University of Strathclyde Department of Bioengineering

Sensory function; Use in assessment of spinal cord function and its role in neural control of walking in humans.

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2010

This thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the Bioengineering Unit University of Strathclyde, Glasgow, 2010

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Signed: Date:

We shall not cease from exploration,

And the end of all our exploring

Will be to arrive where we started

And know the place for the first time.

T. S. Eliot

Acknowledgement

I would like to thank all the staff at the Bioengineering Unit at Strathclyde University for providing high quality teaching and excellent research facilities without which my PhD would not have been possible. I would like to also thank Professor B.A Conway (Bernie) for his valuable supervision and guidance and Dr Sujay Galen who worked with me tirelessly in the hospital. I also received a large amount of help and support from my friend and colleague Dr Gopal Valsan in writing scripts and learning the practical aspects of EEG.

During this study I spent many hours at the Queen Elizabeth Spinal Injuries Hospital in Glasgow. I would like to thank all the staff for their hospitality and guidance as well as the providing me with much needed space and time with patients in a very demanding unit. Many thanks go to the patients and their families from the Queen Elizabeth Spinal Injuries Hospital who gave up a lot of their time to be involved in the study.

I would also like to thank the volunteers from the Bioengineering unit who completed the early studies which were essential in the development of the methodologies produced. Thanks also for the volunteers who completed the walking tests for your time, patience and assistance during the many testing protocols.

I would also like to thank my family for their constant support and special thanks to my husband Chris, who is my everything.

Thank you.

Abstract

Tests of spinal cord function are required to assess interventions and provide common outcome measures across international studies for rehabilitation of incomplete spinal cord injury (iSCI). These tests need to be sensitive, reliable and reproducible. Tests which provide a predictive measure of functional outcome may also help clinicians to prescribe the most effective form of intervention to each patient.

The primary aim of this study was to validate sensory test procedures and outcome measures set out in the first phase of a clinical initiative (Ellaway et al., 2004) in iSCI patients after a period of intervention. The secondary aim was to evaluate the somatosensory pathway and modulation of sensory processing during phases of the gait cycle during normal walking.

18 iSCI patients completed 6 weeks Lokomat training. Functional ability was measured using Walking Index for Spinal Cord Injury II scale (WISCI II) and temporal gait analysis. Neurological function was assessed using the protocol set out by the American Spinal Injuries Association (ASIA). Electrical and Vibration perception thresholds (EPT, VPT) and Somatosensory Evoked Potentials (SEP) were validated as possible assessments of spinal cord function. Improvements in ambulatory capacity were seen in iSCI patients after 3 weeks of Lokomat training. The EPT and VPT assessments can give additional detail on the level of the lesion in iSCI. The Posterior Tibial (PT) nerve SEP may provide some predictive value of ambulatory capacity after Lokomat training.

Modulation of cortical potentials was seen during phases of the gait cycle. During the swing phase cortical components evoked by PT nerve stimulation were present. In other phases the early components were abolished. This may suggest supraspinal pathways are involved in the modulation of sensory information during the swing phase. These finding suggest that rehabilitation methods for iSCI patients should focus on presenting sensory stimulus at the correct phase of the gait cycle.

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1 INTRODUCTION

It was said to me many times as a child that I should walk before I run, meaning that one should accomplish the easier task before moving on to the harder task. This parable also demonstrates how the art of walking is perceived in the general public. We take it for granted. As we have been able to walk for nearly as long as we can remember, we do not need to put any effort into walking and assume that we can walk when concentrating on a multitude of other tasks. But walking is a complex task involving the coordination of many muscles and joints. The cyclic event which creates locomotion involves changes in limb direction, power and timing of muscle activity. As our walking is not consistent all of these parameters must be adaptable to overcome changes in the floor surface, speed, obstacles or any unexpected events.

The way in which we walk and how it is controlled has intrigued many people and research has been applied to this field of work for over 100 years. Work on animal and humans subjects during normal walking as well as observations after stroke and spinal cord injury (SCI) have provided understanding of movement and how it is controlled. After an injury such as stroke or SCI functional walking is sometimes lost. Reasons why some people recover better than others and what type of treatment is more useful to a type of injury is still unclear. This thesis has concentrated on the ability and recovery of walking in patients after an incomplete SCI.

SCI affects many people across the world, with injuries commonly due to road traffic accidents, violence, falls, sport and disease. In the UK 825 new cases of SCI were admitted to Spinal Injury Centres in the year 2000. This figure is lower than the total estimated annually as it does not include those treated in general hospitals within the UK. After discharge from the hospital a patient with a SCI can live for many years and it was estimated in 2006 that 253,000 people were living with a SCI in the USA (Spinal Cord Information Network).

Most patients with a SCI will have deficit in mobility. The degree of deficit in ambulatory capacity can vary greatly from no ability, i.e. wheelchair bound to functional walkers who are able to walk with their community setting with or without

the use of aids and braces. The physical ability of each patient may be improved with physiotherapy rehabilitation. For many years this rehabilitation was done to develop compensatory methods, such as using non-affected limbs or muscle groups to do the function of the limbs that have been affected. Compensatory methods were encouraged as it was believed that the CNS could not adapt or change to prevent recovery. However it is now known that the CNS is not rigid and can undergo changes after an injury which may lead to functional improvement. This ability of the CNS to adapt is termed neural plasticity (Cooke and Bliss, 2006) for review, (Ward and Cohen, 2004).

The discovery that the adult CNS is highly adaptive has led to a change in rehabilitation methods from compensation to methods that may induce plastic recovery. The current understanding of the neural control of walking has led to rehabilitation methods that are task specific, repetitive and which induce motion related sensory feedback.

The efficacy of these rehabilitation methods is required to ensure the best possible outcome for individual patients is achieved. To enable these types of rehabilitation methods to be assessed against each other and against other forms of SCI intervention, such as nerve growth promoters and stem cell research, accurate and reproducible tests of spinal cord function need to be available (Ellaway et al., 2004).

The International Spinal Research Trust (ISRT) established a research programme to identify a batch of tests that could be used to monitor changes in spinal cord function of spinal cord injured patients over a period of intervention within its Clinical Initiative funding cell. During the first phase of this initiative Professor Ellaway and his colleagues in London, UK developed a series of sensitive, accurate and reproducible assessments into neurological function (Ellaway et al., 2004). The second phase of the initiative was to independently validate the motor and sensory assessments and outcomes measures in the context of an established intervention. This thesis reports on a component part of the 2nd phase of the Clinical Initiative and focuses on the role of sensory function in the restoration of ambulatory capacity after robotic gait training in iSCI. The level of improvement in ambulatory capacity over the period of the trial for each patient was determined using gait analysis and

walking indices. Observations of any correlations between the changes in ambulatory function and underlying physiology determined by the sensory assessments may provide evidence to the nature of the ambulatory recovery, i.e., compensatory, neural repair or plasticity. In this thesis the series of sensory tests described by Ellaway et al (2004) and supplemented by additional electrophysiological measure of sensory function which may provide sensitive reliable and reproducible measures of spinal cord function.

The current study used a Robotic Gait Driven Orthosis (RGDO) called the Lokomat as the intervention. This use of an RGDO was developed from studies in the healthy and complete spinliazed mouse (Leblond et al., 2003) and in humans (Behrman and Harkema, 2000) demonstrating the importance of repetitive task specific training during which normal motion induced sensory feedback is obtained(Harkema, 2001, Leblond et al., 2003). The results from this type of training differs in the current literature between the animal and human SCI subjects as over ground walking in complete SCI humans has never been achieved but is achieved in the animal models. This thesis additionally reports on modulation of sensory information within phases of the gait cycle during treadmill walking. This modulation demonstrates that sensory feedback is not processed in the same way during each phase of the gait cycle. The modulation of sensory information reported within this thesis was assessed in healthy subjects to identify the role of transcortical pathways in conveying sensory information during each phase of the gait cycle. The identification of supraspinal sensory processing during gait may enhance rehabilitation methods used to provide recovery of walking within iSCI and lead to increased functional ability of iSCI patients.

2 LITERATURE REVIEW

In this chapter I will explain the terminology of spinal cord injury and the affects of such an injury focusing on walking ability. I will then review the literature on how walking is controlled through complex neural circuits and how this understanding has led to new technological methods in walking rehabilitation. Finally I will discuss the concept of using physiological assessments to assess the neurological changes that may occur as walking ability is improved and whether the ability of a patient to walk after rehabilitation can be predicted. At the end of the chapter I will outline the aims and objectives of this project concluded from the literature review.

2.1 SPINAL CORD INJURY

Spinal Cord Injury (SCI) is termed as damage to the spinal cord which can be caused by either trauma or by disease. The injury which is a lesion within the spinal cord can cause a loss of function in mobility or sensation or both. The amount of function that is lost is dependent upon the location and size of the lesion. To determine the extent of the lesion clinical examinations are used; a detailed review of these techniques is discussed later in this chapter. Once the extent of the lesion is determined the lesion is categorized so that the patient can receive the correct treatment for their specific injury.

2.1.1 DEFINITIONS OF SPINAL CORD INJURY

The size of the lesion affects the amount of tracts that have been damaged, when the lesion affects the whole of the spinal cord width and no tracts have been spared this is classified as a complete Spinal Cord Injury (cSCI). With this type of lesion a complete loss of function is seen below the level of the lesion with no voluntary movement or conscious sensation present. If any part of the spinal cord is spared then the lesion is termed as an incomplete Spinal Cord Injury (iSCI). An iSCI patient will have some function below the lesion but the type and amount is dependent on what ascending and descending tracts have been spared.

The level of the lesion, its position in the spinal column is also grouped and defined. The higher the lesion the greater the amount of the body is affected. The level of injury is described by the level of the lesion in the spinal cord not the level of the vertebral column. In Figure 2-1 the relationship of the spinal cord to the vertebrae column is shown. It can be seen that the spinal cord segmental levels do not always correspond to the vertebral segment. The spinal cord has nerve roots which enter and exit the spinal column between each of the vertebral segments. In the cervical region the spinal nerves exit above the vertebral segment that shares its name. In all other regions the spinal nerve exits below the vertebral segment. This explains the presence of the spinal nerve C8 when there is no C8 vertebra.

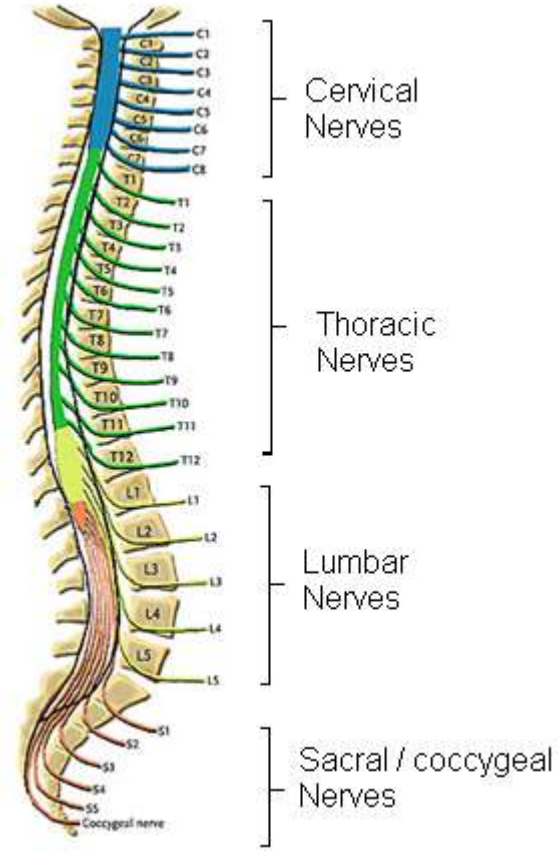


Figure 2-1: shows the relation of the spinal cord to the vertebrae. The spinal nerve exist above the vertebra tin the cervical region. Between C7 and T1 vertebra the spinal nerve is C8. In the thoracic, lumbar and sacral regions the spinal nerve exists below the vertebra. [Adapted from http://www.maturespine.com]

Tetraplegia (also known as Quadriplegia) is defined as the impairment or loss of motor and or sensory function due to an injury in the cervical segments of the spinal cord containing the spinal nerves (C1-C8). All four limbs are affected in tetraplegia.

Paraplegia occurs if an injury is below the first thoracic vertebra (T1) and is defined as the impairment of motor and or sensory function in the thoracic, lumbar or sacral segments of the spinal cord. A paraplegic patient has impaired function in the lower limbs but normal function is preserved in upper limbs.

2.1.2 EFFECTS OF SPINAL CORD INJURY

Although the most commonly known effect of a SCI is the loss of sensation and or motor function it is only a part of the overall effects of SCI. Other effects, which are dependent upon the location of the lesion, include irregular heartbeat, low blood pressure, blood clots, spasms, autonomic dysreflexia, pressure sores, pain, bladder and bowel functions, reproductive and sexual problems. This thesis is concerned with ambulatory capacity that is affected by an iSCI and hence the other affects will not be discussed further.

Research shows that some degree of recovery of ambulatory capacity is seen in up to 87% of iSCI patients (Harkema, 2001). The level of assistance needed to complete a walking task varies across iSCI patients and may include the use of braces, crutches and / or help from others to no assistance needed for full ambulatory capacity (Scivoletto and Di Donna, 2009). However in cSCI patients there has been no reported case of a patient regaining functional ambulatory capacity over ground. Some ability to walk over ground can be achieved in complete paraplegic patients with injuries between T6 and T12. This is done through abdominal muscle control to move the legs forward whilst taking their body weight through their arms and balancing on the other leg with help from leg braces which fixes the knee.

In the iSCI population there is a large variation in the outcome of ambulatory capacity. It has been suggested that the outcome depends upon age, gender, and factors relating to the injury, such as level and severity of the lesion (Scivoletto and Di Donna, 2009). However it remains unclear why some patients improve more than others and why some rehabilitation methods work better for some patients than others.

The early prediction of ambulatory capacity is important to the patient and the health workers to ensure the correct care and rehabilitation is given at the correct time. In patients where limited function is predicted timely adaptations to living arrangements can be made. This ensures that the patient is able to return to their own home as early as possible. It is also important for the patient to know what he or she may expect and not to have their hopes raised or diminished with false predictions.

To enable further discussion over the ambulatory capacity of iSCI patients first the pattern of normal walking and how this is controlled must be understood.

2.2 LOCOMOTION

The gait cycle is determined by the pattern of muscle activity and movements during walking. It can be studied using techniques of motion analysis, inverse dynamics, and multichannel Electromyography (EMG). The gait cycle of most animals and humans is well documented within the literature (Winter, 2009) however only the gait cycle for human walking is presented in this thesis. When the neural control of walking is described later in this thesis reference to animal models of pattern generation are made. It should be noted that humans walk differently to these animals. We walk on two legs (bipedal) and the sole of our foot is placed onto the floor (known as plantigrade) whereas cats and many other vertebrates which are quadripeds walk with 4 limbs and only make contact (generally) with the ground with their toes (known as digitigrades). However cat and rat models have been extensively used to understand the neural control of walking and many aspects of human walking are referenced to these studies.

2.2.1 THE GAIT CYCLE

The human gait cycle starts as one heel strikes the ground and ends with the consecutive heel strike of the same limb. The cycle is composed of 2 phases; stance and swing. Stance occurs when the limb is on the ground and swing occurs when the limb is swinging forward (See Fig 2-2). The movement of the two limbs is synchronized so that during stance phase of the left limb the right limb is able to swing forward in the swing phase. Fig 2.2 shows this synchronization with the right

limb in black and the left limb in red. This synchronization is needed to progress forward transferring body weight between limbs and to maintain balance.

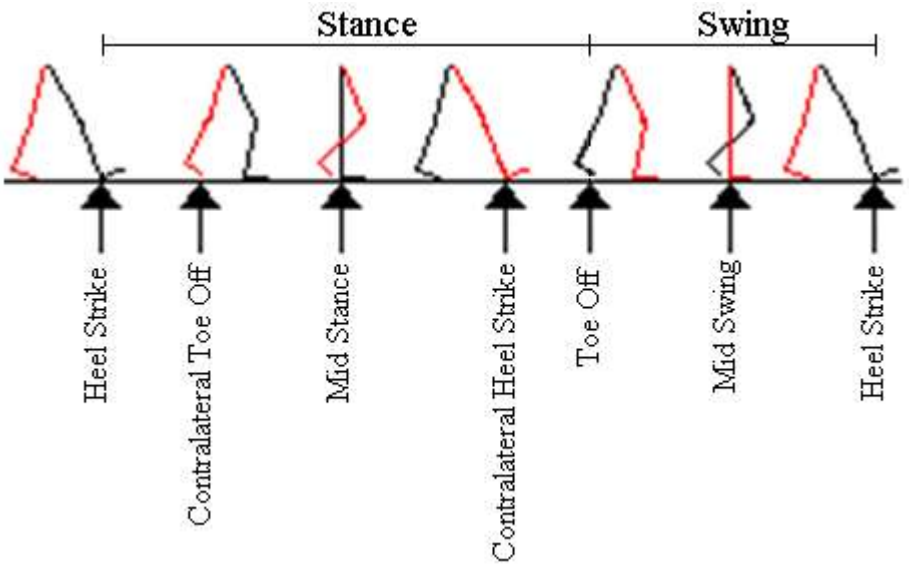


Figure 2-2: The gait cycle during normal walking. The gait cycle is composed of 2 phases, stance and swing. Heel strike (HS) and Toe Off (TO) of a single limb indicates the transition between the 2 phases. Within each stance phase there are 2 periods of double and single support occur. Right limb shown in black left limb in red.

When the limb is not in contact with the ground it is in the swing phase of the gait cycle. After the limb leaves the ground, at toe off it accelerates to catch up with and pass the torso. The limb then decelerates to correctly position the foot and to reduce heavy foot fall on heel strike.

During the gait cycle the movements at the hip, knee and ankle joints are out of phase with each other (Capaday, 2002). The position of the hip, knee and ankle joints in each phase of the gait cycle is dependent upon the activity of the lower limb and trunk muscles as well as external forces. The muscles around the joints contract and then relax to move the joint centres into the correct positions and create the stepping rhythm. The muscles are classified anatomically as either flexors or extensors according to whether the function of the muscle is to reduce or to increase the angle around a joint.

The main muscles active during human locomotion (shown in Table 2-1) flex and extend the hip, knee and ankle during each of the phases of the gait cycle. At the start of the stance phase (heel strike) gluteus maximus, quadriceps and tibialis

anterior muscles contract to stiffen the lower limb. As the stance phase progresses the gluteus maximus extends the hip while the quadriceps controls the passive flexion of the knee and tibialis anterior controls the passive plantar flexion of the ankle. At the start of the swing phase, contractions of the iliopsoas and tibialis anterior produce hip and ankle flexion so that the leg can swing through without the toes dragging on the ground.

Muscle	Flexor / Extensor	Active during gait cycle
Gluteus Maximus	hip extensor	Late Swing to mid Stance
Lisopsoas	hip flexor	Late Stance to mid Swing
Quadriceps	knee extensor	Late Swing to early Stance
Hamstrings	knee flexors	Mid Swing to early Stance
Triceps Surae	ankle extensors	Early Stance to Late Stance
Tibialis Anterior	ankle flexors	Early swing to early Stance

Table 2-1: Simplified activity of the large muscle groups during normal gait.

Although these are the main muscles involved during the gait cycle this is a very simplified and superficial view. The actual muscles involved are numbered in the tens and involve upper limb and torso muscles to provide stability. Synchronization of erector spinae muscles has been shown during walking demonstrating some involvement during walking (Catton and Conway, 2005). Variations are also seen in the muscle output between subjects as well as within subjects at different speeds.

By looking at the phases of the gait cycle, the joint centres and muscle activity the complexity of human walking is revealed. There is a good understanding in the literature about the mechanics of how we walk, but this does not explain how walking is controlled. To understand this, the thesis now looks at the role of the central and peripheral nervous system in the neural control of walking in animals and humans.

2.3 NEURAL CONTROL OF WALKING

2.3.1 CENTRAL PATTERN GENERATOR IN THE SPINAL CORD

Early research into the understanding of the neural control of walking was initiated by Sir Charles S Sherrington (1857-1952) and Thomas Graham Brown (1882-1965). In 1911 Brown demonstrated for the first time the existence of networks of neurons in the spinal cord that could generate the rhythmic activity seen in walking. Brown (Brown, 1911) isolated the spinal cord from supraspinal input by transecting the spinal cord, and lumbar sensory input by cutting the dorsal roots of the spinal cord (deafferenated). Figure 2-3 shows the recording of the alternating contractions of flexor and extensor muscles similar to the patterns seen during walking. The importance of this work was to demonstrate that spinal circuits alone can generate sustained rhythmic output without any input from either supraspinal structures or from sensory receptors. Prior to this work by Brown (Brown, 1911) the theory proposed by Sherrington (Sherrington, 1910b) that stepping movements could be initiated and coordinated by a series of reflex actions from sensory feedback was the consensus. The work by Brown advanced the understanding of neural control of walking and gave rise to the theory of central pattern generators (CPG) in the control of rhythmic movements like walking.

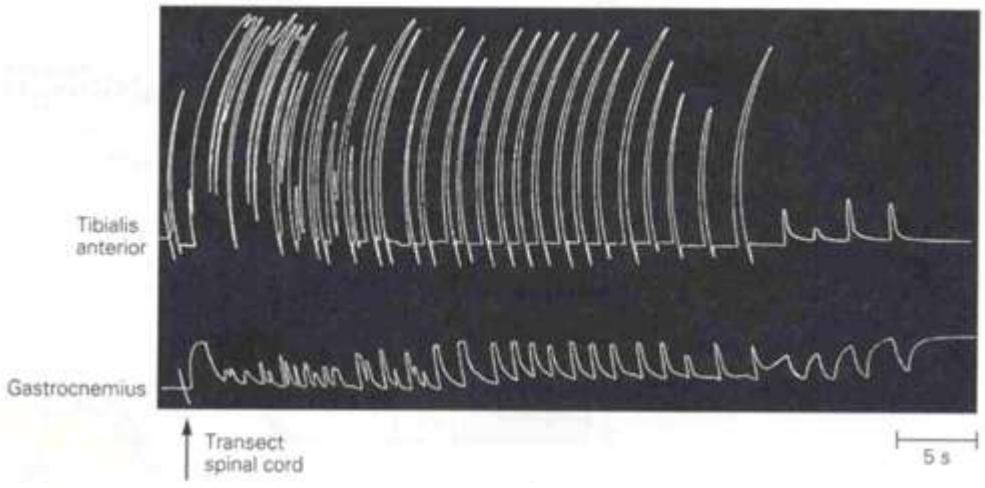


Figure 2-3: Rhythmic activity generated from an isolated spinal cord of the cat. Implicates the existence of a neural network within the spinal cord that can generate walking like patterns. [Modified from (Brown, 1911)]

Graham Brown (Brown, 1914) proposed a model termed the "half-centre" to illustrate how the spinal circuits could generate the rhythmic movements of walking. In the development of this simple model shown in Figure 2-4, each limb is controlled by a half centre that contains two groups of excitatory interneurons. These interneurons project to either the pool of flexor or extensor motorneurons. The model shows mutual reciprocal inhibitory connections between the active flexor and extensor "half-centres". As the two groups of excitatory interneurons are connected by mutual reciprocal inhibition, only the flexors or extensors could be active at one time (Brown, 1924). In his original model he proposed that as the active group of excitatory interneurons fatigues the reciprocal inhibition to the inactive group of excitatory interneurons decreases and allows it to become active which activates the antagonistic muscle group (Stuart and Hultborn, 2008).

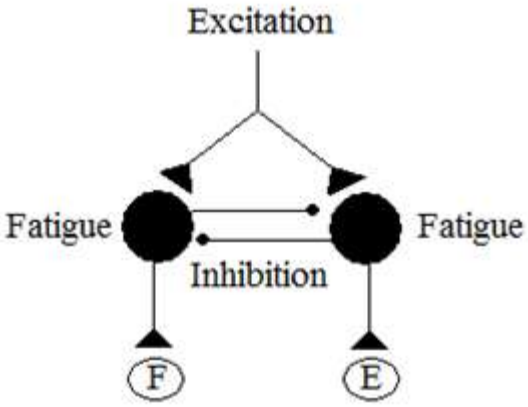


Figure 2-4: Half centre model by Graham Brown (1914). The circles represent the spinal interneurons projecting to the flexor and extensor motorneurons. The excitatory and inhibitory connections are shown by lines ending with triangles and small circles respectively.

Brown also recognised that the key role of sensory feedback in his model is to provide adaptations to the gait pattern to account for environmental changes and external perturbations. The Graham Brown half centre model therefore has the expectation that the cycle symmetry can be modulated through interneurons by sensory input. Models of the spinal pattern generators for mammalian locomotion have become progressively more complex but they mostly still include a half-centre component (Stuart and Hultborn, 2008).

The presence of the mutual reciprocal inhibition, key to Brown's model was demonstrated by Lundberg, Jankowska, and their colleagues through studies of the Flexor Reflex Afferent (FRA) system in cats and the monoaminergic innervations of the spinal cord. The FRA system was originally described by Sherrington in decebrate cats (Sherrington, 1910, Sherrington and Sowton, 1915) but is commonly demonstrated in text books by the model of a person standing on a pin. The FRA is a collective name given to afferent systems that when stimulated tend to produce a reflex withdrawal of the stimulated limb and a crossed extension reflex of the contralateral limb. In general the afferents are considered to comprise those with a high threshold to electrical stimulation and therefore could be considered to include groups II, III and IV afferents. In the model of a person standing on a pin the reflex withdraws the limb from the painful stimulus while straightening the opposite limb to ensure that balance is maintained (See Fig 2-5). The stimulation of the FRA (by the pin) leads to a short latency response in the ipsilateral flexor muscles and inhibition of ipsilateral extensor muscles, which causes the limb to be withdrawn from the site of stimulation. At the same time the extensors of the contralateral limb are stimulated and the flexor muscles are inhibited to straighten the leg and allow it to bear weight.

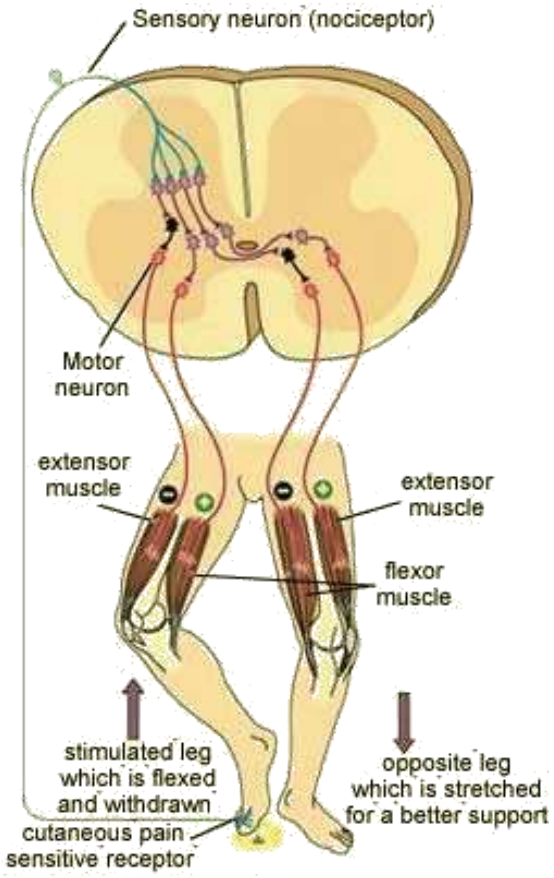


Figure 2-5: Crossed extensor reflex. When the ipsilateral FRA is stimulated the ipsilateral flexor muscle and the contralateral extensor muscle is contracted (excited) whilst the ipsilateral extensor and contralateral flexor are inhibited. [Modified from http://thebrain.mcgill.ca/flash/index_a.html].

The FRA system was subsequently studied by Lundberg and colleagues using intracellular recording techniques to investigate spinal networks that may be involved in the control of Locomotion. The study investigated what role monoaminergic innervations to the spinal cord had on motor circuits. In the acute spinal cat FRA stimulation generated a short latency, short lasting flexion reflexes described in the crossed extensor model above, however this was lost when the animal was injected with L-DOPA (L-dihydroxyphenylalanine) (Hultborn and Nielsen, 2007). The L-DOPA caused an increase in the release of noradrenalin from nerve terminals of descending fibres from reticulospinal centres. Injection of L-DOPA suppresses the short latency FRA effects and releases long latency and long lasting flexion reflexes with mutual extensor inhibition (Jankowsk et al., 1967). The long lasting response was observed as an excitation in the ipsilateral flexor (Fig 2-6B) and contralateral extensor motoneurons (Fig 2-6E) (as seen in the classical flexor

reflex response but considerably delayed). The change in the state of the reflex behaviour suggests a role of the monoaminergic innervation in the CPG.

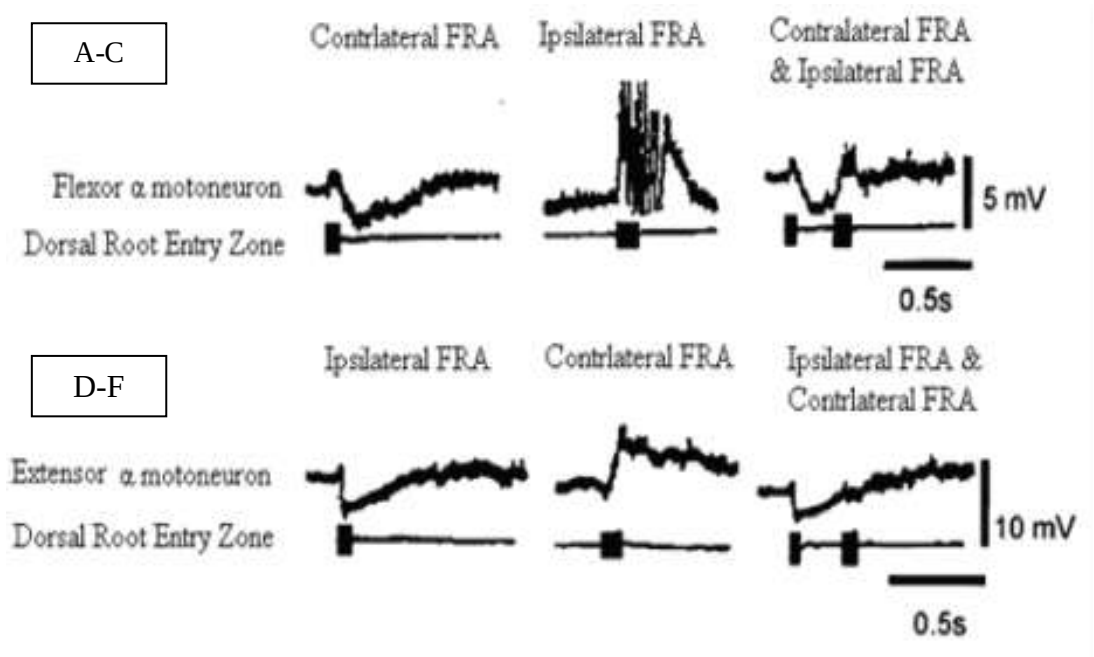


Figure 2-6: Tracings A-C show the activity in the flexor motoneurons and the lower tracings, D-F show activity in the extensor motoneurons. The upper records show the intracellular recordings from motoneurons and the lower records show the dorsal root entry zone. When the ipsilateral FRA is stimulated the ipsilateral flexor motoneuron (B) and the contralateral extensor motoneuron (E) shows a excitatory post synaptic potential. This effect is inhibited if a stimulus to the ipsilateral FRA is preceded by stimulus from the contralateral FRA (C). [Modified from (Jankowsk et al., 1967)].

The stimulus was then applied to the ipsilateral and contralateral FRAs using the spatial facilitation technique where stimuli are presented with short delays between each (Jankowsk et al., 1967, Grillner and Zangger, 1974). The effect was to inhibit the excitatory response in the ipsilateral flexor and contralateral extensor motoneurons. Figure 2-6C shows the inhibited response after an ipsilateral FRA stimulation in the flexors when the stimulation was preceded by a stimulation on the contralateral FRA. This response suggests that the flexor motoneuron is inhibited during the excitation of the extensor motoneuron and vice a versa, demonstrating the mutual reciprocal inhibition first hypothesized in interneuronal circuits proposed in Browns 'Half centre' model. These findings led Lundberg to propose that the FRA interneuronal pathway is part of a complex neural network that has the capacity to operate in a manner similar to Browns half centre model. This type of complex network of neurons is now termed central pattern generator (CPG).

A second experimental set up by Lundberg and colleagues (Lundberg, 1979) was used to further demonstrate the role of these spinal circuits in locomotion. When the DOPA was administered to the spinal transected cats after Nialamide (a monoamine oxidase inhibitor) the effects of DOPA were prolonged. Spontaneous bursts of activity occurred in the interneurones which led to bursts of motoneuronal discharges in the flexor and extensor pools. When the FRA was stimulated during these bursts of motoneuronal discharges it caused alternating activity in the flexor and extensor motoneurons as shown in Fig 2-7. The bursts of muscle activity seen looked like steps or part of steps and were termed 'spinal stepping'. This reinforced the belief that the interneurons in the FRA pathway are utilized by the spinal networks to create stepping.

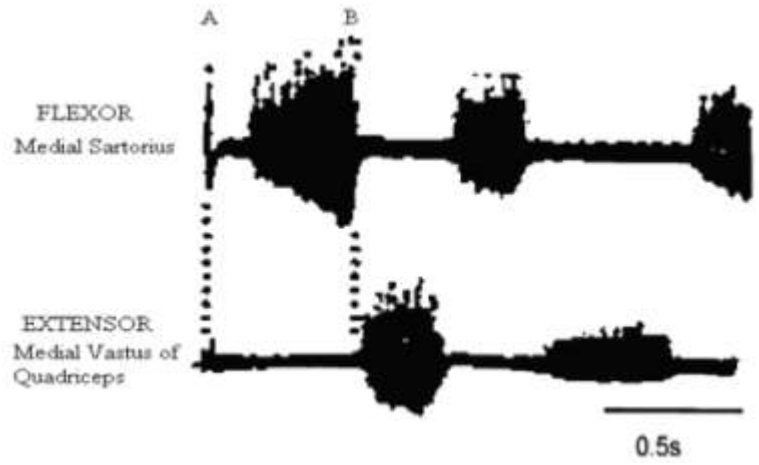


Figure 2-7: Alternating discharges in flexor and extensor efferents after Nialamide and DOPA. Recordings from nerves to medial sartorius, a flexor muscle and medial vastus of the quadriceps, an extensor muscle. Stimulation of the cutaneous nerve (A) ipsiplateral and (B) contralateral evokes alternating activation of the flexor and extensor muscles. [Rearranged from (Lundberg, 1979)].

L-DOPA stimulates the synthesis and release of neurotransmitters such as noradrenalin from presynaptic terminals of monoaminergic neurons in the spinal cord (Andén et al., 1966). As fictive locomotion can be stimulated after an injection of L-DOPA it suggests that the descending monoaminergic pathways from the brain stem activate the spinal circuits responsible for locomotion (Duysens and Van de Crommert, 1998).

Sten Grillner and his colleagues confirmed that the CPG is present in the spinal cord and is able to produce locomotion using the following experimental setup. The

control of the hind limbs was removed by a spinal transaction while leaving the forelimbs under normal descending control. These spinal cats, with external support for weight bearing and balance were able to walk on a treadmill with a near normal stepping pattern (Grillner and Shik, 1973). In this preparation the spinal cat received sensory input from the periphery and demonstrated the ability of the spinal cord to generate locomotor activity in the hind limbs without supraspinal control demonstrating the presence of the CPG within the spinal cord.

Further details on how sensory feedback provides adaptations to the central pattern are discussed later in this thesis under the section, 'role of sensory feedback during locomotion'. First it is necessary to discuss the possible existence of CPG in humans as this thesis is to focus on the recovery of locomotion in spinal cord injured humans. The existence of a CPG for locomotion in humans is more difficult to demonstrate and the evidence presented here and throughout the literature is indirect.

CENTRAL PATTERN GENERATOR IN HUMANS

When a patient presents with a complete spinal cord lesion movement below the level of the lesion is not possible and walking is lost. This observation remains a strong argument against the presence of a spinally located CPG for locomotion in humans. An example of rhythmic EMG activity modulated by peripheral stimulation in a complete SCI patient has been described by Bussel et al (Bussel et al., 1996). However only occasionally and after flexor afferents were stimulated was alternating activity observed between the two limbs similar to that seen in locomotion. The alternating activity only lasted for a single cycle, unlike the spinal stepping seen in the cat.

A case describing involuntary rhythmic locomotor activity in an incomplete SCI patient was reported by Calancie et al (Calancie et al., 1994) to show evidence of the CPG for stepping in the adult human. Movements were observed when the patient was supine and their hips and knees were extended. The movement was reduced when the hips and knees were flexed. As the subject was unable to voluntary initiate or interrupt these movements it was suggested that a spinal CPG was responsible for these movements. However as the patient had an incomplete SCI the influence of

supraspinal input cannot be eliminated and so this case study does not in itself provide conclusive evidence of a spinally located human CPG. Nadeau et al (2010) reported rhythmic activity in a T5 complete SCI patient. Activity was seen in trunk muscles and flexor and extensor muscles of the lower limb. This patient had possible pain below the level of lesion due to coxotemporal arthritis. This afferent feedback may have triggered the bouts of activity which lasted 2-3 days. The presence of alternating activity which could be interrupted by additional afferent input (by pinching the skin) is related to the co-activating of a CPG for locomotion. The patient in this study was on baclofen which may hyperpolarise the neurons within the spinal cord.

The studies into spinal cord stimulation provide the most compelling evidence for the presence of a CPG in humans. Spinal cord stimulation was first developed as a clinical method to control severe spasticity in chronic spinal cord injured patients (Dimitrijevic et al., 1998) but was adapted to investigate the locomotor capabilities of the lumbar cord in humans (Gerasimenko, 1996). Figure 2-8a/b shows the rhythmic locomotor activity observed in the EMG of the lower limbs of a single cSCI patient during tonic spinal cord stimulation at L2. Similar results were observed in 6 cSCI patients. In 4 cSCI patients extension and flexion movements of one limb was also observed and provides some evidence that involuntary locomotor like patterns can be produced in humans with no supraspinal input (MacKay-Lyons, 2002). It demonstrates that the lumbar spinal cord was capable of initiating locomotor like activity (Dimitrijevic et al., 1998, Minassian et al., 2004).

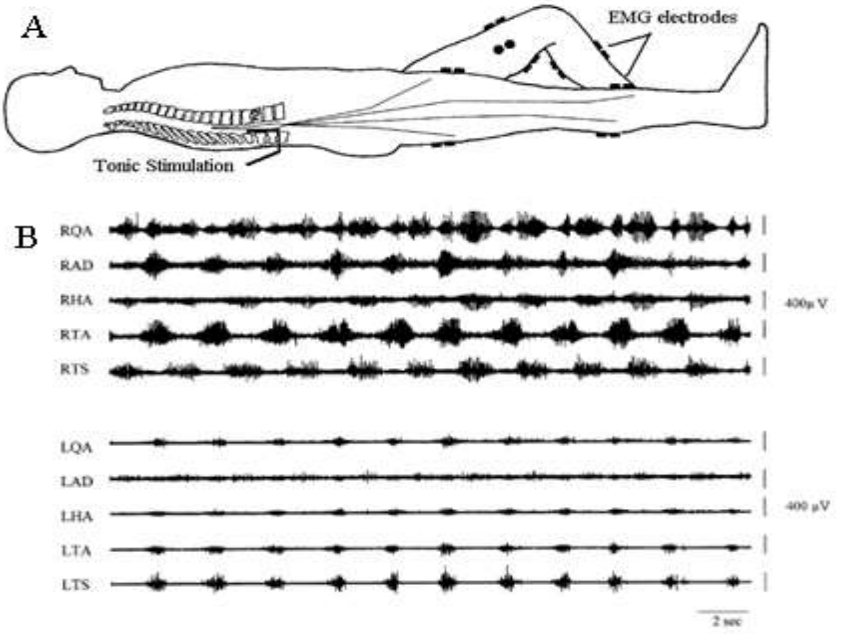


Figure 2-8a/b: Locomotor-like EMG activity in the lower limbs during spinal cord stimulation above the L2 segment. The subjects were tested in the supine position with the stimulating epidural electrode placed within the spinal canal, above the posterior lumbar cord structures (A). A train of stimuli of 30 Hz and 9 V on the right side was applied. EMG recording were placed over left and right quadriceps (QA), adductors (AD), hamstrings (HA), tibial anterior (TA), and triceps surae (TS) muscle groups. Figure B shows locomotor-like EMG activity in the right lower limb and simultaneous contralateral recording of EMG responses all muscle groups. The vertical marker for amplification is 800 μV, with the exception of RHA and LHA, for which the vertical marker for amplification is 400μV. [Rearranged from (Dimitrijevic et al., 1998)].

The work on the FRA by Lundberg and co-workers on spinal cats (Jankowsk et al., 1967) was investigated in a comparative study of complete SCI patients by Roby-Brami & Bussel (Roby-Brami and Bussel, 1987, Roby-Brami and Bussel, 1990) to determine if a simple pattern of reflexes exist in patients and which could possibly relate to a substrate for a human CPG. In these patients early and late flexor reflexes were observed in ipsilateral muscles after electrical stimulation of the FRA. The early reflex occurring at 100 ms was similar to the flexion reflex observed in healthy individuals. The later response, occurring after 200ms is thought to be a separate reflex directly activated by the afferent volley. These findings on the late reflex are similar to the late flexion reflex described in the acute spinal cat injected with DOPA (Andén et al., 1966). These studies by Roby-Brami hypothesised those patients with a complete SCI display similar long latency spinal reflexes to those seen in the acute spinal cat injected with DOPA. This work is potentially significant since this reflex which is mediated via interneurons is involved in the half centre organization and

related to spinal stepping seen in cats and suggests the presence of a CPG in the human spinal cord. The long latency flexion reflex described by Roby-Brami has also been used in Functional Electrical Stimulation (FES) gait restoration programmes to provide the swing phase of stepping (Andrews et al., 1991, Field-Fote, 2001, Granat et al., 1993, Kralj and Grobelnik, 1973). The long latency flexion reflex causing the flexion of the hip, knee and ankle occurs after stimulation of the sural, peroneal or saphenous nerve of the foot while the quadriceps of the contralateral limb are activated by of the electrical stimulation. To complete the swing phase the quadriceps of the ipsilateral limb is stimulated which straightens the knee while the hip continues to flex. However the reflex response diminishes with repetition so only a small number of steps can be accomplished (Andrews et al., 1990, Granat et al., 1991, Nicol et al., 1998).

It has been shown that the spinal cord (of animals) without any supraspinal control can centrally generate locomotor like activity without any sensory input though a central pattern generator. Although indirect in humans, the evidence does suggest that a CPG is present and provides a substrate for the stereotyped locomotor movements (Grillner, 1975). This patterned movement needs to be adaptable to enable a change of speed, negotiate an obstacle, adjust load or to react to any unpredictable perturbations from the external environment. This adaptation is mediated via the sensory input from external and internal feedback.

2.3.2 ROLE OF SENSORY FEEDBACK DURING WALKING

It has been shown that locomotor patterns can be achieved when all sensory inputs have been removed. This demonstrates that sensory input is not required to generate the basic locomotor rhythm. However, during real walking sensory interaction with the CPG is required to overcome changes that occur due to external stimuli (Rossignol et al., 2006). The following literature review shows how the sensory input is involved with the correct positioning of the feet, assists in switching from one phase of the step cycle to the next, influences the speed of the gait cycle and compensates for external disturbances. An extensive review of the role of afferent input in locomotion was recently published by Rossignol et al (2006).

CORRECT POSITING OF THE LIMB

Cats are able to walk and place their feet correctly on a treadmill after cutaneous inputs from the foot pads were removed (Bouyer and Rossignol, 2003). The denervated cats showed normal walking patterns with only small changes to the gait pattern apparent after a detailed gait analysis. However when the cats were required to complete a more difficult walking task, such as walking over a horizontal ladder they were unsuccessful. This suggests that sensory cues from the foot are required for the correct and precise placement of the foot during challenging locomotion. In this study improvement in the cats' ability to walk over the ladder was seen after some training, demonstrating compensation via other sensory inputs and the plastic properties of the neural network. Further examples of improvements in ambulatory capacity in animals are discussed later in "plasticity of the central nervous system" and "locomotor training in animals".

CONTROL OF THE PHASES OF THE GAIT CYCLE

The importance of afferent input in the control of the phases of the gait cycle, i.e., from stance to swing and swing to stance was demonstrated by Grillner & Rossignol (Grillner and Rossignol, 1978). Afferent information interacts with the CPG to initiate the transition between the phases of the gait cycle in cats. They demonstrated that the position / angle of the hip is critical for the transition between the stance and swing phase of the gait cycle. To determine the hip angle required for the initiation of the swing phase the movement of the hip while the cat walked on a moving treadmill was restricting by holding the hindlimb during stance and preventing it from extending (Grillner and Rossignol, 1978). Figure 2-9 shows the effect on the muscle activity of both hindlimbs when the ipsilateral hip angle was held constant in the middle section of the graphs. The muscle activity in the ipsilateral extensors (iG) persists and the ipsilateral flexors (iST) are silent which prevents the initiation of the swing phase.

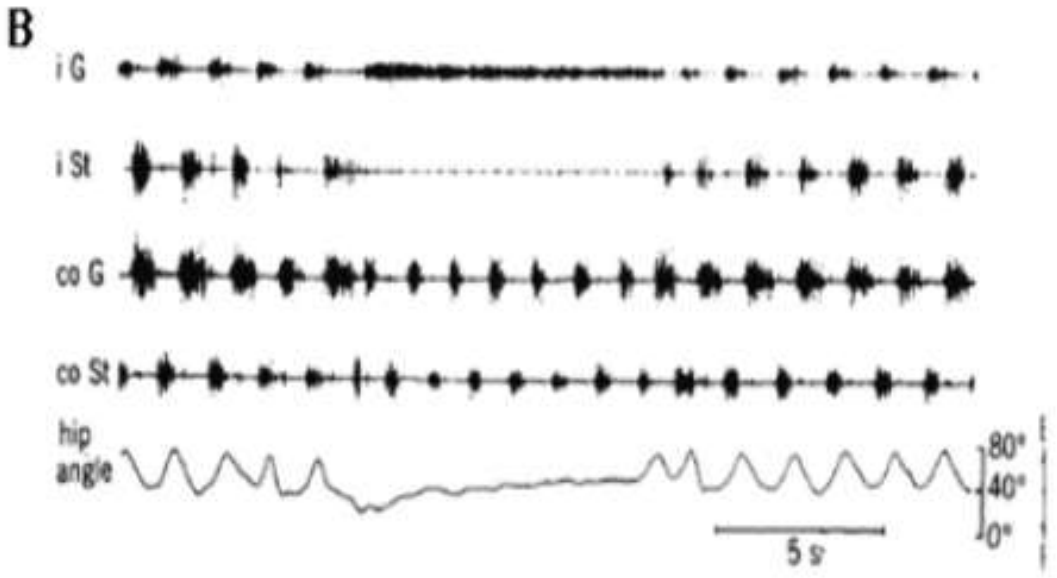


Figure 2-9: EMG and hip movements during perturbations on treadmill locomotion in spinal cat. EMG and hip angle of the Ipsilateral (i) and contralateral (co) gastrocnemius (G) and semitendinosus (St) muscles. During the period where the ipsilateral limb is held iG is tonically active and iSt is silent while the contralateral leg continues to walk. The continuous trace representing the hip angle was derived from markers on the hip and knee joint. [Modified from (Grillner and Rossignol, 1978)]

The swing phase was initiated again once the hip angle was increased by moving the limb backward (mimicking the mid to late stance). Figure 2-9 shows the muscle activity in the ipsilateral extensors (iG) stop and activity in the ipsilateral flexors (iST) start which initiates the swing phase and normal walking is continued. This suggests that the prioprioceptors in the muscles, ligaments and joint capsule around the hip signal the position of the limb and this influences the CPG directly.

This study by Grillner & Rossignol (1978) also demonstrated that the hip angle of the ipsilateral limb was not the only parameter that would prevent the initiation of the swing phase. The contralateral limb must also be a load bearing position. Without this the ipsilateral limb remains in stance with the afferent drive from the triceps surae muscle operates to maintain the muscle activity. This prolonged delay in the initiation of swing when the limb is loaded prevents the animal from falling. Once the contralateral limb is loaded and the ipsilateral limb unloaded the initiation of swing phase in the ipsilateral limb can occur (Duysens and Pearson, 1980). Duysens and Pearson (1980) showed that is the unloading of extensors of the ankle that is

required to initiate swing and not the loading of the contralateral limb. The loading of the extensors creates an inhibition of the flexor muscles.

Further to this work Conway et al (Conway et al., 1987) demonstrated in spinal cats how afferent information interacts with the CPG to reset the phase of the gait cycle in spinal cats. An electrical pulse train was delivered to the extensor group I afferents in the spinal cat during extensor and flexor activity. When the stimulation was applied to a limb during flexor activity (Fig 2-10A) the flexion was stopped in the ipsilateral limb (SAR) and an early flexor burst was initiated in the contralateral limb (CoPBST). However, when the stimulation was presented during an extensor burst (Fig 2-10B) it enhanced the extensor activity (MG) and delayed the onset of the flexor burst (PBST) and therefore the transition to the next phase within the gait cycle.

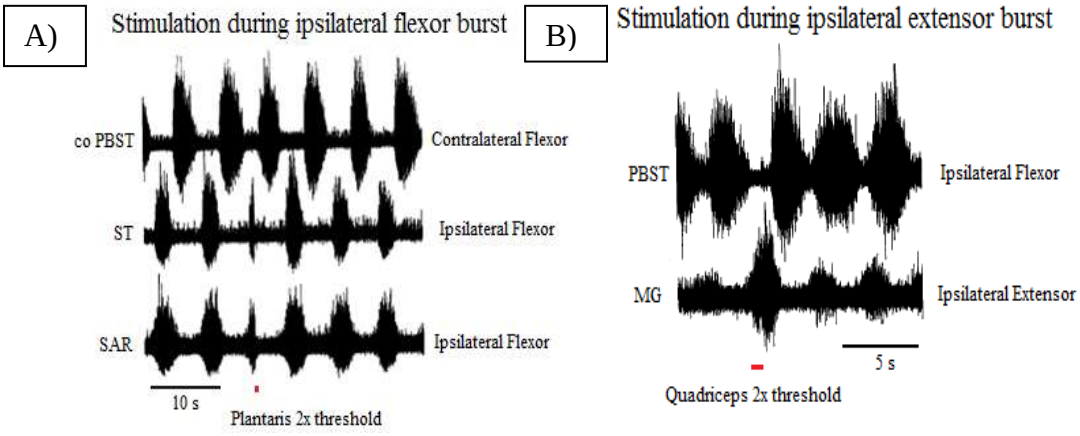


Figure 2-10: Resetting of locomotor rhythm by short electrical pulse to extensor group I afferents in the spinal cat during extensor and flexor activity. **A**: The stimulation is given during an ipsilateral flexor burst, causing its termination. A early flexor burst is initiated in the contralateral flexor nerve. The rhythm of locomotion then continues from this reset position. **B**:The stimulation is given during an ipsilateral extensor burst. The duration and amplitude of the extensor burst is increased whilst delaying the onset of the ipsilateral flexor burst. [Modified from (Conway et al., 1987)].

To identify if this response is mediated via the group Ia or Ib pathway electrical intramuscular stimulation was used to evoke a twitch in the muscle. This twitch activates the Ib afferents whilst silencing the Ia spindle afferents as the muscle is shortened. The findings demonstrated that Ib afferent feedback not the Ia leads to inhibition of flexor centres and excitation of extensor centres producing the muscle bursts. This indicates that the extensor group Ib afferents have access to CPG for

locomotion. The afferent feedback resets the phase of the gait cycle by exciting the extensor half centre proposed in Brown's model and may be of importance in the reflex regulation of stepping (Hultborn and Nielsen, 2007).

The inhibition of the flexor burst activity and the promotion of the extensor burst activity in the ipsilateral limb was later suggested by Pearson and colleagues (Donelan and Pearson, 2004) (Pearson and Collins, 1993, Pearson et al., 1992) to be conveyed via the Golgi tendon organs and the group Ib afferent pathway. By reducing the activity in the Ib afferents near the end of the stance phase the GTO may be involved in regulating the stance to swing transition.

Studies continue to date in human subjects to determine if similar afferent pathways are involved in the neural circuit for locomotion (Af Klint et al., 2010, af Klint et al., 2009, Bachmann et al., 2008, Grey et al., 2007, Duysens et al., 2000, Sinkjaer et al., 2000, Stephens and Yang, 1999, Yang et al., 1991, Yang et al., 1998). Indirect evidence to determine the contribution of the length sensitive group II afferents and the force sensitive group Ib afferents in phase transition in human walking has been investigated using an unload response (Af Klint et al., 2010, af Klint et al., 2009, Bachmann et al., 2008, Grey et al., 2007, Sinkjaer et al., 2000, Stephens and Yang, 1999, Yang et al., 1998). The unload response is described as a depression in the soleus activity following unloading of the ankle extensors. This unloading is triggered experimentally by a stretch device attached to the lower limb (Andersen and Sinkjaer, 2003) and creates a planter flexion during mid and late stance of normal treadmill walking (Grey et al., 2007) and treadmill walking with BWS (Af Klint et al., 2010). The onset of the unload response corresponds to the timing of the group Ib pathway and suggests that the decline in group Ib activity towards terminal stance is involved in the regulation of transition from stance to swing during gait in humans.

This work has shown that peripheral input has a role in the transition between the phases of the gait cycle. The afferent input can either induce or delay the transition from one phase to the next to affect the frequency of locomotion. This is termed as phase-advance or phase-delay and is seen from stance to swing and from swing to stance. These studies of human locomotion have highlighted the importance of load

during walking and this knowledge has been incorporated into the design of locomotor training methods in patients with a Spinal cord injury (see locomotor training in humans below).

CONTROL OF THE SPEED OF THE GAIT CYCLE

The frequency of the gait cycle which affects the speed of locomotion is influenced by sensory feedback (Forssberg and Grillner, 1973). This is demonstrated by spinal cats walking on a treadmill at various speeds. When a spinal cat walks on a treadmill that is increasing in speed the cat responds and increases it speed appropriately until a gallop is reached (Forssberg and Grillner, 1973). As the speed of the cat increases the duration of the gait cycle decreases, but the stride length remains the same. As seen in healthy animals the decrease in the gait cycle time is not uniform throughout both phases of the gait cycle. While the duration of the swing phase remained constant the duration of the stance phase was shortened. For the cat to be able to react to the change in treadmill speed the frequency of the gait pattern must be dependent upon sensory feedback (Forssberg and Grillner, 1973) most likely using the mechanisms described in the previous section.

CONTROL OF MUSCLE ACTIVITY DURING THE STEP CYCLE

During normal locomotion an animal or person must interact with their environment and adapt to both expected variations such as the surface of the ground and to unexpected changes such as catching the curb. Sensory information is vital to informing the animal about their environment. If an animal trips a reaction must occur to try and prevent it from falling as well as to continue in its chosen direction.

