The Role of EEG Theta Power and Somatosensory Evoked Potentials in Spinal Cord Stimulator Baseline Responder Selection in Failed Back Surgery Syndrome

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DECLARATION

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ABSTRACT

The aim of the study was to investigate whether patterns of brain activity measured by quantitative EEG (QEEG) absolute power and somatosensory evoked potentials (SSEPs) could predict the therapeutic response to spinal cord stimulation (SCS) in failed back surgery syndrome (FBSS) patients with chronic neuropathic pain. Twenty-seven patients with FBSS underwent a resting state electroencephalography (EEG) and lower limb somatosensory evoked potentials (SSEP) protocol before SCS and every four days after SCS receiving either high frequency, tonic or burst SCS stimulation. Four patients withdrew after the first trial. Responder's with ≥50% pain relief from baseline and non-responders <50% pain relief from baseline were compared for each trial. Absolute theta power at the Pz electrode and SSEP P39 was compared to baseline for each stimulation programme and between responder and non-responder patients. A spectral cortical signature for neuropathic pain in FBSS patients was identified. The spectral pattern consisted of raised absolute theta power over the prefrontal, somatosensory, precuneus and lateral occipital cortical regions forming a ring of absolute theta power with concentric reduced theta power over the motor and somatosensory cortices involved with central function. This pattern was associated with high frequency SCS stimulation in 12 out of 16 responders, with tonic SCS stimulation in 10 out of 14 responders and with burst SCS stimulation in 11 out of 15 responders. ROC analyses revealed the baseline pattern had a sensitivity of 85%, specificity of 67% and accuracy of 81% in identifying responders. This suggests that patients identified with this quantitative EEG (QEEG) pattern may no longer need a screening trial with a temporary implant. Significant differences in absolute theta power from baseline were observed with high frequency SCS and tonic SCS using a relative theta power ratio ($p<0.05$) in responders. The average absolute theta power reduction was lower for high frequency SCS than tonic SCS. High frequency and tonic SCS were observed to modulate the baseline pattern resulting in significant absolute theta power reduction over the somatosensory, precuneus and lateral occipital. Absolute theta power increased over the motor cortex leading to motor cortex reactivation on the Oswestry disability index (ODI). ODI scores associated with physical motor disability improved in patients where the motor cortex was reactivated. Pain Detect scores associated with neuropathic pain symptoms, specifically paraesthesia, crawling and electric shock sensations reduced. In non-responder patients the pattern was absent in 7 out of 11 patients with high

frequency SCS, 5 out of 9 patients with tonic SCS and 5 out of 9 patients with burst SCS. Absence of reduced theta power over the motor cortex was the most common feature (n-5) with raised absolute theta power across frontal, somatosensory and precuneus regions. In these patients, absolute theta power was unresponsive to high frequency and tonic SCS with suboptimal pain relief. Despite a very high sensitivity for identifying burst SCS responders with the absolute theta power concentric pattern, no significant changes in absolute theta power or relative theta power ratio were observed in burst SCS responders. Contrastingly high frequency SCS and burst SCS had no significant effects on lower limb SSEP amplitudes in keeping with neuromodulation of Aδ fibres. A significant difference with nonparametric testing was observed for SSEP amplitude reduction with tonic SCS. The identification of this novel spectral pattern may have considerable benefits to SCS pain therapy and associated cost savings.

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FBSS	Failed back surgery syndrome
QEEG	Quantitative electroencephalography
SSEP	Somatosensory evoked potential
SCS	Spinal cord stimulation
ICD	International classification of disease
NICE	National Institute for Health and Care Excellence
PSP	Persistent spinal pain
Aβ	A-beta nociceptor
Aδ	A-delta nociceptors
AMPA	a-aminio-3-hydroxy-5-metyl-4-isoazolepropionic acid
NMDA	N-methyl-D-aspartate
GABA	Gamma-Aminobutyric acid
NK	Neurokinin
D	Dopamine
WDR	Wide dynamic range
PAG	Periaqueductal grey
VMPo	Ventral medial nucleus
VP1	Ventral posterior nucleus
MOR+	MU opioid receptors
5HT	5-hydroxytryptamine
TNF	alpha Tumour Necrosis Factor alpha
FDA	Food and Drug administration
Tn	Thoracic spinal level, the accompanying number (n) indicates level
Ln	Lumbar spinal level, the accompanying number (n) indicates level
Sn	Sacral spinal level, the accompanying number (n) indicates level
VAS	Visual analogue scale
CLT	Central lateral thalamotomy
MP	Michael Pridgeon
LO	Llwyd Orton
QST	Quantitative sensory testing
ODI	Oswestry disability index
MDT	Multidisciplinary team
EDF	European data format
ROC	Receiver operating characteristic curve
AUC	Area under the curve
DFT	Discrete Fourier Transformation
FFT	Fast Fourier Transformation
CCT	Central conduction time
ms	Millisecond
HSD	Honestly Significant Differences

LIST OF APPENDICES

1. INTRODUCTION

1.1 Failed back surgery syndrome

Chronic pain presents as a major problem for the NHS particularly following spinal surgery with many patients becoming opioid resistant. In the research pain community, there is a growing consensus that lower back related chronic pain is placing a significant hidden economic burden on healthcare services like the NHS (Chan and Peng, 2011; Cho et al., 2017; Treede, 2019; Christelis et al., 2021). The push for opiate free pain management therapies have driven the development of spinal cord stimulation (SCS) as a last resort treatment with the development of new and novel stimulation paradigms (Tonic high density, high frequency and burst SCS) placing a greater emphasis on the need to explore personalised medicine within this patient group to reduce these hidden costs.

Failed Back Surgery Syndrome (FBSS) is heterogeneous by definition and was first described by Burton in 1977 for patients with post laminectomy syndrome. This group of patients were characterised by persistent pain after back surgery an often overlooked post operative symptom. Over the last fifty years the literature has shown a heterogeneous pattern for the definition of FBSS with common definitions linked to post operative lower axial back pain. The most common definitions reviewed include:

- Persistent, new, or recurrent lower back pain following one or more spinal surgeries.
- Lumbar or cervical chronic pain despite surgical intervention.
- Unrelieved pain following the herniation of a lumbar disc.
- Chronic radicular, neuropathic pain favouring the legs following one or more surgeries.

The International Classification of Disease classify chronic pain under the ICD-11 framework (Treede et al., 2015; Treede, 2019; Christelis et al., 2021) as pain that lasts or reoccurs for more than 3-6 months. The ICD-11 framework subdivides lower back pain into chronic post-surgical pain or chronic post traumatic pain. Under this framework post-surgical pain which includes FBSS is defined as being either lumber or cervical radicular pain that either persists despite surgical intervention or appears after surgical intervention that increases in intensity and

severity. This definition when applied to FBSS assumes that all FBSS patients are the result of lower back surgery that either failed or caused the pain and ignores a subset of patient's presenting with neurodegenerative changes or herniated discs.

Christelis et al., (2021) challenged the name "Failed Back Surgery Syndrome" to be more inclusive of the patient population represented by FBSS. They argued that it was unusual to define a syndrome based on the outcome of a treatment (surgery). Chronic pain symptoms in FBSS patients may co-exist as a direct consequence of an underlying degenerative process and not as a direct consequence of surgery (Castillo and Lieberman, 2015 and Christelis et al., 2021).

The alternative definition proposed by Christelis et al., (2021) is referred to as "Persistent Spinal Pain syndrome" (PSP) an alternative syndromic name based on a consensus view from a range of pain experts using the Delphi technique a well-established approach in answering a research question. Christelis et al., (2021) included individuals with recurrent spinal pain, paraesthesia, numbness, stiffness, muscle spasms and weakness and excluded a subset of individuals presenting with chronic primary musculoskeletal pain traditionally included under the ICD-11 definition. This revised definition by Christelis et al., (2021) covers primarily lumbosacral spinal pain however also acknowledges that PSP may also include pain in the cervical and even rarer thoracic regions. Chronic pain under this definition is subdivided into type I, patients that have not received any surgical intervention and type II PSP patients with chronic pain following spinal surgery where surgery has been identified as either a direct or indirect cause of their pain. In older patients PSP type II is more common, ranging between twenty and forty percent of PSP patients (Christelis et al., 2021). Furthermore, Four-fifths of PSP type II patients report low quality-of-life scores, worse than other chronic pain syndromes with a significant impact on daily living, severe to chronic disability and problems with mobility and being unable to work. The chronic pain symptoms experienced can also be exacerbated by unrealistic expectations by the patient especially when treatment fails or is suboptimal in managing pain leading to disappointment, anger, anxiety and stress.

This revised definition is a better descriptor for FBSS patients and acknowledges the two different subgroups who may respond to the different therapies available differently. Despite this improvement the pain research community have failed to adopt this newer definition with studies continuing to favour FBSS terminology in the literature. This may partially be

due to clinical practice therapeutic and treatment recommendations. NICE TAG 159 (NICE committee reviewed 2014, 2008) recommends for SCS chronic neuropathic pain be defined using the ICD-11 framework and recommend this be used in the evaluation of all SCS trials.

The underlying mechanisms that predispose patients to develop lower back pain is poorly understood. One compelling hypothesis is linked to the sustained upright position unique to human bipedalism (Castillo and Lieberman, 2015 and Christelis et al., 2021). From an evolutionary perspective the degree of lumbar spinal curvature is driven by the movement of the upper bodies centre of mass over the hips to stabilise the trunk placing excessive mechanical, compressive, and shearing forces on the human vertebral column, spinal cord, and spinal roots (Figure 1.1). Castillo and Lieberman, (2015) consider the risk factors to be genetic, environmental, psychosocial, and biomechanical. All factors that can influence lumbar spinal curvature leading to shearing forces between adjacent vertebrae and compression. In modern humans' low levels of physical activity and abnormal spine loading predispose the vertebral column and trunk to become weak and unstable. When combined with age related degeneration and other predisposing factors such as obesity, sleeping on a soft mattress, prolonged sitting in a chair or a sedentary inactive lifestyle shearing, and compressive forces can become excessive.

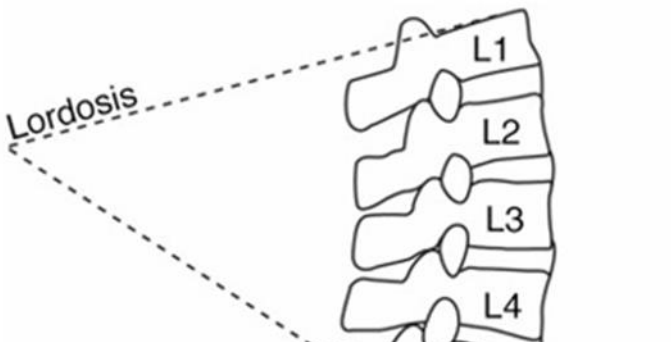


Figure: 1.1: Shearing and compressive forces exerted on the vertebral column due to lumbar curvature taken from Castillo and Lieberman, (2015). Changes in lumbar curvature due to vertebral degeneration alters the curvature of the lumbar spine (lordosis) increasing shearing and compressive forces (downwards) adding to the forces exerted by trunk weight on the intervertebral discs and shearing forces more laterally increasing the risk of disc prolapse. which in turn leads to increased lordosis. Increased lordosis leads to an increased risk of disc herniation, capsule pain, inflammation, further bone degeneration and vertebral displacement.

This is indeed compelling and good evidence to support a predisposing mechanism for the development of chronic lower back pain following back surgery particularly in high-risk surgical procedures that change the lumbar curvature (lordosis) and surgical procedures in older patients complicated with lumbosacral spinal degeneration. Furthermore, this model is good evidence to explain the two subgroups of patients described under the PSP definition.

In support of this model there is good evidence in the literature that lower back pain severity increases with age. The number of spinal surgeries as a therapeutic strategy to manage chronic lower back pain is increasing despite increasing population levels. Between 1990 and 2000 a 220% increase in spinal surgery was seen with a greater proportion of older patients (Chan and Peng, 2011). The most common indication for surgery in these older patients is herniated discs because of increased compressive forces on the degenerative spine. Other causes cited in the literature include foraminal stenosis due to bony spurs or arthritis and/or nerve root injuries either direct or indirect (Chan and Peng, 2011, Markman et al., 2015,

Christelis et al., 2021). All causative factors associated with older age and a degenerative spine. Another causative factor is the number of surgical revisions which may predispose the spine to spinal instability and mechanical compression because of inadequate decompression in multi-level pathology or poor surgical technique (Markman et al., 2015). Intraoperative damage because of poor surgical technique may be related to somatosensory pathway damage because of resection and coagulation near dorsal root ganglia, dura, and spinal nerve roots. It is good clinical practice to use multimodal intra-operative monitoring which includes somatosensory evoked potentials (SSEP) to reduce the risk of intra-operative somatosensory damage. The limitation to this type of monitoring is that SSEPs only monitor for large sensory nerve damage (Aβ nerves) and not the smaller sensory nerves associated with nociceptive pain. This may explain why despite good intra-operative monitoring clinical practice there remains a high proportion of patients who are reporting post operative pain.

Other candidates for intra-operative surgical complications that have been proposed as underlying causes for post operative chronic pain include spondylolisthesis, epidural fibrosis (Figure 1.2), vascular injury, infection, hematoma and lateral resus space compression due to foraminal stenosis (Figure 1.3). The common underlying mechanism in these examples is compression especially compression of spinal nerves below the conus (end of the spinal cord) at spinal levels L4-S2 resulting in entrapment and injury (ischaemic or mechanical).

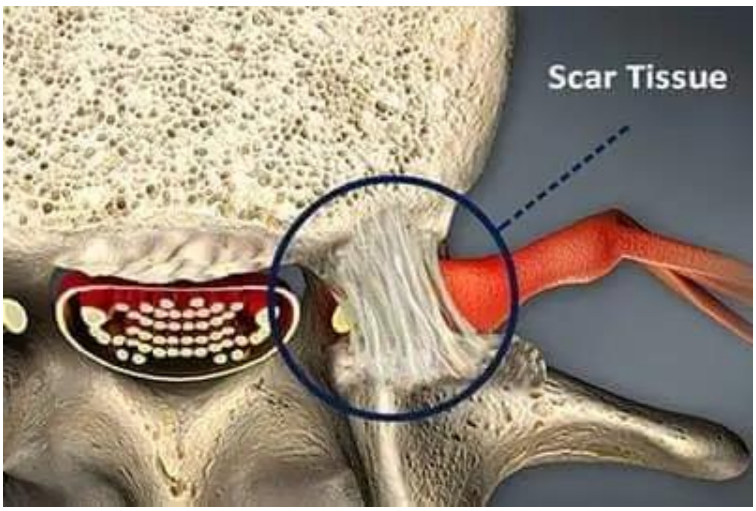


Figure 1.2: An illustration of post operative epidural fibrosis (scar tissue) taken from the International Pain Foundation, (2024). The emerging spinal nerve (orange) is entrapped by scar tissue resulting in local compression of the underlying dorsal root entry zone and spinal nerve trunk.

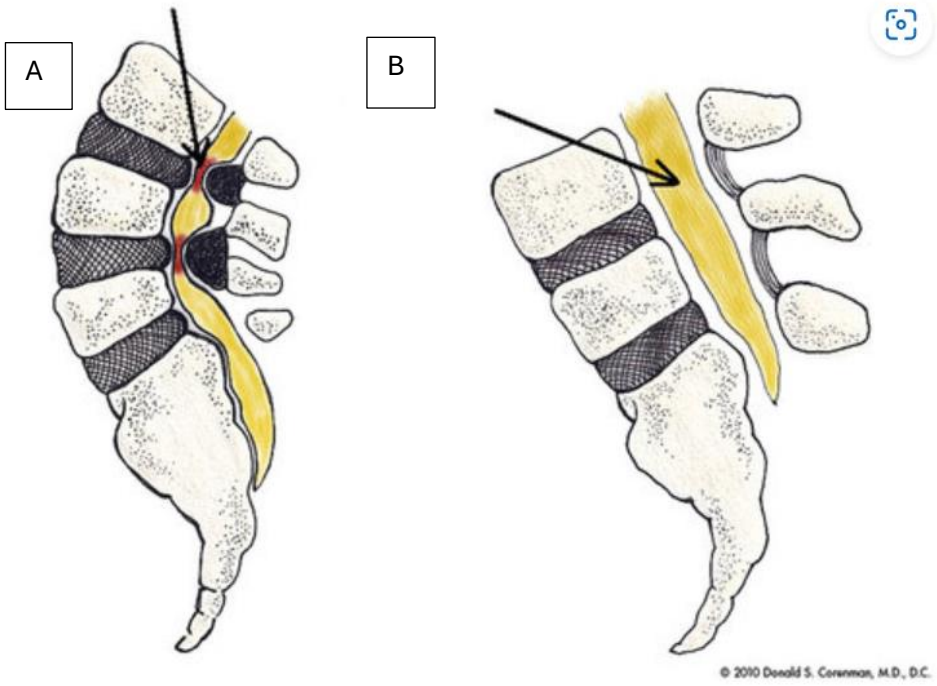


Figure 1.3: An illustration of Lateral resus space compression due to foraminal stenosis taken from Lifecare, (2024). The foraminal space is reduced for exiting spinal nerves leading to compression, entrapment, injury and irritation. A. Degenerative changes lead to spinal cord and foraminal narrowing. B. shows the absence of compression.

However, disc herniation remains the largest cause of both PSP type 1 and PSP type 2 related chronic pain in FBSS. The spinal nerves at greatest risk of entrapment due to lumbar disc herniation are L3, L4, L5 and S1 with the most common entrapments occurring at L5/S1 as a direct result of disc herniations (Dvorak, 1988). S1 nerve impingement is the main cause of sciatica with chronic pain radiating into the leg (Dvorak, 1988), Figure 1.4 and Figure 1.5.

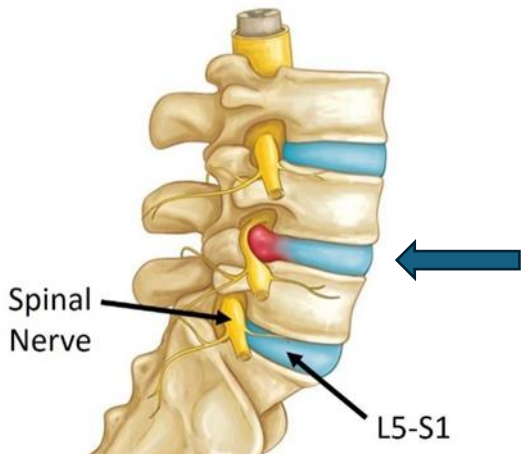


Figure 1.4: An illustration of disc herniation at spinal level L4 taken from Centeno, (2020). The prolapse of disc between L4-L5 leads to entrapment of the emerging spinal nerve, the resultant instability places increased compressive forces on the disc below between L5-S1.

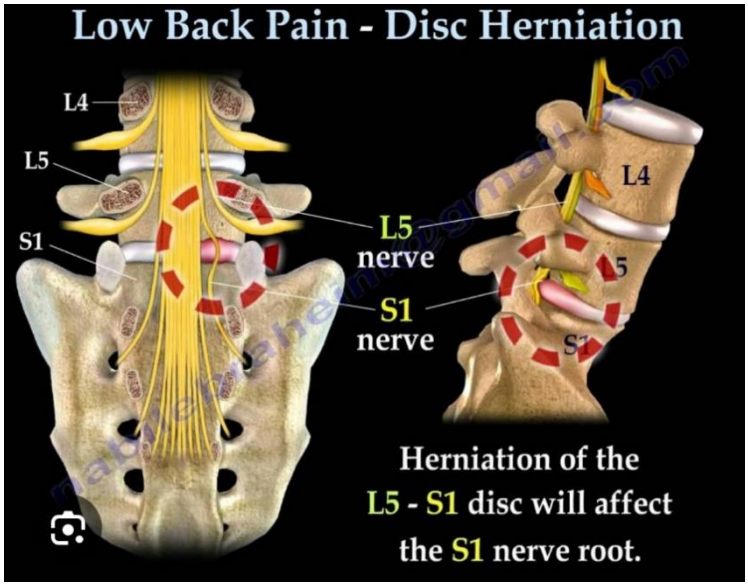


Figure 1.5: An example of lower back pain because of disc herniation between L5-S1 taken from Ebraheim, (2020). The prolapsed disc entraps the S1 spinal nerve placing increased pressure at the dorsal root entry zone, dorsal roots and main trunk of the emerging spinal nerve.

There is limited follow up evidence available on the incidence of chronic pain following lumbar disc surgery. Dvorak, (1988) reported that 70% of patients continued to complain of back pain over a 4-17 year follow up period and that 23% reported chronic pain and 45% described residual radicular pain. This paper is over 36 years old and intra-operative monitoring practices have significantly changed. It is unclear what the impact this has had on the incidence of chronic pain as a result lumbar disc prolapse in this group of patients.

Despite this rather heterogeneous picture of underlying causative factors there is good agreement in the literature that chronic pain due to FBSS is primarily neuropathic pain (Chan and Peng, 2011; Markman et al., 2015; Inoue et al., 2017; Christelis et al., 2021). Post-surgical pain in FBSS patients initially presents as axial lower back pain between the 12th rib and gluteal sulcus in keeping with a lumbosacral spinal nerve compression. However, the pain distribution pattern that develops does not always appear to conform to a single compressed nerve root typically seen with neuropathic radicular pain. Instead, chronic pain is often more diffuse and may frequently not match with a single dermatome. This atypical pattern implies that diffuse small fibre nociceptors (c-fibres) found innervating soft tissue and skin are contributing significantly to the pain profile. The inclusion of small fibre nociceptors may explain why chronic pain in FBSS tends to be persistent, regardless of the absence of neural compression and may be driven by mechanisms associated with local inflammation.

The sensory pain profile for FBSS related chronic pain reported in the literature is heterogeneous with a higher incidence of neuropathic and deep pain phenotypes a further indicator of small fibre (c-fibre) involvement. Ramaswamy et al., (2019) described the sensory pain profile in FBSS as burning, tingling, tactile allodynia, hyperalgesia, electric shock, heat or cold numbness or pressure pain. A mixture of both peripheral and central sensitisation features. Markman et al., (2015) and Cho et al., (2017) reported similar pain phenotypes, adding numbness, paraesthesia, and muscle weakness. What was not clear in the literature was

whether the clinical profile for FBSS changed with progression, pain duration or pain intensity or differed between or during SCS treatment. If pain characteristics change over time then they may be a useful baseline characteristic for treatment evaluation.

