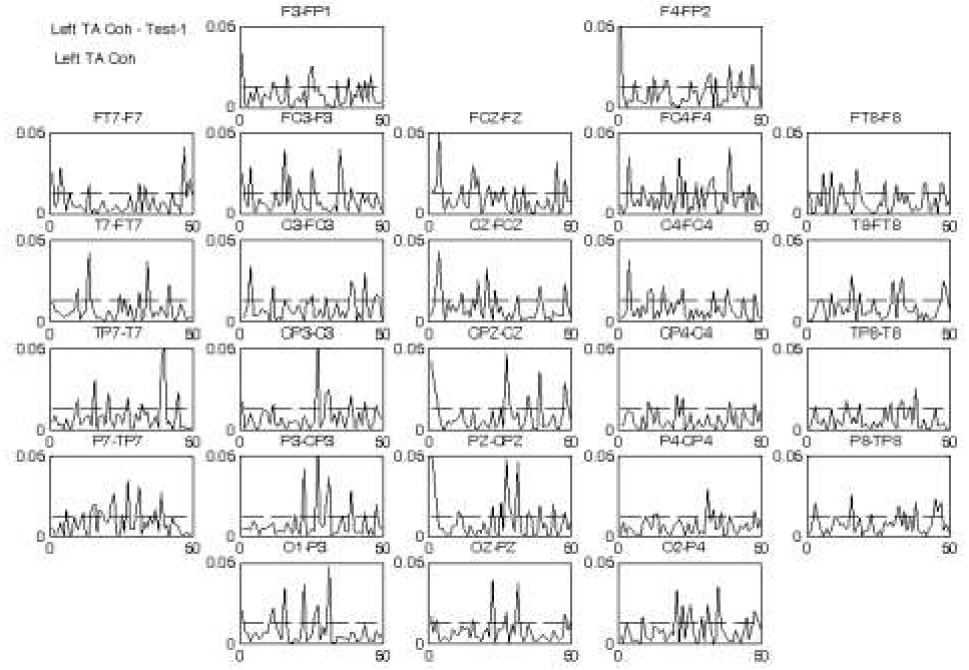


Figure 4.54 shows CMC maps performed for EEG and EMG from right TA muscle during voluntary contraction at two occasions 10 weeks apart between test-1 (**top**) and test-2 (**bottom**). There seen is an appearance of a high coherence at 8-10Hz, during sustained contractions of the right TA muscle, seen at several electrode sites which might reflect activity that is organised into coherent low frequency bursts. *Source:* Field work.

Similar but less obvious changes are seen on CMC plots from contraction of left TA muscle as shown in Figure 4.55.

Test-1



Test-1

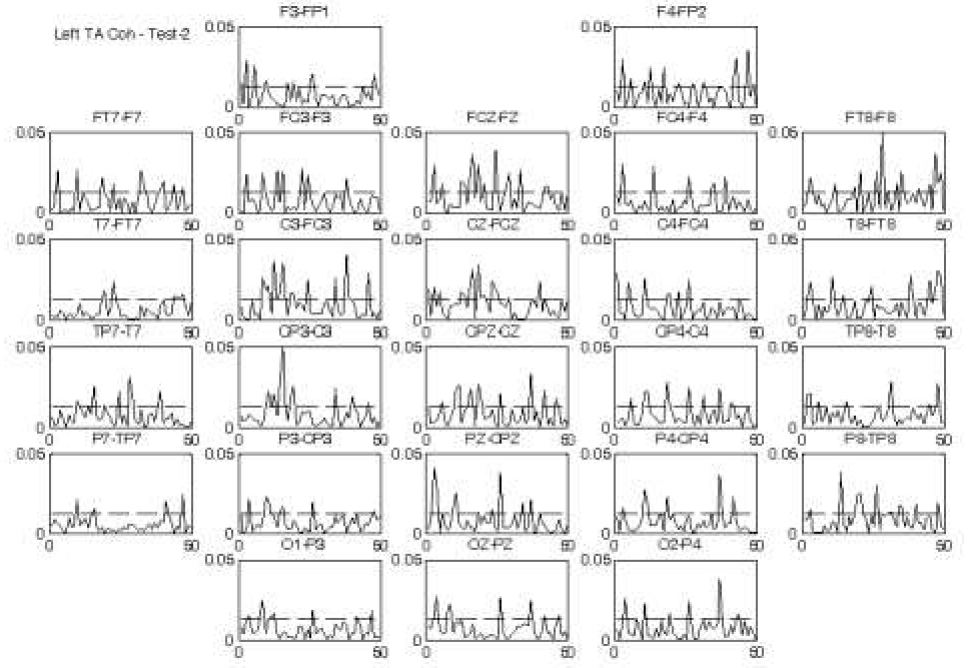


Figure 4.55 shows CMC maps performed for EEG and EMG from left TA muscle during voluntary contraction at two occasions 10 weeks apart between test-1 (**top**) and test-2 (**bottom**), with less obvious CMC map changes in response to sustained contraction of the left TA muscle.

Source: Field work.

4.16 Interpretation of Electrophysiological Results (in light of clinical info):

Electrophysiology for Patient S7 (55-years male with C5 incomplete AISA-D tetra-paresis).

Clinically, the patient showed no significant difference in clinical assessment up to the time of discharge from hospital, scoring no AIS grading difference.

Results of objective tests performed **10 weeks** apart showed changes in SEP waveforms. PTN SEP responses were absent in test-1 but became present in test-2 with latency and amplitude parameters reaching normal. The remaining SEPs and D-SEPs from C5, C6, Median, L2 and L3 were largely similar, but with a marginal growth of amplitudes towards normal for the SEP responses of left Median and PTN. The MEP latency measurements show some shortening of latency which reached statistical significance at some of the stimulation intensities used. The patient was taking **medications** including Gabapentine 400mg x 3, Tramadol 100mg x 1, Baclofen 20mg x 3 and Imipramine 20mg x 1 at time of test-2. These medications need to be considered when interpreting test results especially SEP and D-SEP proximal propagation, cortical processing, CMC calculation and MEPs (largely amplitude related and less on latency changes). This is because these medications are found to be cause suppression of the afferent signalling and reduce cortical responses, which would affect the final results of these tests.

4.16.1 Patient S2 (ASIA-C Incomplete C5 Tetraparesis, tested 3 times):

Clinical Information:

- Patient: 56-years-old male.
- **Injury level** C5 ASIA C – (& the **Neurological** level was **C5**).
- Time Interval – **Injury to Test 1 'initial test'**: 56 days (7 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **C5 ASIA C**.
- Time Interval – **Injury to Test 2**: 154 days (22 weeks).
- ASIA Impairment Scale **on Test 2**: **C5 ASIA C**.
- Time Interval **– Test 1 to Test 2: 15 weeks**.
- Medications at time of Test 2:

  Citalopram 20mg once a day. Tramadol 50mg four times a day.

  Tizanidine 4mg three times a day. Baclofen 25mg four times a day.
- Time Interval – **Injury to Test 3**: 473 days (67.5 weeks).
- ASIA Impairment Scale **on Test 3 'third' test**: **C5 ASIA D**.

- Time Interval – **Test 2 to Test 3: 52.5 weeks**.
- Medications at time of Test 3: Tramadol 50mg x 4 - Diazepam 5mg x 1.

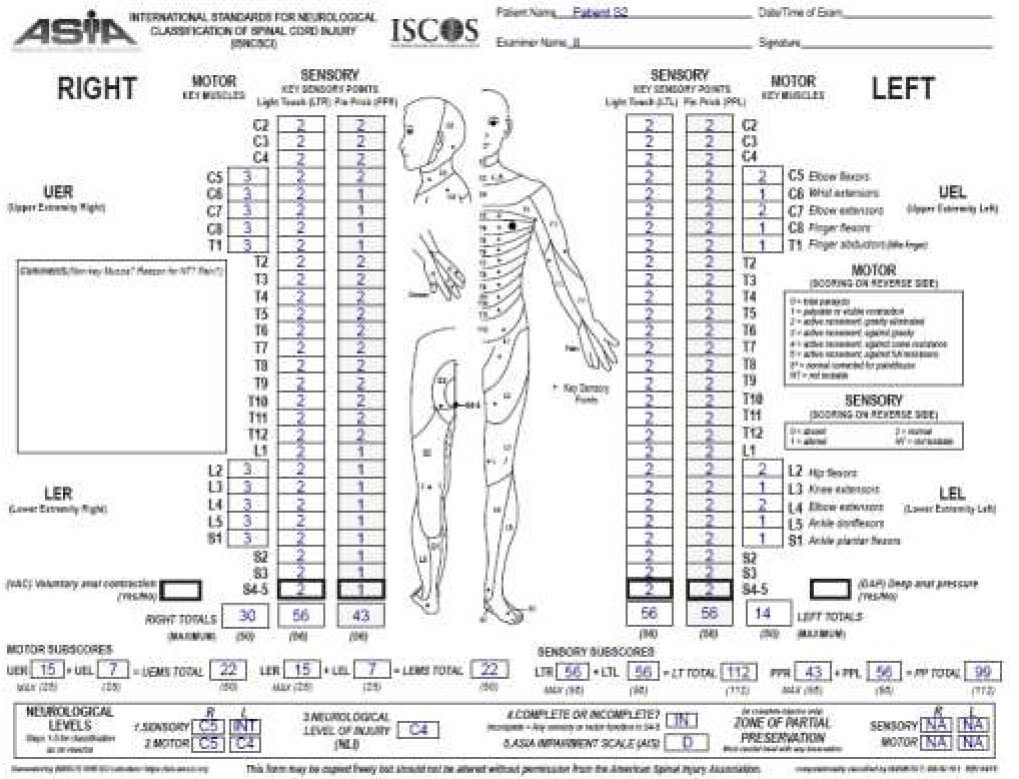
  Gabapentine 300mg x 4 - Baclofen pump – constant Baclofen locally.

- On Discharge: The patient managed the following functional activities:

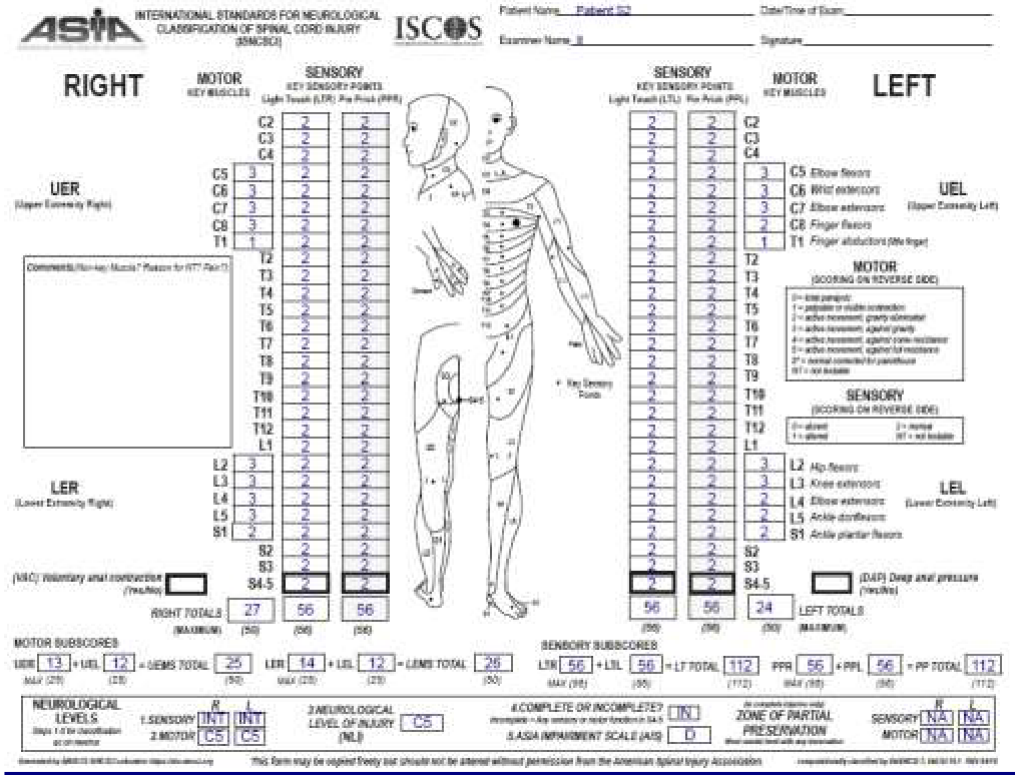
  Use of spoon or fork (right hand), drinking from a cup, can hold mobile phone and speed dial, use of electric razor, use of electric wheel chair indoor, sit in bed and transfer (+ major assistance), stand from sitting (+ major assistance); walk short distances using a gutter frame (+ supervision); feel when in need to pass urine (while still using a urine sheath). Generally, the right arm and right leg have become stronger.

Patient S2 underwent three tests (designated test-1, test-2 and test-3) performed at 15 and 52.5 week follow up intervals, as shown in Figure **4.56** and **4.57** with AIS maps and colour charts for sensory-motor clinical scoring. Test-3 was required due to corruption of data obtained at test-2 necessitating a further test (test-3) to enable comparison with test-1 data. Test-3 was facilitated by patient S2 remaining as an inpatient requiring hospital treatment independent from the purpose of the test.

(A):



(B):



(C):

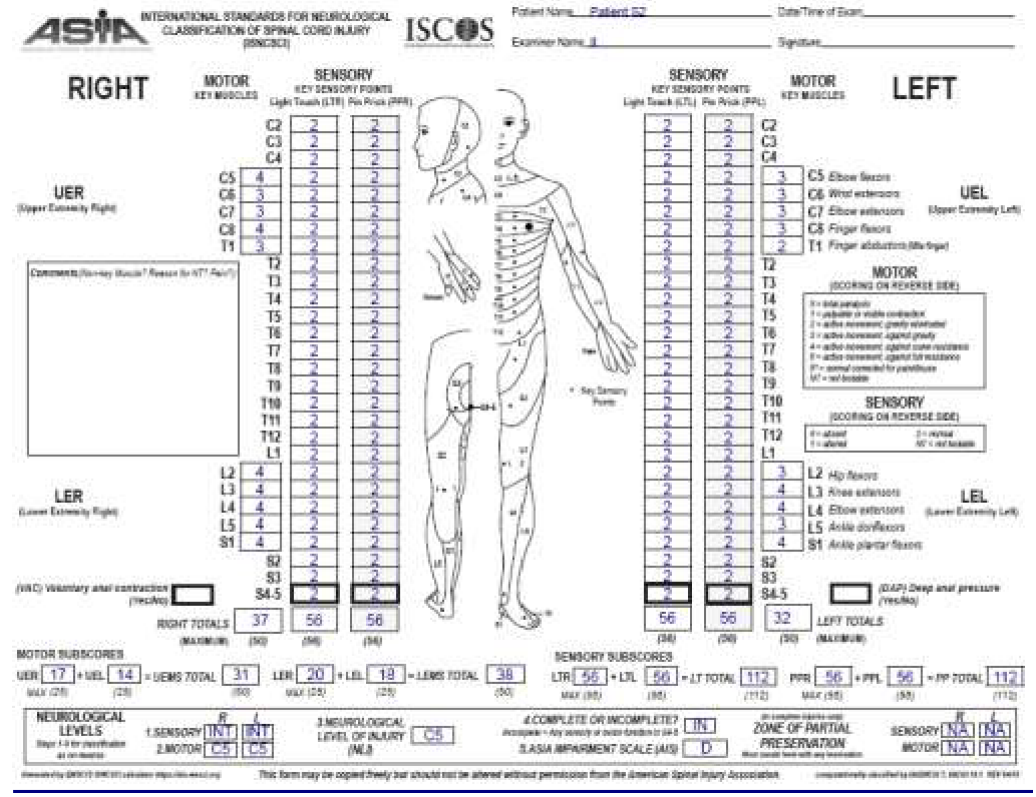
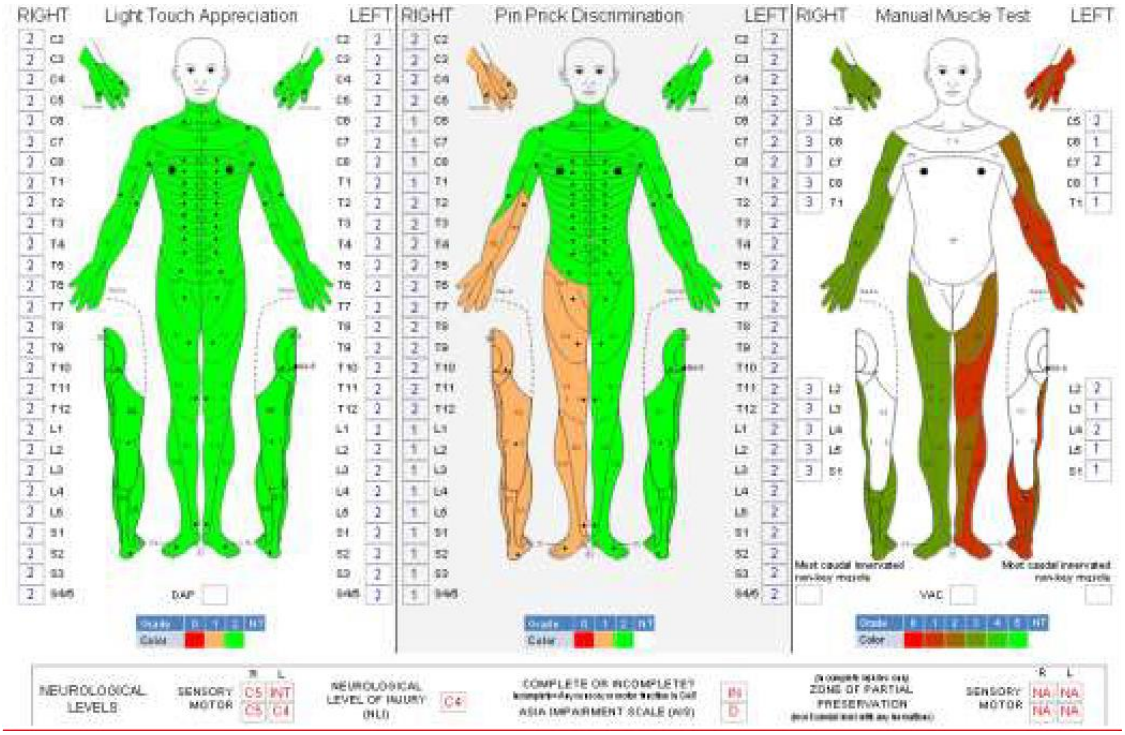
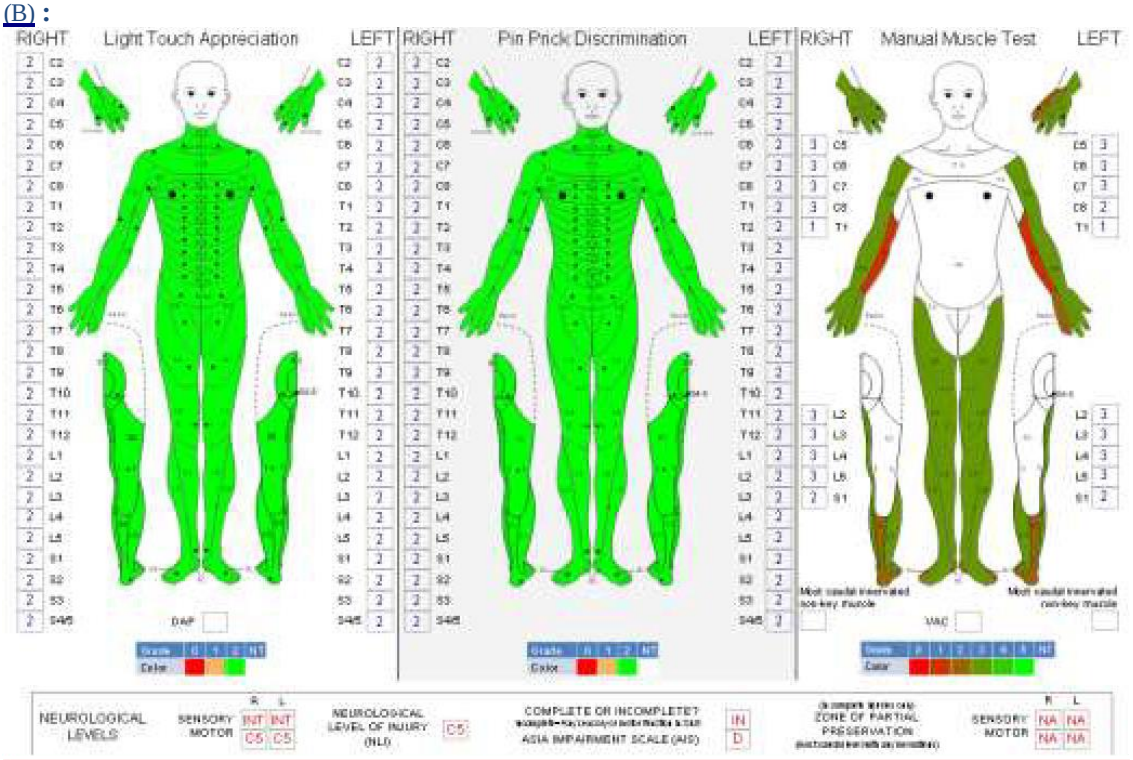


Figure 4.56 (**A**), (**B**) and (**C**) shows ASIA Impairment Scale (AIS) for patients S2 at test-1 (A), test-2 (B) and test-3 (C) examined respectively 15 and 52.5 weeks apart. *Source:* Field work.

(A) :


RIGHT
Light Touch Appreciation
LEFT
RIGHT
Pin Prick Discrimination
LEFT
RIGHT
Manual Muscle Test
LEFT
NEUROLOGICAL LEVELS
SENSORY
MOTOR
NEUROLOGICAL LEVEL OF INJURY (NLI)
C4
COMPLETE OR INCOMPLETE?
ASIA IMPAIRMENT SCALE (AIS)
B
D
ZONE OF PARTIAL PRESERVATION
SENSORY
MOTOR
NA

(B) :


RIGHT
Light Touch Appreciation
LEFT
RIGHT
Pin Prick Discrimination
LEFT
RIGHT
Manual Muscle Test
LEFT
NEUROLOGICAL LEVELS
SENSORY
MOTOR
NEUROLOGICAL LEVEL OF INJURY (NLI)
C5
COMPLETE OR INCOMPLETE?
ASIA IMPAIRMENT SCALE (AIS)
B
D
ZONE OF PARTIAL PRESERVATION
SENSORY
MOTOR
NA

(C):

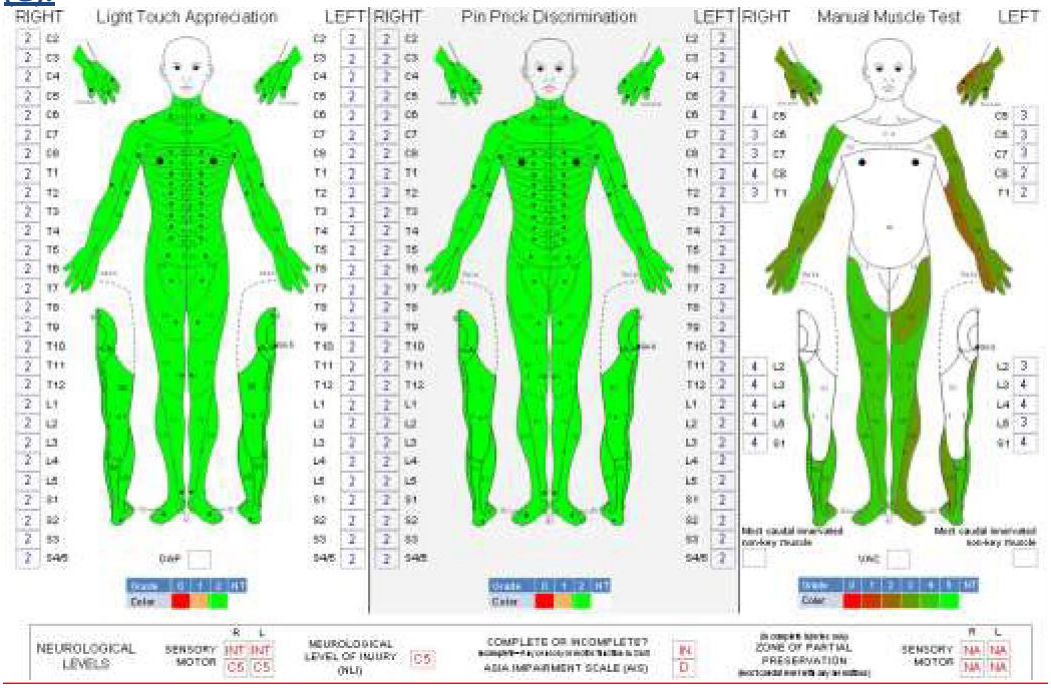


Figure 4.57 (**A**), (**B**) and (**C**) shows cartoon illustrations of colour charts of the sensory dermatomal and motor maps related to clinical sensory-motor scoring values at test-1 (A), test-2 (B) and test-3 (C) for patient S2 performed at 15-week and 52.5-week intervals. *Source:* Field work.

Patient S2 underwent three testing sessions (designated test-1, test-2 and test-3) performed respective 15 and 52.5 week follow up intervals. ASIA charting made at these specified times show changes with gain in scoring of pin prick felt in the right lower limb over 15 weeks follow up. This pin prick scoring remained the same at the time of test-3, with no other measurable clinical sensory changes observed (see cartoons of AIS maps in Figures 4.56 (**A**), (**B**) and (**C**). However, manual muscle power examination showed improvement as represented in muscle power charts obtained at test-3. This is reflected on the overall AIS of patient S2 recovering to ASIA-D at test-3 following being the same at ASIA-C at times of test-1 and test-2. Recovery of pin prick sensation seen on the AIS maps obtained at test-1 and test-2 is reflected on colour sensory-motor scoring charts shown in Figures 4.57 (**A**), (**B**) and (**C**). These changes remained the same at test-2 and test-3 over the remaining 52.5 weeks follow up interval. Clinically, this patient showed some improvement over initial 15-weeks, with minor sensory scoring changes recorded on AIS but obvious functional benefits. Patient S2 was functionally better in activities based on hand function, as well as assisted transfer, standing with major assistance, some sensation on need to pass urine. It was also observed that generally the right arm and right leg became stronger over time. However, patient S2 remained in the same AIS category C from test-1 to test-2, but eventually gaining muscle power that changed AIS from C to D.