The leg muscles proprioceptors respond rapidly to changes in muscle length and force respectively (Duysens et al., 2008). After a perturbation in gait there is usually a change in this proprioceptive activity, which leads to a reflex action on the leg muscles. There are usually two response seen in the muscle activity, a short and long latency response (SLR & LLR). The SLR response which is small but seen in various limb muscles occurs 40-45 ms after muscle stretch (Bastiaanse et al., 2006, Duysens et al., 1996, Zehr et al., 1998). This response provides a short period of

increased stiffness (Duysens et al., 2008) that may contribute to regaining stability. The main response, the LLR is seen later at 85-90ms and produces a larger EMG response in more specific muscle groups than the SLR. This allows corrections to be made to amend the unexpected perturbation (Bastiaanse et al., 2006, Duysens et al., 1996, Zehr et al., 1998).

The neural pathway of the LLR is still unclear. The latency of the response allows ambiguity as to whether it is a long latency spinal pathway mediated by the slower group II afferents (Dietz et al., 1985a) or a long loop supraspinal or transcortical pathway mediated by group I afferents (Christensen et al., 2000, Duysens et al., 2008). By using Transcranial Magnetic Stimulation (TMS) evidence for a transcortical pathway in the LLR was obtained (Christensen et al., 1999, Taube et al., 2006). By applying TMS a magnetic pulse is produced which activates the corticospinal cells and evokes a muscular response. This muscular response can be measured. The size of the muscular response after TMS can be influenced by the excitability of the corticospinal cells. Therefore if the stretch in the muscle which occurs during gait perturbations changes the excitability of the corticospinal cells through a transcortical pathway evidence of this can be obtained using TMS. During experiments to determine this, increased muscle activity was seen in the tibialis anterior (Christensen et al., 1999) and the soleus (Taube et al., 2006) muscles at the latency of the LLR after TMS. This supports the view that a cortical component contributes to the LLR (Christensen et al., 1999, Duysens et al., 2008, Taube et al., 2006) and may provide evidence for supraspinal control during perturbed gait in humans.

Further evidence of supraspinal involvement in the reaction to gait perturbations was demonstrated in spinal cats whilst walking on a treadmill with a hole in the belt. These were a series of experiments termed ‘foot in hole’ which were conducted by Pearson and his colleagues. The corrective reactions of the hind limb of a cat when one foot un-expectantly falls into a hole during walking was studied (Gorassini et al., 1994, Hiebert et al., 1994). In the intact cat the foot was quickly removed from the hole by flexion at the knee and ankle. The stance phase of the contralateral leg was prolonged which enabled the weight of the hind limbs to be supported. Normally

when the foot makes contact with the ground activity in the extensors at the ankle would be seen. When the foot steps into the hole the cutaneous and muscle afferents signal which normally occur due to contact with the ground are not present. However the there was no change in the ankle extensor activity for 3-40ms and flexion did not occur until 70-150ms after the foot stepped into the hole. The long latency before any change to the motor pattern after the foot enters the hole suggests that the flexor burst initiated to remove the foot from the hole is conveyed via a supraspinal pathway (Gorassini et al., 1994). To investigate this Pearson and colleagues repeated the experiments with chronic spinal cats (Hiebert et al., 1994). In the spinal cats the flexion response was delayed by ~100ms (130-350ms after the foot stepped into the hole) and smaller in magnitude compared to the responses seen in the intact cats (Hiebert et al., 1994). The flexor response in the spinal cats was similar to the flexor response seen during the swing phase of the gait cycle in intact cats and was not strong enough to remove the paw from the hole. It was proposed that the flexion response seen in normal cats during stepping into a hole is due to the activation of a spinal system that normal initiates the swing being facilitated by supraspinal pathways. In the chronic cat this is not possible and the spinal circuit provides flexion similar to that seen in swing. This suggests that the facilitation of the LLR is mediated by supraspinal pathways.

The muscle responses that occur after a gait perturbation have also been investigated by recording EMG activity in animal (review by (Rossignol, 1996)) and human studies ((Dietz et al., 1985a, Dietz et al., 1985b, Duysens et al., 1995, Grey et al., 2001, Marchand-Pauvert and Nielsen, 2002, Yang et al., 1991, Zehr et al., 1997). These studies show that the activity of the muscles after a perturbation is not always the same but is dependent upon the phase of the gait cycle in which the perturbation occurs. During the swing phase in intact walking cats, an excitation to the flexor muscles occurs if an obstacle is struck with the dorsum (bottom) of the foot (Forssberg, 1979, Forssberg et al., 1975). A prominent flexion of the knee as well as flexion in the ankle and hip enables the limb to be lifted over and placed in front of the obstacle. During the stance phase when the limb is weight bearing an extensor response is seen after the same cutaneous stimulus is applied to the hind limb. This demonstrates that a stimulus applied during one phase of the gait cycle causes an

excitation in one group of muscles but when the same stimulus is applied in another phase of the gait cycle it causes excitation of the antagonist muscles. This is referred to as phase dependent reflex reversal and has been demonstrated in response to both mechanical and electrical stimuli (Duysens and Pearson, 1976, Forssberg, 1979, Forssberg et al., 1975, Forssberg et al., 1977).

Phase dependent reflex reversal has also been identified in humans where a different response in early swing was observed to that during late swing (Eng et al., 1994, Schillings et al., 2000). In early swing the response is a withdrawal response which sees the limb elevated by flexion at the ankle and knee (Fig 2-11a). In late swing the limb was lowered rapidly to stabilize the body and allow the obstacle to be cleared during the following step (Fig 2-11a).

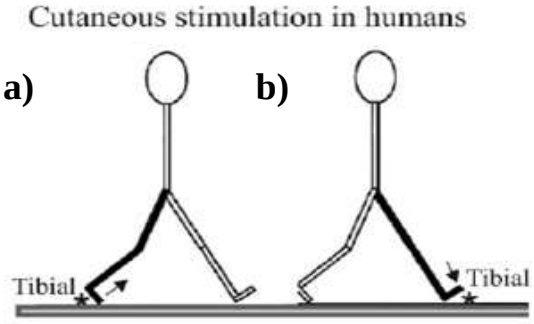


Figure 2-11: Phase dependent reflex reversal in human gait. Effects of cutaneous reflexes from tibial nerve stimulation during a) the transition from stance to swing and b) during late swing. The direction of the induced movements is shown by the arrows. [Rearranged from (Zehr et al., 1997)]

This reflex reversal is functionally important because a single stereotypical reflex response may not be appropriate at all times. These studies show that adaptive reflexes (and sensory information) can be modulated by the CPG in a phase dependent manner (Rossignol et al., 2006). This ensures that the movements produced after afferent input stimulated by a perturbation is correct for the phase of the gait cycle.

The phase dependence of the afferent information is not only seen in the reflex reversal but also in the modulation of the response. This may be because a large volume of sensory information is conveyed during walking and much of it is information from expected events. To ensure the sensory information of the expected events does not drown out the information that occurs during unexpected

events the "gain" of the sensory information can be modulated. The LLR which has been suggested to have a transcortical pathway may lead to gating or modulation of sensory information at supraspinal levels.

MODULATION OF CORTICAL POTENTIALS

Cortical components which reflect sensory processing can be detected using EEG and evoked potential methods. By a applying a stimulus to the periphery a response can be recorded from scalp electrodes that is time locked to this response. This technique is referred to as somatosensory evoked potential (SEP), further details of this test are described later. By using this test indirect measurement of the sensory information arriving at the cortex can be determined.

This technique has demonstrated that during voluntary movement in the upper and lower limbs cortical components are depressed (Applegate et al., 1988, Cheron and Borenstein, 1987, Cohen and Starr, 1985a, Cohen and Starr, 1985b, Nishihira et al., 1996). The cortical potentials seen during standing are similar to those seen at rest (Dietz et al., 1985a, Dietz et al., 1985b) although attenuation of the amplitude has been reported (Applegate et al., 1988). It is now accepted that gating of SEPs takes place when the limb which is being stimulated is voluntarily moved (Wasaka et al., 2006).

Showing evidence of this modulation of cortical components during gait has not been as well documented. In the 1980s and 90s three main groups (Duysens, Dietz, and Nielsen) recorded cortical potentials after electrical stimulation to peripheral nerves during gait (for review see (Brooke et al., 1997)). When the posterior tibial (Dietz et al., 1985a, Morita et al., 1998) or sural (Altenmuller et al., 1995, Morita et al., 1998) nerve were stimulated with an electrical pulse or a perturbation caused by a sudden treadmill acceleration (Dietz et al., 1998a) occurred during gait the cortical potentials recorded had longer latencies and attenuated amplitudes compared to those seen at rest. The attenuation was modulated over the phases of the gait cycle. The attenuation was stronger immediately following heel strike and weaker in the swing phase (Altenmuller et al., 1995, Duysens et al., 1995) indicating that the sensory processing is modulated dependent upon the phase of the gait cycle. The

mechanisms by which this modulation occurs is unknown. These studies did not analyse early components of the SEP which reflect the sensory volley arriving at the thalamus. New recording methods in EEG and EP studies may provide further details of this modulation and the physiological mechanisms operating during gait.

This review has demonstrated that complex neural circuits exist in the spinal cord that are able to produce rhythmic locomotor movement without supraspinal or peripheral input. But has also shown how the sensory input is vital to allow interaction with the environment and to control locomotion. The sensory information interacts with a spinal interneuronal network for pattern generation and to adapt muscle output to the external conditions. The sensory information is modulated at spinal and cortical levels during the phases of the gait cycle. The current understanding of neural control was summarised by Dietz in 2009 "the CPG and the afferent inputs interact so that a single or synergistic muscle response is produced at the correct strength and is dependent upon the actual task". This is the current level of understanding of the neural control of walking in humans. Work is continuing by many groups in an effort to improve the rehabilitation methods used, by focusing on, and implementing the understanding of normal neural control of walking into rehabilitation methods.

Although extremely complex the CNS also has the ability to change and adapt after injury. This process is often referred to as neuroplasticity. This means that function may be regained in some spinal cord injured people. Any changes that do occur may alter the neural network for control of locomotion. By understanding the CNS's ability to change, termed as plasticity we may be able to provide better rehabilitation methods to regain ambulatory capacity

This review continues by looking at the plasticity of the CNS and the training which is aimed at creating the conditions for plasticity to improve ambulatory capacity in animals and humans.

2.4 PLASTICITY OF THE CENTRAL NERVOUS SYSTEM

For many years it was believed that the CNS was hardwired, unchangeable and unable to repair its self. This has lead to rehabilitation strategies for SCI patients to be compensatory, using unaffected muscle groups or limbs in conjunction with assistive devices to learn new techniques to complete a task like dressing or standing. It is now recognised that plasticity can occur within the CNS. Curt and colleagues (Curt and Dietz, 1999) suggested that the reorganization of the spared neural pathways is the contributing factor for improvement in locomotor recovery in mammals with SCI. Sensory input is involved with the long term adaption of locomotion (Hultborn and Nielsen, 2007).

In the study by Bouyer and Rossignol (Bouyer and Rossignol, 2003) cats had their cutaneous inputs from their footpads removed and then re-taught to walk on rungs of a horizontal ladder. These cats were then spinalized at T13. These cats did not then recover the ability to walk on the rungs. However spinalized (T13) cats that had not had their cutaneous inputs from their footpads removed were able to correctly place the foot and recovered the ability to walk on the rungs. Spinal cats with partial cutaneous denervation could adapt their locomotion so that, even with a minimal cutaneous input, spinal cats could 'learn' to correctly place the foot on the horizontal ladder rungs. The role of sensory inputs thus appears to be crucial for the expression of spinal locomotion and probably for the recovery of locomotion after spinal cord injury.

The knowledge of the neural circuits involved in the control of gait has led to the possibility that by retraining the neural circuits involving afferent feedback, locomotor function may be restored after SCI. The initial work on this hypothesis was completed on animals but studies on humans, led by the work of Barbeau and his colleagues have been completed over the last 20 years. .

2.4.1 LOCOMOTOR TRAINING IN ANIMALS

Initial work into the effect of treadmill training with spinalized kittens was done by Grillner and colleagues (Forssberg et al., 1974, Forssberg and Grillner, 1973). Once

spinalized, kittens immediately lost locomotor function in the hind limbs. The kittens regained locomotor ability in the hind limbs after daily training on a treadmill. After training the EMG patterns and kinematics in these cats were similar to those seen in intact cats (Belanger et al., 1988, Belanger et al., 1996). These improvements were also seen in adult spinalized cats after training (Barbeau and Rossignol, 1987). This demonstrated that plasticity was not limited to the immature spinal cord. However to enable the training and to induce improvements in the adult cat body weight support (BWS) was required. The BWS was given to the cats by suspending the cat by the tail above a treadmill which also provided the cat with additional help in postural control and balance. As the cats' gait improved the amount of BWS provided was reduced. Several authors have demonstrated that using this training method in spinalized acute and chronic adult cats walking ability similar to intact animals can be regained (Barbeau and Rossignol, 1987, Edgerton et al., 1992, Lovely et al., 1986, Lovely et al., 1990).

Rossingol's group (Barriere et al., 2008) demonstrated how treadmill training can shape plasticity in the spinal cord after incomplete lesions in cats. After a partial lesion at T10 to T11 the cats were split into a two groups. One group received locomotor training the other did not. Both trained and untrained cats regained locomotor abilities (although at different rates). The cats then underwent a complete spinal transection at T13 to L1 and then all the cats received treadmill training. After the first few days the cats that had previously received training showed a bilateral stepping pattern whereas the previously untrained cats showed a unilateral pattern of locomotion on the side of the lesion. The difference in the two groups reflects the changes that were induced by the locomotor training that did not occur in the untrained cats even though they still regained locomotor ability. This demonstrates that functional reorganization of the spinal circuitry is induced by locomotor training after an incomplete lesion in adult cats (Barriere et al., 2008).

The changes that occur are also specific to the type of training given (Edgerton et al., 1997). Although adult spinalized cats with incomplete lesions improved locomotor function if they were not given locomotion training (Barriere et al., 2008, Lovely et al., 1986) they did not regain locomotion if taught a different task i.e. standing

(Edgerton et al., 1997). When the cats were taught to walk after being taught to stand they regained locomotor function but lost the ability to stand. This demonstrated the need for task specific training (Edgerton et al., 1997).

The most successful outcome in locomotor capacity was seen in cats which were given repeated (Lovely et al., 1990) task specific training (Edgerton et al., 1997) at regular intervals (Lovely et al., 1990) early after spinal transection (Hodgson et al., 1994).

2.4.2 LOCOMOTOR TRAINING IN HUMANS

If humans have similar neural mechanisms for locomotion as animals then locomotor recovery after SCI may be promoted with repeated and intensive task specific training (Behrman and Harkema, 2000), such as BWS treadmill training.

Barbeau and colleagues (Barbeau and Rossignol, 1987, Barbeau et al., 1993) were first to report on the feasibility of using treadmill training with BWS for rehabilitation of people with a SCI. Early studies were then reported by many groups using BWS locomotor training for patients with SCI using a harness to support the patient over the treadmill and a therapists to provide assistance in moving the limb when required (Barbeau and Rossignol, 1994, Behrman and Harkema, 2000, Dietz et al., 1994, Dietz et al., 1995, Dietz et al., 1998b, Dobkin et al., 1995, Dobkin et al., 2006, Thomas and Gorassini, 2005, Wernig and Phys, 1992, Wernig et al., 1995, Wernig et al., 1998). Physiotherapists manually moved the lower limbs when needed to give forward momentum to the limb through swing and held the limbs to stabilize the knee during the stance phase. The duration of these sessions varied in the studies and across patients from 10 minutes (Behrman and Harkema, 2000) to 30 minutes (Wernig and Phys, 1992) depending upon the level of physical assistance the patient required. The number of sessions per week and in total also varied across these studies.

After completing treadmill training the walking capacities of iSCI patients were significantly improved compared to conventional therapy (Dobkin et al., 2006, Wernig and Phys, 1992, Wernig et al., 1995). In a large multicentre Dobkin et al

(06) found no difference between iSCI patients treated with BWSTT and over ground mobility training. However both groups showed significant improvements in ambulatory capacity. In a study by Wernig et al (Wernig et al., 1998) 80% of non ambulatory chronic iSCI became independent walkers after completing BWS training for at least 30 minutes per day for 5 days a week and progressing onto training in parallel bars. Improvements were seen in gait parameters such as walking speed and duration in both iSCI (Wernig and Phys, 1992) and in stroke patients (Barbeau and Visintin, 2003). Gait symmetry and modulation was assessed using EMG analysis of the lower limb muscles. An improvement in the EMG activity was seen including an increase in the activity of the leg extensors with a decrease of BWS (Dietz et al., 1994, Dietz et al., 1998a). The EMG modulation improved to look similar to that seen in healthy subjects (Dietz et al., 1994, Wernig et al., 1995) although the amplitude was reduced (Dietz, 2009). Follow up studies show that the improvements gained after treadmill training was retained (Wernig et al., 1998).

Chronic complete SCI patients gained better mobility after locomotor training (Wernig et al., 1995) although this has not led to over ground walking (Dietz, 2009, Dietz et al., 1994, Wernig et al., 1995). This difference in improvement between incomplete and complete patients suggests a greater requirement for supra-spinal input to the CPG for locomotion in humans compared to the cat (Dietz, 2009).

Although improvements are seen this form of training is very intensive for the patient and therapist team with up to 3 people needed per patient per training session (Behrman and Harkema, 2000). The physical effort needed is also intensive and limits the number of patients and amount of time that training can be carried out for (Wirz et al., 2005). To increase the duration of training by facilitating the therapist a Driven Gait Orthosis (DGO) was developed by Hocoma AG, and the Rehabilitation Centre ParaCare of the University Hospital Balrist in Zurich, Switzerland called the Lokomat (Colombo et al., 2001, Jezernik et al., 2003). By using an online computer to control the active hip and knee joints a preset reproducible gait pattern can be achieved for each step during a session and between sessions (Colombo et al., 2001). The Lokomat allows walking to be practised by patients in a repeatable way during

each training period and provides symmetric and coordinated gait patterns suited to each patient (Wirz et al., 2005).

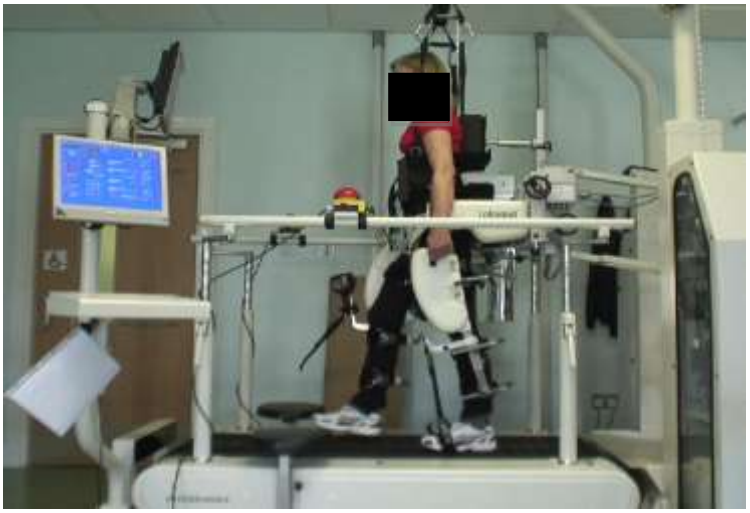


Figure 2-12: A patient on the Lokomat during training. The Lokomat is a driven gait orthosis (DGO) developed by Hocoma, Switzerland.

To enable the task to be specific it must ensure the correct sensory feedback is given during each phase of the gait cycle (Dietz et al., 2002, Harkema, 2001). These cues are of critical importance in the functional improvement of patients with iSCI (Dietz et al., 2002, Dietz and Harkema, 2004).

Similar statistical and functional changes were seen in patients after Lokomat training compared to BWS Treadmill Training (Wirz et al., 2005). After Lokomat training the patients who were the most impaired showed the greatest improvement (Wirz et al., 2005).

It has been suggested that the improvements seen in ambulatory function is due to the sensory feedback (de Leon et al., 1998a, de Leon et al., 1998b) and not on the training effects to the muscular system (Roy et al., 1998). The treadmill training, by BWS and a therapist or by Lokomat training provides repetitive sensory stimulation which plays a role in the ability to regain functional walking capacity after iSCI (Barbeau and Rossignol, 1987, de Leon et al., 1998a, de Leon et al., 1998b, Harkema, 2001, Leblond et al., 2003, Lovely et al., 1986). This highlights the importance of sensory feedback in task specific training. In both cats and humans it has been shown that progressively increasing the amount of body weight carried

improves walking capacity (Barbeau et al., 1987, Barbeau and Rossignol, 1987, Edgerton et al., 1992, Harkema et al., 1997) and the group Ia, group Ib and group II afferents activated during the stance phase of locomotion may have a role within locomotion recovery.

This chapter has reviewed the neural control of locomotion and how knowledge of this and plasticity has developed the rehabilitation methods used in SCI. The review now continues by looking at the assessments of SCI currently used and how they may reflect the physiological changes that are occurring during a period of intervention developed to promote plasticity. This may provide information as to how the CNS changes and may also provide predictive indicators of ambulatory capacity after a period of rehabilitation.

2.5 ASSESSMENT OF SPINAL CORD INJURY

An assessment of a SCI needs to define the neurological deficit in a reliable, accurate and reproducible way. This information allows the appropriate care to be given at the correct time and can give patients and carers information on possible outcomes. The current assessments of SCI available to research and the clinical setting fit into 3 main categories, neurological, functional and electrophysiological assessments. This review will look at the Frankel scale and the American spinal injuries association scale (ASIA) as neurological assessments, the functional independence measure and WISCI II for functional assessments and somatosensory evoked potentials and QST for electrophysiological assessments.

Neurological assessments look at the neurological deficit suffered as a result of a SCI. These assessments use scales of either numbers or letters to characterise the motor and sensory function. Many assessments of this type have been developed including the Frankel scale (Frankel et al., 1969), Lucas and Ducker's Neurotrauma Motor Index (Lucas and Ducker, 1979), American Spinal Cord Injury Association (ASIA), University of Miami Neuro-Spinal Index (UMNI) (Klose et al., 1980), Yale Scale (Chehrazi et al., 1981), and Sunnybrook Cord Injury Scales for assessing neurological injury and recovery from spinal cord injury (Tator et al., 1982) and the National Acute Spinal Cord Injury Studies (NASCIS) scale (Bracken et al., 1985).

However, only the Frankel scale and the ASIA scale are commonly referred to in the literature. The other assessments have not been taken up by clinical establishments as routine tests and therefore will not be discussed further here.

The functional assessments look at how the patient functions with activities for daily living (ADL) and is a measure of performance. These scales include the Modified Barthel Index (MBI), Functional Independence Measure (FIM), Spinal Cord Independence Measure (SCIM) and the Walking Index for Spinal Cord Injury (WISCI). The scales that are most relevant to walking ability in SCI are the FIM, and WISCI and they are discussed here.

2.5.1 FRANKEL SCALE

The Frankel scale developed in Stoke Mandeville Hospital by Frankel was the first scale to assess the neurological deficit in SCI patients (Frankel et al., 1969). It described the extent of the neurological and functional deficits (Curt and Dietz, 1999). The scale had 5 grades from A to E. Group A were complete SCI, group B had only sensory function below the level of the lesion, group C had both motor and sensory function below the level of the lesion. The motor function in group C was described as useless and in group D as is not fully recovered but not useless. In group E the motor function is normal. Although this scale was widely used in the 1970s and 80s the classification groups were very broad. Improvement in function could be observed in a patient without their Frankel scale grade improving (ASIA 1984). As the repeatability and specificity of this test is poor it is no longer used as an assessment tool for SCI but was incorporated into the scale developed by the American Spinal Injury Association.

2.5.2 AMERICAN SPINAL INJURY ASSOCIATION

The American Spinal Injury Association (ASIA) developed the international standards for neurological assessment and classification of SCI and is often referred to as the gold standard (Marino, 2005) clinical measure. It is a fast and simple semi-quantitative assessment of neurological deficits in SCI (Curt and Dietz, 1999). There are two parts to the protocol; examination and classification. In the examination

sensory and motor components as well as completeness of the injury are assessed. The sensory component is made up of the pin prick and light touch tests at the key points in each of the 28 dermatomes on both sides of the body. The pin prick test is usually carried out with a disposable safety pin and the touch test with a piece of cotton. For the motor component the key muscles in the 10 paired myotomes are examined. The muscles were selected as they are consistently innervated by the documented spinal nerves (Maynard et al., 1997). The motor levels; C1 to C4, T2 to L1 and S2 to S5 are not testable using this method of examination (Maynard et al., 1997). The completeness of the injury is assessed and confirmed by a rectal examination to assess the presence or absence of voluntary anal contraction.

The classification determines the sensory and motor levels, the completeness of injury, the zone of partial preservation (for complete injuries) and the ASIA Impairment Scale grade (AIS grade). The protocol identifies and scores the sensory deficits for all dermatomes, and the degree of preserved motor functions in the most important muscles both at the lower and upper extremities (Curt and Dietz, 1997). The motor and sensory level of injury is defined as the lowest normal segment and may differ on each side of the body (Maynard et al., 1997).

The AISA impairment scale is broken into 5 parts, A is defined as complete SCI, B – D are incomplete with different levels of preserved function and E is normal (see table 2.2).

Grade	Severity	Comments
A	Complete	No motor or sensory function is preserved below the lesion including the sacral segments
B	Incomplete	Sensory but not motor function is preserved below the neurological level and includes sacral segments S4-S5
C		Motor function is preserved below the neurological level, and more than half the key muscles below the neurological level have a muscle grade less than 3
D		Motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade of 3 or more
E		Motor and sensory function is normal.

Table 2-2: AISA Impairment scale (AIS). Grades range from A to E with A being the most severe injury and E has no neurological impairment.

The ASIA scale was first published in 1982 and has been revised in 6 editions to improve the reliability of the assessment and classification (Marino et al., 2008). The last major revision of the ASIA assessment was completed in 1992, which included the introduction of the key muscles and the sensory tests of pin prick and light touch. The Functional Independence Measure (FIM) was also incorporated to assess the impact of the SCI on the patient's functional capabilities (See Below). Studies have been carried out at determine the reliability and repeatability of the ASIA assessment in SCI (Cohen and Bartko, 1994, Jonsson et al., 2000, Marino et al., 2004, Marino et al., 2008, Savic et al., 2007).

The studies have shown that the AISA assessment provides reliable measures of sensory and motor scores in spinal cord injuries when used by professionals trained in both skills; examination and classification (Marino et al., 2008). ICC between examiners was found to be >0.98 for light touch, pin prick and motor scores in SCI patients (Savic et al., 2007).

The examination is not as repeatable in incomplete SCI compared to complete SCI (Cohen and Bartko, 1994) and the total scores of sensory and motor components have a greater reliability than the individual scores (Cohen and Bartko, 1994, Jonsson et al., 2000). Hence caution should be applied before putting emphasis on the results of single dermatomes (Jonsson et al., 2000). The light touch element of the sensory testing provides greater reliability than the pin prick test (Marino et al., 2008) this may be because the pin prick test is more difficult for the patient as they need to differentiate between sharp and dull sensations. The patients understanding of the test and willingness to cooperate may also incorporate errors into the assessment. Repeatable and reliability of the international standards when completed by trained assessors meets or exceeds those needed for clinical trials (Marino et al., 2004).

The ASIA assessment, although developed as a classification system is now often used as outcome measures to determine the effectiveness of different rehabilitation methods (Marino, 2005). When using the sensory and motor scores to assess changes after intervention it should be noted that the scales of assessment are ordinal and have ceiling effects. When the amount of improvement is displayed by the

improvement in scores it can be misleading if the patients did not start at the same baseline level. A patient with an initially high score cannot improve as much as another patient with a lower baseline score as he will reach the highest score of the test.

2.5.3 FUNCTIONAL INDEPENDENCE MEASURE

The functional independence measure (FIM) is an 18 item scale developed to evaluate a patient's ability to complete activities in self care. This allowed the burden of care and level of assistance for each patient to be determined. The FIM is a functional assessment and focuses on 6 areas, self-care, sphincter control, mobility, locomotion, communication and social cognition. For each of these areas questions are answered on a scale of 1-7, where 1 is defined as needing total assistance through to 7 which is defined as completely independent (See Table 2-3). The rating of the FIM is complex and requires the assessor to undergo training. When patients are left to assess themselves using FIM significant differences were found compared to assessments made by trained professionals (Marino and Cohen, 1998). However when completed by a trained professional the repeatability of the FIM is high (Ottenbacher et al., 1996).

LEVELS	7 Complete Independence (Timely, Safely)	No Helper
	6 Modified Independence (Device)	
	Modified Dependence	Helper
	5 Supervision	
	4 Minimal Assist (Subject = 75%+)	
	3 Moderate Assist (Subject = 50%+)	
	Complete Dependence	
	2 Maximal Assist (Subject = 25%+)	
	1 Total Assist (Subject = 0%+)	

Table 2-3: Functional Independence Measure (FIM) scale.

For the assessment of locomotion two activities are assessed; walk/wheelchair and stairs. For each activity a single level is denoted. The patient can receive the same score whether they are walking or are in a wheelchair as it only assess the level of assistance needed not the method in which the task is completed. The locomotion items within the FIM scale are the least sensitive to change (Catz et al., 1997) and lacks sensitivity to detect changes associated with the return of function after SCI

(Anderson et al., 2008). The Walking Index for Spinal Cord Injury (WISCI) was developed as a more specific test for ambulatory capacity in SCI (Ditunno et al., 2000) and is more sensitive to walking recovery in SCI than the FIM (Morganti et al., 2005).

2.5.4 WALKING INDEX FOR SPINAL CORD INJURY.

The Walking Index for Spinal Cord Injury (WISCI) is a scale to measure the walking ability of SCI patients that incorporates the use of physical assistive device required for walking (Ditunno et al., 2000, Ellaway et al., 2004). The scale was developed so that physical assistance could be integrated with walking aids and braces to better reflect the ambulatory capacity of SCI patients and to identify improvements in walking ability resulting from neurological improvements after SCI (Marino et al., 2010)

The test is mainly completed by physiotherapists within the clinical setting. The patient is asked to complete a ten meter walkway while any walking devices, braces or assistance required is recorded (Ditunno et al., 2000). The results are recorded on a 21 point scale (0 to 20) with 0 given to a patient who has no walking ability and 20 for normal walking ability, i.e., without the use of any device, brace or assistance (Dittuno and Ditunno, 2001). If the patient is unable to walk 10m then further assistance is given until they are able to complete the test. If they are unable to complete 10m but are walking then a score of 1 is given.

Level	Devices	Braces	Assistance	Distance
0				Unable
1	Parallel bars	Braces	2 persons	Less than 10 meters
2	Parallel bars	Braces	2 persons	10 Meters
3	Parallel bars	Braces	1 person	10 Meters
4	Parallel bars	No braces	1 person	10 Meters
5	Parallel bars	Braces	No assistance	10 Meters
6	Walker	Braces	1 person	10 Meters
7	Two crutches	Braces	1 person	10 Meters
8	Walker	No braces	1 person	10 Meters
9	Walker	Braces	No assistance	10 Meters
10	One cane / crutch	Braces	1 person	10 Meters
11	Two crutches	No braces	1 person	10 Meters
12	Two crutches	Braces	No assistance	10 Meters
13	Walker	No braces	No assistance	10 Meters
14	One cane / crutch	No braces	1 person	10 Meters
15	One cane / crutch	Braces	No assistance	10 Meters
16	Two crutches	No braces	No assistance	10 Meters
17	No devices	No braces	1 person	10 Meters
18	No devices	Braces	No assistance	10 Meters
19	One cane / crutch	No braces	No assistance	10 Meters
20	No devices	No braces	No assistance	10 Meters

Table 2-4: WISCI II Scale [Rewritten from Ditunno & Dittuno 2001]

The hierarchical rank order allows the change in walking ability to be assessed in a measurable way using a scale from most to least impaired. It includes the assistive devices used by the upper and lower limbs such as crutches and braces. The scale reflects walking capacity but to fully characterize the ambulatory capacity of a SCI patient additional gait parameters such as walking speed, double support time and energy consumption should be assessed (Marino, 2005).

This scale is seen as the most effective and unambiguous of the scales currently used in SCI assessment and has a high inter-rater and test-retest repeatability (Ditunno et al., 2000, Ellaway et al., 2004). The inter-rater reliability of assigning levels of SCI patients was 100% (Ditunno et al 00) and the inter rater reliability has an ICC of 1.00 (Marino et al 2010). The test is sensitive to change in walking capacity and has been used in longitudinal studies to validate rehabilitation methods (Ditunno et al., 2007).

2.5.5 SOMATOSENSORY EVOKED POTENTIALS

A somatosensory evoked potential (SEP) test can evaluate whether nerves are able to send and or receive sensory information from the periphery to the brain and so assess

functionality of the whole afferent pathway (Kimura, 2001). The evoked potential is the neural response that is triggered by the stimulation of sensory receptors in the peripheral nervous system (PNS) and is recorded in the central nervous system (CNS).

The test is usually completed with the patient lying supine in a comfortable and quiet room. The potential is evoked by stimulating either the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle with an electrical pulse (Baran, 1996). Commonly mixed nerves are used, as innervating a mixed nerve group I and II muscle and cutaneous afferent fibres are excited. This creates sensory volley within the somatosensory which is conveyed to the sensory cortex and a muscle twitch in the muscles that the nerve innervates and allows the examiner to assess the strength of the electrical pulse.

The sensory information evoked by the electrical stimulus is processed along the afferent pathways of the somatosensory system to the somatosensory area of the cerebral cortex. The 2 main systems transmitting these signals are the dorsal column medial lemniscal (DCML) and the Anterolateral System (ALS) (also known as the ventrolateral system) (See Fig 2-13). THE DCML contains the medial lemniscal pathway from the gracile and cuneate fasciculus. The ALS contains the spinothalamic, spinoreticular, spinomesencephalic, spinotectal and spinohypothalamic pathways. The pathways of the ALS are located close together within the spinal cord and are described here as a single pathway, the spinothalamic.

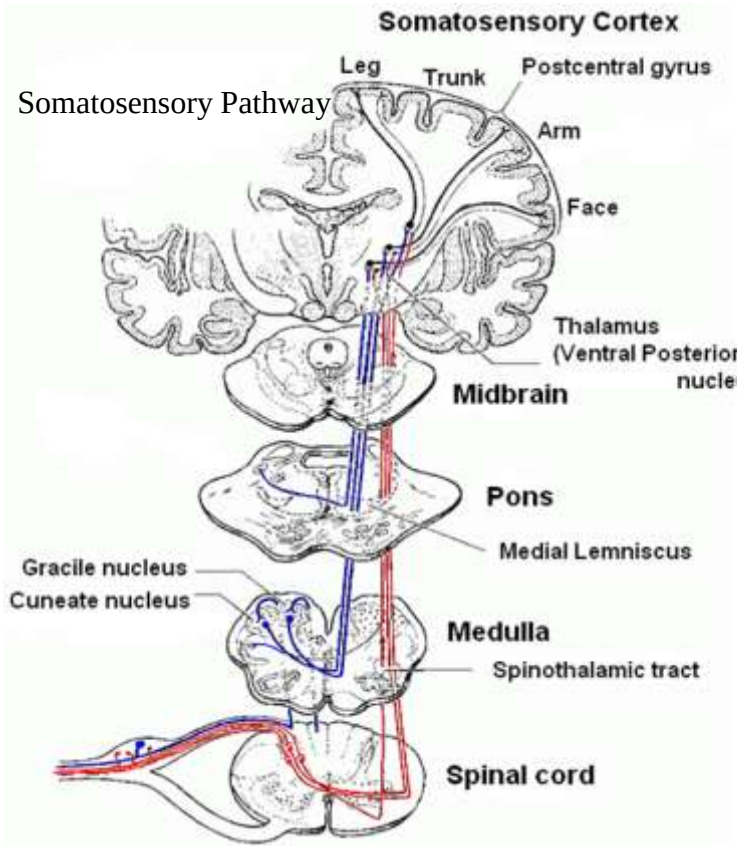


Figure 2-13: The dorsal column medial lemniscal and spinothalamic pathways of the somatosensory system. The medial lemniscal tract (blue) ascends ipsilaterally in the dorsal white matter of the cord, and crosses in the caudal medulla. Spinothalamic tract (red) crosses the midline immediately and ascends in the lateral and ventral white matter of the spinal cord. [Modified from http://instruct.uwo.ca/anatomy/530/530notes.htm]

The ALS carries non discriminate touch, temperature and pain where as the DCML carries fine touch, vibration, pressure, two-point discrimination, stretch and tension. By stimulating a mixed nerve in the periphery it is still not clear what modalities are activated by the electrical pulse. However the nerve fibres in the medial lemniscus pathway have a larger diameter and are myelinated so that the signals travel 2-3 times faster than those in the ALS. As it is the low threshold large diameter myelinated fibres that are activated with stimulus strengths that elicit a muscle response in a mixed nerve it is hypothesised that the afferent volley is conveyed in the DCML pathway. SEP examinations are used in clinical practice to detect any physiological impairment within the DCML pathways.

Both pathways consist of 3 populations of neurons, the first, second and third order neurons. The first order neurons enter the spinal cord via the dorsal roots. In the spinothalamic pathway these neurons ascend the Lissauer's tract before they synapse

in the grey matter 1 or 2 segments above the level of entry. The second order neuron then decussates (crosses the midline) and ascends the spinal cord in the spinothalamic tract to the thalamus where it terminates. In the dorsal column medial lemniscal pathway the first order neuron ascends the spinal cord in tracts known as gracile fasciculus (neurons from the lower body) and the cuneate fasciculus (neurons from the upper body) to the medulla where they synapse in the gacile nucleus and cuneate nucleus respectively. The second order neurons decussates within the medulla then ascend to the thalamus where it terminates in the ventrolateral posterior nucleus (VPL). For both pathways the 3rd order neuron ends in the contralateral somatosensory cortex which is in the post-central gyrus of the parietal lobe just posterior to the central sulcus (See Fig 2-14).

The largest somatosensory receiving area is the primary area (SI) situated in the postcentral gyrus (Brodmann areas 3, 1 and 2). The second somatosensory receiving are (SII) lies within the lateral fissure. Areas 3a, 3b, 1 and 2 all have topographical maps of the body surface (Fig 2-15). Brodmann area 3a & 2 receive a large amount of input from muscle, tendon and stretch receptors. Many of these signals to 3a spread to area 4 of the adjacent motor cortex. Inputs originating from cutaneous mechanoreceptors go to area 3b.

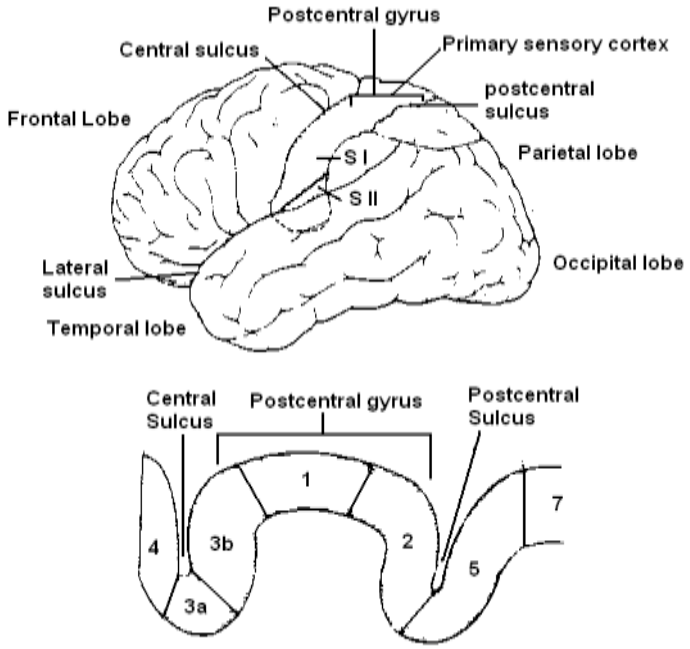


Figure 2-14: Location of the somatosensory Cortex and Brodmann areas.

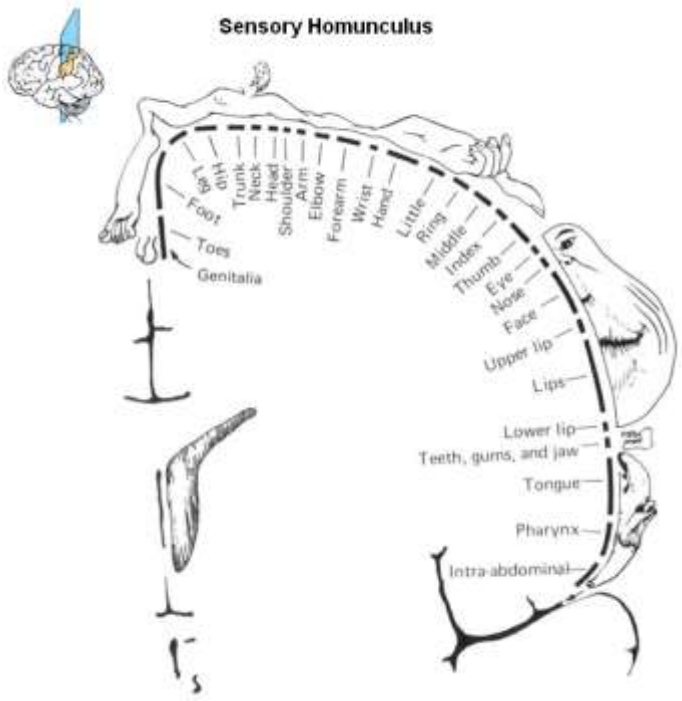


Figure 2-15: The sensory homunculus shows the relative amount of area each body part represents in the somatosensory cortex.

The SEP test procedure has been used to study patients with spinal cord injury since the late 1970's. Although it is restricted to the posterior column of the spinal cord it can provide information to the investigator about the extent (Gruninger and Ricker, 1981) and level of the lesion (Curt and Dietz, 1996) which helps with classification of the injury. The SEP test is more useful than the standard clinical neurological assessment when assessing unresponsive or uncooperative patients (Curt and Dietz, 1997) as the test does not require a verbal or other cognitive response from the patient. It can also provide further information when the neurological history and examination are equivocal (Chiappa, 1997).

Few studies on repeatability and reliability of SEPs have been published to date. To assess the SEP waveform the presence, latency and amplitudes of peaks within the waveform are analysed. The latency of the peak is affected by limb length and body height and normalization should be completed if the data is compared across patients. The absolute latencies are more reliable in indicating damage than the peak amplitudes (Spiess et al., 2008) but inter-peak and inter-side differences have better

reproducibility than the absolute latencies (Beric, 1988). Romani et al (Romani et al., 1996) showed good test to retest reproducibility (R values 0.75) for latencies. Amplitudes of peaks can vary greatly between individuals due to recording set ups but they are reliably for longitudinal studies in individuals (Chabot et al., 1985, Romani et al., 1996). Each lab should use normal values collected from an age matched healthy population taking in the same location using the same set up. If changes over time are to be observed within a patient the recording set up should remain the same during each session. By using this methods SEPs may offer a more sensitive method for assessing sensory function and its recovery following an incomplete SCI (Kimura, 2001).

As SEPs have been shown to have high intra subject reproducibility (Chabot et al., 1985) they can be used to monitor changes in spinal cord function. This provides a record of regeneration which may be induced by an intervention during longitudinal rehabilitation studies (Chiappa, 1997, Dietz and Curt, 2006, Spiess et al., 2008). To monitor changes in function of the spinal cord pathways the changes that occur due to natural recovery must be understood and separated from changes induced by an intervention. Spiess et al (Spiess et al., 2008) described the spontaneous changes that occur in the latency and amplitude of the peaks as well as the presence of the peaks within the SEP waveform over time. The main changes seen in that study were increase in amplitude and a reduction in latency between test sessions taken at 1-15 and 16-40 days post injury. However 60% of patients (n=297) had no SEP; 70% SEP were recordable at each of the five sessions, 10% improved during the sessions and 10% showed recovery of the potential. In 10% the SEP could not be consistently recorded. This shows how the SEP cannot be recorded in all subjects but the spontaneous changes occurred early, <40 days after injury. Repeatability of the SEP should be investigated after this period.

2.5.6 QUANTITATIVE SENSORY TESTING

Quantitative sensory testing (QST) refers to a set of methods that have been developed to extend traditional neurological examinations to evaluate somatic sensations. There are 3 types of modality of somatic sensations; 1) discriminative

touch, 2) pain and temperature and 3) proprioception. Each of these modalities contains multiple types of sensations as shown in table 2-5 below.

Modality	Sensations	Pathway
Discriminative touch	Touch Pressure Vibration	Dorsal column medial lemniscus
Pain and temperature	Itch Tickle Hot Cold	Spinothalamic tract
Proprioception	Muscle movement Joint position Facial expression	Dorsal column medial lemniscus

Table 2-5: Somatic modalities and sensations.

By testing the different modalities specific information about the ability to perceive a stimuli and implied information about the integrity of the pathways in which the modality is conveyed can be obtained. The DCML pathway conveys discriminative touch and conscious proprioception and is assessed with QST of fine touch and vibration. Electrical perception (EPT) is also believed to be conveyed in the DCML pathway due to the large group I fibres recruited at the lower stimuli (Ellaway et al., 2004). The spinothalamic tract conveys crude touch, thermal and pain stimuli.

Although the axons that carry the modalities of pain and temperature are located within the spinothalamic tract, Fitzgerald (Fitzgerald, 1996) noted that they are segregated with thermal axons located more medially and pain axons more peripherally. The ventral spinothalamic tract conveys crude touch and pressure. The lateral spinothalamic tract conveys pain and temperature.

The QST involves a variety of sensations applied to the surface of the skin, these include; temperature, touch, pain, vibration and electrical stimuli. The main methods used in QST are the method of limits, and the forced choice method. The simplest and quickest of these is the method of limits where the stimulus is applied continuously with increasing or decreasing stimuli intensity. The test stops when either the stimuli is perceived or when the stimuli reaches the maximum or minimum value. The main disadvantages to this method are that null stimuli cannot be randomly placed, the response time can vary between patients and across test

sessions and the direction of the stimulus (increasing or decreasing) can affect the perception level.

In the forced choice method the patient is presented with two periods of time noted as "1" and "2". In one of these periods the stimulus will be presented, during the other period no stimulus is presented. The patient must make a choice in which period the stimulus was presented. If the patient correctly identifies the period in which the stimulus was presented the intensity of the stimulus is decreased, if they incorrectly identify the period in which the stimulus was presented the stimulus intensity was increased. An algorithm is used to determine the level of stimuli in each test. In the algorithm the level of stimulus intensity is changed in steps, initially decreasing in intensity by multiples of 4, then 2 and finally multiples of 1. The level for each multiply is decided upon prior to the start of the test, i.e., for electrical perception the multiple may be 0.1mA therefore initially the stimulus will decrease by 0.4mA in each step. Once the patient incorrectly identifies which period the stimulus was presented the stimulus is increased in multiples of 2 until they get another correct response (i.e., they can feel the stimulus). The stimulus is then decreased in multiples of 2 until a wrong answer (the patient cannot feel the stimulus) is given. This pattern continues until a number of turnarounds in multiples of 1 have been completed (see Fig 2-16).

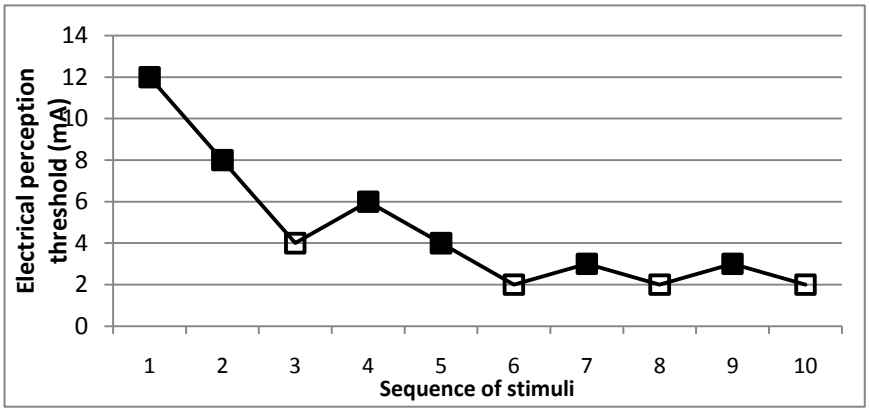


Figure 2-16: Algorithm for forced choice method of sensory testing. The first stimulus is given at a high intensity of the patient can feel it (12mA). The patient correctly identifies the stimulus (shown by a solid box symbol). The next stimulus is reduced by 4mA in intensity. A correct response is given. The third stimulus strength (4mA) is incorrectly identified (shown by a clear box symbol) and the next stimulus is increased by a multiple of 2. Once the stimulus is again correctly identified the stimulus intensity is reduced by multiples of 2. This is repeated for multiples of 1. The perception threshold in this example is 3mA.

This method removes the response time and the result is not affected by the direction of the stimulus. However it can be very frustrating for the patient and they may have to be pushed into making a choice. This method can also be very slow and is not recommended unless only a few areas are to be tested (i.e., to foot in diabetes testing).

The modalities that are tested using QST are; electrical perception threshold (EPT), vibration perception threshold (VPT), touch, cold, warm and thermal pain. EPT assessment was first developed by Davey et al (Davey et al., 2001) as a simple and reproducible means of testing sensory impairment in patients with SCI (King et al., 2009, Savic et al., 2006). Good intra- (ICC 0.56-0.80) and inter-rater (ICC 0.52-0.91) reliability of EPT was found using the method of limits in patients with SCI (King et al., 2009). Krassioukov et al (Krassioukov et al., 1999) however reported that repeated measure were needed over consecutive days to gain accurate perception thresholds when assessing cold, warm, cold pain and vibration perception thresholds when using the method of limits.

By using EPT the level and density of lesion can be determined to a more accurate level than by the ASIA assessment (Savic et al., 2006). This is possible by showing the levels for each modality as well as areas of preserved sensation. The spatial resolution is also improved which means that the assessment is more sensitive in determining preserved sensory function in iSCI compared to the ASIA scores of light touch and pin prick (Hayes et al., 2002, Savic et al., 2006). It should be remembered however that the QST are psychophysical, as an objective physical stimulus is presented but a subjective response is given by the patient (Rolke et al., 2006). This means that QST requires cooperation, concentration and understanding from the patient.

2.6 PREDICTION OF AMBULATORY FUNCTION

The recovery of walking is one of the priorities for iSCI patients and so has become the target for many forms of rehabilitation and interventions. To provide the most efficient training to patients that have the greatest capacity for improvement a prognosis of walking recovery would be advantageous. This prognosis would also

allow the patient to have an indication of the likely amount of independence that they may achieve after training.

The ASIA assessment taken during the patients' first examination will give the completeness of the lesion and a degree of prognosis of functional outcome. An ASIA Impairment Scale (AIS) Grade A given on initial examination gives only a 2.5-20% chance of an improvement in the AIS grade (Chabot et al., 1985) and so the probability of achieving functional walking ability is small (Scivoletto and Di Donna, 2009). In AIS B patients ambulation is achieved in 33% (Katoh and Elmasry, 1995) and this is increased to 87% in AIS C patients (Crozier et al., 1992). The prognosis of regaining functional walking for AIS D is high, between 80 to 100% at the time of discharge (Burns et al., 1997, Scivoletto et al., 2004).

Crozier and colleagues looked at the sensory (Crozier et al., 1991) and motor (Crozier et al., 1992) components of the ASIA assessment for predictors of functional walking ability. They concluded that patients who had preserved sensation to both pin prick and light touch or a muscle grade of 3 or more in the quadriceps at 2 months post injury had a much better probability of ambulation.

The SEP and Motor Evoked Potentials (MEP) have also been studied to see if they might further improve the ability to predict function in SCI. In upper limb function SEPs show a positive relationship with functional outcomes in SCI (Curt and Dietz, 1996). Studies that have used MEPs and SEPs to predict functional ambulatory capacity suggest that the tests do not offer any additional accuracy to that achieved with clinical examination (Chabot et al., 1985, Curt and Dietz, 1997, Curt and Dietz, 1999, Katz et al., 1991). However SEPs do provide an assessment of early prognosis in uncooperative patients that cannot be achieved with ASIA assessment (Curt and Dietz, 1999, Jacobs et al., 1995). A combined approach of SEPs with other neurological tests, such as AISA standards provides the greatest accuracy in predicating function (Feys et al., 2000, Tzvetanov et al., 2005) in the upper limb after stroke.

2.7 PROJECT AIMS

In this review the current understanding of the neural control of walking and its application to rehabilitation methods to improve ambulatory capacity of iSCI patients has been discussed. Further understanding is needed on the underlying physiological adaptations that occur after Lokomat training which lead to an improved functional ability in acute and chronic iSCI patients. Accurate and sensitive tests need to be developed that show the level of functional change as well as to identify the change as compensation, neural repair or neural plasticity.

The prediction of functional outcome will help to correctly allocate rehabilitation resources and may provide further information on why some iSCI patients improve to a greater extent than others. Understanding the optimal time frame for rehabilitation and dosage of training will also benefit training protocols in the clinical setting. With this in mind the aims of this project are:

1. Indentify acute and chronic iSCI patients which improve ambulatory capacity after 6 weeks Lokomat training using the WSIC II scale and temporal gait analysis.
2. Assess the ability of QST and SEP assessments to detect physiological changes that occur in patients with improved ambulatory capacity.
3. Determine the predictive value of QST and SEP assessments for ambulatory capacity after 6 Lokomat training.
4. Indentify cortical potentials that may be evoked during normal treadmill walking.
5. Indentify the cortical potentials evoked by electrical stimulation during 4 phases of the gait cycle.
6. Indentify any modulation to sensory information in transcortical pathways during phases of the gait cycle.

3 METHODS FOR PATIENT STUDY

The aim of the patient study was to evaluate the use of Quantitative Sensory Testing (QST) and Somatosensory Evoked Potentials (SEP) as assessment tools of spinal cord function. To enable this, a set of assessments were completed on iSCI patients before, during and after a period of rehabilitation intervention, using a Driven Gait Orthosis (RGO). The intention was to indentify if the assessments are sensitive to any physiological adaptations that may be induced by rehabilitation. During the course of this project it was hoped that by studying the outcome measures of these tests correlations to functional capacity could be identified and prognostic indication of recovery unveiled.

3.1 ETHICAL APPROVAL

Ethics approval was obtained from the National Health Service (NHS) regional ethics committee and the departmental ethical committee at the Bioengineering Unit, Strathclyde University, Glasgow. 18 iSCI Patients (14 Male and 4 Female) completed the study and 10 healthy volunteers completed the QST assessments to determine normative values. All patients and subjects gave informed written consent and were free to leave the study at any time. Table 5-1 and Table 6-1 (in the results sections) show the demographic details of the patients that participated in the study.