In the pain research community allodynia and hyperalgesia are considered as signatures of typical neuropathic pain. The pain community describe allodynia as *"*pain due to a stimulus that does not usually evoke pain" classified using touch, pressure, pinprick, cold and heat (Jensen and Finnerup, 2014). Hyperalgesia is defined as "increased pain from a stimulus that usually provoked pain". However, in FBSS allodynia and hyperalgesia are often reported as subtle and can escape routine clinical examination suggesting a different pain model to other neuropathic pain syndromes. Furthermore, the pain described by FBSS patients is often greater in pain severity and physical disability than other neuropathic pain syndromes and will often spread to include the legs, perineum, and genitals (Markman et al., 2015; Cho et al., 2017). This profile favours peripheral nociceptor hyperexcitability a characteristic that may be useful in a symptomatic approach in FBSS patients for evaluating baseline chronic pain characteristics and the effects of SCS.

Inoue et al., (2017) in a recent FBSS study reported FBSS related pain as severe (12.3%), moderate (43.6%) or mild (36.2%) and 7.9% of respondents described no pain. Mild symptoms were represented as residual symptoms which included a dull ache (71.1%), numbness (69.8%), cold sensations (43.3%) and paraesthesia with either burning or prickly sensations in the legs or feet (35.3%). In this study pain severity was mild to moderate with only 12.3% representing chronic severe pain. In the mild pain subgroup burning or prickly sensations in the legs or feet were reported clinical markers for nociceptor excitation associated with inflammation. Furthermore, allodynia and hyperalgesia were not reported in this study. This finding is consistent with allodynia and hyperalgesia having a lower prevalence in FBSS patients. Pain reported as moderate or severe were associated with increased burning or prickly sensations or electric shock sensations that dominated the pain profile. This study is good evidence of increased peripheral excitability with increasing pain severity in FBSS patients without significant allodynia or hyperalgesia featuring in the pain profile.

There is growing evidence in the literature that chronic pain in FBSS is associated with lower quality of life scores than other chronic pain syndromes. De Ridder et al., (2022) considered non-pain related symptoms for FBSS which included anxiety, depression, disturbed sleep,

increased suffering which all impact on quality of life. Christelis et al., (2021) agrees adding that residual lower back pain (mild, moderate, or severe) was found to be the most common symptom most closely related to patient dissatisfaction and a low quality of life. This suggests that chronification of pain may have additional effects on other brain networks and warrants further scrutiny of the literature.

Due to the heterogeneity in FBSS, there is much debate on both the incidence and prevalence. Markman et al., (2015) estimated the prevalence of chronic lower back pain with a neuropathic radicular sign in the adult general population to be 4%, in the UK (2024). The prevalence of non-radicular neuropathic pain is thought to be much higher. Chan and Peng, (2011) considered patients undergoing lumbar spinal surgery and reported an incidence of new individuals developing chronic pain following surgery to be between ten and forty percent. Christelis et al., (2021) quoted an incidence of between 20%-40% for the last decade and Ramaswamy et al., (2019) an incidence of between 4% and 50% of back surgery patients. This data although compelling is insufficient to determine the prevalence and incidence of FBSS in the UK population. Existing and preexisting radicular pain in the UK population estimated by Markman et al., (2015) is lower than expected at 4% given the aging population and I suspect there is a significant number of unreported cases. What is clear is that there is a minimal to moderate incidence associated with lower back surgery this may well be much higher due to the under reporting of chronic pain in spinal surgery.

The heterogeneous profile of FBSS poses a serious therapeutic problem as different pain types according to Freynhagen et al., (2006), require different therapeutic approaches. They describe first line treatment tending to favour non-steroidal anti-inflammatory drugs, however there is no clear consensus on the therapeutic effect of this intervention. Other drugs which include opioids, cyclic antidepressants and anticonvulsants have been shown to be equally affective in early intervention. Joosten and Franken, (2020) argue that <50% of patients respond to pharmacological treatments leading to a substantial number of patients that either remain under treated or untreated which led to the development of last resort treatments in chronic neuropathic pain. These so-called last resort treatments include dorsal root ganglion stimulation, SCS, deep brain stimulation (of the periaqueductal grey), transcranial magnetic stimulation and cortical stimulation of the motor/somatosensory

cortex. There remains insufficient evidence in the literature on the long-term benefit of these so-called last resort treatments.

The decision to focus on FBSS patients in this project was influenced by my own clinical practice in intra-operative neurophysiology monitoring and neuromodulation. As a part of my practice, I monitor patients during spinal deformity and tumour surgery. In my experience I have noticed that within the spinal surgery patient group there is a considerable amount of lumbar spinal surgery patients reporting post operative chronic pain on follow up. This patient subgroup is subsequently labelled as having FBSS and referred onto pain management services and neuromodulation. This post operative deficit is often under reported as a significant post operative deficit indicator and treated as an acceptable consequence of spinal surgery. My clinical practice also includes neuromodulation primarily in the treatment of movement disorders (Parkinson's disease, dystonia and essential tremor), spasticity, bladder control and more recently chronic pain using SCS. My limited experience here was in mapping the dorsal column positions for SCS paddle placement. It was here that I noticed that surgical patients labelled with FBSS were being treated with percutaneous SCS due to the less invasive practice associated with these electrodes.

The biggest challenge faced with percutaneous electrodes by the team was identifying SCS responders from non-responders. NICE TAG 159 (NICE committee reviewed 2014, 2008) guidelines recommend using a multi-disciplinary approach for patient selection with a brief trial using a temporary implant to evaluate patient suitability. Trials are expensive, due to the individual cost of the implant, surgical time and resources with additional hidden in-patient costs. Patients are at risk of hospital acquired infection, increased pain due to implantation and psychological and emotional effects because of long waiting lists and cancellations. Currently there are no baseline biomarkers to aid this assessment process.

The initial aim of this project was to explore baseline characteristics (clinical and physiological) of chronic pain in FBSS patients who were undergoing SCS trials and identify any suitable measures that could aid SCS responder evaluation and clinical decision making. The anatomical and physiological mechanisms of nociceptive pain and chronic pain were reviewed initially to identify suitable candidates for baseline biomarkers.

1.2 Anatomy and physiology of human pain pathways

The pain system in humans is complex the current consensus in the pain community is that the pain system can be divided into the ascending pain pathways (lateral and medial spinothalamic tracts) and the descending pain modulating system which incorporates the spinoreticular tract and a descending inhibitory pain pathway from the dorsolateral prefrontal cortex. Pain perception occurs peripherally by nociceptors.

1.2.1. Nociceptors of the peripheral nervous system

There is good evidence in the literature to support FBSS nociceptor pain following surgery as consisting of combination of mechanical compression and inflammation activating two subsets of small fibres nociceptors A-delta fibres (Aδ) and C-fibres (Mertens et al., 2015, St. John Smith, 2018 and Christelis et al., 2021). C-fibres are polymodally sensitive to thermal, chemical, and mechanical stimulation and are located throughout tissues consisting of free nerve endings with extensive branches forming a diffuse and variable network. Aδ fibres are myelinated and have larger diameters resulting in a faster nerve conduction velocity and quicker response to pain. Aδ fibres are sensitive to mechanical and temperature noxious stimulation and have either a high or low threshold. The FBSS pain profile is typically diffuse rather than confined to a single spinal nerve root level favouring excitation of c-fibre nociceptors.

During injury numerous C-fibre branches are stimulated above threshold. Action potential propagation is orthodromic towards the parent axon (Mertens et al., 2015) with simultaneous antidromic stimulation of neighbouring branches. Antidromic activation results in the release of vasoactive neuropeptides that results in vasodilation, assisting the onset of inflammation by increasing blood flow to the damaged tissues.

Inflammatory mediators from the circulatory system and inflammatory cells are released which include vasoactive amines (histamine and serotonin), peptides (bradykinin), eicosanoids (prostaglandins and leukotrienes) and substance P (Omoigui, 2007; Abdulkhaleq et al., 2018). Substance P binds to the neurokinin-1-receptors triggering various cellular responses. The important cellular responses likely to contribute to the baseline FBSS chronic pain profile are those associated with increased pain transmission and promoting further inflammation. Initial responses are serotonin driven which binds to peripheral 5HT receptors increasing the local inflammatory effect and nociceptive transmission (Mertens et al., 2015; Paredes et al., 2019).

1.2.2 Dorsal root ganglion

Aδ and C fibre nociceptors are sensory neurones, and their nuclei reside in the dorsal root ganglion adjacent to the dorsal root entry zone of the spinal cord. Nociceptor fibres within the dorsal root ganglia express neurotransmitters and neuropeptides and can be subdivided into either peptidergic nociceptors that secrete glutamate, neuropeptides, substance P and calcitonin gene related peptides (Cheng, 2010) or nonpeptidergic nociceptors that secrete glutamate. In both these mechanisms glutamate is involved in increasing nociceptive transmission an essential underlying mechanism for the development of a FBSS chronic pain symptomatic profile.

1.2.3 Dorsal horn of the spinal cord

At the nociceptor presynaptic cleft located in the Rexed lamina I and II of the superficial layers of the dorsal horn, glutamate and neuropeptides are released and bind to interneuron post synaptic receptors (Cheng, 2010). There are several glutamate receptors that are involved in the nociceptive peripheral pain network. Cheng, (2010) describes the AMPA receptors, as the primary receptors for the transmission of pain which trigger rapid depolarisation with a reduced repolarisation phase promoting fast synaptic transmission, lowering the firing threshold and exciting nociceptors that are stimulated. Other important receptors to consider include Kainate receptors that mediate post synaptic transmission and inhibit GABAergic interneurons promoting nociceptive transmission, NMDA receptors that mediate and prolong ionic channel opening and membrane depolarisation and metabotropic glutamate receptors which mediate intracellular calcium levels increasing dorsal horn excitability (Cheng, 2010, Mertens et al., 2015). Neuropeptides that are released include substance P, calcitonin gene related peptides, inflammatory mediators, cholecystokinin and neuropeptide Y which are involved in pain modulation and bradykinin involved in pain mediation and inflammation (Cheng, 2010). The net result of this complex range of neurotransmitter, receptors neuropeptides is to increase nociceptor transmission by lowering firing thresholds and promoting nociceptor excitation essential characteristics of the FBSS pain profile.

Cheng, (2010) and Mertens et al., (2015) both explain that Aδ fibres enter the dorsal horn and terminate within lamina I and the ventral portion of lamina II and lamina V (Figure 1.6). Aβ fibres (touch) terminate within lamina III and lamina IV (Cheng, 2010) and pass deep into lamina V and lamina VI (Mertens et al., 2015). C-fibres terminate within lamina I, II and X, concentrating around the central canal.

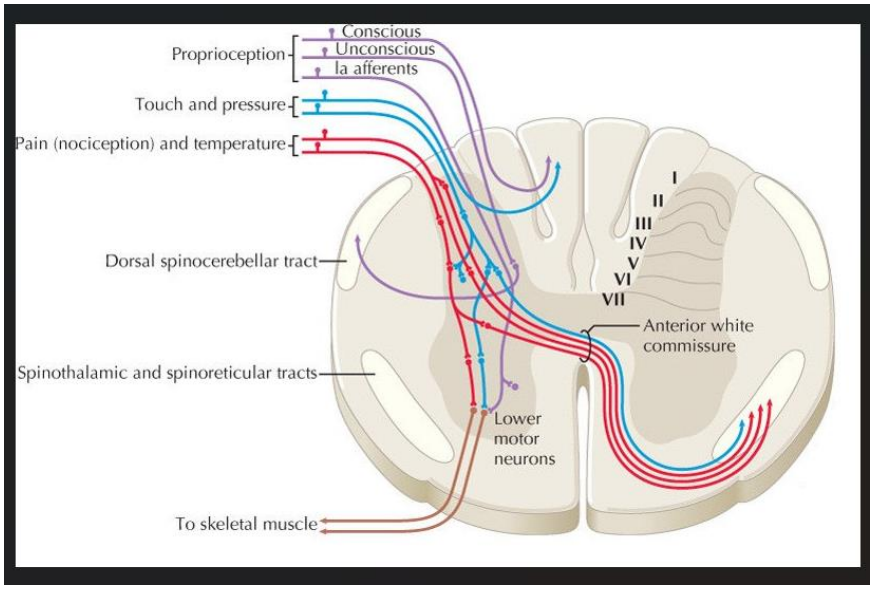


Figure 1.6: A schematic of the dorsal horn architecture of the spinal cord taken from Biswas, (2015). Nociceptive fibres (red), Aδ and c-fibres enter the spinal cord at the dorsal root entry zone passing into the dorsal horn and synapsing with secondary neurones and interneurons primarily within lamina I (marginal zone) and II (substantia gelatinosa). Second order nociceptors cross the midline of the spinal cord as a part of the anterior white commissure to the spinothalamic tracts. Larger Aβ neurones (touch) myelinated neurones (blue) and proprioception fibres associated with consciousness (purple) pass into the dorsal columns. Proprioception fibres associated with unconscious activity (purple) form a reflex with the dorsal spinocerebellar tract and Ia afferents (purple) form a network with lower motor neurones on route to skeletal muscle.

There is good evidence to support that that lamina I first order neurones express the NK1 receptor and are referred to as NK-1 positive neurones and respond to substance P (Cheng, 2010 and Mertens et al., 2015 Megat et al., 2018 and Li et al., 2019). These neurones are located deep in lamina I of the dorsal horn and synapse with peptidergic second order neurones. In Lamina II the first order neurones express as NK-1 negative which synapse with nonpeptidergic second order neurones. A network is formed between dendrites of the NK-1 negative afferents and the deeper NK-1 positive afferents merging the pain signals. The NK-1 negative – NK-1 positive network is modulated by GABAergic and glycinergic interneurons from lamina II and III of the dorsal horn (Cheng, 2010, Mertens et al., 2015).

The synapse between primary and secondary nociceptors in lamina II and other Rexed laminae function as a spinal pain gate which plays a crucial role in the regulation of pain transmission (Cheng, 2010 and Mertens et al., 2015). The excitatory portion of the spinal gate is modulated by serotonin and dopamine (D1 and D5 receptors). Stimulation of larger A-fibres (Aα, Aβ and AϒΥ), closes the spinal pain gate, which according to Mertens et al., (2015) decreases pain perception. In contrast stimulation of nociceptor neurones, Aδ and C-fibres open the spinal pain gate promoting the transmission of pain through lamina I secondary neurones. Inflammation activates dopaminergic neurones via D1 receptors found in lamina I and II which Cheng, (2010), Mertens et al., (2015), Megat et al., (2018) and Li et al., (2019) all agree lowers nociceptor firing thresholds and exciting the pain pathway.

The peripheral and central pain mechanisms limited to the peripheral nervous system spinal cord are driven by inflammation at the site of injury, dorsal root ganglion and dorsal horn. All three anatomical regions that are involved in promoting nociceptor excitability, lowering nociceptor firing thresholds and promoting the transmission of pain. FBSS pain patterns are dominated by pain characteristics associated with nociceptor hyperexcitability. How the initial pain pattern changes in FBSS patients from nociceptive pain to chronic neuropathic pain warrants further investigation.

1.2.4: The Three Pain Pathways

The dorsal horn second order neurones can be subdivided into two groups. Aδ fibres second order neurones located in lamina I of the dorsal horn that are sensitive to heat and ascend in the middle and ventromedial of the lateral funiculus and Aδ fibre second order neurones that transmit sharp pain ascend in the anterolateral funiculus. Together these form the anterolateral spinothalamic tract (Meyerson and Linderoth, 2006, Vedantam et al., 2019, De Ridder et al., 2022, Zhang et al., 2024). C-fibres ascend dorsal to the larger Aδ fibres.

Wide dynamic range neurones (WDR) are the largest population of neurones found in the dorsal horn with the majority being projection second order neurones (Meyerson and Linderoth, 2006, Vedantam et al., 2019, De Ridder et al., 2022, Zhang et al., 2024). WDR neurones are responsible for transmission, encoding and modulation of nociceptive pain. Glutamate enhances their transmission (Meyerson and Linderoth, 2006, Vedantam et al., 2019, De Ridder et al., 2022, Zhang et al., 2024). The WDR neurones are multi-receptive neurones

responding to both light and strong stimuli and receive input from Aβ, Aδ and C-fibres and have polysynaptic connections between C-fibres. The WDR neurones ascend and decussate at 1-2 spinal nerve segments above the point of entry and ascend to the rostral ventromedial aspect of the medulla oblongata forming the anterolateral system. The anterolateral system can be divided into three distinct subdivisions, the lateral spinothalamic pathway and medial spinothalamic pathways both interact with the descending pain modulating system forming a pain regulatory network.

A compelling recent model of chronic pain has been developed, known as the triple network model (Vanneste and De Ridder, 2021; De Ridder et al., 2022) to explain nociceptive pain and the transition to chronic pain. In nociceptive pain this model assumes that WDR neurones in the lateral spinothalamic pathway from lamina I and V ascend to the ventral posterior lateral nucleus of the thalamus passing through the brainstem (medulla oblongata, pons and midbrain). WDR neurones in the medial spinothalamic pathway from lamina I ascend to the posterior part of the ventral medial nucleus (VMpo) and the medial dorsal nucleus. Collateral branches from both these ascending pathways form feedback networks in the brainstem that interact with the descending pain modulating system via the spinoreticular tract that ascends to the reticular formation of the brainstem. The increased ascending afferent nociceptive input is balanced by the descending pain modulating system preventing the development of chronic pain (Vanneste and De Ridder, 2021 and De Ridder et al., 2022).

1.2.5: The lateral spinothalamic pathway

The lateral spinothalamic pathway ascends through the brainstem (medulla oblongata) pons, midbrain and thalamus (Figure 1.7) to terminate on the primary somatosensory cortex. The inferior olivary nucleus located in the medulla oblongata just below the pons receives input from the lateral spinothalamic pathway and forms a subcortical network between the peri-aqueduct grey (PAG), zona incerta of the ventral thalamus and the cerebellum via the spino-olivocerebellar pathway. A subcortical network feedback loop is formed between the lateral spinothalamic pathway, PAG and the descending pain modulating system. This feedback loop connects the ascending lateral spinothalamic pathway to the descending pain modulating system allowing pain modulation with increasing nociception (Vanneste and De Ridder, 2021; De Ridder et al., 2022).

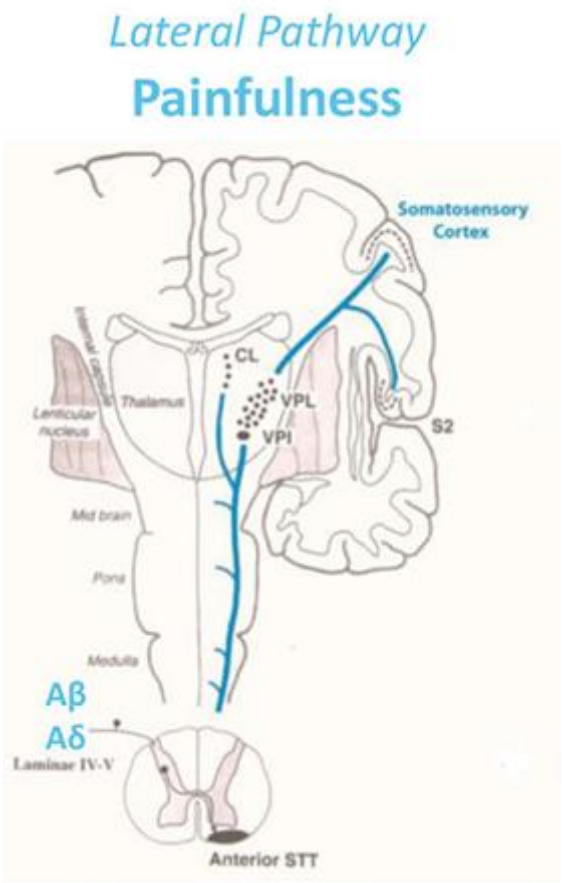


Figure 1.7: The lateral spinothalamic pathway taken from De Ridder et al., (2022). The schematic summarises the anatomical pathway of the lateral spinothalamic pathway (blue). This pathway is associated with the sensation and location of painfulness As the pathway ascends numerous collateral subcortical branches pass into the brainstem creating multiple pain feedback networks to the descending pain modulating system. The lateral spinothalamic pathway as the spinal lemniscus pathway ascend to the ventral posterior lateral nuclei of the Thalamus (VPL, VPI). The lateral spinothalamic pathway projects from the ventral posterior nucleus and posterior nuclei as 3rd order neurones via the internal capsule and corona radiata to the primary somatosensory cortex, located on the post central gyrus of the parietal lobe.

The principle thalamic nuclei of the lateral spinothalamic pathway are found in the dorsal thalamus and are modulated by the zona incerta and the reticular thalamic nucleus, GABAergic nuclei of the ventral thalamus (Yen and Lu, 2013, Vanneste and De Ridder, 2021; De Ridder et al., 2022). Here a thalamic network is formed between the ventral posterior nucleus, posterior nuclei, and lateral nuclei. Yen and Lu, (2013) state that lamina I and II WDR second order

neurones primarily project to the ventral posterior nucleus and posterior nuclei by the spinothalamic tract. They synapse in the medial dorsal, ventral posterior lateral and ventral posterior medial nuclei of the thalamus (Yen and Lu, 2013, Vanneste and De Ridder, 2021; De Ridder et al., 2022 and Zhang et al., 2024). The lateral spinothalamic pathway terminates on the primary somatosensory cortex and encodes for discriminative pain, phenotype, painfulness, and location (De Ridder et al., 2022). Nociceptive processing for location and pain intensity (painfulness) is primarily in the somatosensory cortex. The somatosensory cortex shows strong connectivity with the secondary somatosensory cortex forming a network with the insula, which encodes for nociceptive pain intensity (Reddan and Wager, 2019) and the inferior parietal lobule and precuneus for encoding pain quality.

Numerous authors (Sarnthein et al., (2006); Bushnell et al., (2013); Wolter et al., (2013); Alshelh et al., (2016) and Caylor et al., (2019) agree that the primary somatosensory cortex, precuneus cortex and association areas encode for the location and duration of pain and that the WDR neurones are coupled to the somatosensory cortex and responsible for nociceptive interpretation. Therefore, the somatosensory cortex and parietal network including the precuneus cortex might represent a cortical network region that could be studied. There are two neurophysiological techniques that could be used to evaluate function of this complex cortical network, electroencephalography (EEG) and somatosensory evoked potentials (SSEP). Both could be used to explore somatosensory cortical function as chronic pain develops.

In the literature phasic pain studies (short lasting pain induced in a laboratory setting by electrical or laser stimulation) using EEG have been shown to transiently suppress cortical oscillations in the alpha (8-12 Hz) and beta (13-25 Hz) frequency ranges. Gamma frequency (20-60 Hz+) changes over the somatosensory (post central gyrus, parietal lobe) and neighbouring primary motor areas (precentral gyrus, frontal lobe) have also been observed. Ploner et al., (2017) suggest that the gamma oscillations observed are more closely related to pain intensity encoding. There is convincing evidence that gamma oscillations result from feed forward neuronal network mechanisms and in contrast alpha/beta oscillations from feedback neuronal network mechanisms. Therefore, phasic pain studies imply that nociceptive processing in the somatosensory cortex relies on a feed forward neuronal mechanism (Ploner et al., 2017) and is a potential cortical measure for the differentiation between feed forward and feedback mechanisms of pain.