At the time of test-2, patient S2 was taking (Citalopram 20mg x 1, Tramadol 50mg x 4, Baclofen 25mg x 4, and Tizanidine 4mg x 3), and at time of test-3 (Tramadol 50mg x 4, Diazepam 5mg x 1, Gabapentine 300mg x 4, and Baclofen pump, locally spinal). These are drugs known to cause suppression of afferent signalling, reduced cortical responses including EEG and this may be a factor influencing neurophysiology data.

4.17 SEP and D-SEP (Waveforms and Lat-Amp Measurements):

Analysis of latency and amplitude waveform parameters of averaged SEP and D-SEP from upper and lower limb stimulation sites of dermatomes and mixed nerves are detailed in Table 4.13. Right and left PTN SEP, and right L2 and L3 D-SEP responses were absent (or damaged with filter noise) at test-1, but these became present in test-3 (test-2 data was corrupted and could not be analysed). Left L2 and L3 D-SEP responses were present at test-1, with small L3 response, but these became prominent with marginal gain of amplitudes at test- 3 (test-2 data was lost). SEP and D-SEP latencies show no significant shift, but were noticed to have grown slightly longer (delayed). This might possibly be related to medications or lower temperature in legs after a prolonged state of paralysis (chronic SCI).

Table 4.13: Shows onset latency and amplitude measurements of cortical SEP and D-SEPs responses obtained at test-1, test-2 and test-3 with respective **15** and **52.5 week'** intervals. *Source:* Field work.

Subject No & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 =* ***56 days (7 weeks).***	***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 =* ***154 days (15 weeks).***
S7 56-yrs **Patient S7**	**Acute** **C4** Incomplete Tetraplegia **MagStim Not Done**	***C*** ***Rt: C5 C6 Med L2 L3 PTN*** ***Am:*** *Absent 0.49 0.88 Notch Notch Notch* ***Lat:*** *N/A 22.30 28.00 Notch Notch Notch* ***Lt: C5 C6 Med L2 L3 PTN*** ***Am:*** *Absent Absent Absent 0.43 0.27 Notch* ***Lat:*** *N/A N/A N/A 32.00 34.30 Notch*	***C*** ***Rt: C5 C6 Med L2 L3 PTN*** ***Am:*** *The data was lost.* ***Lat:*** - - - - - - - - - - - ***Lt: C5 C6 Med L2 L3 PTN*** ***Am:*** *The data was lost.* ***Lat:*** - - - - - - - - - -
		Am. = Amplitude ***Lat. = Latency*** ***Rt. = Right – Lt. = Left***	***ASIA impairment at test 3 – Third Test + SEP Measurements*** *Injury to test-3 =* ***473 days (67.5 weeks).***
		Patient S7 *is the only patient to be tested for the* ***3rd test****, to establish comparison of*	***Rt: C5 C6 Med L2 L3 PTN*** ***Am:*** *1.02 0.87 1.40 0.58 0.08 0.62*

		electrophysiological findings at the time of marked clinical improvement seen and make for the lost data on 2nd test. However, ERDS from initial, retest and third tests were available for analysis). *This 'third test' was carried out **473 days** from the onset of SCI (**67.5 weeks**).*	***Lat:** 30.10 22.90 27.30 40.60 38.30 36.80* ***Lt: C5 C6 Med L2 L3 PTN*** ***Am:** 0.72 0.92 1.57 0.23 0.36 0.97* ***Lat:**32.20 32.60 23.90 42.50 41.30 43.00*

4.18 ERSP (Spectral Maps for Slow Sensory Stimulation):

ERSP maps were obtained for upper and lower limb stimulation sites used to obtain SEP and D-SEP responses but at slower stimulation frequency as previously described.

Figure 4.58 (A) shows normal ERSP pattern obtained from a healthy volunteer right Median nerve, while (B) and (C) show 'initial' and 'retest' electrophysiological findings at **6-7 weeks** and **21 weeks**, respectively.

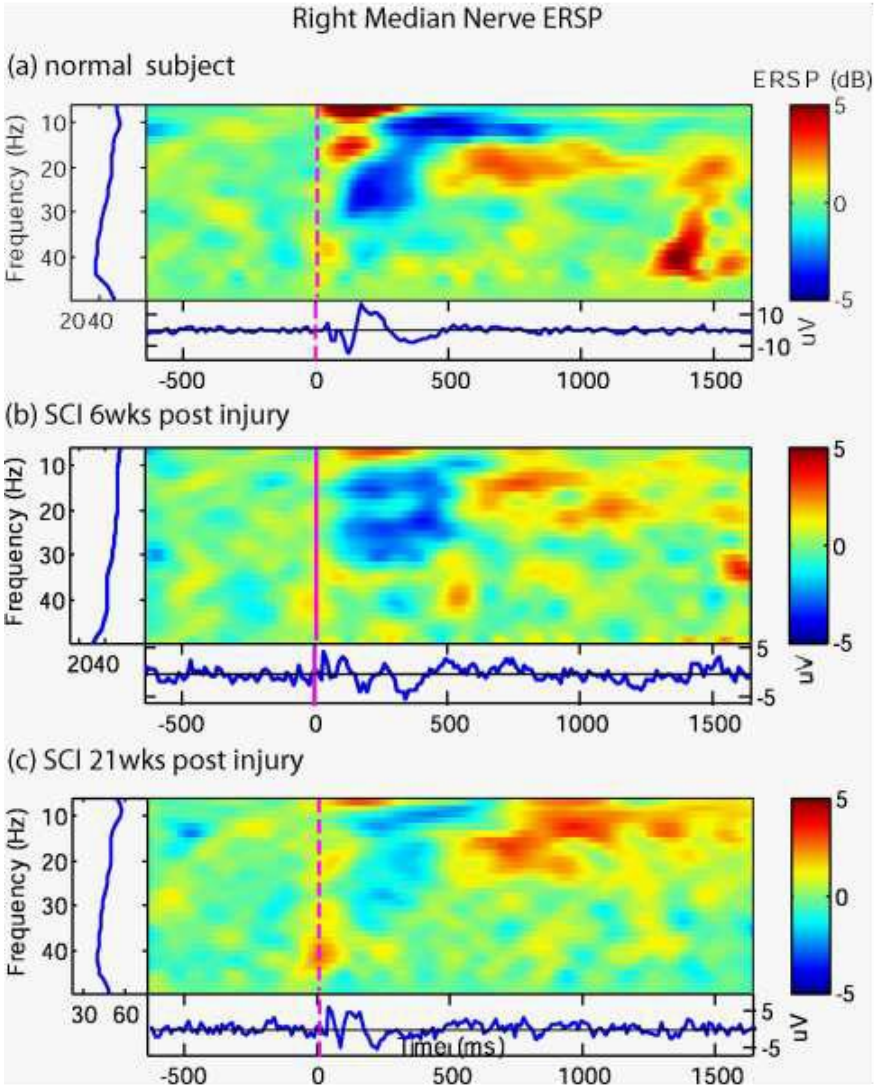


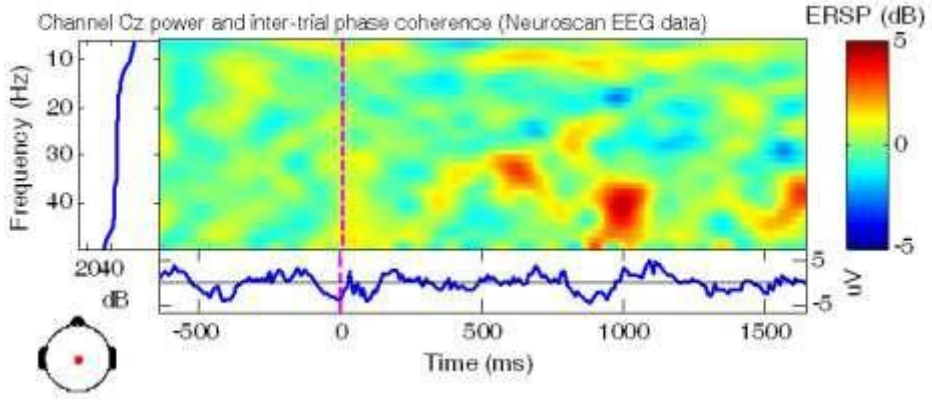
Figure 4.58: ERSP of EEG and EMG signals showing normal ERPS map from a healthy subject (a) in response to right Median stimulation (2x motor threshold). Figures (b) and (c) show ERSP maps SCI patient with ASIA-C Incomplete C5 SCI at 6 and 21weeks post injury. Note the changes in ERSP patterns over time with areas losing bands of desynchronisation and synchronisation at 21 weeks departing from normal ERSP pattern for healthy subject (a). In this patient, decrement in sensory score was seen due to formation of new spinal syringe. Deteriorating sensory signalling is apparent in the lack of EEG desynchronisation in ERSP map estimated from data obtained at time of retest. *Source:* Field work.

These ERSP maps were obtained for Patient S2 with SCI (**ASIA-C C5 Incomplete Tetra-paresis**) at times of test-2 when clinical sensory scores decreased possibly influenced by clinical deterioration caused by the development of a new spinal syringe complicating SCI (newly diagnosed syringomyelia). Although this was not well reflected in the ASIA Impairment Scale (AIS), it has been reflected on the ERSP pattern losing the usual ERD band. This was later on followed by stability then improvement of the clinical scores mirrored with functional improvement. The overall functional recovery obtained by this patient as recorded on discharge from hospital included managing all simple and some medium-skill hand function especially

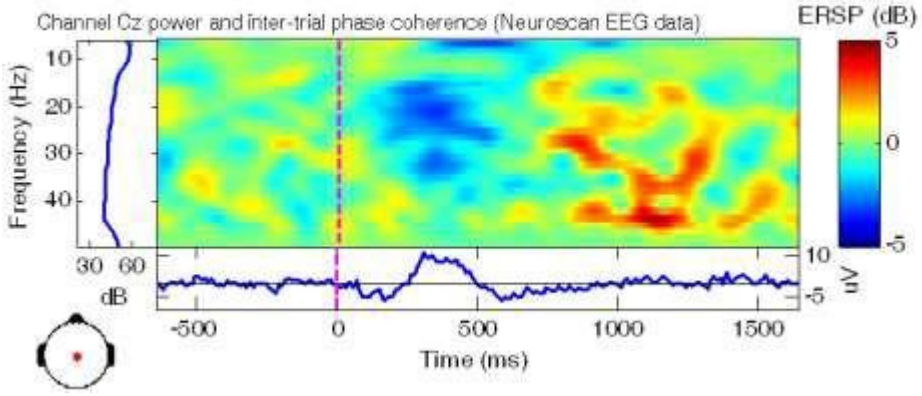
the right side, sitting in bed transferring and standing however with major assistance, short over ground walking using gutter frame and assistance, and sensing desire to pass urine. The right hand and leg appeared on final assessment to be stronger than left and better than previously indicated.

Similarly, ERSP maps were obtained for right and left lower limb stimulation sites used to obtain SEP and D-SEP responses but at slower stimulation, as previously described. Figure 4.59 shows ERSP patterns for Patient S2 obtained from the right PTN at test-1 around 6-7 weeks following SCI (**A**), and comparison to (**B**) at test-2 and (**C**) at test-3 performed 21and 52.5 weeks' intervals, respectively. There are obvious changes in ERSP patterns over time with restoration of some of the areas forming bands of desynchronisation and synchronisation at 21 weeks, which is mirroring the overall functional recovery obtained by this patient recorded on discharge from hospital. Yet, the sensory changes on SEP, D-SEP and ERSP are not reflected on the sensory scores of the AIS maps or coloured charts shown. Measurable clinical recovery involved gain of muscle power with no changes of sensory scores. ERSP map obtained at 52.5 weeks showed deterioration of ERSP pattern with loss of some areas of bands gained earlier during initial clinical recovery. This late deterioration of ERPS pattern is corresponding to clinical deterioration due to a new syringe.

(A) :



(B) :



(C) :

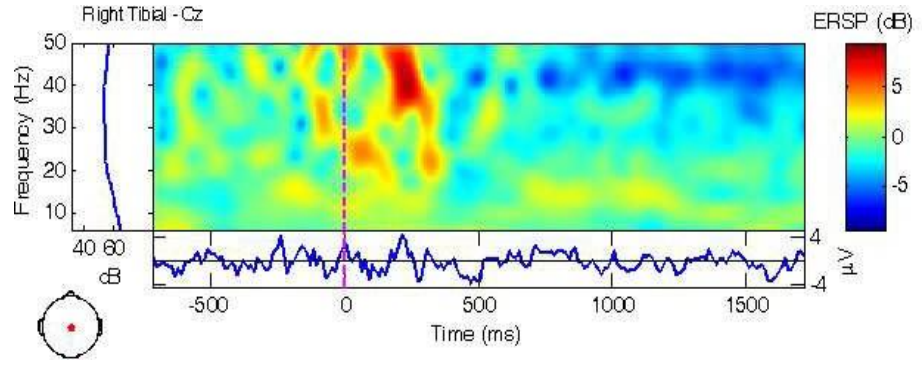


Figure 4.59: ERSP of EEG and EMG signals showing ERPS map from Patient S2 in response to right Posterior Tibial Nerve (PTN) stimulation (2x motor threshold) at 6-7 weeks post-injury at test-1 (**A**), then after 21 weeks at test-2 (**B**) and finally 52.5 weeks later at test-3 (**C**). Changes in ERSP patterns over time are observed with partial restoration of areas forming bands of desynchronisation and synchronisation at 21 weeks (B) compared to less-formed initial patterns in (A). After 52.5 weeks follow up (C), the ERSP map shows deterioration to a less formed pattern, which seems to be corresponding and mirroring clinical deterioration seen lately after initial recovery. *Source:* Field work.

ERSP maps were obtained from opposite left PTN with changes that are largely similar to the right PTN though less prominent. ERSP map with initial recovery of areas and bands later showed significant deterioration, as shown in Figure 4.60.

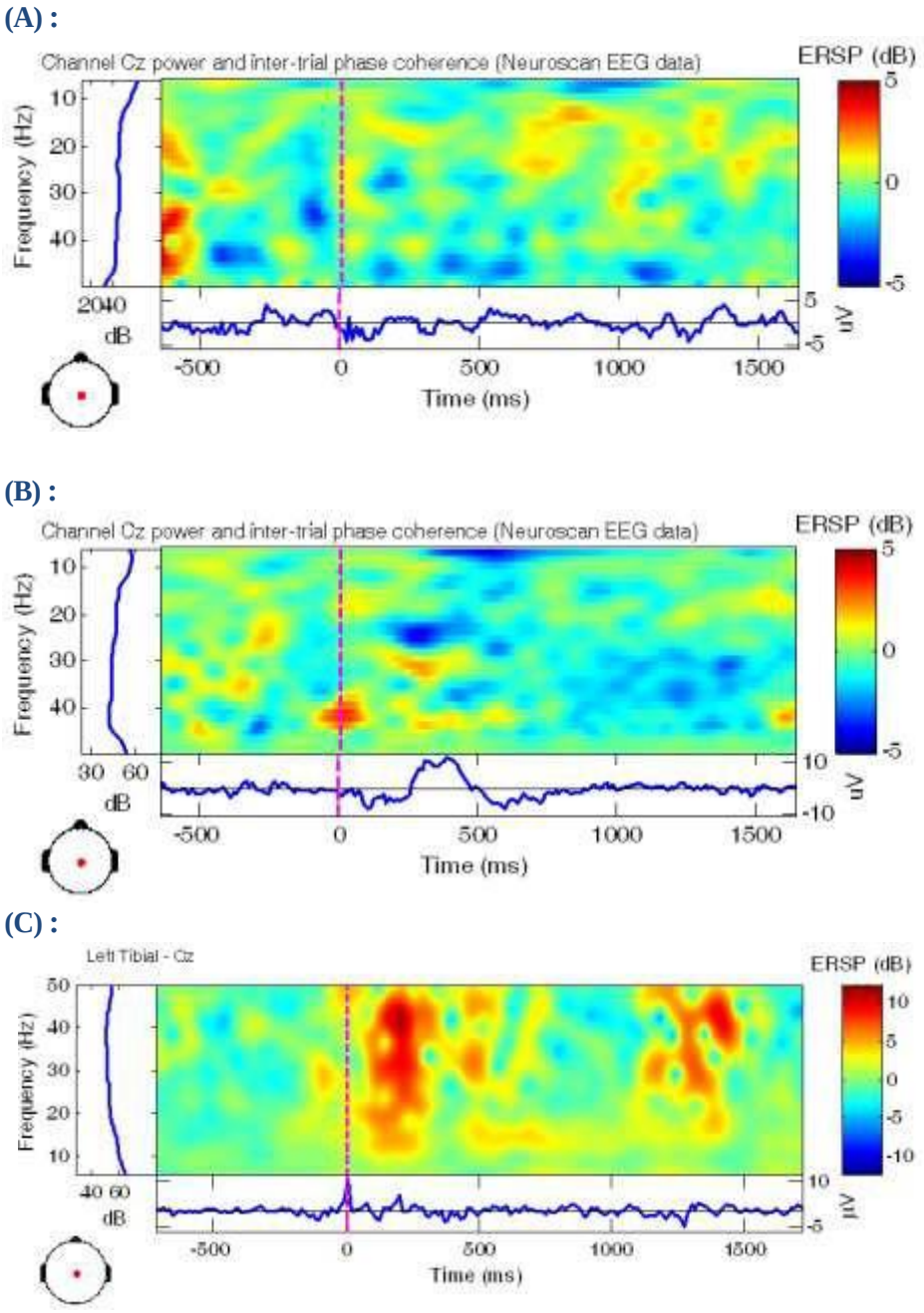


Figure 4.60: ERSP maps from Patient S2 in response to left PTN stimulation (at 2x motor threshold) at test-1 (**A**) performed 6-7 weeks following SCI test-2 (B) 21 weeks and test-3 (C) 52.5 weeks later, respectively. Changes in ERSP patterns over time are observed with partial restoration of areas and bands of desynchronisation and synchronisation at 21 weeks (B) compared to less formed patterns initially (A). With time, the ERSP map obtained at 52.5 weeks (C) shows deterioration, correspondent to observed clinical deterioration, with loss of the usual ERSP map patterns seen earlier in (B) coupled with initial recovery. *Source:* Field work.

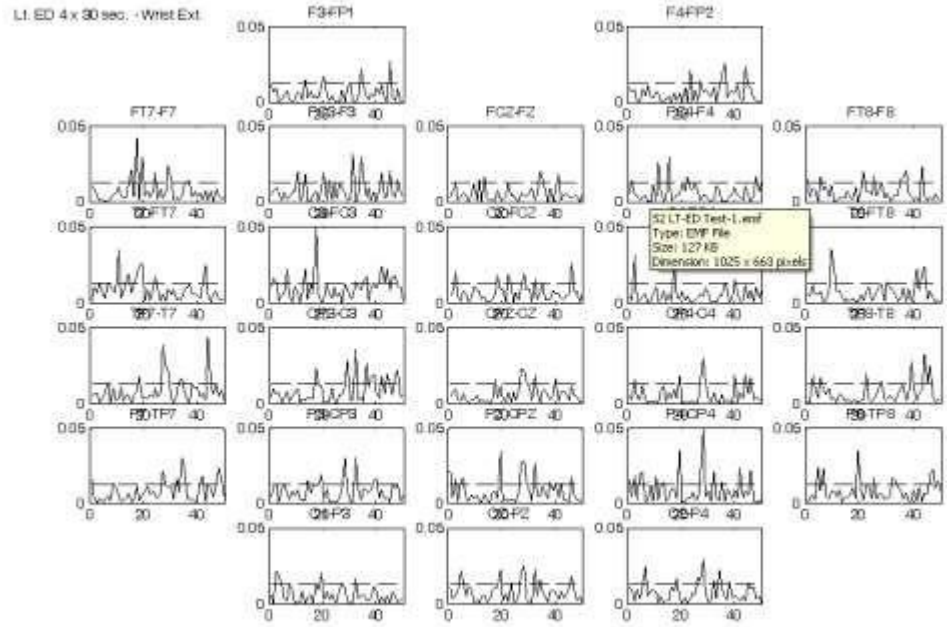
4.19 Trans-cranial Magnetic Stimulation – Motor Evoked Potentials:

TMS was not carried out in this Patient S2 because the patient had an electronic device (Baclofen pump) fitted at the times of initial and retests.

4.20 Cortico-Muscular (EEG-EMG) Coherence – CMC:

CMC analysis for simultaneous recording of EEG and EMG allowed comparisons to be made between data obtained at test 1 and test 3 time points (52 weeks separation). The CMC plots performed at test-1 and test-3 are illustrated for comparison of initial and retesting as shown in figures 4.61 and 4.62, while data obtained at test-2 are lost and not shown. CMC estimates of simultaneous EEG and EMG recordings from upper and lower limb recordings from Patient S2 are obtained and mapped. Patient S2 was able to generate voluntary muscle activity in upper limbs, although these are apparently weak motor responses especially on the left side. As seen on the AIS cartoon maps and coloured charts. The clinically observed muscle movements are minimal (all under grade 3 on MRC scale), and on the left side are down to flickering of fingers and minor limb movements sideways (grade 1 and 2, respectively). At the time of the initial test-1, there is no clear pattern seen to the coherence measurements in frequency bands at which coherence might be seen or EEG electrode sites overlying corresponding cortical areas of the hand as in Figure 4.61 and leg as in Figure 4.62. Data from test-2 was lost in a damaged hard drive, and a further test-3 was carried out as the patient still an inpatient for medical reasons. At the time of test-3 performed 52.5 weeks from test-2, Patient S2 showed clinical recovery with gain of muscle power (over 3 on MRC grade except distally in the left upper and lower limbs).

Test-1



Test-2

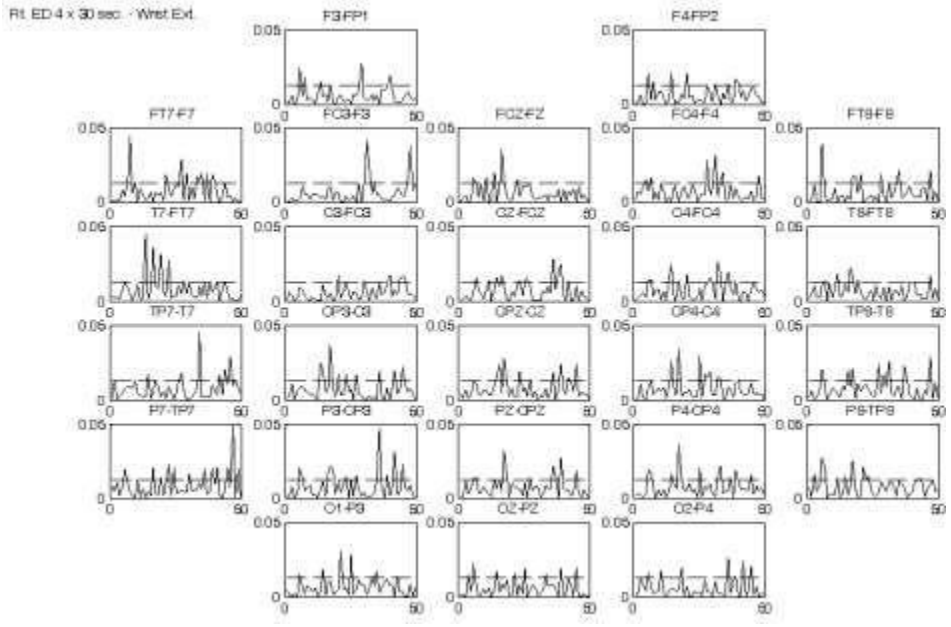
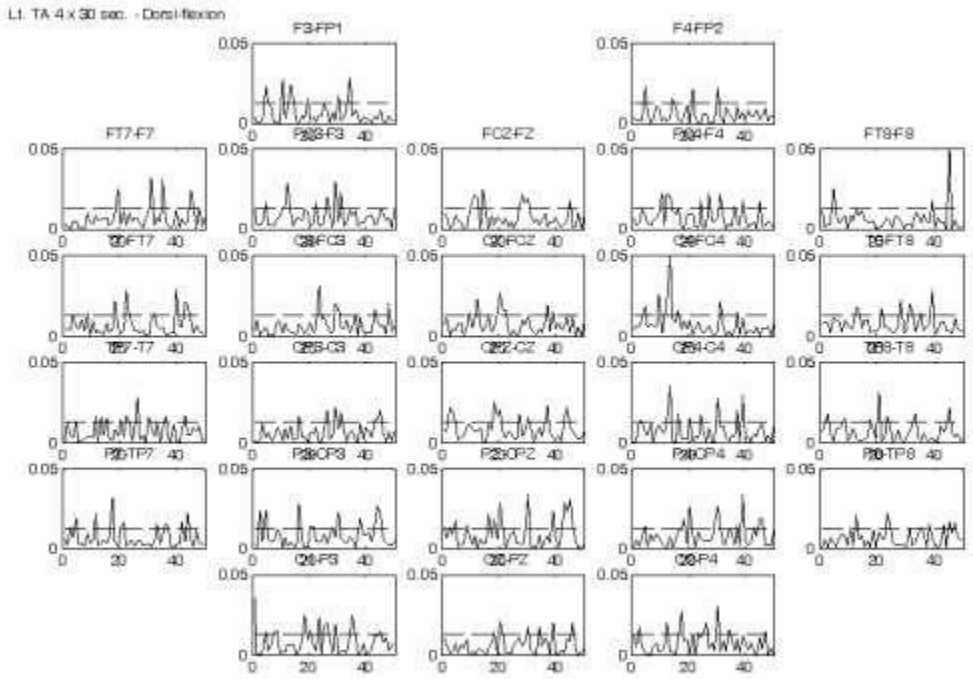


Figure 4.61 shows CMC maps performed for EEG and EMG from left ED muscle during voluntary contraction at two occasions 10 weeks apart between test-1 (top) and test-2 (bottom). There is no clear pattern of CMC could be seen either in frequency bands where coherence might be seen or EEG electrode sites overlying corresponding cortical areas of the hand (ED muscle). *Source:* Field work.