3.2 PATIENT RECRUITMENT

Patients were recruited into the study using the following inclusion criteria:

- SCI treated at Queen Elizabeth National Spinal Injuries Unit (QENSIU), Scotland.
- Subjects with iSCI (acute and chronic) diagnosed with an ASIA Impairment Scale grade (AIS) of C or D.
- Deemed medically stable by their clinician.
- Able to remain upright in a standing frame for 20 minutes.
- Between the ages of 18-65 years.

- No complications requiring immobilization (e.g. fractures and pressure sores).
- No osteoporosis or contractures limiting range of motion.
- Weight under 130kg and thigh length under 44cm (Lokomat restrictions).
- Either inpatients at the QENSIU or able to travel from their place of residence to the QENSIU daily for a period of 6 weeks.

The patients were split into 2 Groups; acute and chronic. The acute group were patients whose injury occurred less than 6 months prior to starting the study and included sub-acute patients. The chronic group had their injury more than 6 months prior to starting the study.

The acute patients were recruited as early as possible after SCI. Once a patient was deemed medically able by their clinician and able to stand upright in a standing frame for 20 minutes they were assessed and approached for inclusion into the study. Being able to withstand being upright in a standing frame for 20 minutes was essential to unsure they could tolerate being fitted into the Lokomat. The chronic patients were recruited from the surrounding area to avoid excessive levels of daily travel.

3.3 PATIENT STUDY DESIGN:

Patients were recruited onto the study for 8 weeks. Recruitment began in January 2007 and ended December 2008. The 8 week period (Figure 3-1) consisted of 3 testing blocks; Baseline, 3 Weeks post Lokomat training, and 6 Weeks post Lokomat training. Rehabilitation training on the Lokomat was conducted from week 2 through to week 7 (inclusively).

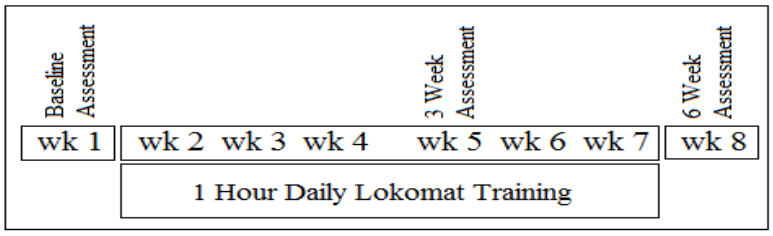


Figure 3-1: Patient study design. Assessments were taken at baseline, during week 1, and after 3 and 6 weeks of Lokomat training in weeks 5 and 8 respectively.

3.3.1 LOKOMAT TRAINING

The patients were measured and fitted into the Lokomat as per the manufactures (Hocoma) instruction manual and training. To comply with the standards written by Hocoma only certified users of the Lokomat are permitted to fit a patient into the Lokomat and operate the device. Prior to training the patient was familiarised with the Lokomat to ensure they understood how it works. The safety features on Lokomat are demonstrated to ensure the patient could activate the stop cord in an emergency. Each patient was fitted into the Lokomat during this session. To enable fitting, measurements of; height, weight, thigh and shank lengths are taken. All measurements were taken while the patient was sitting in their wheelchair. The thigh is measured from the trochanter to the knee joint cavity and the shank from the knee joint cavity to the floor. Both limbs were measured to ensure no variation between the limbs. Three leg cuffs were fitted for the width of the leg. A single cuff was placed on the thigh approximately 8cm from the knee. The remaining two cuffs were placed on the shank, the first approximately 8cm below the knee and the second 8 cm above the lateral malleolus (ankle joint). If patients wore a leg bag (to collect urine) this usually sat on the shank with the tube lying across the thigh. Measurements for the cuffs should take this into account and the patient was asked to empty the bag prior to each training session. The harness was fitted to girth and length of the trunk.

The measurements for the thigh length, shank length and the leg cuffs were applied to the Lokomat exoskeleton. The patient was then fitted into the Lokomat. At this point the back support, hip width, knee angle and ankle support were determined. Final fitting takes about 15 minutes and the patient stands throughout. During the fitting the patient was visual monitored to ensure that they do not faint and are comfortable.

The patient then walked for 2-5 minutes in this session to familiarise themselves with the Lokomat and to confirm the measurements and settings. All settings were recorded on the Patient Records, ‘Lokomat Settings sheet’ and kept in the patient data file.

During the training period (weeks 2 - 7) the aim is for each patient to walk 1 hour daily Monday to Friday. A log of each patient Lokomat session was recorded in the Patient Records, 'Lokomat Training record' and kept in the patient data file, an example is shown in Table 3-1. Non-attended sessions and explanations were also recorded.

	Date	Unloading (kg)	Distance (m)	Time (min)	Comments	Signature
Fitting / Familiarization						
Week 2 Day 1						
Week 2 Day 2						

Table 3-1: Example of the Lokomat Training record held in the patient records. Five days per week for weeks 2,3,4,5 and6 were recorded.

During the first week of Lokomat training the training time was increased gradually from 15 minutes to 1 hour to ensure the patient was not overly fatigued. Each patient walked at a speed of $2kmh^{-1}$ throughout training. The Body Weight Support (BWS) was set at a percentage that was comfortable for the patient and ensured that no knee buckling occurred during the stance phase of the gait cycle. The BWS was reduced in the following session if during the current session they were able to walk for 1 hour without knee buckling during the stance phase. A maximum of 3Kgs was reduced in any one session.

3.4 PATIENT TRIAL PROTOCOLS

Table 3-2 shows the assessments completed at each stage of the trial, which are grouped as 1) neurological assessments using the AISA assessment, 2) ambulatory capacity assessments using the Walking Index for Spinal Cord Injury scale (WISCI II) and Temporal Gait analysis, and 3) integrity of sensory pathways using Quantitative Sensory Testing (QST) and Somatosensory Evoked Potentials (SEP).

Assessment	Baseline	3 Weeks Lokomat Training	6 Weeks Lokomat Training
ASIA	✓		✓
WISCI II	✓		✓
Temporal Gait analysis	✓	✓	✓
Electrical Perception Threshold	✓	✓	✓
Light Touch Perception Threshold	✓	✓	✓
Vibration Perception Threshold	✓	✓	✓
Posterior Tibial Nerve SEP	✓	✓	✓
Median Nerve SEP	✓	✓	✓

Table 3-2: Patient assessments completed at baseline, after 3 and 6 weeks of Lokomat training.

3.4.1 NEUROLOGICAL ASSESSMENT - ASIA

The current American Spinal Injury Association (ASIA) standard for neurological classification of spinal cord injury is the AIS scale. This assessment was used to examine motor and sensory function (See Fig 3-2a/b). The assessment was completed using the methods instructed by the second edition of the ASIA reference manual published in 2003. These methods are outlined below. All ASIA assessments were completed by a trained physiotherapist, Dr Sujay Galen, to ensure no variability was introduced by using multiple assessors (Marino et al., 2008).

The AIS test was completed with the following outcome measures;

1) Upper and Lower Limb motor score

2) Light touch score

3) Pin prick score

4) Single Neurological level

5) AISA Impairment Scale (AIS) Grade

The upper and lower limb motor assessment was completed in full. The muscles that were tested in the 10 myotomes are summarized in the table below (See Table 3-3). Each muscle was scored on a six point scale (see Fig 3-2b) and noted on a ASIA record sheet (Figure 3-2a).

Myotome Nerve	Muscle Action	Muscle
C5	Elbow flexors	Biceps brachialis
C6	Wrist extensors	Extensor carpi radialis longus and brevis
C7	Elbow extensors	Triceps
C8	Finger flexors to the middle finger	Flexor digitorum profundus
T1	Small finger abductors	Abductor digit minimi
L2	Hip flexors	Iliopsoas
L3	Knee extensors	Quadiceps
L4	Ankle dorsiflexors	Tibialis anterior
L5	Long toe extensors	Extensor hallucis longus
S1	Ankle plantar flexors	Gastrocnemius, soleus

Table 3-3: Upper and limb muscles used in the ASIA Motor assessment.

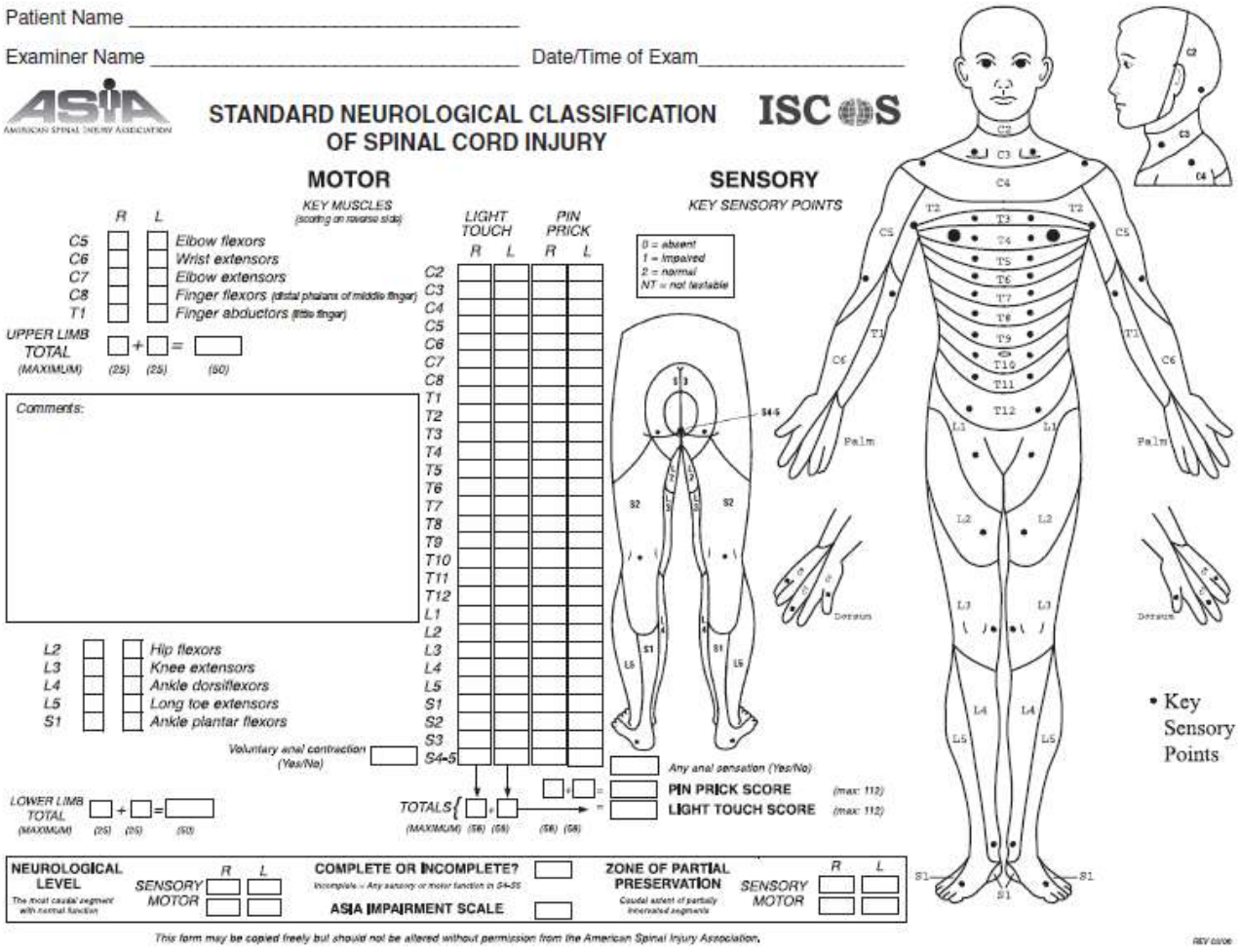
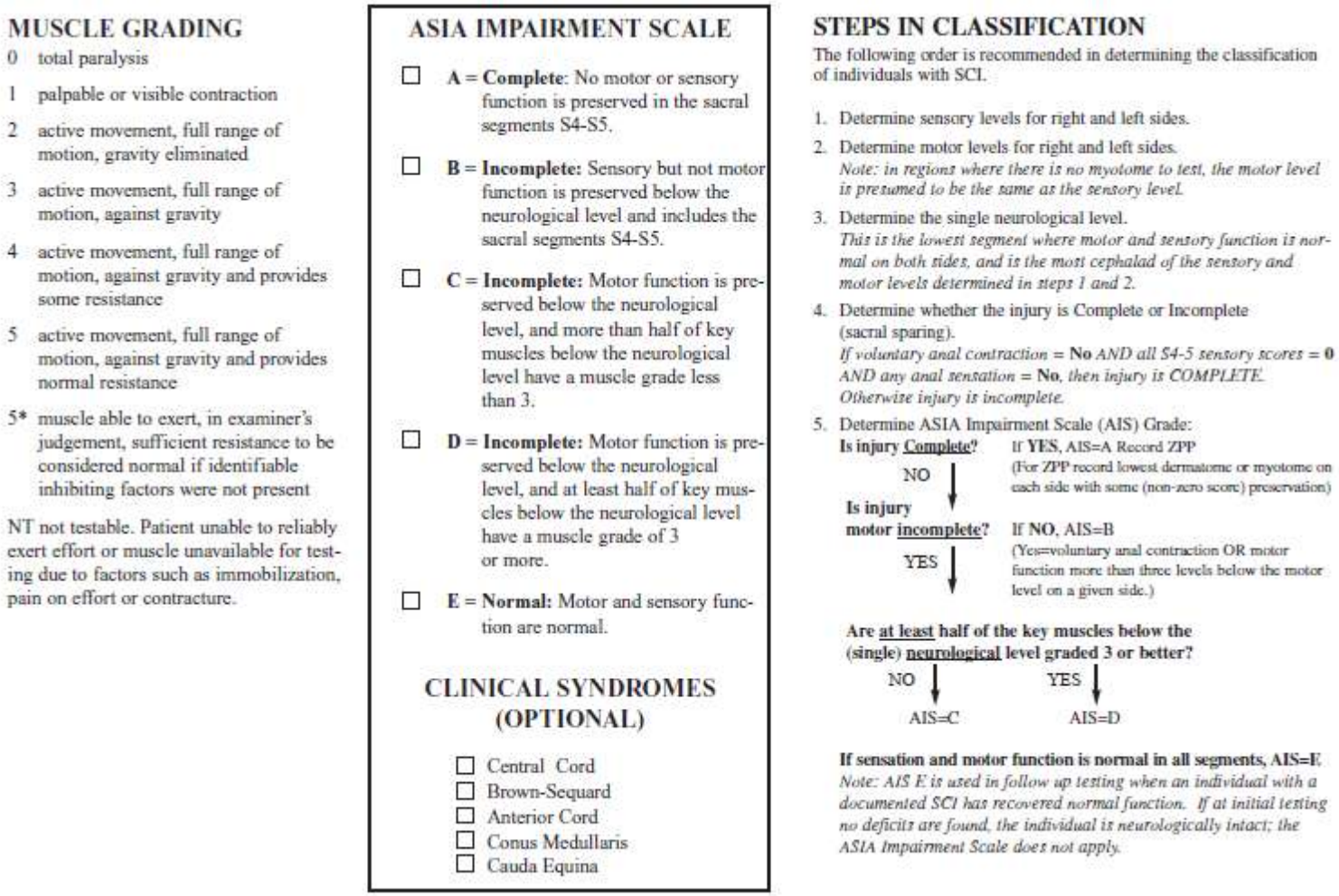


Figure 3-2a: AIS classification form. [Taken from the ASIA reference manual 2003]



MUSCLE GRADING

0 total paralysis

1 palpable or visible contraction

2 active movement, full range of motion, gravity eliminated

3 active movement, full range of motion, against gravity

4 active movement, full range of motion, against gravity and provides some resistance

5 active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

ASIA IMPAIRMENT SCALE

☐ **A = Complete**: No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central Cord
☐ Brown-Sequard
☐ Anterior Cord
☐ Conus Medullaris
☐ Cauda Equina

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores* = **0** *AND any anal sensation* = **No**, *then injury is COMPLETE. Otherwise injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If **YES**, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)

NO ↓

Is injury motor incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)

YES ↓

Are at least half of the key muscles below the (single) neurological level graded 3 or better?

NO ↓ AIS=C

YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Figure 3-2b: ASIA classification form. [Taken from the ASIA reference manual 2003]

The sensory assessment for light touch and pin prick was completed for dermatomes C3 to S2 inclusive. A disposable safety pin was used to test sensitivity to pin prick and cotton wool to test sensitivity to light touch. Each sensory dermatome was scored on the three point scale (See Fig 3-2a) and the result noted on a ASIA record sheet (Figure 3-2a).

The single neurological level was defined using the 'steps in classification' on the ASIA sheet (see Fig 3-2b). It was defined as the lowest segment where motor and sensory function was normal on both sides of the body, (left and right motor score = 5 and pin prick and light touch =2). The motor level was the lowest level in which both sides of the body was recorded as normal motor function. The sensory level was the lowest level that was recorded as normal on both sides of the body for both pin prick and light touch scores.

As the levels above C3 were not tested an AIS grade of C3 was given to patients who motor and sensory scores were normal for C3. The motor assessment does not include muscles from the thorax and accordingly no muscles were tested between the levels of T1 and L2. If the motor score was normal for T1 and abnormal for L2, the true motor level may be between T2 and T12. Therefore the neurological level was assessed as the sensory level on the condition that the sensory score for T1 was normal.

The assessment for sacral sparing is used to assess if a lesion is either complete or incomplete. This part of the AIS test was performed by the clinical team at the QENSIU on admittance of the patient to the spinal unit. It was not repeated during the AIS assessments within the study as it was deemed as an unacceptable intrusion of privacy to the patient by the researcher.

3.4.2 AMBULATORY CAPACITY

WALKING INDEX FOR SPINAL CORD INJURY

Table 3-4 shows the Walking Index for Spinal Cord Injury II (WISCI) scale used to assess the patients ambulatory capacity (Ditunno et al., 2000, Dittuno and Ditunno,

2001). This was completed during a consultation with the patient and the patients physiotherapist at the QENSIU. This test requires each patient to attempt to walk 10m using whatever assistance they require. The outcome of the test provides a score from 0-20 which indicates how much external aid is required by the patient to complete the 10m walk. Once completed the form was filed in the patient data file.

Level	Devices	Braces	Assistance	Distance
0				Unable
1	Parallel bars	Braces	2 persons	Less than 10 meters
2	Parallel bars	Braces	2 persons	10 Meters
3	Parallel bars	Braces	1 person	10 Meters
4	Parallel bars	No braces	1 person	10 Meters
5	Parallel bars	Braces	No assistance	10 Meters
6	Walker	Braces	1 person	10 Meters
7	Two crutches	Braces	1 person	10 Meters
8	Walker	No braces	1 person	10 Meters
9	Walker	Braces	No assistance	10 Meters
10	One cane / crutch	Braces	1 person	10 Meters
11	Two crutches	No braces	1 person	10 Meters
12	Two crutches	Braces	No assistance	10 Meters
13	Walker	No braces	No assistance	10 Meters
14	One cane / crutch	No braces	1 person	10 Meters
15	One cane / crutch	Braces	No assistance	10 Meters
16	Two crutches	No braces	No assistance	10 Meters
17	No devices	No braces	1 person	10 Meters
18	No devices	Braces	No assistance	10 Meters
19	One cane / crutch	No braces	No assistance	10 Meters
20	No devices	No braces	No assistance	10 Meters

Table 3-4: Walking Index for Spinal Cord Injury (WISCI) scale. Version 2 [Taken from Ditunno and Dittuno 2001].

TEMPORAL GAIT ANALYSIS

Temporal gait analysis of the iSCI patients was completed using instrumented insoles. The gait analysis data used for this thesis was collected by Dr Sujay Galen. The patients were tested as they walked along a marked 10m walkway (see Fig 3-3) with instrumented insoles placed in their shoes (Granat et al., 1995).

A body worn gait assessment tool designed and validated among stroke patients (Granat et al., 1995) was modified with a new software interface created to suit assessments of ambulatory capacity of iSCI patients within a clinical environment.

The insoles which had Force Sensitive Resistors (FSRs) (Interlink Electronics Inc., Camarillo, California) attached at the heel, 1st and 5th metatarsal head and the hallux were placed into both shoes of the patient. The FSR's were connected to a junction box containing a 9V battery to power the system. The junction box was secured to the patient by a waist clip. The data was acquired at 100Hz using a National Instruments data acquisition card (NIDAQ (USB-2009), National Instruments inc, USA) and recorded into MS-Excel for processing.

The walkway was marked out at 0, 2, 8 and 10m points and the patients were asked to start and stop at the 0 and 10m points. The patients were instructed to walk at a self selected speed, close to what they regularly used for functional ambulation. The middle 6m (from 2 to 8m) of the walk were considered to represent steady state walking and the first and last 2m as periods of acceleration and deceleration respectively (Wirz et al., 2005).

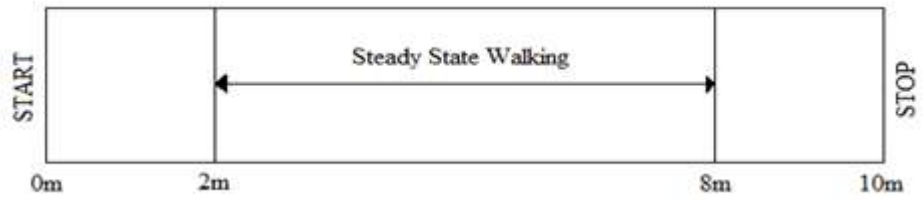


Figure 3-3: 10 Metre walkway used in the temporal gait analysis assessment. Gait analysis was completed over the central 6m so that 2m either side allowed for acceleration and deceleration.

Gait was evaluated by the assessment of 4 temporal parameters; 1) walking speed, 2) double support, 3) stride length, and 4) cadence during the 6m steady state walking.

SIGNAL PROCESSING

The data acquired during the 10m walk test was analysed using a Labview program (version 8.2), 'Foot switch system analyser' written By Dr S Galen. Within the programme the analogue data for each FSR was converted into a discrete on / off signal. Using a pre-defined threshold level the signal was interpreted as either 1 or 2 for on or off respectively.

For each insole; left and right, the discrete signals from the FSRs were encoded into a single four bit number using a binary weighting system (for further details see (Galen, 2006)). This gave 15 possible outcomes, which represents the initial foot contact pattern (first 20ms of the stance phase). For each patient a summary of the initial contact pattern for all recorded steps was shown graphically.

As stated previously the patients gait was evaluated by the assessment of 4 temporal parameters; 1) walking speed (ms^{-1}), 2) double support time (seconds), 3) stride length (meters) and 4) cadence (steps per minute) during a 6 meter walk test as defined in table 3-5. These parameters were calculated within the software after plotting the FSR recordings from the left and right heels.

Temporal Gait Parameters	**Definition**
Walking Speed	The distance (meters) divided by the time (seconds)
Double Support Time	The time (seconds) in which both feet are on the ground during the gait cycle
Stride Length	The distance (meters) covered between 2 consecutive heel strikes
Cadence	The number of steps taken in 1 minute

Table 3-5: Temporal gait parameters assessed using a foot switch system.

3.4.3 QUANTITATIVE SENSORY TESTING

Normative data was collected from healthy volunteers (n=10) at the University of Strathclyde. The protocol was the same as described for the patients (see below) but all tests were completed at the University. Subjects completed each test twice, at least 1 week apart to show repeatability of the test.

The patient QST was conducted in a quiet room within the QENSIU. The patients were made comfortable in the supine position ensuring any pressure points were well padded. Movement to relieve pressure was completed every 15 minutes. Co-operation and alertness by the patient is required throughout these tests. If a patient was lethargic during the test the session was stopped and continued after a suitable break.

For each QST, (electrical and vibration) the dermatomes C3 to S2 inclusive were examined. Dermatomes T4 to T6 were excluded in female patients to avoid potential

unnecessary stress to subjects associated with tests on skin areas considered to be associated with privacy. The ASIA sensory key points were used to ensure the test location of each dermatome was the same for all sessions. For each modality a trial was conducted with each patient at a level above the lesion and at an intensity higher than perception threshold to ensure they could recognise the stimulus during the subsequent test. This also helped to reduce any anxiety by the patient towards the electrical stimulus prior to testing.

ELECTRICAL PERCEPTION THRESHOLD

To assess electrical perception (EPT) an electrical stimulator (Digitimer DS7A) was used to deliver a constant current square wave electrical pulse of 0.5ms duration to the skin via a 20mm fixed bar electrode (See Fig 3-4). The electrode pads were first soaked in distilled water to ensure good conduction. The cathode (-ve) was placed on the ASIA key point and the anode (+ve) placed proximally. The methods of limits described by Davey et al (2001) were used to identify the perception threshold. The stimulus intensity was increased by 0.1mA increments at a frequency of 1Hz until the stimulus was perceived by the patient, or the stimulus reached the test ceiling of 10mA. At the point of perception the patient alerted the assessor, the stimulus was stopped and the stimulus strength recorded. This was repeated 3 times for each dermatome bilaterally. The perception threshold was taken as the average of the 3 data points.

Figure 3-4: Fixed Bar electrode with two soaked electrode pads. The pads are set 20mm apart. The anode (positive) is closest to the wire.

To assess vibration perception, vibration at 100Hz frequency was applied to the dermatome key points using a hand held Neurothesiometer (Arnold Howell, London, UK) as shown in Figure 3-5.

Figure 3-5: Neurothesiometer from Arnold Howell, London, UK

The neurothesiometer is a self contained, electromagnetic device. It delivers vibrations of increasing strength measured in volts per micron to an area of the skin. By increasing the voltage the amplitude of the vibration is increased.

The Neurothesiometer was placed on the skin and held so the weight of the vibrating tip applied a constant pressure to the skin. The method of limits was used to identify the perception threshold. The stimulus intensity was increased by 0.5V increments until the stimulus was perceived by the patient, or the stimulus intensity reached the ceiling of the equipment, which was 50V. At the point of perception the patient alerted the assessor, the stimulus was stopped and the stimulus strength recorded. This was repeated 3 times for each dermatome bilaterally. The perception threshold was taken as the average of the 3 data points.

3.4.4 SOMATOSENSORY EVOKED POTENTIAL

During patient testing the Posterior Tibial (PT) and Medial nerve SEP measurements were taken in a quiet room at the QENSIU. The patients were made comfortable in the supine position ensuring any pressure points were well padded and movement to relieve pressure points was completed every 15 minutes. SEPs were elicited by

applying an electrical stimulation to the PT and medial nerve of the left and right limbs (separately). The stimulus was applied using a DS7A constant current stimulator (Digitimer Ltd Hertfordshire, UK) using a fixed bar electrode (VIASYS Healthcare). The cathode and anode were fixed 20mm apart as shown in figure 3-4.

For the PT nerve the electrode was applied to the skin with the cathode (-ve) placed midway between the Achilles tendon and the medial malleolus. The anode (+ve) was placed distally (below) (see Fig 3-6). For the median nerve the cathode was placed between the tendons of the palmaris longus and flexor carpi radialis muscles, approximately 2cm proximal to the wrist crease with the anode placed distally (see Fig 3-7).

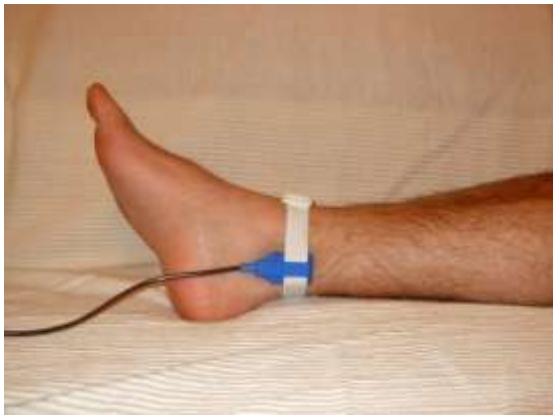


Figure 3-6: Fixed bar electrode placed on the posterior tibial nerve of the right lower limb. The cathode (-ve) placed midway between the Achilles tendon and the medial malleolus. The anode (+ve) was placed distally. The electrode was held in place with an elastic strap.

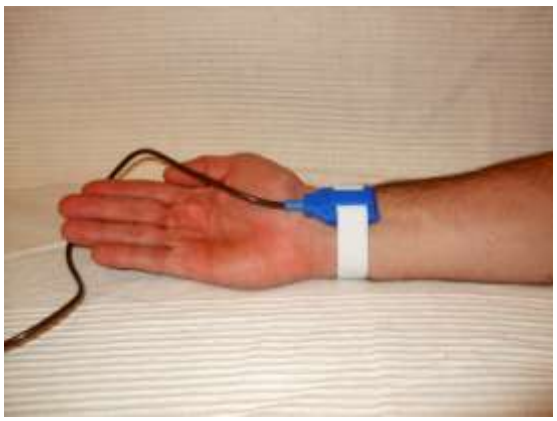


Figure 3-7: Fixed bar electrode placed on the median nerve. The cathode (-ve) was placed between the tendons of the palmaris longus and flexor carpi radialis muscles, approximately 2cm proximal to the wrist crease with the anode (tve) placed distally. The electrode was held in place with an elastic strap.

The stimulus was a square wave pulse of 200μs duration and applied to the left and right limb at separate times. The intensity of the stimulus was adjusted to produce a visual muscle response. The stimulus intensity was then reduced until the movement in the muscle could no longer be seen. The intensity was again increased to the point where a muscle twitch was seen and this point was defined as the Motor Threshold (MT). The intensity of the stimulus was then applied at twice MT during testing. This intensity was applied to a mixed nerve to ensure that both the group I muscle afferent fibres and the low threshold cutaneous afferents were excited (Kimura 2001).

Two recordings at different frequencies were taken at each nerve to allow the data to be analysed in both the time and frequency domains. The timing of the stimuli was controlled using a Digitimer (pulse gennerator) (Ltd Hertfordshire, UK) and the time of stimulation was recorded using SCAN 4.3 software which also captured the EEG. For the time domain analysis the stimulus was applied at 2.5Hz for 1000 stimuli. This frequency allowed a large number of responses to be collected in a short period of time without causing discomfort to the patient. The large number of stimuli is needed to allow acceptable averaging to be performed. By using signal averaging techniques (See below) the cortical component which is time locked to the stimulus event can be determined. The frequency analysis which looks at longer latency components requires the data to be collected at a slower rate as this analysis looks at both short and long components (7s) of evoked response (Pfurtscheller and da Silva, 1999). 100 stimuli were recorded at 0.1Hz which gave periods of 10 seconds between stimulations. Only 100 stimuli were collected due to time constraints. 17 minutes were needed to collect 100 stimuli at 0.1Hz and at this point the patient needs to be moved to prevent pressure sores. The techniques used for time and frequency domain analysis are described later in this section.

The cortical potentials (CPs) of the SEP were recorded using 17 Sliver/Sliver Chloride (Ag/AgCl) sintered electrodes placed on the scalp using an EasyCap (Brain Vision UK). The head of each patient was measured so that the Cz electrode was positioned midway between the left and right preaurical points and midway between

the nasion and inion as shown in Fig 3-8. The cap size was then fitted to each patient. The electrodes were positioned in the cap using the 10-20 international scalp locations as shown in Fig 3-9. The electrode cap and the 10/20 international system was used instead of the prime locations described in the AAEM recommendations. The prime locations are located 2cm posterior to electrode in the international 10/20 system. The cap was used to ensure that during the repeated test session the electrodes were placed at the same site and the sites were consistent between patients (Chiappa, 1997). Using the cap was also preferred to attaching the electrodes directly to the scalp as it reduced preparation time and is more comfortable for the patient.

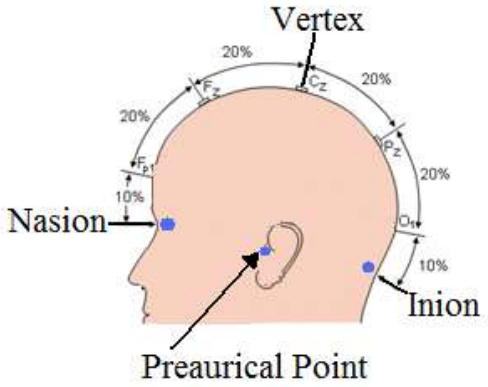


Figure 3-8: Cap size measurement. Cz is located midway between the left and right preaurical points and midway between the nasion and inion.

The electrode recording montage as shown in Figure 3-9 shows the locations of the scalp electrodes used. All EEG channels were recorded as monopolar and referenced to a non-cephalic reference point using clip-on linked ear electrodes. A non-cephalic reference point was used so that the Far Field Potentials (FFPs) which affect all the scalp electrodes nearly equally would not be cancelled out (Yamada et al., 1982).

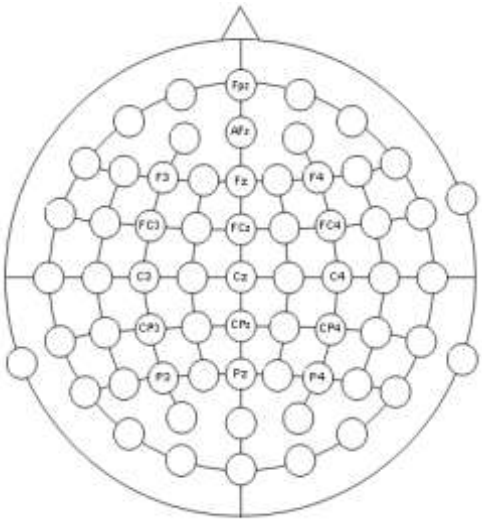


Figure 3-9: Scalp electrode montage. 10-20 International electrode locations.

The electrode impedance was considered acceptable if it was equal to or less then 5kΩ. To enable this, the skin was prepared by abrading the surface of the scalp using a medically approved abrasive solution applied onto the tip of a cotton bud. With the cap placed over the scalp and the electrodes in place the cotton bud was pushed through the hole in the centre of each electrode. A volume conducting gel was then injected into the hole of each electrode so that it sat between the surface of the skin and the electrode. The contact impedance of each electrode was monitored using an application provided with SCAN 4.3 software which controlled the EEG capture and display via the Neuroscan Synamps used in the study. This software illustrates the impedance levels for each electrode using a colour map. The contact impendence of the EEG electrodes after preparation is shown in Fig 3-10.

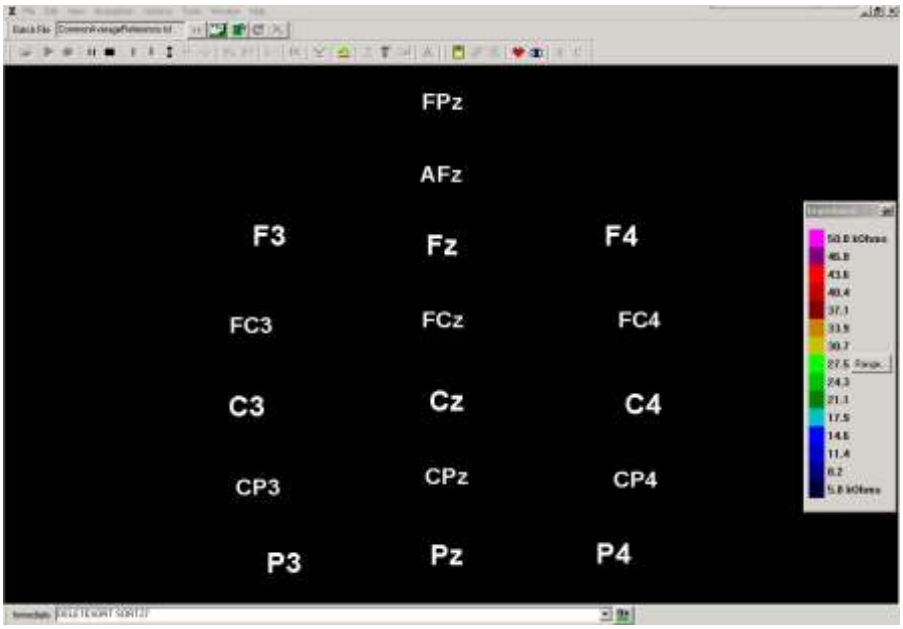


Figure 3-10: Contact impedance of EEG electrodes after experimental set up. The impedance of each electrode in this example is <5kΩ. The colour chart on the right shows the scale of the impedance levels.

SIGNAL PROCESSING - TIME ANALYSIS

As stated above the 17 monopolar EEG channels were recorded using a Synamps (Neuroscan) amplifier controlled by SCAN 4.3 software. The EEG data was recorded as a continuous recorded sampled at 10,000Hz with an amplifier gain of 1000. The time domain data recorded with a 2.5Hz stimulation rate was band-pass filtered 5-2000Hz and the frequency domain data recorded at 0.1Hz was band-pass filtered 0.5-2000Hz. All EEG data was analysed off line using Brain Electrical Source Analysis (BESA) software.

The timing of the stimulus which was recorded with the continuous EEG was used to epoch the data from the point of stimulus using BESA software. The epoch length was -50 to 150ms for the PT Nerve and -50 to 50ms for the median nerve. Stimulus artefact rejection was set from -5 to 2ms. The epochs were averaged and baseline corrected using the pre stimulus data (-50ms to 0ms). This technique is applied to remove the larger background amplitude EEG and reveal the cerebral potential on the hypotheses that the time delay from the stimulus to the cerebral potential is fixed and the background alpha waves in the EEG are not time locked to the stimulus

(Chiappa, 1997, Pfurtscheller and da Silva, 1999). An example of the continuous EEG and epoch data produced are shown in Figure 3-11. The epoched data can be viewed from the 'Top view' to show the epoch for each channel in the electrode position (See Fig 3-12).

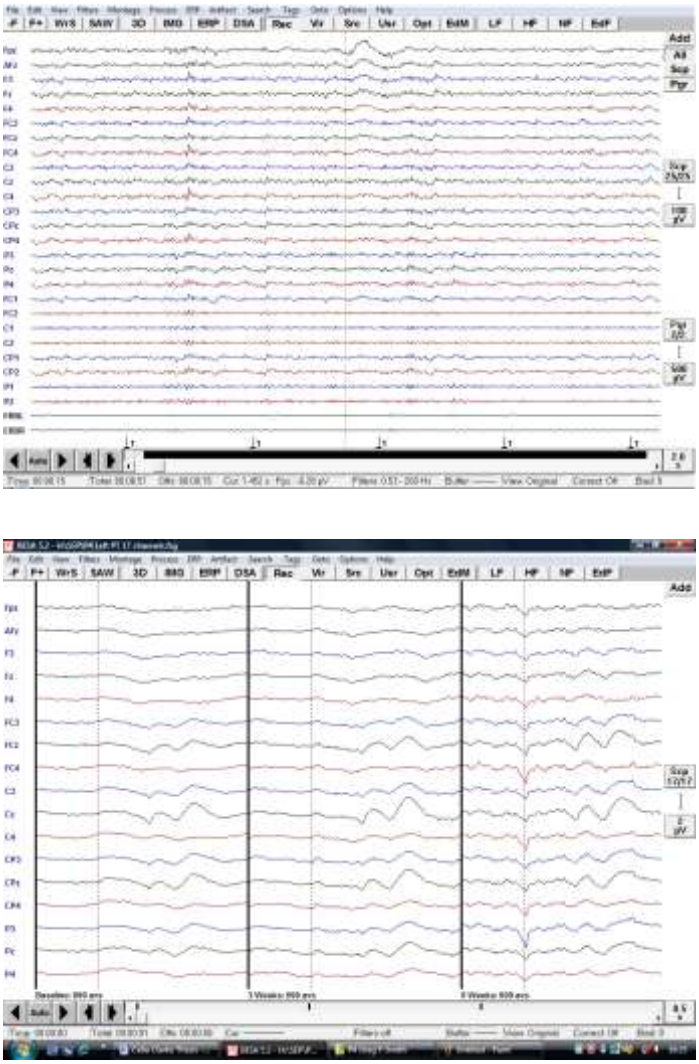


Figure 3-11: Continuous EEG recording from a single patient during left PT nerve stimulation (P4) is shown on the top. The Epoched data is shown on the bottom. The 3 data sets are for the Baseline, 3 weeks lokomat training and 6 weeks lokomat training.

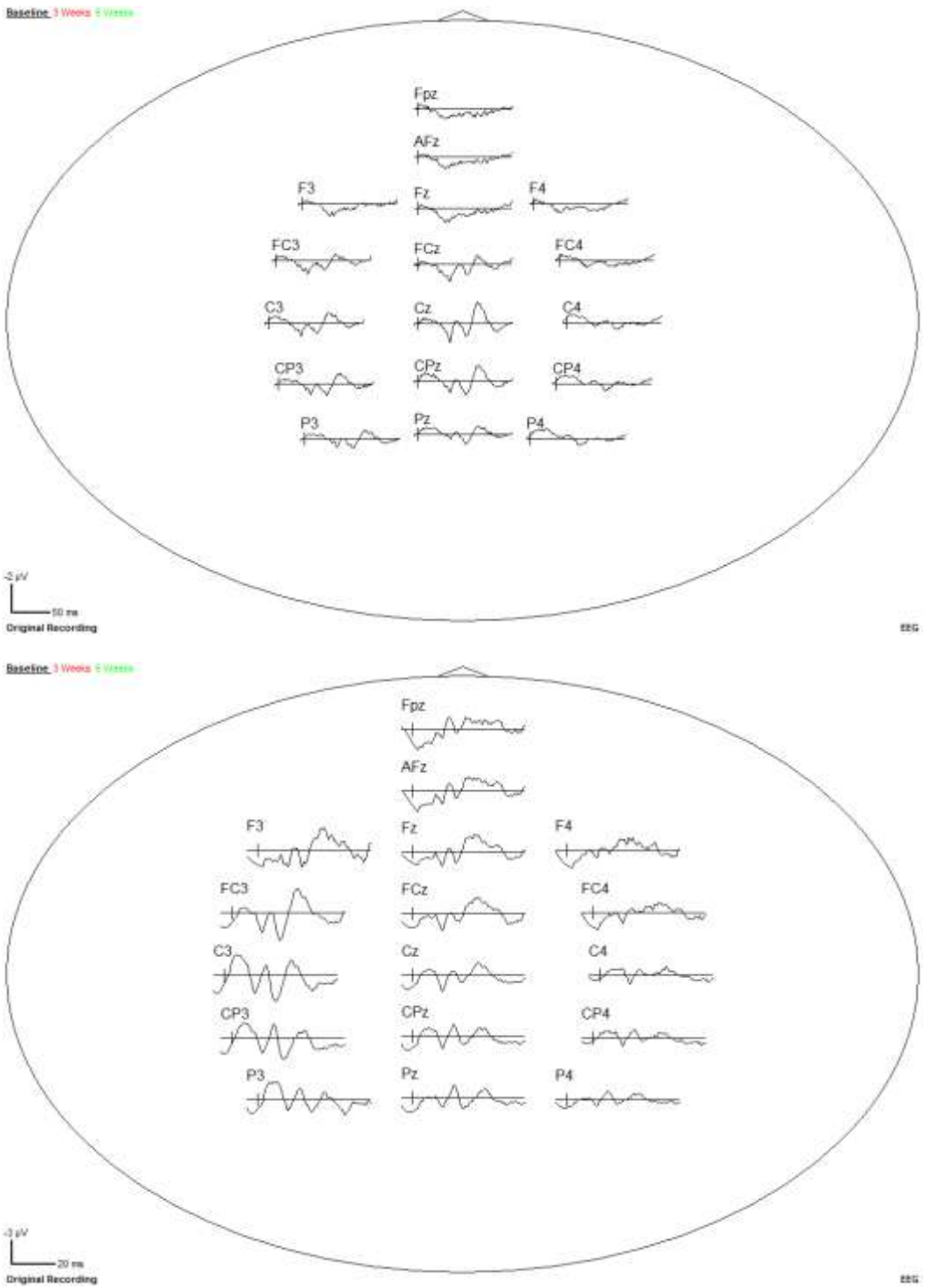


Figure 3-12: Left PT nerve (P4)(top) and Right Median nerve (P14)(bottom) epoched EEG data shown in the top view from a single subject.

This process produces a waveform recorded at each channel on the scalp. The potentials recorded can be termed either near or far field potentials. A far field

potential implies the detection of a stationary potential occurring prior to the signal reaching the recording site, usually by a pair of widely spaced electrodes. The near field potentials represents a potential as it propagates under a pair of usually closely spaced electrodes placed directly over the path of the impulse. By subtracting channels from each other (known as linear derivation) the near and far potentials can be identified. The linear derivation is denoted in the montage.

MONTAGE

During median and PT nerve SEP recording a non-cephalic reference was used. The non-cephalic reference was a linked ear electrode which does not record cerebral potentials evoked by the stimulus. As far field potentials affect all scalp electrodes nearly equally they can be cancelled out if a cephalic reference point is used (Yamada et al., 1982). By using a linked ear electrode as a reference the far field potentials can be identified.

By subtracting one scalp electrode from another a bipolar recording is derived and near field potentials can be identified. During recording the reference electrode was subtracted from the scalp (active) electrode. In the epoched data (Figure 3-12) if the scalp electrode is more negative than the reference electrode it is shown as an upward deflection (Chiappa, 1997).

In the same way as with the active and reference electrode described above, a derived potential from 2 scalp electrodes reflects the positivity or negativity of the first electrode compared to the second. Negativity in the first electrode compared to second electrode is shown as an upward deflection. However the morphology of the derived waveform is affected by the electrode which is subtracted from the active electrode. In Fig 3-13 three electrodes; FPz, Fz and CPz were recorded. The CPz electrode is the active electrode and an example of the waveform is shown after the waveform from FPz and Fz are subtracted from active (CPz) electrode. As some of the early potentials were present in both Fz and CPz these components are cancelled out in the derived montage CPz-FPz. As these components are not present in FPz only the background noise is removed and the potentials are enhanced.

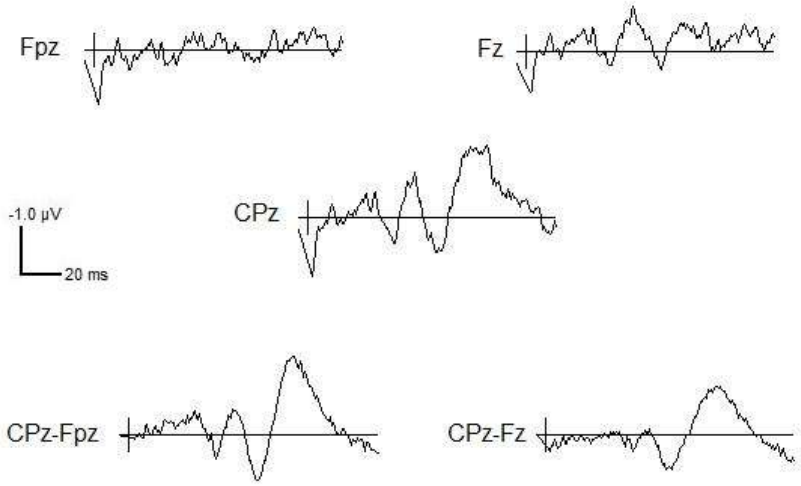


Figure 3-13: Derived waveform. Affect of subtracting different scalp electrodes. The waveform CPz-Fz has reduced amplitude in the early components compared to the wavFPz. This shows how the early component was present in both CPz and Fz. By taking Fz from CPz the early potential is reduced (or worse cancelled out).

To identify how an electrode affects the morphology of the derived waveform the waveforms from individual electrodes were inspected alongside the derived waveform.

The lower limb montage used in this study was compiled from 5 electrodes, Fc, Cz, CP3, CP4 and FPz. To identify the cortical potentials the following linear derivations were used:

Fc

Cz – FPz

CPc – FPz

(where c = contralateral i.e., position 3 or 4).

The upper limb montage used in this study was compiled from 6 electrodes, Fc, C3, C4, CP3, CP4 and FPz. To identify the cortical potentials the following linear derivations were used:

Fc

Cc – FPz

CPc – FPz

Example outputs of these montages are shown in Figure 3-14.

The components in the waveform can be labelled using two common methods. Both methods use a prefix of P or N to denote the polarity of the component as either positive or negative. The prefix is followed by a number. The number is either in numerical order from the time of stimulus (zero time) i.e. P1, P2 or denotes the latency of the peak in ms, i.e. P37, P56. During this study the component from the Fc electrode were labelled with the latency of the peak (i.e. P30). The components measured over the somatosensory cortex using electrodes CPz or Cz for the PT nerve and CPc or Cc in the median nerve were labelled in numerical order (i.e. P1). The suffix c or i defines contralateral and ipsilateral site compared to the stimulus. For example Fc = F4 for left limb stimulation and F3 for right limb stimulation. This method was preferred as it hoped to minimise confusion over which component is being referred to. This is more of a concern in the patient group where the latencies can vary. The labelling used throughout the study is shown in Fig 3-14.

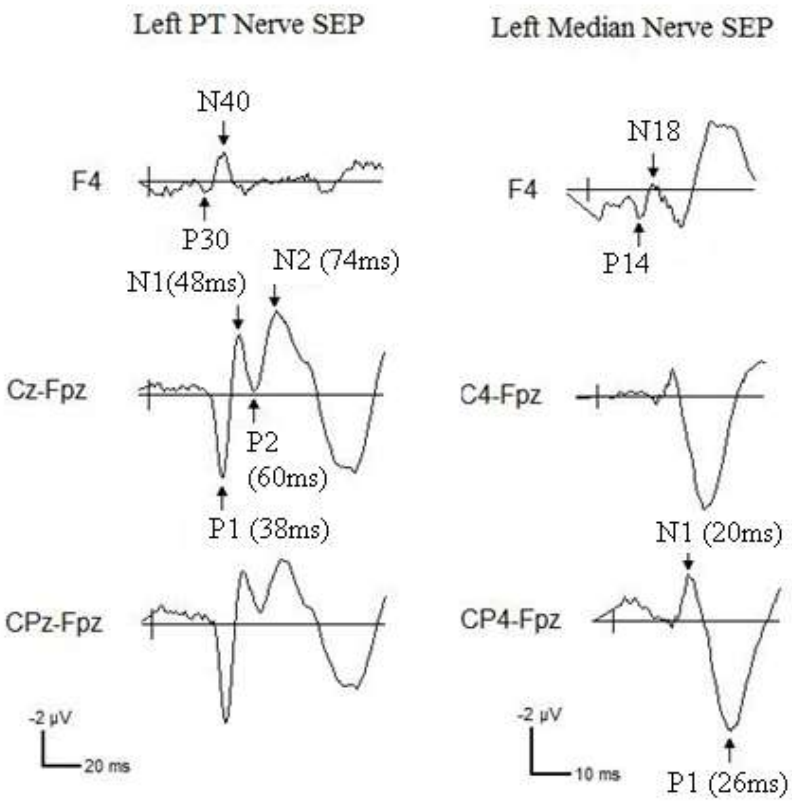


Figure 3-14: Linear derivation montage for Left PT nerve SEP in a single healthy subject.

In the PT nerve SEP 5 components were identified. In electrode Fc; P30 was identified and in the electrode Cz-Fpz; P1, N1, P2 and N2 were identified. The P30 is a far field potential that reflects the activity in the nucleus gracile and medial lemniscus fibres within the lower medulla (Desmedt and Cheron, 1981). The P1 potential, which occurs at around 38ms from the point of stimulus, is shown as a widespread far field potential and is recorded near the mid line. The P1 reflects activity in the primary cortical somatosensory receiving area (American Clinical Neurophysiology Society Guideline 9D). The later components, N1, P2 and N2 recorded in the same electrode reflect cortical-cortical processes, which may include somatosensory to motor areas.

In the median nerve SEP 4 components were identified. In electrode Fc; P14 and N18 and in electrode CPc-Fpz; N1 and P1 were identified. The P14 is analogous to the P30 component of the PT nerve SEP (Desmedt and Cheron, 1981). The N18 reflects activity the brain stem and thalamic structures (Desmedt and Cheron, 1981, Tomberg et al., 1991).

To analysis the components of the waveform in the time domain, the latency and amplitude of components within the waveform were recorded. The latency (ms) was recorded from the point of stimulus to the highest point of the peak, or lowest point of the trough (See Fig 3-15).

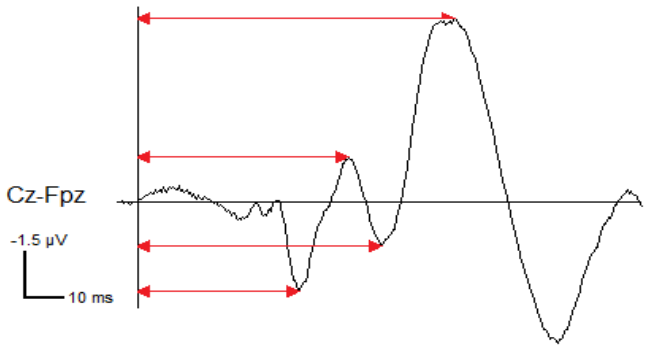


Figure 3-15: Latency analysis of SEP. Time from stimulus to the highest point on the peak, or lowest point on the trough is recorded in ms.

The amplitude (µV) was measured in 2 ways. Firstly the peak height, measured from the zero line (x axis) to the highest point of the peak or to the lowest point of the

trough. Secondly, the peak to peak amplitude measured from the lowest point of the trough to the highest point on the next peak and vice a versa (See Fig 3-16).

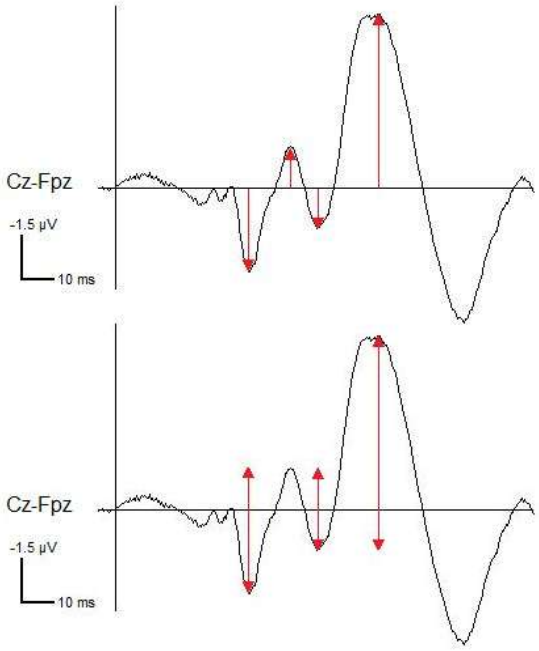


Figure 3-16: Peak amplitude and peak to peak amplitude analysis.

The baseline, 3 weeks and 6 weeks post Lokomat training conditions were overlaid (Fig 3-17) so changes could be observed and time analysis completed. Further analysis was performed by conducting statistical analysis. ANOVA tests on the latencies and amplitudes before and after Lokomat training was completed. Correlations between SEP and ambulatory capacity were determined to investigate the SEP as a predictive indicator of ambulatory capacity after 6 weeks Lokomat training.