1.2.6 The medial spinothalamic pathway

The medial spinothalamic pathway (Figure 1.8) consists of second order WDR neurones arising from C-fibres from lamina I and larger Aβ (touch) from lamina IV-VI.

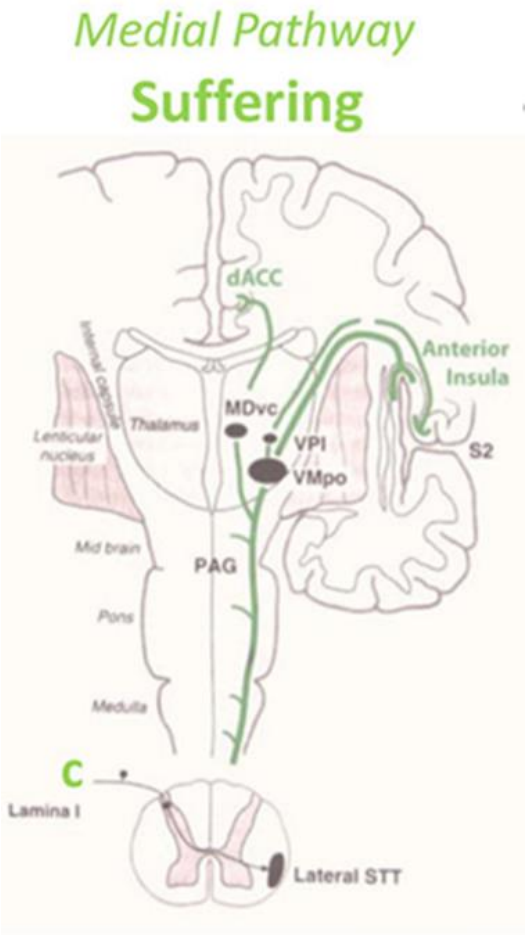


Figure 1.8: The medial spinothalamic pathway taken from De Ridder et al., (2022). The schematic summarises the anatomical pathway of the medial spinothalamic pathway (green). This pathway is associated with emotional interpretation and the sensation of suffering. The medial spinothalamic pathway ascends in the brainstem (medulla oblongata, Pons and Midbrain) with collateral branches providing feedback to the periaqueductal grey (PAG) and the descending modulating pain pathway. The medial spinothalamic pathway ascends to the thalamus synapsing in the posterior part of the ventral medial nucleus (VMPo), the ventral posterior nucleus (VP1) and the medial dorsal nucleus. The ventral medial nucleus (VMPo), the ventral posterior nucleus (VP1) project subcortically to the anterior insula. The medial dorsal nucleus projects subcortically to the anterior cingulate (ACC) encoding for affective pain processing and unpleasantness.

De Ridder et al., (2022) argues that the anterior insula is a critical node in the triple network model as it encodes for the emotional and motivational aspects of pain, cognitive and empathic evaluation of pain, suffering and unpleasantness. The function of the anterior insula and pain as emotional processing (Bushnell et al., 2013; De Ridder et al., 2022; Labrakakis, 2023). Arriving first in the posterior insula and then transferring to the anterior insula for processing in the sensory discriminative sub region of the anterior insula. A subcortical network connects the secondary somatosensory cortices and the dorsal posterior insula.

There is growing evidence that the anterior portion of the insula participates in the subjective experience of pain. The subjective emotional experience of pain varies widely between individuals and heavily influenced by cognitive and emotional factors (Bushnell et al., 2013; De Ridder et al., 2022; Labrakakis, 2023).

The lack of a primary cortical area in the medial spinothalamic pathway makes studying with EEG and SSEP techniques challenging. However tonic pain studies (pain caused by injury) have shown that a surrogate cortical target exists due to connectivity explained by the triple network model (Vanneste and De Ridder, 2021 and De Ridder et al., 2022). Here the EEG profile shows a different pattern to phasic pain studies. The emergence of gamma oscillations over medial prefrontal cortical areas associated with the engagement of the medial spinothalamic tract and emotional processing. This potential surrogate EEG target is the product of connectivity between the medial prefrontal cortices and the anterior cingulate of the medial spinothalamic pathway. Ploner et al., (2017) argues that the evidence from EEG studies in both phasic and tonic pain studies alpha and beta cortical oscillations reduce. This would suggest that pain lasting a few minutes because of injury results in a feed forward shift away from sensory pain encoding cortical areas (somatosensory, precuneus cortices) of the lateral spinothalamic pathway to more emotional – motivational pain encoding areas (prefrontal cortex and anterior cingulate) in the medial spinothalamic pathway. This compelling finding is further evidence to support using EEG to investigate chronic pain in FBSS.

1.2.7 The descending pain modulating system.

The descending pain modulating system (Figure 1.9) balances the two ascending pathways (lateral and medial spinothalamic pathways) in the triple network model and represents the

brains' ability to supress ongoing pain (De Ridder et al., 2022). This may have evolved as a survival strategy during times of severe injury as a part of the sympathetic autonomic nervous systems flight or fight response. The descending pain pathway inhibits pain, through central nervous system pain feedback from the two ascending pain pathways and a strong sympathetic response to injury and supplemented by serotonin due to inflammation.

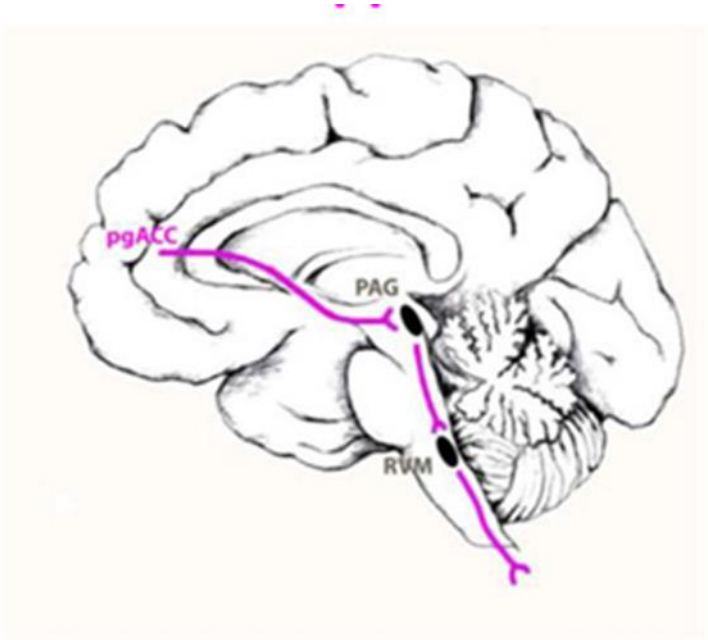


Figure 1.9: The descending pain modulating system (purple) taken from De Ridder et al., (2022), is summarised in the diagram as a descending subcortical network between the anterior cingulate (pgACC), thalamus, Periaqueductal grey (PAG) and rostral ventromedial medulla (RVM). There are extensive feedback connections between the PAG and thalamus which influence pain modulation. Descending connections from the PAG and thalamus also interact with rostral ventromedial medulla (RVM) modulating the spinal gate and pain.

The anterior cingulate has been shown to have strong connections with the dorsolateral pre-frontal cortex (De Ridder et al., 2022; Seminowicz and Moayedi, 2017). Described as a heterogeneous region and a key node to several brain networks involved in complex cognitive processing including nociceptive processing. The dorsolateral pre-frontal cortex acts as an interface for pain regulation (De Ridder et al., 2022; Seminowicz and Moayedi, 2017). The dorsolateral prefrontal cortex is also a key node in the extrinsic mode network (active task and cognitive processing) and the default mode network (active during wakeful rest, detailed thoughts, self-identity, and future planning). Acting as an interface between these two networks and the cognitive control network.

In a normal functioning pain system nociceptive input is suppressed at the spinal gate by a combination of GABAergic, noradrenergic (sympathetic system) and opioidergic mechanisms due to the descending pain modulating system suppressing ongoing pain. The spinal gate is modulated by the descending pain modulating system.

The top-down approach of the triple network model (Vanneste and De Ridder, 2021 and De Ridder et al., 2022) assumes anterior cingulate is the key node of the descending pain modulating system. The rational for this is related to the strong connections with the reticular nucleus of the thalamus. A collection of GABAergic neurons that also receives input from the Para hippocampus and hypothalamus and the Periaqueductal grey (PAG) and critical in driving pain inhibition. There are two neuronal firing patterns associated with activation of the reticular nucleus, tonic and burst (Li et al., 2020). A tonic firing pattern is associated with depolarisation and burst firing pattern with membrane hyperpolarisation and inhibition. Increased activation of the medial spinothalamic pathway results in anterior cingulate activation. This downstream effect increases the activation of the bursting firing pattern and a descending inhibitory effect.

Second order neurones from the thalamic reticular nucleus descend to the PAG within the midbrain. There is good pre-clinical evidence to suggest that the PAG can modulate descending output and is dependent on the ascending pain input like the reticular nucleus of the thalamus and subsequent output from the reticular nucleus (Harper et al., 2018). Stronger conditioning painful stimuli increase the connectivity between the PAG and rostral ventromedial medulla and dorsal pons resulting in pain inhibition. This observation can be explained by the numerous descending second order neurones that project to both the rostral ventromedial medulla, dorsal pons, and the dorsal horn of the spinal cord.

The hypothalamus contributes to the descending pain modulation pathway by projecting dopaminergic second order neurones from the hypothalamic A11 nucleus to the dorsal horn of the spinal cord and trigeminocervical complex. Modulating both peripheral and trigeminal pain by activating postsynaptic dopamine D2 receptors (Megat et al., 2018 and Li et al., 2019). There are five types of dopaminergic receptors expressed in the dorsal horn. It is the D2 receptors that are involved in descending pain inhibition. When activated the D2 receptors induce an anti-nociceptive effect on the opposing the D1 receptors found in lamina I and II inhibiting nociceptors.

Pain inhibition at the level of the dorsal horn of the spinal cord is modulated by four neurotransmitters, opioids primarily from the PAG within the midbrain, serotonin from rostral ventromedial medulla, dopamine from hypothalamus and noradrenalin from locus coeruleus nucleus in the pons. Collectively this is referred to as the inhibitory portion of the spinal gate (De Ridder et al., 2022; Loyd and Murphy, 2014; Megat et al., 2018; Li et al., 2019).

Persistent pain activates the release of endogenous opiates from the PAG. PAG neurones are sensitive to Mu opioid receptors. Approximately 27%-50% of PAG neurones project to the rostral ventromedial medulla and dorsal horn and interact with MU opioid receptors (MOR+). MOR+. The net effect of MOR+ activation is analgesia at the dorsal horn. MOR+ neuronal density shows huge sexual dimorphism at the rostral ventromedial medulla and dorsal horn, with females having greater densities of MOR+ neurones. Despite having a greater density of MOR+ neurones males tend to show a greater level of opioid mediated analgesia on activation. One explanation is that perceived pain intensity in females fluctuates across the ovarian cycle, pregnancy, and menopause. Loyd and Murphy, (2014) explain that PAG and dorsal horn neurones contain both oestrogen and androgen receptors that are required for analgesia activation. In males there are greater densities of androgen activated neurones compared to the oestrogen activated neurones which are activated with a metabolite of testosterone. In contrast females show fluctuating levels of oestrogen due to the ovarian cycle, pregnancy and menopause varying the analgesic response of the PAG neurones. This may explain why female patients are reported in the literature to be at a greater risk of developing chronic pain disorders than males and why female patients may show greater variability in their response to SCS.

In addition to MOR+ opioid dorsal horn inhibitory network there is a serotoninergic network mediated by 5HT+ (serotonin) neurones found in the rostral ventromedial medulla, when stimulated 5HT is released into the dorsal horn (Carr et al., 2014; Li et al., 2019).

Serotonin pain inhibition portion of the descending pain system is driven by inflammation (Cortes-Altamirano et al., 2018) and subsequent activation of the reticular formation through the spinoreticular tract. Multiple brainstem reticular nuclei are innervated. It is the raphe magnus nucleus that appears to be the most important nucleus in this network. The raphe magnus nucleus projects serotonin (5-HT+) neurones from the brainstem to laminae I and II of the dorsal horn of the spinal cord. $5HT_{1B}$ receptor sensitivity is increased when activated by

5HT+ neurones making lamina I and II neurones more sensitive to serotonin mediated analgesia. This initial effect likely supplements the inhibitory effects from the PAG and sympathetic system on initial injury assisting in modulating pain intensity at injury.

In rat animal models, dorsal horn lamina I projection neurones and lamina II excitatory interneurons are MOR+, $5HT_{1A,}$ $5HT_{1B}$ + and $5HT_3$+ (Carr et al., 2014; Cortes-Altamirano et al., 2018). The activation of $5HT_3$ receptors found in lamina II (substantia gelatinosa) and $5HT_{1B}$ receptors found on WDR neurones suppresses neuronal responsiveness.

The sympathetic portion of the descending pain modulating system is through the locus coeruleus nucleus of the Pons. A primary node of the noradrenergic pain system and forms a network between A5, A6 and A7 ascending and descending noradrenergic neurones (Carr et al., 2014, Taylor and Westlund, 2017 and Li et al., 2019). Primary innervation to the dorsal horn is through the A6 noradrenergic neurones and supplemented by A5 and A7 neurones. Noradrenergic A5, A6 and A7 neurones are inhibitory acting on neurones found in lamina I and II.

1.3: Pathophysiology of chronic pain

Chronic lower back pain consists of two components, a nociceptive component, and a neuropathic component to pain (De Ridder et al., 2022; Freynhagen et al., 2006; Mertens et al., 2015; Omoigui, 2007; St. John Smith, 2018). The nociceptive component is dominant at initial injury and is gradually replaced by the neuropathic component. FBSS pain profiles reported in the literature appear to favour the neuropathic component of chronic pain. This would suggest that chronic pain in FBSS is driven by the transition from acute nociceptive pain due to injury or compression to muscles, tendons, nerves or ligaments to chronic neuropathic pain over a prolonged period.

The pain profile for nociceptive pain is described as localised pain that is sharp, aching or gnawing and occurs initially at injury accompanied by inflammation. Localised pain primarily refers to the activation of the lateral spinothalamic pathway with characteristics that are sharp or aching. In contrast, the neuropathic pain phenotype is described as burning, tingling, shooting or electric shock type pain sensations that develop over time, may be spontaneous. These symptoms are more in keeping with dysfunction of the lateral spinothalamic pathway and are associated with an emotional response (medial spinothalamic pathway), aspects of

suffering and a reduction in quality of life. Chronic neuropathic pain is driven by both peripheral and central sensitisation.

1.3.1 Peripheral sensitisation

There is good agreement in the literature that prolonged stimulation for more than 3-6 months leads to the onset of chronic pain and is characterised by the transition from nociceptive pain to neuropathic pain (Omoigui, 2007; Treede, 2019; Vanneste and De Ridder, 2021 and De Ridder et al., 2022). The triple network model (Vanneste and De Ridder, 2021; De Ridder et al., 2022) describes this transition as an imbalance in the two ascending spinothalamic pathways (lateral and medial) and the descending pain modulating system responsible for suppressing pain. The transition observed would suggest that the descending pain modulating system is impaired with prolonged stimulation.

The transition to chronic pain is marked by inflammatory mediators releasing GABA neuropeptides and neurotransmitters and raised levels of macrophages. Prolonged inflammation stimulates the release of interleukin-6 and Tumour Necrosis Factor alpha (TNF-alpha). TNF-alpha has been shown to damage the myelin of larger A-fibres reducing nerve conduction velocities and exposing axons to damage and irritation triggering further inflammation. Phospholipase A2 an enzyme involved in the phospholipid-arachidonic acid cycle of inflammation (Omoigui, 2007) is activated promoting further inflammation.

In FBSS the degeneration of disc tissue and disc herniation have been shown by Omoigui, (2007) to be associated with profound inflammatory changes due to the release of prostaglandin and nitric oxide inflammatory mediators. This would suggest that in addition to biomechanical stress and physical compression there are neurochemical changes that drive the transition of pain in FBSS patients. Omoigui, (2007) describes how degenerative disc tissue synthesises TNF-alpha damaging myelinated somatosensory (Aβ fibres) and nociceptors (Aδ fibres) accelerating the inflammation process. This rapidly leads to the development of chronic inflammation accelerating nociceptive mechanisms associated with lowering neuronal firing and increasing nociceptor excitability. This compelling finding hints at TNF-alpha accelerating the initial onset of chronic pain in FBSS patients and may explain why the neuropathic pain profile is dominated by hyperexcitable nociceptor characteristics.

If excess TNF-alpha is driving the pain process in FBSS myelin damage may well be higher in FBSS patients than other neuropathic pain syndromes and detectable with SSEP or sensory nerve conduction studies. There is strong evidence in the literature that increased nociceptor excitability due to ephaptic transmission and axonal irritation is augmented by the lowering of Aδ and C-fibre neuronal firing thresholds. This may explain the neuropathic pain phenotype for FBSS being dominated by burning, tingling, shooting or electric shock type sensations and further evidence of a potential baseline phenotype signature using clinical pain characteristics. This process is described as peripheral sensitisation (Berger et al., 2021; Cheng, 2010; Gomez-Varela et al., 2019; Ji et al., 2013). Here nociceptor excitability is amplified at the dorsal root ganglion due to an increase in T-cells and macrophage concentrations within the dorsal root ganglion and supportive glial cells altering nociceptor neuronal properties. Concentrated T-cells and macrophages begin to synthesise an excess of inflammatory mediators. Supportive glial cells begin to promote a series of changes in ion channel receptor and signalling protein properties within the dorsal root ganglion. This results in a rise in intracellular calcium concentration altering post synaptic dorsal horn excitability through a multitude of altered chemical processes and upregulation of gene expression leading to multiple epigenetic changes. Gomez-Varela et al., (2019) and Descalzi et al., (2015) argue that it is the epigenetic changes of gene expression that are most significant in chronic pain development. The most significant epigenic changes that may influence the baseline chronic pain profile in FBSS patients is lowering of nociceptor thresholds, nociceptor hyperexcitability and a prolonged sensation of pain. This compelling finding may explain why FBSS pain characteristics are dominated by painful electric shock and burning sensations. Another important epigenic change is histone acetylation which has been shown to promote gene transcription in the dorsal horn of the spinal cord enhancing pain intensity and pain duration (Descalzi et al., 2015; Berger et al., 2021). There are over 67 regulatory proteins that have been identified for regulating pain within the dorsal root ganglion. The net effects of these regulatory proteins are a lower nociceptor threshold, enhanced pain intensity and prolonged pain duration all clinical characteristics of FBSS. This is known in the pain community as hyperalgesia priming and induces neuroplasticity changes mediated by inflammatory mediators (Berger et al., 2021; Descalzi et al., 2015; Li et al., 2019) in the dorsal horn.

1.3.2 Central sensitisation in the spinal cord

Hyperalgesia priming induces neuroplastic changes that result in a desensitisation of dorsal horn opioid receptors in lamina I and II of the dorsal horn (Megat et al., 2018). This results in a reduction of opioid mediated analgesia and an amplification of pain intensity experienced called pain chronification a clinical feature associated with FBSS.

In the dorsal horn the larger Aβ fibres (touch), located in laminae III and IV begin to sprout due to increased levels of TNF-alpha and cytokines released from microglia and astrocytes which stimulates neurotrophic factor expression (Lu and Gao, 2023). A new dorsal horn network is created with second order neurones in laminae I and II, bypassing the spinal gate (Cheng, 2010). Under these circumstances the sensation of touch (Aβ transmission) stimulates a pain response (Aδ / C-fibre transmission) this is known as allodynia and is a clinical biomarker for the onset of neuropathic pain. This process is described as synaptic plasticity and is driven by a reduction in GABAergic and glycinergic interneurons due to a combination of apoptosis and impaired function (Cheng, 2010; Lu and Gao, 2023). Prostaglandin release is also associated with hyperalgesia development. In FBSS allodynia is reported as subtle or even absent suggesting that dorsal horn plasticity changes are not a typical clinical characteristic in FBSS. It is unclear why FBSS patients are not associated with moderate to severe allodynia symptoms even in patients who have suffered with chronic pain for many years. This is unusual given the excess TNF-alpha seen in FBSS patients due to disc degeneration and herniation.

Recent compelling evidence from Lu & Gao, (2023) relating to excess TNF-alpha and the cytokines released from microglia and astrocyte offer an alternative explanation. Astrocytes and microglia become reactive under prolonged painful conditions driven by inflammation and alter glutamate receptor expression. GluR2 receptors are converted to GluR1 receptors enhancing calcium permeability and further augmenting hyperalgesia. NMDA receptors become blocked by magnesium ions triggering an influx of calcium ions which in turn maintains sodium channels to remain in an open state. Ion channel conductance is enhanced and membrane depolarisation prolonged. This recent evidence offers a good model to explain the FBSS pain profile. It is unclear on the circumstances other than inflammation why TNF-alpha and cytokinin related changes favour hyperalgesia over allodynia. Changes in glutamate receptor expression and the blocking of NMDA receptors may be two important underlying mechanisms in FBSS.

This is intriguing however it is unclear from the literature if FBSS is associated with an increased number of astrocytes in a reactive state than other pain syndromes. Mild reactive astrocyte changes have been associated with increased intracellular calcium ions which lower nociceptor thresholds. More prolonged changes result in astrocyte hypotrophy and translational regulation protein synthesis amplifying painful sensations. These are certainly characteristics of FBSS. Lu and Gao (2023) described an extensive list of different signalling molecules associated with reactive astrocytes that contributes to nociceptive transmission by promoting calcium ion influx, phosphorylation, and the release of glutamate. Reactive astrocytes and microglia also regulate neuronal function, neuronal and synaptic plasticity through neurotrophic growth factor release. This finding suggests that reactive astrocytes are also involved in controlling intercellular communication and intracellular downstream signalling and synaptic plasticity.

More recent evidence from Zhang et al., (2024) suggests that prolonged sensory stimulation of Aδ and C-fibre WDR neuronal networks in the dorsal horn results in hyperexcitable spontaneous neuronal firing without peripheral stimulation. FBSS pain chronic pain profiles in the literature are dominated by ectopic spontaneous firing the so-called electric shock sensations. This finding is in keeping with an excited WDR network in the lateral and medial spinothalamic pathways and would explain the increased afferent input required to destabilise the descending pain modulating system as described by the triple network model.

The evidence presented favours prolonged inflammation as driving the chronic pain process in FBSS along with excess TNF-alpha in the degenerative spine of older patients. The combination of these two processes may lead to astrocytes to become reactive stimulating the nociceptor - WDR neuronal network in the afferent pathways of the spinal cord.