Hence, the CMC results from Test 1 reveal no clear pattern of coherence in the range of frequencies normally where coherence could be expected between EEG and contralateral EMG recordings, as shown in corresponding figures from test-1.

Test-1



Test-2

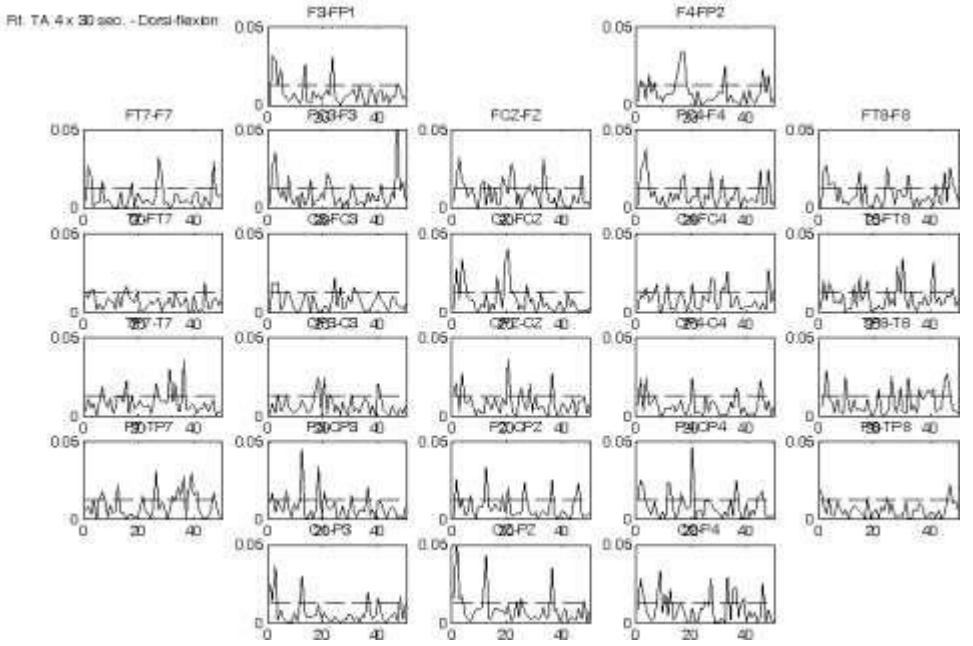


Figure 4.62 shows CMC maps performed for EEG and EMG from left TA muscle during voluntary contraction at two occasions 10 weeks apart between test-1 (top) and test-2 (bottom). There is no clear pattern of CMC could be seen either in frequency bands where coherence might be seen or EEG electrode sites overlying the corresponding cortical areas of the leg (TA muscle). During sustained contractions of left TA muscle, an intermittent coherence at variable frequencies is seen at several electrode sites with questionable significance. *Source:* Field work.

Looking at CMC maps, results from test-3 could not be located.

4.21 Interpretation of Electrophysiological Results (in light of clinical info):

Clinically, the patient displayed significant clinical improvement represented by transformation into AIS grade D over a period of approximately a year between initial and final testing. Nevertheless, there was no measurable clinical information to reflect on AIS maps which remained ASIA-C at initial and retest some 21 weeks later. Upon discharge, the patient managed many functional activities of daily living collectively related to managing all simple and medium-skill hand function especially on the right side, sitting in bed, transferring and standing however with major assistance, short distance of assisted over ground walking using gutter frame and sensing desire to pass urine. The right hand and leg appeared on the final assessment to be stronger than left and better than previously indicated. At initial test-1, manual muscle test was grade 3 out of 5 MRC scale in the right upper and lower limbs. This recovered at time of test-3 performed at the final stages of hospital treatment to grade 4 out of 5 MRC scale in some of C5 and C8 muscles of the right upper limb but all of the right lower limb muscles assessed by AIS. It is worth mentioning that the clinical sensory scores decreased due to the development of a new spinal syringe as a complication of SCI, but this was not well reflected in AIS, however was picked-up and nicely illustrated by the **ERSP pattern** losing the usual ERD band and familiar overall scalp ERSP map.

Averaged **SEP and D-SEP** waveforms were obtained and generally showed normalisation of latency and amplitude parameters from both left and right upper and lower limbs over time. This patient was retested with a 52 weeks' interval between test dates (Test-1 and Test-3). At the time of test-1, waveforms were both of small amplitudes, slightly abnormal latencies and some were completely absent. At the time of test-3, SEP and D-SEP waveforms appeared with well-defined amplitudes and robust latencies.

This patient had two phases of ASIA follow-up recorded with different clinical outcomes. The first-time interval of 15 weeks spanned from test-1 to test-2 which was featured by the development of spinal syringe leading to deterioration of the sensory scores on the clinical AIS. The ERSP map from the time of test-2 regained the usual ERD band with familiar overall scalp ERSP map picking up nicely in comparison to disturbed ERSP pattern at initial test. However, over the second time interval of 52.5 weeks from test-2 to test-3 clinical improvement and functional recovery was evidenced.

4.21.1 Group C – Patients with Incomplete SCI and Measurable Recovery:

Patient S6 (ASIA-C Incomplete T12 Paraplegia):

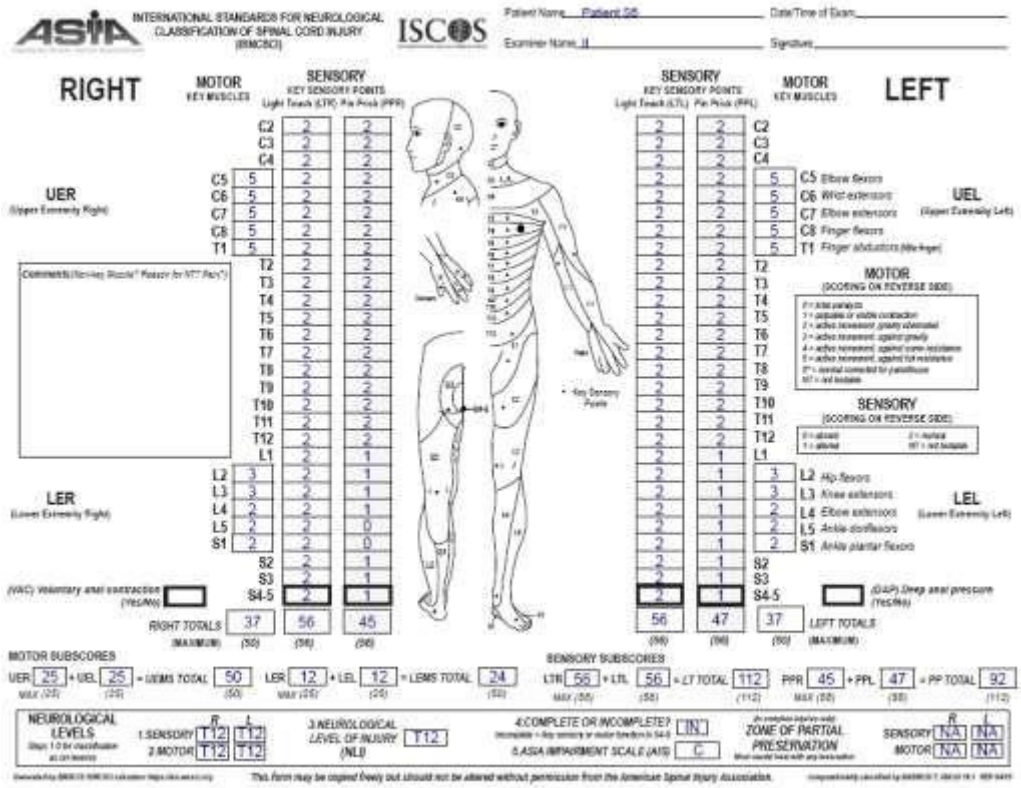
Clinical Information:

- Patient: 67-years-old female.
- **Injury level** L1 ASIA C – (& the **Neurological** level was T12).
- Time Interval – **Injury to Test 1 'initial test'**: 42 days (6 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **T12 AIS C**.
- Time Interval – **Injury to Test 2 'initial test'**: 147 days (21 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **T12 ASIA D**.
- Time Interval **– Test 1 to Test 2: 15 weeks**.
- Medications at time of Test 2:

  Temazepam 10mg at night – Tramadol HCl 50mg 4 times a day.
- On Discharged: was able to walk using crutches (4+ /5 on most muscles).
- Other information or comments: None.

Patient S6 had two tests performed at two occasions 6 and 21 weeks apart, respectively, with 15 week follow up time interval. Corresponding clinical assessment in the form of AIS maps are shown in Figure **4.63** and the colour charts for sensory-motor clinical scoring are shown in Figure **4.64**. For this SCI patient, ASIA charting clinical tools show clear recovery changes over the follow up period between times of test-1 (A) and test-2 (B) as illustrated in Figures **4.57** and **4.58**. The changes were scored over time in sensory and manual muscle power testing as shown in AIS maps and colour cartoons of the sensory-motor scoring charts. These scores of clinical recovery reflected on the AIS maps moving from AIS-C to AIS-D and paralleled sensory and motor improvement with functional improvement experienced by the patient over 15 weeks longitudinal follow up period. The functional recovery reflected in Patient S6 as an ability to walk using crutches, with muscle power of 4+ on MRC scale on most muscles. On discharge, the patient was taking (Temazepam 10mg x1 and Tramadol 50mg x 4) which might affect some electrophysiology tests.

(A):



(B):

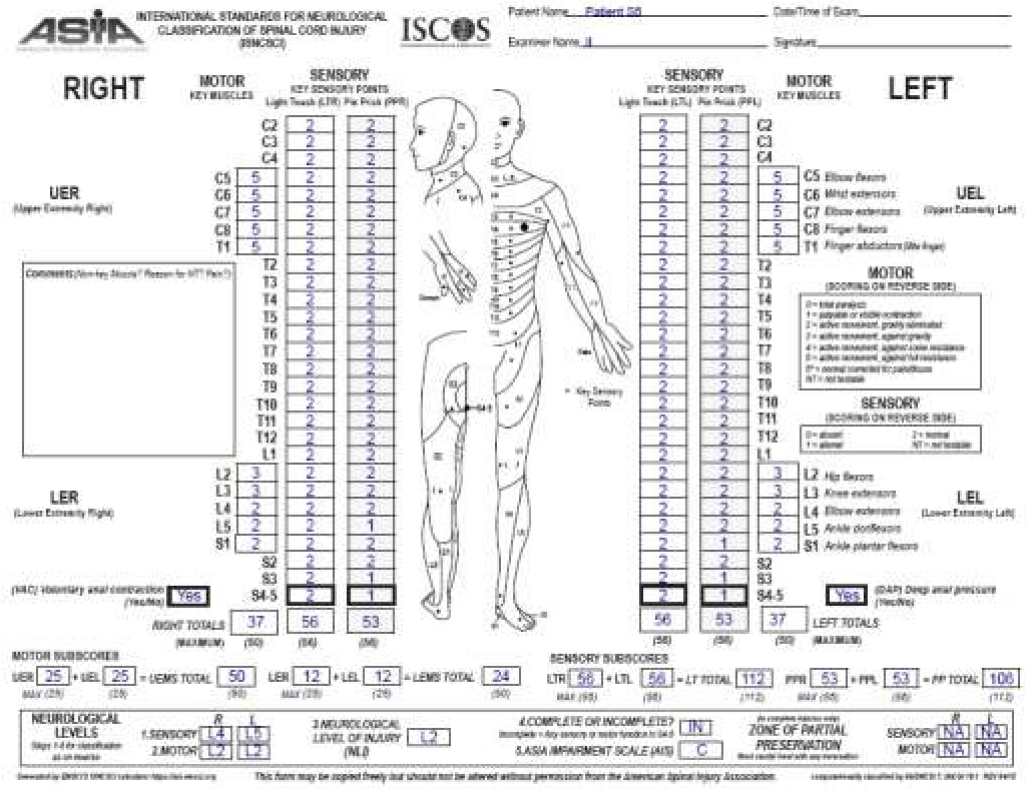
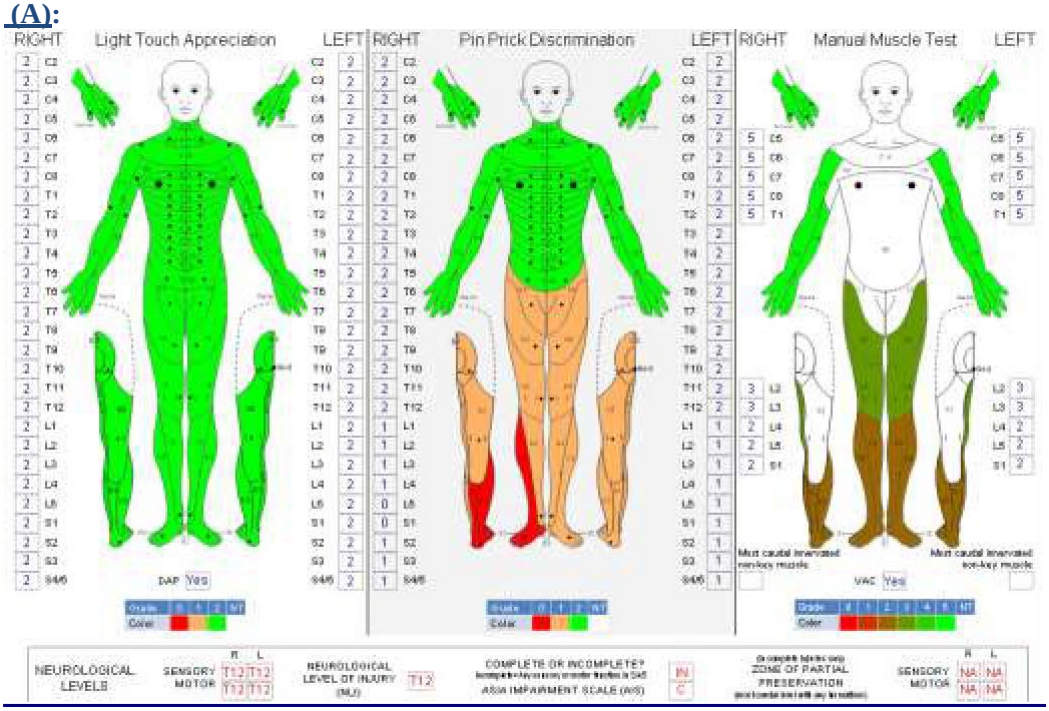


Figure 4.63 (**A**) and (**B**) shows ASIA Impairment Scale (AIS) for Patient S6 obtained at the time of test-1 (**A**) and test-2 (**B**) performed 6 and 21 weeks, respectively, following SCI with the two tests being 15 weeks part down the longitudinal follow up. *Source:* Field Work.

(A):



(B):

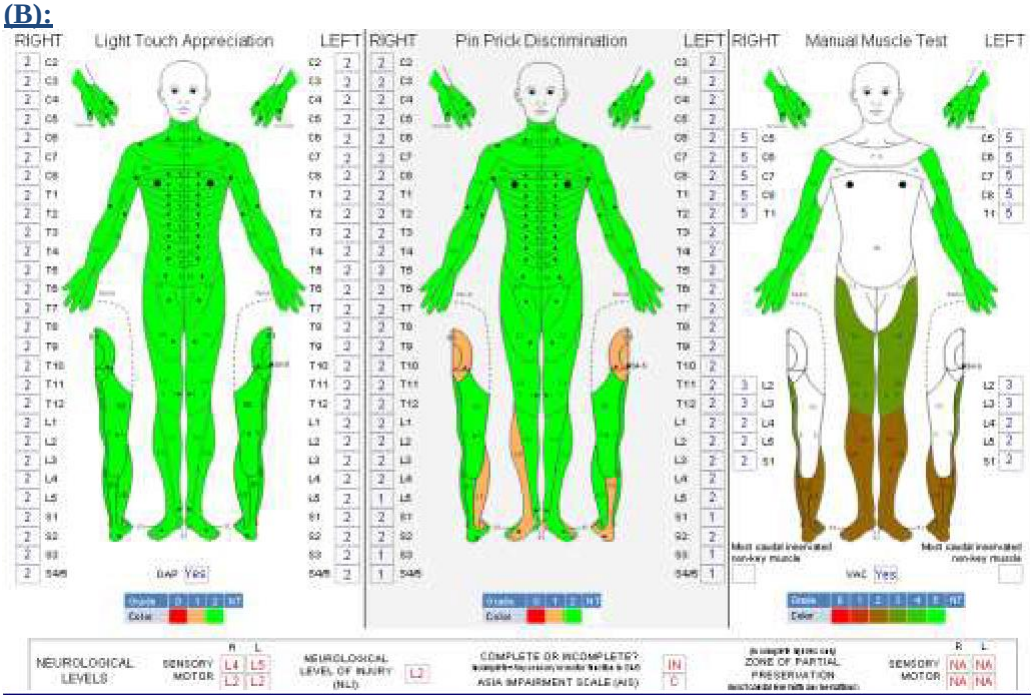


Figure 4.64 (**A**) and (**B**) shows cartoon illustrations for colour charts of the dermatomal sensory and motor maps based on clinical sensory-motor scoring values at test-1 (**A**) and test-2 (**B**) performed at 6-weeks and 21-week' intervals, respectively (15 weeks apart). *Source:* Field Work.

4.21.2 SEP and D-SEP (Waveforms and Lat-Amp Measurements):

The clinical presentation of this patient showed **marked improvement** over the course of this investigation and this improvement resulted in a change of status from AIS C to D. The change seen in the ASIA assessment was largely improved sensory scores associated with pin

prick tests below the level of the lesion but in addition the patient experienced marked **improvement in balance** (sitting, standing and walking) even although muscle test scores were unchanged over the dates of testing. These clinical improvements although not reflected in AIS chart but likely contribute to have a significant impact on the functional outcomes and ADL for the patient. At the time of test-2 this patient was taking (Temazepam 10mg x 1 and Tramadol 50mg x 4). These are drugs that are known to cause suppression of cortical responses, EEG and might affect recorded amplitudes, though less likely to be directly attributable to major latency changes.

Averaged SEP and D-SEP waveforms were obtained by stimulation of right and left Posterior Tibial nerves (PTN) and the L2 and L3 dermatomes respectively. In Figure 4.65, right PTN SEP traces are plotted from test-1 (red trace) and test-2 (black trace) performed **15 weeks** apart. These 'initial' and 'retest' traces show no clear short latency SEP responses were recorded on either test, indicating no significant electrophysiological changes of underlying sensory pathways examined. However, the lack of a short latency SEP response is confounding in relation to the patient ASIA score for light touch at sites innervated by the PTN to be 2 (ie normal sensation). Similar findings are seen in measurements of the corresponding right L2 and L3 D-SEP waveforms as shown in Figure 4.66 (**A**) and (**B**). These figures show no measurable responses obtained from right L2 D-SEP responses (**A**), however looking at the right L3 D-SEP waveforms, there might be a trace of a dispersed and delayed response. This might represent early recovery of this D-SEP response reflecting changes seen on sensory scoring on clinical assessment (sensory scores normalised).

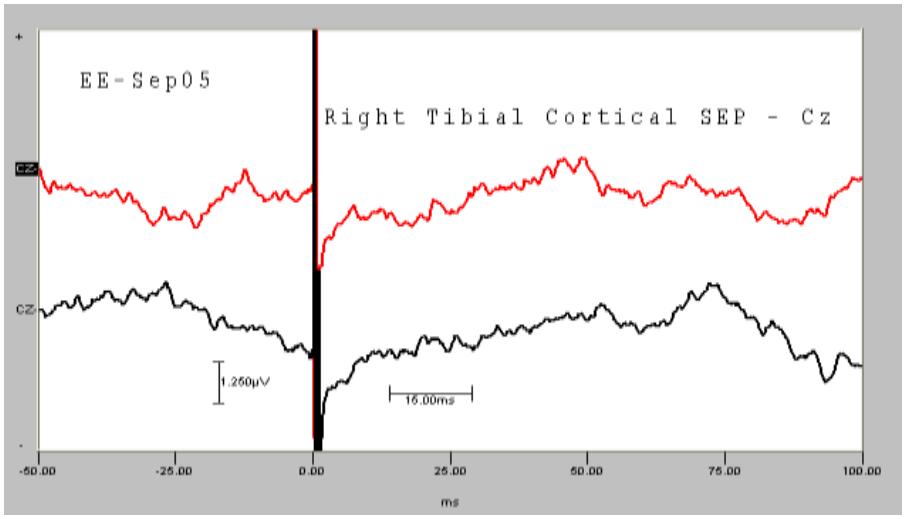
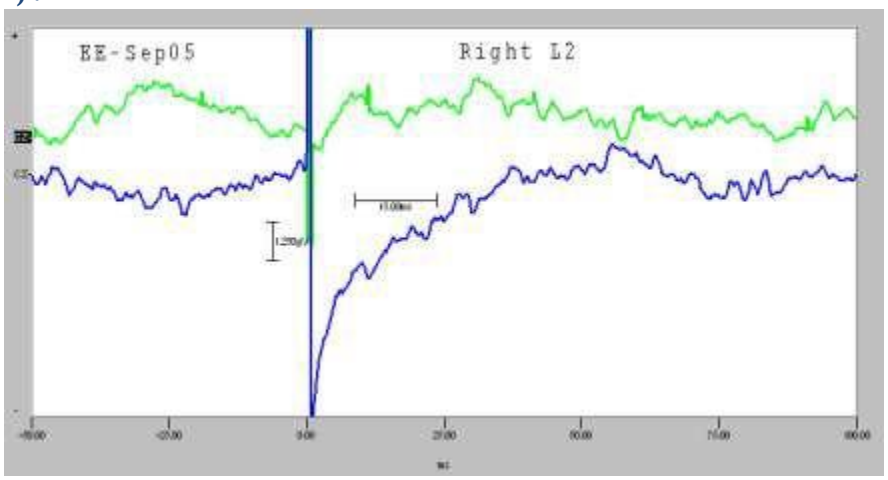


Figure 4.65: Shows averaged SEP waveform recordings of right PTN from this patient with incomplete SCI. **Red** trace represents test-1 and **black** represents test-2 performed **15 weeks** apart with no measurable SEP responses seen on either test. *Source:* Field work.

(A) :



(B) :

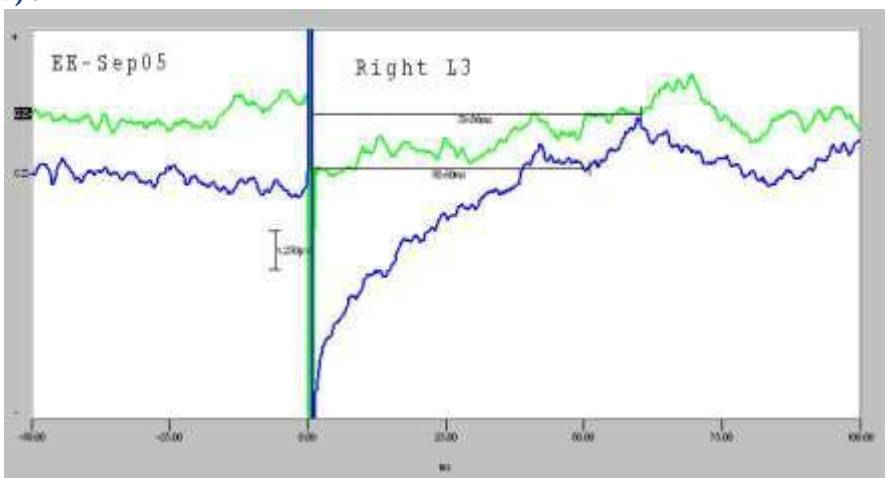


Figure 4.66 (**A**) & (**B**): shows averaged D-SEP waveform recordings of left L2 (A) and left L3 (L3) dermatomes obtained from Patient S6. **Green** trace represents test-1 and **blue** represents test-2 performed **15 weeks** apart. No measurable D-SEP responses seen on either test on right L2, however the right L3 show a dispersed delayed response. *Source:* Field work.

SEP and D-SEP waveform parameters from lower limb stimulation sites are shown and detailed in table 4.14. Latency and amplitudes parameters of PTN SEP and L2 and L3 D- SEP responses are shown. Right L2 D-SEP responses were absent at test-1 but became recordable at test-2. However, the remaining SEP and D-SEP waveform parameters were largely similar in test-1 and test-2 performed 15 weeks apart, however with marginal variation in values recorded for latencies and amplitudes.

Table 4.14: details of measured values for amplitude and inter-peak latency parameters from right and left lower limb SEP and D-SEP waveforms recorded at test-1 and test-2 performed **10-weeks** apart. The upper limb (UL) study findings were not included here. *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 = **42 days**.*						***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 = **147 days**.*						
	Acute	***C***						***D***						
S6	**T12**	***Rt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***	***Rt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***
	Incomplete Paraplegia	***Am:***	--	--	--	*Absent*	*0.43*	*0.25*	***Am:***	--	--	--	*0.40*	*0.14*	*0.30*
67-yrs	**UL** not Included here	***Lat:***	--	--	--	*N/A*	*49.30*	*39.60*	***Lat:***	--	--	--	*43.80*	*49.70*	*42.70*
		Lt:	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***	***Lt:***	***C5***	***C6***	***Med***	***L2***	***L3***	***PTN***
Patient S6	**Complete Test x 2**	***Am:***	--	--	--	*0.65*	*0.30*	*0.47*	***Am:***	--	--	--	*0.45*	*0.45*	*0.61*
		Lat:	--	--	--	*28.80*	*33.70*	*38.70*	***Lat:***	--	--	--	*32.60*	*34.10*	*41.50*

4.21.3 ERSP (Spectral Maps for Slow Sensory Stimulation):

ERSP maps were obtained for lower limb PTN SEP and D-SEP stimulation sites. Figures 4.67 and 4.68 show 'initial' and 'retest' ERSP patterns performed at times of test-1 and test- 2, respectively. ERSP maps for right PTN stimulation obtained for test-1 and test-2 (as shown in these two figures below), show no clear periods of either event related synchronisation or de synchronisation. ERSP maps for 'initial' and 'retest' with stimulation of left PTN are in the appendix, showing similar results with no identifiable patterns relating to normal ERSP maps initially and following 15 weeks follow up.