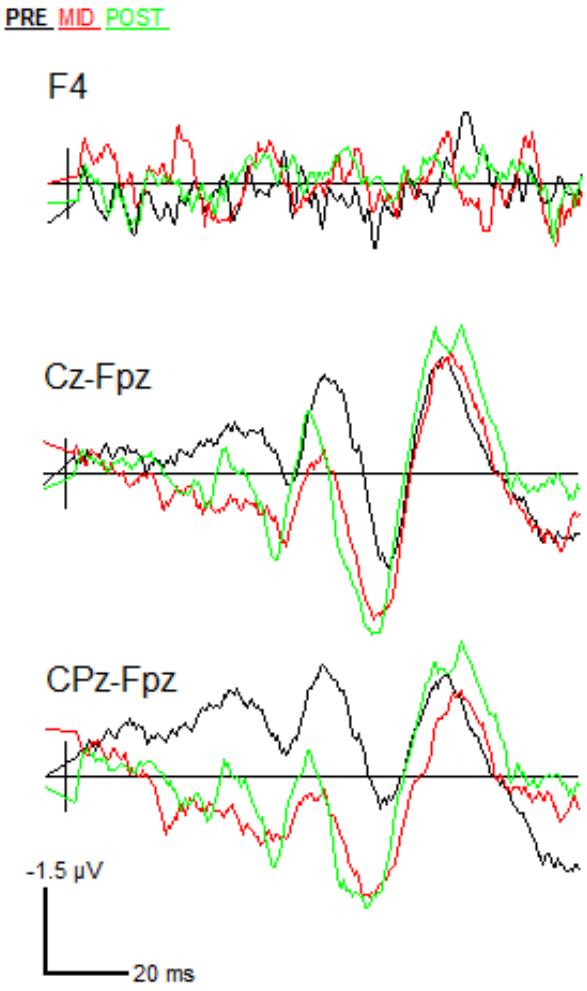


Figure 3-17: Left PT nerve SEP from baseline (blue) after 3 weeks Lokomat training (red) and after 6 weeks Lokomat training (green) from a single patient (P8).

SIGNAL PROCESSING - FREQUENCY ANALYSIS

As stated above the 17 monopolar EEG channels were recorded using a Synamps (Neuroscan) amplifier controlled by SCAN 4.3 software. The EEG data was recorded as a continuous recorded sampled at 10000Hz with an amplifier gain of 1000 and band-pass filtered 0.5-2000Hz. All EEG data was analysed off line using BESA software.

Late components may also occur after SEP testing that are not included in the epoch window of the time analysis. By extending the epoch window these later components may not be identified in averages as phase locking to the stimulus may

be absent and the components cancelled out by time domain analysis (Pfurtscheller and da Silva, 1999).

The late components are a form of event releated potentials that appear as enhancements and attenuations of the EEG. They are often referred to as periods of event-related synchronization (ERS) and event related desynchronization (ERD) respectively and shown in Fig 3-18.

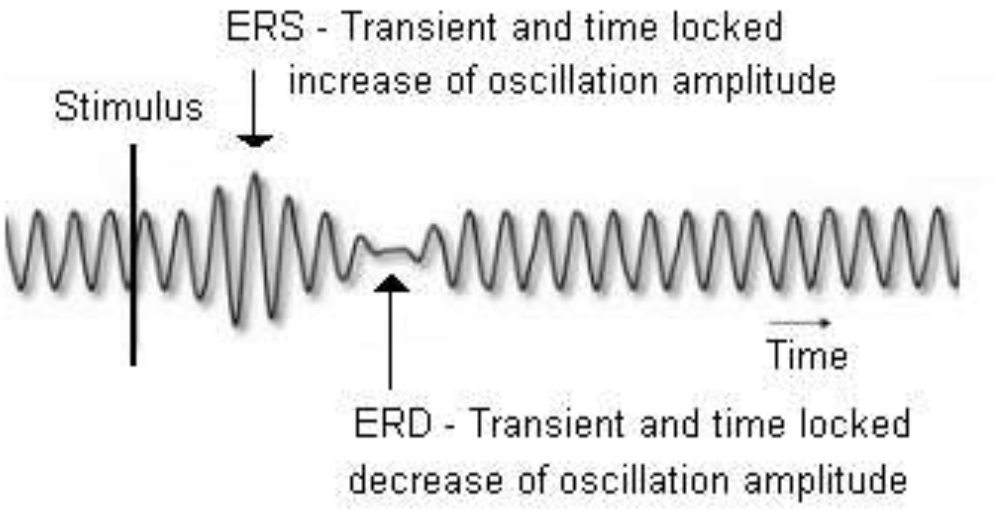


Figure 3-18: Increases and decreases in the ongoing EEG know as Event related synchronization (ERS) and Desynchronization (ERD).

Conventional studies of ERD/S focuses on frequency domain analysis of narrow frequency bands (Pfurtscheller and da Silva, 1999). To monitor changes over time a wider frequency band was considered necessary for this study. Accordingly the Event Related Spectral Perturbations (ERSP) estimate was used. This test measures the changes in the power spectrum over the entire sampling range bandwidth after an event (Delorme and Makeig, 2004, Makeig, 1993) and allowed frequency domain analysis of cortical potentials evoked by PT and median nerve SEP.

The EEG data collected (described the Methods section) was epoched from -1000 to 3000ms using SCAN 4.3 software. The ERSP was computed using a Fast Fourier Transform (FFT) within EEGLAB (Version 4.515) (Delorme and Makeig, 2004). EEGLAB is a tool box which runs within MATLAB. The ERSP is calculated by

first computing the power spectrum over a sliding latency window and then averaging across the data trials (Delorme and Makeig, 2004). The EPSP equation is;

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

where F_k (f ,t) is the spectral estimate of trial k at frequency f and time t for n trials as (Delorme and Makeig, 2004).

Channels Cz and CPz were analysed for the PT nerve SEP, and channels Cc, CPc for the median nerve SEP. Periods of synchronization and desynchronization were shown graphically using a colour intensity map. The hotter or colder the colour, the greater the synchronization or desynchronization. Red shows periods of synchronization and blue periods of desynchronization. An example of an SEP measured this way at Cz is shown in Figure 3-19. The white box indicates a period of desynchronization from 0 to 800ms in the frequency band 12-16Hz seen in healthy subjects evoked by lower limb stimulation.

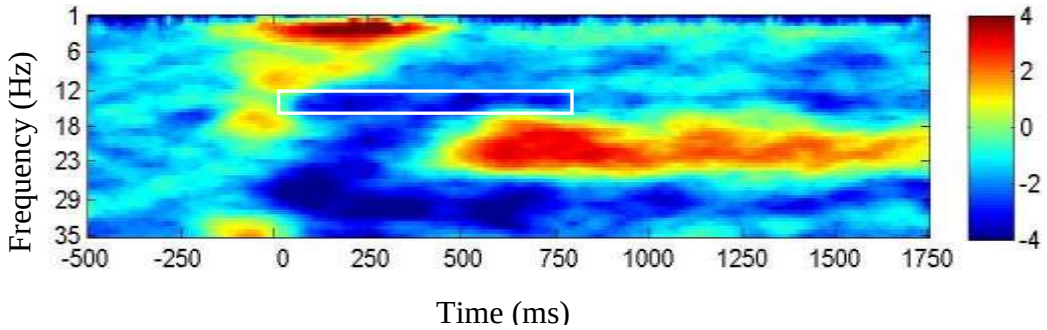


Figure 3-19: ERSP of Cz and in a healthy subject after PT nerve SEP. The colour indicates power (in dB) at a given frequency and latency relative to the time locking event. Synchronization is shown in red and desynchronization in blue.

4 METHODS MODULATION OF CORTICAL POTENTIALS DURING WALKING

The aim of the subject study was to identify and report the cortical evoked responses observed during normal treadmill walking and during treadmill walking with stimulation of the PT nerve in healthy subjects at different parts of the gait cycle. By comparing the morphology and timing of these evoked responses during normal treadmill walking, sitting and standing any gating or modulation of the waveform could be determined and used to provide insight into cortical sensory processing during gait.

4.1 ETHICAL APPROVAL

Ethics approval was obtained from the departmental ethical committee at the Bioengineering Unit, Strathclyde University, Glasgow. All subjects gave informed written consent and were free to leave the study at any time. 10 subjects (6 male 4 female) completed the study. Table 6-1 (in the results section) show the demographic details of the subjects that participated in the study.

4.2 SUBJECT STUDY DESIGN

PT nerve SEPs were recorded while sitting, standing and during treadmill walking. Each subject completed all tests shown in Table 4-1 during one session. The supine and standing were completed to enable a comparison of these postures to the results obtained during walking in the same subject. To determine evoked potentials that occur during normal (non perturbed gait) each subject completed walking trials without the stimulus applied to the PT nerve. Each subject completed the trials in the same order; supine, standing and walking. During the walking trials the subjects walked in 5 minute blocks, alternating non stimulation and stimulation trials. This enabled more manageable size data files to be recorded as well as allowing the subject frequent rests.

Test	Posture	Stimulation	Time
1	Supine	2.5Hz 1000 pulses	10 minutes
2	Standing	2.5Hz 1000 pulses	10 minutes
3	Treadmill Walking	Phase dependent stimulation (randomised) *****No stimulus applied*****	25 minutes (5 x 5minutes)
4	Treadmill Walking	Phase dependent stimulation (randomised)	25 minutes (5 x 5minutes)

Table 4-1: Trials completed by each subject during the test session.

4.2.1 SOMATOSESNORY EVOKED POTENTIALS

SEPs were elicited by applying an electrical stimulation to the Posterior Tibial (PT) nerve of the right leg only. The stimulus was applied using a DS7A constant current stimulator (Digitimer Ltd Hertfordshire, UK) and a fixed bar electrode (VIASYS Healthcare) to the PT nerve at the ankle. The electrode was attached to the skin and held in place with an elastic strap and micro-pore tape.

The stimulus intensity was applied at twice MT during sitting, standing and walking assessments. The MT was determined using the protocol described for the patients (see Chapter 3). The stimulus applied was a square wave pulse of 200μs duration. In the sitting and standing tasks the pulses were applied at 2.5Hz for 1000 pulses. During walking a maximum of 1 pulse was given per step cycle (right heel strike to right heel strike). Details of the stimulation protocol during walking are explained in detail later in this section.

The cortical potentials (CPs) of the PT SEP were recorded using 17 monopolar EEG channels using an easyCAP and a Synamps EEG system. The recording montage used was the same as recording montage used in the patient PT nerve SEP testing (see Chapter 3).

EMG DATA

EMG was recorded simultaneously with the EEG using 3 bipolar channels of the Synamps. EMG was collected from muscles on the right lower limb and foot. These were 1) Abductor Hallucius (AH), 2) Medial Gastrocnemius (GM) and 3) Tibialis

anterior (TA) as shown in Fig 4-1. The AH muscle was recorded from the right foot to monitor the amplitude of the M-wave which reflects the intensity of the stimulus applied to the PT nerve. During walking the PT nerve moves under the skin as the ankle is rotated though the gait cycle. This movement may cause a variation of the intensity of the stimulus applied to the nerve. To monitor the possible change in the pulse intensity the M-wave from the Abductor Hallucius muscle was recorded during each posture and in each phase of the gait cycle. The M-wave was then expressed as a percentage of the M-wave during the supine position.

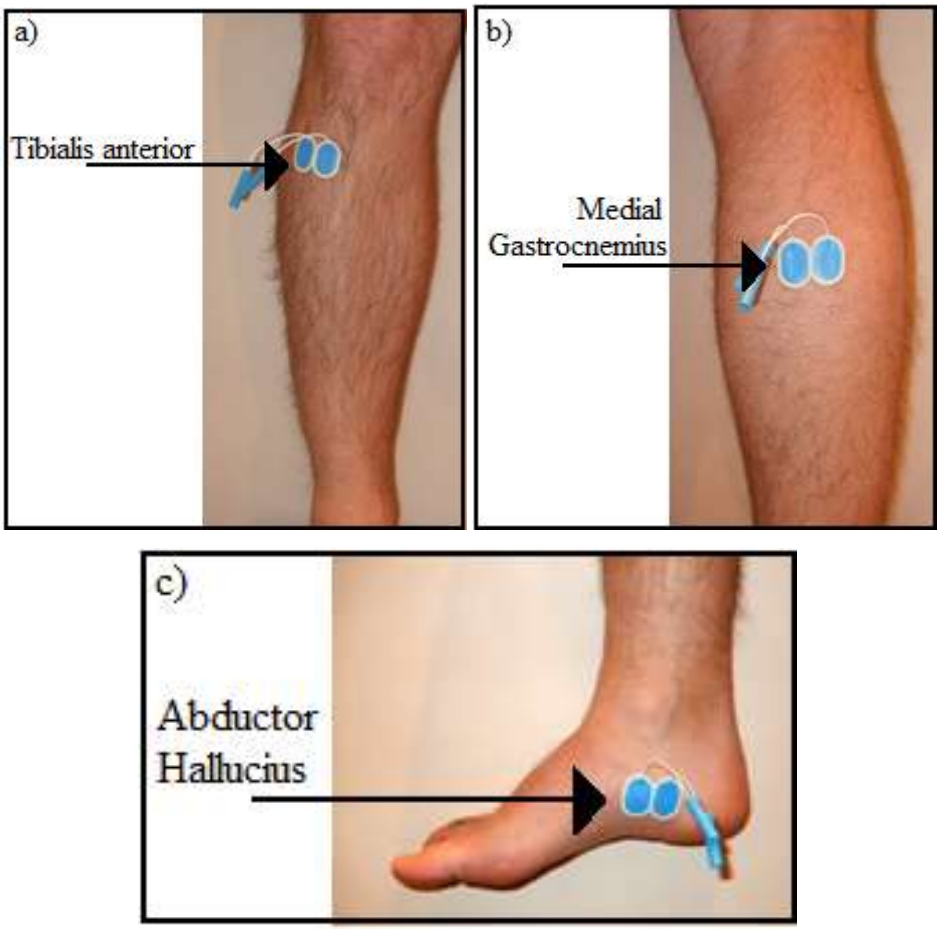


Figure 4-1:Locations of EMG electrodes on Abductor Hallucius (AH), Medial Gastrocnemius (GM), and Tibialis anterior (TA) for the right lower limb.

The muscles were identified by palpation whilst asking the subject to flex and extend their ankle. The skin was prepared with a medically approved abrasive solution

applied using a cotton gauze to insure the contact impedance was below 5kΩ. Disposable self adhesive EMG surface electrodes were placed onto the skin and secured using micro-pore tape.

ELECTRICAL STIMULUS

To establish the timing of the gait cycle for each subject, all subjects completed a 2 minute walk on the treadmill at 4kmh^{-1} with FSRs placed at the heel and 1st metatarsal head on the insoles in their shoes (Fig 4-2). Data from the FSRs were recorded via a CED 1401 controlled via Spike 6 software.

Figure 4-2: Instrumented Insoles.

The timing of heel strike and toe off in consecutive steps was determined to give averaged duration and onset time of the stance and swing phases. An example of the heel strike and toe off data from a single subject is shown in Fig 4-3. The falling edge of the right heel strike signal was used to determine the onset of stance and the rising edge of the right toe off signal was used to determine the onset of swing. This was done prior to testing for each subject and also allowed the subject to be familiarized with the treadmill.

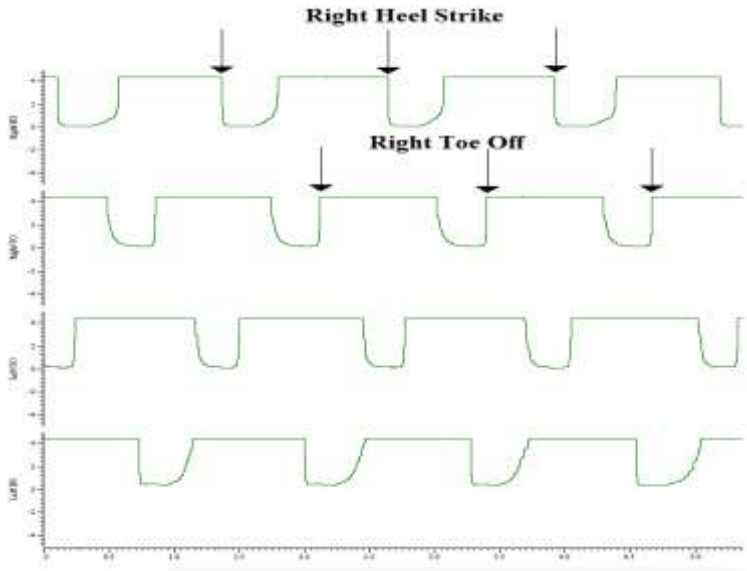


Figure 4-3: Heel strike and toe off timings over 4 consecutive gait cycles in a single subject. The falling edge of the right heel strike signal determined the onset of stance and the rising edge of the right toe off signal determined the onset of swing.

As the timings of the gait cycle varied between the subjects the stimulation was applied at percentage of the stance and swing phase duration. Stimulation was given at 4 different points within the gait cycle (right heel strike to right heel strike);

- Heel Strike (40ms after heel strike)
- Mid Stance (50% of stance duration)
- Toe Off (40ms after toe off)
- Mid Swing (62% of swing duration)

These timings enabled periods of planter-flexion, dorsi-flexion, load bearing and non load bearing to be assessed. A programme written using Spike software determined the points of heel strike and toe off for the left and right foot. The timings for PT nerve stimulation were calculated using this programme from the 2 minute treadmill walking data. The timings were then used during all the walking tasks. A stimulus was applied during each gait cycle to maximise the number of once evoked potentials during each test session. The stimulus was given in a random order determined by the programme. This meant that a stimulus at mid swing could be followed by a stimulus at heel strike on the next consecutive step. As the time between these points

in the gait cycle is >200ms and the cortical potentials of interest are < 90ms the cortical potentials are not affected by this short stimulus interval.

The timing of the stimulus was recorded with the EEG and EMG data using SCAN 4 software. This allows the EEG and EMG to be epoched from the time point of the PT nerve stimulus. The stimulus points were recorded with a predefined number, which identified the phase within the gait cycle that it was presented. This enabled the epochs from each phase of the gait cycle to be averaged (See Signal processing for details).

A schematic of the data collection set up for PT nerve stimulation during walking is shown in Figure 4-4. During normal treadmill walking, i.e. without stimulus, the set up remained the same but the stimulator output to the subject was switched off. The time points in the gait cycle that would have been stimulated were recorded. This allowed the same methods of data processing for the normal treadmill walking and the stimulated walking.

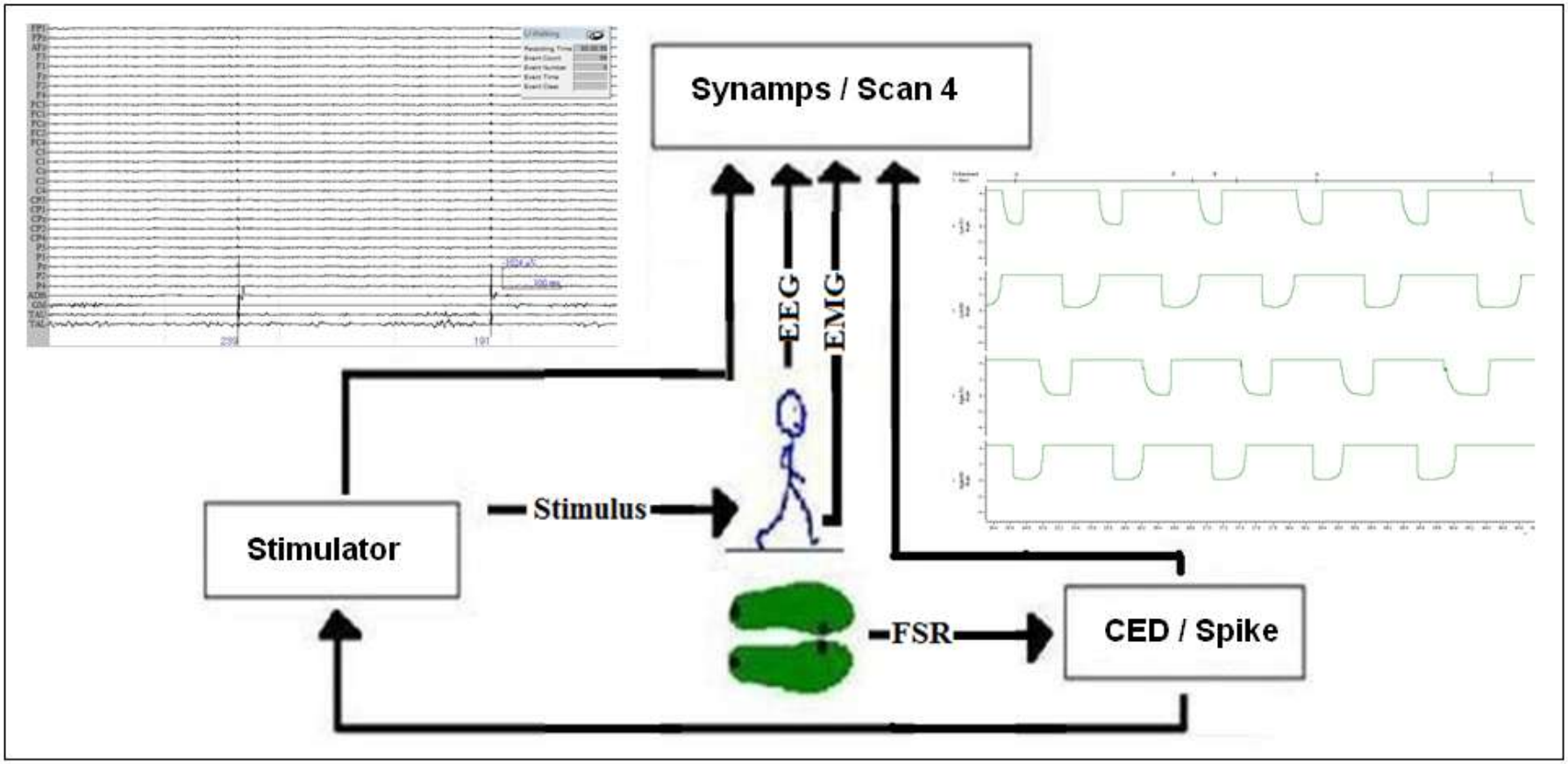


Figure 4-4: Recording set up for SEP during treadmill walking.

4.3 SIGNAL PROCESSING

The EEG recorded during the supine and standing postures were processed in the time domain using the same methods described for the iSCI patient study (See Chapter 3). The EEG recorded during treadmill walking was also analysed in the time domain, however the data was epoched for the phase of the gait cycle using the stimulus triggers.

During treadmill walking the time of the stimulus was logged with the EEG data by the SCAN 4.3 software. Depending upon the phase of the step cycle in which the stimulus was applied a different number was logged (See Fig 4-5). During the trials when the stimulus was not given to the subject the timing of the stimulus was still recorded. This enabled the EEG collected during normal treadmill walking to be epoched using the same methods. The EEG data was separated into 4 sets of epochs (-50 to 150ms) associated with the 4 points of stimulation in the gait cycle. Each set of epochs was averaged to produce a single waveform for each phase of the gait cycle.

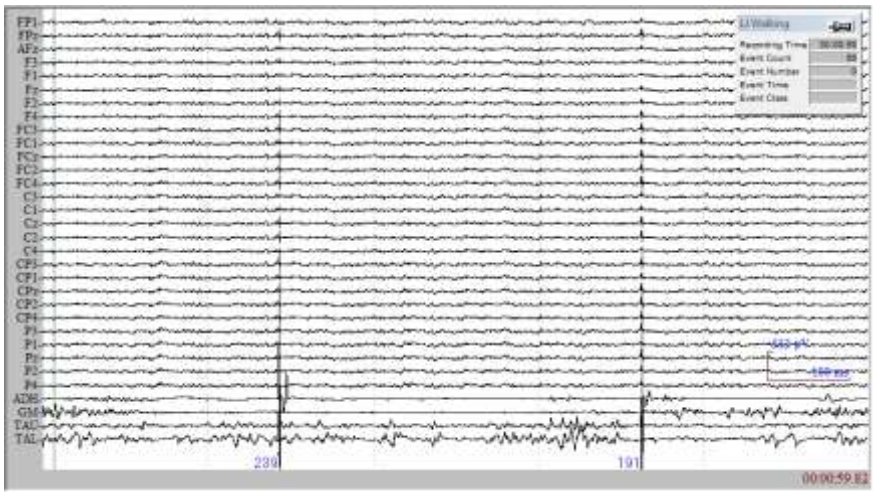


Figure 4-5; EEG with stimulation triggers. Stimulus triggers 239 and 191 are shown which represent toe off and heel strike respectively. By recording the stimulus triggers with the EEG and EMG and waveforms can be epoched from each stimulus type.

The averaged epoch of the stimulated and non stimulated steps for each phase of the gait cycle were then plotted with the sitting SEP waveform overlaid, as shown below

in Figure 4-6. The latency and amplitude of the component peaks were recorded for further analysis using the methods described for the patient study (see chapter 3).

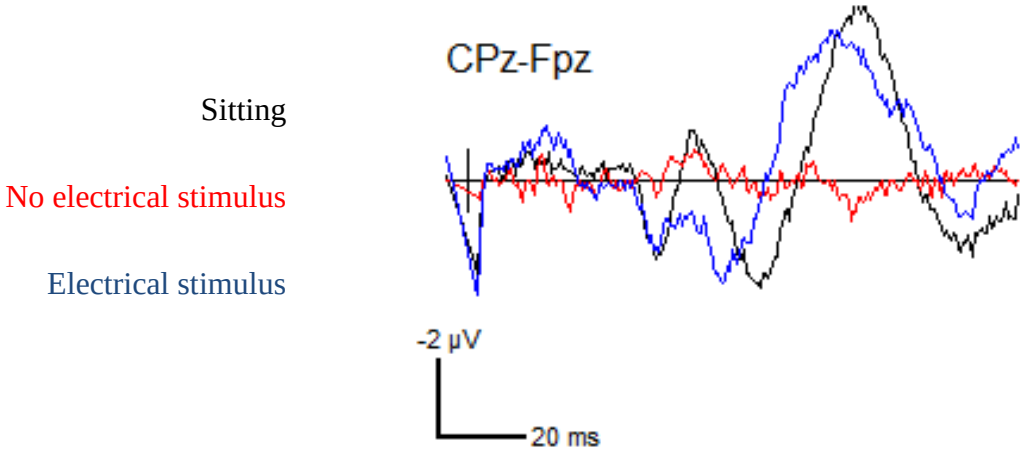


Figure 4-6: Right PT nerve SEP recorded at CPz-FPz in a single subject during sitting, and treadmill walking. The stimulus was applied during the swing phase and shown in the black line.

EMG activity can give a representation of the stimulus intensity applied to a nerve that innervates the muscle. The amplitude of an M-Wave after stimulation is depended upon the intensity of the stimulus. During each posture the EMG activity in the ADH muscle was recorded to monitor the amplitude of the M-wave. The ADH EMG data was epoched and averaged using the methods applied to the treadmill walking EEG data (see above). In each averaged epoch the M-wave was identified (Fig 4-7). The amplitude of the M-wave was recorded for each posture and phase of the gait cycle. The M-wave was presented for each phase of the gait cycle as a percentage of the sitting and standing M-wave.

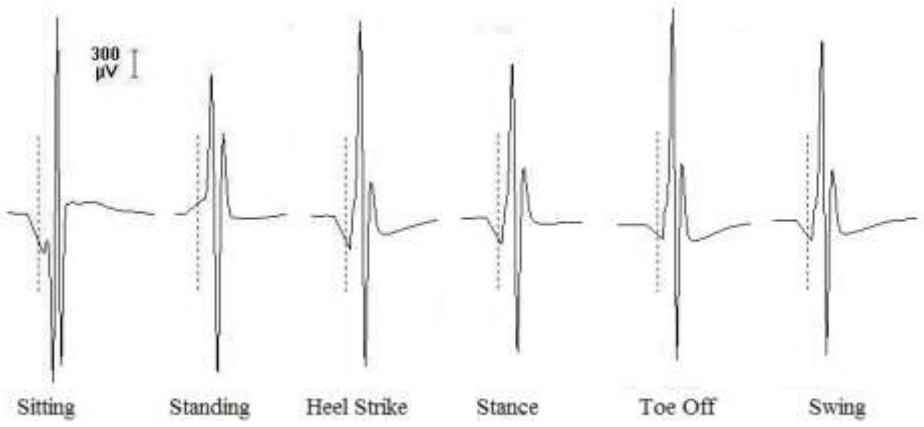


Figure 4-7: Averaged M-Wave for sitting, standing and 4 phases of the gait cycle during treadmill walking after PT nerve stimulation recorded in the Abductor Hallucius muscle.

Averaged rectified EMG waveforms for the GM and TA muscles during the gait cycle were constructed using the heel strike triggers recorded within Spike 6 software controlled by a CED (Fig 4-8). The points within the gait cycle that the stimulus was applied were superimposed to show the phase of the gait cycle and muscle activity at the point of stimulus.

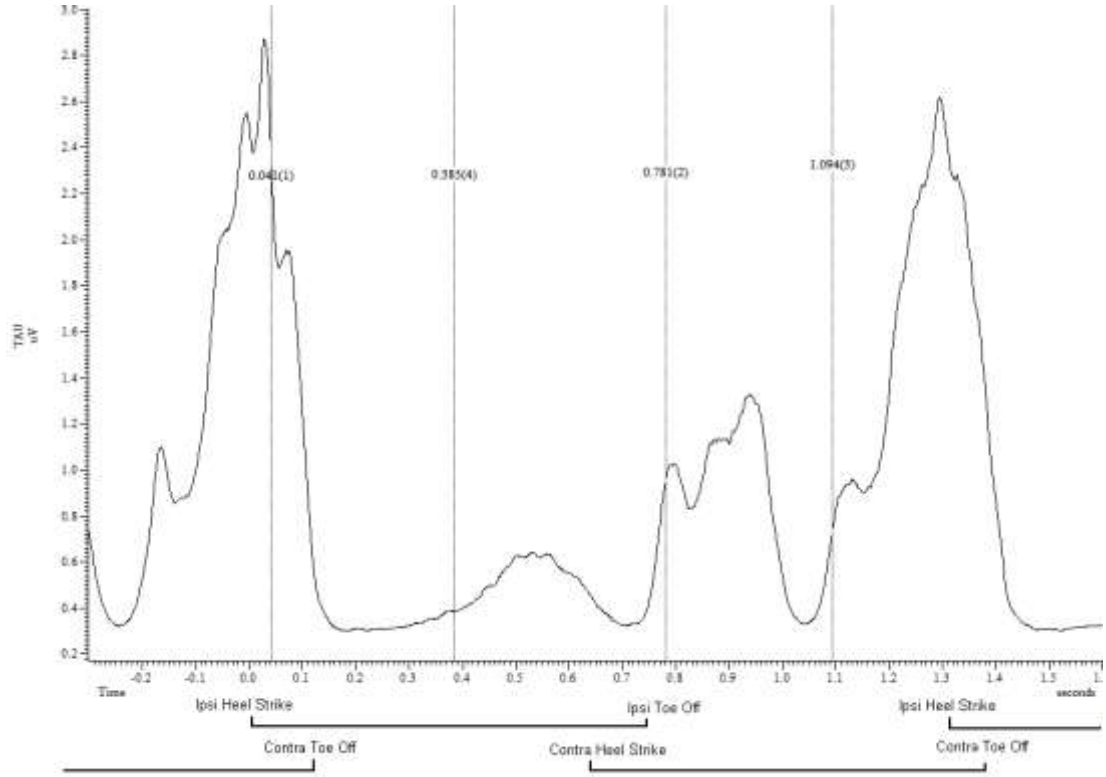


Figure 4-8: Averaged rectified EMG waveform for the right Tibialis Anterior (TA) using the right heel strike as a trigger.

5 RESULTS - ISCI PATIENT STUDY

Within this chapter the results of the 8 week patient trial are presented. Details of the patients that completed the study are shown. The details of the Lokomat training which was completed over the 6 weeks is shown for each patient. Results for the Walking Index for Spinal Cord Injury scale (WISCI II) and the temporal gait analysis are presented to show the improvement in ambulatory capacity of iSCI patients over this period of Lokomat training. The results of the assessments completed before and after 3 and 6 weeks Lokomat training are then presented. A series of case studies are not presented, but results from the patients are selected and used to highlight the positive and negatives points of each of the assessment methods. Correlations between the outcomes of different tests are shown and any predictive value of the test for ambulatory capacity is presented. An overview of these results is presented in (Ellaway et al., 2004).

5.1 PATIENT DETAILS

19 Patients were recruited to the study. 1 patient retired from the study after 3 weeks and was not included in the data analysis. 18 Patients (14 Male and 4 Female) with a mean age of 48.3 (range 26-63) years completed the study.

Table 5-1 shows the demographic details of the patients that completed the study. The patient ID was given to the patient when they were recruited to the study and shows the order in which the patients completed the study. In the table the patients are ordered by the stage of their injury (acute then chronic), AIS grade and neurological level. Further tables within this chapter are ordered in the same manner to highlight any affect that the stage of injury, AIS grade and neurological level has on functional changes after a period of Lokomat training.

Patient ID	Age	Gender	Time post injury (weeks)	Acute / Chronic	AIS Grade	Neurological level
19	31	Female	11	Acute	C	C4
16	42	Female	12	Acute	C	C5
13	57	Female	13	Acute	C	T2
12	42	Male	6	Acute	C	T9
3	61	Male	20	Acute	D	C3
8	59	Male	14	Acute	D	C4
10	30	Male	18	Acute	D	C4
11	63	Male	8	Acute	D	C5
17	57	Male	8	Acute	D	T3
15	44	Male	5	Acute	D	T8
2	49	Male	13	Acute	D	T8
5	48	Female	4	Acute	D	T11
9	58	Male	8	Acute	D	T11
4	30	Male	44	Chronic	C	L1
6	61	Male	26	Chronic	D	C4
1	26	Male	84	Chronic	D	C4
7	59	Male	169	Chronic	D	C4
14	53	Male	110	Chronic	D	C4

Table 5-1: Patient demographic data. Sorted by Acute/Chronic, then ASIA grade and neurological level. A total of 18 patients completed the study.

The patients were split into 2 groups, acute (n=13) and chronic (n=5). The acute group were patients whose injury occurred less than 6 months prior to starting the study and included sub-acute patients. The chronic group had their injury more than 6 months prior to starting the study. The mean time since the injury varied between 10.8 weeks in the acute group to 86.6 weeks in the chronic group.

Of the 13 acute patients 4 were AIS C and 9 AIS D. 6 Acute patients had a lesion at cervical level, and 6 patients had a lesion at thoracic level. Of the 5 chronic patients 1 was AIS C and 4 AIS D. 4 Chronic patients had a lesion at cervical level and 1 patient had a lesion at lumbar level. All patients were considered free from any peripheral neuropathy to the upper or lower limbs.

5.2 LOKOMAT TRAINING

During the study the patients completed Lokomat training as an intervention method for rehabilitation. The patients trained for 1hour per day Monday to Friday for a total of 6 weeks. For each training session the walking speed and duration and amount of Body Weight Support (BWS) provided was noted on the patient training record.

5.2.1 ATTENDANCE OF LOKOMAT TRAINING SESSIONS

The Lokomat training was completed daily but due to illness, national holidays and miscellaneous reasons some sessions were missed by the patients during the six weeks of training. If the patient did not attend a session the reason was noted on the patient training record. A maximum of 30 training sessions were given to each patient. Table 5-2 shows that compliance was good and all patients completed a minimum of 23 sessions (77%). The attendance of the chronic patients (bottom five rows) was high despite the need for daily travel to complete training. Only one session was missed by a chronic patient (P4) due to ill health. The acute patients missed a larger number of sessions due to ill health which was expected as their condition was more unstable compared to the chronic patients.

To complete the Lokomat training the chronic patients were required to commute daily from their residence within the greater Glasgow area to the QENSIU. Table 5-2 shows that only 2 sessions were missed by chronic patients due to miscellaneous reasons and demonstrates both their ability to withstand the intense training regime and their commitment to the Lokomat training.

Patient ID	Acute / Chronic	Time post injury (weeks)	Attended sessions	Unwell	Bank holiday	Misc
19	Acute	11	25	5		
16	Acute	12	28		1	1
13	Acute	13	27		3	
12	Acute	6	25	3	2	
3	Acute	20	26		4	
8	Acute	14	27		3	
10	Acute	18	27	1		2
11	Acute	8	26	4		
17	Acute	8	28	1		1
15	Acute	5	25	3	2	
2	Acute	13	28	2		
5	Acute	4	23	7		
9	Acute	8	26	3	1	
4	Chronic	44	26	1	2	1
6	Chronic	26	28		2	
1	Chronic	84	30			
7	Chronic	169	27		3	
14	Chronic	110	27		2	1

Table 5-2: Lokomat sessions attended by iSCI patients. No sessions were missed due to non compliance.

Although there is some variation in the number of Lokomat sessions completed by the patients the assessments shown in Table 5-3 were completed after 3 and 6 calendar weeks. The results of these assessments are presented later in this chapter.

Assessment	3 Weeks Training	6 Weeks Training
ASIA		✓
WISCI II		✓
Temporal Gait analysis	✓	✓
Quantitative Sensory Testing	✓	✓
Somatosensory Evoked Potential	✓	✓

Table 5-3: Patient assessments completed after 3 and 6 weeks of Lokomat training.

5.2.2 BODY WEIGHT SUPPORT DURING LOKOMAT TRAINING

Body weight support (BWS) was provided by a harness worn by the patient during the Lokomat training sessions. This enabled the patients who were not able to weight bear to receive gait training. All patients wore the harness during the training

session. The amount of BWS provided to the patient was noted at the start of each training session on the patient training record. The BWS was reduced during the 6 weeks to ensure the patient training was progressive (See Table 5-4).

Patient ID	Initial Body weight (Kg)	Body Weigh Support (% of body weight)		
		Baseline	3 Weeks Training	6 Weeks Training
19	60	88	78	65
16	66	86	77	83
13	66	77	76	64
12	65	82	65	46
3	64	80	67	41
8	78	77	29	9
10	72	83	67	57
11	105	76	67	50
17	72	75	58	44
15	70	54	34	18
2	61	85	39	34
5	53	67	34	19
9	93	84	70	39
4	99	81	71	56
6	75	87	73	53
1	68	82	40	7
7	87	54	48	46
14	70	71	40	23

Table 5-4: Amount of BWS provided prior and after 6 weeks of Lokomat Training for each patient.

The rate in which the BWS was reduced was different across the patients. The BWS was reduced in the following session if during the preceding session they were able to walk for 1 hour without knee buckling during stance phase. A maximum reduction of 3Kgs was provided in any one training session. Table 5-4 shows the initial body weight (Kg) of each patient and the percentage of BWS given at baseline and after 3 and 6 weeks of Lokomat training. The greatest % of BWS at baseline was 88% (P19) and least was 54% (P15). The table shows how all patients reduced the percentage of BWS over the 6 weeks of training. The rate of change in BWS over the 6 weeks can be seen for each patient in Figure 5-1.

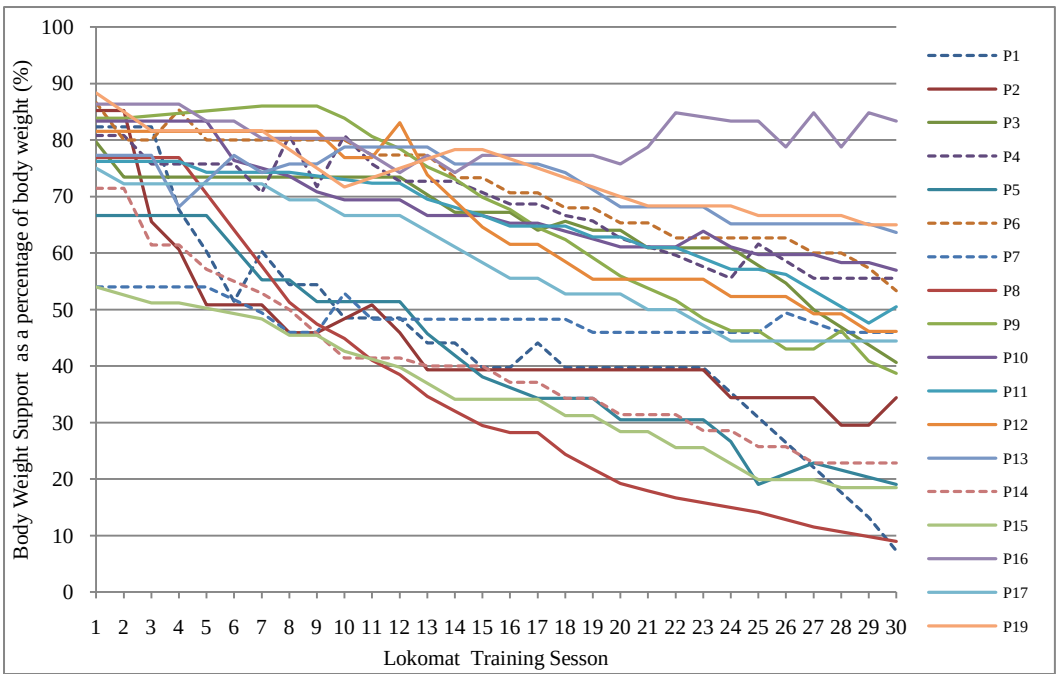


Figure 5-1: Percentage of initial body weight unloaded (BWS) for each subject during each Lokomat training session. --- *show chronic iSCI patient.*

Figure 5-1 shows that the amount of BWS given to each patient during the Lokomat sessions. The first sessions for each patient show no change in BWS as the amount of BWS was not reduced until the patient was able to walk for 1 hour at $2kmh^{-1}$. The amount of BWS was reduced earlier in the chronic patients which may be due to an increased stamina which they developed over time since their injury. All patients show a reduction in their BWS but a large spread (7 - 83%) in the % of BWS provided at the end of the 6 weeks Lokomat training is seen. In P16, BWS was reduced by only 3% (86-83%) over the 6 week period. Reductions in BWS during session 12 and 14 were not sustained (74%) and later sessions required higher levels of BWS. This was due to increased spasticity in the lower limbs that made weight bearing uncomfortable. This Patient did not recovery any over ground walking function.

BWS for P7 reduced by 8% (54-46%) over the 6 week period. P7 is a chronic patient who had functional ambulatory capacity prior to the start of the study. The patient did not want to reduce the BWS as he felt that he became tired over the training period. No changes in ambulatory capacity, as assessed by the WISCI II scale and gait analysis were observed in this patient.

5.3 ASSESSMENT OF AMBULATORY CAPACITY

5.3.1 AMBULATORY CAPACITY ASSESSED BY WISCI II SCALE

The WISCI II scale grades the impairment in walking ability in SCI patients. The ordinal scale is from 0 to 20, where 0 is defined as non walking and 20 as walking unaided. The scale has both floor and ceiling effects. Table 5-5 shows the results of the WISCI II assessment taken at baseline and after 6 weeks of Lokomat training.

Patient ID	WISCI II					Neuro-logical level
	Baseline		6 Weeks Lokomat Training		Change	
19	3	Parallel bars, Braces, 1 Person	12	Two crutches, Braces	9	C4
16	0	Not Walking	5	Parallel bars, Braces	5	C5
13	0	Not Walking	0	Not Walking	0	T2
12	0	Not Walking	12	Two crutches, Braces	12	T9
3	16	Two crutches	16	Two crutches	0	C3
8	8	Walker, 1 Person	20	Walking unaided	12	C4
10	0	Not Walking	0	Not Walking	0	C4
11	0	Not Walking	13	Walker	13	C5
17	0	Not Walking	0	Not Walking	0	T3
15	0	Not Walking	19	One crutch	19	T8
2	0	Not Walking	4	Parallel bars, 1 Person	4	T8
5	8	Walker, 1 Person	12	Two crutches, Braces	4	T11
9	4	Parallel bars, 1 Person	20	Walking unaided	16	T11
4	12	Two crutches, Braces	12	Two crutches, Braces	0	L1
6	8	Walker, 1 Person	11	Two crutches, 1 Person	3	C4
1	16	Two crutches	19	One crutch	3	C4
7	16	Two crutches	16	Two crutches	0	C4
14	12	Two crutches, Braces	16	Two crutches,	4	C4

Table 5-5: WISCI II scores prior and post Lokomat training in iSCI patients.

A non parametric Wilcoxon's signed rank test was conducted to identify if there was a significant change in the WISCI II scores after 6 weeks Lokomat training in the acute and chronic iSCI patients. A significant ($p<.01$) difference in the WISCI II scores after 6 weeks Lokomat training was seen in the acute group. No significant ($p<.05$) changes were seen in the WISCI II scale in the chronic iSCI patient group.

The fourth column of table 5-5 shows the change in WISCI II scale from baseline to the assessment completed after 6 weeks Lokomat training. At the baseline measurement eight acute patients were graded 0 (zero) which is the bottom of the scale and designates them as not walking. 3 of these patients remained graded at 0 (zero) after 6 weeks Lokomat training. This is either due to no change in function or a sensitivity limitation of the scale. When a patient is scored 0 (zero) by the WISCI II scale it is known that the patient is unable to walk. It does not give any detail on their ability to stand. P10 was not able to stand following six weeks Lokomat training. P13 was able to complete sit to stand exercises however increased tone in her lower limbs made it difficult for her to walk in the parallel bars. P17 was able to complete sit to stand exercises and was about to progress to over ground walking therapy as he was able to complete a number of steps in the parallel bars. P16 is shown to improve from 0-5 on the WISI II scale, however this was a maximal effort by the patient that required both legs to be fixed into braces and the patient using their arms and trunk to create locomotion. This was not done routinely in their rehabilitation sessions and was not a preferred method of mobility for the patient, who remained wheelchair bound.

2 acute patients were graded 20 after 6 weeks Lokomat training which designates them as walking unaided. This is the ceiling of the test and no further knowledge is known about their ability to walk unaided for more than 10m or how physically demanding the task is for each patient.

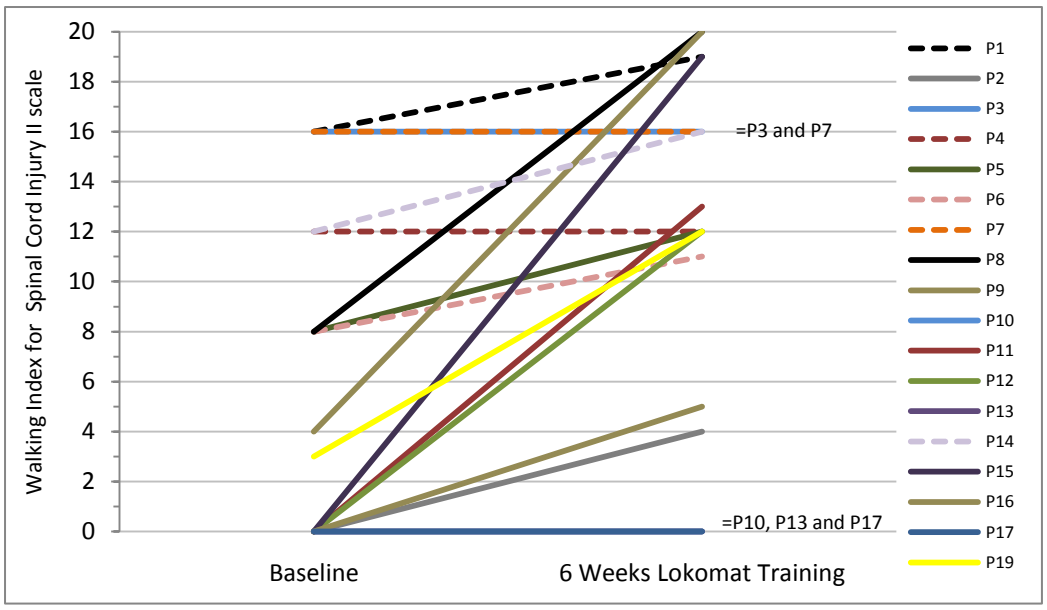


Figure 5-2: WISCI II scores from baseline and after 6 weeks of lokomat training in iSCI patients. *Key: --- show chronic iSCI patient.*

Figure 5-2 above shows the WISCI II scale results graphically. It can be seen from the table 5-5 and figure 5-2 that six patients; four acute (P3,10, 13 and 17) and two chronic (P4 and 7) did not show any improvement in their WISCI II score after 6 weeks of Lokomat training. The other three chronic patients (P1, 6 and 14) showed a small improvement in their WISCI II score increasing by 3 (P1 and 6) or 4 scale points (P14). The amount of improvement in WISCI II scale in the nine acute patients varied from 4 to 19 points on the scale.

The three patients who did not achieve ambulatory capacity at the end of the study (P10, P13 and P17) were all acute tetraplegic iSCI patients (C4, T2, T3). All chronic iSCI patients were ambulatory prior to the start of the study. Of the other eight tetraplegic patients, one (P16) recovered therapeutic ambulatory capacity and seven (P1, 3, 6, 7, 8, 14 and 19) recovered functional walking. All six paraplegic iSCI patients achieved ambulatory capacity. One (P2) recovered therapeutic ambulatory capacity and five (P4, 5, 9, 12 and 15) recovered functional walking.

To present the changes in the WISCI II score in the patient groups; acute and chronic, box plots were drawn (Fig 5-3). The plots show the minimum and

maximum values (at the end of the bar), the lower and upper quartile (top and bottom of the box) and the median WISCI II value (the centre line in the box).

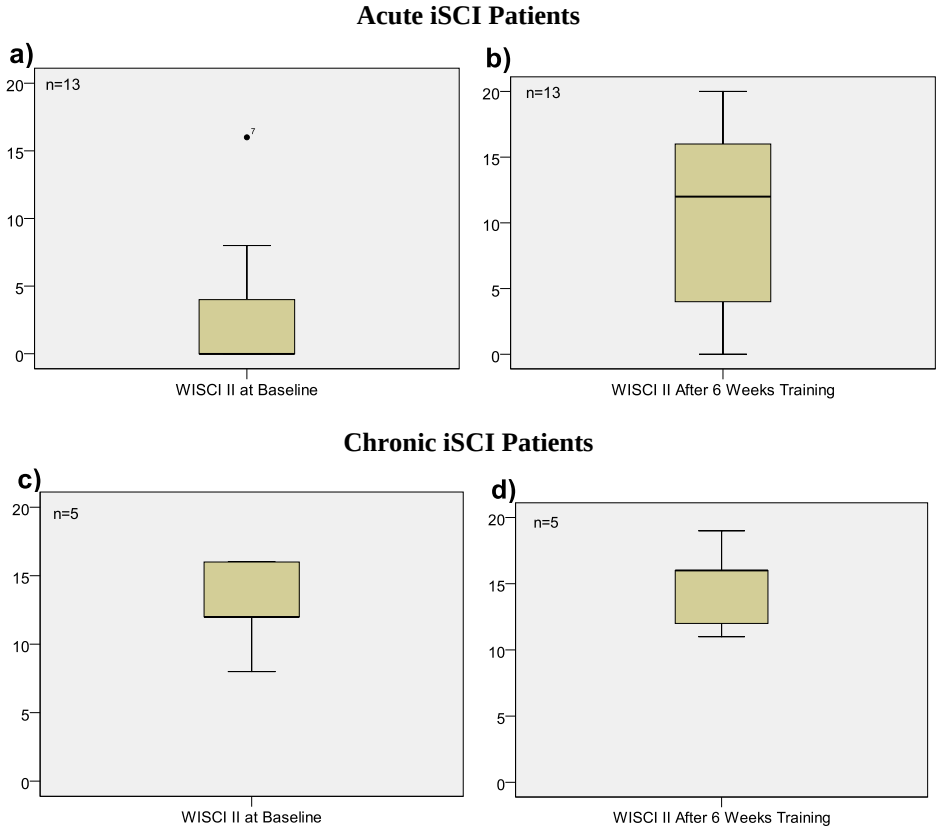


Figure 5-3: Box Plots of WISCI II scale pre and post Lokomat training in acute and chronic iSCI patients. Improvements are seen in the acute group, however the plot shows how not all patients improved. The chronic patients improved very little after the training.

In the chronic patients (Fig 5-3 c and d) it can be seen that there is little change in the median value or spread of the WISCI II score after the Lokomat training. At baseline the acute patient group (Fig 5-3 a) show a floor effect in the WISCI II scale with 8 (62%) patients scoring 0 (zero). After 6 weeks of Lokomat training the acute patients (Fig 5-3 b) show a large spread across the WISCI II score scale. This result suggests that not all patients show an improvement and it appears that acute patients benefit from Lokomat training by a greater amount when assessed by the WISCI II scale. This would imply that time since injury may be an important factor in the prescription of Lokomat training.

5.3.2 AMBULATORY CAPACITY ASSESSED BY TEMPORAL GAIT ANALYSIS

A 10m walk with instrumented insoles was completed to assess walking speed, double support time, stride length and cadence of the patients at baseline and after 3 and 6 weeks of Lokomat training. 10 iSCI patients; 6 acute and 4 chronic completed the 10m walk test (Table 5-6).

Patient ID	Age	Gender	Time Post Injury (weeks)	Acute / Chronic	AIS Grade	Neurological level
3	61	Male	20	Acute	D	C3
8	59	Male	14	Acute	D	C4
11	63	Male	8	Acute	D	C5
15	44	Male	5	Acute	D	T8
5	48	Female	4	Acute	D	T11
9	58	Male	8	Acute	D	T11
1	26	Male	84	Chronic	D	C4
6	61	Male	26	Chronic	D	C4
7	59	Male	169	Chronic	D	C4
14	53	Male	110	Chronic	D	C4

Table 5-6: Demographics of iSCI patients that completed temporal gait analysis.

9 Patients did not complete the 10m walk test as they were unable to walk for 10m outside of parallel bars without using braces. Braces were not allowed to be used during the test to ensure that the orthosis did not affect the walking ability of the patient. Walkers, crutches or sticks were permitted to be used when necessary as they did not change the function of the lower limb. P14 completed the temporal gait analysis, although by the WISCI II scale the patient required braces. This patient was able to walk 10m without the brace and so could complete the test, but preferred to wear it during normal walking and was therefore scored appropriately on the WISCI II scale.

The temporal gait parameter data for the patients was grouped into acute and chronic patient data sets. The result of the group temporal gait analysis is shown graphically in Figure 5-4. The figure shows the percentage change observed in the walking speed, double support time, stride length and cadence after 3 and 6 weeks of

Lokomat training from baseline measures. An improvement in temporal gait parameters is seen by an increase in speed, stride length and cadence and a reduction in double support time. An increase in the gait parameters is shown by an upward bar and a decrease by a downward bar.