1.3.3 Imbalance between pain pathways

The main driver of chronic pain according to the triple network model proposed by De Ridder et al., (2022) is the onset of central sensitisation. De Ridder et al., (2022) argues that central sensitisation creates an imbalance between the two ascending pain pathways (lateral and medial spinothalamic pathways) and the descending pain modulating system. The

changes in Aδ, C-fibre and WDR neurones excitability observed in FBSS would support this claim.

The onset of central sensitisation proposed by the triple network model is underpinned by the onset thalamocortical dysrhythmia a pathophysiological process that has been associated with abnormal thalamic neuronal firing in chronic pain (Alshelh et al., 2016; Vanneste and De Ridder, 2021; De Ridder et al., 2022; Sarnthein et al., 2006 and Yen & Lu, 2013). There is good agreement that thalamocortical dysrhythmia results from the imbalance of the lateral spinal thalamic pathway due to an increase in afferent ascending volleys. Thalamocortical dysrhythmia is characterised by spontaneous firing of the ventral posterior nucleus of the thalamus which adopts a bursting firing pattern. There is good agreement that the observed bursting pattern is a result of deafferentation of the afferent inputs on thalamic relay neurones (Sarnthein et al., 2006; Alshelh et al., 2016; Vanneste and De Ridder, 2021; De Ridder et al., 2022). The thalamocortical white matter network becomes compromised resulting in cellular membrane hyperpolarisation. The resultant hyperpolarised state deactivates calcium T-channels causing thalamic neurones to fire in bursts within the theta frequency range (4-7 Hz) the biological signature thalamic dysrhythmia. PET and neuroimaging studies compliment these findings by showing evidence of reduced activity within the thalamus (Iadarola, 1995 and Sarnthein et al., 2006). Furthermore Bushnell et al., (2013) observed grey and white matter atrophic changes in the suspected compromised thalamocortical white matter networks.

An alternative hypothesis that is growing in popularity since the emergence of the triple network model argues that thalamocortical dysrhythmia onset results from the excitation of the reticular nucleus (Taylor & Westlund, 2017; Li et al., 2020 and De Ridder et al., 2022). In lower back pain nociceptive activation can persist a long time after initial injury. It has been suggested that long term nociceptive activation leads to an imbalance between noradrenergic ascending and descending neurones from the locus coeruleus nucleus (Taylor & Westlund, 2017 and Li et al., 2020). There is growing evidence that this imbalance creates a dominant ascending facilitatory effect exciting the dorsal reticular nucleus in the thalamus and excitation of the medial prefrontal cortex. The reticular nucleus is critical in regulating thalamocortical interactions in pain processing and may lead to the onset of thalamocortical dysrhythmia (Taylor & Westlund, 2017; Li et al., 2020 and De Ridder et al., 2022). The triple

network model (De Ridder et al., 2022) favours the reticular nucleus model for thalamocortical dysrhythmia and assumes that excitation of the reticular nucleus in the thalamus drives subcortical coupling between the two ascending pain pathways. This is indeed intriguing and favours reticular nucleus excitation as the underlying mechanism for thalamocortical dysrhythmia onset. The disruption to the reticular nucleus may also disrupt the sleep wake cycle in chronic pain patients resulting in fragmented poor-quality sleep. It is unclear whether sleep disruption plays a major role in the quality of life of FBSS patients. However, this intriguing finding may suggest that FBSS patients are at an increased risk of excessive levels of sleepiness which may limit the reliability of EEG biomarkers. This compelling finding warrant more scrutiny in the literature.

Therefore, the thalamocortical compromise model and characteristic theta bursting signature may reflect the effects of prolonged thalamocortical dysrhythmia resulting in thalamocortical network compromise and damage to the lateral and medial spinothalamic pathways. More studies are required to better understand the role the reticular nucleus plays in thalamocortical dysrhythmia.

There are numerous studies that link prolonged chronic pain to neuroplastic changes at the cortical level (Dos Santos Pinheiro et al., 2016; Koyama et al., 2018; Sarnthein et al., 2006; Telkes et al., 2020; Vanneste et al., 2018 and Vuckovic, 2014). There is good agreement between these studies that chronic pain neuroplasticity occurs at the primarily somatosensory cortex. This compelling finding can be explained by thalamocortical network compromise. Over time coupled cortical areas with the thalamus and wider pain network become inhibited leading to both cortical and subcortical plasticity changes and the evolution of characteristic EEG signatures. There is good agreement that brain cortical oscillations firing between 4-7 Hz (theta frequency) are linked to inhibited cortical areas forming a cortical signature of cortical plasticity (Ploner et al., 2017; Telkes et al., 2020 and Vanneste et al., 2018). The subsequent reduction in lateral inhibition in neighbouring cortical areas results in a shift towards faster beta (13-25 Hz) and gamma (20-60 Hz+) frequencies.

In chronic pain studies, alpha cortical oscillations are gradually replaced by slower theta cortical oscillations primarily over the somatosensory, precuneus and frontal cortical areas coupled to the bursting discharges of thalamocortical dysrhythmia. The evidence here suggests a potential cortical signature for chronic pain with EEG exists that could be used to

measure chronic pain progression. Potential EEG signatures could include transitioning from alpha power to theta power over the somatosensory cortex and the wider parietal network or coupled cortical areas showing increased theta activity in characteristic theta power patterns. Beta cortical oscillations in chronic pain studies have been observed to increase over the frontal brain areas creating a cortical border between theta and beta cortical oscillations (Ploner et al., 2017 and Telkes et al., 2020). This EEG signature is called the edge effect and is considered as further evidence of cortical inhibition due to prolonged pain. The work published by Ploner et al., (2017) relates to general chronic pain how these changes relate to FBSS patients warrants further scrutiny of the literature. Similar findings for lower back pain have been reported by Dos Santos Pinheiro et al., (2016); Jensen & Finnerup, (2014); Koyama et al., (2018); Sarnthein et al., (2006) and Telkes et al., (2020).

SSEPs have also been used to explore somatosensory cortical reorganisation, and neuroplasticity changes and strengthens the need to explore this second potential measure for evaluating changes due to chronic pain in FBSS patients. This warrants further study in the literature.

The triple network model (De Ridder et al., 2022 and Labrakakis, 2023) argues that the onset pain transition from nociceptive to chronic pain is triggered by excitation of the medial spinothalamic pathway. An ascending imbalance is created primarily observed in the anterior insula. Strong evidence from tonic pain studies suggests that pain processing shifts away from the sensory discriminative sub region of pain processing (lateral spinothalamic pathway) to the affective sub region that encodes for motivational-affective components of pain processing, disconnecting from the secondary somatosensory cortex with prolonged pain. Connectivity increases within the dorsal anterior cingulate cortex (Horn et al., 2012 and Labrakakis, 2023). This shift in cortical connectivity moves away from the initial pain experience to a more general viscero-motor -sensitive pain experience. The painful experience becomes associated with unpleasantness and empathy engaging the pre-frontal cortex. Increased activation between the pre-frontal cortex and anterior cingulate cortex leads to cognitive processing of more complex emotional reactions like frustration, depression, and anger.

Anatomical evidence supports these observations with grey matter atrophy observed in the anterior cingulate cortex and insula important nodes of the medial spinothalamic pathway (Bushnell et al., 2013). Grey matter atrophy has been suggested by Bushnell et al., (2013) to

represent damage caused by excessive prolonged nociceptive input to dendrites impairing synaptic function. Similar changes have been observed in the white matter tracts associated with these areas resulting in a degradation or disruption of white matter function and neuronal transmission. The anatomical evidence presented by Bushnell et al., (2013) is good evidence in favour of medial spinothalamic compromise because of increased afferent nociceptive input.

Grey matter atrophy changes have also been observed throughout the descending pain modulating system in support of impaired function. The most important areas were the dorsolateral and medial pre-frontal cortex, anterior cingulate cortex, insula and PAG (Bushnell et al., 2013; Harper et al., 2018). Grey matter atrophy changes in the PAG are of particular importance and may represent a loss of MOR+ neurones leading to the subsequent impairment of the opiate response to pain. This is supported by decreased connectivity between the PAG, rostral ventromedial medulla and dorsal horn (Harper et al., 2018), evidence to support decreased opiate mediated analgesia and pain inhibition. The anatomical evidence presented favours a failing opioidergic system to suppress pain. The surviving MOR+ neurones in the dorsal horn due to decreased connectivity become desensitised (Li et al., 2019) by the activation of D1 and D5 dopaminergic receptors. Grey matter atrophy in the rostral ventromedial medulla due to prolonged chronic pain has been shown to reduce the number of 5HT releasing neurones further impairing pain inhibition at the dorsal horn (Harper et al., 2018).

The anatomical evidence presented in these studies nicely demonstrates how subsequent neurochemical changes influence the descending pain modulating systems ability to suppress pain at the spinal gate. Evidence in favour of the triple network model proposed by De Ridder et al., (2022) for chronic pain.

1.3.4 The triple network model for chronic pain

The triple network model assumes that over time there is increased subcortical connectivity between the primary somatosensory cortex and the default network. Self-representational processing becomes coupled with pain processing. Engaging this network can lead to fear worry and anxiety and further coupling with the amygdala, dorsomedial prefrontal cortex and the anterior cingulate cortex. There is good evidence from the triple network model to

support FBSS associated anxiety and depression resulting from a strengthening in connectivity between the default network and the medial spinothalamic pathway (De Ridder et al., 2022). Increased anxiety and depression create increased sympathetic nervous system pressure on the descending pain pathway leading to sympathetic nervous system compromise.

The triple network model offers an intriguing explanation for sympathetic nervous system compromise driven by the increased subcortical connectivity between the default network and the medial spinothalamic pathway. To save energy consumption from fear, depression and chronic anxiety the default network and overlying parasympathetic system disconnect from the energy consuming sympathetic system (De Ridder et al., 2022). This important stage of the triple network model results in inhibition of the descending pain modulating system (Figure 1.10).

The anterior cingulate cortex is deactivated, with increased connectivity with the medial spinothalamic pathway leading to further inhibition of the noradrenaline portion of the descending pain modulation system. Subsequent failure of the descending pain modulating system leads to the activation of A1 and A2 noradrenergic neurones driving an inhibitory effect on the descending pain modulating system. A5, A6 and A7 noradrenergic neurones at the dorsal horn are impaired (Taylor & Westlund, 2017; De Ridder et al., 2022). A similar mechanism is observed for the trigeminal pain network seen in facial pain models. This process has been described as feedback inhibition and may promote the onset of neuropathic pain by exciting the prefrontal cortex. This underlying process has been proposed for all types of chronic pain including lower back pain and is compelling evidence for the underlying mechanism of chronic pain in FBSS.

Therefore, measuring anxiety and depression in chronic pain studies may allow an indirect measurement of subcortical coupling in chronic pain. Assessing anxiety and depression in FBSS patients before and after SCS therapy may be useful biomarkers for identifying SCS responders and warrants further scrutiny of the literature.

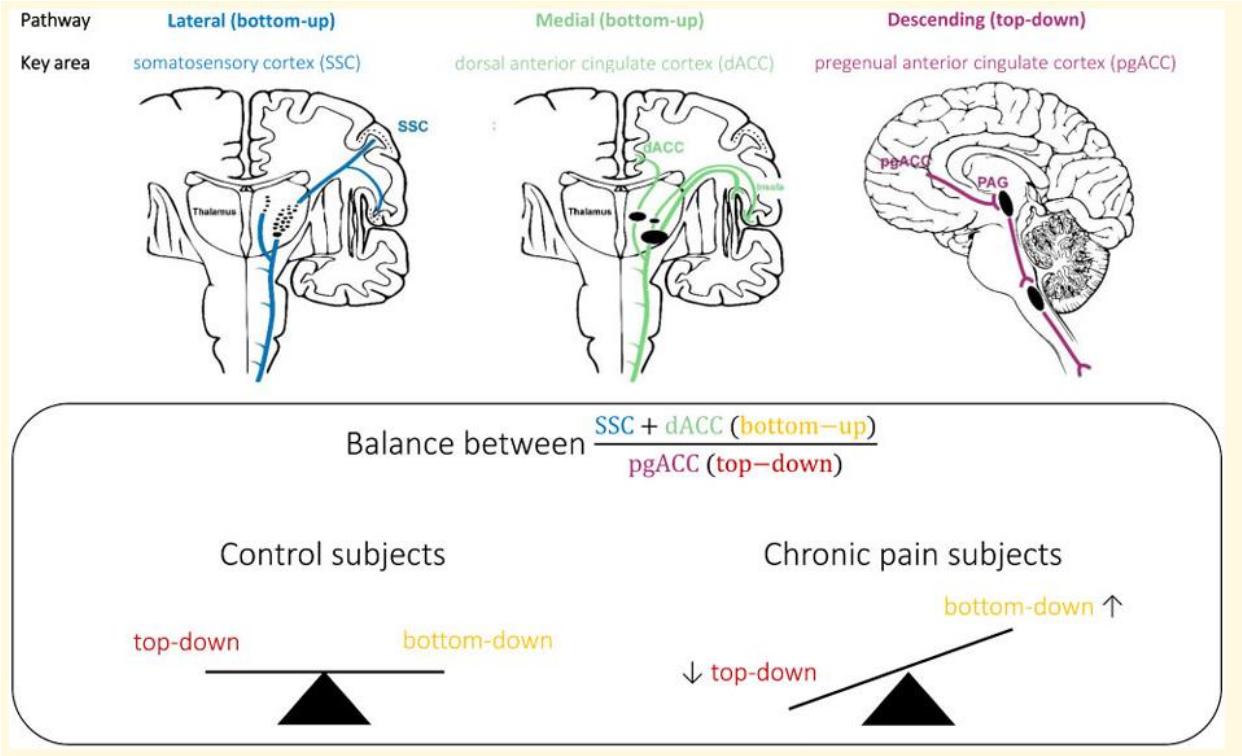


Figure 1.10. The Triple network model, taken from Vanneste & De Ridder, (2021) shows the three pain pathways, the lateral spinothalamic pathway (blue), the medial spinothalamic pathway (green) and the descending pain modulating system (purple). The two ascending pathways work on a bottom-up approach of ascending nociception, the descending pain modulating system operates on a top-down approach driven by feedback. An imbalance in the lateral and medial spinothalamic pain systems (Vanneste & De Ridder, (2021) due to prolonged pain input leads to increased coupling with the default network and inhibition of the sympathetic portion of the descending pain system. Increasing the severity of ascending pain input experienced (bottom down) and inhibiting the effects of the descending pain modulating system (top down). Pain transitions from nociceptive pain to chronic neuropathic pain.

The triple network model (De Ridder et al., 2022) argues that the main consequence of coupling with the default network is suffering and a significant decrease in the quality of life, physically and cognitively. This would imply that prospective studies involving FBSS patients may benefit from the addition of a quality-of-life questionnaire.

Anatomical evidence of functional network coupling and reorganisation in lower back pain is limited and has been reported in a single human brain imaging study (Cauda et al., 2014) as additional grey matter changes. In this paper grey matter changes were primarily observed in the dorsal medial prefrontal cortex and posterior cingulate, anatomical evidence for enhanced connectivity with the default network and thalamus. Signs of atrophy in the insula, opercula-insula cortex, somatosensory and motor cortical areas and the hippocampus were more common. In the insula an increase in grey matter was observed in the dorsal anterior insula and a decrease in the ventral anterior insula. This pattern suggests an increase in connectivity between the default network, the somatosensory cortex medial spinothalamic pathway and a decrease in connectivity with the descending pain modulating system. This single study represents strong anatomical evidence to support the triple network model for chronic pain in lower back pain patients and compliments the observations by Bushnell et al., (2013) and Harper et al., (2018).

In summary EEG may be useful in measuring thalamocortical dysrhythmia in FBSS patients and SSEPs to evaluate cortical reorganisation, both require further investigation and benefit inclusion in a scoping review of the literature. To better understand the effects of SCS on these potential neurophysiological measures the literature was reviewed in terms of the different SCS methods used in clinical practice for the treatment of FBSS.

1.4 Spinal cord stimulation

SCS is recommended by (NICE, 2014) for severe, prolonged neuropathic pain. SCS is an FDA approved treatment for managing chronic and intractable neuropathic pain. The British Pain Society (2015) consider SCS early in the patient's pain management pathway and not as a treatment of last resort. This is to ensure more patients respond to the intervention.

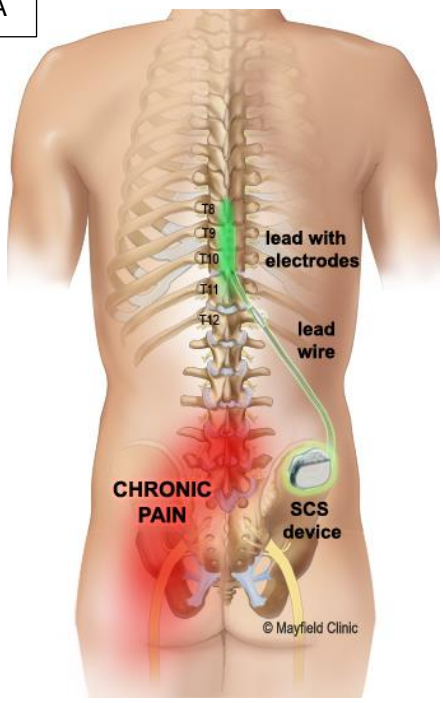
SCS involves stimulation of the dorsal columns (Figure 1.11) either by an extradural percutaneous stimulating electrode or a larger multi-contact paddle / strip electrode placed

through a laminectomy in the epidural space on top of the dura mater (De Ridder et al., 2013; Dones and Levi, 2018; Joosten and Franken, 2020; Telkes et al., 2020).

In my clinical experience SCS for FBSS has moved away from the larger paddle electrode in favour of the less invasive percutaneous electrode reducing the risk of infection. The limitation to this technique is that percutaneous electrodes are at a greater risk of migration once implanted and positioning uses X-ray guidance rather than intra-operative neurophysiology mapping. Recommendations in the literature suggest that the stimulating electrode (paddle or percutaneous) is positioned above the level of lower back pain.

In FBSS patients' pain in most patients starts at T12, between the 12th rib and gluteal sulcus. Therefore, it is not surprising that there is good agreement in the literature that stimulating electrodes for the treatment of FBSS axial lower back pain are placed tip to T8 allowing an adequate T8 to T12 coverage.

A



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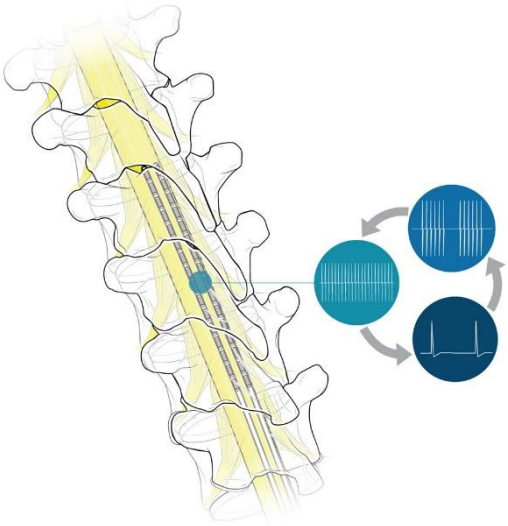


Figure 1.11. An illustration of SCS placement for the treatment of chronic lower back pain taken from the Research and planning Consultants, (2022). Image A shows the placement of the multi-contact paddle (green) a less invasive percutaneous electrode can also be placed over the same region above the level of chronic pain. The SCS implantable device is connected by a lead wire. Image B shows the position of the electrode on the dorsal columns of the spinal cord allowing either tonic, high frequency or burst stimulation. Modern devices can deliver all three stimulation programmes.

NICE, (2014) report that there is a gradual loss of pain control over 4-years, in FBSS patients this is reported as 48% at 6 months and 35% at 12 months with a 3.24% per annum withdrawal rate. The cost implication from failed stimulators and / or withdrawal is unknown and therefore it is recommended that a brief trial prior to permanent implantation be undertaken to identify true clinical responders and differentiate from non-responders.

The Accident Compensation Corporation (2012) and NICE, (2014) and The British Pain Society (2015) both recommend that a trial should be performed over a minimum of seven days during which time different stimulation programmes are evaluated in terms of delivering the best pain relief. In current clinical practice there are three common stimulation programmes that are evaluated prior to permanent implantation, tonic stimulation, high frequency stimulation and burst stimulation. Due to restrictions on time related to waiting pressures it is often two SCS programmes that are trialled. In my clinical experience trials tend to favour tonic and high frequency stimulation. This is largely due to the type of device delivering therapy. Nevro have produced an interface that allows all three programmes to be delivered in one patient. This raises the possibility of trialling all three programmes. This observation is supported by two studies in the literature (Thomson et al., 2017; Hayek et al., 2015). Rarely are all three trialled together, with responders evaluated using subjective methodology primarily from a visual analogue scale (VAS) or numeric pain scale.

The British Pain Society, (2015) do not advocate any specific stimulator programme over another due to insufficient long term follow up evidence available in the literature The British Pain Society, (2015) recommend SCS for FBSS patients with neuropathic back or leg pain of more than 6 months duration with a VAS score >5. A change in the VAS score post stimulation trial of ≥50% or a reduction of at least three or more divisions on the scale as indicators of a "clinical responder". The treatment effect size is reported in the literature as

percentage pain relief calculated from the change in VAS scores from the baseline (stimulation off or not implanted).

SCS has variable clinical effectiveness with a percentage pain relief being heterogeneous ranging between 50% to 70% (Hayek et al., 2015; Joosten and Franken, 2020; The Research and planning Consultants, 2022; Thomson et al., 2017). Many studies fail to report follow up data and therefore there is insufficient evidence available on the long-term role of SCS in this group of patients.

1.4.1 Tonic stimulation.

Tonic stimulation is the most common programme cited in the literature and is often the first stimulation programme evaluated in clinical practice. Tonic SCS is described in the literature as low frequency stimulation (1-60 Hz), (De Ridder et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020; Provenzano et al., 2021 and Gmel et al., 2021). Tonic SCS is defined as stimulating the dorsal columns to create areas of paraesthesia over the area of chronic pain. The stimulation characteristics are illustrated in Figure 1.12.

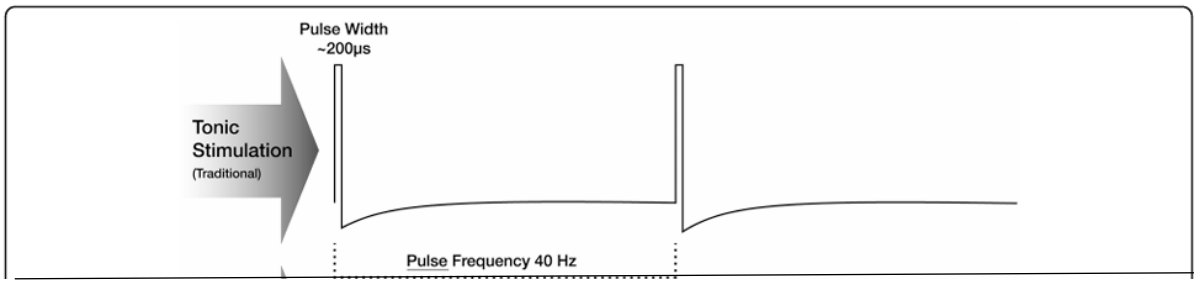


Figure 1.12: Tonic stimulation paradigm taken from Slavin et al., (2016), in this example the stimulus programme is set to a repetitive single stimulus delivered at 40 Hz with a 0.2 ms pulse width.