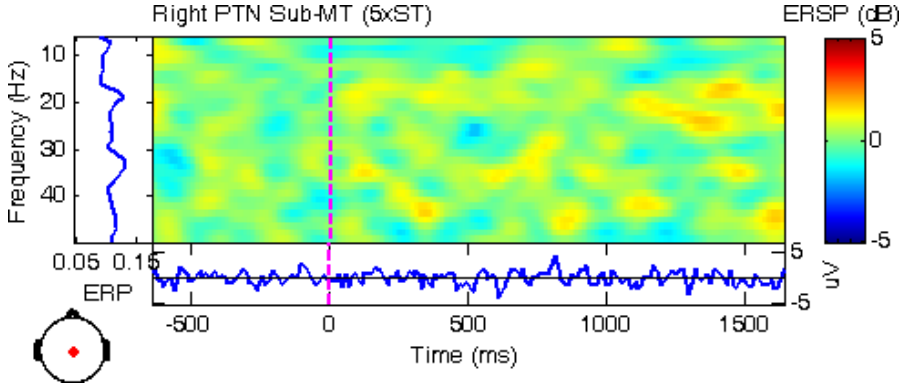


Figure 4.67: shows (**initial**) ERSP map obtained from SCI patient with T12 Paraplegia using bi-polar montage recording of cortical responses at Cz electrode in response to stimulation of right PTN. There were no formed patterns of ERD or healthy ERSP maps observed at this occasion (from Field work).

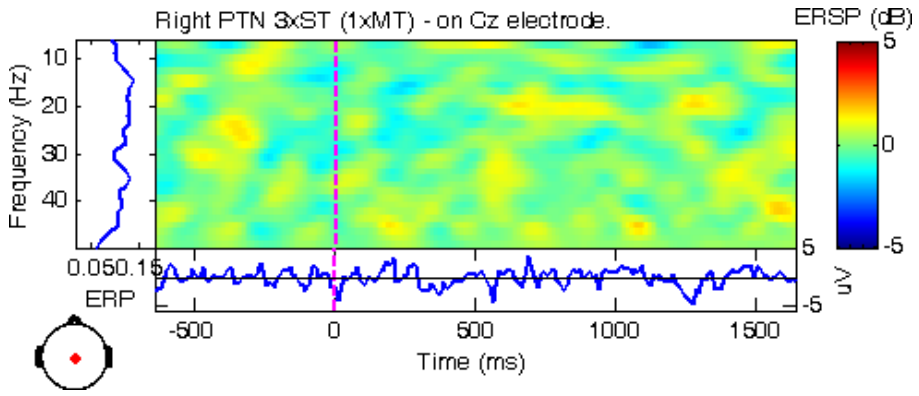


Figure 4.68: shows (**follow-up**) ERSP map obtained the same SCI patient described above with the previous ERSP shown using same standard testing parameters. Normal ERSP pattern was consistently absent at the 'initial' test as previously described (***as shown Figure 4.61***) as well as this 'retest' performed after **15-weeks'** time interval along the follow-up period. *Source:* Field work.

4.21.4 Trans-cranial Magnetic Stimulation – TMS (Motor Evoked Potentials – MEP):

In this T12 paraplegic patient TMS was directed to cortical sites expected to activate the TA muscles of left and right legs. In Figure **4.69**, example MEP recordings for test-1 (black trace) and test-2 (red trace) from the left TA muscle obtained is shown. The time interval separating test-1 from test-2 was **15 weeks** along the follow-up period. In both cases the stimulation intensity is 55%. In describing these averages, it would appear that the retest MEP is more synchronised than the MEP seen on test 1 and appears with a shorter latency.

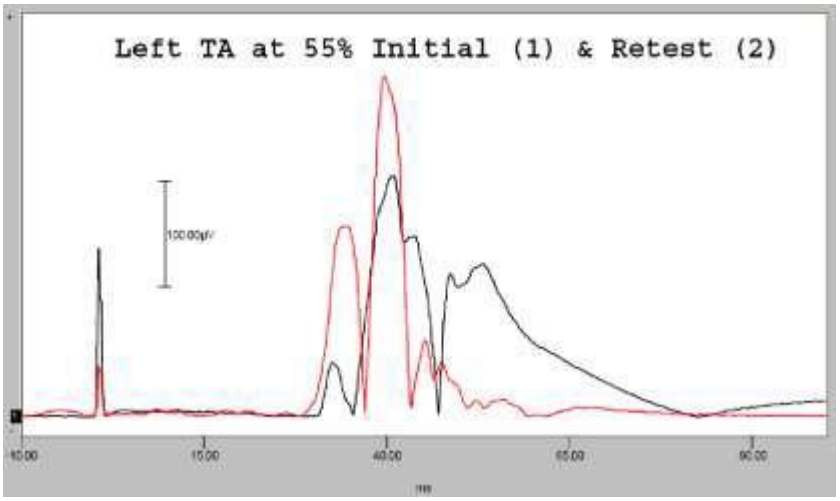


Figure 4.69: MEP responses from EMG recording of left *Tibialis Anterior* (TA) muscle obtained using TMS at 55% stimulation intensity directed at Cz cortical electrode, on two separate occasions **15 weeks** apart. Rectified MEP responses at test-2 (red trace) achieved larger amplitude, slightly shorter (faster arriving) latency and more synchronous MEP. *Source:* Field work.

When TMS-obtained MEP responses were studied for Latency measurements, obvious changes at test-2 compared to test-1 are shown in Figure 4.70 (**A**) and (**B**). At test-1 with the patient clinically recorded as ASIA-C, MEP latencies were delayed and irresponsive to incremental TMS intensities. In contrast, at test-2 with the patient clinically recorded as ASIA-D, correspondent MEP latencies improved to reach normal levels and became responsive to TMS.

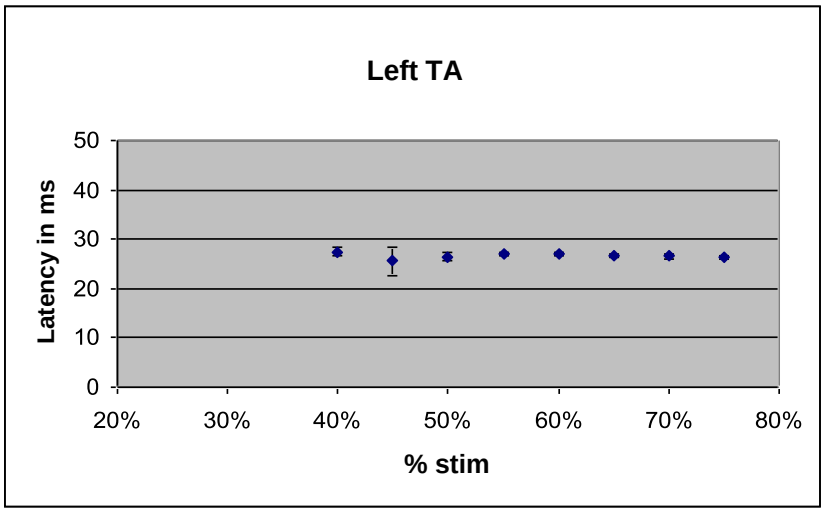


Figure 4.70 (**A**): MEP responses from left TA muscle obtained at incremental TMS intensities, however with no response to incremental stimulation with MEP latencies seen at abnormally delayed measurements at all levels of stimulation. *Source:* Field Work.

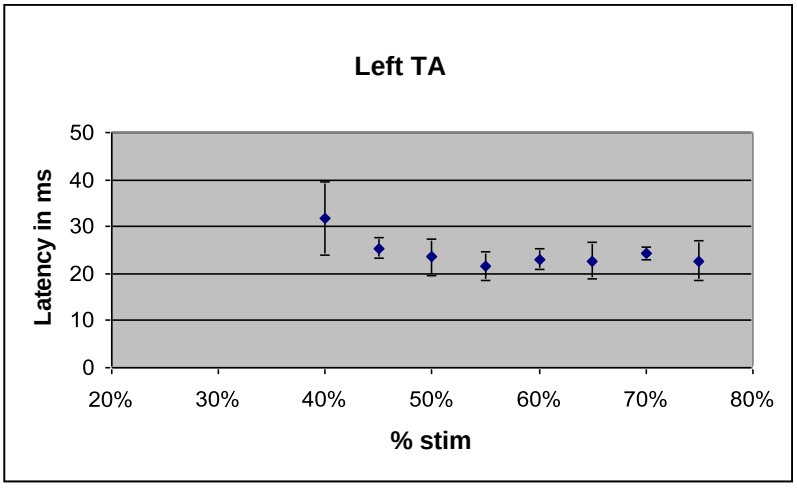


Figure 4.70 (**B**): MEP responses from left TA muscle obtained at incremental TMS intensities, with obvious response to incremental stimulation with the MEP latencies seen to build-up with incremental intensities from 40% to maximum tolerated. *Source:* Field Work.

Changes observed in MEP latencies of the left TA muscle recordings at test-2 compared to test-2 were visually obvious, and reached statistical significance at most stimulation intensities over 50% intensities, as shown in Figure 4.71.

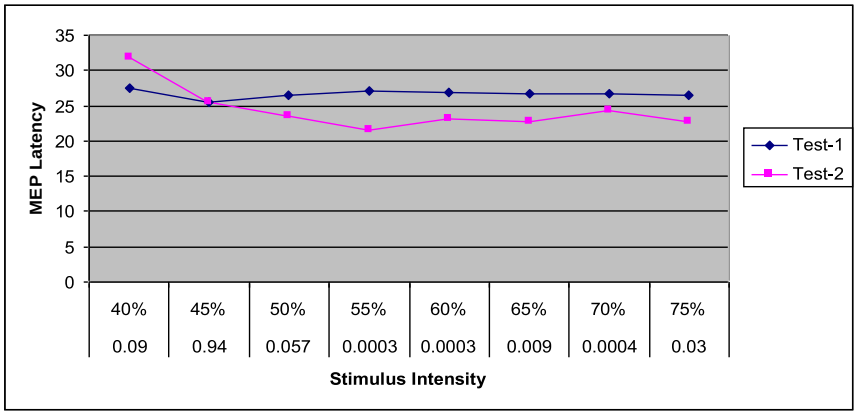


Figure 4.71: MEP responses from left TA muscle obtained at incremental TMS intensities, with significant shortening latency (quicker arriving amplitude) seen at most TMS intensities higher than 50% reaching statistical significance. *Source:* Field Work.

Similar comparison was made for the MEP amplitudes obtained for test-1 and test-2 shown in Figure 4.72 (**A**) and (**B**). As the AIS for Patient S6 scored some clinical improvement to ASIA-D at test-2 from initial ASIA-C at test-1, the corresponding MEP measurements showed improvement with growth of the amplitudes (MEP sizes) as shown in Figure 4.72 (**A**) from earlier test-1 and (**B**) from follow up at test-2 15 weeks later. Therefore, MEP measurements demonstrated recovery as seen on MEP latencies as well as amplitudes obtained at test-2 compared to those from test-1 performed 15 weeks earlier.

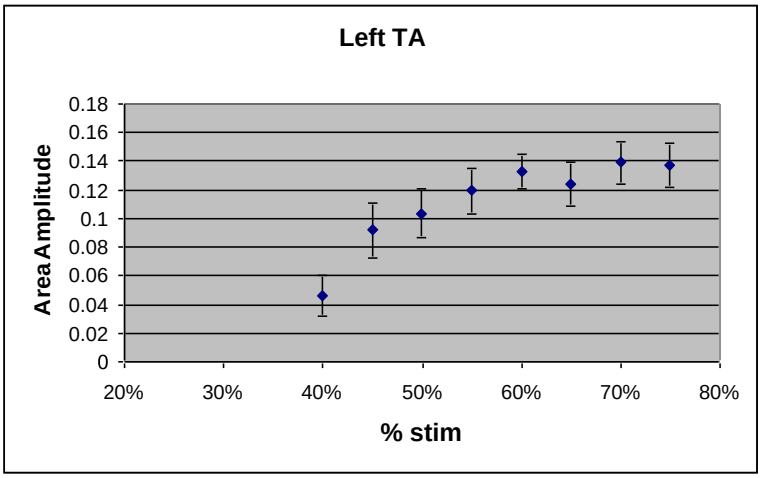


Figure 4.72 (**A**): MEP responses from left TA muscle obtained at incremental TMS intensities, however with no response to incremental stimulation with MEP latencies seen at abnormally delayed measurements at all levels of stimulation. *Source:* Field Work.

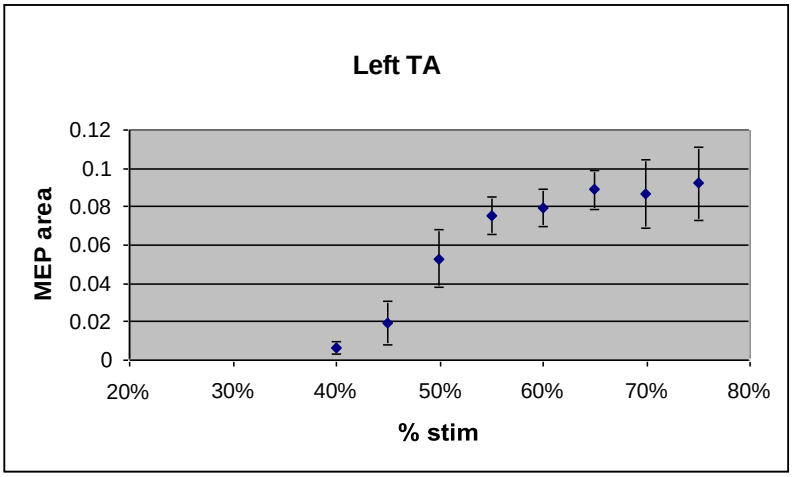


Figure 4.72 (**B**): MEP responses from left TA muscle obtained at incremental TMS intensities, with obvious response to incremental stimulation with the MEP latencies seen to build-up with incremental intensities from 40% to maximum tolerated. *Source:* Field work.

MEP sizes or amplitude findings from Figures 4.72 (**A**) and (**B**) were plotted in a single graph (Figure 4.73), which instantly illustrates obvious difference in the amplitude responses (MEP size) at test-1 and test-2 recorded 15 weeks apart. During this elapsing time interval, the patient improved clinically scoring ASIA-D from ASAI-C with power (4+/5) in most lower-limb muscles, coupled with significant functional improvement enabling walking using crutches. The patient was on (Temazepam 10mg x 1 and Tramadol 50mg 4 x 1), medications that suppresses muscles and CNS, but not preventing the gain observed in amplitude.

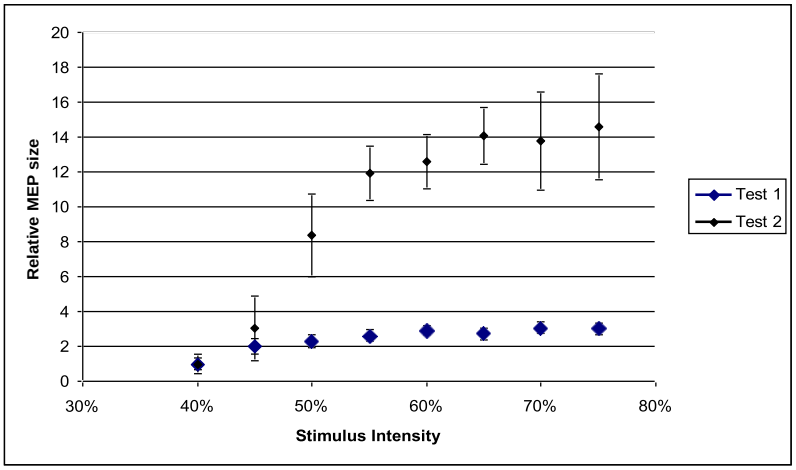


Figure 4.73: Relative MEP recruitment curve for left TA muscle for SCI patient with T12 Paraplegia tested at 6 and 21weeks post injury. MEP size is the average area of 10 responses to TMS delivered using a double-cone coil positioned over the vertex. *Source:* Field work.

On the other hand, although at test-2 this patient clinically scored ASIA-D which is a significant improvement from the previous ASAI-C scored at test-1, the MEP latencies seen from the right TA muscle recording were apparently similar at these two testing occasions. This might suggest that the SCI lesion in this patient might not be symmetrical, with the right side being less affected remaining similar in findings while the left side with much improvement being much more severely affected at the onset. Figure 4.74 (**A**) and figure 4.74 (**B**) shows similarities of MEP latency recordings of test-1 and test-2.

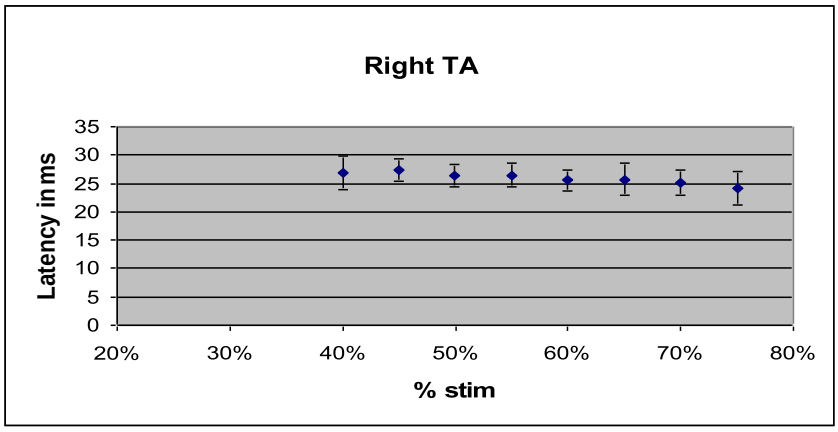


Figure 4.74 (**A**): MEP responses from right TA muscle obtained at incremental TMS intensities (test-1) with no obvious shortening of MEP latencies (seen at normal levels). *Source:* Field work.

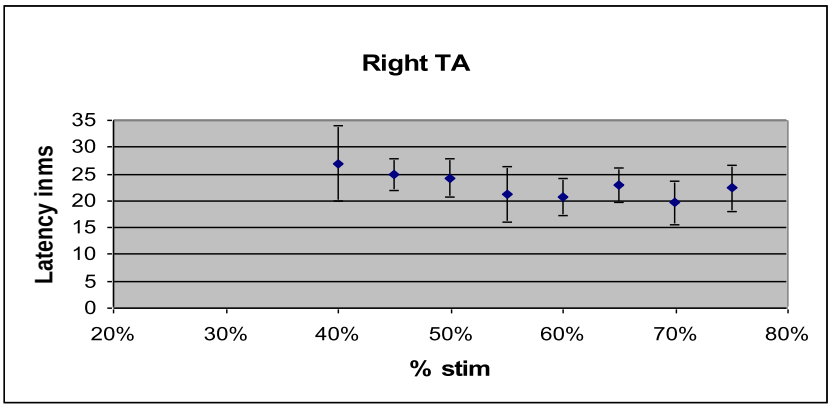


Figure 4.74 (**B**): MEP responses from right TA muscle obtained at incremental TMS intensities (test-2) with no obvious shortening of MEP latencies (seen at normal levels). *Source:* Field work.

However, the calculation of statistical significance of the MEP response of the right TA for latency measurements shows some difference between test-1 and test-2 as shown below in Figure **4.75**. In this figure, MEP latencies obtained from right TA muscle recordings were visually similar but reached statistical significance at stimulations intensities from 55% to 70%.

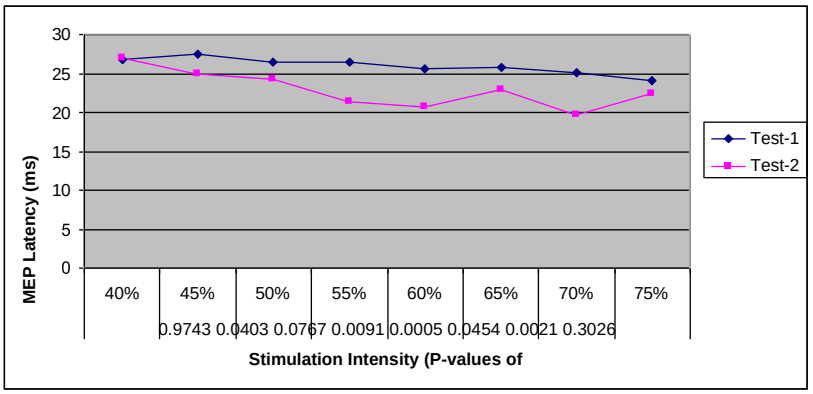


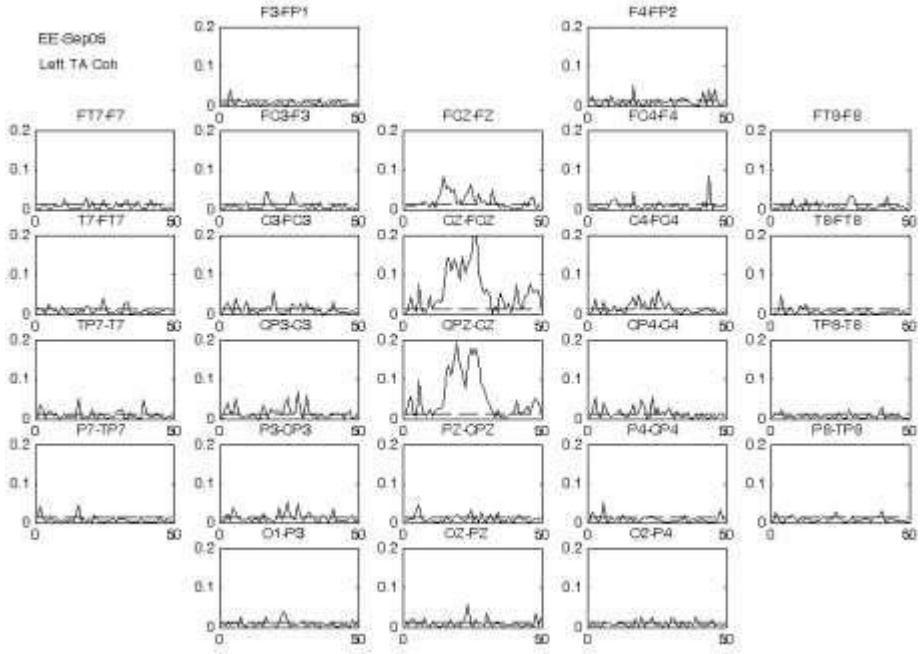
Figure 4.75: MEP responses from right TA muscle obtained at incremental TMS intensities, with significant shortening latency (quicker arriving amplitude) seen with incremental TMS intensities above 55% (however variable at certain intensities). *Source:* Field work.

Seemingly, Patient S6 scored some clinical recovery reflected in AIS climbing from ASIA-C to ASIA-D over 15 weeks follow up, mainly a recovery in the area of gain of muscle power, mirroring recovery of MEP latency measurements and amplitude that is statistically significant. However, the right and left sides were not symmetrical largely in relation to the initial AIS reflecting the SCI.

4.21.5 Cortico-Muscular (EEG-EMG) Coherence – CMC:

CMC for simultaneous EEG and EMG from left and right lower limb muscles were obtained. Coherence data is shown in figures below which displays maps of CMC from montage of bi-polar electrode recordings covering the entire scalp. Maps for left Tibialis Anterior (TA) muscle are shown in Figure 4.76 (**A**) and (**B**), with maps for the right TA muscle shown in Figure 4.77 (**A**) and (**B**). For left and right TA, the peak CMC appears at bipolar scalp recordings overlying the vertex at Cz. This Patient S6 with (ASIA-C T12 Incomplete Paraplegia), demonstrated an improved motor score over the follow-up period from test-1 to test-2, yet the CMC for this patient in the beta frequency band is smaller during test-2 compared with test-1. This might in part be related to medications taken by the patient and how these medications might influence the magnitude of oscillatory components within the EEG or EMG recordings obtained. It is worth mentioning that (at time of Test-2, the patient was on small to moderate doses of Temazepam and Tramadol). But may also represent a change in the way motor-units are recruited over the course of time resulting in less dependency on oscillatory coupling. Interpreting results of CMC require considerations to be given to medications being used, however the presence of coupled oscillatory activity between EEG and EMG seen in this CMC cortical map, suggests that the corticospinal tract (CST) in this subject is capable of sustaining relatively normal motor activation patterns.