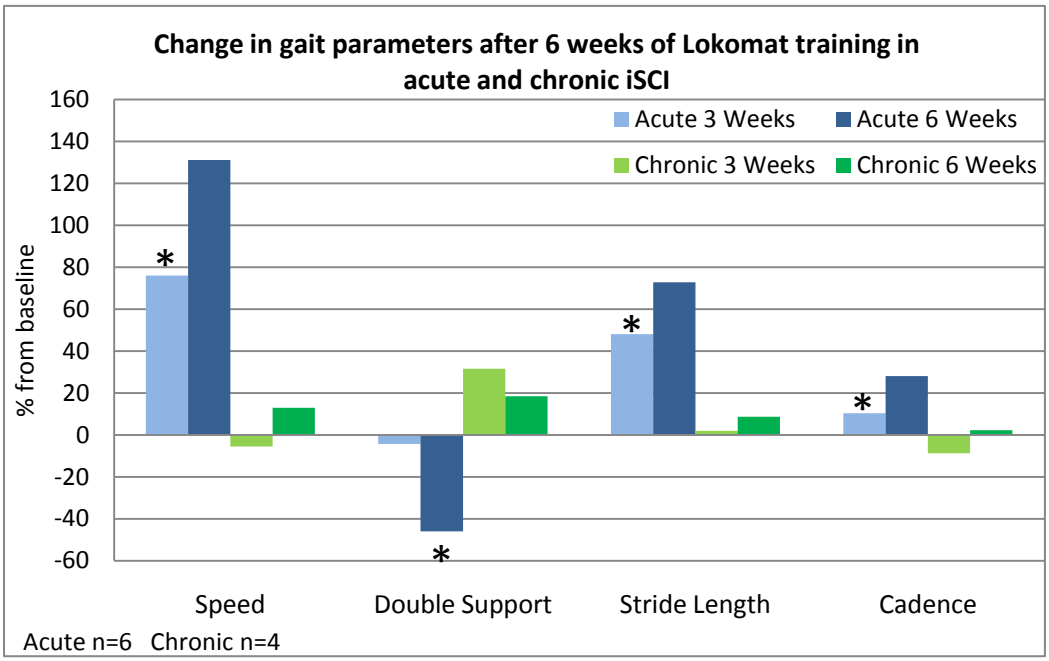


Figure 5-4: The change in gait parameters after 6 weeks of Lokomat training in acute and chronic iSCI patients. Improvement is seen in all categories for the acute patients. In the chronic patients the speed, stride length and cadence showed very little change from baseline. Significant difference between baseline to 3weeks and to 6 weeks training are shown by *. No significant changes between 3 weeks and 6 weeks of Lokomat training were observed in either group.

In Figure 5-4 significant changes (highlighted by the *) are shown between the group temporal gait analysis from baseline to 3 weeks after Lokomat training and from 3 weeks Lokomat training to 6 weeks Lokomat training. Significant changes (using a Post hoc pair-wise T-test) were seen in the walking speed (p=.017), stride length (p=.015) and cadence (p=.014) after 3 weeks of Lokomat training in the acute patients (in light blue). Further improvement in the temporal gait parameters were seen between the 3 and 6 week assessment points in the acute patients (dark blue). However no significant changes were seen between the 3 and 6 week assessments, which suggest that a larger amount of improvement in temporal parameters was seen during the first 3 weeks of Lokomat training in acute iSCI. This may have an implication on the advised dosage of Lokomat training for acute iSCI patients.

The duration of double support was significantly different (p=.006) after 6 weeks of Lokomat training in the acute iSCI patients. This suggests either additional rehabilitation time is required to regain balance and therefore reduce the double support time. Or the Lokomat does not train the patient in balance and balance training is completed later through self initiated over ground walking once adequate weight bearing can be achieved.

The chronic iSCI patient group, shown in green in Figure 5-4 shows smaller changes in the temporal gait parameters assessed after 3 and 6 weeks of Lokomat training. The double support time increased after 3 weeks of Lokomat training. After 6 weeks of training the double support time had decreased, but still remained longer than at baseline. This increase may be due to the chronic patients using different compensation methods. The WISCI II scale recorded for the chronic patients shows a reduction in walking aids needed to complete the 10m walk. Patients went from; a walker to two crutches (P5), 2 crutches to 1 crutch (P1) and braces to no braces (P14). The change in the walking aids used by these patients may have initially caused the patient to be less stable. This may have increased their double support time to enable them to become stable before shifting their body weight. As their stability improved with practice the double support time was then also reduced.

From the WISCI II and temporal gait analysis assessments it can be seen that functional changes occurred in the acute iSCI group after 6 weeks of Lokomat training. The amount of improvement observed varied across the patients. In table 5-7 the amount of improvement for each subject after 6 weeks of Lokomat training was determined subjectively from the change in WISCI II score and their temporal gait analysis data. Example data from 3 patients is presented below to highlight issues from these tests in indentifying the main outcome measure of ambulatory capacity in the assessment of iSCI patients.

Change in Ambulatory Capacity	Patient ID	
	Acute	Chronic
Large Improvement (with Braces)	8, 9, 11, 15, (12, 19)	
Improvement (with Braces)	3, 5, (2, 16)	1, 6, 14
No Improvement (with Braces)	10, 13, 17	7, (4)

Table 5-7: Changes in ambulatory capacity determined by the WISCI II scale and gait analysis.

Figure 5-5 shows the results of the temporal gait analysis from the foot switch system in a single acute patient (P9). No data is shown for baseline measurement as the patient was unable to walk at this point in the study. A large increase in all temporal parameters is seen after 3 weeks of Lokomat training from a zero baseline. Further improvements are seen between the 3 and 6 week assessments. The gait analysis data complements the WISCI II score which improved by 16 points for this patient (see table 5-5 P9).

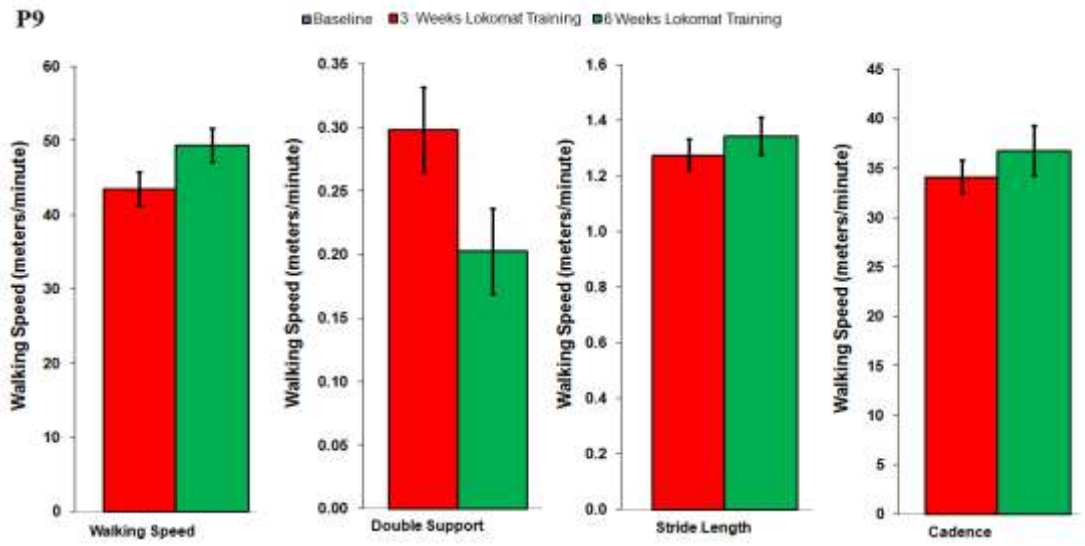


Figure 5-5: Example of a large improvement in gait parameters measured after 3 and 6 weeks Lokomat training in a single iSCI patient (P9). No baseline measure are shown as patient was non ambulatory at start of the trial.

For 2 patients, showing improvement (P3 and P6) the WISCI II scores and gait analysis initially seemed to be contradictory. For P3 the WISCI II scale showed no improvement with the score staying at 16 (two crutches, no braces and no assistance) following 6 weeks of Lokomat training. However improvement in gait was seen in the foot switch analysis (Figure 5-6). Improvement in all parameters tested is evident. For this patient to improve their WISCI II score they would need to change

from using 2 crutches without help to using 1 crutch with or without help. This patient was not able to walk with one crutch and no help but could walk with 1 crutch and 1 person to help. For the patient independent walking was of greater importance than walking with a single crutch and therefore they remained using 2 crutches. This shows how the gait analysis can complement the WISCI II score especially at the top end of the scale.

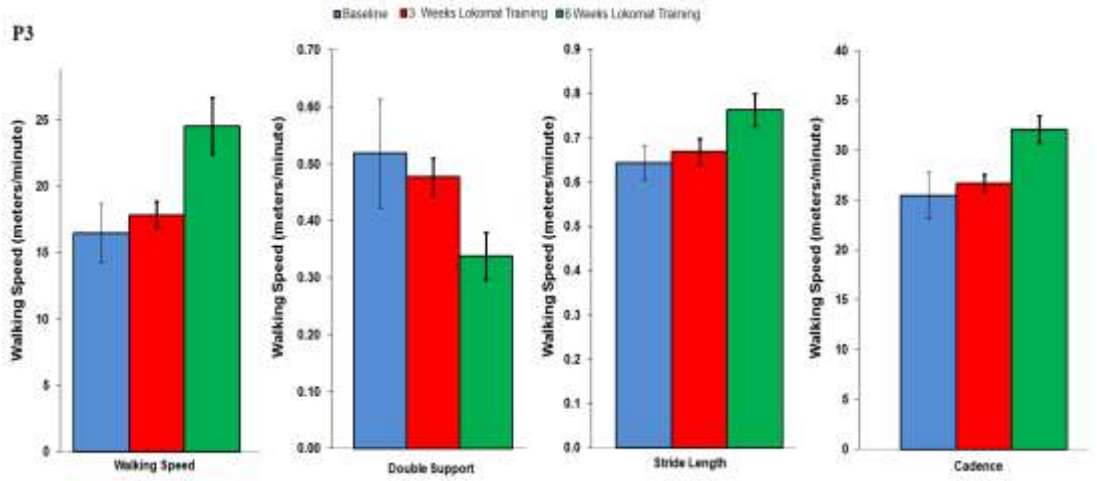


Figure 5-6: Example of a small improvement in gait parameters measured after 3 and 6 weeks Lokomat training in a single iSCI patient (P3). In this patient the WISCI II did not change from baseline to that taken at 3 or 6 Lokomat training.

For P6 the WISCI II score improved by 3 points (8 to 11) however the initial temporal gait analysis shows a decrease in ambulatory capacity (Fig 5-7). The WISCI II score was improved by 3 points by changing from a walker to double crutches. The temporal gait analysis (Fig 5-7) shows a decrease in speed, and cadence as well as an increase in double support time. It is logical that the patient has reduced his walking speed to compensate for the reduction of stability provided by the crutches compared to the walker. During the period from 3 to 6 weeks of Lokomat training the gait parameters tested improved this may indicate an improvement in the patient's ability to walk with the double crutches. This has shown how the temporal gait parameters changed in conjunction with the change of the walking device used.

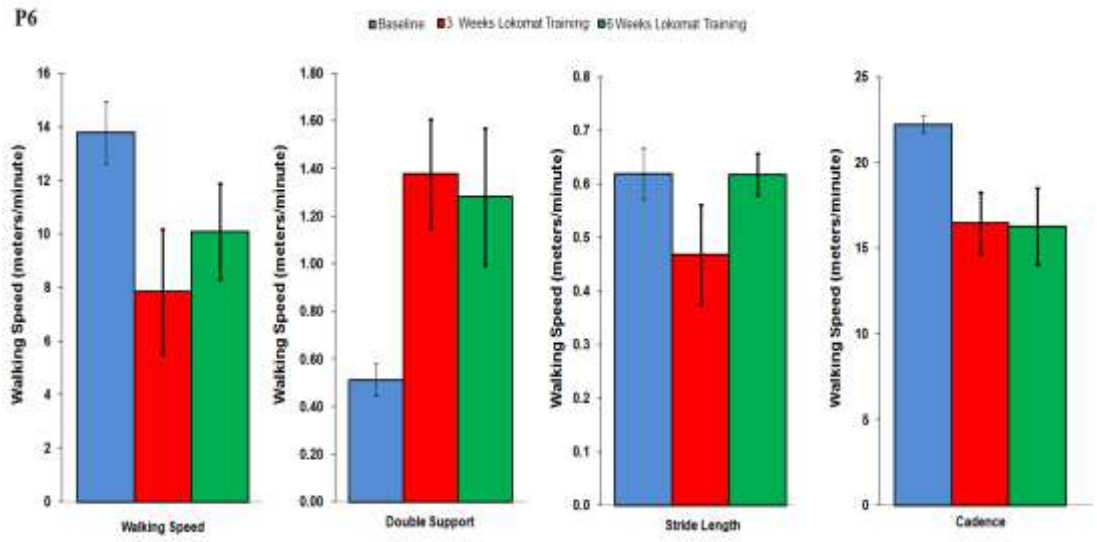


Figure 5-7: Change in temporal gait parameters. Decrease in stability after 3 weeks and improvement after 6 weeks. P6 foot switch data.

The patients that used braces (identified in table 5-7) to enable them to walk were excluded from temporal gait analysis. Their improvement in WISCI II score (Table 5-5) may have been gained by methods of compensation rather than neural plasticity or neural repair. For P2 and P6 they were able to walk in parallel bars with help and without help respectively after 6 weeks of Lokomat training compared to no ambulatory ability at baseline. If these changes had been purely compensatory (i.e using their arms to weight bear and their truck to swing the legs through), no changes in the ASIA or electrophysiology tests are expected. P2 showed small improvements in the ASIA light touch and pin prick scores (see Table 5-9) and EPT. P16 showed no improvement in the ASIA light touch and pin prick scores or EPT and VPT. An improvement in the morphology and latency of the early cortical component of the PT nerve SEP (Left side) was observed in P16.

P12 and P19 showed a large amount of improvement in the WISCI II scale from 0-12 and 3-12 respectively (see Table 5-5). An improvement in the ASIA light touch and pin prick scores was seen in both patients (Table 5-7) however no change in the EPT, VPT or PT nerve SEP was observed.

The changes in the ASIA and electrophysiological assessments may provide detail into how these patients have improved, however video and biomechanical analysis of

their walking within the parallel bars, or with crutches may provide further information as to which mechanisms have lead to this improvement.

For patients that were able to complete both the WISCI II scale and temporal gait analysis changes in ambulatory capacity were seen in acute and chronic iSCI patients. Figure 5-8 and 5-9 show the change in WISCI II score from the time of injury for acute and chronic patients respectively. The degree of change in ambulatory capacity as assessed by the WISCI II is larger in acute iSCI patients compared to chronic iSCI patients. However some acute patients did not show any functional change in their ambulatory capacity using these assessment measures.

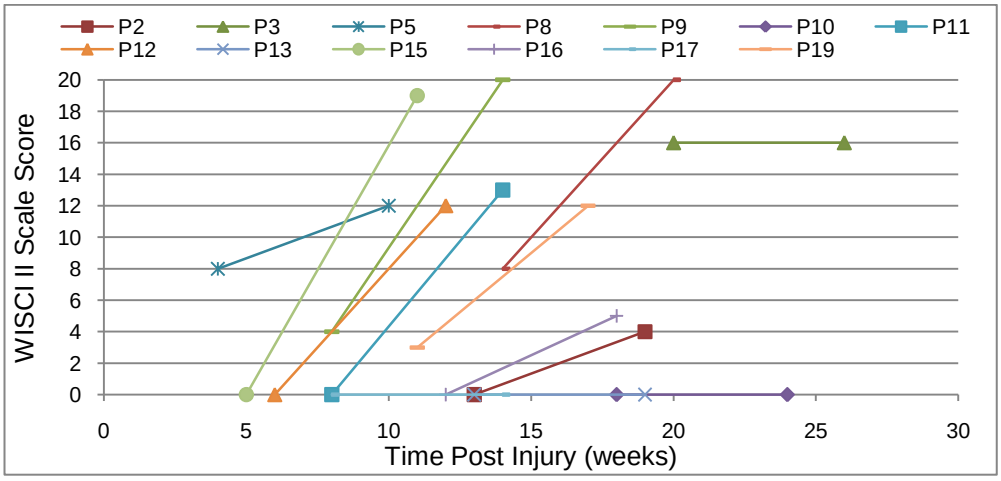


Figure 5-8: Changes in WISCI II scale score in acute iSCI from the time of injury. Assessments completed at baseline and week 6 of Lokomat training are shown.

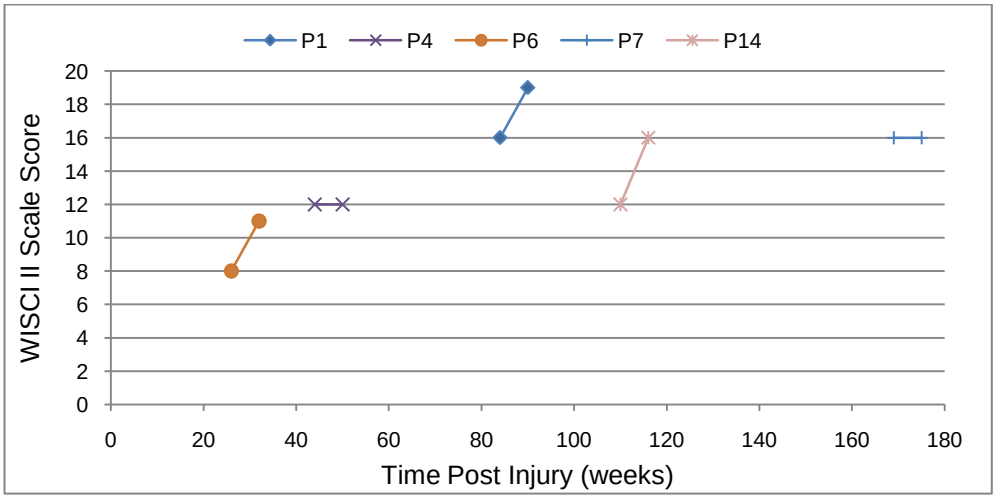


Figure 5-9: Changes in WISCI II scale score in chronic iSCI from the time of injury. Assessments completed at baseline and week 6 of Lokomat training are shown.

Having identified the patients that showed improvement (without the use of braces) over the 6 weeks of Lokomat training we now turn to the neurological tests to establish if this improvement can be identified in the function of their sensory pathways, and if these tests may have a predictive value of ambulatory function.

In the following sections sample data from each of the patient's assessments is used to highlight the issues of sensitivity, repeatability and reliability identified during this study with each of the assessment methods.

5.4 ASIA SCORES

The American Spinal Injury Association (ASIA) standard for neurological classification was completed at baseline and after 6 weeks of Lokomat training. Table 5-8 and 5-9 show the results of the upper and lower limb ASIA examinations respectively. Improvements are shown in red.

Patient	Acute / Chronic	Baseline								6 weeks Lokomat Training							
		ASIA Grade	Neurological level	Motor		Sensory				ASIA Grade	Neurological level	Motor		Sensory			
						Light Touch		Pin Prick						Light Touch		Pin Prick	
				Left (25)	Right (25)	Left (36)	Right (36)	Left (36)	Right (36)			Left (25)	Right (25)	Left (36)	Right (36)	Left (36)	Right (36)
19	A	C	C4	16	19	30 (30)	30 (30)	13 (30)	19 (30)	D	C5	19	22	30 (30)	30 (30)	29 (30)	30 (30)
16	A	C	C5	17	17	22 (30)	23 (30)	18 (30)	19 (30)	C	C5	21	20	24 (30)	23 (30)	17 (30)	20 (30)
13	A	C	T2	25	25	27 (30)	29 (30)	19 (30)	28 (30)	D	T3	25	25	29 (30)	29 (30)	22 (30)	28 (30)
12	A	C	T9	25	25	33	34	31	32	D	T9	25	25	34	34	33	33
3	A	D	C3	19	17	24	27	18	21	D	C3	22	22	28	29	19	26
8	A	D	C4	12	10	33	33	13	30	D	C4	16	13	31	29	19	27
10	A	D	C4	19	13	26	28	13	21	D	C4	20	12	26	27	14	23
11	A	D	C5	20	19	36	36	19	19	D	C5	20	25	36	36	26	18
17	A	D	T3	25	25	27	29	28	28	D	T4	25	25	28	28	28	28
15	A	D	T8	25	25	35	34	36	33	D	T8	25	25	36	35	36	32
2	A	D	T8	25	25	36	36	35	30	D	T9	25	25	36	36	36	33
5	A	D	T11	25	25	36	35	36	35	D	T11	25	25	36	35	35	35
9	A	D	T11	25	25	36	36	36	35	D	T12	25	25	36	36	36	36
4	C	C	L1	25	25	36	35	36	35	C	L1	25	25	36	35	36	36
6	C	D	C4	18	17	35	32	24	24	D	C5	21	19	31	32	28	32
1	C	D	C4	22	17	30	29	20	26	D	C5	17	24	22	29	23	27
7	C	D	C4	15	17	26	24	17	15	D	C4	16	20	32	27	17	20
14	C	D	C4	20	19	34	31	35	35	D	C5	21	21	35	36	34	34

Table 5-8: Upper Limb ASIA scores at baseline and after 6 weeks of Lokomat training. Improvements are shown in red.

Patient	Acute/ Chronic	Baseline								6 weeks Lokomat Training							
		ASIA Grade	Neurological level	Motor		Sensory				ASIA Grade	Neurological level	Motor		Sensory			
						Light Touch		Pin Prick						Light Touch		Pin Prick	
				Left (25)	Right (25)	Left (14)	Right (14)	Left (14)	Right (14)			Left (25)	Right (25)	Left (14)	Right (14)	Left (14)	Right (14)
19	A	C	C4	6	10	4	11	1	1	D	C5	8	13	8	13	6	4
16	A	C	C5	9	9	12	9	6	6	C	C5	15	14	7	10	4	6
13	A	C	T2	14	2	14	11	0	10	D	T3	16	4	14	13	0	9
12	A	C	T9	2	6	7	7	0	1	D	T9	4	19	14	7	6	4
3	A	D	C3	14	23	11	10	1	4	D	C3	18	23	13	13	0	9
8	A	D	C4	21	19	14	11	1	5	D	C4	25	20	13	13	0	6
10	A	D	C4	10	9	9	9	0	1	D	C4	13	11	8	8	0	0
11	A	D	C5	12	18	12	12	9	3	D	C5	19	23	14	14	11	3
17	A	D	T3	10	15	7	7	5	2	D	T4	13	18	7	7	5	4
15	A	D	T8	14	13	11	9	3	5	D	T8	21	19	11	12	9	3
2	A	D	T8	14	14	8	3	6	0	D	T9	18	18	9	3	11	1
5	A	D	T11	21	18	8	4	3	2	D	T11	22	21	7	5	3	3
9	A	D	T11	16	19	7	7	3	4	D	T12	24	21	8	7	5	3
4	C	C	L1	6	7	11	12	8	6	C	L1	7	8	11	13	7	10
6	C	D	C4	19	16	11	11	5	7	D	C5	23	20	11	10	10	11
1	C	D	C4	24	20	0	5	0	7	D	C5	25	23	0	5	0	7
7	C	D	C4	17	20	7	7	0	0	D	C4	16	20	7	9	1	0
14	C	D	C4	16	20	6	7	7	7	D	C5	20	21	7	7	6	8

Table 5-9: Lower limb ASIA scores at baseline and after 6 weeks of Lokomat training. Improvements are shown in red.

The first parameter of the AISA assessment is the neurological level of lesion. In eight iSCI patients (5 acute, 3 chronic) the neurological level of lesion improved by one spinal level (Table 5-8). For each of the chronic patients the level improved from C4 to C5. This improvement in the chronic patients was unexpected as it is assumed that a chronic patient will have a stable level of neurological lesion. In the acute patients changes in the level of lesion were seen from as high as C4 down to T11. Of the 8 patients 2 did not improve ambulatory capacity (P13, P17). These patients improved from T2 to T3 and T3 to T4. However 4 of the patients that improved ambulatory capacity went from C4 to C5.

The second parameter of the AISA assessment is the ASIA Impairment Scale (AIS). In three acute patients the AIS grade improved from a grade C (more than half of the key muscles below the neurological level have a muscle grade less than 3) to a grade D (more than half of the key muscles below the neurological level have a muscle grade of 3 or more) 2 of these patients (P19 and P12) showed large improvement in ambulatory capacity. The other, P13 showed no improvement. None of the chronic iSCI patients showed a change in the AIS grade after the 6 weeks of Lokomat training.

The neurological level and AIS grade is determined from a set of tests that includes the results of the motor and sensory investigations. The motor and sensory tests are completed on both the upper and lower limbs. The upper limb motor score is determined by muscle groups innervated from C5 to T1. The upper limb motor function is not assessed between T2-T12 using the AISA motor test. This is due to difficulty in assessing the thoracic area for motor control. Therefore the paraplegic patients (lesion at or below T4; P12, 15, 2, 5, 9 and 4) all had maximum score of 25 for upper limb motor function although they may have some motor impairment in the upper limbs. For this reason the analysis of the upper limb motor score included only the tetraplegic patients (n=11). The level of change in the sensory (light touch and pin prick) and motor scores that is clinically relevant has not been determined in the literature. However in a reliability study (Savic et al., 2007) it was shown in 95% of repeat tests the light touch score would differ by less than 4 points and less than 8

points in the pin prick score for the whole body. 5 patients (P19, P12, P3 P11 and P6) show a change greater or equal to 8 points on one side of the body during the pin prick test and 8 patients (P19, P12, P3, P15, P6, P1 P7 and P14) show a change greater to or equal to 4 points on one side of the body during the light touch test. Although this level of change is more likely to reflect physiological changes it remains unclear if this level of changes provides a clinically significant change to the patients. The scores in patients that show changes less than these values may reflect the sensitivity and reliability errors in the test.

Figure 5-10 shows an improvement trend in the tetraplegic iSCI patients' upper limb motor score after 6 weeks of Lokomat training. Improvement in the upper limb motor score was seen in all patients that did not start at the ceiling of the test (P17) (Table 5-8 and Fig 5-10). The change observed in the upper limb motor function was similar in both acute (solid lines Fig 5-10) and chronic (dashed lines Fig 5-10) iSCI patients. In the acute patients natural recovery processes may have influenced this recovery. Rehabilitation may have also influenced recovery in both sets of patients. The acute patients completed hand function rehabilitation with their occupational therapists as part of their conventional rehabilitation and although the chronic patients did not complete any formal upper limb rehabilitation, exercises at home were not restricted.

Of the patients that showed the largest improvement in ambulatory capacity (see Table 5-7) only P8 and P11 are tetraplegic patients and included in Fig 5-10. P8 showed large improvements on both sides and P11 improvement on the right side.

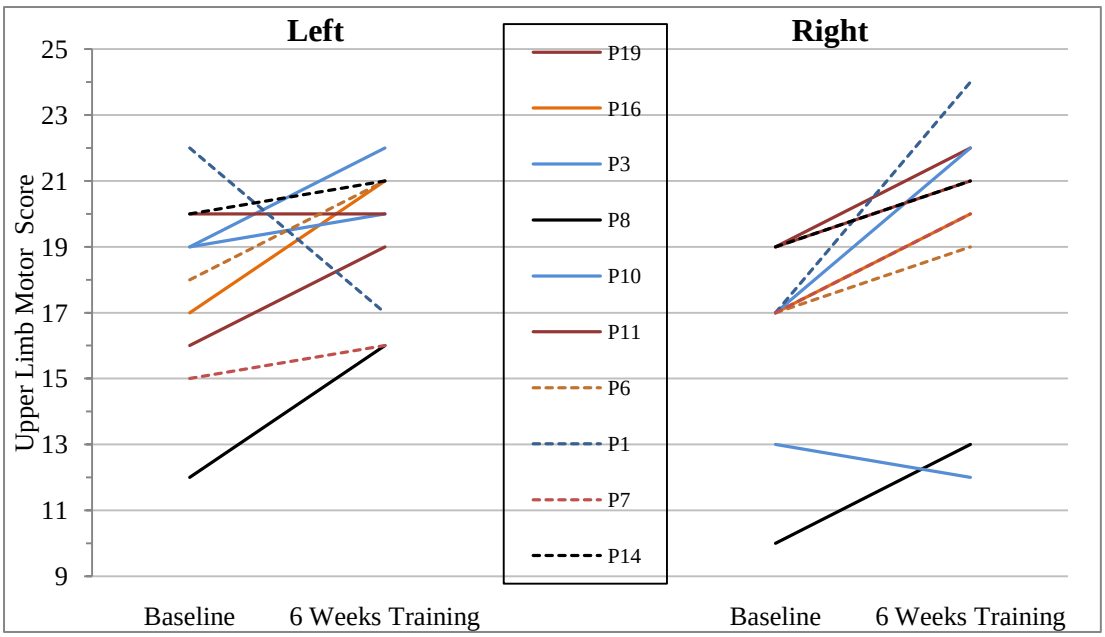


Figure 5-10: Upper Limb Motor Scores from the ASIA assessment in tetraplegic patients (n=10). Results for the left and right limb of each patient are shown. Acute and chronic iSCI patients show a trend of improvement after 6 weeks of Lokomat training compared to their baseline results. *[Dashed line- - - shows chronic iSCI patients]*.

The lower limb motor score is determined by muscle groups innervated from L2 to S1. Both tetraplegic and paraplegic patient groups were included in the lower limb motor score analysis (n=18). Improvement was seen in 17 (out of 18) iSCI patients (Table 5-9 and Fig 5-11). The improvement was significant in the acute iSCI patients (n=13, $p<0.01$ Wilcoxen signed ranks test). In the patient (P7) that did not show improvement the lower limb motor score decreased by 1 point following 6 weeks of Lokomat training. This patient did not show any functional improvement in ambulatory capacity as assessed by the WISCI II scale or temporal gait analysis.

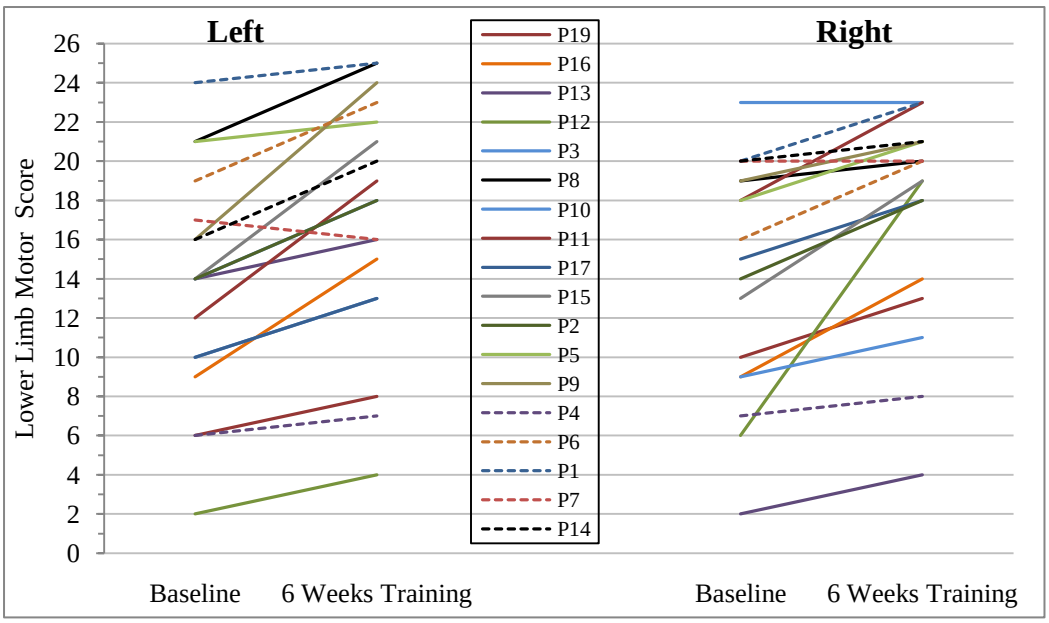


Figure 5-11: Lower Limb Motor Scores from the ASIA assessment. Results for the left and right limb of each patient are shown. *[Dashed line- - - shows chronic iSCI patients]*.

The patients that showed the largest improvement in ambulatory capacity (see Table 5-7) showed a large improvement in the lower limb motor score. When all the patients (not including those who wore braces) are ordered by the level of improvement in lower limb motor score the patients with the greatest improvement in ambulatory capacity (P15, P11 and P9) are the top three patients (Table 5-10). P8 is in the middle of the group however as this patient had a high baseline score (40) a limited level of change could be obtained.

Table 5-10 also shows that the patients (not wearing braces) that did not show any improvement in WISCI II scale score did improve their lower limb motor score (P17, 10 and 7). P17 and P10 remained at a WISCI II score of 0 following the 6 weeks of Lokomat training but had an increase of 6 and 5 points respectively in their lower limb motor score. P17 was able to complete sit to stand exercises and take a few steps within the parallel bars. However P10 was unable to stand. The difference between the lower limb motor score and the WISCI II score may reflect sensitivity limitations in the WISCI II scale. Functional changes in these patients may have occurred but not detected by using the WISCI II score and temporal gait analysis assessments.

Large improvement in ambulatory capacity (Table 5-7)

Lower Limb Motor Score			
Patient Number	**Baseline**	**6 Weeks Lokomat training**	**Change**
15	27	40	13
11	30	42	12
9	35	45	10
6	35	43	8
17	25	31	6
8	40	45	5
10	19	24	5
14	36	41	5
13	16	20	4
3	37	41	4
5	39	43	4
1	44	48	4
7	37	36	-1

Table 5-10: Change in lower limb motor score after 6 weeks of Lokomat training. Patients with a larger improvement in lower limb motor score have a larger improvement in ambulatory capacity.

To assess the function of the lower limb motor score to predict the WISCI II scale score after 6 weeks Lokomat training a Spearman's correlation coefficient of the two scores was completed. A Spearman's correlation coefficient test was completed as the WISCI II data is ordinal and therefore non parametric. A graphical representation of the results of the statistical analysis is shown in Figure 5-12. All patients who were able to walk without the use of braces (n=13) are shown. The data set shows 2 separate groups. Patients who score 0 on the WISCI II scale after 6 weeks Lokomat training and patients who score was greater than 0 (shown by +). A significant Pearson correlation between the WISCI II score taken after 6 weeks of training and the lower limb motor score at baseline ($r=0.591$, $p<.05$) is evident and suggests that baseline motor score may give an indication to the WISCI II score following 6 weeks of Lokomat training. When patients who scores 0 in the WISCI II scale were removed from the analyses no significant correlation ($r=0.202$, $p=.57$) was found. This shows that there is no correlation (in this study) between the LLMS at baseline and the WISCI II score after 6 weeks training when the patient is able to walk (WISCI II score >0).

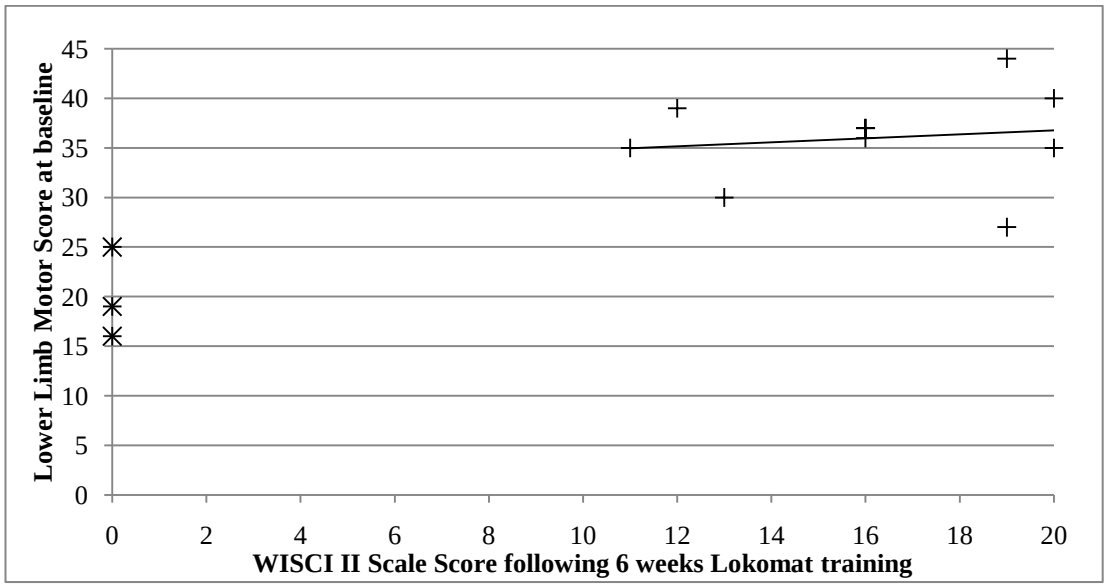


Figure 5-12: Baseline Lower Limb Motor Score (sum of Left and right limbs) against the WISCI II score after 6 weeks of Lokomat training. 13 Patients who were able to walk without braces are shown. The long trend line accounts for all data points (n=13) and a significant Spearman's correlation ($p<0.05$) is seen between the lower limb motor score at baseline and the WISCI II score after 6 weeks Lokomat training. The short trend line accounts for all data points with a score above 0 on the WISCI II scale (as shown by the + markers). No significant correlation is seen in this group.

The remaining part of the AISA assessment is the Sensory function test. Unlike the motor function test each dermatome (C3-S2) can be tested. As the sensory scores are completed on each dermatome, all patients with a lesion between C3 and T12 may show some improvement in the upper limb sensory score. All patients with a lesion above T12 were included in the upper limb analysis (n=17).

The sensory test was split into two parts; light touch and pin prick. In the upper limb 8 iSCI patients showed improvement (on at least 1one side) in light touch sensation and 14 iSCI patients showed improvement (in at least one side) in pin prick sensation (Table 5-8 and Fig 5-13 and Fig 5-15). 6 patients improved in both sensory perception tests in the upper limb.

The level of improvement seen in the upper limb perception of light touch and pin prick was between 1 and 4 points in light touch and between 1 and 11 points in pin prick. 5 patients showed an increase in their upper limb light touch perception and 5 patients showed an increase in their upper limb pin prick perception. Only 1 patient

(P8) had an increased upper limb perception to both light touch and pin prick. The increases were between 2-8 points in the light touch and 1-3 points in the pin prick.

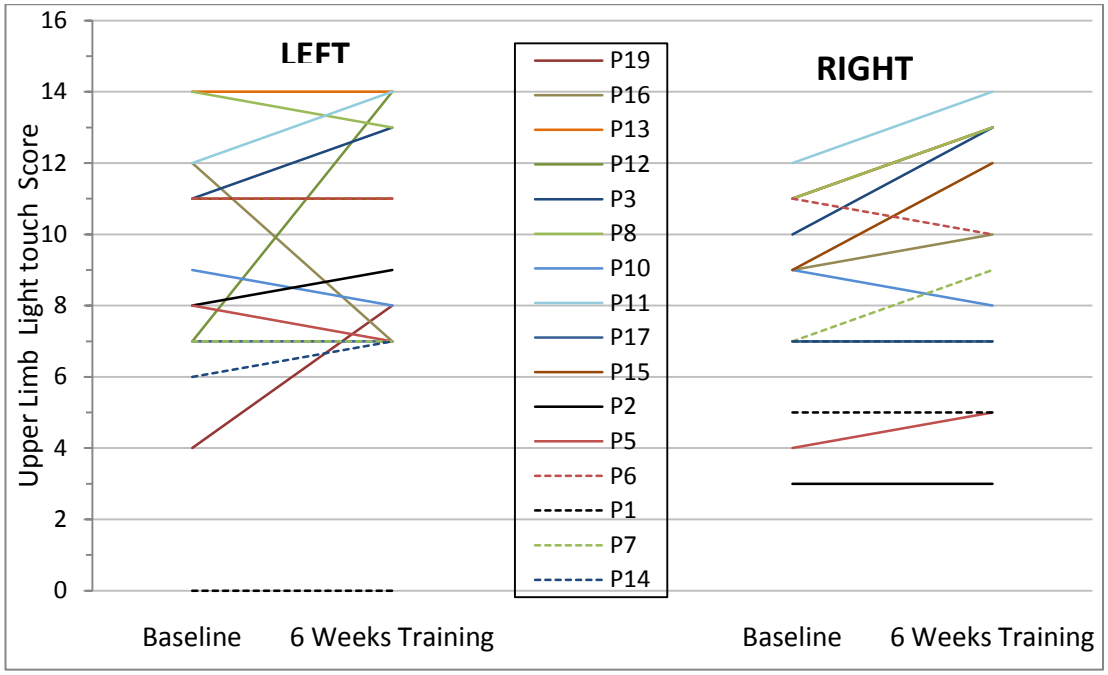


Figure 5-13: Upper Limb Light Touch Scores from the ASIA assessment. Results for the left and right limb of each patient (n=16) are shown. *[Dashed line- - - shows chronic iSCI patients]*.

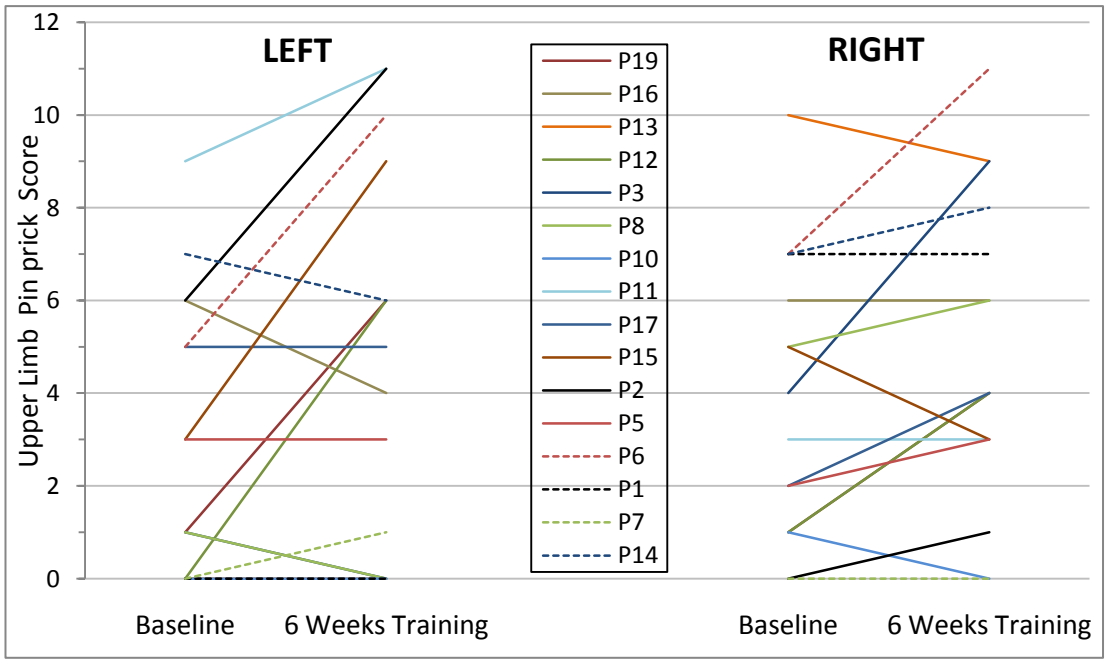


Figure 5-14: Upper Limb Pin Prick Scores from the ASIA assessment. Results for the left and right limb of each patient (n=16) are shown. *[Dashed line- - - shows chronic iSCI patients]*.

For the lower limb light touch and pin prick analysis all patients were included in the analysis (n=18). Improvements were seen in at least one side of the body in 14 iSCI patients in the lower limb light touch (5-15 points) and 13 iSCI points in the lower limb pin prick scores (5-16) after 6 weeks Lokomat training. 11 patients improved sensory perception in both the light touch and pin prick tests. The level of improvement was between 1-4 points in the light touch and 1-6 points in pin prick.

The lower limb light touch scores were reduced on either the left or right side of the body after 6 weeks of Lokomat training in 5 patients (P16, 8, 10, 5 and 6). Reduced scores were also seen on either the left or right side of the body in the pin prick scores after 6 weeks of Lokomat training in 9 patients (P16, 13, 3, 8, 10, 15, 9, 4 and 14). This could be due to neurological reasons such as a reduction in sensory perception to these modalities or may be due to inaccuracies of the test that may affect the tests reliability and repeatability measures. The scores were reduced by either 1 or 2 points across the lower limb score that has a total of 14 points.

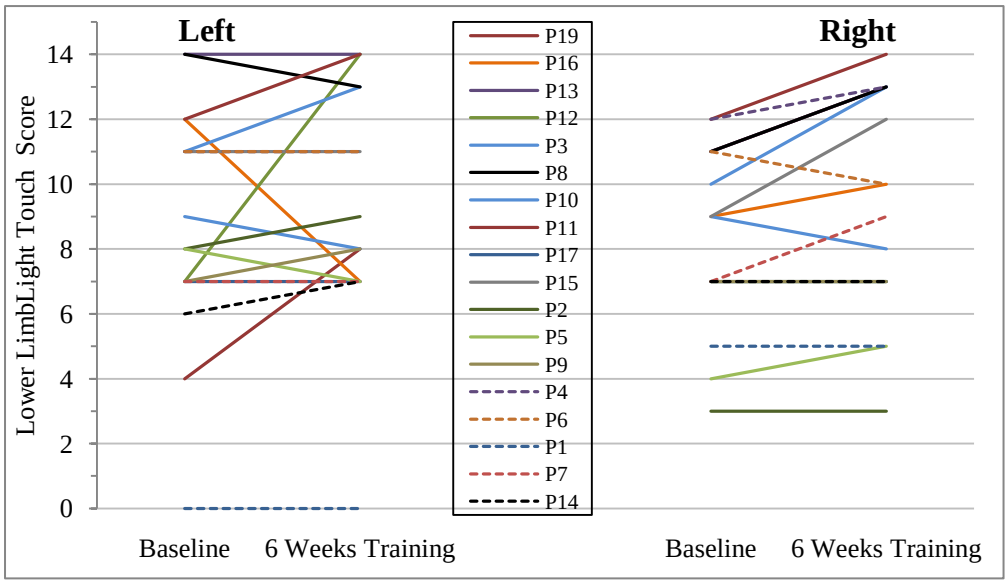


Figure 5-15: Lower Limb Light Touch Scores from the ASIA assessment. Results for the left and right limb of each patient are shown. *[Dashed line- - - shows chronic iSCI patients]*.

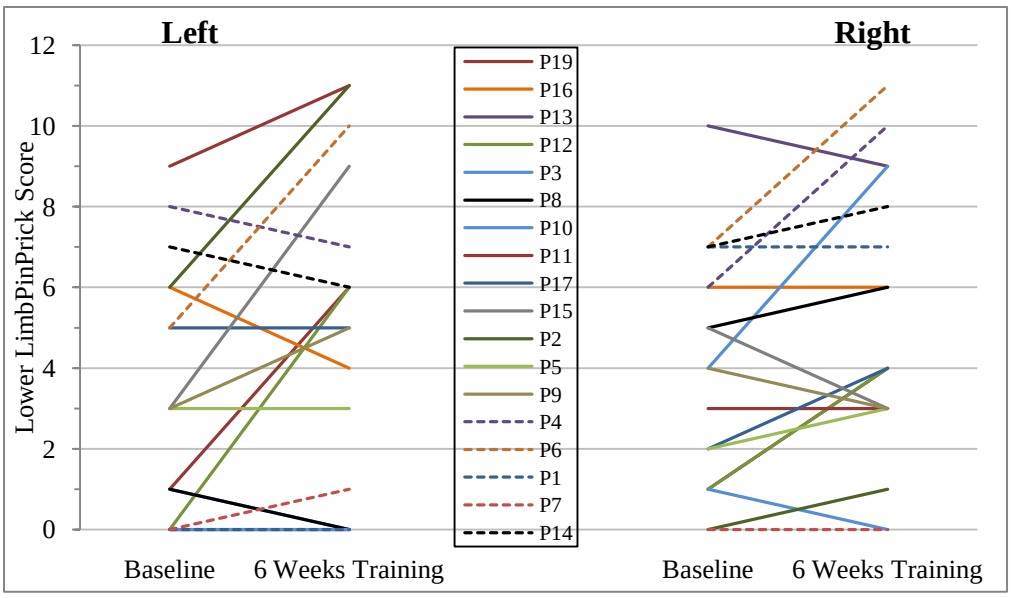


Figure 5-16: Lower Limb Pin Prick Scores from the ASIA assessment. Results for the left and right limb of each patient are shown. *[Dashed line- - - shows chronic iSCI patients]*.

The patients that showed the largest improvement in ambulatory capacity (see Table 5-7) did not show a large improvement in the lower limb light touch or pin prick scores compared with the other patients.

The pin prick scores were analyzed to determine if they could be used as a prognostic tool for ambulatory capacity after 6 weeks Lokomat training. Figure 5-17 shows the WISCI II score for each patient after 6 weeks Lokomat training against the lower limb pin prick score taken prior to the Lokomat training. The pin prick scores did not show any prognostic value for ambulatory capacity in the iSCI patients after 6 weeks of Lokomat training. Patients with low pin prick scores still achieved high WISCI II scores indicating functional ambulatory capacity in these patients. In patients with high pin prick scores the full range of WISCI II scores, from 20 to 0 were observed. This result is contrary to the study by Crozier et al (Crozier et al., 1992) who found a better ambulation outcome in patients with pinprick and light touch than light touch only. However in his study the patients (n=17) were all motor complete as assessed by clinical examination and the outcome measure taken 1 year post injury.

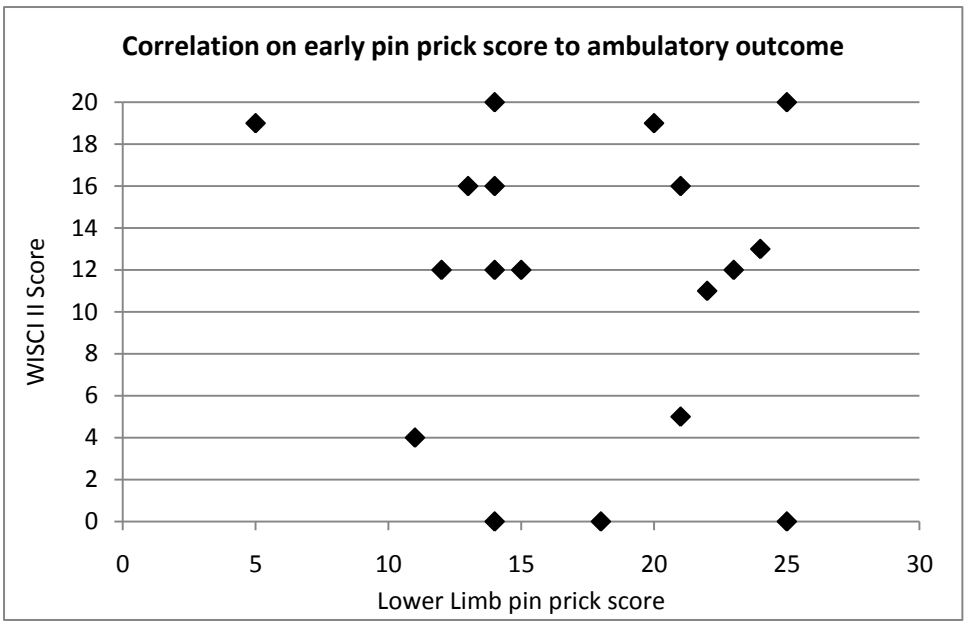


Figure 5-17: Correlation of pin prick scores and walking outcome measured by WISCI II scale.

5.5 QUANTATITIVE SENSORY TESTING

The QST test provides a quantitative value of perception threshold that can be measured on a continuous scale (only limited by the sensitivity of the stimulating equipment). The perception threshold measurement remains subjective, as the test is dependent upon subject / patient concentration and compliance.

The control group for the QST consisted of 10 healthy volunteers. 5 volunteers completed the vibration perception threshold and 5 completed the electrical perception threshold tests. QST testing was completed on the dermatomes from C3 to S2 on both sides of the body. For each dermatome tested, an average of the three values recorded using the method of limits was calculated for both left and right sides (see methods pp 61-63).

In the healthy volunteers a very strong correlation was found between the left and right sides in the electrical (Pearson correlation coefficient $r=0.833$, $p<0.01$) and vibration tests ($r=0.835$, $p<0.01$). The two sides were not statistically different (paired sample t-test $p>0.05$) for either test. The normative data was calculated for each dermatome as the mean ± 2 SD from all subjects from both sides (total of 10

sides) and this is illustrated in Figure 5-18. This mapping method of illustration and analysis is in line with the development of the EPT introduced during the first phase of the clinical initiative (Ellaway et al., 2004). The intra and inter subject repeatability of the EPT testing has been published by Ellaway's group (King et al., 2009) and was not repeated during this study.

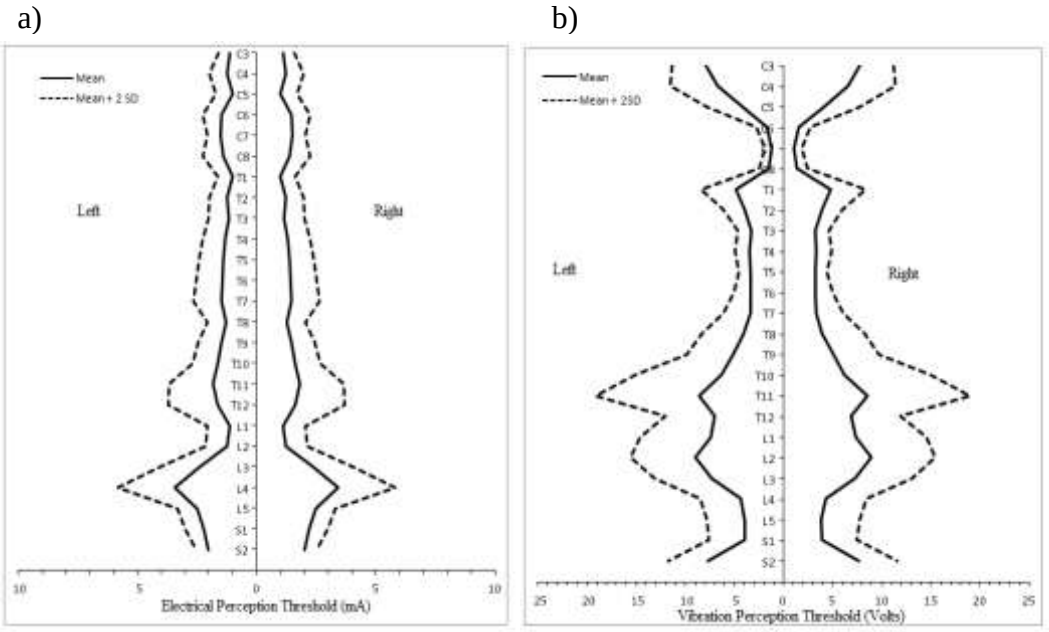


Figure 5-18: Normative values of EPT (a) and VPT (b) in normal subjects. (n=10 sides). The solid line shows the mean data from 10 sides (5 people left and right) and the dashed line 2 SD from the mean. Values of perception and variability at each dermatome is shown. Values across the dermatomes vary within the normal subjects.

The mean perception threshold in the normal volunteers varied across the dermatomes. Figure 5-18 shows the normative values (mean plus 2 SD) of perception threshold to electrical and vibration stimulus in each dermatome. Figure 5-18a shows the electrical perception was lowest at C5 (0.99 ± 0.35) and highest at L4 (3.42 ± 1.20). Figure 5-18b shows the vibration perception was lowest in C7 (1.08 ± 0.38) and highest in L2 (11.52 ± 2.63).

The variability (as assessed by the SD) in electrical and vibration perception thresholds also varied across the dermatomes. The SD is shown in Figure 5-18a/b by the dashed line, it ranges from 0.24 to 1.20 at C3 and L4 respectively in the EPT (Fig 5-18a) and from 0.38 to 5.46 at C7 and T11 respectively in the VPT (Fig 5-18b). A

larger variation was seen in the vibration perception threshold compared to the electrical perception threshold. This may be due to methods of applying the stimulus to the subjects. The pressure in which the Neurothesiometer is applied to the skin was not measured during the study. By applying different pressure it is possible that different receptors were activated by the vibration. The vibration is also transmitted through tissue and bone and large vibration amplitudes may be detected in adjacent dermatomes to the one tested. To compensate for this variability during patient testing any response larger than the mean + 2SD of the normative data was termed abnormal. This reduces the sensitivity of the test but increases the reliability by reducing the number of false negatives reported (defined as abnormal when normal).