Currently there is insufficient evidence in the literature to determine the optimum therapeutic stimulation settings for tonic SCS in lower back pain FBSS patients. The main aim of tonic SCS is to create substantial paraesthesia that overlaps the painful areas. Frequency and pulse duration have been used to vary the size of paraesthesia (De Ridder et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020; Provenzano et al., 2021 and Gmel et al., 2021).

Increasing frequency (up to 60 Hz), intensity or pulse width increases the size of paraesthesia field generated. Paraesthesia is generated by the activation of the larger non-nociceptive Aβ fibres responsible for touch which follows a linear relationship (De Ridder et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020 and Gmel et al., 2021). An unwanted side effect of Aβ fibre stimulation is the generation of unpleasant "pins and needles" or "tingling" sensations. Increasing frequency (up to 60 Hz), intensity or pulse width increases the unpleasant sensations experienced by the patient. Tolerance to the unpleasant side effects varies and is one of the greatest challenges faced with tonic SCS. However, altering these parameters allows the paraesthesia field to be modulated. The movement from paddle stimulation to percutaneous electrode stimulation has increasingly relied on the ability to adjust the size of the paraesthesia field with stimulation parameters to offset against placement accuracy over the dorsal columns. Balancing therapeutic pain relief with unwanted side effects is extremely challenging and may lead to inadequate paraesthesia coverage and inadequate pain relief (Van Buyten et al., 2013; Provenzano et al., 2021). In FBSS patients covering both axial lower back and leg pain can be difficult. Stimulation at spinal cord levels T8-T12 can lead to unwanted paraesthesia fields over the chest wall leading to unpleasant sensations in the thorax. Increasing the intensity, frequency, and duration can augment these sensations impacting on daily living. Furthermore, there is an increased thickness of dorsal cerebral spinal fluid over T8-T9 and the size difference between L1 and L2 dermatomes compared to T12 dermatome making adequate individual coverage challenging (Van Buyten et al., 2013). The dorsal columns are also in close association with the dorsal roots and can be indirectly stimulated. Aδ and C-fibres at the dorsal horn and dorsal root with dorsal column stimulation in rats reduces nerve hyperexcitability and attenuate perceived pain, with suboptimal results observed with electrode migration. In percutaneous SCS unwanted and often unpleasant side effects can result due to electrode migration (Van Buyten et al., 2013).

In clinical practice frequency and pulse duration is controlled by the neuromodulation team and is referred to as paraesthesia mapping. Intensity remains in the control of the patient and adjusted for comfort. SCS is undertaken above the patient's sensory threshold and therefore will depend upon comfort and tolerance creating individual variation.

In the literature tonic SCS is reported to not be superior to placebo stimulation for pain suppression in FBSS patients and appeared not to suppress back pain significantly (De

Ridder et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020; Provenzano et al., 2021 and Gmel et al., 2021). This may be one explanation for tonic SCS non-responders another explanation may be patient comfort. Pain relief is reported as heterogeneous ranging between 50% - 70% (Joosten and Franken, 2020; Tapias Pérez, 2022; Goudman et al., 2020; Van Buyten et al., 2013). Long term follow up effectiveness is insufficiently reported with limited evidence suggesting 50% - 58% over 2 years (Tapias Pérez, 2022; Goudman et al., 2020). There is agreement that over 71% of FBSS patients experience uncomfortable sensations on tonic SCS one of the main contributing factors to tonic SCS failure.

Tonic SCS creates both antidromic and orthodromic stimulation volleys (Caylor et al., 2019; Joosten and Franken, 2020). Antidromic activation Aβ fibres in the dorsal horn leads to retrograde activation of inhibitory interneurons located in laminae I and II of the dorsal horn, these in turn releases excess GABA. Simultaneous orthodromic activation of the dorsal column activates supraspinal inhibitory loops from the brainstem that modulate dorsal horn neurotransmitter release. GABA and acetylcholine receptor function is enhanced whilst simultaneously reducing glutamate and NMDA receptor function (Caylor et al., 2019) "closing the spinal gate" and triggering GABA mediated pain inhibition. A combined effect of antidromic induced GABA neurotransmitter release and orthodromic GABA receptor activation contribute to the local pain relief experienced over the paraesthesia field. Glutamate and NMDA receptors are deactivated reducing the intracellular calcium ion influx which has been shown to decrease the effects of central sensitisation (Caylor et al 2019; Joosten and Franken, 2020). The effects of central sensitisation are reduced by $GABA_A$ receptor agonism (Caylor et al 2019; Joosten and Franken, 2020). Individual variability in GABA receptor function may explain why some individuals are either responders or non-responders to tonic SCS. Joosten and Franken, (2020) report that tonic SCS non-responders can be converted into tonic SCS responders through the administration of low subeffective doses of intrathecal baclofen a derivative of GABA. This increases the amount of available GABA and assists in the activation of $GABA_B$ receptors responsible for presynaptic $GABA_B$ inhibition effects. This would suggest that in non-responders there is a deficiency of available GABA activated at the spinal gate (Joosten and Franken, 2020). Similar findings have been reported with subeffective doses of intrathecal ketamine a NMDA antagonist. In tonic SCS non-responders' calcium ion influx remains high; an NMDA antagonist will help promote the

development of a magnesium ion channel block reducing calcium ion influx and central sensitisation.

This evidence is compelling as explanation for responders and non-responders to tonic SCS. However, it remains unclear on what affect GABA receptor variability will have on baseline profiles.

Another competing mechanism in addition to spinal gate modulation is WDR neuronal modulation (Caylor et al., 2019). WDR neurones receive non-painful input from Aβ fibres and painful input from Aδ and C-fibres when stimulated. This creates a graded imbalance between Aβ, Aδ and C-fibres input and in turn inhibits the hyperexcited WDR neurones and their connected pathways particularly to the somatosensory cortex (Caylor et al., 2019). This compelling evidence may suggest that thalamocortical dysrhythmia is inhibited with tonic SCS because of WDR neuronal modulation. This inhibitory effect may be measurable using EEG absolute theta power.

There is convincing evidence from imaging studies that tonic SCS activates the lateral spinothalamic pathway and modulates the somatosensory cortex directly reversing cortical plasticity changes associated with chronic pain and wider pain network. (Caylor et al., 2019; Joosten and Franken, 2020). Both EEG and SSEPs may be able to measure the cortical plasticity changes suggested by this model. EEG theta rhythms induced by thalamocortical dysrhythmia should decrease over the somatosensory cortex and parietal network with tonic SCS. Augmented SSEP amplitudes due to cortical plasticity and hyperexcitability may decrease with successful tonic SCS. This warrants further study in the literature and be inclusion in the scoping review.

There is good consensus that in higher stimulation frequencies >60 Hz (60 Hz-100 Hz) the paraesthesia field size starts to decrease (De Ridder et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020; Provenzano et al., 2021 and Gmel et al., 2021). This is due to the activation of noradrenergic spinal inhibitory loops involved in noradrenergic and opioidergic mechanisms. Under these higher frequencies paraesthesia is replaced by analgesia. There is growing evidence that in higher frequency tonic SCS programmes a tolerance to opioidergic recruitment may develop leading to a ceiling effect of maximum benefit and increased failure to suppress pain another potential mechanism to explain non-responders (De Ridder

et al., 2013; Caylor et al., 2019; Joosten and Franken, 2020; Provenzano et al., 2021; Solanes et al., 2021 and Gmel et al., 2021). The findings reported would suggest that in tonic SCS frequency plays an important role in modulating the firing rate of nerve fibre size.

1.4.2 High frequency stimulation

High frequency SCS is defined as 10 kHz with a pulse width of 0.3 ms although any frequency >1000 Hz could be used (Caylor et al., 2019; Heijmans and Joosten, 2020; Joosten and Franken, 2020 and Sdrulla et al., 2018). In clinical practice high frequency stimulation is undertaken at 10 kHz.

Unlike tonic SCS, high frequency SCS doesn't activate Aβ fibres in the dorsal column. Instead Aδ and C-fibres which terminate in laminae I and II of the dorsal horn are activated (Joosten and Franken, 2020). Due to the close association of the dorsal root and dorsal horn at spinal cord levels T8-T12 high frequency SCS creates an electrochemical disturbance or block at the dorsal root entry zone and dorsal horn. The reversable depolarisation block desynchronises dorsal horn neuronal signals, membrane integration and glial neuronal modulation. This in turn desynchronises the spinal gate and activates opioidergic mechanisms of the descending pain inhibitory system resulting analgesia (Heijmans and Joosten, 2020; Joosten and Franken, 2020). Temporal summation of the high frequency train of impulses is one mechanism proposed which leads to neuronal activation and subsequent desynchronisation whilst another advocates hyperpolarisation of superficial dorsal horn neurones (Sdrulla et al., 2018). There is currently insufficient evidence to determine which mechanism is correct. The resultant reversable depolarisation block prevents further propagation of nociceptive action potentials from Aδ and C-fibres. Blocking the ascending nociceptive volley in the lateral spinothalamic tract and reversing thalamocortical dysrhythmia. Like tonic SCS this change may be measurable using either EEG or SSEPs as a biomarker for thalamocortical dysrhythmia cortical effects.

High frequency stimulation offers no unpleasant stimulation side effects and comfortable night-time use an advantage over traditional tonic SCS and is referred to as Paraesthesia free pain relief. NICE, (2019) recommend high frequency stimulation as an alternative when tonic stimulation fails or becomes unpleasant. Caylor et al., (2019) reports that there is convincing class 1 evidence from randomised control trials that high frequency stimulation is superior to

tonic stimulation in axial lower back or leg pain. In one FBSS study consisting of 83 patients 88% (72 out of 82) of patients enrolled had positive clinical results with high frequency stimulation and at six-months follow up 74% of patients experienced 50% pain reduction. Van Buyten et al., (2013) states that 85% of patients enrolled in their study would recommend high frequency stimulation to others. In another study by Kapural et al., (2015) in 198 patients enrolled on their randomised control trial one-third of patients who receive high frequency stimulation eliminated their opioid analgesic intake. This study was a randomised control trial undertaken by a company invested in SCS sales. Van Buyten et al., (2013) and Kapural et al., (2015) consider high frequency stimulation to be superior to tonic stimulation in controlling long-term treatment of axial lower back and leg pain.

This seems to be compelling evidence that high frequency SCS is a suitable alternative to tonic SCS in FBSS patients (Van Buyten et al., 2013; Kapural et al., 2015; Caylor et al., 2019; NICE, 2019; Joosten and Franken, 2020). However, there remains many studies that fail to report long term follow up data and limited to small case series driven by SCS sales and clinical validation.

1.4.3 Burst stimulation

Burst stimulation has emerged into routine clinical practice as a contender to tonic and high frequency SCS. Burst SCS was developed by De Ridder et al (2013) and consists of intermittent high frequency bursts or trains of five stimuli at 500 Hz per burst (one millisecond, inter-spike interval and pulse width of one millisecond) applied forty times per second (40 Hz), as detailed in figure 1.13.

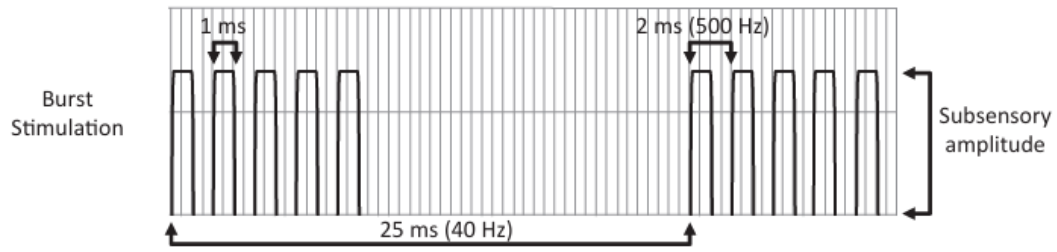


Figure 1.13: Burst stimulation taken from Schu et al., (2014) consisting of a brief train of 5 stimuli with each stimulus having a pulse duration of 1 ms and a interstimulus interval of 2.0 ms (500 Hz). The inter-train interval is delivered at 40 Hz and allows for a cumulative charge

to be balanced in what is called a passive recharge phase leading to a desynchronisation of the bursting pattern in second order neurones travelling in the lateral and medial spinothalamic pathways.

Burst stimulation aims to disrupt the natural "bursting pattern" in the two ascending pathways and at the thalamus disrupting cortical dysrhythmia. Burst stimulation desynchronises the natural bursting firing patterns of the Aδ and C-fibre WDR neurones creating variation within the dorsal column, lateral and medial spinothalamic pathways (Chakravarthy et al 2019; De Ridder et al 2013 and Schu et al., 2014). Larger Aβ fibres travelling in the dorsal column are not activated resulting in paraesthesia free pain relief. In rat studies WDR neuronal firing rates in the dorsal horn have been shown to reduce. Stimulation intensities at 60% of the motor threshold were found to significantly reduce pain perception and hyperalgesia suggesting that both the stimulus pattern (train) and intensity were involved in pain reduction and a reduction in central sensitisation (Chakravarthy et al 2019 and De Ridder et al 2013). EEG may be useful in detecting the disruption of cortical dysrhythmia in the lateral spinothalamic tract by measuring EEG changes over the coupled somatosensory cortex and parietal network. I suspect the modulation effects on the medial spinothalamic tract may be less obvious due to the subcortical components in that network and confined to raised EEG theta power over the prefrontal regions. The role of EEG evaluation with burst SCS requires further evaluation from the literature.

More recent evidence from rat animal models suggests that increasing the number of impulses in a train, pulse width and intensity reduces WDR neuronal firing rates with a linear relationship seen between increasing the total charge per burst and reduction in WDR firing rates (Chakravarthy et al., 2019). The passive recharge phase and balanced cumulative charge is critical in reducing dorsal horn neuronal firing rates.

There is growing evidence that burst SCS decreases C-fibre excitability (De Ridder et al., 2015), dorsal horn excitability (De Ridder et al., 2013; Crosby et al., 2015; Caylor et al., 2019; Kirketeig et al., 2019) and promote analgesia (De Ridder et al., 2013; Crosby et al., 2015; Caylor et al., 2019; Kirketeig et al., 2019). There is limited evidence from Schu et al., (2014) and Chakravarthy et al., (2019) that burst SCS provides better analgesia in patients with FBSS than high frequency SCS. There is limited yet compelling evidence that burst SCS induces plasticity changes between the thalamus and anterior cingulate (Chakravarthy et al 2019 and

De Ridder et al 2013). Simultaneously stimulating both the medial spinothalamic pathway and the descending pain modulating system to activate supraspinal noradrenergic and opiodergic mechanisms at the spinal gate. There is no evidence of GABAergic activation at the spinal gate suggesting that burst stimulation activates a non-GABA dependent neuro-signalling mechanism.

The triple network model shows strong connectivity between the anterior cingulate, pre-frontal cortex and the default network with chronic pain transition. Chakravarthy et al., (2019) argues that recent evidence suggests that the biological signature for this is likely to be an oscillatory firing pattern between the thalamus and anterior cingulate cortex linking perceived pain, memory, pain induced fear and anxiety together. Disruption of this hypothesised oscillatory firing pattern with burst stimulation may play a role in decoupling these areas and reversing the transition of acute pain to chronic pain. This is supported by clinical observations that show a reduction in pain related disability and successful burst stimulation (Chakravarthy et al., 2019).

Crosby et al., (2015) demonstrated in a rat model that larger pulse widths incrementally increased analgesia and increasing the number of pulses in a train correlated to reduced dorsal horn activity. However, a ceiling effect was noted beyond 6-7 pulses per train. Increasing stimulus intensity showed a similar decrease in dorsal horn excitability (Crosby et al., 2015). Increasing the frequency of bursts promotes non-GABAergic opioidergic mechanisms that increase analgesia (De Ridder et al., 2015). Burst stimulation was also statistically superior at supressing pain than tonic and high frequency stimulation in back pain than placebo studies (De Ridder et al., 2013; Kirketeig et al., 2019).

In summary all three SCS programmes appear to affect the lateral spinothalamic pathway and that SCS affects may be measurable using either EEG or SSEPs neurophysiological biomarkers. Both neurophysiology techniques are strong candidates for a useful clinical biomarker and warrant further study in the literature.

1.4.4 Treatment in FBSS

There remains insufficient evidence in the literature on the clinical effectiveness of SCS. Telkes et al., (2020) highlights that there remains a sizeable portion of patients that receive either suboptimal or inadequate pain suppression with success rates varying widely across

studies and clinical practice. One reason for this might be that current therapies are not optimised for individual neural and/or spinal segmental features of pain. In my clinical practice I would agree suboptimal, or inadequate pain suppression is the biggest challenge faced in SCS clinical practice.

SCS is reported by Hayek et al., (2015); Thomson et al., (2017) and Koyama et al., (2018) to be beneficial in 50%-60% of patients, who they all describe as responders. Thomson et al., (2017) reported that in 60% of responders, a trial of a different stimulation modality was effective in another 10-15% of patients. Thomson et al., (2017) and Hayek et al., (2015) both agree that despite a successful trial of at least 50% pain reduction, only 50-70% of true responders maintain a sustained benefit after permanent implantation. Therefore, there is an argument to trial all three modalities prior to implantation to personalise the treatment being offered to an individual patient. EEG and SSEP are promising candidates for a personalised approach to SCS evaluation. It remains unclear whether all three SCS programmes have been studied and compared in the literature with EEG and SSEP. This warrants further scrutiny. Personalised medicine for treatment delivery is growing in popularity. There is a need to better understand how patients individually respond to different treatments to improve individual treatment efficacy (Vicente et al., 2020).

FBSS neuropathic back or leg pain places considerable economic burden on healthcare (Cho et al., 2017, Duarte & Thomson, 2019; NICE, 2014 and NICE, 2019). SCS is more cost effective than conventional medication or repeat surgery (NICE, 2014). The estimated cost effectiveness of tonic SCS to treat FBSS is approximately £10,490 per QALY assuming the implanted stimulator has a longevity of 4 years with an average stimulator cost of £9000. In contrast NICE, (2019) state that high frequency SCS using rechargeable devices can provide further cost savings of £2,292 per patient when compared to tonic stimulation and £7,755 per patient for non-rechargeable devices over a 15-year period.

The lack of available follow up evidence in the literature makes it difficult to determine if SCS should be classified as a last resort intervention treatment or be considered earlier in patient treatment plans.

In summary based on the clinical, anatomical and physiological evidence presented in the narrative literature review two potential candidates (EEG and SSEP) for neurophysiological

measures have emerged and warrant further study through a more detailed scoping review. Both present as candidates for baseline biomarkers of chronic pain in FBSS patients and may be useful in predicting SCS responders in clinical practice.

It was hypothesised that EEG theta power increases with chronic pain and SSEP amplitudes become enhanced due to cortical plasticity and excitability. Effective SCS (responders) was hypothesised to reduce EEG theta power and SSEP enhanced amplitudes when using either high frequency, tonic, or burst SCS and this may aid in patient selection.

Baseline pain characteristics may change with pain duration and intensity in FBSS leading to changes in baseline EEG theta spatial patterns or enhanced SSEP amplitude profiles. These signatures may be useful in predicting SCS responders and non-responders.

To inform this work, a scoping review and meta-analysis was undertaken to draw together evidence from primary sources allowing a concise and evidence-based decision on the role of neurophysiological biomarkers (EEG and SSEP) in neuropathic pain and the effects of SCS on these biomarkers as a treatment for chronic pain. This provided metrics to assist in the design and analysis of the meta-analysis.

1.5 Over all aims and objectives

Aim: to investigate whether baseline patterns of brain activity measured by QEEG and SSEPs could predict the therapeutic response to SCS in FBSS patients with chronic neuropathic pain.

Objective 1: Synthesise evidence in the literature for QEEG spectral power changes in chronic neuropathic pain.

Objective 2: Synthesise evidence in the literature for SSEP measures in chronic neuropathic pain.

Objective 3: Combine and compare evidence in the literature as a meta-analysis for changes in QEEG and SSEP measures with SCS.

Objective 4: To explore spatial profiles of baseline QEEG and SSEP amplitudes in FBSS patients alongside clinical characteristics to determine their usefulness in responder selection for SCS for a given patient.

Objective 5: To explore the changes in absolute theta power with SCS to a given modality during the trial.

Objective 6: To explore the changes in SSEP amplitude reduction with SCS to a given modality during the trial

Objective 7: To explore clinical characteristics to determine usefulness in responder selection for SCS

Objective 8: To explore the ability to predict a sustained response at 6 months post implantation

2. SCOPING REVIEW AND META-ANALYSIS

2.1 Introduction

Quantitative EEG (QEEG) and SSEPs are the two most common neurophysiology techniques used to evaluate cortical hyperexcitability and assess and measure the effects of thalamocortical dysrhythmia and somatosensory cortical plasticity in chronic neuropathic pain patients.

QEEG evaluation has been used to assess the effects of thalamocortical dysrhythmia and cortical plasticity changes in a range of chronic pain disorders, which includes lower back pain (Dos Santos Pinheiro et al., 2016; Telkes et al., 2020). QEEG is the transformation of scalp EEG recordings from the time domain into the frequency domain using Fast Fourier Transformation (FFT). FFT is an algorithm that deconstructs the EEG recordings made in the time domain into discrete frequency components by Discrete Fourier Transformation (DFT). The FFT algorithm is more efficient and faster method of calculating the DFT.

Scalp EEG is a non-invasive recording that utilises scalp electrodes to record from cortical neurones orientated perpendicular in the cortex. The EEG detects neuronal interactions between the excitatory pyramidal neurones and surrounding inhibitory post synaptic interneurons. The thalamus drives periodic synchronisation between the six layers of neocortex via the thalamocortical network generating cortical oscillations (Ploner et al., 2017). EEG recordings of these oscillations can be transformed from the time domain into the frequency domain using FFT and the spectral content visualised and displayed using absolute or relative power. Absolute power is defined as the amount of activity in a chosen frequency band and relative power as the activity in a chosen frequency band divided by the total activity from all the frequency bands (Park et al., 2020). Relative power in therapeutic studies have also described relative power as being relative to the baseline power when looking for a therapeutic change (Telkes et al., 2020).