(A) :



(B) :

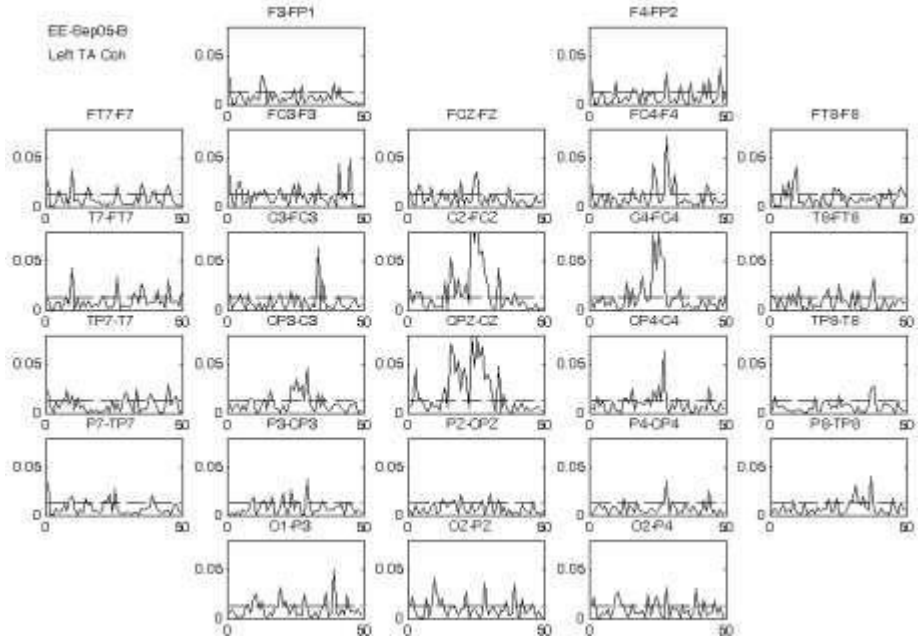
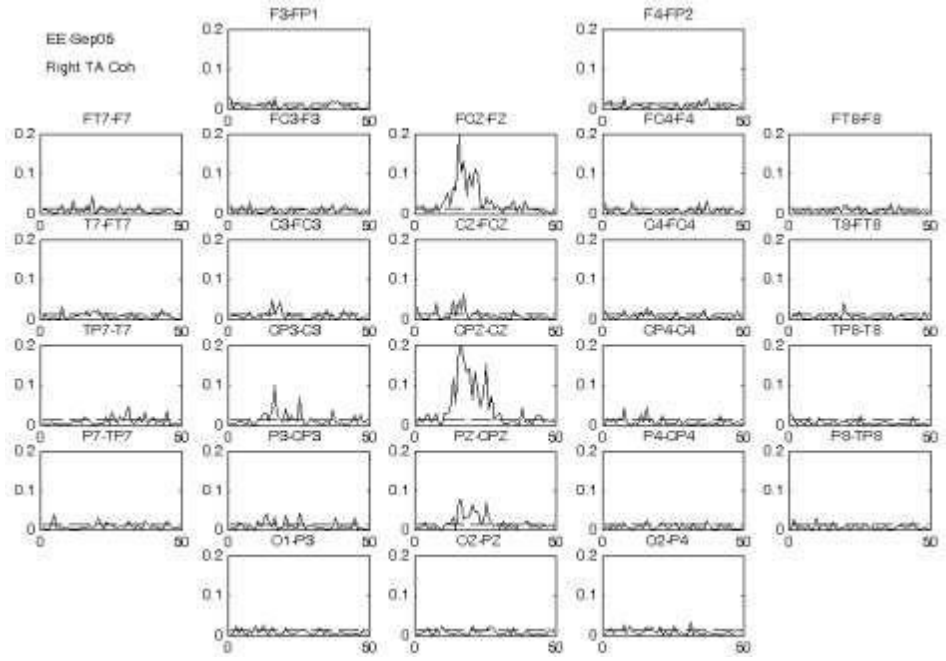


Figure 4.76 (**A**) and (**B**): Cortico-muscular coherence estimated between selected bipolar EEG channels and the left TA muscles during repeated short-lasting periods of voluntary ankle dorsi- flexion. Recordings are from SCI patient tested approximately 6 weeks and 21 weeks post injury. Noted here is that the peak coherence occurs in the beta range of the EEG frequency. In general, the magnitude of calculated CMC decreases over time, in addition to evidence of change in the distribution of electrode pairs that show significant coherence being recorded. At test-1, Patient S6 with ASIA-C T12 SCI had a motor score of 2 MRC on ankle dorsi-flexion (**A**). After 15 weeks, the AIS improved to ASIA-D with a motor score of 3 MRC on ankle dorsi-flexion (**B**).

Source: Field work.

(A) :



(B) :

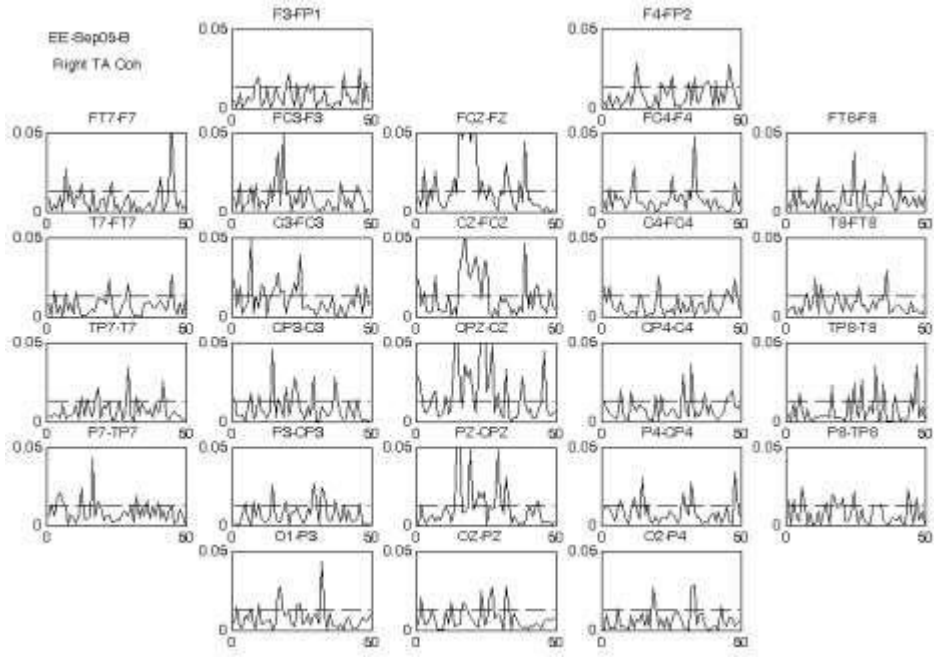


Figure 4.77 (**A**) and (**B**): Cortico-muscular coherence estimated between selected bipolar EEG channels and the right TA muscles during repeated short-lasting periods of voluntary ankle dorsi- flexion. Recordings are from SCI patient tested approximately 6 weeks and 21 weeks post injury. Noted here is that the peak coherence occurs in the beta range of the EEG frequency. In general, the magnitude of calculated CMC decreases over time, in addition to evidence of change in the distribution of electrode pairs that show significant coherence being recorded. At test-1, Patient S6 with ASIA-C T12 SCI had a motor score of 2 MRC on ankle dorsi-flexion (**A**). After 15 weeks, the AIS improved to ASIA-D with a motor score of 3 MRC on ankle dorsi-flexion (**B**).

Source: Field work.

4.22 Interpretation of Electrophysiological Results:

The findings from all electrophysiological tests performed for Patient S6, who is 67-year-old SCI female with (**ASIA-C Incomplete T12 Paraplegia**) show **a** significant improvement in most muscles grades (4+/5) contributing to AIS transformation into of AIS C to D. There was also significant functional improvement enabling the patient to walk using crutches.

The results of the **objective tests** performed **15 weeks** later on the longitudinal follow up period **indicated** obvious recovery and change of electrophysiological parameters towards normality. Looking at the **SEP and D-SEPs**, the right L2 D-SEP responses were absent at test-1 but became recordable at test-2, while the remaining SEP and D-SEP waveforms were remaining largely similar to test-1 15 weeks later. Marginal variation of the values of recorded latency and amplitude responses were seen. The **ERSP** patterns were however less informative and over the 15 weeks of the follow-up period, remained featureless and carry little resemblance to the patterns of the normal ERSP maps. The **MEP** waveform measurements show robust growth (improvement) of amplitude sizes at test-2 performed 15 weeks later compared to test-1. The

amplitude changes were associated with latency shift (shortening with earlier arrival of MEP response) reaching statistical significance at several TMS intensities used for various muscles being tested. The **CMC calculations and analysis** showed smaller CMC during test-2 compared with test-1, which might be in part be related to medications being used at the time of test-2 affecting the magnitude of oscillatory components of EEG and EMG signals. In this recovering ASIA-C becoming ASIA-D patient with T12 Para-paresis, for the left and right TA muscles, the peak CMC appears at bipolar scalp recordings overlying the vertex at Cz. The presence of this CMC indicative of coupled oscillatory activity between EEG and EMG signals, suggests that the corticospinal tract (CST) in this patient is capable of sustaining relatively normal motor activation patterns.

This patient was taking **medications** including (Temazepam 10mg once per day and Tramadol 50mg four times per day) which might have some influence on **CMC calculations**, **sensory propagation**, **cortical responses** of **SEPs and D-SEPs parameters** and **MEP responses**, although these medications are less likely to abolish SEP D-SEP or especially MEP responses. Caution and careful considerations with allowance for the effects of medications is important in correct interpretation of electrophysiological findings obtained in patients taking these medications.

4.22.1 Patient S1 (ASIA-C Incomplete C5 Tetra-paresis):

Clinical Information:

- Patient: 49-years-old male.
- **Injury level** C5 ASIA B on addmission
- Time Interval – **Injury to Test 1 'initial test'**: 50 days (7 weeks).
- ASIA Impairment Scale **on Test 1 'initial test'**: **C5 ASIA C**.
- Clinical Information at time of Test 1:

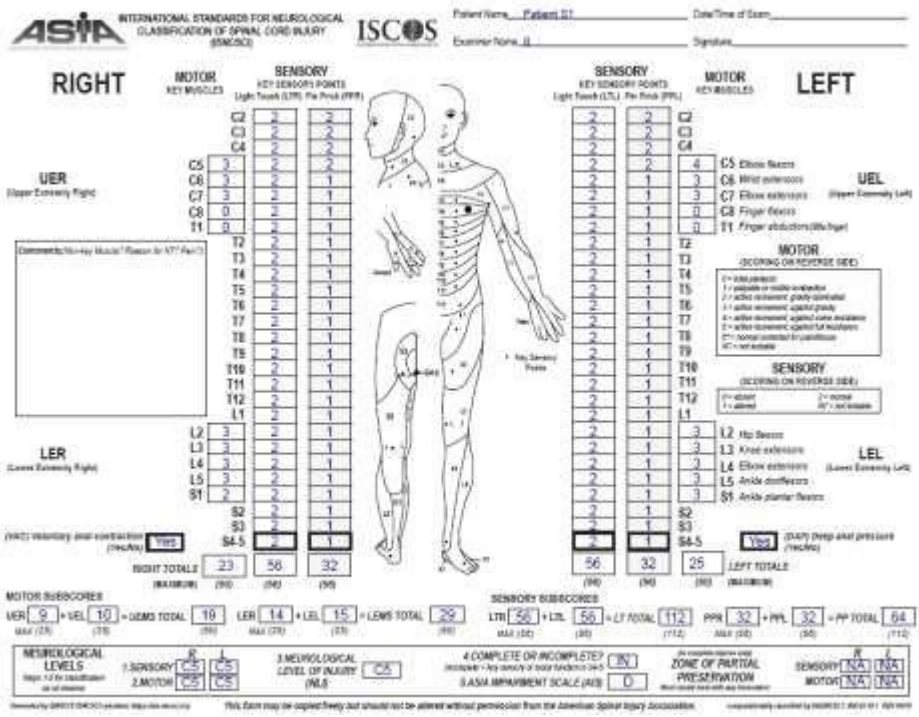
  Upper limbs: Right 3- to 3+ /5 proximally and 0/5 distally.
  Left 3- to 4 /5 proximally and 0/5 distally.
  Pin prick was normal proximally and reduced distally.

  Lower limbs: Right 2+ to 3- /5 and Left 3 to 3+ /5, with pin prick sensation was reduced on both sides.
- Time Interval – **Injury to Test 2 'initial test'**: 147 days (21 weeks).
- ASIA Impairment Scale **on Test 2 'retest'**: **C5 ASIA D**.

- Time Interval – **Test 1 to Test 2: 14 weeks**.
- Medications at time of Test 2: Diazepam and Temazepam.
- On Discharged: Clinical improvement & Independence with most ADL.
- Other information: None.

Patient S1 had test-1 and test-2 performed at 7 and 21 weeks, respectively, with 14 weeks follow-up time interval separating the two tests. Corresponding clinical assessment in the form of AIS maps are shown in figure 4.78 and colour charts for sensory-motor clinical scoring are shown in Figure 4.79. For this SCI patient, clinical tools in the form of ASIA charting show recovery changes over 14-week follow up period span between times of test-1 (A) and test-2 (B) illustrated in figures below. The functional recovery reflected in Patient S1 scoring clinical improvement and gaining independence with most activities of daily living. On discharge, patient was taking (Diazepam and Temazepam) which might affect some electrophysiology tests.

(A) :



(B) :

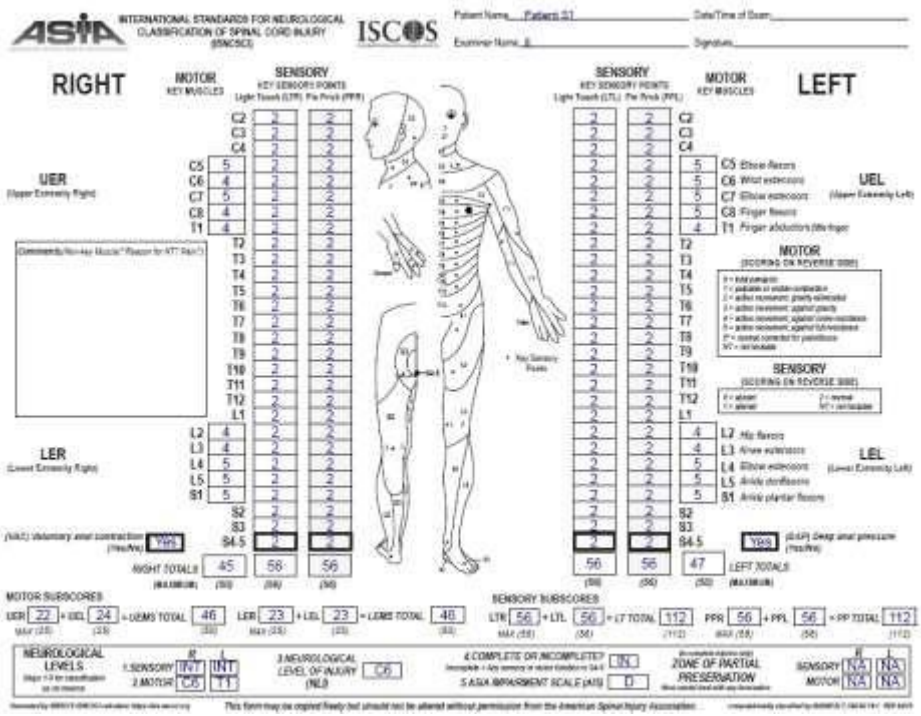
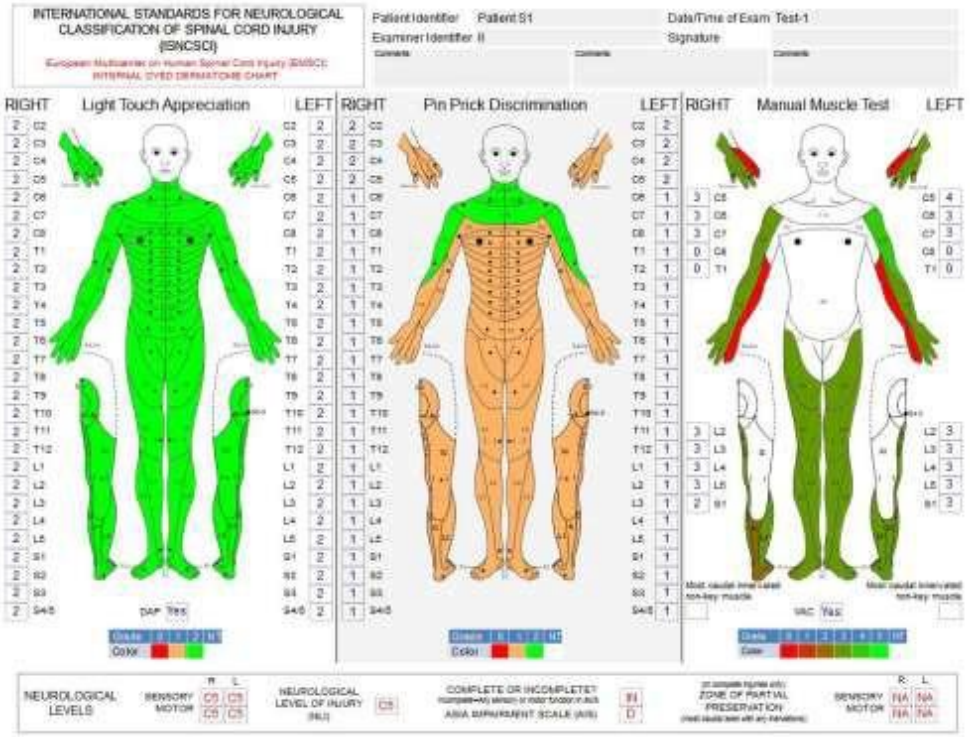


Figure 4.78 (**A**) and (**B**) shows ASIA Impairment Scale (AIS) for Patient S1 obtained at the time of test-1 (**A**) and test-2 (**B**) performed 7 and 21 weeks, respectively, following SCI with the two tests being 14 weeks part down the longitudinal follow up period. *Source:* Field work.

(A):



(B):

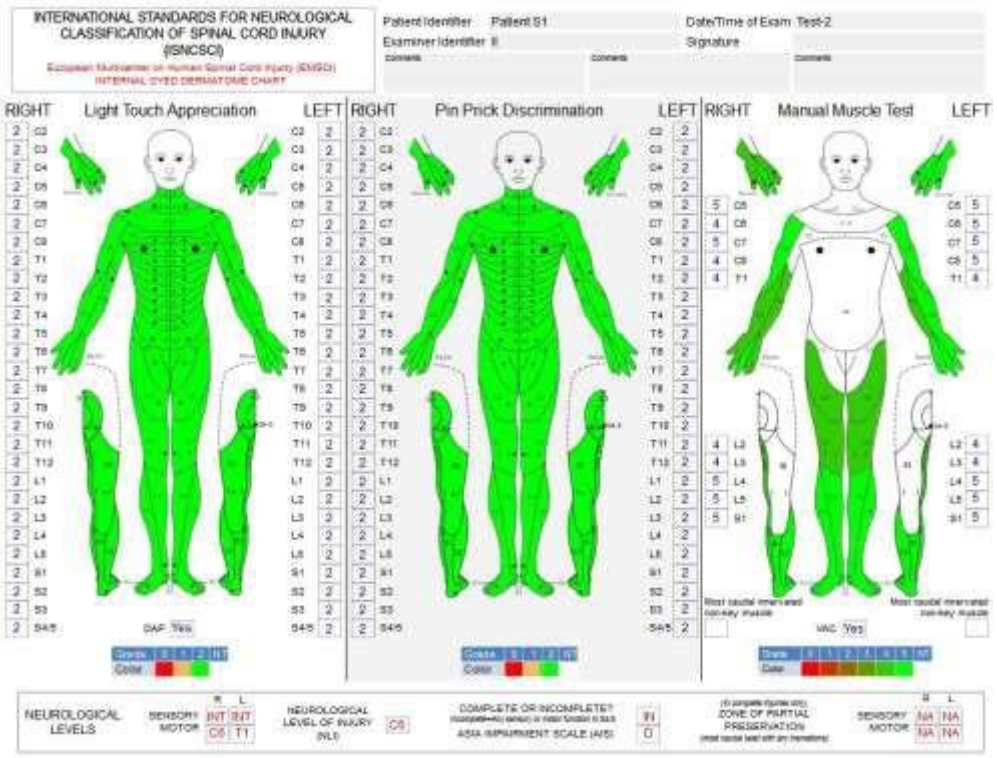


Figure 4.79 (**A**) and (**B**) shows cartoon illustrations of colour charts for the dermatomal sensory and motor maps based on clinical sensory-motor scoring values obtained at test-1 (**A**) and test-2 (**B**) performed 14 weeks apart at 7 and 21weeks intervals, respectively. *Source:* Field work.

4.23 SEP and D-SEP (Waveforms and Lat-Amp Measurements):

Averaged SEP waveforms were obtained by stimulation of left and right Median and Posterior Tibial nerves, and D-SEP waveforms from L2, L3, C5 and C6 dermatomes. In Figure 4.80, left and right median nerve SEP traces from test-1 and test-2 are plotted (red = test 1, black = test 2). In all cases a clear short latency SEP is visible. On retest there is a slight shortening of the early component of the left SEP and also clearer and sharper late components.

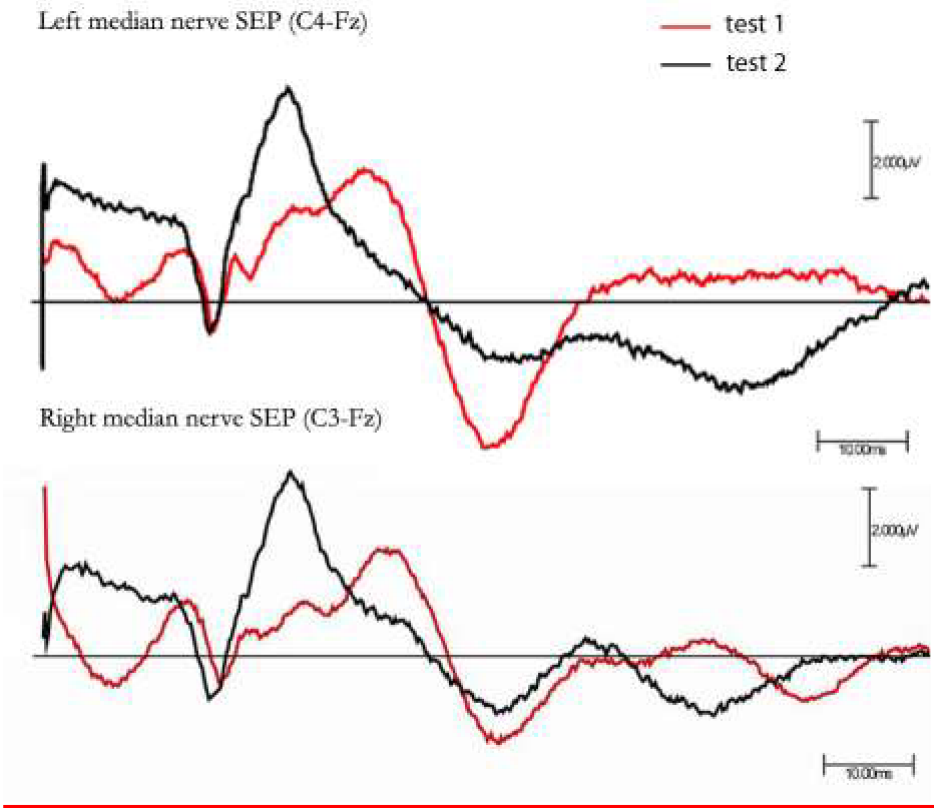


Figure 4.80: Shows averaged SEP waveform recordings of left and right Median nerve from **ASIA-C C5 Incomplete SCI patient**. The **red** trace represents test-1 and **black** trace represents test-2 performed **14 weeks** apart, showing measurable differences. It has been noted that there is a decrease in latencies and increase in amplitudes of SEP components on the right side over ***14 weeks*** follow up period. *Source:* Field work.

Measurements of latency and amplitude parameters of SEP and D-SEP response waveforms summarised in Table 4.15 for comparison of initial and retest outcomes. The findings obtained from observation of the SEP and D-SEP waveform parameters included regain of some of the upper and lower limb responses, and improvement of the waveform parameters especially for the mixed nerve SEP parameters for the Median and Posterior Tibial nerves.

Table 4.15: Shows onset latency and amplitude measurement values obtained from the cortical SEP and D-SEP waveforms obtained for test-1 and test-2 which were recorded **14 weeks** apart (note that **Am** = Amplitude, **Lat** = Latency, **Rt** = Right, **Lt** = Left). *Source:* Field work.

Subject Age & Code	**Diagnosis & Neuro-Level**	***ASIA impairment at test 1 – Initial + SEP Measurements*** *Injury to test 1 = **50 days (7 weeks).***	***ASIA impairment at test 2 – Re-Test + SEP Measurements*** *Injury to test 2 = **147 days (21 weeks).***
S6 49-yrs	**Acute** **C4** Incomplete	***C*** ***Rt:*** ***C5 C6 Med L2 L3 PTN*** ***Am:*** *1.16 0.74 3.40 Notch Notch Notch*	***D*** ***Rt:*** ***C5 C6 Med L2 L3 PTN*** ***Am:*** *0.84 2.74 5.53 0.64 Absent 1.22*
Patient S6	Tetraplegia **MagStim Not Done**	***Lat:*** *16.50 28.60 24.20 Notch Notch Notch* ***Lt:*** ***C5 C6 Med L2 L3 PTN*** ***Am:*** *0.86 0.64 2.81 Notch Notch Notch* ***Lat:****19.50 18.90 25.60 Notch Notch Notch*	***Lat:****19.90 27.10 23.70 32.00 N/A 34.50* ***Lt:*** ***C5 C6 Med L2 L3 PTN*** ***Am:*** *1.50 0.52 4.74 0.19 Data was lost.* ***Lat:*** *19.70 22.00 23.10 43.00 Data was lost.*

4.24 ERSP (Spectral Maps for Slow Sensory Stimulation):

ERSP maps were obtained for upper and lower limbs at slower stimulation frequency as described in the testing methods. Figure 4.81 (**A**) shows the normal ERSP pattern obtained from a healthy volunteer, while (**B**) and (**C**) show 'initial' and 'retest' electrophysiological examinations performed intervals of **7 weeks** and followed by **22 weeks** afterwards, respectively. ERSP maps were obtained for Patient S6 with SCI (**ASIA-C C5 Incomplete Tetra-paresis**) at times of test-2 when scored clinical improvement is observed in comparison to the time of test-1, reflected on an improvement shift of ASIA Impairment Scale (AIS) score from C to D over the follow-up time period. The described obvious clinical and electrophysiological improvement of the testing parameters assessed, was mirrored with obvious functional recovery experienced by the patient enabling independence in most activities of daily living (ADL), remaining with unpleasant but decreasing sensory symptoms.