In the patient group the tests were completed at baseline and after 3 and 6 weeks of Lokomat training. To highlight features of the sensitivity and reliability of the tests, example graphs from the patient data are shown. Using examples from EPT and VPT analysis the graphs are presented in 3 sections; above the lesion, the level of the lesion and below the lesion.

5.5.1 ABOVE THE LEVEL OF LESION

Figure 5-19 illustrates the results of the EPT assessment above the level of the lesion in one patient taken at each assessment. The mean of the three readings taken at baseline (blue), after 3 weeks of Lokomat training (red) and 6 weeks Lokomat training (green) for each dermatome, for the left and right side of the body are shown. The dermatomes above the level of lesion to one level below are shown. The level of the lesion (T9), as determined by ASIA assessment is shown by the horizontal black line. The normative values (mean + 2 SD) from the healthy subjects are superimposed, shown by a dashed line.

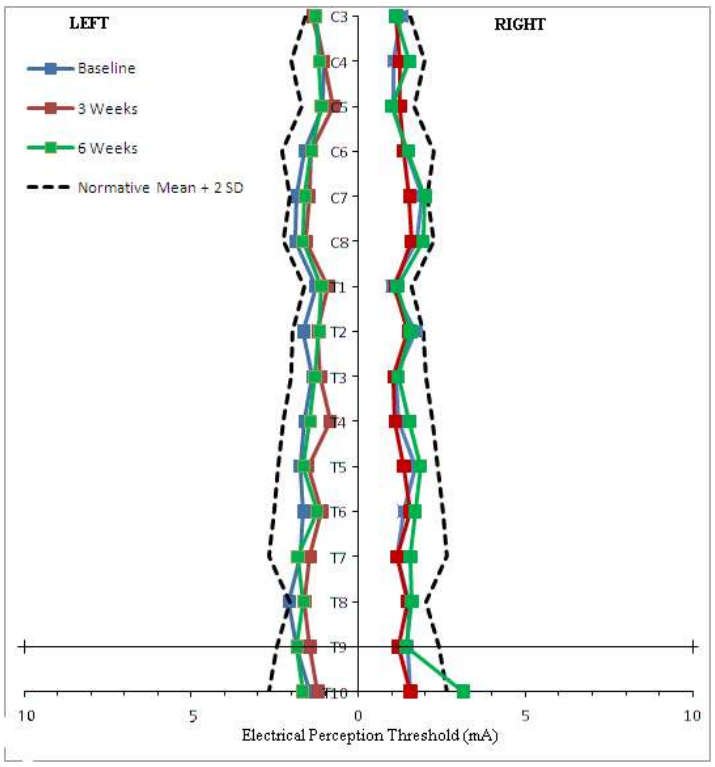


Figure 5-19: EPT from baseline and after 3 and 6 weeks training in a single patient (P12). Normal mean + 2SD vales shown in the dashed black line. Level of lesion is shown with the horizontal line (T9).

Above the level of the lesion it was expected that the perception thresholds for each dermatome and each patient would be within the normative data range (central to the dashed line on the left and right side). This is illustrated in figure 5-19 where the values for each dermatome above the level of the lesion are within the normal range (mean plus 2 SD).

If the perception level is greater than the range determined from the control subjects above the level of the lesion it may indicate a sensory deficit and can be detected using the EPT and VPT measurements. Figure 5-20 illustrates raised electrical perception thresholds in dermatomes at T7 and T8 on the left side of the body which are above the level of lesion.

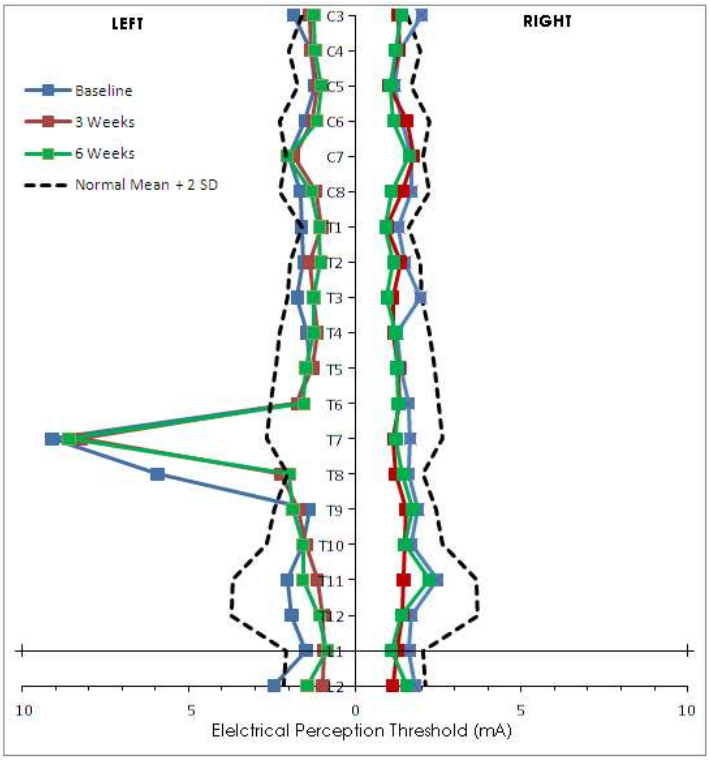


Figure 5-20: EPT above the level of lesion from baseline and after 3 and 6 weeks training (P4).

The raised levels are seen at baseline (blue), and after 3 (red) and 6 (green) weeks Lokomat training. The other dermatomes above the lesion (L1) are within the normal range. The test has identified an area of sensory loss that would not be expected from a lesion at L1. The cause of this sensory impairment may be due to a surgical procedure (thoracotomy) at T7 performed on this patient. This invasive surgery may have damaged sensory nerves at this level and caused an area of reduced sensation.

The results of the VPT analysis above the level of lesion for this patient (P4) is shown in figure 5-21. The figure illustrates how the area of sensory impairment identified in the EPT (Fig 5-20) is not as clearly defined in the VPT. This may be due to the differences in the methodology of the two tests. The EPT uses a bipolar stimulus which means the stimulation in focused whereas the vibration may have spread to adjacent segments. The receptive field for vibration perception may also be larger than the receptive fields for electrical perception.

This result may have indicated impaired perception to vibration across dermatomes with normal electrical perception. However the AISA light touch and pin prick scores for this patient were only abnormal at T7.

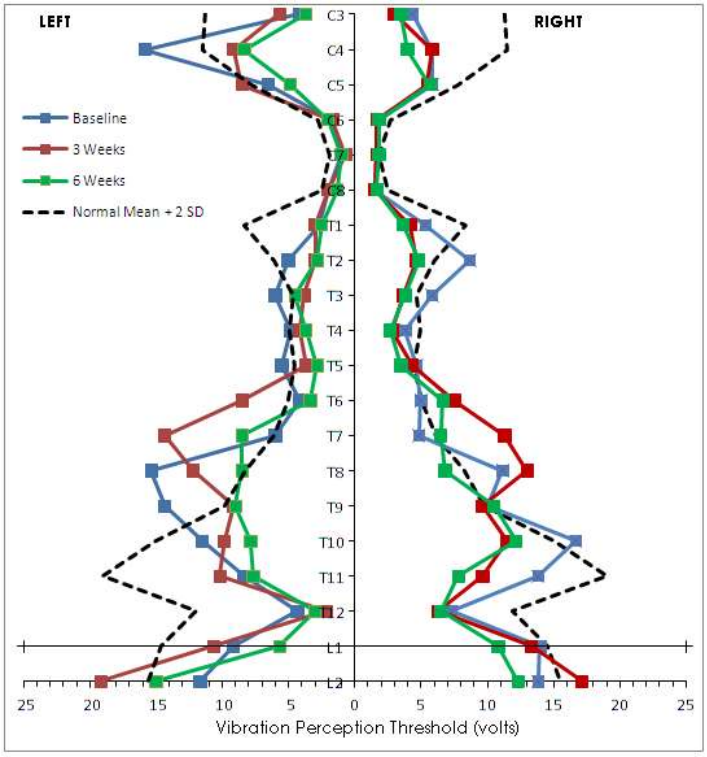


Figure 5-21: VPT above the level of lesion from baseline and after 3 and 6 weeks training (P4).

5.5.2 THE LEVEL OF THE LESION

The EPT and VPT tests may provide additional information to the ASIA assessment on the level of sensory impairment. As shown above the results of the perception threshold above the level of the lesion are normally within the healthy range. By identifying the point at which the results are not within this range the level of the lesion can be determined. The sensory level of the lesion can also be determined using the ASIA scale by the light touch and pin prick assessments for each side. For each assessment; ASIA and perception threshold, the level of lesion is determined as the most caudal spinal segment with normal sensory function. In the ASIA assessment this spinal segment must have normal sensory function in both tests (light touch and pin prick).

The level of lesion determined by the ASIA assessment was compared to the level of lesion determined by the EPT and VPT assessments. Table 5-11 shows the neurological level for each patient as assessed by the AISA scale, EPT and VPT assessments. The EPT and VPT are shown as the number of levels from the ASIA level. A positive number illustrates the number of levels below and a negative number illustrates the number of levels above the ASIA neurological level. The table demonstrates how the sensory level of impairment changes in each patient depending upon the sensory assessment used. As the assessment identifies the impairment of a different modality within the same functional pathway, the dorsal column medial lemniscal pathway, this result was unexpected. It highlights that the EPT and VPT assessments should be used to compliment the ASIA assessment to increase the sensitivity of sensory impairment tests.

Patient Number	ASIA	EPT	VPT
19	C5	---	**19** (L4)
16	C5	---	**9** (T6)
13	T3	**3** (T6)	**-1** (T2)
12	T9	**0** (T9)	**2** (T11)
3	C3	**0** (C3)	**0** (C3)
8	C4	**1** (C5)	**0** (C3)
10	C4	**2** (C6)	**1** (C5)
11	C5	**6** (T3)	**5** (T2)
17	T4	**0** (T4)	**-1** (T3)
15	T8	**1** (T9)	**-12** (C4)
2	T9	**-7** (T2)	**-2** (T7)
5	T11	**-4** (T7)	**2** (L1)
9	T12	**0** (T12)	**-3** (T9)
4	L1	**4** (L5)	**1** (L2)
6	C5	**1** (C6)	**1** (C6)
1	C5	**-1** (C4)	**-1** (C4)
7	C4	---	**-1** (C3)
14	C5	**-1** (C4)	**0** (C5)

Table 5-11: The difference in sensory level of impairment as determined by the AISA assessment compared to the EPT and VPT tests after 6 weeks Lokomat training. A positive number shows the number of levels below the ASIA classified lesion and a negative number show the number of levels above the ASIA classified lesion. Where no number is given in the EPT no level showed a raised threshold above the healthy mean +2SD. The table shows that the sensory level changes in each patient dependent upon the sensory test used.

5.5.3 BELOW THE LEVEL OF LESION

Below the level of the lesion the interpretation of the EPT and VPT graphs are more difficult. The perception at each dermatome depends upon the location and severity of the patient's injury. Below the level of the lesion the area of sensory impairment should be spread across many dermatomes. Figure 5-22 shows how the results of the EPT and VPT are different at each dermatome and at each test session. Although improvements can be seen at single dermatomes (e.g.T9 in the EPT and T5 on the right in the VPT) there are also dermatomes that do not show improvement (e.g.T2 in the EPT and C7-8 in the VPT). The change is not constant to the chronological order of the tests. If improvement was seen it would be expected that the perception threshold after 3 weeks of Lokomat training would be lower than the perception threshold recorded at baseline. The perception threshold at 6 weeks should be lower than the perception threshold recorded at the 3 week point, i.e. the points should be blue, red and green from the outside to the centre line off the graph. Figure 5-22 shows that this is not the case in many of dermatomes. This makes it difficult to interpret and show where changes in sensory perception have occurred. It is also difficult to refer these changes in perception threshold to any functional change that may be due to an intervention. No pattern in the improvement of ambulatory capacity observed in the patients of this study and their changes in EPT or VPT was found.

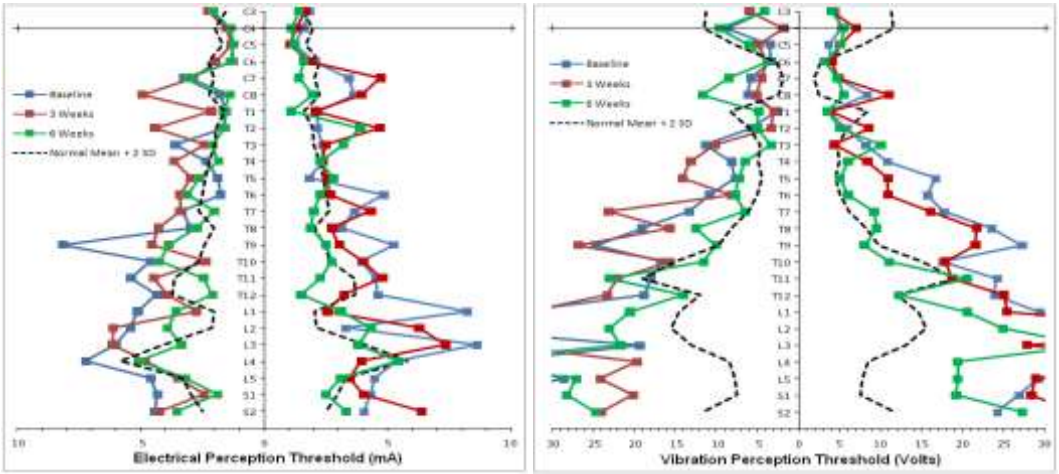


Figure 5-22: EPT and VPT from baseline and after 3 and 6 weeks training (P6).

5.5.4 CORRELATION OF EPT AND VPT

The final point to note about the EPT and VPT is that it is believed that they assess similar pathways at low stimulus levels. Figure 5-23 shows the EPT and VPT of a single patient. The EPT is normal in all dermatomes tested and the VPT shows increased perception threshold in all dermatomes tested.

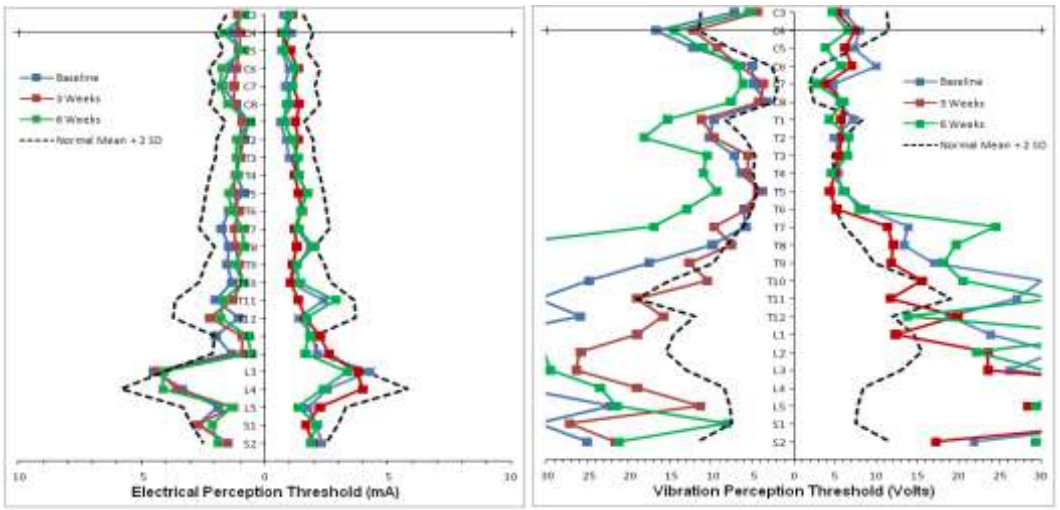


Figure 5-23: EPT and VPT results from a single patient (P7). Results from the EPT show normal perception thresholds at baseline (blue) and after 3 (red) and 6 (green) weeks of Lokomat training. The VPT show higher perception values than normal in all dermatomes.

To assess the correlation between the electrical and vibration perception the EPT results for each dermatome, on both sides of the body, for each patient were plotted against the VPT result (Fig 5-24). The results from dermatomes below the level of the lesion are shown in the blue and those from above the level of the lesion are shown in red. A broad range of vibration perception thresholds compared to the EPT results is evident in levels above and below the lesion. Raised perception levels in one modality can result in raised or normal perception in the other modality.

The spread of perception in the EPT and VPT above the level of lesion (red) are within normal range. The lack of correlation in the normal range may be due to the different level of perception at the different dermatomes as shown by healthy subjects in graphs 5-18a/b.

The results may also suggest a lack of sensitivity in one or both tests, or that the modalities may be conveyed in other spared sensory pathways.

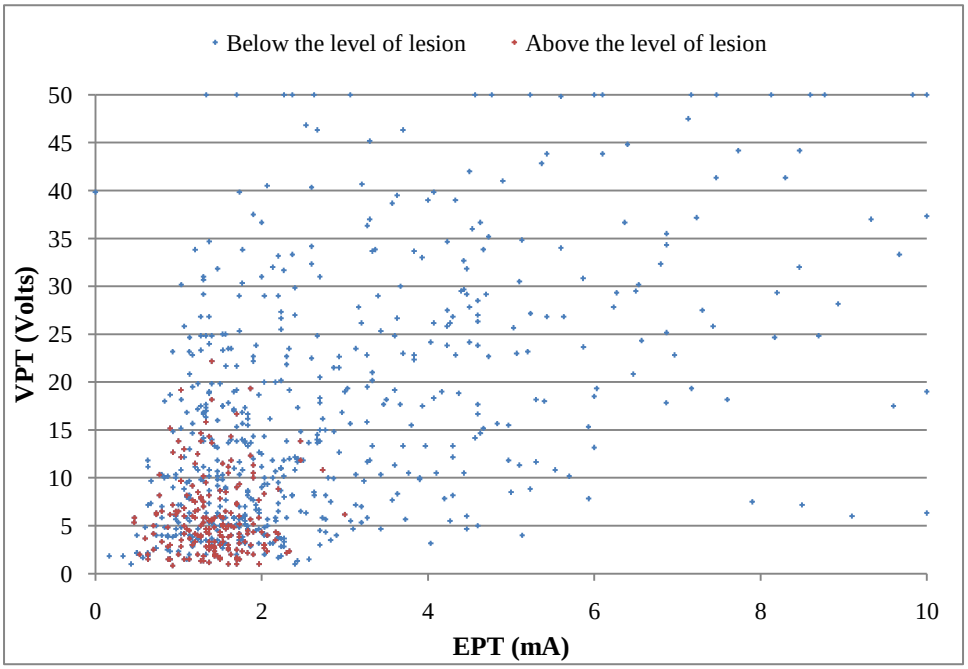


Figure 5-24: Correlation between EPT and VPT in iSCI taken at dermatomes above and below the level of the lesion. Above the lesion the values can be considered as within the normal range.

5.6 SOMATOSENSORY EVOKED POTENTIALS

SEP testing was completed on the median and posterior tibial (PT) nerve at Baseline, and after 3 and 6 weeks of Lokomat Training. 15 iSCI patients completed the SEP testing protocol. 3 Patients did not complete all three test sessions and so their results are not included. For each nerve tested (left and right) two sets of data were recorded. The stimulus intensity was the same for each data set but presented at different frequencies (2.5Hz and 0.1Hz). The higher stimulus rate data was analysed in the time domain and the slower frequency in the frequency domain (see Methods for details). The results for the time analysis are presented first, followed by the frequency analysis.

5.6.1 TIME ANALYSIS

Time analysis is the commonly used method in data processing of SEPs. It provides latencies and amplitudes of the peaks and troughs which can be compared against

normative data. The SEP latency and amplitude is known to be affected by height, gender and age. During this study we compared the Median and PT nerve SEP taken prior to Lokomat training to the SEP taken after 3 and 6 weeks of Lokomat training. This analysis compared results within patients. No between patient analysis was completed therefore the data was not normalised for height, gender or age.

PT NERVE SEP CORTICAL COMPONENTS

The cortical components measured from the PT nerve SEP waveforms for each patient at baseline and after 3 and 6 weeks Lokomat training are illustrated in Figure 5-25. The front contralateral electrode (right SEP = F3, left SEP=F4) was analysed for the P30 component. The electrodes over the central line of the somatosensory cortex (Cz and CPz) were used to analyse P1, N1, P2 and N2 components for the left and right PT nerve SEP.

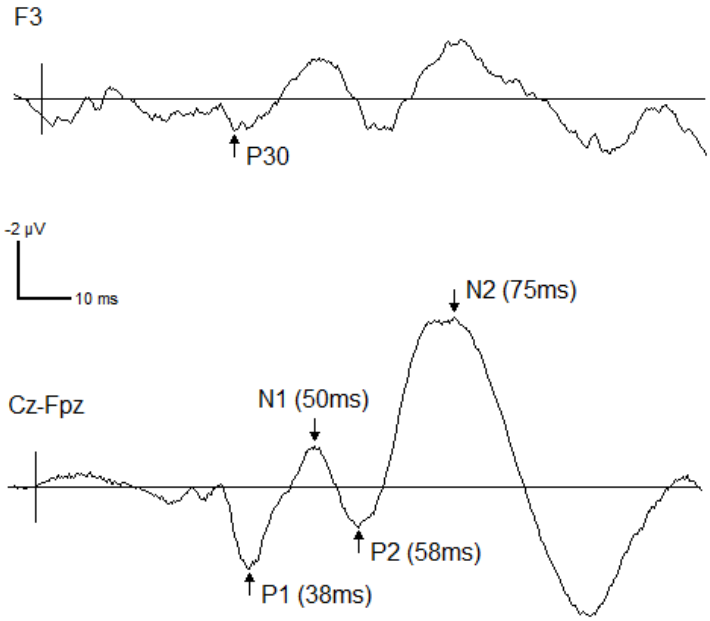


Figure 5-25: Components of the PT nerve SEP. Each measured for latency; time from stimulus, and amplitude; height from baseline.

Figure 5-26 shows the components measured in the median nerve SEP. The front contralateral electrode (right SEP = F3, left SEP=F4) was analysed for the P13 and N18 components. The electrodes over the contralateral side of the somatosensory cortex (Cc and CPc) were used to analyse the N1 and P1 components.

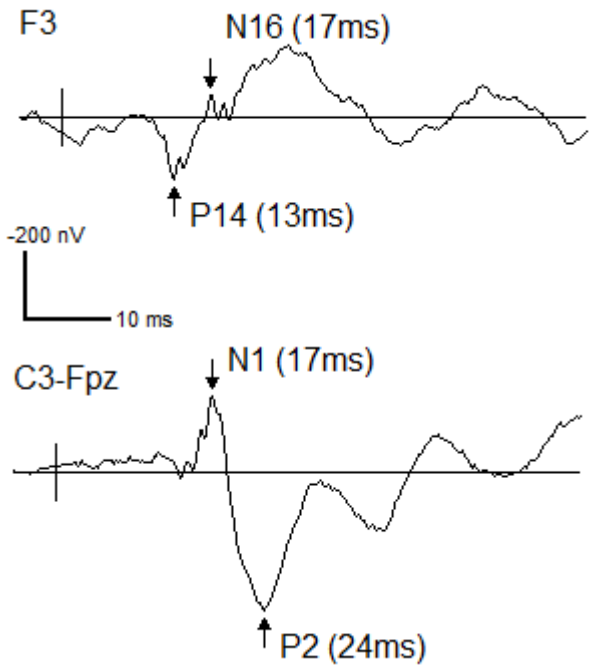


Figure 5-26: Components of the median nerve SEP. Each measured for latency; time from stimulus, and amplitude; height from baseline.

For each component the latency (ms) was measured from the point of stimulus (zero) shown by the vertical bar to the highest point of the peak or lowest point of the trough respectively. The amplitude was measured from baseline to the highest point of the peak or the lowest point of the trough respectively. The inter-peak latency and amplitude of P1-N1 and N1-P2, in the PT nerve SEP and of P14-N18 and N1-P1, in the median nerve SEP was calculated from the peak values.

CHANGES IN PT NERVE SEP AFTER LOKOMAT TRAINING

The data recorded at baseline was used to identify changes that may have occurred after 3 and 6 weeks of Lokomat Training in each patient. The earliest cortical component to be seen after a PT Nerve SEP is the P30 shown in figure 5-27 recorded from the contralateral and frontal electrode (F3 for right PT nerve). It is a far field potential that originates in the lower brain stem. The anatomical structures that generate the P30 are the nucleus gracilis and the lemniscal sensory fibres of the lower limb somatosensory pathway below their decussation in the medulla (Tinazzi et al., 1997).

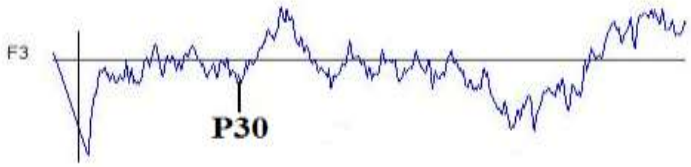


Figure 5-27: P30 recorded at F3 with reference electrode on the earlobe after right PT nerve SEP in a single healthy subject.

The 3 waveforms obtained at baseline and after 3 and 6 weeks Lokomat training were overlaid to see the changes in the latency, amplitude and morphology of the waveform. Figure 5-28 shows an example from a single patient (P3) of the 3 waveforms recorded at F3 (baseline (blue), 3 weeks Lokomat training (red), 6 weeks Lokomat training (green)).

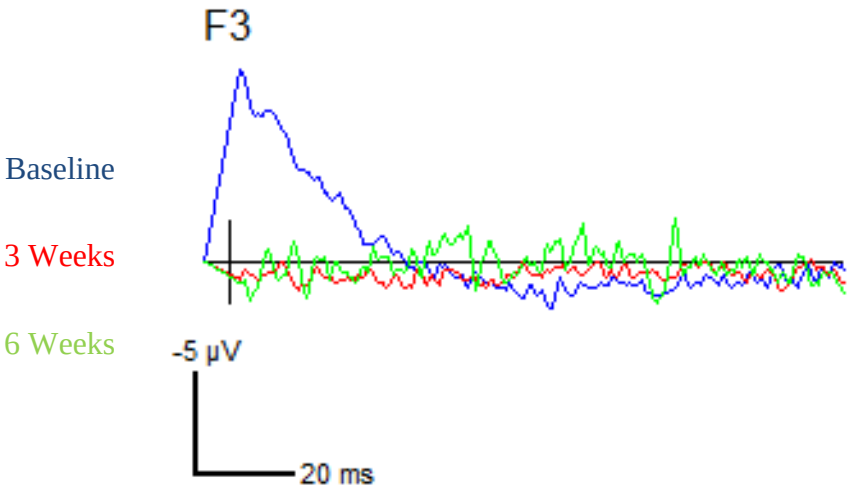


Figure 5-28: Right PT nerve SEP recorded at F3 (P3). No P30 component is identifiable in the 3 waveforms taken at baseline (blue), after 3 weeks Lokomat training (red) and 6 weeks Lokomat training (green).

The P30 component is not observed in any of the three waveforms in this patient. For the patient data a total of 90 waveforms were analysed (15 patients *3 trials *2 sides (left and right)) and the P30 component was only identified in 26 waveforms. No patient had an identifiable P30 in all 3 waveforms. Figure 5-29 illustrates the percentage P30 cortical components present and absent at each stage (baseline, 3 weeks and 6 weeks Lokomat training) for the acute and chronic iSCI patients. The percentage within the groups does not change over the 3 test sessions for either group. In the chronic group the P30 is present in over 60% of the PT nerve SEP

waveforms compared to the acute group where it is present in under 23% of the waveforms.

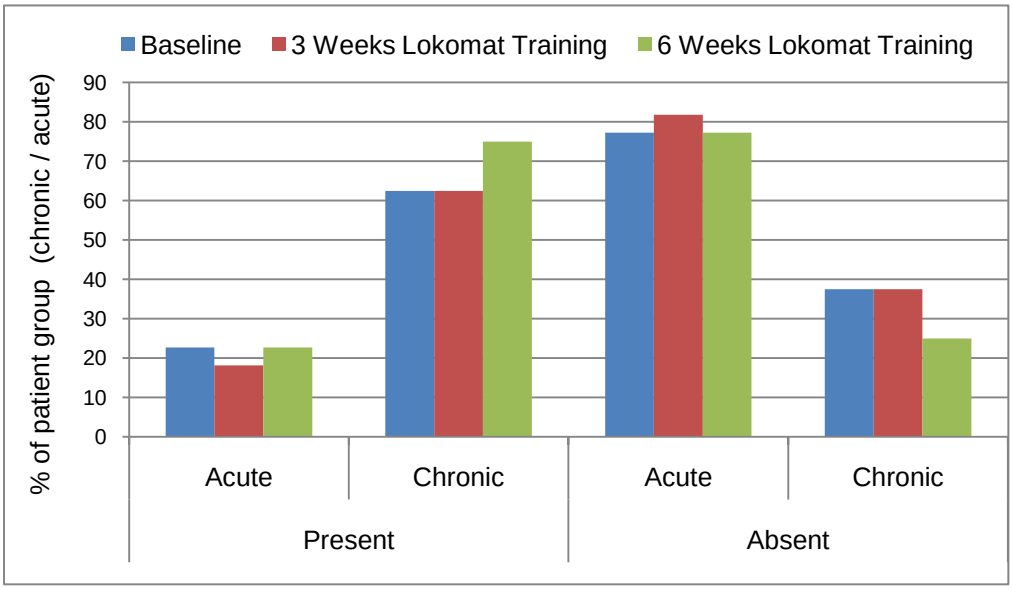


Figure 5-29: The Presence and absence of the PT nerve SEP P30 cortical component in acute and chronic patients at baseline and after 3 and 6 weeks Lokomat training. Within the acute and chronic groups the % of P30 components present does not change over time. The P30 is present in over 60% of chronic patients and under 23% of acute patients.

Due to the inconsistency in identifying the P30 component no further analysis was completed on the latency or amplitude of the P30 component after PT nerve SEP.

The four components (P1, N1, P2 and N2) recorded from CPz-Fpz and Cz-Fpz are larger in amplitude and width which makes them more easily identifiable in the morphology of the SEP waveform. Figure 5-30 shows the PT nerve SEP waveform after 6 weeks Lokomat training from a single patient recorded over the midline of the somatosensory cortex. The cortical components are easily identifiable in this patient. Although the latencies of the components are slightly delayed compared to the healthy subjects all 4 cortical components are present and the morphology of the waveform is normal.

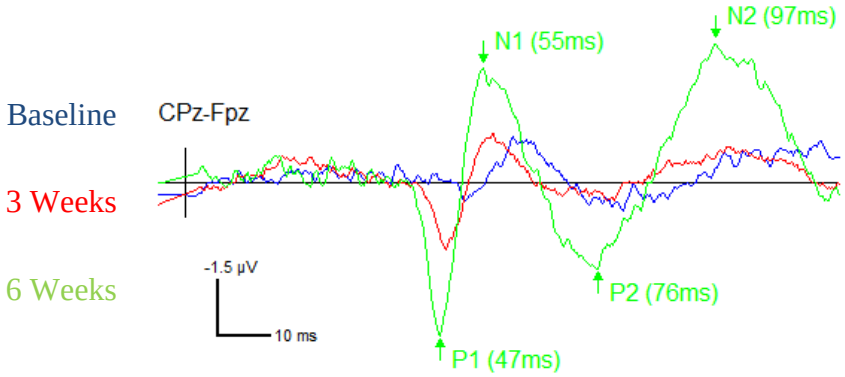


Figure 5-30: Right PT tibial nerve from a single iSCI patient (P3) taken at baseline (blue) after 3 weeks (red) and 6 weeks (green) Lokomat training.

In SCI patients the cortical components are not always present and the latencies of the components that are present may be delayed. This makes the identification of peaks in abnormal SEP waveforms more difficult. Not all peaks and troughs are present which can lead to ambiguity in which peak is present. Figure 5-31 shows the PT nerve waveform in a single patient (P15) taken at baseline (blue), and after 3 weeks (red) and 6 weeks (green) Lokomat training. The waveform is present in each test. However P1 could be placed at 2 latencies in each test, but a clearer peak is identified in the 6 week Lokomat test (green). N1 and P2 peaks at the 3 weeks Lokomat test (red) are small and difficult to identify. Peaks that have a plateau such as seen for the N2 component at 6 weeks Lokomat training (green) can create ambiguity in defining the latency of the peak. Identification of the peak was completed subjectively by one investigator. The highest point of a peak was determined using BESA software. This method of analysis adds subjectivity into an otherwise objective test.

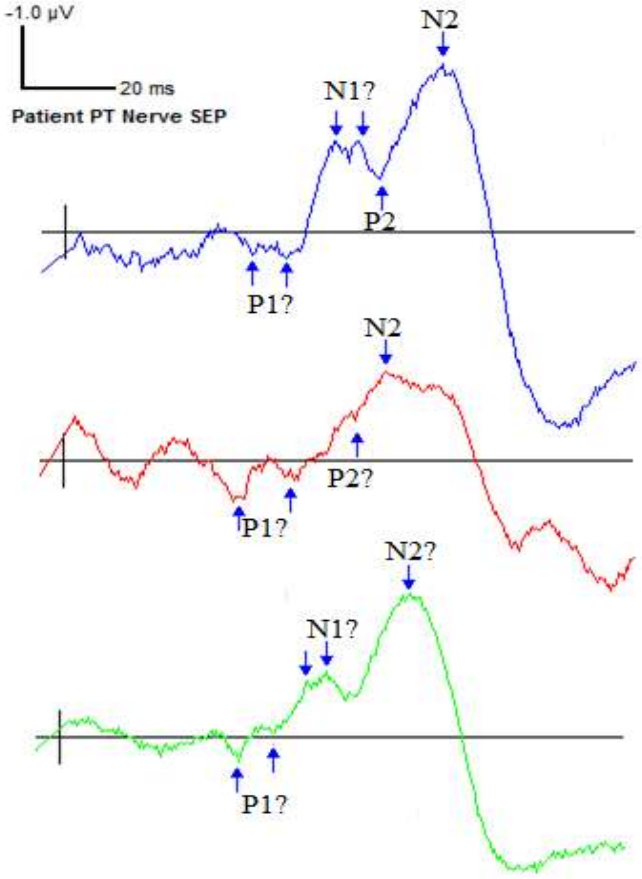


Figure 5-31: PT nerve SEP in a single acute iSCI patient (P15) with a lesion at T8. 3 Trials are shown; baseline (blue) after 3 weeks Lokomat training (red) and after 6 weeks Lokomat training (green). 4 Components are identified in each (normal) waveform, P1, N1, P2 and N2. Ambiguity in the identification of the peak components occurs in abnormal SEP waveforms.

To identify any changes in the latency or amplitude of components within the PT SEPs after Lokomat training statistical analysis was used. The latency and peak amplitude of P1, N1, P2 and N2 as well as the and inter-peak latency and amplitude of P1-N1, N1-P2 and P2-N2 taken at baseline were compared to those taken after 6 weeks of Lokomat training using a repeated measures ANOVA. The patient data was spilt into 2 groups; chronic and acute to identify if changes occurred in either group.

After 6 weeks of Lokomat training no significant changes to the peak or inter-peak amplitudes were seen in the acute or chronic patient groups.

After 6 weeks of Lokomat training the latency of the P1 component was significantly different (p=.009) in the acute iSCI patient group. No significant changes were seen in the inter-peak latencies after 6 weeks Lokomat training in the acute iSCI patient group.

In the chronic iSCI patient group no significant changes were seen in the peak latencies after 6 weeks Lokomat training. The inter-peak latency; N1-P2 was significantly different (p=.009) after 6 weeks of Lokomat training in the chronic iSCI patient group.

A Post hoc pair-wise (T-test) comparison was performed to ascertain if the changes observed in P1 latency of acute iSCI patient group in the PT nerve occurred between baseline and 3 weeks of Lokomat training and / or between 3 and 6 weeks of Lokomat training. Figure 5-32 shows the average latency of the P1 component taken at baseline and after 3 and 6 weeks of Lokomat training in the acute and chronic iSCI patient groups. A reduction in the latency of the P1 component is seen in the acute patients (black bars). The P1 latency was significantly different after 6 weeks of Lokomat training (p=.010) from baseline. However the P1 latency was not significantly different after 3 weeks of Lokomat training (p=.057) from baseline and no significant difference was seen between 3 and 6 weeks Lokomat training (p=.114) either. This shows a trend of improvement of the period which becomes significant at 6 weeks.

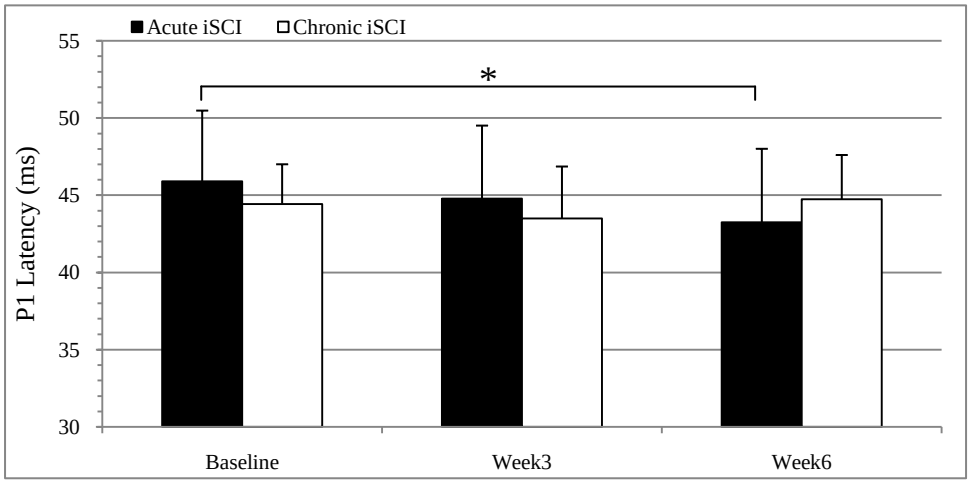


Figure 5-32: Latency of the P1 component in the PT nerve SEP in acute and chronic iSCI patients. (*p<0.05)

A Post hoc pair-wise (T-test) comparison was performed to ascertain if the changes observed in N1-P2 inter-peak latency of the chronic iSCI patient group in the PT nerve occurred between baseline and 3 weeks of Lokomat training and / or between 3 and 6 weeks of Lokomat training. Figure 5-33 shows the average inter-peak latency of the N1-P1 component taken at baseline and after 3 and 6 weeks of Lokomat training in the acute and chronic iSCI patient groups. The N1-P1 inter-peak latency is significantly different after 3 weeks of Lokomat training (p=.000) from baseline, and from 3 weeks to 6 weeks Lokomat training p=.041). However no significant difference was seen between baseline and 6 weeks Lokomat training (p=.757).

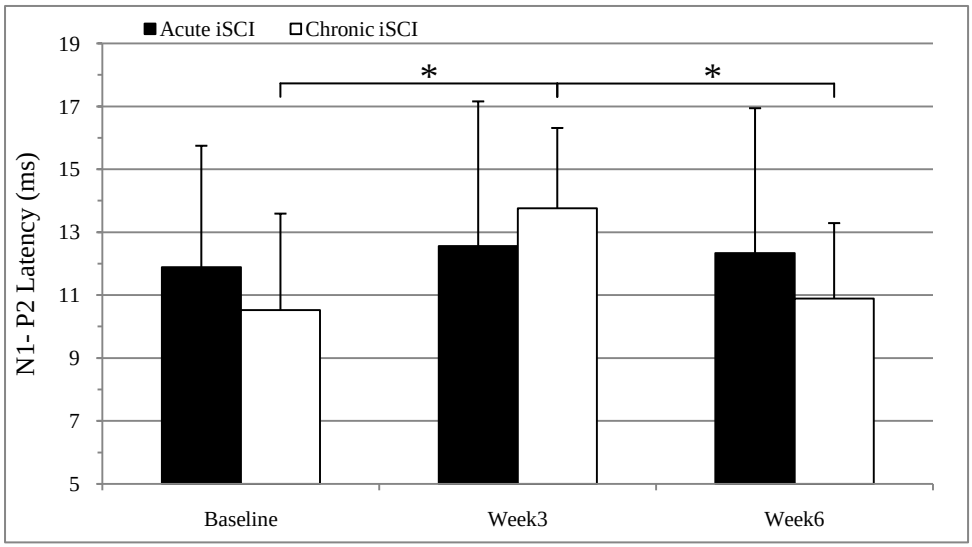


Figure 5-33: Inter-peak latency of the N1-P2 component in the PT nerve SEP in acute and chronic iSCI patients. (*p<0.05)

It has been reported in this thesis that some of the chronic iSCI patients improved their ambulatory capacity (P1,6 and 14) and some acute iSCI patients did not improve their ambulatory capacity after 6 weeks Lokomat training as assessed by the WISCI II scale and temporal gait analysis (P10, 13, 17). Analysis of the PT nerve SEP was therefore repeated with the patients split into three groups, based on the amount of improvement in their ambulatory capacity.

The presented results above show that the P1 latency of the PT nerve SEP appears to change after 6 weeks Lokomat training in the acute iSCI patient group. This analysis looked at the patients in two groups, acute and chronic. To identify the changes that may occur with the improvement in ambulatory capacity as assessed by the WISCI II scale and temporal gait analysis the P1 latency was identified in the 3 groups. The groups were large improvement, some improvement and no improvement in ambulatory capacity.

Figure 5-34 shows the latency of the P1 component of the PT nerve SEP (left and right side) in each patient. The lines are colour coded to the amount of improvement seen in ambulatory capacity as assessed by WISCI II scale and temporal gait analysis; black indicates the most improved group, red indicates the patients which showed some improvement and green indicates the patients that showed no improvement in ambulatory capacity after 6 weeks Lokomat training. The longer the latency of the P1 component at baseline the larger the improvement in ambulatory capacity is seen after 6 weeks in Lokomat training. This result is unexpected although it may indicate that the patients with larger functional impairment benefit more from the Lokomat training.

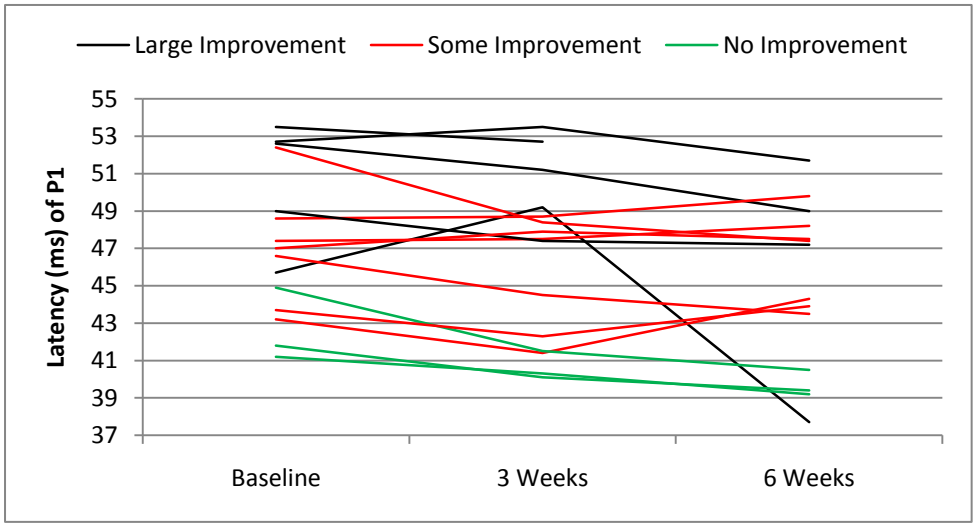


Figure 5-34: Latency of P1 component in the PT nerve SEP at baseline and after 3 and 6 weeks Lokomat training. The patient data is colour coded to the amount of improvement seen in ambulatory capacity as assessed by WISCI II scale and temporal gait analysis.

The patients that had a large improvement in their ambulatory capacity after 6 weeks of Lokomat training had an average, reduction in P1 latency of 0.9ms (n=4). The P1 latency was also reduced in the patients that had some improvement in ambulatory capacity (Avg. 0.09ms n=7) and the patients that showed no improvement in ambulatory capacity (Avg. 0.48ms n=4). Although the greatest change in P1 latency was seen in the patients who had the largest improvement in ambulatory capacity a direct relationship between the two parameters is not clearly evident.

PREDICTION OF AMBULATORY CAPACITY WITH PT NERVE SEP

The PT nerve SEP has been studied to determine whether it might be able to predict the outcome of lower limb function (Curt and Dietz, 1997, Curt and Dietz, 1999, Jacobs et al., 1995, Katz et al., 1991, Li et al., 1990, Ziganow, 1986). The presence or absence of the early components in the PT nerve SEP has been shown to be predictive of ambulatory outcome (Curt and Dietz, 1997). Only three patients (P10, P13 and P17) within this study failed to recover any ambulatory capacity. Figure 5-35 shows the waveforms from the left PT nerve SEP in the three iSCI patients that did not recover ambulatory capacity. In the waveform of P17 (Fig 5-35a) the four peak components (P1, N1, P2 and N2) could not be identified during any of the three test sessions; baseline (blue), after 3 weeks (red) and 6 weeks Lokomat training (green). In P10 the waveform was present but the morphology of the waveform was abnormal as P1 cannot be identified or N2 (at baseline and 6 weeks) (Fig 5-35b) and in P13 the waveform was normal (Fig 5-35c). The presence or absence of the early components as a prediction of outcome could not be determined in this study due to small number of patients that did not recover ambulatory capacity.

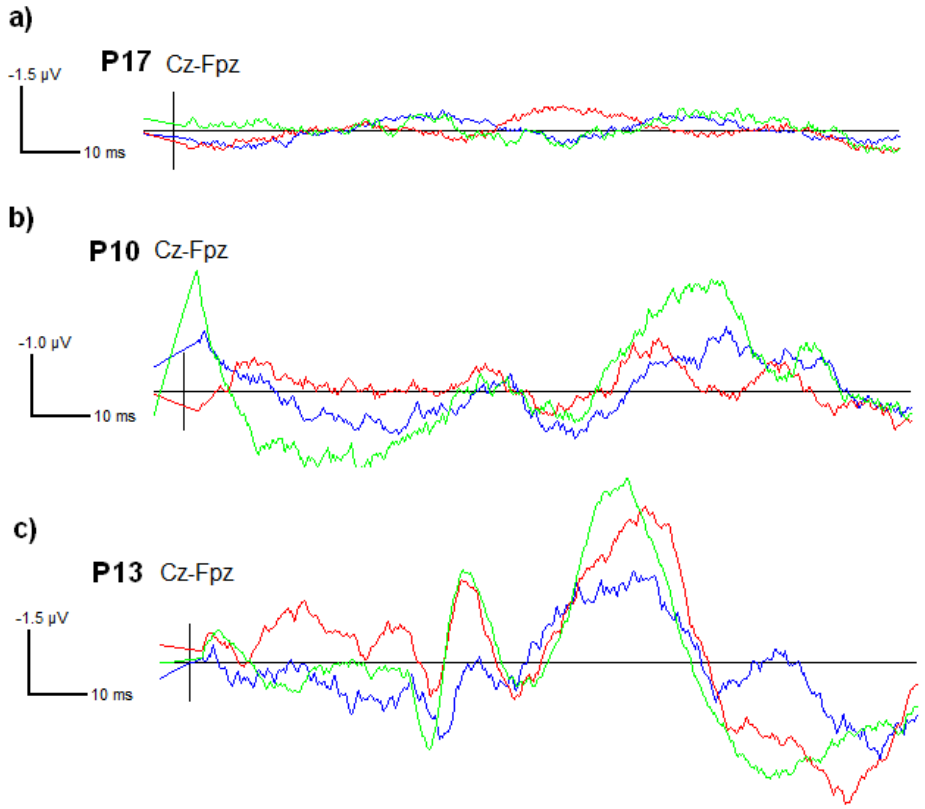


Figure 5-35: Left PT nerve SEP in 3 non ambulatory iSCI patients. a) No components are present (P17), b) waveform is abnormal (P10) and c) normal PT nerve SEP waveform (P13).

To identify any predictive value of the PT nerve SEP for ambulatory capacity in iSCI a statistical analysis was completed. A spearman's correlation coefficient was estimated to identify if any correlations between components within the baseline PT nerve SEP and ambulatory capacity after Lokomat training could be identified.

The ambulatory capacity was assessed using temporal gait analysis after 3 and 6 weeks of Lokomat training in 10 iSCI patients. Of these 10 iSCI patients 8 (5 acute, 3 chronic) patients also completed PT nerve SEP. Therefore data from only 8 patients (shown in Table 5-12) was used in the statistical analysis of temporal gait parameters and PT nerve SEP data.

Patient ID	Age	Gender	Time Post Injury (weeks)	Acute / Chronic	AIS Grade	Neurological level
3	61	Male	20	Acute	D	C3
8	59	Male	14	Acute	D	C4
15	44	Male	5	Acute	D	T8
5	48	Female	4	Acute	D	T11
9	58	Male	8	Acute	D	T11
6	61	Male	26	Chronic	D	C4
7	59	Male	169	Chronic	D	C4
14	53	Male	110	Chronic	D	C4

Table 5-12: Patient demographics (n=8) who completed temporal gait analysis and PT nerve SEP testing.

For each patient both the left and right PT nerve SEP was recorded, giving a result for P1, N1, P2 and N2 for the left and right side. The four components were identified in 5 patients on both sides (left and right limb). In 3 patients some or all of the components could not be identified. This further reduced the number of data points in the analysis. The gait analysis identified the patients walking speed, duration, cadence and double support time. These temporal parameters are not limb (left and right) specific. To enable a statistical analysis the results for the temporal gait assessment for each patient was entered for the left and right limb (i.e. double analysed).

After 6 weeks of Lokomat training significant correlations were seen between the double support time and the N2 component latency ($r = .670$, $p < .01$) and between walking speed and the P1-N1 inter-peak latency ($r = -.602$, $p < .02$) of the iSCI patient group. Correlations are strongest at 1 or -1 so although the results are highly significant the correlations are not strong. The data was reanalysed in 2 patient groups; acute (5) and chronic (3).

In the chronic iSCI patient group significant correlations were seen between the latencies of cortical components and the temporal gait parameters. Figure 5-36 illustrates the correlations between each of the temporal gait parameters; walking speed (Fig 5-36a), double support time (Fig 5-36b), stride length (Fig 5-36c) and cadence (Fig 5-76d) with each of the cortical components (P1, N1, P2, N2). Significant correlations were seen between the P2 peak component latency shown in

green in Fig 5-36a-d and all the gait parameters tested; walking speed (r= -.863, p<.01 (Fig 5-36a)), double support time (r= .973, p<.001 (Fig 5-36b)), stride length (r= -.863, p<.01 (Fig 5-36c)) and cadence (r= -.973, p<.001 (Fig 5-36d)). Correlations were also seen in the chronic group between the N2 peak component latency and the double support time (r= .949, p<.01) (Fig 5-36b) and cadence (r= -.949, p<.01) (Fig 5-36d).

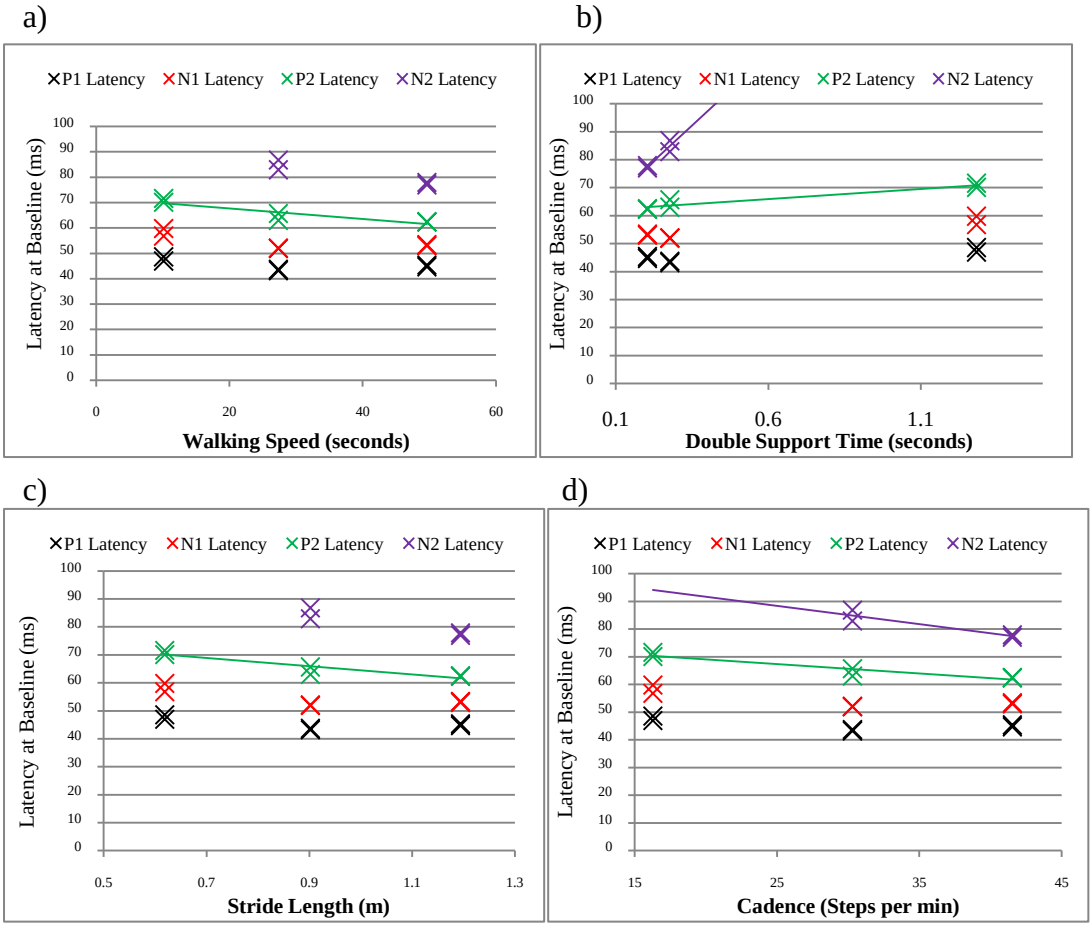


Figure 5-36: Correlation of cortical components and temporal gait parameters in chronic iSCI patients. Walking speed (a), double support time (b), stride length (c) and cadence (d) against the peak latency (ms) of P1 (black), N1 (red), P2 (green) and N2 (purple). See text for significant correlations.

Figure 5-37 shows the latencies of the PT nerve components for the acute iSCI patients. In the acute patient group significant correlations were seen between the N2 peak component latency and the double support time (r= .982, p<.00) shown in purple in Fig 5-37b and between the N2 peak component latency and cadence (r= -.788, p<.02) shown in purple in Fig 5-37d.