Initial nociceptive pain signals in the somatosensory cortex are dominated by feedforward corticocortical interactions (Dos Santos Pinheiro et al., 2016; Ploner et al., 2017). In chronic pain at rest there is an increase in power at lower frequencies and feedback cortical mechanisms. In chronic pain beta frequencies become more numerous over the frontal regions and the dominant gamma frequencies are abolished. Alpha frequencies decrease and are replaced by slower theta frequencies (4-7 Hz) primarily over the somatosensory areas (Dos Santos Pinheiro et al., 2016; Ploner et al., 2017 and Telkes et al., 2020). The transition from nociceptive pain to chronic pain is marked by a change from feedforward interactions to feedback interactions (Ploner et al., 2017).

In pain research there is agreement that in phasic pain studies the EEG is characterised by the suppression of alpha (8-12 Hz) and beta (13-29 Hz) EEG frequencies with gamma (30-40+ Hz) frequencies induced over the sensorimotor cortical areas. Gamma (30-45+ Hz) frequencies have been correlated with nociceptive pain perception. Indeed, gamma frequencies are more numerous in the supragranular layer of the neo cortex (cortical layers II and III) and can be considered as a QEEG signature for corticocortical feedforward interactions (Figure 2.1). Supragranular layer feed forward interactions start in cortical layers II and III, driven by the external pyramidal layer neurones and terminate in cortical layer IV (Figure 2.1).

Alpha oscillations (8-12 Hz) and beta oscillations (13-29 Hz) are more numerous in the infragranular layer of the neocortex (cortical layers V and VI) and can be considered as a QEEG signature for corticocortical feedback interactions (Figure 2.1). Infragranular layer feedback interactions start in cortical layers V and VI driven by the inner pyramidal layer neurones and terminate in cortical layer IV.

Both feedforward and feedback corticocortical interactions terminate in cortical layer IV, the internal granular layer, which contains both stellate and pyramidal neurones and is the primary site for thalamocortical afferent and intra-hemispheric corticocortical afferent neuronal interactions.

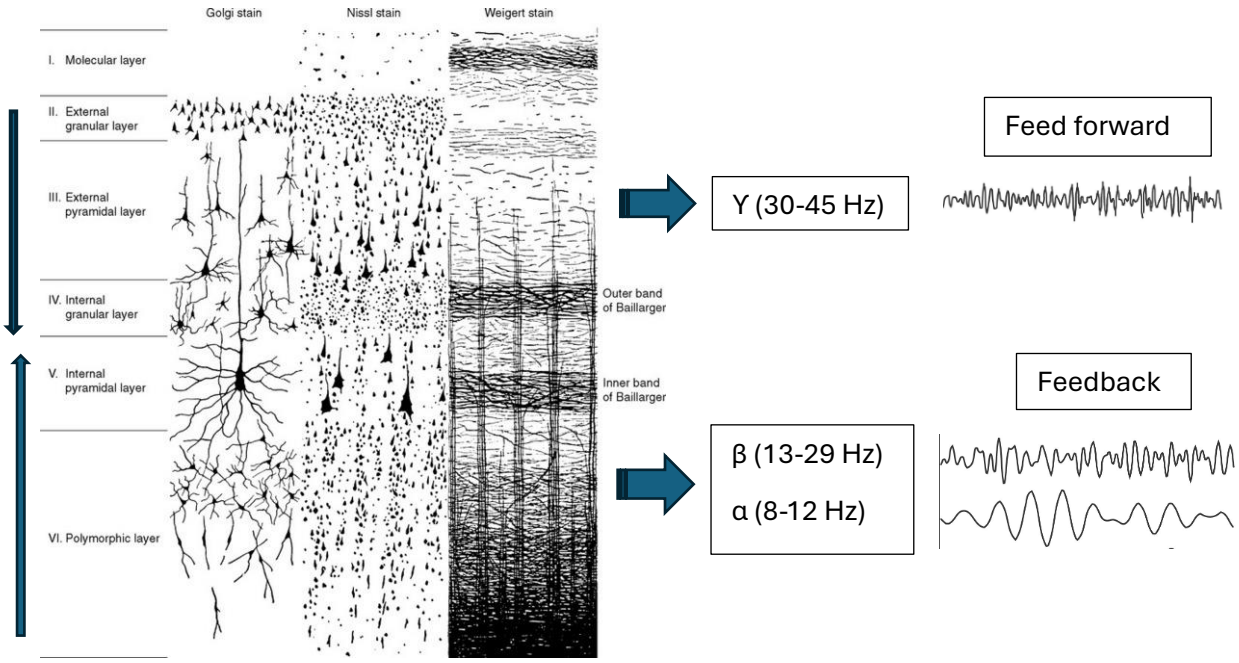


Figure 2.1: A schematic of a section of human neocortex taken from Brodman, (1909) showing the six layers with pyramidal neurone distribution. Feed forward ϒ (gamma) cortical interaction occur between layers II, III to VI and feedback α (alpha) and β (beta) cortical interaction between layers V, VI to IV. EEG waves forms were taken from (Jeong, 2011).

Thalamocortical dysrhythmia observed in chronic pain can be used to explain the decrease of alpha frequencies and the emergence of slower theta frequencies. Thalamocortical dysrhythmia is the abnormal firing of thalamic relay neurones due to hyperpolarisation, firing in a bursting pattern at 4-7 Hz. Thalamocortical afferents interact with the neocortex at layer IV resulting in transient plasticity changes in the WDR neurone network. Pyramidal neurones in cortical layer V synchronise with thalamic relay neurones and adopt the bursting theta signature. Alpha activity is replaced by theta activity. An increase in theta power (absolute or relative) or a decrease alpha power (absolute or relative) can be considered as a QEEG signature for thalamocortical dysrhythmia and chronic pain (Ploner et al., 2017; Sarnthein et al., 2006 and Telkes et al., 2020). Sarnthein et al., (2006) investigated thalamocortical dysrhythmia in patients with chronic neurogenic pain who were treated with a central lateral thalamotomy (CLT) by lesioning the medial thalamus. They observed that CLT treatment resulted in a decrease in relative theta EEG power with significant pain relief reversing the effects of thalamocortical dysrhythmia. They attribute this to thalamocortical dysrhythmia inhibition caused by the therapeutic surgical lesion.

In spinal cord injury patients in the relaxed awake state chronic neuropathic pain is characterised by increased EEG power in both the theta and alpha frequency bands with alpha frequencies shifted towards the lower portion of the alpha frequency band (Wydenkeller et al., 2009; Jensen and Finnerup, 2014 and Vuckovic, 2014). These EEG changes are primarily localised over the somatosensory and parietal cortical regions (precuneus and lateral occipital cortex) and not restricted to painful somatotropic areas of the body. The slowing observed on the EEG (theta and within the alpha frequency band) was due to sensory deafferentation of thalamic relay neurones leading to cortical hyperpolarisation and a shift towards slower cortical oscillations Wydenkeller et al., 2009; Jensen and Finnerup, 2014 and Vuckovic, 2014). Imaging studies have shown that in spinal cord injury patients' metabolic activity in thalamic nuclei decrease leading to the altered firing pattern associated with thalamocortical dysrhythmia (Wydenkeller et al., 2009). A single study by Wydenkeller et al., (2009) used contact heat evoked potentials (CHEPs) and found that increased theta and alpha power in spinal cord injury patients was also associated with impaired Aδ function.

Another study by Tran et al., (2022) used different virtual reality (VR) therapies with spinal cord injury patients and observed changes in their EEG frequencies with reduced neuropathic pain. They observed a reduction in relative theta power over the frontal and parietal regions. The greatest reduction in relative theta power was noted with three-dimensional (3D) VR therapy which corresponded to the greatest reduction in neuropathic pain. They attributed this finding to reduced thalamocortical dysrhythmia with increased levels of immersion. Alpha power also decreased. Babiloni et al., (2006) observed in chronic pain patients the anticipatory response to pain was exaggerated with increased central alpha frequency power. They attribute this to phase synchronisation of the EEG due the anticipation of a painful stimulus. Lee et al., (2021) used non-invasive painless signalling therapy to stimulate cutaneous nerve in FBSS patients. They found that relative alpha power increased this was most significant over the transverse gyrus of the temporal lobe. Beta activity increased over the frontal regions corresponding to the anterior cingulate gyrus and medial frontal area. Increased beta activity over the anterior cingulate gyrus correlated with reduced pain.

The studies reviewed imply that in chronic pain theta power could be used as a pain signature for thalamocortical dysrhythmia, and alpha and beta power as signatures of corticocortical feedback interactions associated with chronic pain.

Lower limb SSEPs have been used to assess somatosensory hyperexcitability due to cortical plasticity (Egsgaard et al., 2012). Peripheral nerve electrical stimulation is used to stimulate the somatosensory pathway at intensities above the sensory threshold activating Aβ myelinated sensory fibres (Figure 2.2). In lower limb SSEP studies the posterior tibial nerve or sural nerve is the peripheral nerve most often chosen for stimulation. Peripheral nerve stimulation synchronises, time locking the SSEP response.

Scalp electrodes are used to record the evoked and time locked response at the cortex. The SSEP cortical response can be divided up into near field and far field responses. Near field responses represent activated somatosensory pyramidal neurones in the cortex and near the recording electrode and far field responses more distant cortical or subcortical structures that are activated in the cortical-subcortical network (Egsgaard et al., 2012; Passmore et al., 2014; Trenado et al., 2017).

Near field responses are referred to as early responses or short latency responses these are the most reproducible responses of the SSEP complex as they are not influenced by subcortical variability or cognitive factors. In lower limb SSEP studies latencies ≤40 ms +/- 2.0 ms are classified as short latency responses (Egsgaard et al., 2012; Passmore et al., 2014; Trenado et al., 2017). In neurophysiology polarity convention, positive is down and negative is up. Lower limb SSEP short latency responses are measured from the positive onset and amplitude from the latency onset to the negative upward peak.

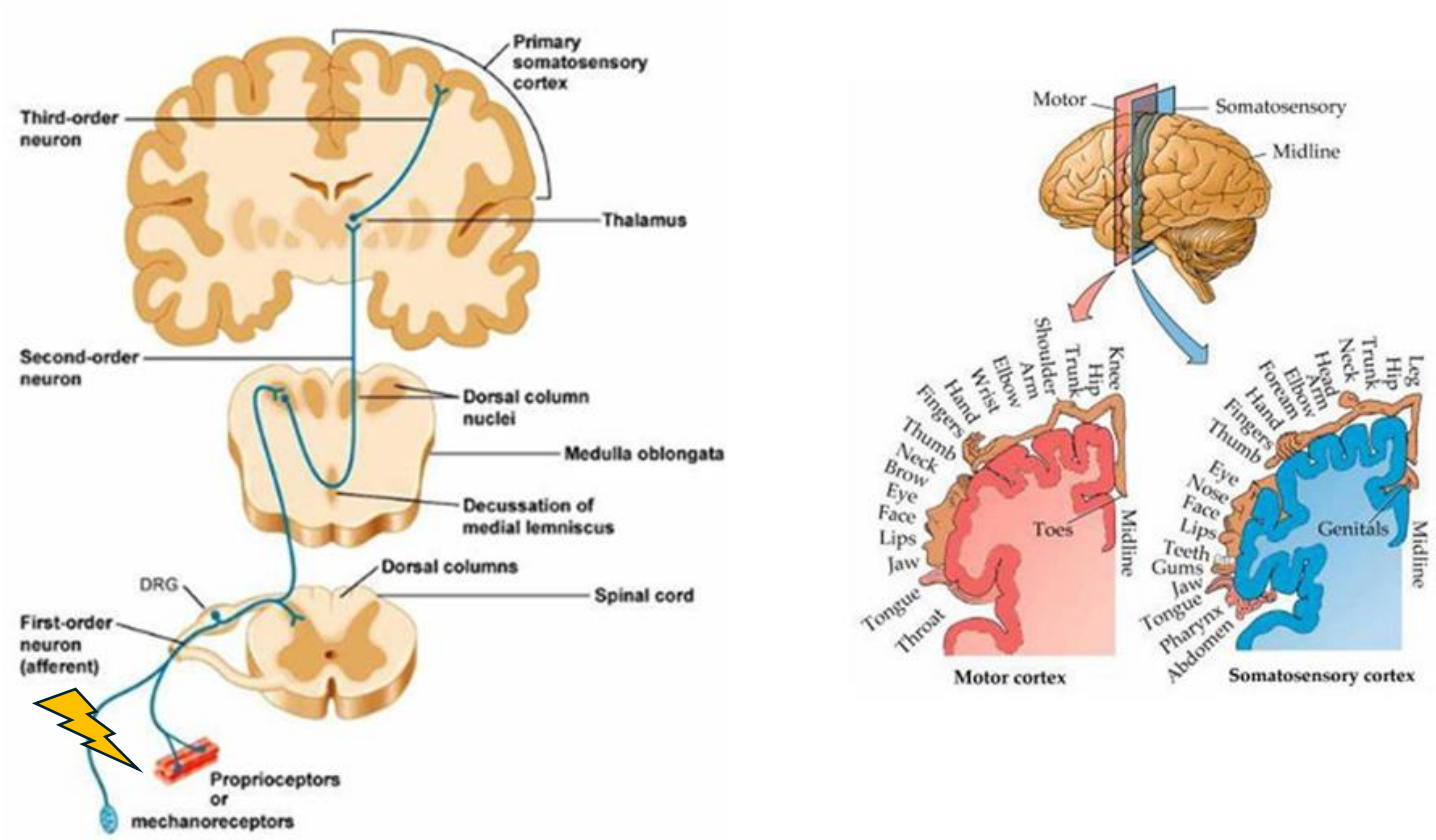


Figure 2.2: Figure 2.2: Somatosensory pathway taken from Bear et al., (2006) and somatosensory cortex topography taken from Oller, (2010) Image (A) is taken from Bear et al., (2006) and shows SSEP orthodromic stimulation (yellow lightning bolt) activating Aβ afferent neurones sending an afferent volley of action potentials up the somatosensory pathway via the dorsal root ganglion (DRG) and dorsal horn of the spinal cord (first order sensory afferents), brainstem (second order neurones), thalamus and primary somatosensory cortex (3rd order neurones) located on the post central gyrus of the parietal lobe. The stimulated pathway is highlighted in blue. Image (B). Taken from Oller, (2010) shows the motor cortex (red) as a slice through the pre-central gyrus and somatosensory cortex (blue) as a slice through the post central gyrus. The somatotopic organisation on the gyrus organised from face to foot following a rostral – caudal organisation. Lower limb somatosensory representation is on the mesial surface of the post central gyrus within the longitudinal fissure.

The IFCN label the early SSEP component as P39 although P37 and P40 are used interchangeably in the literature (Cruccu et al., 2008 Egsgaard et al., 2012; Passmore et al., 2014; Trenado et al., 2017). The SSEP early response is low in amplitude compared to the ongoing spontaneous EEG. Due to the reproducibility of the early response averaging is used to enhance the morphology from the background EEG. The IFCN recommend ≥500 averages as sufficient for recording stable SSEP early responses. (Cruccu et al., 2008).

The amplitude of the early response has been used as a measure of activated pyramidal neurones in the somatosensory cortex and local cortical network. The more excitable the network the more neurones activated and larger the amplitude. Inhibition of the somatosensory cortex reduces the number of neurones activated decreasing the SSEP early response amplitude.

Far field responses are referred to as late responses or long latency responses >40 ms and are influenced by cognitive factors at latencies >45 ms (Egsgaard et al., 2012; Passmore et al., 2014). Long latency SSEP responses have been linked to neighbouring or more distant cortical areas and subcortical areas within the somatosensory wider cortical-subcortical network. Examples of long latency cortical responses include P45, N60 from the somatosensory cortex, P65, N70 from the frontal cortex and P80, P100, P200 and P300 from bifrontal cortices (Trenado et al., 2017). Subcortical long latency SSEPs have been recorded from subthalamic nucleus, thalamus, medial lemniscus and zona incerta (Trenado et al., 2017).

In one study Egsgaard et al., (2012) used long latency responses evoked at N100, P200 and P300 for equivalent current dipole mapping generating dipoles for primary somatosensory cortex, cingulate, thalamus and prefrontal cortex. They used the long latency responses to investigate conditioning pain modulation which is impaired in lower back pain patients due to suppression of the descending pain modulating system. Egsgaard et al., (2012) found that the P300 dipole was in the cingulate cortex and was composed of multiple dipoles. Hypoalgesia following tonic muscle pain reduced the amplitude of P200 long latency response. Electrical stimulation (heterotopic conditioning pain modulation) resulted in short term plasticity changes in the cingulate cortex related to pain perception and pain related emotion (Egsgaard et al., 2012).

The role of QEEG power measures and lower limb SSEP short and long latency responses in the assessment of SCS for chronic lower back pain is unclear. Their role in SCS to assess pain relief is less clear.

This scoping review aimed to explore the role of two neurophysiology techniques and their biomarkers: QEEG and SSEP, in the assessment of chronic neuropathic back pain with SCS.

Objective 1: Synthesize evidence of QEEG spectral power changes in chronic neuropathic pain.

Objective 2: Synthesize evidence of SSEP measures in chronic neuropathic pain.

Objective 3: Combine and compare evidence for changes in QEEG and SSEP measures with SCS.

2.2 Method

The protocol was pre-registered and published on the Open Science Framework (14th January 2024) prior to paper selection (Pridgeon and Orton, 2024).

Literature search:

The search strategy used was constructed using the PICO model (Richardson et al., 1995; Eriksen and Frandsen, 2018; Brown, 2020; Frandsen et al., 2020).

Table 2.1 PICO strategy used for the scoping review.

PICO structure	Search terms
Population	Failed back surgery syndrome OR FBSS OR lumbar spinal pain OR chronic pain after spinal surgery OR neuropathic pain OR post laminectomy syndrome OR persistent spinal pain OR PSPS OR recurrent lower back pain
AND	
Intervention	Spinal cord stimulation OR SCS OR percutaneous spinal cord stimulation OR tonic stimulation OR high frequency stimulation OR burst stimulation OR low frequency stimulation
AND	
Comparison	EEG OR electroencephalography OR quantitative electroencephalography OR QEEG OR SEP OR SSEP OR somatosensory evoked potential OR lower limb SEP OR posterior tibial SEP
AND	
Outcome	Reduction in pain OR improvement in the quality-of-life OR reduced theta power OR increased alpha power OR reduced SEP amplitude

A preliminary search using PubMed was undertaken to define search terms and construct the search thread. The search was performed using three databases: PubMed (filtered for Medline), Scopus, and the Web of Science. There were no restrictions on date providing the methodology was still relevant to current practice. The review was limited to English language and full text papers. The eligibility criteria

are detailed in table 2.2. Any source which was not original research reporting primary data (for example systematic reviews, narrative reviews, book chapters) were excluded. The review was not limited to papers published in any geographic location, or specific healthcare setting. The first search (PubMed filtered for Medline) was performed on 24th January 2024 with subsequent searches on 30th January 2024 (Scopus) and 8th February 2024 (Web of Science).

Table 2.2: Eligibility criteria used for the scoping review

Inclusion criteria	**Exclusion criteria**
Patients presenting with chronic lower back pain, failed back surgery syndrome, lumbar spinal pain, chronic pain after spinal surgery, post laminectomy syndrome, persistent spinal pain syndrome or neuropathic pain.	Patients presenting with any other type of chronic pain – e.g. face, abdomen, bone etc.
Patients of ages ≥ 18 years of age with full capacity.	Patients of ages <18 years of age
Patients of any sex.	Patient with sleep disorders
Patients of any ethnicity.	Patients with epilepsy
All original research papers which attempt to measure either QEEG or SEP biomarkers to measure chronic pain.	Animal studies
All original research papers which attempt to measure either QEEG or SEP biomarkers in chronic pain following spinal cord stimulation (SCS).	Papers where the intervention is not SCS
Only papers which provide a description of the QEEG or SEP methodology	Papers which do not attempt to measure the efficacy of either QEEG or SEP biomarkers to measure chronic pain.
Papers detailing EEG neurofeedback training for chronic pain.	

2.2.1. Study selection.

Papers included in the review were exported into Covidence systematic review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) where duplicate studies were removed.

The title and abstract were first reviewed independently by two reviewers (Michael Pridgeon, lead reviewer and Llwyd Orton, second reviewer). Two reviewers were used to minimise bias in paper selection and was followed by a full text screen of included papers.

Any disagreements were resolved between the two reviewers prior to the completion of each stage with the lead reviewer (MP) having the final decision in the papers included in the review.

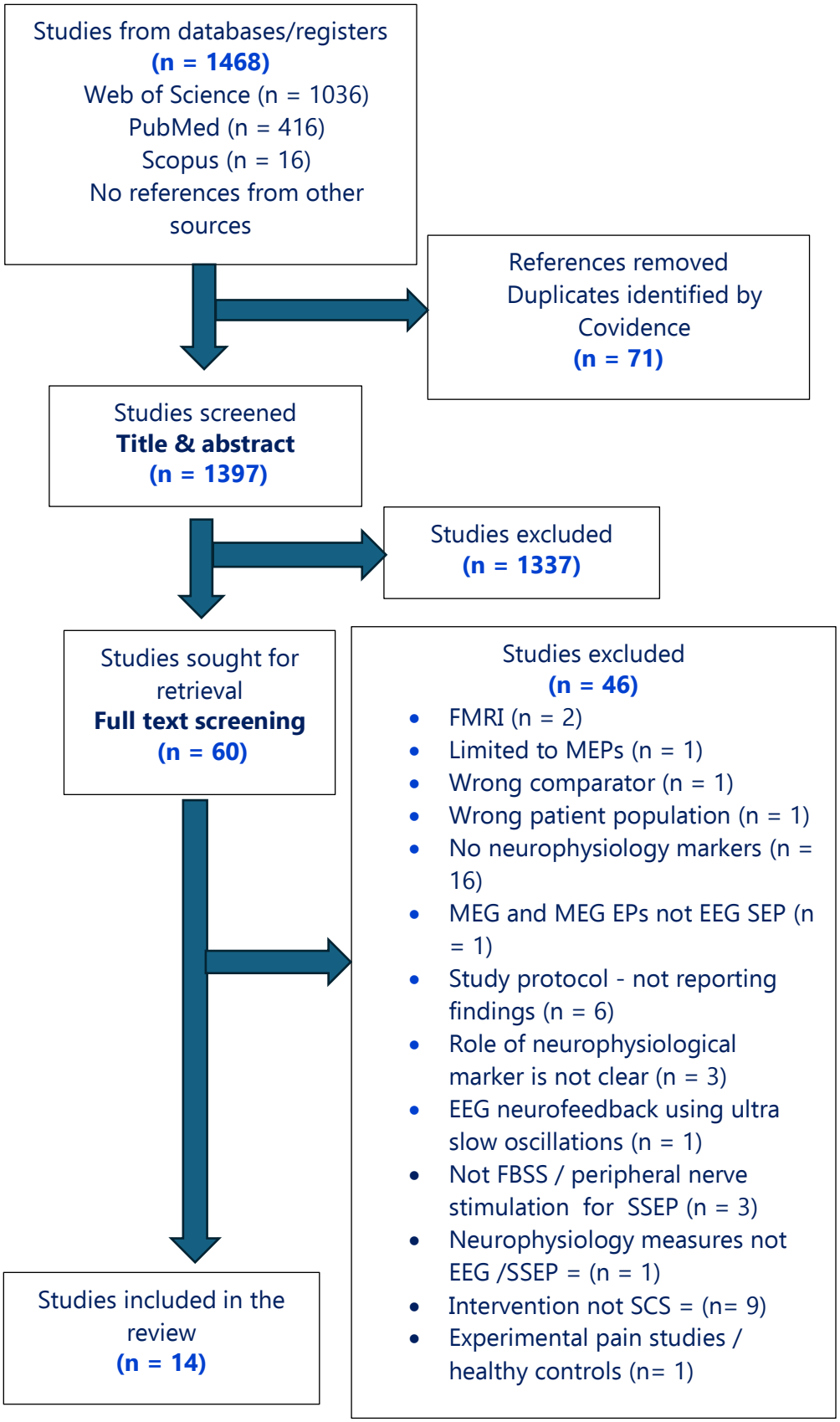


Figure 2.4: PRISMA diagram depicting the flow of information through the scoping review out of 1468 papers retrieved 14 papers were included in the overall review.