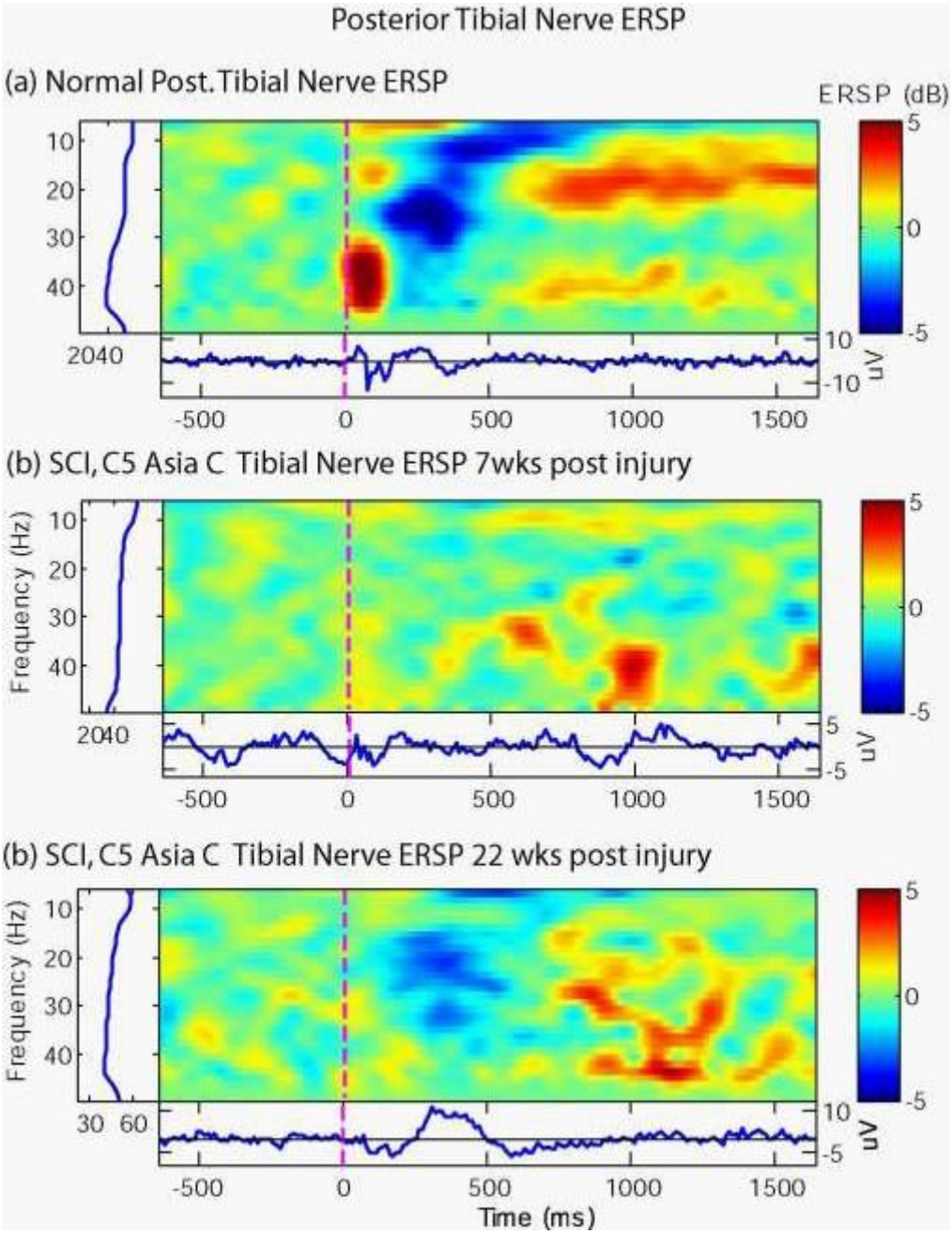
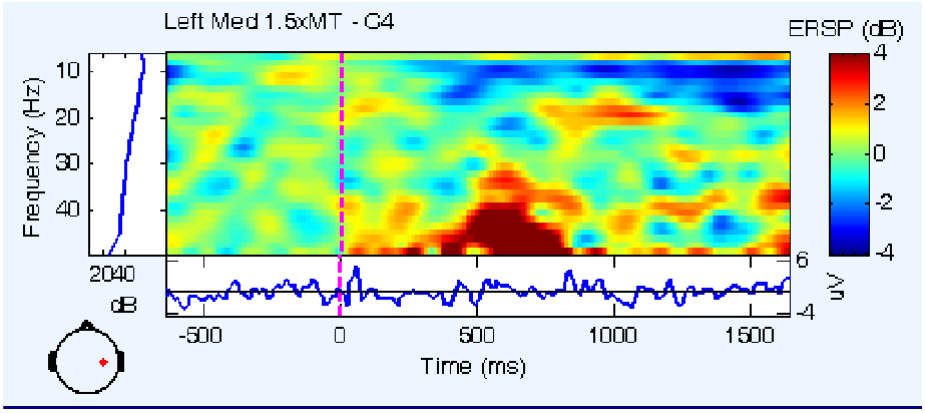


Figure 4.81: Event-related spectral perturbation (ERSP) of EEG showing the normal ERPS map from a healthy subject (a). Figures (b) and (c) show ERSP maps from SCI patient with ASIA-C C5 Incomplete SCI. The EEG recordings show responses to graded electrical stimulation of the posterior tibial nerve (PTN) at 7 (b) and 22 (c) weeks post injury. Note the changes in the ERSP patterns over time with clear areas or bands of desynchronisation and synchronisation occurring at 22 weeks resembling the normal ERSP pattern the healthy subject. The altered pattern of ERSP map which was observed occurred in this SCI patient without a significant observed alteration in the clinical score as measured by AASIA Impairment Scale (AIS). *Source:* Field work.

Similarly, ERSP maps were obtained from left Median nerve graded stimulation as shown in Figure 4.82 (**A**) and (**B**). The ERSP maps for Patient S1 obtained at 22 weeks (**A**) show ERSP patterns with areas or bands of desynchronisation and synchronisation resembling normal ERSP patterns of healthy subjects. However, these patterns were not as clear at the earlier testing time at 7 weeks (**B**).

These electrophysiological changes observed in the ERSP patterns mirror and correlate with the observed status of clinical recovery, with improved AIS gaining scores of the pin prick sensations normalising in all examined dermatomal fields.

(A) :



(B) :

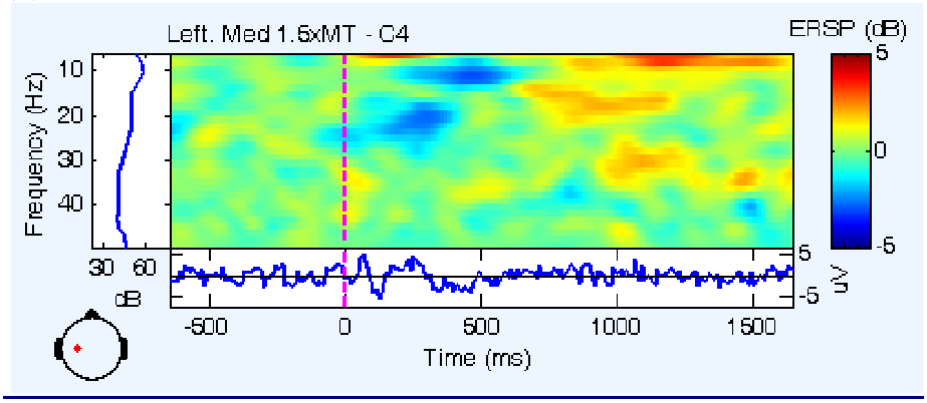
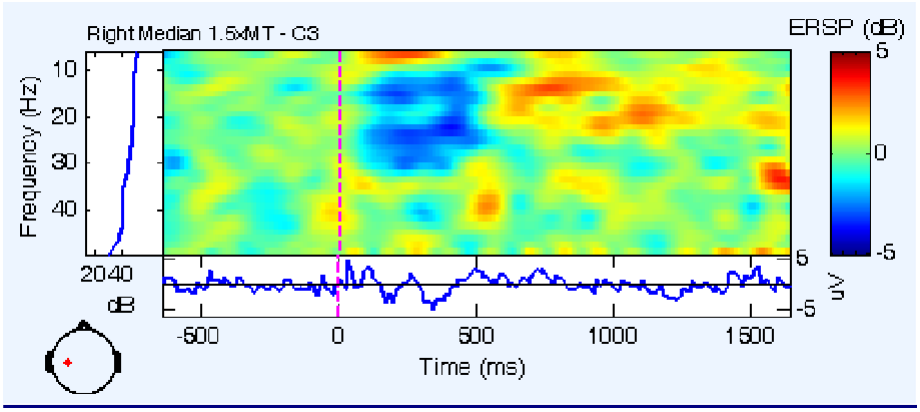


Figure 4.82: ERSP maps for Patient S1 showing responses to graded electrical stimulation of left Median serve at 7 (**A**) and 22 (**B**) weeks post SCI. Changes in ERSP patterns over time are seen with areas or bands of desynchronisation and synchronisation at 22 weeks (**A**), resembling normal ERSP patterns of healthy subject, however these patterns were not clear earlier at 7 weeks (**B**). *Source:* Field work.

In the right upper limb, where obvious clinical recovery is scored in AIS and the colour dermatomal charts, the right Median ERSP maps as in Figure 4.83 (**A**) and (**B**) showed relative stability of the ERSP patterns resembling normal ERSP maps of healthy volunteers. However, the ERSP pattern observed initially at 7 weeks (**A**) is much more in resemblance to normal ERSP patterns with areas or bands of desynchronisation and synchronisation. However, these patterns though generally maintained appeared less distinct/defined at 22 weeks (**B**). This slight electrophysiological change observed in ERSP pattern bears little correlation to the state of recovery seen in Patient S1 over time, with improved corresponding AIS scores gaining in touch and pin prick assessment of right upper limb.

(A) :



(B) :

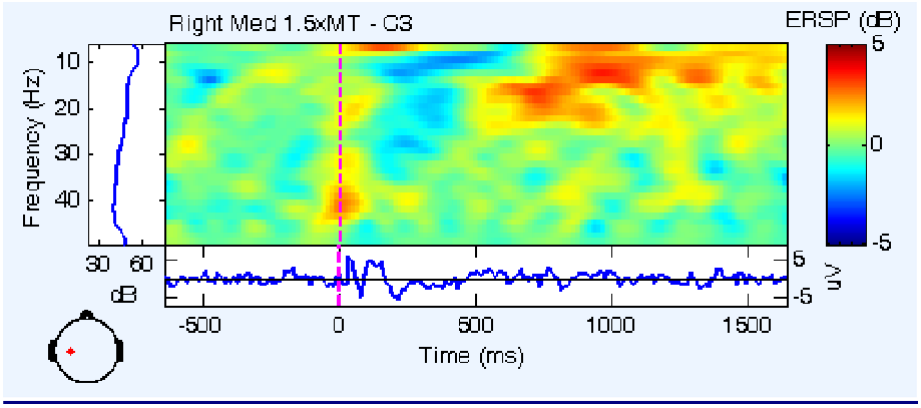
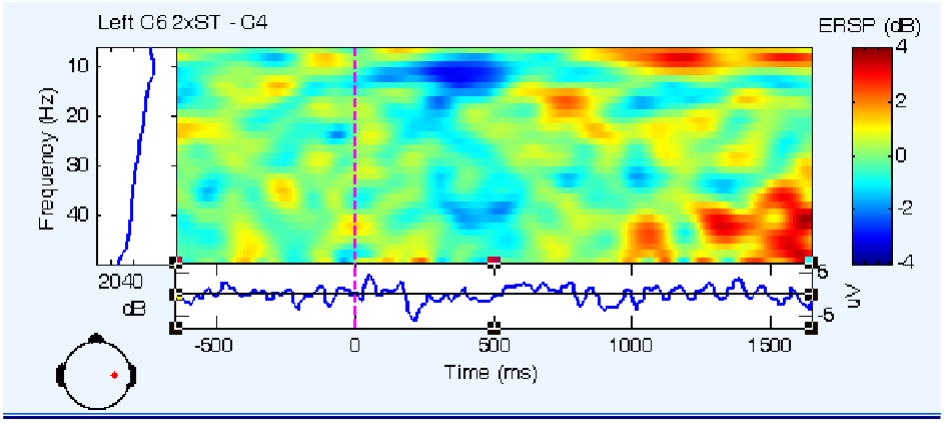


Figure 4.83: ERSP maps for EEG from Patient S1 showing responses to graded electrical stimulation of the left C6 dermatome at 7 (A) and 22 (B) weeks post SCI. There are obvious changes in the ERSP patterns over time with areas or bands of desynchronisation and synchronisation 7 weeks resembling the normal ERSP pattern of healthy subject, with alteration of this pattern at 22 weeks. However, this observed electrophysiological changes had little correlation to improved AIS clinical observations of C6 dermatome gaining scores over time. *Source:* Field work.

Similarly performed ERSP maps for left C6 dermatome of Patient S1 are shown in Figure 4.84 (A) and (B). ERSP maps obtained at 7 weeks (A) show ERSP patterns with areas or bands of desynchronisation and synchronisation with some resemblance to normal ERSP patterns. However, the normal patterns were not very clearly defined at the later testing time at 22 weeks (B) apart from a narrow band of desynchronisation seen at the frequency of around 10Hz seen up to 400ms from stimulation onset. The electrophysiological changes observed in ERSP patterns obviously bear little correlation to state of recovery seen in over-time and reflected in scores for touch and pin prick increasing.

(A) :



(B) :

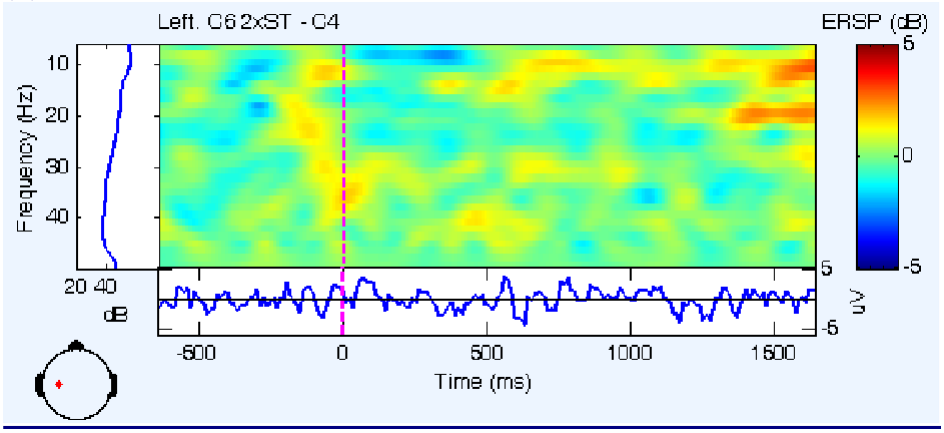


Figure 4.84: ERSP maps for EEG from Patient S1 showing responses to graded electrical stimulation of the left C6 dermatome at 7 (A) and 22 (B) weeks post SCI. There are obvious changes in the ERSP patterns over time with areas or bands of desynchronisation and synchronisation 7 weeks resembling the normal ERSP pattern of healthy subject, with alteration of this pattern at 22 weeks. However, this observed electrophysiological changes had little correlation to improved AIS clinical observations of C6 dermatome gaining scores over time. *Source:* Field work.

4.25 Trans-cranial Magnetic Stimulation – Motor Evoked Potentials:

TMS was not carried out in this Patient S6 because of the fact that this patient had an electronic Baclofen pump fitted for the treatment of spasticity, which would contra-indicate the use of magnetic stimulation in this patient.

4.26 Cortico-Muscular (EEG-EMG) Coherence – CMC:

Cortico-muscular coherence (CMC) obtained from simultaneous recording of mono-polar EEG montage and surface EMG signals was completed in this patient for upper limbs, while lower limb with abnormal and disturbing sensations could not tolerate the electric stimulation to obtain potentials for TA. Upper limb CMC map in a topographic layout for Patient S1 is shown in Figure 4.85, with data for CMC between brain and left ED EMG (**A**) and data for the right

ED (**B**). CMC map of cortical electrode recording sites is shown with significant coherence at varying EEG frequencies distributed over right cerebral hemisphere contra- lateral and synchronous to left ED muscle EMG. Lower limb CMC maps are not shown here.

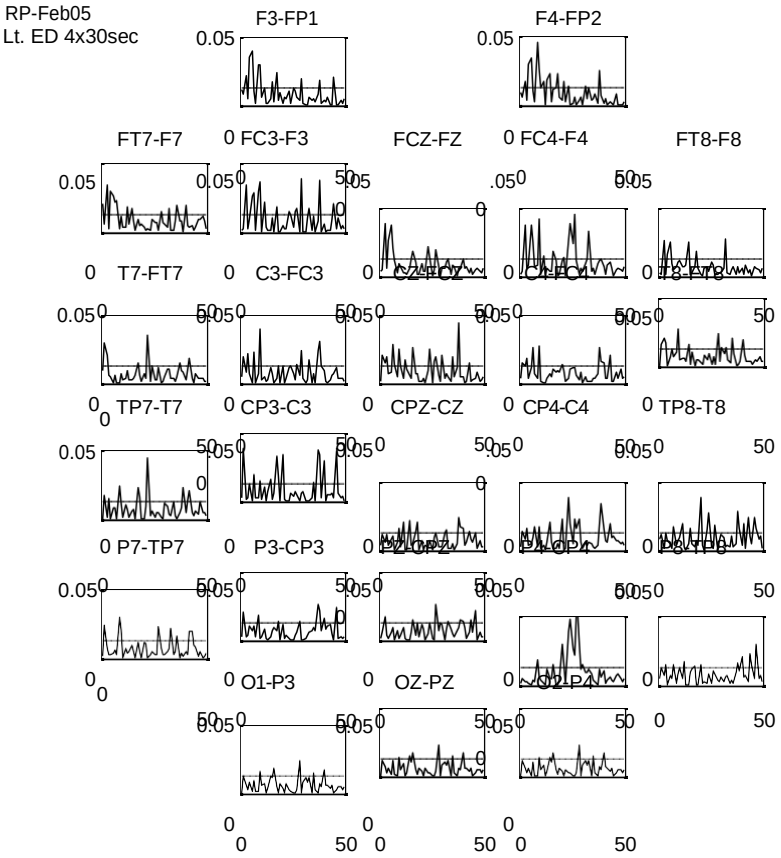
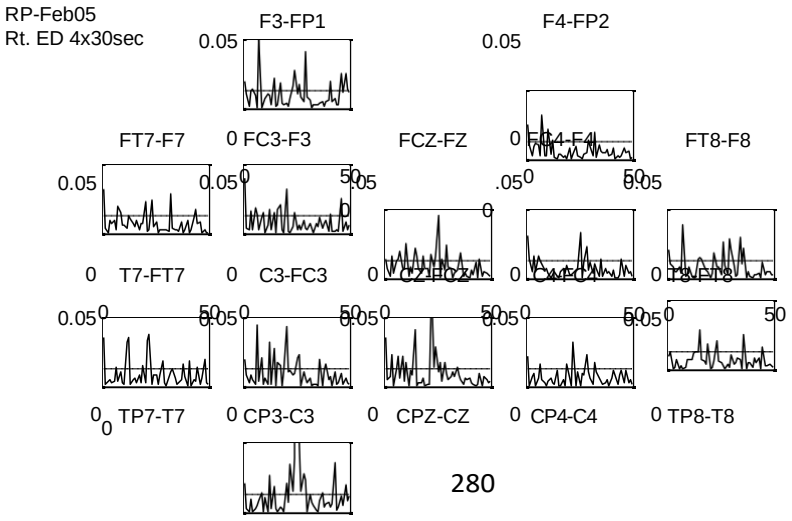


Figure 4.85 (**A**): shows CMC map for SCI Patient S1 with ASIA-C C5 Incomplete Tetra-paresis from calculation of coherence between left ED EMG during sustained contraction and EEG signals. Each small square represents a cortical electrode recording site where the horizontal dashed lines indicate thresholds for significant coherence calculated for the specified site. Significant coherence at varying EEG frequencies is distributed in the right cerebral hemisphere as expected contra-lateral to synchronous to left ED muscle EMG. *Source:* Field Work.



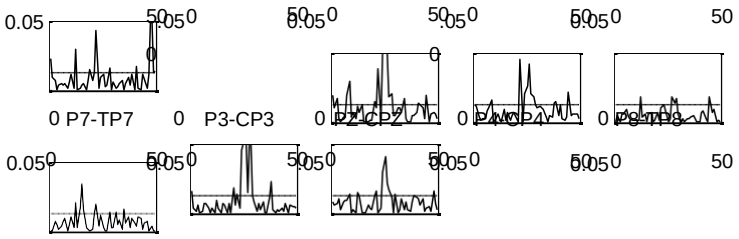


Figure 4.85 (**B**): shows CMC map for SCI patient with ASIA-C C5 Incomplete Tetra-paresis obtained from calculation of coherence of right ED EMG and EEG signals. Noted is the significant coherence at varying EEG frequencies distributed in the right and left cerebral hemispheres as well as some in the midline cerebral cortical areas. *Source:* Field Work.

4.27 Interpretation of Electrophysiological Results (in light of clinical info):

The findings from electrophysiological tests performed for Patient S1 highlight a patient who (**AIS-C Incomplete C5 Tetra-paresis**) was achieving a good clinical and functional recovery.

Clinically, the patient displayed significant improvement represented by transformation from an initial AIS C grade to D over the 14 weeks' test interval. This reported clinical improvement over the longitudinal follow-up period was associated with an improvement in pin prick in all tested dermatomes and significant gains in motor scores for upper and lower limb musculature. A significant improvement was observed enabling functional independence in most activities of daily living (ADL).

The results of objective electrophysiological tests performed **14 weeks** apart over the longitudinal follow up period showed **SEP and D-SEP** responses to improve with time. For instance, the SEP waveforms from left and right Median nerve stimulation showed shorter latencies, displayed a more synchronised waveform and grew in amplitude. Further review of the measurements of SEP and D-SEP latencies and amplitudes values for test-1 and test-2 performed **14 weeks** showed restoration of some of upper and lower limb responses, improvement of waveform parameters especially of the mixed-nerve SEP parameters for Median and PTN.

Initial and follow-up **ERSP patterns** were also obtained over the **14 weeks** follow-up period, and these showed changes in ERSP patterns over time with clear areas of desynchronisation and synchronisation becoming evident at test-2 and beginning to resemble the normal ERSP pattern of healthy subjects. This altered pattern of ERSP map was observed to occur without significant alteration in the clinical score as measured by light touch appreciation. MEP waveforms were not obtained in this patient because **TMS was contra-indicated** due to the fact that this patient was using at the time an electronic (Baclofen) pump implanted to treated spasticity. The **CMC calculations** obtained for this SCI patient show evidence of coherence with peaks seen topographically over scalp bi-polar recordings, indicative of signal coupling and capability of cortico-spinal tracts sustain motor activation. The patient was on **medications** including (Diazepam and Temazepam) which are both Benzodiazepines that might **affect CMC calculations** influencing some of the **cortical responses**.

This patient showed reasonable clinical improvement and significant functional recovery, mirroring some measurable electrophysiological changes evident on test results. Variation observed in different electrophysiological parameters used at different testing sites, suggest the inherit variability in degrees and patterns of improvements seen in different dermatomes or myotomes below SCI lesions or lack of improvement or even deterioration. On the other hand, variability might suggest asymmetry of SCI lesion affecting the left or right-side limbs unequally or variation in distal versus proximal involvement. This might partly explain the discrepancy seen in AIS score changes in different parts of upper and lower limb sensory and motor findings.

4.28 Electrophysiological (SEPs Test) Results (Group Results):

The electrophysiological testing was designed in a way to assess responses from nerves at spinal levels above and below the ASIA level of tested SCI individuals. This has been performed in a way that is relevant to allowing comparisons to be drawn between ASIA scoring and parameters that can be extracted from electrophysiological tests conducted on specific locations (see figure 4.86).

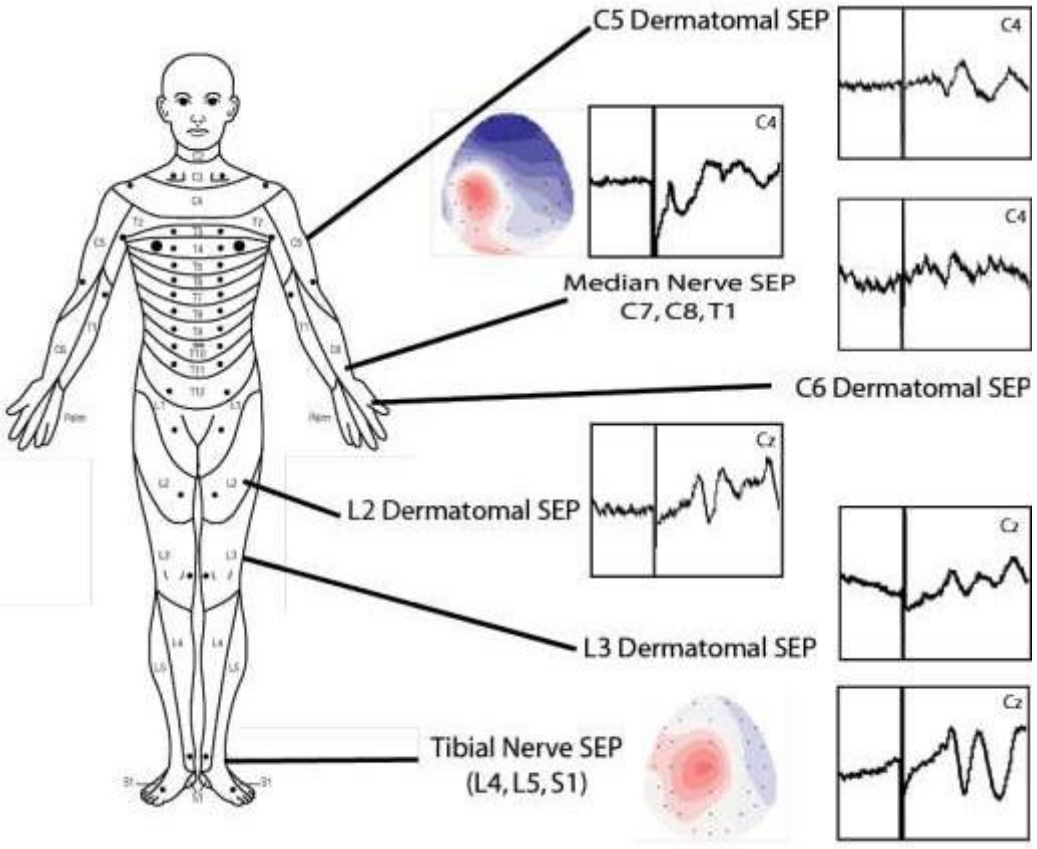


Figure 4.86 Illustrates testing sites of mixed nerves and dermatomal areas above and below given SCI lesions in order to reflect the integrity and function of nerve fibres across the given SCI lesions. These tests were repeated in the same way for the 'initial' test and after a period of longitudinal follow up as 'retest'. *Source:* Field Work.*Is this in normal or an average of SCI patients?*

In Figure 4.87, a schematic summary of changes seen in the responses to left and right SEP and D-SEPs are presented as changes in the latency of the first evoked response peak for each subject. Peak latency measurements values were extracted from SEP and D-SEP waveforms for the purpose of longitudinal charting and this serves as a basis for an initial comparison of clinical grade changes to be considered alongside any measurable electrophysiological outcomes occurring over the initial test to retest period.