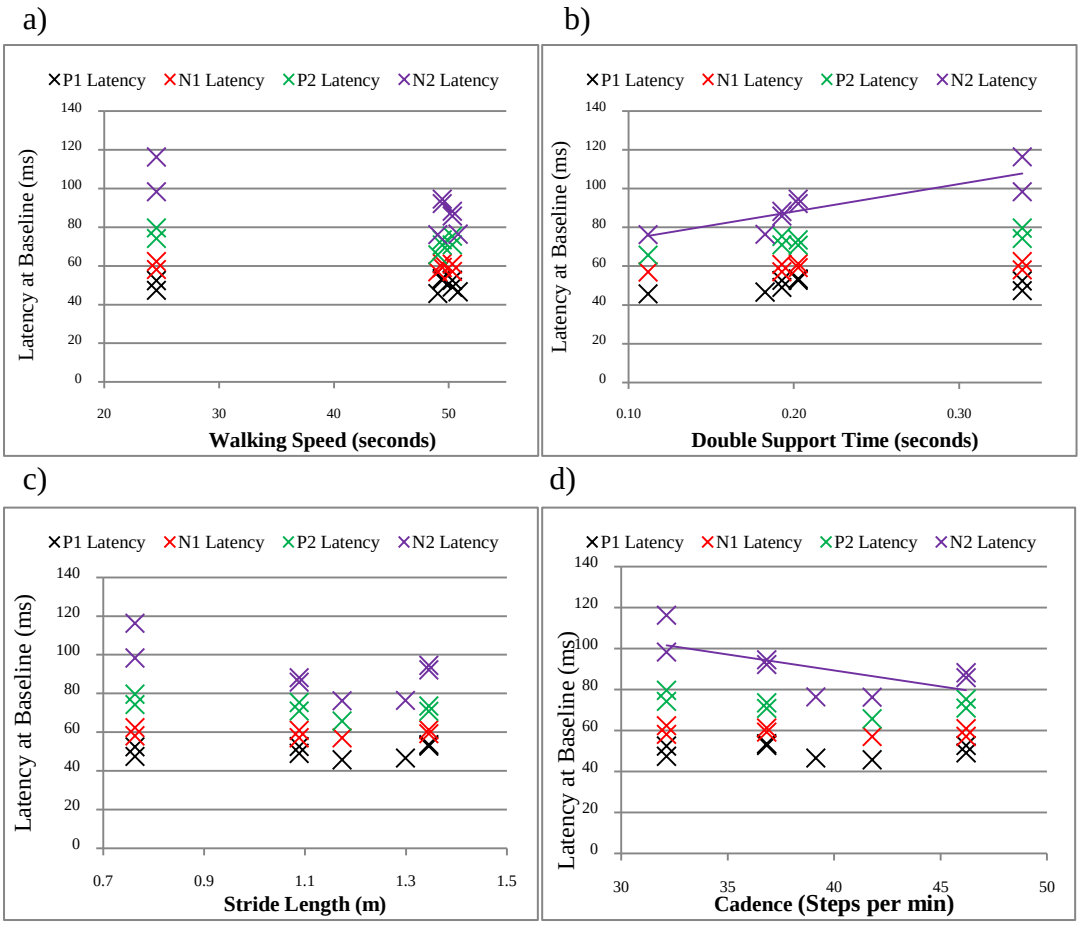


Figure 5-37: Correlation of cortical components and temporal gait parameters in acute iSCI patients. Walking speed (a), double support time (b), stride length (c) and cadence (d) against the peak latency (ms) of P1 (black), N1 (red), P2 (green) and N2 (purple). See text for significant correlations.

After 6 weeks of Lokomat training significant correlations were also seen in the acute iSCI group between the N1-P2 inter-peak latency and the stride length ($r = -.863$, $p < .01$). In the chronic patient group significant correlations were seen between; the N1-P2 inter-peak latency and the double support time ($r = .826$, $p < .02$) and between the N1-P2 inter-peak latency and cadence ($r = -.826$, $p < .02$).

No correlations were seen between the temporal gait parameters after 6 weeks of Lokomat training and the amplitudes of PT nerve SEP cortical components at baseline either the acute or chronic iSCI patient groups.

In summary the double support time is correlated to the 2 latency taken at the initial PT nerve SEP assessment in both groups.

MEDIAN NERVE SEP CORTICAL COMPONENTS

The cortical components which were measured form the median nerve SEP waveforms for each patient at baseline and after 3 and 6 weeks Lokomat training are illustrated in Figure 5-38. The front contralateral electrode (right SEP = F3, left SEP=F4) was analysed for the P13 and N18 components. The electrodes over the contralateral side of the somatosensory cortex (Cc and CPc) were used to analyse the N1 and P1 components.

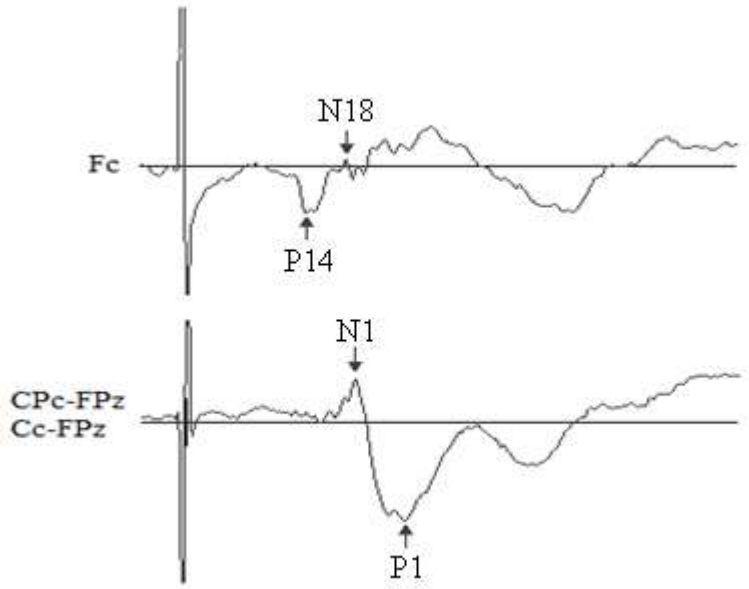


Figure 5-38: Components of the median nerve SEP. Each measured for latency; time from stimulus, and amplitude; height from baseline.

For each component the latency (ms) was measured from the point of stimulus (zero) shown by the vertical bar to the highest point of the peak or lowest point of the trough respectively. The amplitude was measured from baseline to the highest point of the peak or the lowest point of the trough respectively. The inter-peak latency and amplitude of P14-N18 and N1-P1 was calculated from the peak values.

CHANGES IN THE MEDIAN NERVE SEP AFTER LOKOMAT TRAINING

The upper limb SEP was completed on the median nerve at the wrist on the left and right limb at baseline and after 3 and 6 weeks Lokomat training. A lesion at T1 or above may affect the median nerve SEP as the median nerve comes from spinal

nerves C5 to T1 inclusively. The patients were analysed in 2 groups; patients with a lesion below T1 and patients with lesion at T1 or above.

The patients with a lesion below T1 are presented first followed by the patients with a lesion at T1 or above. Table 5-13 shows the patients with a lesion at T2 or below. No significant changes were seen after 3 or 6 weeks of Lokomat training in this group.

Patient ID	Age	Gender	Time post injury (weeks)	Acute / Chronic	AIS Grade	Neurological level
13	57	Female	13	Acute	C	T2
12	42	Male	6	Acute	C	T9
11	63	Male	8	Acute	D	C5
17	57	Male	8	Acute	D	T3
15	44	Male	5	Acute	D	T8
2	49	Male	13	Acute	D	T8
5	48	Female	4	Acute	D	T11
9	58	Male	8	Acute	D	T11
4	30	Male	44	Chronic	C	L1
1	26	Male	84	Chronic	D	C4

Table 5-13: iSCI patients with lesion at T2 or below. (n=10)

The peak latencies and amplitudes and inter-peak amplitudes for the patients with a lesion at T2 or below are shown in Table 5-14.

Median Nerve SEP Component	Latency		Amplitude	
	Mean (ms)	SD	Mean (µV)	SD
P14	13.77	.916	1.81	1.50
N18	16.97	1.13	0.23	.98
N1	19.40	1.05	-2.23	1.33
P1	26.43	3.68	2.45	2.64
P14-N18			1.59	.85
N1-P1			4.69	3.32

Table 5-14: Median nerve SEP (n=41) Mean and SD from 7 iSCI patients with lesion at or below T2. P14 and N18 were attained from Fc. N1 and P1 were attained from CPz-Fpz.

The patients with a lesion at T1 or above are shown in Table 5-15.

Patient ID	Age	Gender	Time post injury (weeks)	Acute / Chronic	AIS Grade	Neurological level
19	31	Female	11	Acute	C	C4
16	42	Female	12	Acute	C	C5
3	61	Male	20	Acute	D	C3
8	59	Male	14	Acute	D	C4
10	30	Male	18	Acute	D	C4
6	61	Male	26	Chronic	D	C4
7	59	Male	169	Chronic	D	C4
14	53	Male	110	Chronic	D	C4

Table 5-15: iSCI patients with lesion at T1 or above. (n=8)

In the median nerve SEP the early cortical components are the P13 and N18 shown in Figure 5-39 and are recorded from the contralateral and frontal electrode (F3 for right median nerve). It is the equivalent of the P30 in the PT nerve SEP. The P13 and N18 were observed in 7 (of the 8) patients with a lesion at T1 or above. Figure 5-39 is from P14 who has a C4 lesion. The P13 and N18 are clearly identifiable in all three test sessions; baseline (blue) and after 3 weeks (red) and 6 weeks (green) Lokomat training.

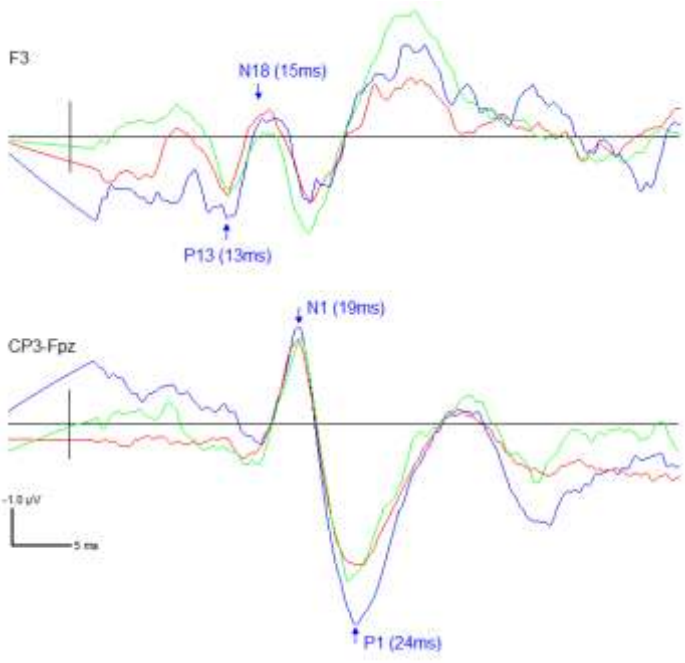


Figure 5-39: Right Median nerve SEP (P14) taken at baseline (blue) and after 3 weeks (red) and 6 weeks (green) Lokomat training.

In the median nerve SEP no significant changes ($p<0.05$) were observed in the peak latency, amplitude or inter-peak latency in either the chronic or acute patient group after 6 weeks Lokomat training.

5.6.2 SEP AND QST

The results of the PT and median nerve SEP were examined to identify any correlations to the quantitative sensory tests (EPT and VPT). The SEP is conveyed in the dorsal pathways (Curt and Dietz, 1999). Vibration which is also conveyed in the dorsal pathways has been shown to be correlated to the SEP delivered to the L4 dermatome (Hayes et al., 2002). Unlike the vibration stimulus the electrical stimulus is not detected by specific receptors but may be conveyed by different populations of nerve fibres and tracts. Correlations between EPT and dermatome SEP (Kramer et al., 2008) have demonstrated a relationship between the two stimuli and suggests that the electrical perception in also conveyed in the dorsal columns.

In this study we correlated the latency of the P1 cortical component of the PT nerve with the EPT and VPT results at L4 and L5 bilaterally. This gave 70 data points in the lower limb. Previous studies had looked at the P1 in categories; non affected, pathological and abolished and found raised thresholds for electrical perception when the SEP is pathological and raised further when the SEP is abolished (Kramer et al 2008). In this study this was not found which may be due to a smaller number of participants within the study. When each point (rather than a group mean) was analysed correlation between the latency of the P1 component in the PT nerve SEP and the EPT at L4 ($r=.421$ $p<.00$ Fig 5-40) and L5 levels ($r=.352$ $p<.00$ Fig 5-40) and VPT at L4 ($r=.353$ $p<.00$ Fig 5-41) and L5 ($r=.436$ $p<.00$ Fig 5-41) levels and were identified. This correlation suggests that the same pathway, DCML pathway is used to convey the afferent volley when elicited by either cutaneous vibratory or cutaneous electrical stimulation or electrical stimulation of a mixed peripheral nerve.

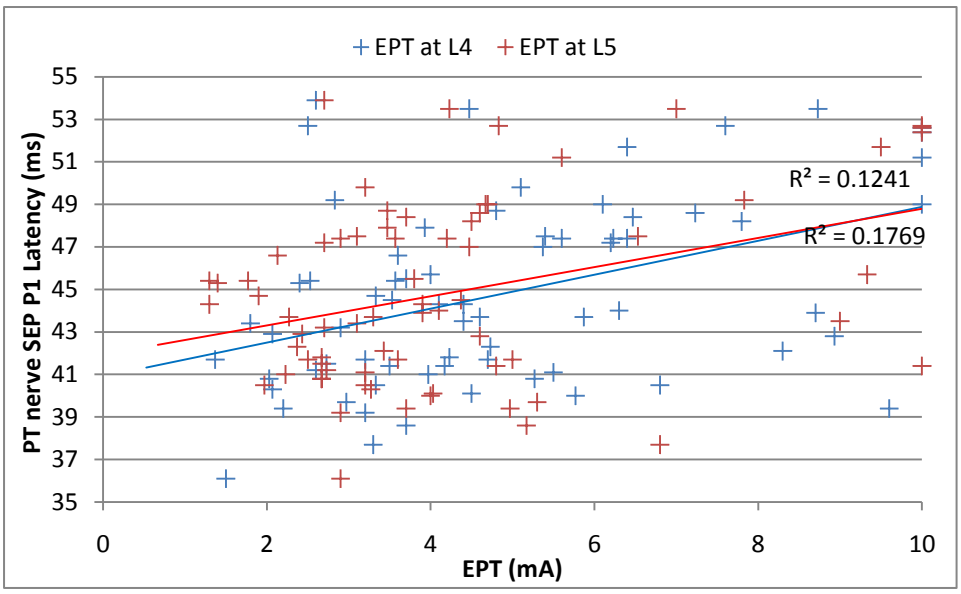


Figure 5-40: EPT (ms) for the left and right side at dermatomes L4 and L5 in iSCI patients against the left and right PT nerve SEP P1 latency (ms). The red points indicate the EPT taken at L4 and the blue EPT taken at L5. (n=70).

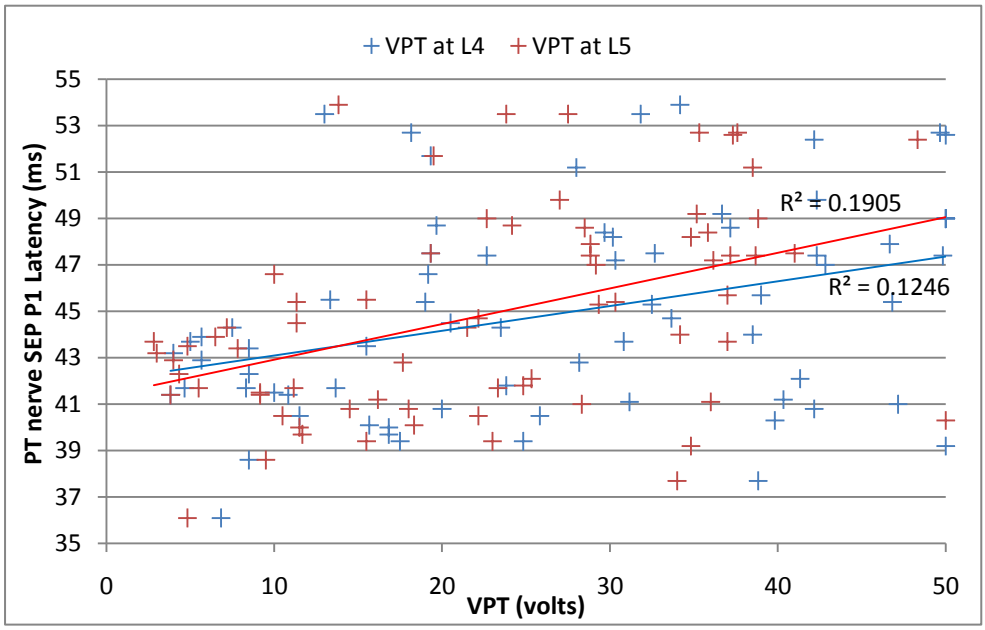


Figure 5-41: VPT (volts) for the left and right side at dermatomes L4 and L5 in iSCI patients against the left and right PT nerve SEP P1 latency (ms). The red points indicate the VPT taken at L4 and the blue VPT taken at L5. (n=70).

For the upper limb the N1 cortical component of the median nerve SEP was compared to the EPT (Fig 5-42) and VPT (Fig 5-43) values taken at dermatomes C5 and C6 bilaterally which gave 88 data points for the upper limb. 2 data points were identified as outliers. The statistical analysis was conducted with and without these

data points. The QST and SEP data are parametric so a Pearson correlations coefficient was calculated between the median nerve SEP and the electrical perception. At levels C5 (r=.612 p<.00 Fig 5-42) and C6 (r=.573 p<.00 Fig 5-42) significant correlations between the SEP and EPT data are seen. The correlation was also significant when the outliers were kept in the analysis; C5 (r=.622 p<.00 Fig 5-42) and C6 (r=.620 p<.00 Fig 5-42). Correlations between the median nerve SEP and the vibration perception at C5 (r=.593 p<.00 Fig 5-43) and C6 (r=.672 p<.00 Fig 5-43) are seen.

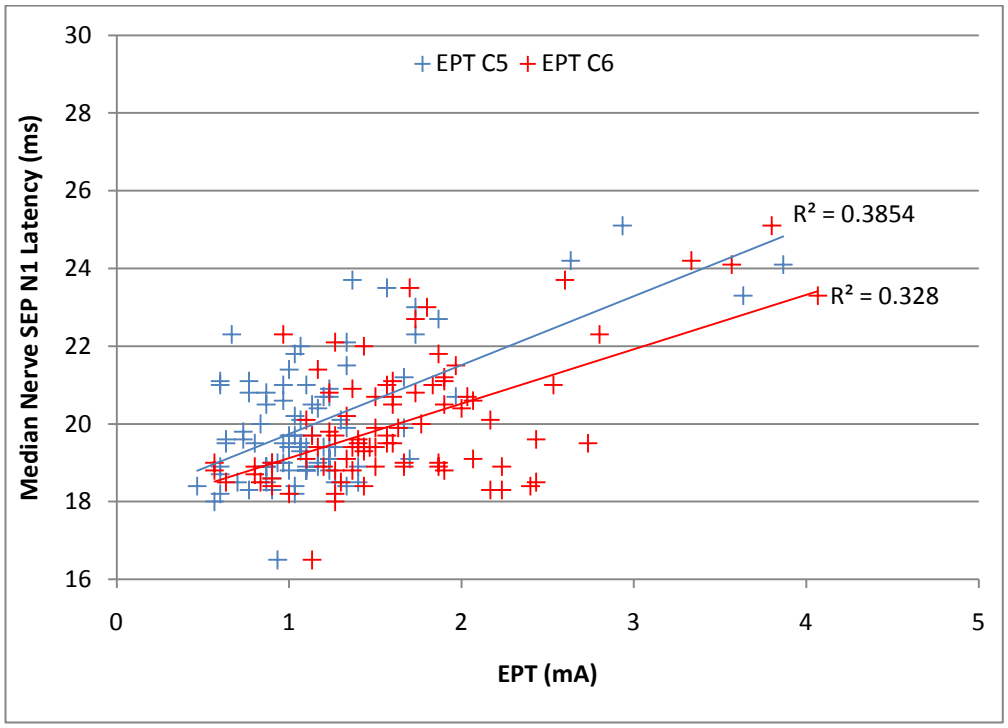


Figure 5-42: EPT (ms) for the left and right side at dermatomes C5 and C6 in iSCI patients against the left and right PT nerve SEP P1 latency (ms). The red points indicate the EPT taken at C6 and the blue EPT taken at C5. (n=86).

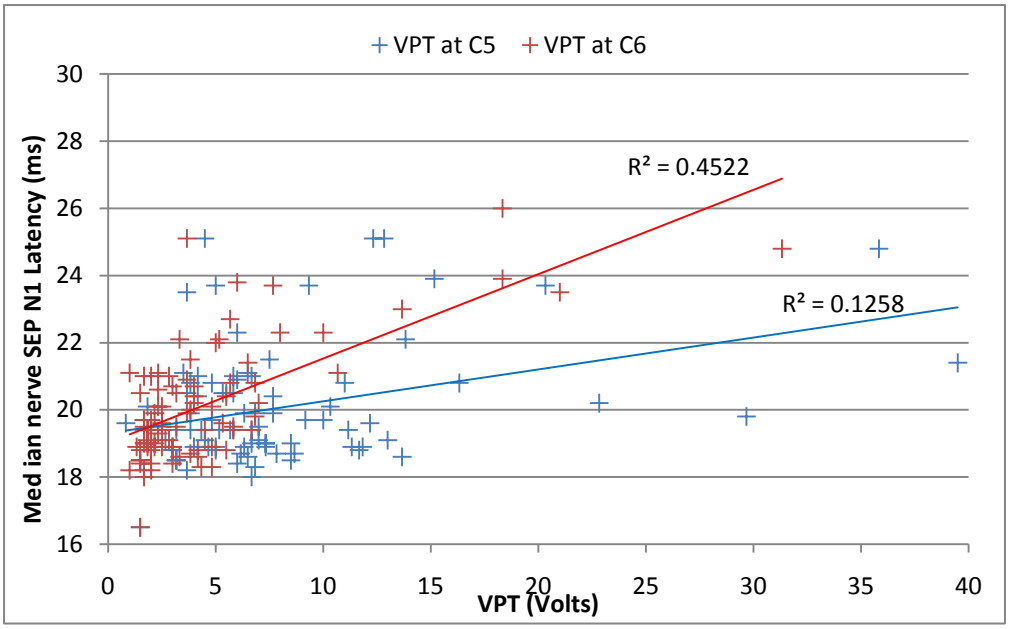


Figure 5-43: VPT (volts) for the left and right side at dermatomes C5 and C6 in iSCI patients against the left and right PT nerve SEP P1 latency (ms). The red points indicate the VPT taken at C6 and the blue VPT taken at C5. (n=88).

5.6.3 SEP FREQUENCY ANALYSIS.

Frequency analysis is not commonly used in the data processing of SEPs. However if done it provides additional information to the time analysis (see signal processing for further details). For each electrode a graph is produced which shows the frequency (from 1-35Hz) and timing of desynchronization and synchronization of neural activity underlying the electrode. This graph is termed the Event Related Spectral Perturbation (ERSP).

Figure 5-44 shows the ERSP for a single healthy subject. The areas of desynchronization are shown in cold colours and areas of synchronization in hot colours. The stimulus was applied at time zero. A period of desynchronization is present in healthy subjects after PT nerve stimulation (Neuper et al., 2006)from the point of stimulus (zero time) to 800ms between the frequencies 12 and 16Hz as shown by the white box. This test was completed in the iSCI patients to identify if this period of synchronization is present and if it is not present does it return with improved ambulatory capacity.

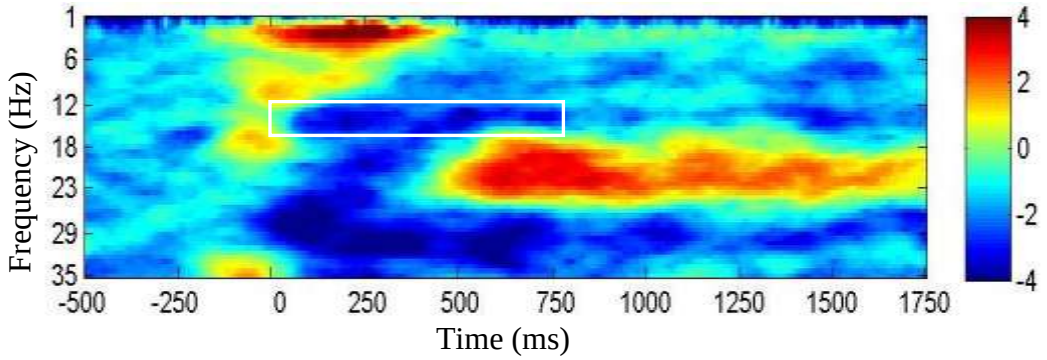


Figure 5-44: ERSP in a single healthy subject recorded at Cpz. Activity prior to the stimulus time (zero) is seen. This is created by the overlapping of the 200ms windows to create this plot.

During this study changes in the ERSP were not identified in the iSCI patients after 6 weeks of Lokomat training. Fig 5-45 shows an example of the ERSP taken in 3 patients at baseline and after 6 weeks Lokomat training. The first figures (Fig 5-45a) are from a patient who had a large improvement in their ambulatory capacity as assessed by the WISCI II scale and temporal gait analysis. The second and third figures (Fig 5-45b and c) are from patients who had a small improvement and no change in their ambulatory capacity respectively. By visual inspection there is no change in the desychronization between 0-800ms in the frequency band 12-16Hz in any of these patients. No difference were observed between patients that improved ambulatory capacity and those that did not.

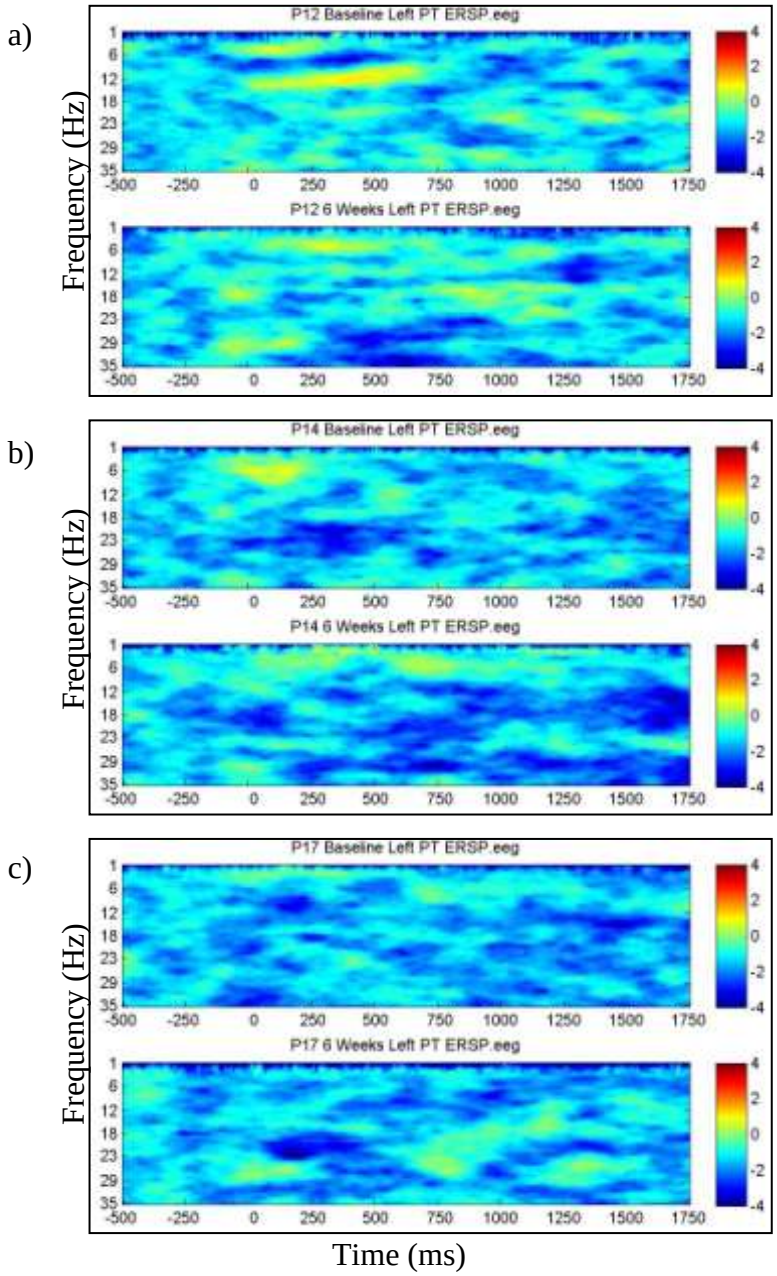


Figure 5-45: ERSP graphs from 3 iSCI patients; a) patient who had a large improvement in ambulatory capacity, b) small improvement in ambulatory capacity and c) no change in ambulatory capacity after 6 weeks of Lokomat training as assessed by the WISCI II scale and temporal gait analysis.

Fig 5-45 shows no clear visual changes in the ERSP after 6 weeks of Lokomat training. To determine if any statistical changes occurred in the ERSP a t-test was completed between each patient's baseline and 6 weeks assessment. The t-test was completed in MATLAB and compared each voxel at baseline to each voxel after Lokomat training. The MATLAB code was written by Dr Gopal Valsan at

Strathclyde University. Fig 5-46 shows an example t-test result. Significant changes between the top two panels are shown in the bottom panel in blue, the darker the blue the more significant the difference as shown by the colour panel on the right of Fig 5-46. No significant changes in the ERSP between 0 - 800ms at frequencies between 12 - 16Hz as shown by the white box are observed. No significant changes in this time and frequency band were observed in any of the iSCI patients after 6 weeks Lokomat training.

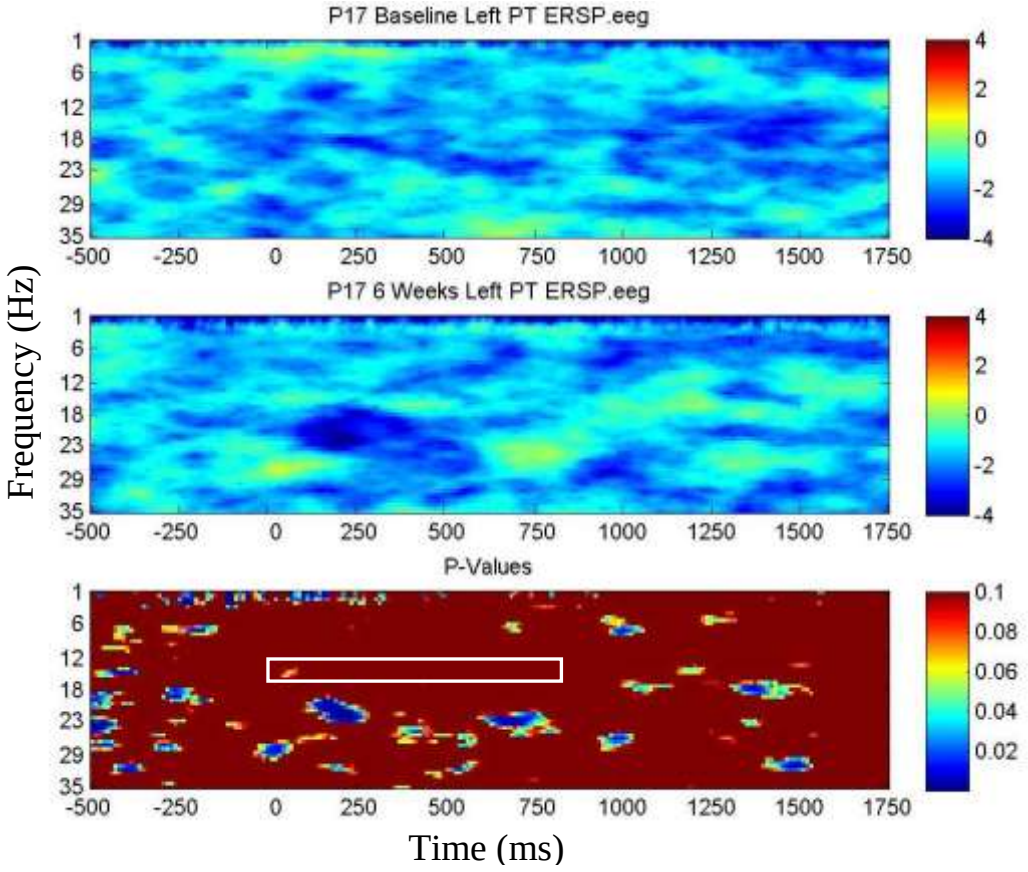


Figure 5-46: T-test of the ERSP graphs from an iSCI patients taken at baseline and after 6 weeks of Lokomat training. Significant changes between the top two panels are shown in the bottom panel in blue, the darker the blue the more significant the difference. No significant changes were seen between 0-800ms in the frequency band 12-16Hz as shown by the white box. Desychronization is seen in this time and frequency band in healthy subjects after lower limb stimulation.

6 RESULTS - MODULATION OF CORTICAL POTENTIALS DURING WALKING

The PT nerve was stimulated in healthy subjects during sitting, standing and treadmill walking to identify and report the cortical evoked responses observed. The morphology and timings of these evoked responses during treadmill walking were compared to the evoked responses observed during sitting and standing to determine if any gating or modulation of the waveform occurs during walking.

6.1 SUBJECT DETAILS

10 healthy volunteers (6 Male and 4 Female) with a mean age of 29.8 years (range 23-41) participated and completed the study. 9 Subjects were right handed and 1 left handed.

Subject	Age	Gender	Left / Right Handed
1	27	Female	Left
2	23	Female	Right
3	32	Male	Right
4	29	Female	Right
5	33	Male	Right
6	29	Male	Right
7	28	Male	Right
8	41	Male	Right
9	28	Female	Right
10	28	Male	Right

Table 6-1: Subject demographic data. (n=10)

6.2 TIMING OF THE GAIT CYCLE

Each subject completed a 2 minute familiarization walk at a constant speed of 4kmh^{-1} on the treadmill during which the duration of their gait cycle time was calculated. The timing of heel strike and toe off in consecutive steps was recorded. The averaged duration of a complete gait cycle and the averaged duration of the stance

and swing phases were calculated from the heel strike and toe off timings taken over 10 consecutive steps during a period of steady state walking on the treadmill. Table 6-2 shows the duration of the gait cycle time and the duration of the stance and swing phase for each subject. The range of gait cycle time in 10 healthy volunteers was 0.342 seconds (0.999-1.341). Large variation in gait cycle times means that the time duration of the stance and swing phase also varied between subjects. The percentage of the stance and swing phases were calculated for each subject and shown in Table 6-2.

Subject	Gait cycle duration (s)	Stance phase duration (s)	Stance phase % of gait cycle	Swing phase duration (s)	Swing phase % of gait cycle
1	0.999	0.602	60.3	0.397	39.7
2	1.074	0.652	60.7	0.421	39.2
3	1.085	0.627	57.8	0.457	42.1
4	1.123	0.637	56.7	0.49	43.6
5	1.140	0.661	58.0	0.48	42.1
6	1.160	0.694	59.8	0.465	40.1
7	1.206	0.717	59.5	0.502	41.6
8	1.217	0.715	58.8	0.502	41.2
9	1.237	0.734	59.3	0.502	40.6
10	1.341	0.775	57.8	0.567	42.3
Average	**1.16**	**0.68**	**59**	**0.48**	**41**

Table 6-2: Gait cycle duration from 10 healthy subjects during treadmill walking at 4kmh^{-1}

As the gait cycle time varies between subjects the timing of the stimulation was applied at a percentage of the gait cycle rather than a fixed time after heel strike or toe off. The stimulus was applied at 50% of stance duration and termed 'Mid Stance' and 62% of swing duration, termed 'Mid Swing'. The 62% of swing duration was used to enable the period of unloaded dorsiflexion, i.e., TA activity in the swing phase.

6.3 EMG ACTIVITY

The four points within the gait cycle where stimulus was applied were plotted on the averaged EMG activity during the gait cycle to show the timing of the stimulus points.

The EMG activity of the ankle flexors (TA) and extensors (GM) were recorded during normal walking and during stimulated steps. The right heel strike was used to construct averaged rectified EMG waveforms for the TA and GM muscles during the gait cycle for each subject during normal walking. Figure 6-1 shows an example of the average gait cycle of rectified EMG waveforms for the TA and GM muscles for a single subject during normal treadmill walking.

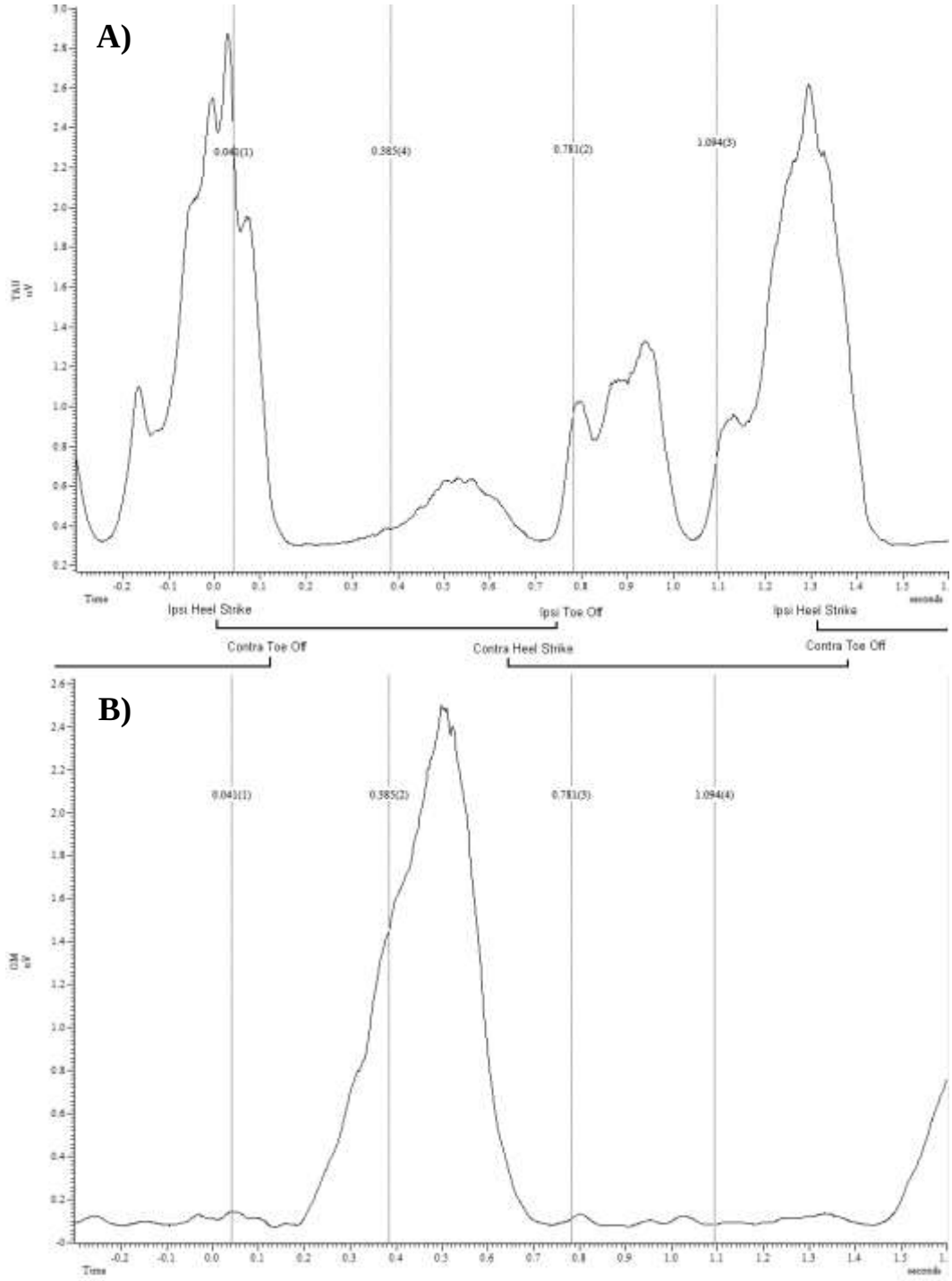


Figure 6-1: EMG activity in a) the ankle flexors (Tibialis Anterior TA) and b) the extensors (Gastrocnemius GM) during the gait cycle.

The timings of the 4 stimulus points applied are shown by the vertical lines. The first stimulus within the gait cycle (point 1 in Fig 6-1a) was applied during the ipsilateral TA muscle burst occurring after heel strike. The second stimulus was applied during

mid stance when the limb is fully loaded and the TA muscle was quiet and the GM muscle was active. The third stimulus was applied after toe off during the second burst of activity in the TA muscle. The final stimulus to be applied within the gait cycle was during mid swing with the TA muscle active during terminal swing and early stance. The stimulus points occurred at the same points within the gait cycle for each subject.

6.4 SITTING AND STANDING SEP WAVEFORM

For each task (sitting, standing, treadmill walking) the stimulus was applied to the right PT nerve at twice motor threshold (2x MT). The MT was determined whilst the subject was sitting (see Methods p65). The intensity of the stimulus during each task was reflected in the amplitude of the M-wave recorded in the Abductor Hallucius (ADH) muscle. During each test the EMG from the Abductor Hallucius muscle was collected. An average waveform for each task was calculated and the M-wave identified. The amplitude of the M-wave during standing and each phase of the gait cycle were compared to the amplitude of the M-wave during sitting.

Large variations in the amplitude of the M-wave were seen between sitting and standing tasks. This change in M-wave amplitude may reflect a change in the intensity of the stimulation seen by the nerve. The output, i.e., stimulus strength from the stimulator remains constant throughout, however if the nerve moves away from the electrode which is taped to the skin the nerve will detect a smaller stimulus intensity. The variation in stimulus strength was not reflected within the morphology, latency or amplitude of the cortical components of the PT nerve SEP. Figure 6-2 shows the cortical component of the PT nerve SEP evoked during sitting and standing tasks in a single subject. The latency and amplitude of the component peaks are the same in each posture but the M-wave observed during standing was 38% of the amplitude of that observed during sitting.

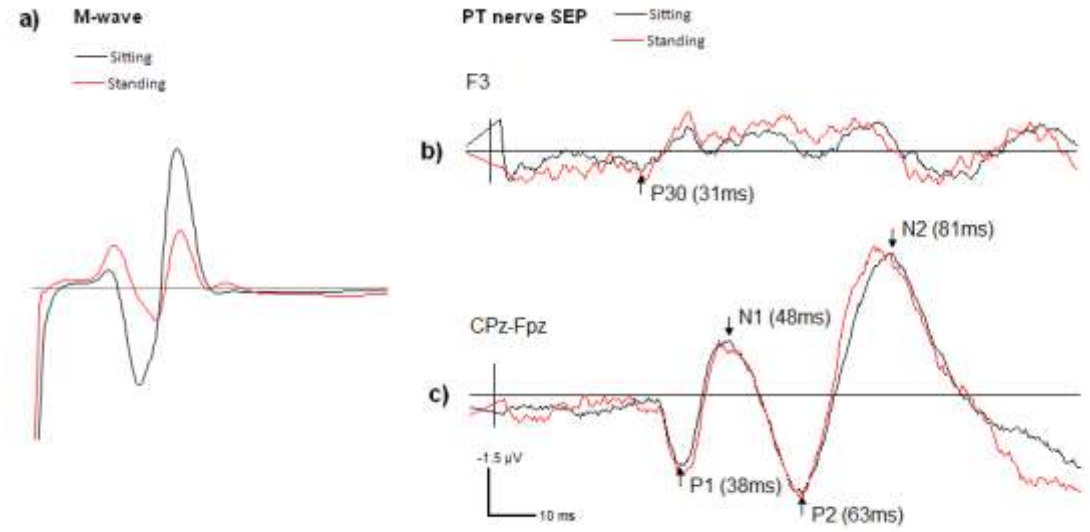


Figure 6-2: M-Wave from ADH (a) and cortical components of the PT nerve SEP from sitting (black) and standing (red) postures recorded at F3 (b) and Cpz-Fpz (c) in a single subject (S5).

In Figure 6-2c the components of the PT nerve SEP waveform, P30, P1, N1, P2 and N2 can be identified. To identify any differences between the sitting and standing tasks the latencies and amplitudes of the components were recorded for both tasks in each subject and the averaged data was complied and shown in Table 6-3.

The earlier component observed in F3 (P30) represents the arrival of the volley at the thalamus. By identifying this component during different postures may reflect if modulation of the sensory processing is supraspinal or spinal. In PT nerve SEP evoked during sitting the P30 had a mean latency of 30.12ms and during standing the mean latency decreased to 29.73ms. No significant difference between the latency of the P30 component in the 2 postures was seen (p=.387). However, the amplitude was significantly different (p=.006) between the mean sitting amplitude (0.60µV) and mean standing amplitude (1.10µV).

Of the components recorded from CPz-FPz the latency of the P1 component was significantly different during standing when compared to sitting (p=.047). However the change in latency was not greater than 1 SD from sitting. No other significant differences were observed.

Cortical Component	Sitting			
	Latency		Amplitude	
	Mean (ms)	SD	Mean (μV)	SD
P30	30.12	1.31	0.56	0.26
P1	38.31	1.51	3.03	1.85
N1	48.05	1.77	-1.59	1.14
P2	60.05	2.71	1.40	1.32
N2	74.18	6.83	-2.89	2.30

Cortical Component	Standing			
	Latency		Amplitude	
	Mean (ms)	SD	Mean (μV)	SD
P30	29.73	1.31	1.10	0.51
P1	39.19	1.65	2.65	1.55
N1	49.16	1.71	-1.50	1.00
P2	59.72	2.59	1.71	1.16
N2	75.52	6.43	-2.94	1.56

Table 6-3: Average latencies and amplitudes (n=10) of cortical components after stimulation of the PT nerve in the sitting and standing tasks.

6.5 NORMAL WALKING PHASE DEPENDENT WAVEFORM

Prior to identifying the cortical potentials evoked by PT nerve stimulation this study aimed to identify any cortical potentials that are evoked during normal treadmill walking (i.e., in absence of electrical stimulus).

For each of the four phases of the gait cycle (heel strike, mid stance, toe off and swing) an averaged epoched waveform was produced. This shows the activity that occurs during the 4 phases of the gait cycle during non stimulated (normal) treadmill walking. The waveform for each phase was produced and the sitting waveforms were overlaid for comparison (Fig 6-3).

The gait initiated cortical components evoked during normal treadmill walking were not clearly identified in all subjects. Figure 6-3a-d shows the waveforms during normal walking in red for a single subject (S8) with the PT nerve SEP evoked during sitting superimposed in black. At heel strike event related potentials are observed that have components similar to those seen in the PT nerve SEP evoked during the

sitting task. There is an early and late component that may be initiated by sensory synchronization in proprioceptive and cutaneous afferents due to heel strike. The early component is similar to the P1 component shown in fig 6-3a which was observed in 3 subjects. The late component is similar to the N2 component shown in fig 6-3a which was observed in 4 subjects. The remaining subjects did not show any identifiable components during the normal walking tasks.

The afferent volley during the non stimulated walking will not have the tight synchronization that is generated by the electrical stimulation and this could explain why the cortical components are smaller in amplitude but with wider duration and why they are not present in all subjects. These components may reflect physiological activity in the sensory pathways or may be caused by movement artefact as the foot strikes the ground. Identification of this component as either physiological or not is important in understanding the processing of sensory information during normal, unperturbed walking. It is unlikely however to be an artefact created by the foot striking the floor as the early peak occurs at ~80ms after heel strike and the late component ~120ms after heel strike.

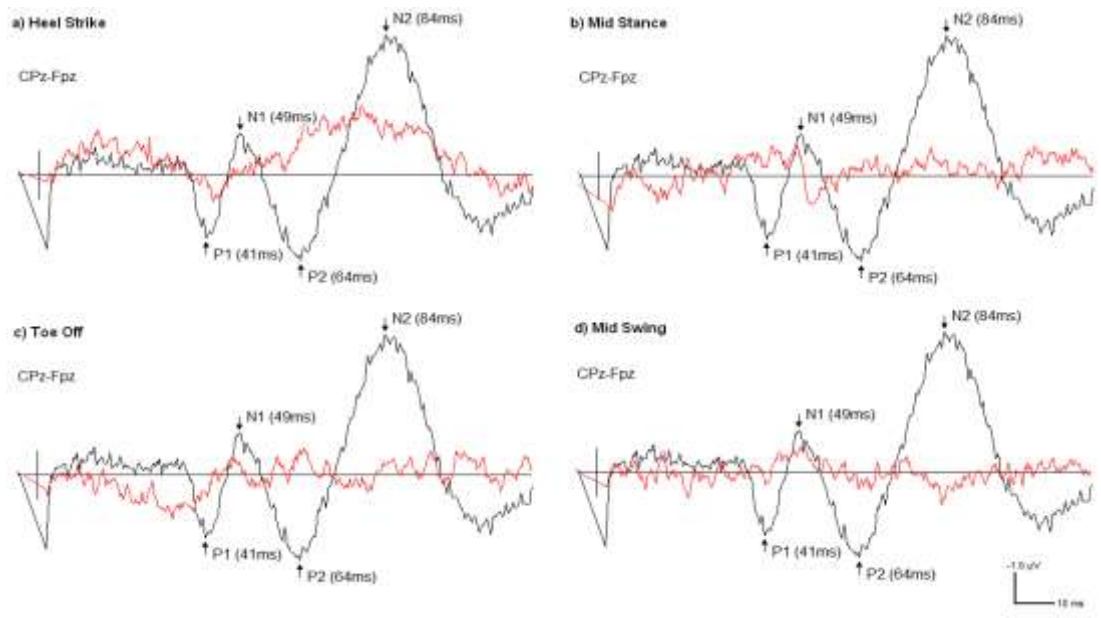


Figure 6-3: Non stimulated phases of the gait cycle (red) and sitting cortical components from PT nerve in black from a single subject. Clockwise from top left; a) Heel strike, b) mid stance, c) toe off and d) swing. (Subject 8)

6.6 STIMULATED PHASE DEPENDENT WAVEFORM

During the four phases of the gait cycle the amplitude of the M-wave was consistent within each subject. Figure 6-4 shows the M-waves for a single subject at each phase of the gait cycle. This suggests that the intensity of the stimulus was relatively constant throughout the four phases of the gait cycle. The presence of the SEP waveform in any phase of the gait cycle would indicate that the stimulus intensity was at an intensity to produce the waveform at each stage of the gait cycle, assuming no modulation of sensory information.

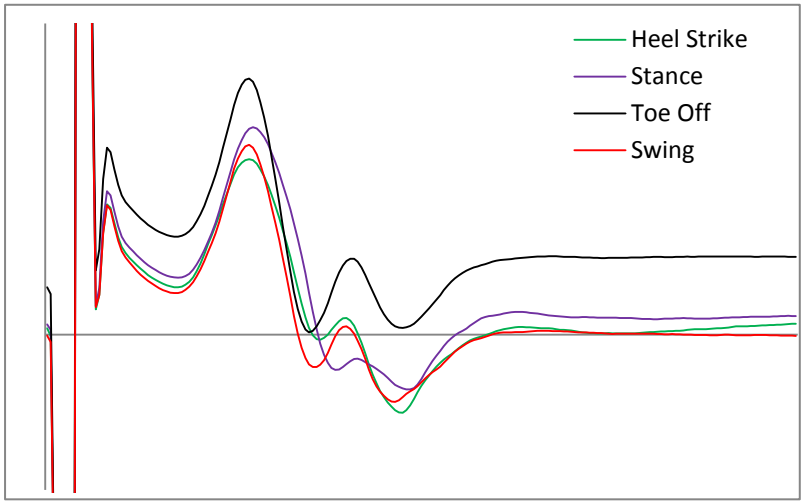


Figure 6-4: M-wave from ADH muscle evoked by stimulation of the PT nerve at the ankle during standing and 4 phases of the gait cycle. (Subject 8)

The EEG waveform during the four phases of the gait cycle was epoched from the four point of stimulus. The cortical potential, P30 seen in the PT nerve SEP during sitting and standing, was not identified in the healthy subjects during any of the four phases of the gait cycle. The component was not observed but may have been present, movement artefact or the small number (~100) of stimuli presented during walking may have led to the waveform not been observed within the time analysis techniques. Further trials are required to determine if this component is present or absent during gait. The resultant waveforms from Cpz-Fpz are presented with the sitting PT nerve SEP waveform overlaid for comparison in Figures 6-5a-d.

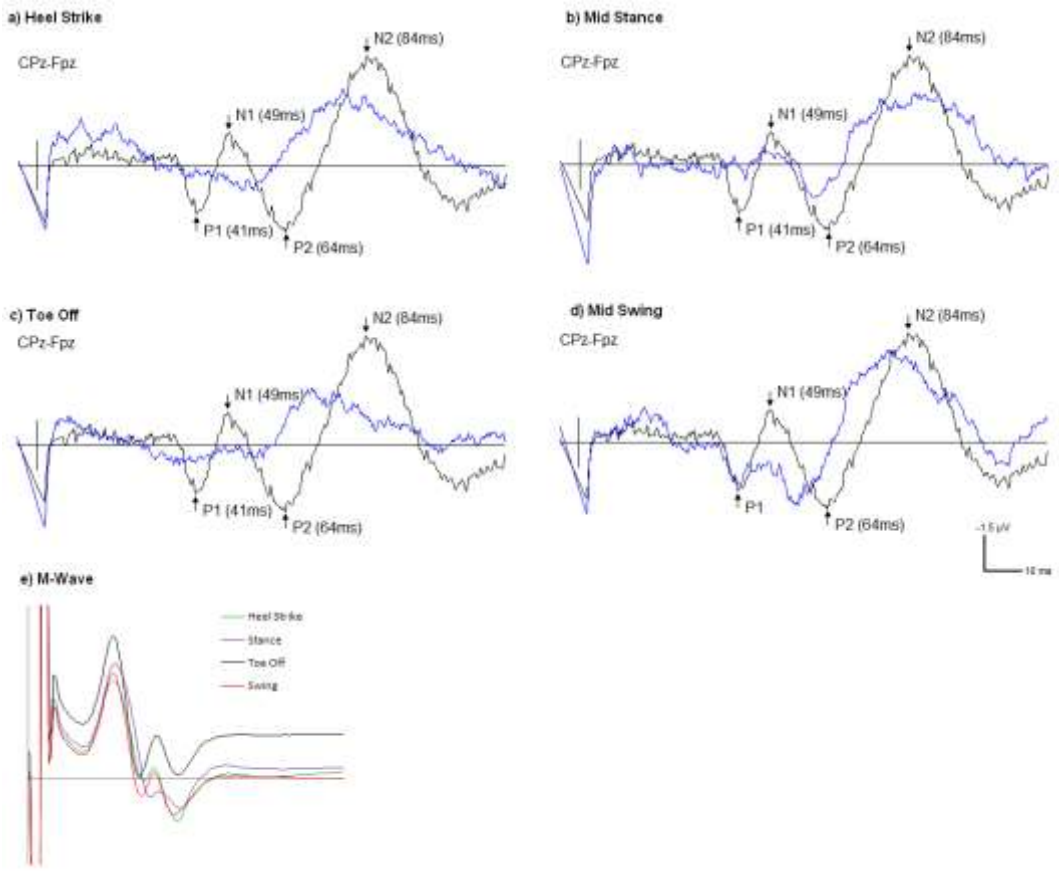


Figure 6-5: Cortical components evoked during treadmill walking with stimulus (blue) at the PT nerve during four phases of the gait cycle recorded at Cpz-Fpz. 4 Phases of the gait cycle from top left; a) heel strike, b) stance, c) toe off and d) swing. The PT nerve SEP taken during sitting is superimposed (black).