2.2.2. Data extraction and management.

Data extracted from all 14 eligible studies were managed in Microsoft Excel. Data extraction was undertaken by the lead reviewer (MP) and then discussed with the second reviewer (LO). Five papers identified studied EEG spectral power changes in chronic neuropathic pain and nine papers identified studied SSEP measures in chronic neuropathic pain.

Generic study characteristics were extracted from all 14 papers. The generic study characteristics extracted included: year of publication, study design, study sample size, duration of pain, pain phenotype and list of pain symptoms, methods used to subjectively quantify pain (questionnaires for pain, quality of life or disability), medication, assessment of anxiety, depression, and sleepiness, SCS intervention used, with stimulation parameters, type of SCS electrode, location of stimulation in relation to spinal cord and SCS study protocol.

EEG study characteristics were extracted from 5 papers. The EEG study characteristics extracted included: electrode measuring system used, type and number of electrodes used EEG reference position, electrode impedances, EEG technical parameters (Nyquist rate, filters), EEG test protocol, EEG duration, EEG data analysis (artefact removal, data processing and epoch size), EEG measure used to quantify pain with a summary of the results and the EEG frequency ranges investigated.

SSEP study characteristics were extracted from 9 papers. The SSEP study characteristics extracted included: SSEP montage and choice of reference, electrode impedances, SSEP technical recording parameters (sampling rate, filters, number of averages), stimulation technical parameters (peripheral nerve stimulated, type of stimulation, frequency, pulse width and intensity and SSEP measures used to quantify pain with a summary of the results.

2.2.3. Quality assessment and risk of bias

The 14 papers included in the review consisted of twelve cases series and two case studies. Assessing the methodological quality of primary studies is very important as studies with poor study design, analysis or interpretation are at risk of bias which can mask the true underlying effect (Guo et al., 2016; Ma et al., 2020). Case series and case studies report novel occurrences which Ma et al., (2020) consider belong to descriptive studies. Guo et al., (2016) adds that case series are uncontrolled describing a single group of patients that receive an

intervention. This type of study design doesn't allow for statistical comparison to a control sample. Guo et al., (2016) developed a twenty-criterion quality checklist for appraising case series primary studies, with ten criteria assessing how the study was undertaken which included hypothesis testing (risk bias) and ten criteria evaluating how the study was reported and overall quality. Guo et al., (2016) argues that their checklist allows readers to assess validity and applicability of the case series studies being reviewed. One criticism of the checklist is that there is no cut off scores to separate high quality from low quality studies.

For this scoping review each "yes" answer was scored as one and "no" answers were scored as zero. The total score available was therefore twenty. Three sub-groups were constructed from these scores with cut off values of 6/7 and 14/15. High quality scores were 15 and above with a low risk of bias, moderate quality scores between 7 and 14 with a moderate risk of bias and low-quality scores between 0 and 6 with a high-risk of bias.

Studies that scored as low quality and a high risk of bias were at risk of significant bias. These studies were of poor study design, with missing data and/or discrepancies. Studies scoring a moderate risk of bias and moderate quality were susceptible to some bias but probably not enough to invalidate the results. Studies scoring low risk of bias and high quality were studies that were well designed and minimise bias especially selection bias, these studies were valid.

2.2.4. Statistical analysis

A meta-analysis was performed for percentage pain relief after SCS for each of the three stimulation programmes and theta power and SSEP amplitude ratios. The analysis was conducted on Meta Essentials version 1.5 (Hak et al., 2016) and presented using forest plots. A random effects model was used for the meta-analysis. Forest plots displayed on the X-axis the effect size estimate as a point and a 95% confidence interval and each study displayed on subsequent rows. The combined effect size was displayed at the bottom of the Forest plot.

The extent of heterogeneity across studies was evaluated using the Q-statistic with a p-value; I^2 statistic; Tau^2; and Tau. A moderator analysis on the effect size and publication bias analysis using a funnel plot, standardised residual histogram and Galbraith plot were used to assess outliers.

In SCS studies and chronic pain the most common effect size measure used to represent the impact of the intervention was percentage pain relief using a visual analogue scale (VAS) score to compare pain relief post intervention to the baseline pain level. The precision of a study was weighted by sample size. Additional effect size measures for EEG and SSEP measures included theta power ratio, for EEG consisting of theta power post intervention compared to theta power at baseline and for SSEP, an SSEP amplitude ratio was chosen consisting of SSEP amplitude after intervention compared to the baseline SSEP amplitude value. Precision was measured with respect to with sample size.

Numerical study characteristics were summarised using mean, median, standard deviation, variance and range. EEG study characteristics were compared to current clinical standards from the International Federation for Clinical Neurophysiology (IFCN) (Nuwer et al., 1999; Peltola et al., 2023) and quantitative EEG standards (Hammond et al., 2004). Lower limb SSEP cortical study characteristics were compared to the current IFCN clinical standards last reviewed in 2023 (Cruccu et al., 2008).

2.3. Results

The combined search returned 1,468 studies, 1,026 from the Web of Science, 416 from PubMed and 16 from Scopus of which 71 were duplicates, 1,397 studies were screened by title and abstract and 1,337 didn't meet the inclusion criteria and were removed. A full text review of 60 remaining studies for eligibility was undertaken and 46 studies were removed leaving 14 studies to be included in the meta-analysis. The 14 included studies, 5 used EEG measures and 9 studies used SSEP measures.

2.3.1. Risk of bias and quality of the included studies

The fourteen included studies were scored against a case series quality assessment check list (Guo et al., 2016). The quality scores can be visualised as a variance graph (Figure 2.5).

Most studies assessed scored as a moderate risk of bias (85% of studies). The mean quality score across all 14 studies was 8.71, the quality score variance was 8.83 with a standard deviation 2.97 indicating that all included studies had quality scores within two standard deviations from the mean. Seven studies (50%) scored above the mean quality score (Sindou

et al., 2003; De Andrade et al., 2010; Buonocore et al., 2012; Wolter et al., 2013; Goudman et al., 2020; Telkes et al., 2020; Niso et al., 2021) with three studies (21%) scoring the highest quality scores (De Andrade et al., 2010; Goudman et al., 2020; Telkes et al., 2020) of up to 13/20 in keeping with a moderate risk of bias.

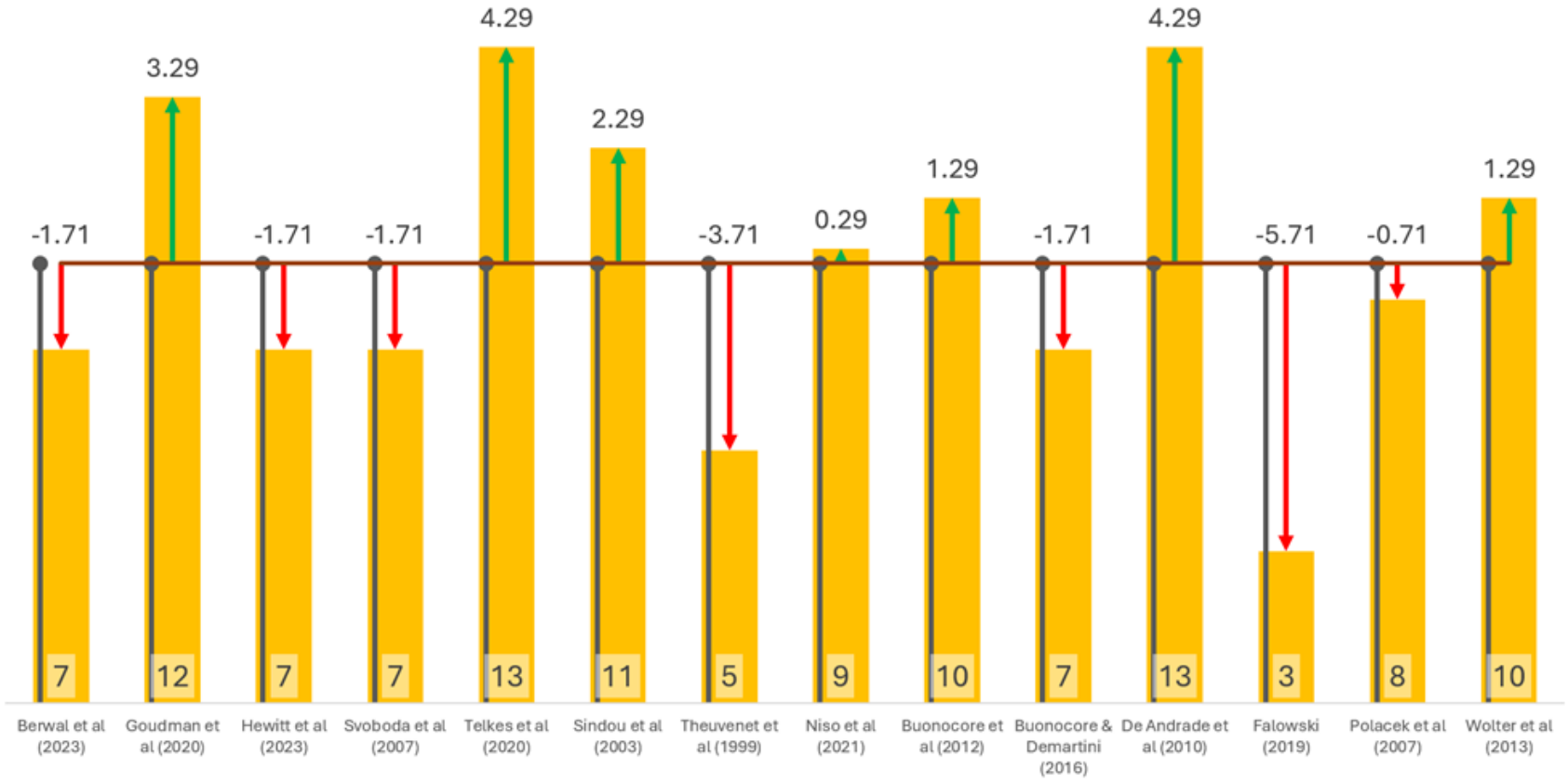


Figure 2.5: A variance graph summarising the quality scores (QS) for the fourteen included papers in the scoping review

All studies were conducted prospectively as either a case series or case study and were collected from a single centre with small sample sizes for lower back pain. Four studies showed mixed neuropathic pain conditions. Of these lower back pain or FBSS patients contributed to the overall sample size as a small cohort. The largest was Sindou et al., (2003) who reported 95 participants in their study but only 24 participants were lower back pain patients. Sarnthein et al., (2006) reported 17 patients with 7 being lower back pain patients.

Study characteristics were reported in 71% (10/14) of studies and SCS (intervention) was fully described in 64% (9/14) of studies. Neurophysiology (EEG or SSEP) measures were described in 64% (9/14) of studies and were described as an outcome measure with measurements made at baseline before SCS and following intervention. In 78% (11/14) of studies the correct statistics were used with the results supporting the conclusions in 71% (10/14) of studies.

A wide range of pain durations were reported throughout the studies often ranging over many years and varying in severity, with participants entering each study at different points making comparison difficult. In 35% (5/14) of studies recruitment was not performed consecutively and often unclear how selection was made. In 42% (6/14) studies the aims, objectives or hypothesis were not clearly stated or only partially reported. In most studies the outcome assessors were not blinded.

Only 21% (3/14) of studies had follow up periods reported Berwal et al., (2023) followed their participants up at 3 months and Sindou et al., (2003) and Sarnthein et al., (2006) were followed up at 1 year. SCS protocols tended to be limited to on/off paradigms with only brief periods of either on or off stimulation. Stimulation therapeutic wash in and wash out effects were not considered. No studies reported losses to follow up or adverse events due to SCS. Only 28% studies (4/14) reported estimates of random variability in their data sets (standard error, standard deviation, or confidence intervals). Two studies were at high risk of bias (Theuvenet et al., 1999; Falowski, 2019).

The study undertaken by Falowski, (2019) scored 3/20, this study was prospective, the intervention of interest was clearly described, and declaration of interests reported. The author worked as a consultant conducting research for Abbott, Medtronic and Nevro three

spinal cord stimulator companies. This is evidence of confirmation bias confirming the beliefs of the customers preconceived notions to influence spinal cord stimulator sales.

The study of Theuvenet et al., (1999) scored 5/20. This study was prospective and consisted of a case series of 8 patients. However, only 3 patients were discussed and of these only 2 patients had spinal cord stimulators in-situ for lower back pain. The two patients were reported as separate case studies within the paper. The aim, objectives and hypothesis were not clear, and the study lacked detail on the study characteristics. Instead, a brief historical summary was listed for each patient. There was no technical or protocol details for SCS and the technical details for SSEPs used in the study was limited to the characteristics of the type of peripheral nerve stimulation used.

2.3.2. Study characteristics.

Studies included were published within the last 25 years, with 7 studies within the last 10 years and 6 studies within the last 5 years. The oldest study was published in 1999 and the newest study in 2023. The 14 papers included in the review consisted of twelve case series and two case studies. Table 2.4 shows the basic study characteristics.

The largest cohort SCS for lower back pain / FBSS was 24 (Sindou et al., 2003) this cohort was a part of a larger study consisting of 95 participants. The smallest case series was 2 (Theuvenet et al., 1999) and essentially consisted of two case studies. Also included were two individual case studies (Buonocore and DeMartini, 2016; Berwal et al., 2023). The combined mean sample size across all fourteen studies was 10 patients (10.4), median, 9 patients (9.5), standard deviation 7.0 and variance 49.9. Primary studies that use neurophysiology biomarkers for lower back pain and SCS were small cohorts consisting of either case series or case studies. Case studies and case series occupy a low position in the hierarchy of evidence and represent a weak study design (Guo et al., 2016). Nevertheless, these were the only primary sources of evidence available in the literature to assess neurophysiology EEG or SSEP pain measures against SCS intervention.

None of the included studies reported using pain definitions recommended by the International Association for the Study of Pain (IASP) or the ICD-11 framework. None of the included defined chronic pain as per NICE TAG 159 for SCS therapy.

Participant pain duration and severity varied across the studies. Mean pain duration ranged from 3-11 years with a combined mean of 6.8 years, median of 6.3 years, standard deviation of 2.69 and variance 7.2. Four studies reported the different pain phenotypes as a part of their study characteristics (Sindou et al., 2003; Poláček et al., 2007; De Andrade et al., 2010; Buonocore and DeMartini, 2016). The pain phenotypes listed were all stereotypical for neuropathic pain and represent pain at baseline prior to any intervention. No studies reported on the pain phenotype after SCS.

Table 2.4: A summary of the basic study characteristics

Author	Year of publication	Study type	Sample size	Mean duration of pain / years	Pain phenotypes
Berwal et al.,	2023	Case study	1	3	NR
Goudman et al.,	2020	Case series	8	NR	NR
Hewitt et al.,	2023	Case series	21	10.5	NR
Svoboda et al.,	2007	Case series	10	8.2	NR
Telkes et al.,	2020	Case series	7	5	NR
Sindou et al.,	2003	Case series	24	4.8	Burning, crushing, continuous pain
Theuvenet et al.,	1999	Case series	2	NR	NR
Niso et al.,	2021	Case series	12	11	NR
Buonocore et al.,	2012	Case series	6	NR	NR
Buonocore & DeMartini	2016	Case study	1	7	Hyposthenia and continuous pain
De Andrade et al.,	2010	Case series	20	4.5	Shooting, stinging. paraesthesia, allodynia, burning, freezing, paroxysmal electrical shocks, dysaesthesia and tingling
Falowski	2019	Case series	15	NR	NR
Polacek et al.,	2007	Case series	9	8.7	Shooting and burning
Wolter et al.,	2013	Case series	10	5.6	NR

NR = Not reported

The main subjective measure of pain used in most studies was the VAS (8/14 studies included). Two studies in addition to VAS used the pain catastrophising questionnaire (Goudman et al., 2020; Telkes et al., 2020) and two studies simply asked patients if they were pain free or not - a binary subjective measure of pain (Theuvenet et al., 1999; Buonocore et al., 2012). Other studies used Pain Detect (Hewitt et al., 2023), Oswestry Disability Index (ODI) (Telkes et al., 2020), central sensitisation inventory (Goudman et al., 2020) and the McGill pain questionnaire (Telkes et al., 2020). Two studies used a battery approach using multiple subjective questionnaires which included VAS, pain catastrophising questionnaire, central sensitisation inventory, the McGill pain questionnaire and Oswestry Disability Index (Goudman et al., 2020; Telkes et al., 2020). Three studies didn't report using any subjective measures (Svoboda et al., 2007; Buonocore and DeMartini, 2016; Berwal et al., 2023). The results indicate that the preferred subjective measure used alongside neurophysiology objective measures is the VAS, which is considered by many to be a gold standard pain measure. Pain Detect and ODI are both measures used in lower back pain assessments following surgery.

Neurophysiology biomarkers, especially EEG power, were at risk of bias from medication and sleep, where elevated or suppressed levels of theta power in different brain areas may be the result of certain analgesics or poor sleep quality and not spinal cord stimulation. SSEP measures especially amplitude was found to be more robust than EEG measures to these changes. Anxiety, depression and poor sleep are recognised symptoms of chronic pain that are often overlooked in primary pain research and could be used as physiological markers of reduced pain in SCS. Therefore, it would be good research practice to include these variables in primary research studies.

Table 2.5: Study characteristic, subjective pain measuring systems, medication, anxiety and depression and sleepiness NR = Not reported

Author	Subjective pain measures / questionnaire	Medication	Anxiety	Depression	Sleepiness
Berwal et al.,	NR	NR	NR	NR	NR
Goudman et al.,	VAS, pain catastrophizing questionnaire, central sensitisation inventory	Opioids, non-opioids and antidepressants	NR	NR	NR
Hewitt et al.,	Pain Detect	NR	NR	NR	NR
Svoboda et al.,	NR	Opioids and non-opioids	NR	NR	NR
Telkes et al.,	VAS, McGill Pain Questionnaire, Oswestry Disability Index (ODI), and Pain Catastrophizing Scale	NR	NR	Beck's depression inventory	NR
Sindou et al.,	VAS	Antiepileptic, opioids and non-opioids	NR	NR	NR
Theuvenet et al.,	Subjective scale (pain free or not)	NR	NR	NR	NR
Niso et al.,	VAS	Co-analgesic antidepressants, anti-epileptic drugs, opioids	NR	NR	NR
Buonocore et al.,	Subjective scale (pain free or not)	NR	NR	NR	NR
Buonocore & DeMartini	NR	NR	NR	NR	NR
De Andrade et al.,	VAS	Opioids, non-opioids, antidepressants, and anti-epileptic	NR	NR	NR
Falowski	VAS	NR	NR	NR	NR
Polacek et al.,	VAS	Opioids, non-opioids, antidepressants and anti-epileptic	NR	NR	NR
Wolter et al.,	VAS	NR	NR	NR	NR

Six studies from the fourteen included listed the type of medications used by participants. Opioids and non-opioid pain medications were the two most common analgesics used in these studies. Co-analgesic antidepressants and anti-epileptic medications were listed in four studies. Six studies didn't list the medications being used by participants, two studies from this group were investigating EEG measures (Telkes et al., 2020; Berwal et al., 2023). Both these studies were undertaken during intra-operative monitoring with patients under general anaesthesia which may mask any changes in theta power. Both studies reported that theta power remained unaffected in the somatosensory region. Telkes et al., (2020) reported an alpha frequency band power increase with SCS.

No studies assessed anxiety or sleepiness at baseline or following SCS. One study assessed depression (Telkes et al., 2020) and used the Beck inventory scale although these scores were not reported on or included in the published paper. Details of SCS was reported in most papers and summarised in Table 2.6 and Table 2.7. All studies primarily investigated tonic SCS with neurophysiology measures. Eleven studies reported the frequencies used for SCS. These showed a heterogeneous picture with frequency settings ranging from 5 Hz to 120 Hz. All had participants receiving tonic stimulation over the range associated with paraesthesia therapeutic effects (1-60 Hz). Three studies reported higher frequencies up to either 100 Hz or 120 Hz. At these frequency levels paraesthesia effects decrease and analgesic effects increase. The mean frequency used was 59.4 Hz, with median and mode values of 60 Hz. The standard deviation for the frequency range was 32 and variance was 1027 suggesting large variability with frequencies used across studies within a 2x standard deviation range. The mean, median and mode values are all similar and correlate with 60 Hz frequency typically used within clinical practice.