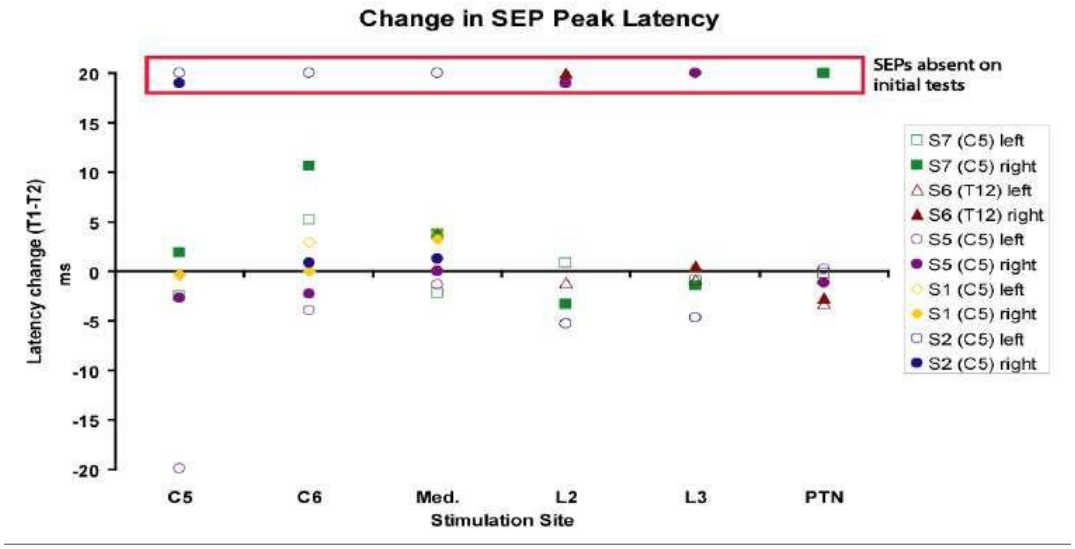


Figure 4.87 summarises results of SEP and D-SEP measurement parameters defined by Peak Latency for 7 SCI patients who completed this testing modality at the time of test-1 'initial' and test-2 'retest', performed several weeks apart in the course of longitudinal assessment and follow-up of this study. The figure shows changes of peak latencies of SEP from different stimulation sites in the SCI patients studied. Positive values represent a shortening of latency while negative values represent lengthening of latency (or slowing of the peaks). In a number of SCI patients, SEPs were absent on test-1 'initial' test, but could be clearly observed after longitudinal follow up assessment 're-tests'. However, there were no incidences where SEPs were present on test-1 'initial' testing but not being observed on 'retest'. *Source:* Field Work.

The data in **Figure 4.87** show measurable electrophysiological changes obtained for individual SCI patients to compare/contrast with simultaneous clinical assessments:

4.28.1 Patient S7 (C5 ASIA D remained ASIA D on retest):

- **Clinical Scores (**sensory**)** largely remained the same (with marginal increment of Pin Prick scores from **36** to **39**),
- **Electrical Tests (**sensory**)** are variable (with some improvement on the right but largely remained with similar latencies both sides),
- **Functional Outcome** showed improvement in sitting and standing balance and increased sensory perception.

4.28.2 Patient S6 (T12 ASIA C improved to ASIA D on retest):

- **Clinical Scores (**motor**)** improvement (power 4/5 in most muscles) and **(**sensory**)** improvement from 45Right/47Left to 53 Right/Left,
- **Electrical Tests (**sensory**)** showed no major sensory changes,
- **Functional Outcome** showed improvement, and on discharge the patient was able to walk on crutches, and continued to improve.

4.28.3 Patient S5 (C5 ASIA C remained ASIA C on retest):

- **Sensory Scores (**motor**)** no difference on assessment, and (sensory) largely no improvement (only from 39R/39L to 41R/41L.
- **Electrical Tests (**sensory**)** showed same or marginal worsening of sensory latencies (especially right), with some absent responses.
- **Functional Outcome** showed no significant difference in retest.

4.28.4 Patient S1 (C5 ASIA C improved to ASIA D on retest):

- **Sensory Scores (**motor**)** showed improvement, and **(**sensory**)** shows maintained normal Touch scores at 56, with marginally improved Pin Prick scores from 52 to 56 on both Left and Right sides.
- **Electrical Tests (**sensory**)** showed some marginal improvement on sensory latencies especially on left Ct6.
- **Functional Outcome** improved significantly with independence on performing most activities of daily living (ADL).

4.28.5 Patient S2 (C5 ASIA C remained ASIA C on retest):

- **Sensory Scores (**motor**)** showed slight gain in muscle power of 0.5-1 on MRC scale, and **(**sensory**)** improvement of Pin Prick from 43 to 56 (Right) while these remained the same at 65 (Left).
- **Electrical Tests (**sensory**)** showed slight improvement of Median and C6 (Right) sensory responses, while slightly deteriorated L2 and L3 (Left) sensory responses. Left Median, C6, C5 remained absent.
- **Functional Outcome** showed improvement on few ADL activities including sitting balance and use of hands, forearms and arms.

4.29 Summary of Findings in SCI Patients Tested

1. **Length of follow-up periods** obtained for SCI patients participating in this study potentially carry advantages and disadvantages. Shorter follow-up durations are practical as they enable more testing to be achieved; however, they potentially miss out on changes that might take place later-on down the line. Long follow-up durations might be impractical and hard to achieve in a single study even though they are much more likely to identify most changes that might be encountered during the full time span of neuronal recovery. The average duration of follow-up period elapsing

between test-1 and test-2 in all seven tested SCI patients was **14.7 weeks,** with the shortest duration **10 weeks** and longest **17.5 weeks**. The single exception to this is a SCI patient who had test-3 at **52.5 weeks** from test-2 when data from it was accidentally damaged and lost.

2. **Clinical assessments** might be reflective of the residual function of the underlying sensory-motor spinal cord tracts, however might fall short of capturing the actual status of connectivity and functionality of these tracts.
3. **In some studied SCI patients,** clinical changes were observable and were detectable by clinical assessment methods. The clinical methods scored changes which altered grading AIS grading when significant variation in **sensory scores** or **motor function** (on manual muscle testing scores) were readily detectable. However, frequently this has not been the actual case.
4. **In many instances, significant functional improvement** (reflected on individual patient's ability to perform activities of daily living) were not detectable by conventional or standard clinical methods and hence not reflected on the AIS grading and not charted as clinical changes.
5. **Use of evoked potential analysis** in studying the sensory pathways in patients with SCI shows means of improving subjective clinical measures in assessing SCI lesion. These methods almost exclusively studied dorsal column pathways informing of the changes in conduction and organisation of this complex pathway post SCI (nociceptive and autonomic pathways largely not investigated in these current electrophysiological assessments).
6. **Standard time-domain averaging (SEP and D-SEP)** as well as **spectral analysis of evoked activity (ERSP)** are quantifiable and usable within the contexts of measuring the functions of (ascending spinal tracts) as well as (cortical processing) of any activation resulting from the related stimuli.
7. **SEP D-SEP** & **ERSP analysis** have the ability of revealing improvements and deterioration taking place in sensory conduction and related cortical processing, thus providing greater sensitivity than the subjective clinical testing methods.
8. **TMS and EEG/EMG (Cortico-Muscular) Coherence (CMC)** are the electrophysiological **motor assessment methods** used to examine the motor pathways of the spinal tract in patients with SCI.
9. **In general, MEP measurements obtained through TMS parameters** are largely reliable in the assessment of changes observed in motor pathways. In this instance,

relative increase in MEP size (amplitude) with increasing TMS intensity appear to correlate with ASIA manual muscle power on clinical testing. Latency measurements show changes in relation to incremental TMS intensities however latencies are less reliable as indicators of changes of clinical motor function.

10. **Combination of sensory and motor electrophysiological methods** carry best chances of obtaining representative information on possible changes in an underlying SCI or residual connectivity or functionality therein. This is usually made on top of baseline clinical assessments that pave the way for appropriate and relevant electrophysiological methods to take place.
11. **The effect of medications usually on board at the time of test-2** needs to be kept in mind. Most of the medications used in the later or chronic phases of SCI are usually suppressive to the nervous system, used to treat symptoms related common chronic complications, primary SCI lesion or secondary injuries such as spasticity, flexor spasms, abnormal movements, bladder instability or neuropathic pain and annoying sensory symptoms. Some of these medication groups include but not exclusively Narcotic analgesias such as Tramdadol and long-acting morphine (MST), some of the Benzodiazepines, GAB agonists and tri-cyclic anti-depressants (TCA). These medications influence the propagation and processing of sensory signals as well as the magnitude of oscillatory components within the EEG or EMG recordings in the process of calculating the EEG/EMG coherence. Consideration should be made to the medications taken by the patient when interpreting results of the electrophysiological tests assessing both sensory and motor pathways, and this is especially true with test-2 results coinciding with the time of arrival of complications which necessitates the use of large number of medications to control undesirable symptoms.

4.30 Overall flow of tests and data obtained for SCI patients Tested:

Table 4.16: shows a summary of the clinical information of all SCI patients, as an overall flow chart for the clinical progress of SCI patients who were tested along the longitudinal follow-up period documenting variable clinical changes seen with some changes indicating neurological recovery observed over this time period. Source: Field work.

Group A:
Patient S3: *ASIA-**A** T10* ***– remained ASIA-A*** ***– 16.5 weeks***
Patient S4: *ASAIA-**A** T4* ***– remained ASIA-A*** ***– 17.5 weeks***
Group B:
Patient S5: *ASIA-**C** C5* ***– remained ASIA-C*** ***– 15 weeks***
Patient S7: *ASIA-**D** C5* ***– remained ASIA-D*** ***– 10 weeks***
Group B':
No MEP Data (one refused & one contra-indicated)
Patient S2: *ASIA-**C** C5*
– remained ASIA-C at Test-2 *(lost some data)* ***– 15 weeks***
– recovered to ASIA-D at Test-3 *(some displayed)* ***– 52.5 weeks***
Group C:
Patient S6: *ASIA-**C** T12* ***– recovered to ASIA-D*** ***– 15 weeks***
No MEP Data (one refused & one contra-indicated)
Patient S1: *ASIA-**C** C5* ***– recovered to ASIA-D*** ***– 14-weeks***

5. DISCUSSION

This chapter covers discussion and conclusions of the results and outcome of this research project and aims to draw the findings of the work done into learning that applies to the clinical electrophysiological assessment of sensory and motor systems in patients with traumatic spinal cord injury.

As previously indicated, there remain challenges in establishing reliable and quantifiable diagnostic tools suitable for use in the clinical setting for patients with SCI. The challenges apply to both sensory and motor evaluation of patients where conventional and routine clinical assessment is most commonly based on scoring of dermatomes and key muscle groups of the limbs together with the AIS assessment injury completeness. Developed and updated since its introduction the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) outcome measure has been adopted as the most widely used clinician administered exam for patients with spinal cord injury[5].ISNCSCI has become widely adopted for a number of reasons but importantly it does not require specialist equipment and can be completed at the bedside. In the most recent version the results can be entered into a software package that computes the motor and sensory scores and presents a visualisation of the assessment result (as was done retrospectively with the assessments performed and presented in this thesis). The ISNCSCI algorithm is available online here (http://isncscialgorithm.azurewebsites.net/). Its use further reduces the time for completing and recording the test results and might also reduce errors relating to completing these charts. However, even with experienced assessors the test can be time consuming (>1 hour for ISNCSCI and AIS) and in busy clinical centres the results can be inaccurate if the assessor is inexperienced and does not follow the test guidance fully (Jonsson et al., 2000). Nevertheless, the assessment method has become established as the default and core tool used in the clinical examination of neurological function after SCI and an essential part of clinical trials aimed at improving neurological outcomes for patients with SCI. In this context because the ISNCSCI and AIS are psychometric tests it is important to take into account variability and reliability associated with the use of such outcome measures. Furthermore, it is critical that for the patient and clinician, what constitutes a change that is clinically or functionally meaningful is also critical. This has recently been investigated by Scivoletto et al. (2013) who

[5] American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2002. 2002. Chicago, IL, American Spinal Injury Association. http://www.ncbi.nlm.nih.gov/pubmed/9160449

highlight that following the natural recovery profile post injury a change of 5 points in motor and sensory scores is most likely necessary to achieve a minimal clinically significant outcome but this needs to be carefully evaluated against the time points of initial and retest assessments post-date of injury. In the work making this thesis, the first examination (Test-1) of SCI patients post injury took place after an average of 7.5 weeks (ranging from 3 to 11 weeks). This means that some of the initial clinical and electrophysiological changes taking place in the crucial early post injury days might not have been registered by Test-1. Time interval taken to perform retesting (Test-2) averaged 12.4 weeks (ranging from 10 to 17.5 weeks), which is reasonably timed and likely to capture most recovery changes that takes place in the first six months post SCI. Testing SCI patients earlier than the stated 3-weeks proved very challenging and was frequently impossible in the acute setting.

From the work done by Scivoletto et al. (2013), it has been estimated that the Minimal Clinically Important (MCI) Difference for total motor or sensory scores are 4.48 and 5.19, respectively. In these estimates, an upper extremities motor score (UEMS) of 2.72 and lower extremities motor score (LEMS) of 3.66 were considered as minimal for clinical improvements related to hand function or walking capacity, respectively. Table 5.1 provides a summary of the ISNCSCI data obtained for SCI patients participating in this study. Data for the change in total Sensory Scores and total Motor Scores, further stratified for upper (UEMS) and lower (LEMS) extremities, are shown for each individual SCI patient.

Table 5.1: shows values of Minimal Clinically Important (MCI) Difference between test-1 and test-2 sensory and motor scores, performed for all 7 patients at two testing occasions several apart down the longitudinal follow-up period. Significant MCI difference, according to set levels by Scivoletto et al. (2013), is indicated by (**S**) and insignificant by (**I**): *Source:* Field Work:

	Sens Touch	Sens PP	Motor UL	Motor LL	ASIA-1	ASIA-2
S1 C5	R56-56=N L56-56=N Normal	R52-56=4 L52-56=4 Total = 8 **S**	R9-22=13 L10-24=14 Total=27 **S**	R14-23=9 L15-23=8 Total=17 **S**	C	D
S2 C5	R56-56=N L56-56=N Normal T	R43-56=13**S** L56-56=0/N Total = 13 **S**	R15-13=-2 L7-12=5 Total = 3 **S**	R15-14=-1 L7-12=5 Total = 4 **S**	C	C
S3	R34-38=4	R36-39=3	R25-25=N	R0-0=0	A	A

T1 0	L34-34=0 Total = 4 **I**	L34-34=0 Total = 3 **I**	L25-25=N Normal UL	L0-0=0 Total = 0 **I**		
S4 T4	R24-24=0 L24-24=0 Total = 0 **I**	R24-24=0 L24-24=0 Total = 0 **I**	R25-25=N L25-25=N Normal UL	R0-0=0 L0-0=0 Total = 0 **I**	A	A
S5 C5	R56-56=N L56-56=N Normal T	R39-41=2 L39-41=2 Total = 4 **I**	R10-13=3 L11-14=3 Total = 6 **S**	R0-0=0 L0-0=0 Total = 0 **I**	C	C
S6 T1 2	R56-56=N L56-56=N Normal T	R45-53=8 L47-53=6 Total = 14 **S**	R25-25=N L25-25=N Normal UL	R12-18=6 L12-18=6 Total = 12 **S**	C	D
S7 C5	R56-56=N L56-56=N Normal T	R36-39=3 L36-39=3 Total = 6 **S**	R14-18=4 L11-16=5 Total = 9 **S**	R21-24=3 L21-23=2 Total = 5 **S**	D	D

From these data, SCI patients in this study fall into three categories:

A. **Patients** who did not meet criteria for MCI difference and remained in same ASIA grade after a time period of longitudinal follow-up. This is concordant with outcome of work done by Scivoletto et al. (2013), and this category includes patients S3, S4 and S5.

B. **Patients** with evidence of changes in ISNCSCI scores that surpass the Scivoletto et al. (2013) MCI difference but remained in the same AIS grade. For instance, patient S2 with motor score changes of 3 for UEMS and 4 for LEMS did not change AIS nor show functional improvement even though pin prick sensation also was raised by 13 points. Another confounding example is patients S7 with borderline MCI difference with scores of 9 for UEMS, 5 for LEMS and 6 for sensory score, but no change of AIS grade observed over the test interval periods.

C. **Patients** with significant MCI difference and therefore an expected improvement in functional outcome and AIS grade. This applies to patients S1 and S6.

Accordingly, taking a simple view of ISNCSCI changes is valuable but even when the change is seen to exceed what average or pooled data suggests is a MCI difference other factors need to be taken into account. For example, although Scivoletto et al. (2013) highlight that following the natural recovery profile post injury a change of 5 points in motor and sensory scores is most likely produce a minimal clinically significant outcome this needs to be carefully evaluated against the time points of initial and retest assessments post-date of injury. What should be the timeframes of an initial versus follow up assessment is not clearly established.

The general view by centres who have adopted the ISNCSCI and AIS measures is that it should be regarded as a core assessment tool given that it is non-invasive, has moderate to high validity and high inter-rater reliability for sensory and motor components (Jonsson et al., 2000; Marino et al., 2008). It has moderate correlation with other outcome measures on walking (6 and 10m walk tests, WISCII) and functional independence (FIM). But it shows floor and ceiling effects in a large percentage of patients suggesting that for those patients where small changes in neurological status occur the ISNCSCI and AIS measures lack sensitivity and specificity in relation to function (van Middendorp et al., 2009). This may be an important factor in clinical trials of new interventions where physiological or biological change may not be of a size to influence the ISNCSCI outcomes or AIS. The ISNCSCI and AIS tests by focusing on a patient's perception of sensation (fine touch and pain) and being limited to only motor tests of key upper and lower limb muscles inevitably reduces the ability to identify sensory recovery that is not measurable by perception or of crude measures of muscle contractions.

The most effective diagnostic tools are meant to be sensitive, objective, non-invasive, reproducible, preferably quantitative and most of all applicable to the clinical context, risk and management of acute SCI patients. Diagnostic tools applicable for use in the clinical context of SCI has been emphasised in many studies phasing technology into clinical trials (Ellaway et al., 2011). This study used non-invasive electrophysiological methods to assess integrity and

connectivity of ascending and descending spinal tracts in patients diagnosed with SCI. Furthermore, the tests used were brought together as a potential diagnostic battery of electrophysiological methods to assess severity of SCI. Use of complementary tests with sensitive and quantitative markers helped to detect small changes in integrity and function of individual spinal segments and across SCI lesions. SCI patients were tested at separate occasions over time to enable monitoring of subtle and sub-clinical changes in spinal tracts in longitudinal follow-up down the course of natural recovery and any possible neurological improvement that sets in.

5.1 Justification of these Electrophysiological Tests:

With above concepts in mind, this study focussed on a choice of electrophysiological tests that in common have a good level of quantification parameters for the measured changes whether at a given stage of SCI lesion or at a time point along the recovery pathway (Kramer et al., 2010). This collection of tests is therefore designed to explore the possibility of obtaining biomarkers that relate to well-known physiology or anatomy and have the potential for sensitive and reliable detection and prediction of an individual's potential for natural recovery or a positive response to novel therapy. It is however worth mentioning that electrical tests are considered exploratory tools within the common data elements (CDEs) for SCI clinical research (Biering- Sørensen et al., 2015) and together with core tests are believed to offer higher reliability than can be achieved when either set is done alone. Nevertheless, electrical tests including the ones chosen in this study cohort even when individually used have the potential for sensitive detection and reliable prediction of changes marking or underlying CNS recovery SENS-MTOR CHANGES (Costa et al., 2007). Furthermore, combining individual tests and exploring methods to augment sensitivity further will increase their value and acceptance within clinical practise.

5.2 Recruitment of SCI Patients:

Recruitment of the SCI patients was initiated through consultant identified inpatients admitted with acute SCI subjects to the Queen Elizabeth National Spinal Injuries Unit. At the time of starting this study, 22 patients with SCI were deemed to be suitable according to the recruitment criteria based on acute SCI with potential for recovery and absence of significant comorbidity. Out of these, only 12 patients gave unconditioned written informed consent for performing the tests according to the agreed protocol. During the study, three patients withdrew before starting the first set of measurements (test-1), leaving only 9 patients to be tested. One of these withdrawals was for personal reasons, and another due to development of autonomic dysreflexia which is a low-risk contraindication to electrophysiological stimulation in our ethics submission. Autonomic dysreflexia is a medical emergency that complicates SCI and contra-indicates most of the electrophysiological tests planned for this study.

A further two recruited patients only participated in part of the full protocol (test-1 basic and partial testing; SEP, D-SEP and Coherence) but were unwilling to complete the retest (test-2) due to personal reasons, largely related to inability to come back for retesting following their discharge from hospital. The remaining (7) patients were studied on two separate occasions (test-1 and test-2) over a follow-up period that spanned a time frame where natural recovery or progress of rehabilitation should be most evident. The longest interval between tests was 17.5 weeks, the shortest 10 weeks. In a single patient a third testing date was arranged (test-3), which took place 30 weeks following test-2. Compliance to the experimental programme (i.e. completion of all test assessments at both test points) was challenging as described below. Out of the 7 patients undertaking test-1 and test-2, 5 completed all testing modalities that were specified in the experimental protocol but 2 patients could not participate in TMS retesting. For one patient TMS was discontinued on request due to discomfort. While in the second patient the implantation of an electronic Baclofen pump, as part of treatment of severe spasticity, meant that

TMS was not appropriate due to the risk of damage to the implanted pump. Accordingly, out of a total of 22 suitable recruits only 5 patients completed the full protocol planned for this study. Each of these 5 subjects participated in all designed electrophysiological tests at two occasions at the start and end of a follow-up. The initial electrical examination (test-1) took place after an average of 7.5 weeks post SCI (ranging from 3 to 11 weeks). Test-2 took place averagely 12.4 weeks after the time of test-1 (ranging from 10 to 17.5 weeks).

Participation was demanding on the time of the volunteers on the day of the tests and because of a need to have at least one follow up testing session recruitment sustainability was difficult to achieve. It should not be underestimated how the duration of an experimental investigation of the type performed in this work influences patients' opinions on participation, cooperation and compliance. It is therefore obvious that recruitment to this study was difficult and in the end achieved less than the expected numbers of clinically suitable patients. In addition, the recruitment rate proved to be slow also making it difficult to judge whether protocols were realistic and practical across cohorts of patients. Despite significant initial interest from patients to participate in the study, many were put off by the amount of time they would necessarily have to commit to completing the assessments at a single test session. To adequately perform the tests, approximately 4-hours was necessary for recording with additional time required for preparation prior to testing and subsequent cleaning of the patient after testing. Use of EEG recording gels meant that subjects required a hair shampoo at the end of the test and this often required the assistance of nursing staff. In general, subjects were very tolerant of the electrophysiology but became impatient and inconvenienced by the total duration of time they were expected to commit to.

In the process of recruitment, once experiments are explained in face-to-face interviews, it is evident that already ill and disabled patients are vulnerable and easily put off by these factors. Time taken by the test also posed a difficulty for the recruited patients who tended to lose

concentration or drop asleep following a period of testing due to general tiredness or the effects of medications. Any tests that require active involvement or collaboration with instructions might be affected by these factors. One important instruction during EEG recording was to the need to sustain low levels muscle contraction simultaneously with the recorded EEG. Achieving stable levels of EMG proved difficult for many of the patients. In some other clinical instances, streamline sensory or motor recording were interrupted by frequent involuntary flexor spasms or muscle jerks and these artefacts made analysis more difficult.

Accordingly, this is something researchers need to consider carefully in designing protocols where non-standard tests are incorporated into studies with SCI patients, besides issues of interpreting the SEP results (Aminoff, 1984). In this study, the initial decision to try to complete all the assessment measures within a single session was both difficult for the patients to comply with, was tiring and difficult to timetable in relation to ongoing clinical care and rehabilitation. Splitting the assessments up into more appropriate time slots (maximum 1 hour) spread over a number of days would have potentially improved the recruitment and retention. Nevertheless, the positive outcome of the schedule adopted was that there were no adverse incidents to report as a consequence of the tests conducted.

The recruitment challenge faced by this study ultimately lead to a final small number of SCI patients participating compared to inpatient load accessing QENSIU. The small numbers also present a range of additional challenges when reviewing the data. The patient group is inhomogeneous in relation to demographic factors, lesion, level and extent. In addition, the low numbers highlight that a population statistical analysis is not appropriate. However, the individual cases investigated and the variability observed between cases can provide valuable guidance and knowledge for future studies investigating recovery and what tests can add useful information on patients' progress.

5.3 Demographic of SCI Patients and Healthy Volunteers:

The demography of the chosen SCI patients who were recruited to this study differs from that of healthy volunteers tested for obtaining the controls. The standard normal results (normative data) were obtained from relatively younger group, with an average age of 29.9- years compared to an older age average of 48.6 for the SCI patients. This fact might be accounting for some of the observed variability of results obtained from SCI patients in comparison to normative data obtained from younger healthy controls. It was not possible to abolish these age differences between healthy volunteers used for control and SCI patients participating in this study.