An SEP waveform that is similar in morphology with 4 components present (n=5) to that seen during rest was seen when the stimulus was applied during mid stance and mid swing, shown in figure 6-5b and d respectively. The amplitudes of the 4 components of the waveform are reduced compared to the P1, N2, P2 and N2 cortical components seen in the sitting PT nerve SEP. During heel strike and toe off, figure 6-5a and c respectively, a late component similar to N2 (n=5) was seen. The early components similar to the P1 and N1 in the sitting PT nerve SEP were not present in these phases in 3 subjects. The P1 and N1 were present in 4 subjects in the Toe off phase but were not present in the Heel strike phase.

The PT nerve SEP waveforms displayed for sitting, normal walking without stimulus and during stimulated steps show the clear differences between the tasks and phases of the gait cycle (Fig 6-6a-d). In the mid stance and swing phase of the gait cycle the

morphology of the waveform shows four components present. This suggests that the intensity of the stimulus is large enough to produce a PT nerve SEP waveform. It can also be seen that during these phases of the gait cycle that in the non stimulated steps no naturally evoked SEP waveform is present. During heel strike and toe off the late component, N2 is present but the early components are not. This may suggests a modulation of the sensory information conveyed during heel strike and toe off. As the early components are not present the modulation may occur within the thalamus or within the spinal cord. By determining the presence or absence of the P30 component (recorded in a front contralateral electrode evoked from PT nerve stimulation) that reflects the arrival of the volley in the thalamus more detail over the location of any modulation may be gained.

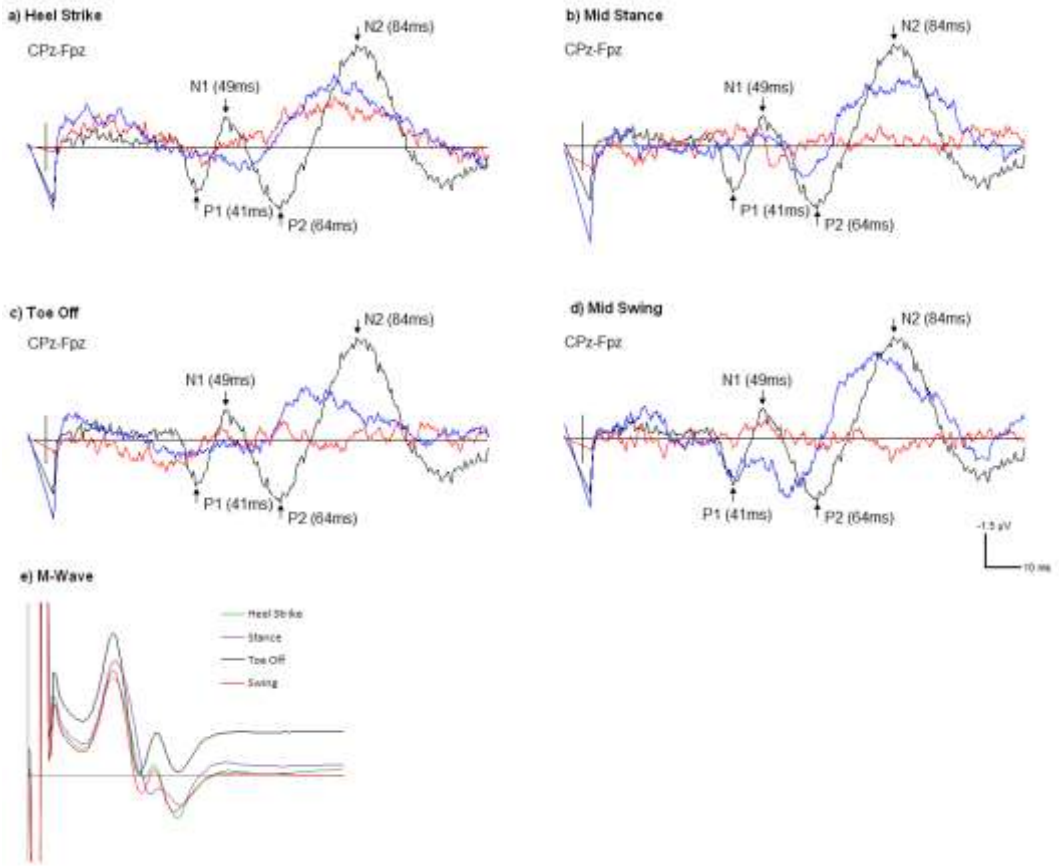


Figure 6-6: Cortical components walking with (blue) and without stimulus (red). 4 Phases of the gait cycle from top left heel strike, stance, toe off and swing. The PT nerve SEP taken during sitting is superimposed (black).

7 DISCUSSION

This study in two parts has looked at the sensory assessments of spinal cord function in relation to recovery of ambulatory capacity in iSCI patients and the evidence of sensory information processed via a transcortical pathway during locomotion. The sensory assessments used are discussed in relevance to their reliability and sensitivity to detect physiological changes that occur with improved function after Lokomat training. This chapter first discusses the patient recruitment, intervention used and the assessment of ambulatory capacity. The cortical potentials evoked during treadmill walking are then discussed focusing on the methods used and the results observed. The chapter will then close with the discussion of how the presence of modulation in the cortical potentials and the significance of the PT nerve SEP as a predictor of ambulatory capacity reflects the role of afferents in the neural control of gait and how this may direct future methods of rehabilitation.

In this study 18 iSCI patients were assessed over a six week period of repetitive, task dependent, functional rehabilitation programme using a driven gait orthosis (the Lokomat). Functional assessments were used to identify which iSCI patients showed improvements in ambulatory function after Lokomat training.

7.1 PATIENT RECRUITMENT

19 iSCI patients were recruited on to the study and 18 completed the study. Of the 18 patients 5 were chronic iSCI patients and 8 acute iSCI patients. Recruiting chronic iSCI patients was difficult as they needed to be living within a commutable distance to the QENSIU in Glasgow. The patients needed to be physically able and willing to commute into the hospital on a daily basis for testing and Lokomat training. During the testing weeks (weeks 1, 5 and 8) the patients were required to be at the hospital from 9am till 5pm Monday to Friday. During the weeks when only Lokomat training was completed (i.e. no testing sessions) the patients were required to be at the hospital for 2 hours per day, Monday to Friday. The travel distance and associated costs limited the geographical area in which the patients could be

recruited from and hence reduced numbers of chronic iSCI patients recruited into the study.

The acute patients were recruited from inpatients at the QENSIU. Although travel was not a consideration for these patients a commitment by both the patient and the clinical staff was required to ensure the patient was available for early morning training and testing throughout the day. Careful time management and awareness of the patients' clinical procedures, physiotherapy and occupational therapy was important to ensure the acute patient did not miss out on any form of their treatment due to participating on the study. Due to the intensive nature of this form of rehabilitation, the patient's ability to complete such a programme should be considered carefully prior to future studies involving iSCI patients.

7.1.1 PATEINT DEMOGRAPHIC

The aim of this study was to evaluate the use of Quantitative sensory testing (QST) and Somatosensory Evoked Potentials (SEP) as assessment tools to evaluate spinal cord function. 18 Incomplete SCI patients completed the study. The patients demographic spread was large. The patients were; male and female, aged from 30 to 63 years old, acute and chronic, AIS C and D, and the level of the lesion was from C4 to L1. With a large variation in the type, extent and level of the lesion the functional outcome and efficacy of the intervention was also varied across the patient group. Trials studying iSCI patients with specific injuries may provide more specific data but are also extremely difficult to recruit the patient numbers needed.

One main aspect that may have an effect on the patients' improvement is the period of time since their injury. This study looked at the changes that occurred over a 6 week intervention. The period of intervention was not at the same point in time from the injury for each patient. By looking at these assessments over a longer period of time and linking the assessment to the time of injury the progress of natural recovery and intervention induce recovery may be identified.

7.2 LOKOMAT TRAINING

The Lokomat training was provided for each patient on a daily basis for a total of 30 sessions in a 6 week period. The dosage of training (number of training sessions) for optimal recovery is unknown. 6 weeks Lokomat training was decided upon with an assessment block halfway through the training period. To indentify the optimal dosage of training further work with functional assessments made at regular and shorter time intervals is required.

Although 30 sessions were set out in the protocol for each patient not all sessions were completed by the patients. The number of sessions completed by the patient varied across the group due to illness and bank holidays. Sessions were missed due to ill health more often in the acute patient group than the chronic patient group. This was expected as their injury is not stable and the patients are more disposed to periods of illness. In one patient (P5) 7 days were taken as ill health. This patient found the supporting straps of the Lokomat harness to be extremely uncomfortable, although no skin damage was seen by visual inspection some sessions were aborted due to this discomfort.

Although there is variation in the number of Lokomat sessions completed by the patients the assessments were completed after 3 and 6 calendar weeks in all patients. This may have had an effect on the degree of improvement seen in some of the patients. However it should be noted that throughout the study the acute patients also underwent physiotherapy and the chronic patients were not restricted in their daily activity. Therefore the amount of rehabilitation and physical activity each patient completed was different and this may have altered the level of improvement seen between the patients. The aim of this study was not to assess the Lokomat as a form of functional rehabilitation of iSCI as this has been previously documented (Colombo et al., 2001, Dietz et al., 1998), but by using sensitive and reliable test measures set out in the first phase of the clinical initiative it was hoped that any physiological changes that occur with the improved (or regained) ambulatory capacity could be identified. This may provide physiological explanations as to why

some iSCI patients improve better than others after Lokomat training and guide the methods for rehabilitation.

As well as the number of Lokomat training sessions it is not known what the optimal duration of each Lokomat session should be to promote recovery. In this study the patients progressed from 15 minutes walking time to 1 hour within the first week. Progressive training was needed to increase the patients stamina and to enable the skin to become resistant to the pressure from the harness straps. One hour of training was selected as a compromise between training time and the patients' physical and mental endurance for the task. During the training the patients were required to assist the Lokomat in moving their legs and this was physically tiring for the patient. With increased body weight (reduced body weight support) more effort was required by the patient. This study did not assess the effectiveness of the training session duration however it is important to ensure effective use of both the patients and the Lokomat time. Future work to assess the efficacy and dosage of the Lokomat in acute and chronic iSCI patients is needed to resolve this outstanding issue.

During this study the ambulatory capacity of the patients was assessed after 3 and 6 weeks of Lokomat training. This enabled observations to be made on the effect of 3 and 6 weeks Lokomat training on the ambulatory capacity of iSCI patients. The results of the WISCI II scale and temporal gait analysis suggest that the first 3 weeks of Lokomat training provide the greatest amount of improvement in ambulatory function. The statistical significance of 3 weeks of Lokomat training on the temporal gait parameters may have implications on the advisable training period for an acute iSCI patient on the Lokomat. After an initial 3 weeks of training the patient (if capable) could be transferred to over ground walking rehabilitation methods.

During the Lokomat training sessions the amount of body weight support was reduced to make the training progressive. The amount of body weight support provided to each patient was dependent upon their ability to sustain knee extension through the stance phase and follow a normal gait pattern. The BWS was reduced as the patient improved resulting in each patient completing a training protocol tuned to

their own rate of progress. For each patient the training was progressive and allowed them to train at an intensity suitable for them. However this method allowed the rate of change in BWS to be different across the patient group. The start and end percentage of BWS was also not standardised. The difference in the rate of change in BWS may be a cause or an effect of improvement in ambulatory capacity. However it is believed that as the BWS was reduced to suit each patient's ability and the smaller change in BWS in the patients who did not improve ambulatory capacity was an effect due to no improvement in the ambulatory capacity.

During the Lokomat training sessions the BWS was the only parameter that was changed. The walking speed of the Lokomat was set at $2kmh^{-1}$ throughout the training sessions and the guidance provided by the Lokomat was set to 100% for all training sessions. During the first session the walking speed was increased from $1kmh^{-1}$ to $2kmh^{-1}$ to enable the patient to become accustomed to the movement. The walking pace of $2kmh^{-1}$ enabled the patient to concentrate on different parts of the gait cycle, such as lifting their toes prior to heel strike and straightening the leg through the stance phase. Higher speeds would have given the benefit of a larger number of repetitions (steps) during a single training period however higher walking speeds would have made concentrating on parts of the gait cycle more difficult. The walking speed of $2km^{-1}$ was also similar to the speeds the iSCI patients were walking at during over ground training and assessments. Further work to identify the most effective traning speed is required to guide training protocols.

The guidance provided to each limb by the Lokomat was set at 100% to ensure that the steps were repeatable and the gait pattern could be 'taught'. It is possible to be in the Lokomat and walk for 1 hour without expending energy or putting effort into walking. No measurement of patient effort or difficulty in completing the training session was recorded during this study. If the Lokomat teaches the CNS to walk again does this need physical effort? From observations within the study patients put different levels of effort into their training. Further work is again required to understand if physical effort or mental concentration is needed to optimize recovery whilst using the Lokomat.

7.3 ASSESSMENT OF AMBULATORY CAPACITY

The ambulatory capacity of the iSCI patients was assessed using the Walking Index for Spinal Cord Injury (WISCI II) scale and temporal gait analysis. The largest improvement in ambulatory capacity was seen in the acute group after the first 3 weeks of Lokomat training. The rate of improvement seen over the first 3 weeks strongly suggests an effect of Lokomat training and not simply natural recovery. The assessments used to identify the functional capacity of the iSCI patients is now discussed in this chapter.

7.3.1 WALKING INDEX FOR SPINAL CORD INJURY

The WISCI II scale was the simplest assessment used in this study. It does not require specialist equipment or training and can be completed within 30 minutes. The assessment can be conducted in a normal physiotherapy training period which causes less disruption to the patient. The WISCI II scale assessment is an inclusive assessment that can be completed on patients that are unable to complete more complex gait analysis. All patients, including 8 iSCI patients who were unable to complete temporal gait analysis within this study were able to complete the WISCI II scale at each stage of the study. This is important as it allows us to monitor the patient's ambulatory capacity during the early stages of recovery.

The WISCI II scale was sensitive to the changes in the ambulatory capacity of the iSCI patients during this study. Improvements were seen in both the acute and chronic iSCI patients after 6 weeks of Lokomat training. Larger improvements in the WISCI II scale were seen in the acute iSCI patients, however 4 acute patients did not show any improvement in their ambulatory capacity as assessed by the scale. Changes in ambulatory capacity in some patients were not observed in the WISCI II scale but were identified in the temporal gait analysis (e.g. P3). It is recommended from this study that the sensitivity of the test at the lower and higher ends of the scale may be improved with the addition of temporal gait analysis.

At the end of this study 3 acute iSCI patients had not recovered any form of ambulatory capacity. No changes could be identified in the WISCI II scale and the 3 patients were unable to complete temporal gait analysis. Any changes that occurred in their function such as improved ability to weight bear or sit to stand were not recorded in either test. To gain an improvement in the WISCI II scale (from 0 to 1) the patient needed to be able to walk less than 10m. However it is unclear what is the minimum activity required to be classed as walking. Can a single step be classed as walking or is a full gait cycle required? Additional comments and possible scale increments at the bottom of the scale may add to the sensitivity of this test.

The WISCI II scale was completed as per the guidelines of the assessment set out by Ditunno et al (Ditunno et al., 2000) ensuring the level was assigned by a therapist after the 10m walk was attempted. However it is not stated in the guidelines of the test if the ambulatory capacity used during normal daily living of the patient is being assessed or the patient's best effort. Patients may be able to achieve a greater WISCI II scale score during the test but does not reflect their normal ambulatory capacity. This may be due to the effort needed to complete the 10m walk or personal preference in how they complete ambulation during normal daily living. If the WISCI II scale is to be used to assess change of ambulatory capacity in patients after treatment it should be stated if normal daily use (self selected) or best effort (maximal) is applied. The assessment of both self selected and maximal ability by WISCI II scale is highly reliable (Marino et al 2010). During this trial the patient was asked to walk at a self selected comfortable pace. The patients used the devices and assistance that they preferred. This may have led to differences within the patient tests especially between patients with low and high motivation or ambition to regain functional ambulatory capacity. By testing both self selected and maximal walking ability with the addition of temporal gait analysis the sensitivity of this test could be increased.

The WISCI II scale is hierarchical and can indicate if a patient is a therapeutic or functional walker. The levels are placed on an ordinal scale which assigns a rank to different levels of ambulatory capacity. An improvement by a single point at one

level of the scale is not equal to a single point at other levels on the scale. As with any scale the WISCI II scale has a floor and ceiling effect. If a patient starts with a high score they are unable to improve by the same amount on the scale as a patient who started with a low score. Caution in applying statistical significance on the change in scale is required and other tests may be used to complement the WISCI II scale particularly at either end of the scale.

7.3.2 TEMPORAL GAIT ANALYSIS

The temporal gait analysis was completed using an instrumented foot switch system that identified changes in ambulatory capacity in iSCI patients after 3 weeks and 6 weeks of Lokomat training. The results gave details on how patients gait improved by looking at walking speed, double support duration, stride length and cadence. This assessment may identify if patients were using compensation methods or showing recovery toward normal gait patterns. Although more sensitive to change in ambulatory function than the WISCI II scale the assessment has two main drawbacks for use in clinical trials.

Firstly out of the 18 iSCI patients that completed the study only 10 patients (6 acute and 4 chronic) completed temporal gait analysis. Half of the acute iSCI patients that completed temporal gait analysis were unable to walk outside of parallel bars and therefore unable to complete the assessment at the start of the study. To complete the temporal gait analysis assessment the patients were required to walk 10m without the support of parallel bars and the use of braces. The number of patients unable to complete the assessment highlights the main drawback of using this form of gait analysis in monitoring early recovery of ambulatory capacity in SCI.

Secondly the assessment requires specialist equipment and training to perform the test and analyse the data. During this study a foot switch system designed by Granat et al (Granat et al., 1995) was used which allowed the assessment to be completed within the clinical setting and the software produced the outcome measures without the need for further analysis. This system reduced the need for technical equipment, expert knowledge, and research space. With minimal training this assessment could

be completed by the physiotherapist during a normal training session and so minimises this drawback.

If the temporal gait analysis system can be used it can identify changes in ambulatory capacity that are not identified using the WISCI II scale. The results of the temporal gait analysis provided sensitive qualitative data that identified changes in ambulatory capacity of each patient. By showing the changes that occurred between the assessment points the rate of improvement was identified. By using the temporal gait analysis assessment and WISCI II scale after each week of Lokomat training an optimal number of Lokomat training sessions for iSCI patients may be obtained.

The temporal gait analysis has shown that the parameters of gait did not all improve at the same time in the acute iSCI patients after Lokomat training. Walking speed, stride length and cadence were significantly different after 3 weeks of Lokomat training in the acute iSCI patient group but the duration of double support was not significantly different until after 6 weeks of Lokomat training. The delay in improvement in double support time may be due to the Lokomat not having an impact on balance control. During Lokomat training the patient's trunk is fixed in position and is not moved over the weight bearing limb as occurs during normal walking. After a period of training in the Lokomat the amount of bodyweight support was reduced and the patients, if able began over ground walking training during their physiotherapy sessions. During the periods of over ground rehabilitation balance may have been improved. These sessions only occurred when the patient was able to load bear and commonly did not occur until after the first 3 weeks of Lokomat training. Further work to identify the requirement of rehabilitation to include balance control to promote recovery is required.

From the assessment of ambulatory capacity after Lokomat training in iSCI patients in this study, it is recommended that the WISCI II scale and the temporal gait analysis assessment is used in conjunction to monitor changes of functional capacity over a period of intervention. This is inline with Marino et al (2010) findings that suggest a greater sensitivity in ambulatory assessment is achieved whrn WISCI II

scale is supplemented with a 10m walking speed test. By using both WISCI II scale and temporal gait analysis it is possible to identify the patients who improve ambulatory capacity by means of compensation and patients who improve by other physiological means. The neurological and sensory tests used in this study aimed to identify the physiological changes that occurred in this later group of patients.

7.4 ASIA

The ASIA assessment was used to give the neurological classification for each patient and identified the level of lesion and areas of motor and sensory deficits. For each patient the ASIA assessment was completed at baseline and after 6 weeks of Lokomat training.

The greatest change in the ASIA assessment after 6 weeks of Lokomat training was seen in the Lower limb motor score. An increase in the lower limb motor score was seen in 17 (out of 18) patients over the 6 weeks Lokomat training. The change in lower limb motor score was correlated to the change in ambulatory capacity as assessed by the WISCI II score and temporal gait analysis. The patients that had a larger increase in their lower limb motor score had the greatest improvement in ambulatory capacity. However as the lower limb motor score has a ceiling, the patients with an initial high lower limb motor score were unable to improve by the same amount as a patient with a low initial score. The greatest change in the lower limb motor score was seen in patients with a low starting score. The improvement seen in the more impaired patients during this study may be due to a ceiling effect of the test. However the significant correlation of the WISCI II score and the lower limb motor score suggests that the patients with greater voluntary control of the lower limb muscles had a greater ambulatory capacity.

The lower limb motor score taken at baseline was correlated to the WISCI II score after 6 weeks of Lokomat training and therefore may provide some predictive value of ambulatory capacity after Lokomat training. However a patient with a WISCI II score of 12 which indicates the patient is a functional walker may not have good

lower limb function. The high score may be due to good upper limb function and the use of devices and braces rather than good lower limb motor control. Low WISCI II scores were also seen in patients with scores above 20 on the lower limb motor scale suggesting that patients with high lower limb motor scores cannot be guaranteed to be functional or therapeutic walkers.

Sensory scores of the lower limbs did not show the same improvement seen in the lower limb motor scores. Patients were shown to improve, remain the same and get worse after Lokomat training. Two reasons may account for this, either some of the patients' sensory perception to light touch and pin prick was reduced after Lokomat training or the test produced false positives. The latter is more likely. From unreported observations the patients can find the identification of the sensory stimuli very difficult. This may have lead to the patient guessing and although this test looks at each dermatome changes at each level are not reliable (Cohen and Barko 2004). To increase the reliability of the test the total score for the lower limbs on both sides can be added together which off sets for small fluctuations in individual dermatomes. This study has shown that testing sensory perception remains highly subjective and depends on the patient understanding co-operation and concentration and hence should only be used to monitor changes in spinal cord function over time with caution. The motor assessment is less subjective as the patient needs to complete a task to demonstrate the motor ability. This may account for the better reproducibility of the motor score.

7.5 QUANTITATIVE SENSORY TESTING

7.5.1 METHODS

The QST allowed an assessment of sensory perception to be made on a continuous scale unlike the ASIA scale where each dermatome was given a value of 2 for normal or 1 for impaired or 0 for absent sensation. By using a continuous scale rather than the ordinal scale of ASIA the test does not have a ceiling effect and changes can be assessed using statistical analysis.

During this study the dermatomes from C3 to S2 were tested on each side of the body. For both the EPT and VPT tests the intensity was started at 0 and was ramped up until perceived or the intensity reached a maximum level. For areas below the level of the lesion the level of sensory perception may by elevated, not present, hypersensitive or allodynia (painful sensation from a normally non painful stimulus). In cases where the sensory perception is elevated or not present the time taken for the intensity to reach perception or maximal level is much longer than in a patient with normal sensory perception. In a patient with a high lesion, C3 for example with sensory impairment the QST test can take up to 1.5 hours for each side of the body. This duration is longer than the preferred duration of a test (<40mins) and levels of concentration can reduce which may reduce the sensitivity and reliability of the test as the test progresses. By studying a select number of dermatomes it may be possible to increase the reliability of the data collected.

The method of limits was used for QST assessments within this study. For this protocol the intensity of the stimulus was increased until the patient notified the examiner of it presence. This method includes the reaction time of both the patient and the examiner, as the patient tells the examiner verbally and the examiner then stops the stimulus. The result using this method can be affected by two parameters, firstly by the patients (and assessors) alertness and secondly, by the rate of stimulus increase. If the patient is not alert they may not be concentrating on the stimulus which may elevate the perception threshold. Once the patient perceives the stimulus they may also have a slower reaction time to reporting it that will also elevate the perception threshold. When carrying out the QST tests it is recommended that the alertness of the patient is monitored and beaks are given as often as necessary. The number of dermatomes tested below the level of the lesion is recommended to be reduced from this study.

The rate in which the stimulus was increased may also affect the recorded perception threshold. By having a faster increasing rate of stimulus strength with the same reaction time the perception threshold could be increased. By increasing the intensity manually during this study the rate of increase was not constant for each

patient or each test and may have led to errors in the perception threshold. However by manually increasing the stimulus strength the rate of intensity can be increased at low stimulus strengths until the stimulus intensity is close to the patients' perception threshold. This makes it more difficult for the patient to estimate and guess the time delay from when the stimulus was applied to perception.

The incremental step of the stimulus is an important parameter in collecting perception thresholds. During testing it was seen that many patients will wait for the next stimulus to confirm to themselves that they felt the previous stimulus prior to reporting the stimulus to the assessor. If there is a large increment between stimulus intensities the level of perception will be increased. It is recommended to repeat each stimulus intensity twice as this may reduce this error, however the time required for the test to be completed will increase.

The method of limits was repeated 3 times for each dermatome and an average of three readings was used to calculate the perception threshold. The lowest of the 3 readings may indicate the true perception threshold and may be lower than the average of the 3 readings. However the lowest value may also be a false positive. The variation in the three recordings taken during a single session was small and using the average did not increase the perception level significantly.

EPT

The testing protocol used in the electrical perception threshold was different from those described by the first phase of the clinical initiative (Ellaway et al., 2004). During this study a fixed bar electrode was used at each dermatome. The anode and cathode were set 20mm apart. Ellaway and colleagues placed the cathode on the key point in the dermatome (to be tested) and the anode on the forearm for all dermatomes. Ellaway used self adhesives electrodes for the cathode on each dermatome. The methods used in this study were preferred as the spread of the electrical field created by the stimulus was reduced and removed the need for disposable resources. By using the fixed electrode held on the skin the pressure applied to the skin may vary across the test sessions. The self adhesives electrodes

used by Ellaway would remove this variable. During this study care was taken not to place any pressure onto the electrode. The author could find no published data to demonstrate changes in electrical perception threshold with changes in pressure applied to the skin. Also as a constant current stimulator was used modest changes in electrical impedance that may be created by changes in pressure should not have changed the stimulus intensity.

VPT

The methods for the vibration perception test were also different to those described by Ellaway and colleagues in the first phase of the clinical initiative (Ellaway et al., 2004). Ellaway and colleagues placed the vibrating head on the bony prominences and spinous processes within each dermatome. Within this study non bony areas were used as patients and subjects reported the sensation in other areas of the body when bony prominences were used. This was also reported by some patients if high levels of vibration are used in dermatomes with sensory impairment. This can make it difficult for the patient to determine when the vibration is felt in the dermatome being tested. In both studies the pressure applied to the skin by the hand held probe was not measured. Different pressures may activate different sensory receptors and lead to altered perception levels. Care was taken during the study to rest the probe on the skin but not to place any pressure on the skin. Measuring the pressure applied to the skin may improve the sensitivity of this test.

A large variation in SD of sensory perception to vibration was seen in the healthy subjects during this study. The reasons for this may include those discussed above. By having a large SD in the normal values the sensitivity of the test in patient population is reduced.

7.5.2 INDENTIFYING FUNCTIONAL CHANGE WITH QST

Previous studies have shown a correlation between the EPT and VPT (Ellaway et al., 2004) and between the EPT and the sensory scores from the ASIA assessment (Savic et al., 2006). This suggests similarities in the pathways used to convey electrical

perception to those that convey vibration and touch. Vibration is detected by specialised receptors in the epidermis and subcutaneous layers of the skin. The pacinian corpuscles are located in the subcutaneous layers of the skin as well as skeletal joints and detect high frequency low amplitude vibration. The meissner's corpuscles are located deeper in the epidermis and respond to low frequency vibration. Detection of the vibration stimuli by both receptors is conveyed by large myelinated fibres within the dorsal column medial lemniscal pathway. It remains unclear what sensory receptors or pathways are involved in conveying the electrical stimuli. During this study no correlation between the perception thresholds in the EPT and VPT assessment at levels above or below the lesion were seen. This may suggest that the electrical stimulus is not detected and conveyed in the same manner as the vibration stimulus. This difference between the studies may be due to the methodologies used for both EPT and VPT.

Both the EPT and VPT gave addition information on the level of the lesion in iSCI patients compared to using the ASIA assessment independently. As discussed the vibration and touch perception is conveyed in the DCML pathway. As each modality is conveyed in the same pathway the same level of sensory impairment across the modalities would be expected. The difference may be due to the locations of the axons within the pathway carrying the individual modalities. Fitzgerald (Fitzgerald, 1996) noted that the thermal axons are located more medially than the pain axons within the spinothalmaic tract and this organisation by modality may be present in the DCML pathway. A second hypothesis is the variation in size of the receptor fields for each modality. If the receptor field is large the stimulus may be detected by axons within nerves above the level of the lesion. A third hypothesis is that the variability in the level of the lesion is due to the difference in the sensitivity of the tests. With the ASIA light touch and pin prick scores each dermatome is described as either normal, impaired or absent. However the EPT and VPT are classed as normal until the perception threshold is greater than the mean plus two standard deviations of the perception level in the healthy subjects. This may mean that a patient has raised perception in a dermatome that is then classed as abnormal in AISA but is still below the mean plus two standard deviations in the QST

assessment. This may explain why a large variation in the level of lesion is seen across these tests and highlights the increased sensitivity of the QST assessment compared to the ASIA sensory score. By using these tests additional information on the sensory impairment can be identified compared to using the ASIA assessment alone.

Below the level of the lesion the EPT and VPT show no clear time related changes in the patients with improved ambulatory capacity (or patients with no change in ambulatory capacity). This may be due to the large levels of trial to trial variability that seems to increase with distance below the level of the lesion. Previous repeatability and reliability studies of QST in SCI patients have only looked at selective dermatomes in the lower limb (King 09, Savic 06, Hayes 02). The intra-rater and inter-rater reliability was reduced in iSCI in the levels below the lesion (King 09). Further information on the repeatability and sensitivity of the test for dermatomes below the level of a SCI is required.

This study has shown the QST tests can be used to assess the perception of sensory stimuli in dermatomes around the level of the lesion to gain a more sensitive evaluation of the sensory impairment. Further work to identify the repeatability of the tests in levels below the lesion is required prior to using QST as an assessment to monitor changes in level of perception over time or an intervention.

7.6 SOMATOSENSORY EVOKED POTENTIALS

7.6.1 METHODS

The EEG activity was recorded from 17 Sliver/Sliver Chloride (Ag/AgCl) sintered electrodes placed on the scalp using an EasyCap (Brain Vision UK). The locations on the scalp of the 17 electrodes described as the montage used is this study was compiled to ensure essential data was recorded but with consideration to the patient comfort and time required to set the test up. The montage recommend for lower (Baran, 1996) and upper limb (Clarke Stevens, 1997) SEP by the AAEM is to use Cz prime, which is located 2cm behind Cz. This is approximately half way between Cz

and CPz (depending upon the size of head). In this study the electrodes Cz and CPz (plus the other 15 electrodes) were recorded and analysed for the SEP waveform. This enabled both sites to be recorded and also allowed the use of a electrode cap to fix the electrodes on place. This method is quicker and preferred when recording from a large number of electrodes.

Spinal electrodes were trialled in a number of patients before being removed from the montage. These electrodes were difficult to attach to the patient as they required the patients to sit up with minimal support (or additional help from a physiotherapist or nurse), which could not always be done. Once the electrodes were attached the patient was then resting on them when in a supine position. This was uncomfortable and may have led to skin damage if left for long periods of time. For these reasons all the spinal electrodes recommended by AAEM were removed from the montage in this study.

By excluding the spinal electrodes the subcortically generated potentials evoked from median nerve stimulation (N11 and N13) and PT nerve stimulation (N17 and N20) were not recorded. The components in the median nerve SEP reflects the arrival of the volley in the 1st order neurons near the dorsal root entry zone (Favale et al., 1982) and the postsynaptic activity in the cervical cord (Emerson et al., 1984). Although by removing these electrodes these components are not detected they are not commonly used in clinical diagnosis because as they are not always identified in healthy subjects. The components in the PT nerve (N17 and N20) reflect the volley as it ascends the spinal cord and may provide additional information on the level of the lesion in these patients. However as patient comfort and skin care is of high priority in this group this data was not attained.

The reference electrode used by AAEM is the Fpz prime or Fz. In this study we have used Fpz as the reference electrode which is situated on the midline above the nasion (as shown in Fig 3-9). The location of Fpz prime in the diagram shown in AAEM (Baran, 1996) is located 2cm behind Fz. By using the more frontal electrode in this study it was hoped that the components of the median and PT nerve SEP

waveform would be more clearly identifiable. The average data from the healthy subjects within the study using Cpz- Fpz were comparable to those reported by AAEM.

7.6.2 PT NERVE SEP

Changes in the early components (P30) of the PT nerve SEP after 6 weeks Lokomat training in iSCI patients could not be identified in this study. The P30 component, which is a far field potential originating from the lower brain stem, is a small potential recorded from the contralateral frontal electrode. In the healthy subjects this component was identified. In the iSCI patients the P30 component was not consistently identified. It is not clear why the incidence of this component is lower in the patient group studied. However, if a lesion within the spinal cord causes the afferent volley to be less synchronized on reaching the brain stem from the point of stimulus the component will be lost by using time averaging techniques. However, as this component is associated with thalamic activation (Tinazzi et al., 1995) its absence may point to different pathways other than the dorsal column activating later cortical potentials. The P30 component if identifiable in the patient group may add further understanding of how the PT nerve SEP changes over time. If it is stable when other components change it may indicate changes in higher centres, however if the latency or amplitude of the P30 component changes over time it may indicate changes in the transmission of the PNS and spinal cord.

The cortical components evoked from stimulation of the PT nerve are; P1 (38ms), N1 (48ms), P2 (60ms) and N2 (74ms). In the PT nerve SEP the P1 potential is shown as a widespread far field potential that reflects activity in the primary cortical somatosensory receiving area and is recorded near the mid line (American Clinical Neurophysiology Society Guideline 9D). However the location where this potential is maximal varies between patients reflecting the differences in the location and orientation of the cortical representation of the foot within the somatosensory cortex. Previous studies have recorded and reported the cortical component P1 from a single midline electrode (Dickstein et al., 1997, Iseli et al., 1999, Nelson et al., 2000). In

this study the montage used included electrode placed at Cz, CPz and Pz to ensure the maximum amplitude of the component was identified. In the patients with identifiable P1 cortical component it was present in both Cz and CPz electrodes but the amplitudes and morphology of the waveform differed. This suggests that activity at both electrodes should be recorded, analysed and presented when assessing the integrity of the DCML pathway or identifying any changes in the waveform after a period of intervention.

The cortical components (P1, N1, P2 and N2) recorded in the Cpz-Fpz were difficult to indentify in patients with abnormal waveform morphology. Abnormalities in the waveform can be seen as delayed peak or inter peak latencies, reduced peak or inter peak amplitudes or the absence of a potential. If a peak has a delayed latency and reduced amplitude it may be difficult to identify from the back ground noise. If some components are missing and peaks are present at latencies different from those expected in a normal waveform ambiguity in what component of the waveform corresponds to what component of the normal PT nerve SEP waveform is probable. No standard method of peak analysis is described in the literature. This makes this test subjective. High quality data is needed to minimise misinterpretation of the results.

7.6.3 INDENTIFYING FUNCTIONAL CHANGE WITH PT NERVE SEP

Statistical analysis was used within this study to identify any changes in the PT nerve SEP after 3 and 6 weeks of Lokomat training. The results showed no significant changes in the peak or inter peak amplitudes of the components after 3 or 6 weeks of Lokomat training. A large variation in the peak amplitudes and inter peak amplitudes of the cortical components was seen across the patients and within patient tests repeated after 3 and 6 weeks Lokomat training. This large variation in the amplitude of the cortical components may reduce the reliability for monitoring change after a period of intervention. In a previous study, Romani et al (Romani et al., 1996) suggests that the peak amplitudes are reliable for longitudinal studies, however the repeatability of the amplitudes was assessed in healthy subjects in this

study. A more recent study in SCI patients by Spiess et al (Spiess et al., 2008) found a greater reliability of the latencies compared to the amplitudes of cortical components to indicate damage to the dorsal columns, which supports the observations made in this study.

In this study the latency of the P1 cortical component in the acute iSCI patient group was significantly different (shorter) after 6 weeks of Lokomat training. However the subsequent peak potential, N1, was not significantly different after 6 weeks Lokomat training. This would suggest that the inter peak latency of the two components would be increased, however this was not seen. This is an anomaly of the statistical analysis. By looking at larger data sets it may be shown if the whole waveform has shifted to the left after training, i.e a reduction in all peak latencies or that the early components shift to the left and the inter peak latency is increased. Curt and colleagues (Curt and Dietz, 1997, Curt and Dietz, 1999, Curt et al., 2008) have shown that the peak latencies are stable in iSCI and no significant changes are seen over time. In the present study the significant reduction in the latency of the P1 potential in the PT nerve SEP of acute iSCI patients may suggest a degree of neural recovery accompanying the Lokomat training period. The difference between this study and those conducted by Curt and colleagues, who do not find any change in the P1 potential may be the numbers participating in the study or the use of the Lokomat. In the studies conducted by Curt and colleagues data was pooled from patients from over 16 specialized European SCI centres (Curt et al., 2008) which has led to patient numbers of 1140 acute iSCI. Studies with greater patient numbers and the use of the Lokomat as the intervention may identify the differences between this present study and those of Curt and Colleagues.

The PT nerve SEP may also be used to identify patients that would benefit most from Lokomat training. In this study the patients with the longest P1 latency showed the greatest improvement in ambulatory capacity after 6 weeks of Lokomat training as assessed by the WISCI II scale and temporal gait analysis. This result may suggest that the patients with larger functional impairment benefit more from Lokomat training. The patients that had abolished P1 cortical potential were not included in

this analysis. Therefore although the SEP was pathological in the patients that improved the most it was present, which suggests that some integrity in the pathway may be required to facilitate recovery with Lokomat training in iSCI.

The PT nerve SEP was also analysed within this study to determine if the outcome of ambulatory capacity after Lokomat training can be predicted. Previous studies (Curt and Dietz, 1997) have shown that the presence or absence of the early components (P1) of the PT nerve SEP is a good prognostic indicator of recovery of gait. In these studies they grouped patients SEP results as either non affected, pathological (amplitude and or latency) or abolished and reported that 80% of patients with abolished PT nerve SEPs did not regain any ambulatory capacity. This study was unable to confirm this finding as only 3 patients did not recover any form of ambulatory capacity and the PT nerve SEP was unaffected in the first patient, pathological in the second patient and abolished in the third patient. By including a greater number of AISA C's within the study this correlation could have been repeated.

Temporal gait analysis was assessed to determine if there were any correlations with the PT nerve SEP that may provide a prognostic indicator of ambulatory recovery. High correlations with functional ambulatory capacity as measured using temporal gait analyses was seen in the late components of the PT nerve SEP in both acute and chronic iSCI patients after 6 weeks Lokomat training. The double support time and cadence was highly correlated to the N2 component in both groups. The P2 cortical component was highly correlated to the walking speed, double support time, stride length and cadence in the chronic group. These late components represent cortical-cortical activity. It is hypothesised that interneurons relaying information from the somatosensory cortex to the motor cortex to control movement may play a role in these potentials. With locomotor training after neural damage it is possible that new synapses between inter neurons are created. Previous studies have not looked at the late components of the SEP and the role of the late potentials and emerging late potentials during recovery is unclear and requires further study.

The PT nerve SEP was also analysed in the frequency domain. A clear period of desynchronization is seen in the healthy subject around 15Hz between 100 and 750ms after PT nerve stimulation in an electrode placed over Cpz. It was hypothesized in this study that this period of desynchronization may change with change in ambulatory capacity. However no changes in the ERSP were seen in any of the patients studied. This was unexpected as changes in the late components in the time domain show some predictive value of ambulatory capacity.

7.7 SEP AND QST

Correlation analysis of the component latencies evoked from the PT nerve and median nerve SEP with the perception thresholds recorded at dermatomes L4 and L5 for electrical and vibration stimuli were completed to identify any similarities in the pathways in which the modalities are conveyed. Correlation between the latency of the P1 (38ms) component in the PT nerve SEP and the EPT and VPT levels at L4 and L5 were identified. Correlations were also identified in the median nerve SEP component, N1 (20ms) with the EPT (at levels at C5 and C6) and VPT (at C6). This supports the belief that the EPT volleys are conveyed in the dorsal columns. However individual patients did show abnormal electrical and vibration perception threshold levels and normal cortical components evoked from PT nerve and median nerve SEPs. Accordingly, other pathways may also convey afferent information to the cortex which influences perception.

7.8 MODULATION OF PT NERVE SEP DURING WALKING.

In the literature, reviewed early in this thesis, the modulation and reversal of reflex activity during phases of the gait cycle has been shown. This work has contributed to our understanding of the role of cutaneous, muscle and joint afferents in the neural control of human locomotion. The involvement of supraspinal networks in the control of human locomotion has been demonstrated in humans using TMS (Christensen et al., 1999, Duysens et al., 2008, Taube et al., 2006). The modulation of transcortical afferent information during phases of the gait cycle has not been

comprehensively studied. By using SEP techniques an indirect measurement of the sensory information arriving at the cortex via transcortical pathways during phases of the gait cycle can be determined.

In this study SEP components reflecting cortical potentials evoked by PT nerve stimulation were recorded during sitting, standing and 4 phases of the gait cycle. Possible event related cortical potentials from activity of normal gait, such as heel strike were recorded to reflect the processing of sensory information during normal (non perturbed) treadmill walking. A comparison was made between the cortical potentials evoked during each phase of non-stimulating walking. The cortical potentials recorded during each phase of the gait cycle that were evoked by PT nerve stimulation were compared to the non-stimulated cortical potentials.

7.8.1 STIMULUS INTENSITY

To enable a comparison of the cortical components evoked by PT nerve stimulation during each task the intensity of the stimulus during each task was compared. The intensity was monitored by recording the amplitude of the M-wave in the ADH muscle of the right foot. As the PT nerve may move relative to the skin stimulation site during walking it is possible that the distance from the electrode to the nerve may vary during phases of the gait cycle. The electrode which applies the stimulus can also move relative to the skin and nerve, however, this was reduced by attaching it to the limb securely with micropore tape. The amplitude of the M-wave was not constant when comparing the sitting and standing tasks within this study. The P1 latency was significantly longer ($p=.047$) in the sitting posture compared to the standing posture. As the M-wave was smaller in sitting the stimulus would be less compared to standing. Therefore in standing all groups of fibres may have been recruited and caused this small delay in latency. It however has been reported that the early components of the median SEP are not affected by the change in stimulus above motor threshold in healthy subjects (Parain and Delapierre, 1991). When studying dermatonal SEPs Kromer et al (2010) fond when stimulating well above perception threshold the latency of the first cortical component was consistent with

activation of large diameter group I fibres. This suggests that the variation seen in this study is not due to the intensity of the stimulus.

During the four phases of the gait cycle the M-wave was similar in amplitude during each phase of the gait cycle. In this study the M-wave was described as a percentage of the M-wave evoked during the sitting task. To ensure stability in the stimulus intensity the M-max at each phase of the gait cycle should be obtained and the walking M-wave described as a percentage of the M-max for the phase of the gait cycle. Further work into the effect of the stimulus intensity on the cortical components of the PT nerve SEP evoked in different postures is required.

7.8.2 SITTING AND STANDING PT NERVE SEP

Significant differences in the amplitude of the early cortical component (P30) of the PT nerve SEP was seen in the standing task compared to the sitting task. These changes were observed in the group statistics. The amplitude of the earliest cortical component, P30 was reduced during the standing task compared to the sitting task supporting observations from previous studies (Applegate et al., 1988, Dietz et al., 1985a). This reduction may reflect the attenuation of the valley during standing. As the P30 reflects the arrival of the afferent volley in the thalamus the modulation of this potential may occur in the spinal circuits. Down regulation of the spinal circuits may be required to inhibit the stretch reflex during standing.

7.8.3 TREADMILL WALKING NATURALLY EVOKED POTENTIALS

This study identified the cortical components evoked during normal treadmill walking in healthy volunteers. Four phases of the gait cycle were studied, heel strike, mid stance, toe off and swing.

At heel strike event related potentials were seen that have components similar to those seen after stimulation of the PT nerve SEP during the sitting task. Two components were identified which are early and late components similar to P1 and N2 components respectively. These components may reflect the activity of propricopetive and cutaneous afferents due to heel strike. They may also be on

movement artefact created by heel strike. However as the response must be time locked to the event and the double peak it is unlikely to be due to movement artefact.

In previous studies cortical components evoked during normal walking were recorded (Applegate et al., 1988, Dietz et al., 1985a), to subtract the SEP waveform from the SEP waveform elicited by electrical stimulation recorded at each of the phases of the gait cycle. However the non stimulated cortical components were not presented or discussed (Altenmuller et al., 1995). Dietz and colleagues (Dietz et al., 1985a) stated that the EEG recorded during the non stimulated phases of the gait cycle only created small changes in the EEG from baseline. However the electrode montage used subtracted an electrode from an ipsilateral electrode (C1-C3) which may have removed some cortical components especially if smaller in amplitude and may explain the different results from this study. The results from this study during non stimulated walking are therefore difficult to compare to published work.

7.8.4 TREADMILL WALKING PT NERVE SEP

During gait the PT nerve was stimulated at four points within the gait cycle, these were at heel strike, mid stance, toe off and mid swing. When the stimulus was presented during the mid stance and mid swing phases of the gait cycle the four components, P1, N1, P2 and N2 were all present. When the stimulus was presented at heel strike and toe off only the N2 component was present. The N2 potential had a reduced amplitude and wider base compared to the N2 component seen at rest. A similar study stimulating the sural nerve during standing and treadmill walking (Duysens et al., 1995) identified the early components (P1(50ms) N1(80ms) equivalents) evoked during gait and these components had smaller amplitudes than when evoked during standing. Duysens and colleagues (Duysens et al., 1995) reported the presence of these potentials in each phase of the gait cycle however the early components were attenuated just after heel strike compared to during late swing. The differences between these two studies may due to the selection of the stimulating nerve and or the stimulating method. In the study by Duysens and colleagues (Duysens et al., 1995) the nerve was stimulated by a train of five 1ms

pulses rather than the single pulse of 200μs. The sural nerve contains cutaneous group II afferents, whereas the PT nerve contains muscle group I afferents (Burke, 1981). The reduction in amplitude and shift in latency are consistent with a gating effect at cortical levels (Duysens et al., 1995). Modulation of spinal circuits during heel strike and toe off may occur to ensure the correct response to the increase load and strength.

During heel strike and toe off sensory information about loading and unloading of the limb is expected, where as in mid swing no sensory information about the external environment is expected during a normal unperturbed step. During the swing phase the limb is not in contact with the floor and so will only convey sensory information about its external environment if an unexpected event occurs, such as tripping over raised ground or an obstacle. Therefore the presences of the early cortical components of the PT nerve SEP during mid stance and mid swing may indicate a greater need for sensory information to allow correct adaptations of movement to ensure continuing stability. During heel strike and toe off which although are important events within the gait cycle the sensory information is expected and is part of the 'normal' sensory feedback. This feedback may therefore be inhibited or modulated so as not to overload the system with sensory information that does not need cortical processing.

7.8.5 SUMMARY

During normal (non stimulated) treadmill walking the late cortical component similar to the N2 component was observed after heel strike. This component is similar to the cortical component seen by stimulating the PT nerve in each phase of the gait cycle. This may suggests that the response evoked by the PT nerve stimulation is due to excitation of the cutaneous, muscle and joint afferents that are activated naturally during heel strike. During the PT nerve SEP study with iSCI patients presented in this thesis theN2 cortical potential was found to have a significant correlation to the outcome of ambulatory capacity. The presence of this potential during each phase of the gait cycle and its correlation to ambulatory capacity suggests that the cortical

potential reflects activity in cortical – cortical pathways involved in the neural control of locomotion.

7.9 APPLICATION FOR AMBULATORY REHABILITATION OF ISCI PATIENTS

Previous studies have shown the importance of the transcortical pathway (Capaday et al., 1999, Christensen et al., 1999, Taube et al., 2006) and the corticospinal tract (Barthelemy and Nielsen, 2010, Petersen et al., 2001, Petersen et al., 2002) in the control of muscle activity during the gait cycle. The importance of the corticospinal tract is seen in iSCI patients who have poor dorsiflexion of the ankle during the swing phase of gait cycle. Termed as foot drop, it is commonly believed to be due to a lesion within the corticospinal tract (Calancie et al., 1994, McKay et al., 2005, Nathan, 1994, Thomas and Gorassini, 2005). The pattern of activity in the muscles during the gait cycle controlled via corticospinal tract may also be influenced by the sensory information that is conveyed to the somatosensory cortex during loading in the stance phase (Dietz and Harkema, 2004) and during the forward propulsion in the swing phase of the gait cycle.

The work presented in this thesis has shown that the cortical components evoked during treadmill walking in healthy subjects are modulated during the gait cycle. Early cortical components evoked by stimulation of the PT nerve were present during the swing phase of the gait cycle and attenuated during heel strike and toe off. This suggests that sensory information during the swing phase of locomotion influences the motor response conveyed via the corticospinal tract. The up regulation of the sensory information during swing may be functionally significant as the limb is in its least stable position. A significant correlation between the latencies of the cortical potentials evoked at rest and the functional ambulatory capacity after training in iSCI patients in this current study suggests a relationship between the integrity of the somatosensory pathway and functional ambulatory capacity.

Rehabilitation strategies for iSCI patients are being developed to focus on the critical sensory cues that are processed by the spinal cord and supraspinal centres. This thesis has demonstrated that the cortical potentials evoked after heel strike during normal (un-stimulated) gait is similar to the late cortical potentials evoked during PT nerve stimulation during walking. This suggests that a transcortical pathway conveys the sensory information relevant to heel strike and implies that heel strike during normal unperturbed walking is a critical sensory cue and should be included in rehabilitation strategies for iSCI patients.

Rehabilitation methods such as the Lokomat training, used in this study may promote the recovery of function by providing this key sensory information during corresponding phases of the gait cycle. Adding additional emphasis on these key sensory points by stimulating cutaneous or muscle and joint afferents during walking or by increasing the cortical excitability using TMS or theta burst stimulation of the primary somatosensory cortex which has been shown t effect the excitability of the intracortical circuits generating the SEPs (Katayama et al 2010) may also provide key sensory information which may enhance functional recovery. By assessing the presence of evoked potentials during Lokomat training from PT nerve stimulation during the stages of rehabilitation a prognostic indicator of ambulatory outcome after a period of Lokomat training may be identified.

8 CONCLUSION

This study has taken 18 iSCI patients through an intensive programme of rehabilitation using a driven gait orthosis, the Lokomat. The ambulatory ability of each patient was assessed at the start of the study and monitored through the 6 weeks of Lokomat training using clinically known and approved tests, including the ASIA assessment and the WISCI II scale. Additional sensitivity of ambulatory capacity testing was given by assessing temporal gait parameters in the ambulatory patients.

The trial identified the acute and chronic iSCI patients which improved after Lokomat training. Improvement was seen in both acute and chronic patients. The improvement in the chronic patients was assessed during over ground walking, demonstrating the transfer of functional ability from treadmill training to over-ground walking which has not been previously documented.

An extensive batch of tests were completed on each patient before, at the middle point and after the 6 weeks of Lokomat training to identify any functional changes in spinal cord function. By using sensitive and reliable test measures set out in the first phase of the clinical initiative it was hoped that any physiological changes that occur with the improved (or regained) ambulatory capacity could be identified. And highlight possible physiological explanations as to why some iSCI patients improve better than others after Lokomat training.

8.1 SUMMARY OF THE STUDY

The key findings of the patient study are:

- Improvement in ambulatory capacity was seen in 10 acute and 3 chronic iSCI patients after 6 weeks of Lokomat training.
- The greatest change in ambulatory capacity was seen in the first 3 weeks of Lokomat training.

- The WISCI II scale is sensitive to changes in ambulatory capacity in iSCI after Lokomat training. Additional comments at the low and high ends of the scale may improve its sensitivity.
- Temporal gait analysis provides additional detail to the WISCI II scale although difficulties were found in using this test in early iSCI patients.
- The ASIA motor scores were more repeatable and reliable than the sensory scores in iSCI patients. Summation of the motor scores for each lower limb better described the functional deficit than the individual dermatome motor scores.
- The ASIA motor score was sensitive to change in function after 6 weeks Lokomat training.
- Pin prick score did not provide in this study any prognostic value of ambulatory outcome after 6 weeks Lokomat training in the ASIA C and D patients.
- EPT and VPT can give additional information on the level of the lesion and any sensory impairment above the level of the lesion. More work is needed before the EPT and VPT tests can provide further information on functional changes below the level of the lesion.
- No correlation between EPT and VPT was found. Further work into what receptors and pathways are conveying the electrical stimulus is required to identify what is being tested when using an electrical stimulus.
- Further work to identify a useable montage to detect sub cortical potentials in PT nerve SEP may help to identify if changes are occurring the spinal cord or higher centres.
- Identified a need for standardized methods for peak detection in SEP waveforms.
- Significant changes in P1 potential latency in the acute iSCI after 6 weeks Lokomat training.
- The longer (more abnormal) the P1 latency the greater improvement in ambulatory capacity was seen after 6 weeks Lokomat training.

- Significant correlation between the latency of the N2 potential and the temporal gait parameter of double support time and cadence in the acute iSCI patient group.
- Significant correlation between the latency of the P2 potential and all the temporal gait parameters; double support time, walking speed, stride length and cadence in the chronic iSCI patient group.

The present study indicates that the recovery of ambulatory capacity (or improvement of) may be due to compensation, neural repair and / or neural plasticity. As the conductivity within the spinal cord may have changed as shown by the significant reduction in the latency of the P1 potential in the PT nerve SEP of acute iSCI patients it is possible that neural repair after Lokomat training has occurred.

The key findings of the modulation of sensory information study are:

- Methods for SEP recordings during different phases of the gait cycle during treadmill walking.
- Stimulus strength is indicated by the amplitude of the ADH M-wave but further work into the effect of stimulus strength during phases of the gait cycle is required.
- The PT nerve SEP waveform is modulated during the gait cycle. Cortical potentials that reflect activity in the thalamus were not observed during heel strike and toe off phases of the gait cycle.

The present study indicates modulation of sensory information during the gait cycle in humans. This may indicate the role of supraspinal centres in the modulation of sensory information relayed within the complex neural pathways involved with the neural control of walking in humans.

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