5.4 Clinical Assessment Methods:

As reviewed previously, clinical assessment methods, using scores of perceptual sensory testing and key muscle power assessments as represented by ISNCSCI, constitutes the standard bedside evaluation tools used in hospital settings caring for patients with acute SCI. These conventional clinical assessment methods are however subjective, lacks precision and sensitivity that is required to detect subtle changes underlying potential recovery (Cohen et al., 1996). For these reasons, this study combining electrophysiological methods with the above-mentioned conventional clinical assessment, was done.

5.5 Electrophysiological Testing of SCI Patients:

The electrophysiological measures used in this study can be difficult to perform in isolation but more so when used in a compiled battery of tests serving the purpose of measuring specific connectivity and conduction in sensory or motor spinal tracts. Each of these electrophysiological tests requires a high level of combined expertise both in technical aspects of these tests as well as the clinical sensitivity of the patients being tested. Some of the clinical issues are related to the fact that patients admitted with acute SCI are on complete bed rest and cared for in settings of intensive care or high dependency units, ICU and HDU respectively. Complete bed rest is sometimes an issue for reducing the risk or preventing complications like autonomic dysreflexia

as well as immobilising an injured spinal cord. In some patients, immobilisation devices used to fix the spinal cord (e.g. Halo Brace) limit or preclude some of the tests or prevent the easy use of devices like EEG electrode caps. As alluded to in the section above the individual tests and the complied battery of tests takes a long time to perform, generally estimated as 4-hours net recording time for each testing occasion of test-1 and test-2 with at least another hour for electrode donning and doffing. The time required for tests, the very delicate patient-test interface and the volunteers resolve to complete the test programme. The value of the information recovered from electrophysiological testing has to be high for it to be adopted widely. Electrophysiological measures are additive to the information obtainable from the conventional clinical methods based on ISNCSCI and AIS. However, integrating these potentially useful electrophysiological measures should be done in a selective way only when certain tests may be necessary to do in order to gain specific insights into surviving spinal tract conduction. In other words, electrophysiological measures are best deployed to suit measurement of specific spinal functions for specific patients.

5.5.1 Advantages of the Electrophysiological Tests:

Electrophysiological methods employed in this study detected subclinical changes following SCI and therefore assisted in giving deeper insights on post-injury changes and mechanisms underpinning observed neurological recovery following SCI. The main results of this study shows variations in outcome and concordance of the components of the electrophysiological tests and their parallel clinical assessments performed in the context of AIS. These variations are discussed in the sections below.

Compared to findings of the clinical assessment performed in parallel, the electrophysiological measures used in this study fall in two categories.

In ***the first category***, the electrophysiological measures bear no significant correlation to the outcome of clinical methods indicating no concordance between the two measures. This might

suggest that clinical assessment methods used were not as sensitive as their counterpart electrophysiological tests. Or conversely, the electrophysiological measures simply do not have a simple correlation to the type of measurements that make up the clinical assessment. This is possibly a factor in those cases where clinical scores are close to ceiling or floor values.

In ***the second category,*** a clear fit between electrophysiological measures and clinical assessments, indicating good concordance of outcome of clinical assessments are revealed through the parallel electrophysiological tests. In this category, an example of good concordance is seen in **Patient S1** (**AIS-C Incomplete C5 Tetra-paresis**) who achieved good clinical and functional recovery over 14 weeks follow up interval with transformation from an initial AIS C grade to D. Improvements in pin prick sensation in all tested dermatomes and gains in motor scores for upper and lower limb muscles is also coupled with functional independence in most activities of daily living (ADL). **The electrophysiological tests** showed improvement of **SEP and D-SEP** responses with time. For instance, SEPs of left and right Median nerve stimulation showed shorter latencies, displayed more synchronised waveforms and grew in amplitude. There is an overall improvement of waveform parameters especially the mixed-nerve SEP parameters for Median and PTN. This would suggest improved transmission in the dorsal column pathway contributed to the recovery profile for this patient. The **ERSP patterns** showed changes, with clear areas of desynchronisation and synchronisation becoming evident over time and beginning to resemble normal ERSP patterns obtained for healthy subjects. The **CMC calculations** also showed evidence of coherence with peaks seen topographically over scalp bi-polar recordings, indicative of signal coupling and capability of cortico-spinal tracts able to sustain motor activation. However, **TMS** was unfortunately not performed in this patient because it was contra-indicated for medical reasons as previously discussed.

Some of the electrophysiological test results were even in tandem with the functional outcome

of given SCI lesion picking subtle changes that were not scored by the clinical methods. For instance, in Patient S2 ***as shown in Figure 4.59***, the ERSP maps from the time of test-2 (***B***) regained the usual ERD band with familiar overall scalp ERSP map picking up nicely in comparison to the disturbed ERSP pattern at initial test (***A***). This was not fully picked up by clinical testing with AIS grade remaining the same as C. However, the results of the electrophysiological measures in the second category, seem to only align with certain aspects of the clinical assessments indicating enhanced sensitivity while not with the others. For instance, some tests of the motor functions such as the CMC and MEP measurements seem to correlate well with findings of the bedside clinical assessments. For instance, in Patient S6, the MEP waveform measurements show robust growth (improvement) in amplitude at 15 weeks follow-up (***shown in Figure 4.73***) and associated with MEP latency shortening shift (***shown in Figure 4.70***). For the same patient, the **CMC** calculations and analysis showed smaller yet maintained CMC reaffirming oscillatory components of EEG and EMG signals (***as shown in Figures 4.76 and 4.77***). In the same time, other tests only reflect the overall functional outcome displayed by SCI patients performing activities of daily living. However, it was common to find that the functional outcomes do not well reflect specific gains on clinical scores of motor or sensory examination represented in the AIS charts. In instances where electrophysiological measures detected subtle changes, these measured changes might also potentially predict functional outcomes of tested patients after a given SCI lesion. In assessing SCI patients, some of the scored electrophysiological changes were in line with some functional outcomes of upper or lower limbs, while clinical assessments using AIS detected no measurable changes. An example is seen in patient S2 with the return of ERSP maps towards resembling normal patterns, mirrored by some functional gain and no measurable clinical change.

5.5.2 Shortcomings of the Electrophysiological Tests:

Some of the results of the electrophysiological tests are only reflected or represented by the outcome of the overall functional gain displayed by SCI patients performing activities of daily living at different stages of recovery. Though there might be some potential for prediction of functional recovery and insight into functional outcomes, as mentioned above, there is no specific or reliable correlation that reflects functional outcomes of the recovering spinal tracts. The outcomes seen in the functional activities of recovering SCI patients were not specifically reflected on any motor or sensory scores represented by the clinically based AIS charts. Furthermore, these functional outcomes are not represented by the electrophysiological measures described in this study. To accurately measure the functional outcome of SCI, it might be essential to combine clinical and electrophysiological tests performed in this study with measures of functional ability and mobility outcome following SCI. One of the measures of functional outcome is the Walking Index for Spinal Cord Injury (WISCI), which reflects any progress made in ambulatory capacity that is otherwise not addressed (Burns et al., 2011). Another global assessment method that captures functional recovery is the Functional Independence Measure (FIM) as a widely used measure of disability (AlHuthaifi et al., 2016). FIM encompasses assessment of several activities of daily living (ADL) that are not otherwise adequately covered by clinical or electrophysiological methods. The assessed skills and measures of ADL include functional activities such as grooming, bathing, dressing upper or lower body, toileting, and sometimes include combined motor, sensory, coordination and reflex functions which are hard to measure otherwise. The Functional Assessment Measure (FAM) adds items to FIM augmenting some specific cognitive and psychosocial assessment measures; therefore, abbreviating the overall modified Functional Assessment Measure to (FIM+FAM) (Turner-Stokes and Siegert, 2013). The lack of such FIM+FAM format in the assessment of the functional outcome of SCI and subsequent recovery is therefore an area of potential future improvement. This might be achieved by the complementary use of FIM+FAM format with the existing clinical and electrophysiological methods.

When electrophysiological measures do not detect changes expected in given SCI lesions or predicted by clinical or functional outcomes, potential changes might have been masked by medications taken by SCI patients at the times of follow-up tests. This has been highlighted in previous work on patients with chronic SCI or following recovery from acute SCI (Almad Jamil, 2017). An example for this is CMC between EEG and EMG from muscles which scored clinical recovery represented by AIS and functional outcomes; however, resulting CMC measures do not reflect this progress or recovery due to effects of medications. An example of this is seen in drug information on medications most frequently used in settings of SCI suggesting that these medications could suppress EEG and EMG signal power, affect processing and transmission of cortical responses to peripheral sensory stimuli. Medications might also influence CMC measures through effects on its precursors of EEG and EMG recordings. The listed medications used for SCI frequently include Baclofen, a few Benzodiazepines, Tizanidine, Gabapentin, Tramadol and Tricyclic Anti-depressants such as Imipramine. All these medications were used for clinical reasons at the time of test-2, with variable effects on the electrophysiological test modalities. For instance, **Baclofen** was found to increase the amount of slow brain wave activity, as described in studies outlining its activity at cortical and subcortical levels (Badr et al., 1983). The **Benzodiazepines** exemplified by the use of Diazepam showed to increase delta slow wave activity (Urata et al., 1996). Furthermore, **Tizanidine** which is one of the frequently used medications in the context of SCI, has been shown to cause strong depressive action on reflex responses and background activity of electromyographic muscle action (Mackel et al., 1984). **Gabapentin** has been associated with significant decrease of the peak frequency of posterior (alpha) rhythm, with a greater effect observed with prolonged use and higher doses, with reduced performance on cognitive assessments (Salinsky et al., 2002). **Tramadol** has been shown to produce dose-related decrease in the amplitudes of somatosensory evoked potentials, with increase in the estimates of side effects such as drowsiness which could affect the concentration of SCI patients and their overall performance (Thürauf et al., 1996). **Tricyclic Anti-depressants**

(TCA) such as **Imipramine** were used for SCI patients and were associated with inconsistent effects on EEG. This might involve an aggravation of EEG patterns or otherwise slow EEG rhythms, with similarly variable clinical effects including variable incidence of seizures (Escande et al., 1976).

5.5.3 Outcomes of the Electrophysiological Tests:

Electrophysiological tests offer sensitive and objective measures which are valuable in mapping and detecting subtle changes that might reflect plasticity taking place post SCI. These subtle electrophysiological changes might not be marked by observable or scored by measurable clinical recovery other than the minor electrical changes reported therein. This is an added value that justifies the use of electrical tests alongside the existing battery of clinical tools to comprehensively assess patients with SCI. Therefore, this makes the case for adding these electrophysiological tests in the assessment of SCI patients for predictable complementary value if not superiority over clinical methods. There is an added value of detecting subtle yet important changes that might be relevant to the overall outcome of SCI and subsequent recovery.

However, an important factor is variability of results of these electrophysiological testing methods which would be discussed in sections below. This means that individual tests might show different electrophysiological outcomes or interpretations when assessing the integrity and function of underlying CNS fibres being tested. However, some of these electrical tests are complementary to each other and need to be combined in assessment for augmenting relevant findings. In this context, it is worth noting that there is no clear picture of what might be the minimally important improvement in SEP, TMS or coherence measure terms. Hence, it is difficult to judge how any of the observed or measured changes translate into function or functional outcomes when viewed or assessed in isolation from the other electrophysiological tests. The individual electrophysiological tests would be explored and discussed below.

5.5.4 Individual Electrophysiological Tests:

This section would go over individual parameters of each electrophysiological testing method as follows:

Sensory Methods:

SEP and D-SEP: Methods assessing the sensory modalities show that changes in latency, amplitude and spatial organisation of SEPs and D-SEPs monitor changes in sensory pathways in SCI patients. These results could potentially provide useful information that supplements results of the clinical perceptual sensory tests based on methods of the ISNCSCI scales. For instance, SEP and D-SEP changes based on latency and amplitude measurements reflect significant clinical changes of sensory function and might detect sub-clinical changes that are not represented by AIS. Hence, these electrophysiological changes might better resonate with functional recovery and the outcome of SCI more than the AIS clinical scores, as previously shown in studies that SEPs might predicts future ambulation (Jacobs, et al., 1995). It was also highlighted that SEPs have the ability to correlate with functional outcome where upper limb SEPs predicted outcome of hand function post SCI (Curt and Dietz, 1996). The above-mentioned SEP and D-SEP changes might be in the form of change in height of amplitude and length of latency. Based on robust mixed-nerve stimulation, SEP measurements are made reliable and reproducible enabling longitudinal follow-up.

SEPs obtained from Median and PTN stimulations provide little or no information on the level of SCI and therefore offering no reliable assessment of CNS fibres across given SCI lesion. Though some studies claims some gain from upper limb SEPs from Median and Ulnar in indicating the level of injury (Curt and Dietz, 1996).

Meanwhile, D-SEP measurements are anatomically better placed to more accurately assess the level of SCI. This is because D-SEP utilises multiple-site dermatomal stimulations to map sensory functions at tested levels, enabling level mapping with potential monitoring capability

(Kramer et al., 2010). D-SEPs have been shown to be useful and reliable non- invasive tool assessing tract function when spinal cord imaging is normal (Prieto and Esteban, 1995). However, these relatively more anatomically precise D-SEP response measurements are inherently less reproducible and hence less reliable compared to SEPs. However, both SEP and D-SEP measurements are subject to significant ***variability*** seen in individual tests and their results which affect these results and the significance of information drawn from them (Turazzini et al., 1994). A further challenge for SEP and D-SEP measurements is the lack of strong and reliable link or ***relevance*** of these tests to ***functional*** outcome of the SCI lesion, though some studies suggested relevance of specific SEP measurements to limb function (Curt and Dietz, 1996). An additional challenge is that medications which are frequently used for SCI patients affect the SEP and D-SEP measurements. Effects of medications, as discussed above, add to the described degree of SEP and D-SEP variability depending on type and dose of medications used at times of test-1 and test-2 down the follow-up period. Finally, a peripheral nerve integrity factors seen in patients with chronic SCI also contributed to variability of responses obtained from peripheral nerve stimulation (Tankisi et al., 2015). However, most changes affect motor nerve components with abnormal spontaneous activity, reduced reflex activity, reduced nerve length and occasional entrapment of fibular nerve across the knee and sciatic nerve.

All these technical concerns raise a question of how to overcome SEP and D-SEP testing challenges to improve reliability of electrophysiological information gained, and it includes listing any drugs taken close or during the time of SEP or D-SEP tests. Another technical improvement might involve recording of SEP and D-SEP volleys at key points in the sensory pathways which might advantage gained information. For instance, obtaining recordings from the spinal nerve entry points and cord dorsum potential at C1 would potentially be valuable in identifying peripheral and central lesion effects. This has not been independently attempted in this study.

ERSP (ERS & ERD): Using ERSP (ERS & ERD) estimates provided further information into sensory cortical processing which combines with and complements relevant SEP and D- SEP measurements that may better assess recovery of sensory tracts. ERSP estimates were attempted beside conventional SEPs amplitude/latency measurements and found to be technically beneficial for prompt and reproducible additional information in sensory assessments (Hu et al., 2011). Moreover, ERSP estimates were readily identifiable with stable waveforms suggesting that the peak power is a more reliable monitoring parameter than amplitude but not superior to latency measurements (Hu et al., 2003). A clear advantage of the ERSPs, is that these estimates are focused on a longer time scale than the conventional SEP measurements, thereby have the potential of being more revealing in terms of the central processing of sensory signals. In this study, both standard SEPs time domain averaging and ERSP spectral time-frequency analysis measures of evoked activity used. The combined methods were quantified and used as a measure of function of ascending tracts as well as the cortical processing of resulting higher activation. This combination potentially increased the amount of gained information on the tested sensory pathways. This study, by employing SEP, D-SEP and ERSP, almost exclusively studied dorsal column pathways by means of the electrical stimulation described in methods sections. There is no firm extension of the electrophysiological examination to assessment of the nociceptive pathways. This was primarily due to time constraints and other limitations posed by patients' clinical status, likely compliance and studying pain pathways in the hospital settings. Some of these limiting factors are listed in the section detailing the limitations faced by this clinical and electrophysiological study.

Motor Methods:

MEP Measurements: Outcomes of testing motor functions show that the MEP measurements seem to correspond well with physical motor ability tested clinically by muscle scores according to ISNCSCI. It has been previously shown by motor evoked potentials performed

alongside somatosensory evoked potentials correlating with the functional outcome of SCI patients predicting prognoses of lesions and aiding plans for therapeutic approaches and rehabilitation (Curt and Dietz, 1997; Curt, 2000). MEPs below a given SCI lesion as a percentage of MEPs above the same lesion showed a significant correlation with ambulation recovery as a potential predictor of longer term functional recovery in animals and humans (Levy et al., 1987). A systemic review found out that MEP measurements from TMS are highly accurate biomarkers that, beside elucidating neural repair mechanism and identify therapeutic targets, are able to assess the extent of neural damage and predict clinical outcomes in patients with SCI (Nardone et al., 2015). In the context of corresponding with physical motor abilities, MEP amplitude is much more robust than latency, which is in keeping with previous studies, showing that the amplitude changes are much easier to monitor while latency changes were small and more conspicuous (Levy et al., 1987). The MEP amplitude demonstrates the correlation between MEP as an electrophysiological test on one hand and clinical recovery with resulting functional outcomes on the other. MEP amplitude assessments besides latency measurements continue to form the basis for MEP methods of assessing integrity and function of the descending spinal tracts across SCI lesions (Weinzierl et al., 2007). It seems that the use of simple TMS measures appears promising. Furthermore, the production of MEP recruitment curves in response to stimulus intensity increments show changes that correlate with altered motor functions over the follow-up period.

CMC Calculations: Although there is a clear need for careful interpretation of cortico- muscular coherence (CMC), analysis of CMC measures threw more light on functionality of cortico-spinal tracts sub-serving these motor functions. In patient S6, **CMC** analysis showed smaller yet maintained CMC calculations (***in Figures 4.76 and 4.77***), reaffirming the oscillatory components of EEG and EMG signals. Other electrophysiological tests for this patient reflected the overall functional outcome displayed by the SCI patient performing activities of daily living, but not well reflected by specific gains of clinical motor or sensory scores represented by the

AIS charts. The utility of cortico-muscular coherence measures as a testing method remains highly variable from subject to subject which might be further debated to be reliably established. The technical difficulties with CMC estimates are partly from its potential reliance on sensory feedback mechanisms but also susceptibility to drugs used to manage spasticity, physical or mental health symptoms common in patients at various recovery and rehabilitation phases of SCI past the acute/sub-acute stages.

Combined Sensory & Motor Tests: Similarly, it could be stipulated that combing both sensory and motor electrophysiological methods to assess integrity and function of ascending and descending spinal tracts across SCI lesions would be complex. This combination, which is successfully attempted in this study, obviously gave the added value of obtaining more information on all examined spinal tracts. However, created added complexity of issues described under sensory and motor assessment methods, including time constraints and interpretation issues.

6. Closure of Discussion

The discussion of this thesis could be drawn into conclusions and recommendations highlighting major areas of potential improvements of the electrophysiological tools examined in this study in the assessment of patients with traumatic spinal cord injury.

An obvious conclusion is that electrophysiological tests carried out for SCI patients in acute hospital settings are extremely challenging. This study demonstrated that these electrophysiological tests are both technically difficult and time consuming. Difficulties relating to these tests are shared by all parties involved including physiologists performing tests, SCI patients and clinicians providing services to these patients. This constitutes a major limitation that needs to be overcome to enable a smooth utility of these potentially useful tools. The described difficulties and limitations raise a valid and fundamental question of how these electrophysiological tests could be brought into the acute clinical setting caring for SCI patients with some sensitive and demanding clinical service needs. From the experience of this study, a practical way of implementing these tests might be through establishing a dedicated electrophysiological unit at the same acute site caring for SCI patients, purposefully equipped for these tests and tailored to address the clinical needs of SCI patients. The tests are ideally performed by appropriately trained physiologists, with the knowledge and technical skills. Trained physiologists competently perform electrophysiological tests and handle SCI patients, with sound understanding of the unique and delicate entity of SCI especially at the early stages of acute and subacute phases. A dedicated electrophysiological unit with a trained operator would be crucial for the smooth running of tests especially when they are not required for clinical care of SCI. The onsite 'ready-to-go' setting, with a trained physiologist dedicated to the unit, enables these tests to be carried out at specified points of time useful to the overall follow-up. For instance, these tests could be done at the crucial early stages of acute SCI as well as later on during their progress and possibly before discharge from hospital. The capacity to perform these tests at

specified chosen times along the care pathway, with ability to repeat them when required, would enable smooth longitudinal follow-up. ***Quality repeatability*** of these tests shall inform the clinical team of the progress of the SCI patients as well as collect useful data for analysis to improve learning about the electrophysiological changes underlying the clinical developments. Hence, it would be useful for both clinical services and data collection for research purposes.

Therefore, electrophysiological tests could be ***attempted with improvements*** including provision of dedicated testing unit settings, trained physiology personnel and flexible timing. This is best done with the recommended modifications gathered from lessons obtained from this study and aiming at improving tests, overcoming the previously described difficulties and limitations. For instance, ***shorter blocks of testing times*** would be much better tolerated by patients suffering acute SCI and less disruptive for the clinical care planned for them.

Of the individual electrophysiological tests examined by this study, the standard or conventional SEP measurements are relatively straightforward and should be done as part of assessing SCI patients. An improvement area is that the SEP measurements are combined with electrophysiological means of assessing the integrity of peripheral nerves. This would exclude any peripheral nerve degeneration or muscle denervation that is separate or related to the process of SCI as evidence shown this possibility. One way of obtaining information on peripheral nerves in the context of SCI might be through screening various limb muscles for denervation, which could be attempted by performing EMG in search of spontaneous activity (SA) or reduced F-wave reflex activity. This focus on peripheral nerve conduction is in line with work done by Curt showing useful utility of peripheral screening methods used in the context of SCI. The screening for peripheral nerve degeneration could be attempted at upper cervical and lumbosacral muscle region to clear upper limb SEPs, as well as lower limb SEPs, respectively. In the lower limbs, standard NCS might also be useful in excluding any forms of nerve entrapment

or length-dependent peripheral neuropathy that might affect the outcome of SEPs relevant to the affected nerves. The peripheral nerve screening in the context of SEPs for patients with SCI might eventually proof very useful and would appraise SEP measurements, especially with aging populations patients affected by SCI. D-SEPs are generally less reliable that standard mixed-nerve SEPs; however, utility of improved D-SEP measurements brings into play anatomical assistance in detecting information relevant to level of SCI. The D-SEPs might be attempted with the addition of quantitative sensory testing such as thermal methods, however time constraints need to be observed and managed. Therefore, tests should be stratified and carried out based on scientific or clinical needs (need to do test) basis. Similarly, linking D-SEP measurements to intra-operative monitoring (IOM) needs to be argued for with potential benefits. Improved D-SEP measurements, using quantitative methods (perceptual sensory threshold with heat or electrical stimulation), have been used in IOM with useful insights and reliable information into levels (Curt et al). Peak frequency estimates or studies as part of ERSP estimates are reliable and sensitive adding to and supplementing assessment of sensory pathways and sensory cortical processing following peripheral stimulation (cite ERSP in D-SEP and +/- IOM).

In improving SEP measurements, there is a need for ***improving reporting*** of abnormalities of SEPs, leading to improving specificity of knowledge of deciding abnormal results. These improvements are related to developing specific Amplitude and Latency parameters to establish abnormalities. For instance, percentage increase of SEP measurements relative to normal, or mean of normal values, might be helpful, estimating degrees of deviation from normal (e.g. based on standard deviation).

Besides standard SEPs, MEP measurements are another reliable electrophysiological measure of motor function, used as a reliable concordant in clinical AIS scores and potentially relevant to functional outcomes following SCI. Improvement of MEP measurements, like SEPs, is also related to the need to improve reporting abnormality, among other improvement measures.

Another area of improvement is the estimation central conduction time (CCT) to allow detection of any peripheral nerve abnormality or degeneration that might affect results of MEP measurements. MEP measurements are shown in this study to correlate with clinical AIS scores (manual muscle testing) and relate to recovery of neurological motor function. An area of improvement is to attempt multiple muscle recordings at the same time, possibly testing several muscles in the same limb or upper limb with lower limb. The correlation between MEP measurements and manual muscle examination could then be studies to better inform of the MEP. Correlation of MEP of key muscle groups and possibly compare with information gained from clinical motor scores through AIS manual estimates and information from reflex F-waves and SA assessments, which all look at accurately informing of the functional motor outcome following SCI.

These MEP measurements with the possible improvements described above, need to be performed on site by trained physiologists, and done early in the in the acute phase of SCI and repeated at specific times. This would enable the repeatability necessary for these tests to be reliably used for longitudinal follow-up assessment. MEPs could also be improved by use of TMS navigation system to accurately place the stimulating coil on the exact scalp with underlying cortical site each time, to enable reliable repeatability of tests enforcing significance and sensitivity of results gained from the MEP measurement methods.

SEPs and MEPs performed as described above detailing specifics of setting, operator, specified times and repeatability to detect changes that are taking place, would enable sound longitudinal follow-up. These could then be cross referenced to clinical progress and potentially relate to functional outcome. Combining improved SEPs and improved MEPs for better information on sensory and motor function and pathways, respectively, carry the best chance of obtaining reliable information on injured spinal cord tracts or their respective recovery.

CMC is not easy to obtain due to clinical factors relating to the paralysis of muscles and use of medications that affect consciousness, alertness, orientation, concentration and ability of SCI patients to follow testing instructions. There is an added difficulty of interpreting test results in the context of acute SCI. These CMC measures are not ready to be introduced in the clinical setup and need further work and refinement. It might be useful establishing better ways of utilizing coherence measurements to improve then use at less linear stages of muscle function in patients with SCI. For instance, their use for patients with recovering muscle function being tested at time intervals for longitudinal comparison.

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