Table 2.6. SCS study characteristics. NR = Not reported

Author	SCS	Settings	Type of SCS electrode	Placement	Protocol
Berwal et al.,	Tonic	60 Hz, 0.03 ms	Paddle	T9-T10	SCS off - SCS on / 1 minute with 30 seconds off
Goudman et al.,	Tonic	60 Hz, 0.21 ms	Percutaneous	T8-T11	BL preop - Tonic 1 month-HD tonic 1 month
	HD Tonic	500 Hz, 0.5 ms			
Hewitt et al.,	Tonic	40-50 Hz	Percutaneous	T8-T12	40 min (SCS off) - testing SCS on tonic/burst - 2 minutes
	Burst	Train of 5 pulses at 500 Hz, 1.0 ms delivered at 40 Hz			
Svoboda et al.,	Tonic	45-100 Hz, 0.2-0.4 ms	Percutaneous	T9-T11	SCS on/off
Telkes et al.,	Tonic	60 Hz, 0.3ms/1 ms	Percutaneous	T8-T10	SCS on/off
	High frequency	10 kHz			
Sindou et al.,	Tonic	NR	Paddle	T11-L1	SCS 1 hour three times per day or 10 minutes every hour during the day and at night
Theuvenet et al.,	Tonic	NR	Paddle	T10-T12	NR
Niso et al.,	Tonic	30-120 Hz, 0.25 ms - 0.5 ms	NR	NR	Sham-tonic-burst or burst-tonic-sham
	Burst	Train of 5 pulses at 500 Hz, 1.0 ms delivered at 40 Hz			

Table 2.7. SCS study characteristics continued. NR = Not reported

Author	SCS paradigms	Settings	Type of SCS electrode	Placement for lower back pain	Protocol
Buonocore et al.,	Tonic	NR	Paddle	T9-T12	1 hour off (T0) - SCS on (T1)- SCS off (T2)
Buonocore & DeMartini	Tonic	60 Hz, 0.25 ms	Percutaneous	T8-T10	SCS off 1 hour / SCS on
	High frequency	10 kHz, 0.20 ms			
De Andrade et al.,	Tonic	50 Hz, 0.1 ms	Percutaneous	NR	3 hr-on-3 hr off cycle testing started either 60 min after on or 60 min after off
Falowski	Tonic	5-10 Hz, 0.25 – 0.35 ms	Percutaneous	T8-10	NR
	High frequency	10 k Hz, 0.3 ms			
	Burst	Train of 5 pulses at 500 Hz, 1.0 ms delivered at 40 Hz			
Polacek et al.,	Tonic	40-100 Hz	Percutaneous	T9-T10	SCS on/off 2 min on/off
Wolter et al.,	Tonic	80-100 Hz, 0.24 - 0.45 ms	NR	NR	SCS on/off

Tonic stimulation pulse duration intensities were reported in five studies with mean, median and mode values for pulse duration being the same (0.2 ms) ranging from 0.03 ms to 0.35 ms. Standard deviation was 0.1 and variance 0.01 in keeping with low variability in the values used.

High frequency and burst stimulation were studied far less frequently. Three studies used high frequency stimulation (Buonocore and DeMartini, 2016; Falowski, 2019; Telkes et al., 2020) and three studies used burst stimulation (Falowski, 2019; Niso et al., 2021; Hewitt et al., 2023). The studies that used high frequency all used the standard high frequency setting from the literature 10 KHz. The studies that used burst stimulation all used the standard burst frequency settings recommended in the literature, train of 5 pulses at 500 Hz, 1.0 ms delivered at 40 Hz.

Eight studies used percutaneous electrodes and four paddle electrodes; two studies didn't report the type of stimulating electrode. Electrodes for lower back pain were placed tip to T8 or T9 with most studies covering a range of T8-T12 consistent with the wider literature for axial lower back pain stimulation. One study extended down from T11 to L1 and another study T10-T12. Three studies didn't report the location of SCS.

Ten studies used a SCS on/off paradigm for their studies, the on or off periods were either 1, 2 or 3 hours and in 1 study the stimulator on/off setting was for 2 minutes. Only one study looked at longer term effects Goudman et al., (2020) they kept the spinal cord stimulator on in the tonic mode for 1 month before testing. Two studies failed to disclose the paradigm used.

The wash in / wash out therapeutic effects were not considered with many of the SCS protocols being limited to on/off paradigms. Ahmadi et al., (2021) recommend a minimum wash in and wash out period of 72 hours (3 days) for tonic stimulation.

Hewitt et al., (2023) agrees that for tonic stimulation the wash in and wash out period may be significant. However, adds that the wash in and wash out period for burst stimulation is poorly understood. Evidence from dosing burst stimulation paradigms (alternating periods of stimulation on/off) suggests that for burst stimulation the effects of stimulation outlast the stimulus by only a few minutes. They used a short washout period between trials of 2 minutes because tonic stimulation trials were short (4 seconds on, 4 seconds off, 40 cycles)

and found this to be adequate for their study design. Despite limited evidence there is consensus in the literature that high frequency stimulation is like burst stimulation with regards to wash in / wash out effects.

Goudman et al., (2020) compared two types of tonic stimulation the traditional tonic stimulation and high dose tonic stimulation. They designed their protocol around prolonged wash in / wash out periods for the two types of tonic stimulation. Their protocol stated wash in and wash out periods from baseline to tonic stimulation (trial 1) at 1.5 months and from tonic stimulation to high dose tonic stimulation (trial 2) at 2.5 months. In their results section there was considerable deviation from the protocol with the first trial occurring 76 days +/- 26 days (2.5 months) and second trial at 176 days +/- 58 days (5.8 months). There was significant inter-trial variability in terms of the return trials. There was no explanation on why the study deviated from the protocol.

Therefore, when comparing stimulation paradigms, the study protocol should be designed around tonic stimulation given this has the largest and most significant wash in / wash out period.

2.3.3. EEG study characteristics

Technical protocols varied between the five studies that were included that reported EEG data. The ten-twenty measuring systems is the gold standard in EEG clinical practice (Nuwer et al., 1999; Peltola et al., 2023). Three studies reported using the ten-twenty system, one study used a quadrant system with electrodes placed 2.5 cm apart on the scalp. The other study failed to report the measuring system used.

The IFCN recommend a minimum of 19 electrodes (Nuwer et al., 1999; Peltola et al., 2023) for EEG data collection. The number of electrodes used to collect EEG data in the five studies varied ranging from 10-111 electrodes (mean = 55, median = 60, standard deviation = 33.9, variance = 1,149. The number of electrodes was different in each study. The study that used 10 electrodes (Telkes et al., 2020) used this montage due to the intra-operative neurophysiology setting. Three studies used a common reference, although the common electrode site chosen was not stated. Three studies failed to disclose the choice of reference used.

The IFCN recommend that electrode impedances should be equal and <5 KΩ, impedances <10 KΩ are considered acceptable however are at risk of electrode impedance imbalance, compromising the common mode rejection ratio and the amplifiers' ability to reject noise. Impedances >10 KΩ are unacceptable and indicate shunting through a salt bridge on the scalp. Such conditions are at risk of excessive noise and artefact (Peltola et al., 2023). Two studies had electrode impedances exceeding clinical practice guidelines of <5 KΩ. Hewitt et al., (2023) reported impedances values of <50 KΩ which would suggest that noise would be a limiting factor to this study. Goudman et al., (2020) reported impedance values of <20 KΩ suggesting noise contamination would be high. Impedance was not reported in the other studies.

The IFCN recommend a minimum Nyquist rate of 250 Hz. High Nyquist rates should be multiples of 50 or 64 (Nuwer et al., 1999; Peltola et al., 2023). A range of different Nyquist were reported most ranging from 128 Hz to 2,048 Hz (median 1,024 Hz and mean 1,050 Hz), no study used the same Nyquist rate, and one study used 38.4 KHz. Higher Nyquist rates enhance the resolution within the EEG bandwidth. All studies analysed data in the delta, theta, alpha beta and gamma frequency range (1-45 Hz), frequencies higher were not analysed. All Nyquist rates reported were either a multiple of 50 or 64.

The IFCN recommend a filter bandwidth of 0.5 Hz – 70 Hz, although lower frequency limits of 0.16 Hz are acceptable and preferred (Nuwer et al., 1999; Peltola et al., 2023). The filter bandwidths used across studies varied significantly ranging from 0.01 Hz to 1 Hz for the low frequency filter and 45 Hz to 200 Hz for the high frequency filter. No study used the same filter bandwidth settings to analyse their data. The filter bandwidths chosen were all adequate for analysing EEG signals across a 1-45 Hz range.

All five EEG studies were all recorded in the eyes closed condition enhancing alpha frequencies. Two studies were undertaken at electrode implantation in the operating theatre with general anaesthesia. EEG study length was reported in three studies and varied from 5 minutes to 15 minutes. Study length was different for each of the three studies.

The removal of eye movements, eye blinks, muscle and ECG are recommended as a minimum for artefact free EEG for quantitative EEG power analysis (Hammond et al., 2004). All five studies used artefact rejection using EEGLAB toolbox (MATLAB) removing eye blinks

or eye movement, ECG artefact, muscle artefact and 50 Hz contamination using a Notch filter. One study reported removing amplifier desaturations (Telkes et al., 2020).

The recommended minimum epoch size for quantitative EEG analysis is 60 seconds (1 minute) following artefact removal and 90-120 seconds (1.5 minutes – 2 minutes) for power analysis (Hammond et al., 2004). Two studies reported epoch length for frequency analysis, these were within the recommended minimum standards, the epoch lengths were 12 minutes (Berwal et al., 2023) and 3 minutes (Goudman et al., 2020). All five studies analysed the raw EEG data via independent component analysis using power spectral density estimates calculated using Welch's method with a Hanning window of 1 second and overlapping of 0.5 seconds.

All five studies investigated EEG frequency power, four studies investigated theta and alpha frequency power (relative and absolute). Theta power was expressed as a decrease from baseline values and alpha power as an increase from baseline values. One study described cortical oscillatory changes expressed as dominant frequency over a 10-150 Hz range (Svoboda et al., 2007).

Table 2.8: EEG recording characteristics. NR = Not reported

Author	**Measuring system**	**Number of electrodes**	**Reference**	**Impedance**	**Nyquist rate**	**Filters**
Berwal et al.,	NR	60	Common average reference	NR	38.4 kHz	1-150 Hz
Goudman et al.,	Ten-twenty system	32	Common average reference	<20 KΩ	2048 Hz	1-45 Hz
Hewitt et al.,	Ten-twenty system	63	Common average reference	<50 KΩ	1000 Hz	0.001-200 Hz
Svoboda et al.,	Placed equally on scalp 2.5 cm apart	111	NR	NR	1024 Hz	0.015-200 Hz
Telkes et al.,	Ten-twenty system (extended)	10	NR	NR	128 Hz	0.5-60 Hz

Table 2.9: EEG protocol characteristics. NR = Not reported

Author	**Protocol**	**EEG duration / minutes**	**Artefact removal**	**Epoch duration / minutes analysed**	**Spectral frequencies analysed**	**EEG measure**
Berwal et al.,	Eyes closed	12	50 Hz, EOG, muscle, ECG	12	Delta, theta, alpha, beta, low gamma, and high gamma	Theta and alpha power
Goudman et al.,	Eyes closed	5	Eye blinks	3	Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz), Gamma (30–45 Hz)	Theta and alpha power
Hewitt et al.,	NR	NR	Muscle	NR	Theta (4–7 Hz), Alpha (8–13 Hz), Beta (16–24 Hz)	Theta and alpha power
Svoboda et al.,	Eyes closed	NR	Eye blinks, muscle	NR	NR	Cortical oscillations
Telkes et al.,	Eyes closed	15	ECG, amplifier desaturation	NR	Theta (4–7 Hz) Alpha (8–12 Hz)	Theta and alpha power and peak dominant frequency

2.3.4. SSEP study characteristics

Nine studies investigated SSEP measures for pain. Seven of the nine studies (77%) analysed SSEP amplitude decrease in the early components (P39), one study from this group also looked at the P50/P60 amplitude. One study analysed the late P300 component, and another study analysed central conduction time and P37/P40 latency. The IFCN label the early SSEP component as P39 although P37 and P40 are acceptable labels (Cruccu et al., 2008).

The IFCN recommend the active scalp recording electrode in lower limb SSEP studies to be CPz, 2 cm posterior to Cz and between Cz and Pz (Cruccu et al., 2008). There are two recommended positions for the reference, Fz or a non-cephalic ipsilateral earlobe position. Four studies reported on the scalp electrodes used for lower limb SSEP recordings all four used the recommended CPz as the active electrode with a range of reference electrode positions. A frontal Fz reference was used in three studies and a non-cephalic (linked ear) reference in one study. Two studies used EEG with either 32 electrodes or 111 electrodes and then reconstructed the SSEPs using triggered data. Two studies (Sindou et al., 2003; Falowski, 2019) failed to report the electrodes or montage used for the SSEP recordings and four studies failed to state the reference used.

SSEP recording characteristics (sampling rate, filters, number of averages and electrode impedance) were poorly described. Two studies reported different sampling rates; 5 kHz (Niso et al., 2021) and 1,024 Hz (Poláček et al., 2007).

The IFCN recommend a filter bandwidth of 3 Hz to 2 kHz (Cruccu et al., 2008). Three studies described the filter bandwidths used, these were different for each study with low frequency filters ranging from 1 Hz to 20 Hz and high frequency filters ranging from 20 Hz to 20 KHz. Six studies failed to detail the filter bandwidths used.

The IFCN recommend undertaking 500 averages which are repeated (Cruccu et al., 2008). Five studies reported on the number of averages used, two studies using 500 averages, one study 1000 averages and one study used 900 averages. Another study used a variable number of averages ranging from 190-210 averages (Niso et al., 2021) less than the recommended number. No study stated that the trials were repeated.

The IFCN recommend that electrode impedances should be equal and <5 KΩ (Cruccu et al., 2008). Only two studies reported on electrode impedance, one study was within the recommended <5 KΩ and the other study reported electrode impedance values of <10 KΩ, over clinical practice recommendations by 5 KΩ.

Stimulation characteristics were better documented in the selected studies. The IFCN recommend posterior tibial nerve stimulation for lower limb SSEP studies at the medial malleolus. Stimulation is recommended to be a monophasic square wave pulse (Cruccu et al., 2008). The sural nerve is a recommended alternative. Eight studies used the posterior tibial nerve for lower limb SSEP stimulation, one study used both posterior tibial nerve and sural nerve (Poláček et al., 2007) and one study failed to report the peripheral nerve stimulated (Falowski, 2019). Three studies reported using a monophasic square wave pulse and three studies reported using a biphasic square wave pulse. One study reported 400 impulses in a stimulation block and two studies failed to report the type of stimulation used.

The IFCN recommend a minimum stimulus duration of 0.1-0.2 ms (Cruccu et al., 2008). A range of stimulus durations were used in the selected studies, four studies reported 0.2 ms, two studies 0.1 ms, one study 0.6 ms and one study failed to report stimulus duration.

The IFCN recommend a minimum stimulus frequency of 3-5 Hz (Cruccu et al., 2008) to allow the generation of a stable transient cortical response. Two studies reported 5 Hz, one study 0.6 Hz, one study 1.1 Hz, one study 2 Hz and one study 5.3 Hz. Three studies failed to report the stimulation frequency used.

The IFCN recommend performing stimulation 2-3 times above the sensory threshold, six studies reported intensities 2-3 times above sensory threshold or at motor threshold with a visible toe twitch. Three studies failed to comment on the intensity used.

Table 2.10: SSEP recording characteristics. NR = Not reported

Author	Electrodes	Reference	Sampling rate	Filters	Number of averages	Electrode impedance
Sindou et al.,	NR	NR	NR	NR	NR	NR
Theuvenet et al.,	32 electrodes	NR	NR	NR	NR	NR
Niso et al.,	Cz	NR	5 kHz	HF – 1350 Hz	190-210	<5 KΩ
Buonocore et al.,	Cpz, Fz, ground	Fz	NR	NR	NR	NR
Buonocore & DeMartini	Cz, Fz, ground	Fz	NR	NR	500	NR
De Andrade et al.,	Cz-linked earlobes	Linked ear lobes	NR	20 Hz–20 kHz	500	NR
Falowski	NR	NR	NR	NR	NR	NR
Polacek et al.,	111 electrode cap.	Fz	1,024	1-20 Hz (tibial) 1-40 Hz (sural)	900	<10 KΩ
Wolter et al.,	Cz-Fz	Fz	NR	NR	1000	NR

Table 2.11: SSEP stimulation characteristics. NR = Not reported, MT = Motor threshold

Author	Nerve stimulated	Type of stimulus	Frequency / Hz	Pulse width / ms	Mean intensity / mA	SSEP pain measure
Sindou et al.,	Posterior tibial	NR	NR	NR	NR	Central conduction time
Theuvenet et al.,	Posterior tibial	Square-wave constant current pulses	0.6	0.6	7	SSEP amplitude reduction (P40, P60)
Niso et al.,	Posterior tibial	Square-wave constant current pulses	1.1	0.2	27	SSEP amplitude reduction (P300)
Buonocore et al.,	Posterior tibial	Biphasic square wave pulse	5	0.1	MT	SSEP amplitude reduction (P39)
Buonocore & DeMartini	Posterior tibial	Biphasic square wave pulse	5	0.1	MT	SSEP amplitude reduction (P39)
De Andrade et al.,	Posterior tibial	Square-wave constant current pulses	2	0.2	MT	SSEP amplitude reduction (P40)
Falowski	NR	NR	NR	NR	NR	SSEP amplitude reduction (P37)
Polacek et al.,	Posterior tibial Sural	400 impulses in one block, ISI 5-7s	NR	0.2	NR	SSEP amplitude reduction (P40)
Wolter et al.,	Posterior tibial	Biphasic square wave pulse	5.3	0.2	MT	SSEP amplitude reduction (P40)

2.3.5. Percentage Pain Relief Effect Size Measure.

Percentage pain relief was the preferred effect size measure used in evaluating SCS in chronic lower back pain. Of the fourteen studies selected in the scoping review only five reported individual numerical data that allowed the average percentage pain relief to be calculated with standard error. All five studies reported data for tonic stimulation. One of these studies used a decrease in theta frequency power and an increase in alpha frequency power (Goudman et al., 2020). Three studies used lower limb SSEP P39 amplitude reduction (Poláček et al., 2007; De Andrade et al., 2010; Wolter et al., 2013) and one study used central conduction time combined with the P39 latency (Sindou et al., 2003). There was insufficient data to calculate percentage pain relief for high frequency or burst SCS studies.

A randomised effect model was generated, and the five studies visualised on a forest plot. A combined effect size for the five studies was 63.5% (cis) with a standard error of 6.30 Figure 2.6.

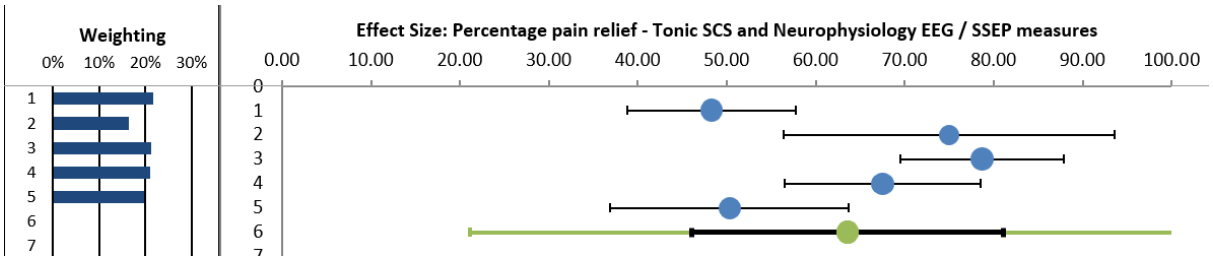


Figure 2.6: Forest plot of the percentage pain relief and neurophysiology pain measures with tonic spinal cord stimulation

The combined effect size (row 6) synthesised a combined percentage pain relief of 63.5% with confidence intervals ranging from 46% - 81%, represented as the black interval line (row 6) and is a measurement of how precise the effect size is in relation to the standard error of the mean (Borenstein, 2023). The standard error was 6.30 indicating a degree of inaccuracy from the true combined mean value due to variation.

The green interval line represents the prediction interval and the amount of dispersion in effects. The prediction interval predicts that 95% of studies comparable to those included in the analysis fall within this interval. Large prediction intervals suggest heterogeneity between studies. In this meta-analysis the synthesised prediction interval was much larger than the confidence interval and is estimated to be 20% to 100%. This finding would favour

heterogeneity between studies with some studies favouring conflicting values from non-responders and a low percentage pain relief.

The Tau statistic (13.94) and Tau^2 (194.31) statistic are in keeping with a large degree of variability between the effect sizes reported in each study. The Q-statistic for percentage pain relief with tonic stimulation was 33.4 (P value <0.001). This result confirms that there is excess variation between the effect sizes included in the meta-analysis and can be attributed to both clinical and methodological heterogeneity between studies. The study characteristics support this with both clinical and methodological heterogeneity being present within the reported study characteristics. This was most apparent in the methodological characteristics for recording EEG and SSEP measures.

The I^2 value was 88.03% and measures the proportion of unexplained heterogeneity. This finding indicates that a large proportion of the variability is attributed to unexplained heterogeneity (Ruppar, 2020). There were many clinical and methodological characteristics that were not reported and the quality assessment for case series highlighted that study designs were at a moderate to severe risk of bias due to study designs being of a moderate quality. Furthermore, there were three different subgroups used in the calculation of percentage pain relief which were modality and methodologically different. The subgroups were: percentage pain relief calculated from a reduction in EEG theta power with tonic stimulation (Goudman et al., 2020), percentage pain relief calculated from a reduction in SSEP P39 amplitude with tonic stimulation (Poláček et al., 2007; De Andrade et al., 2010; Wolter et al., 2013), percentage pain relief calculated from SSEP central conduction time and SSEP P39 latency values (Sindou et al., 2003).

A Forest plot was used to visualise the different subgroups and their contribution to the combined effect size (Figure 2.7).

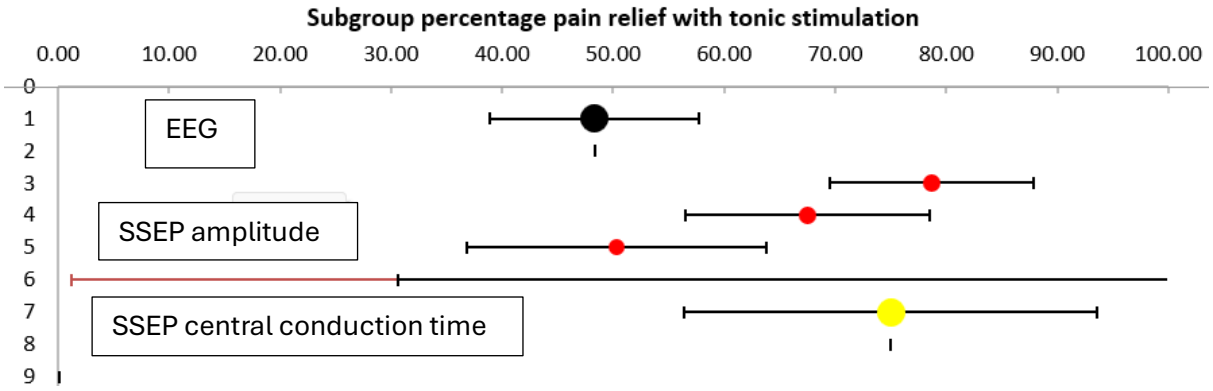


Figure 2.7: Forest plot showing subgroup analysis for pain relief. The EEG (black), (Goudman et al., 2020) and central conduction time (yellow), (Sindou et al., 2003) subgroups represent single studies and have minimal impact on the combined effect size for pain relief. The three SSEP amplitude studies (red) have a combined effect size of 65.9% (cis) with equal weighting in the total group. Methodological heterogeneity remains high between these three studies (Q statistic = 14.8, P = 0.001 and I^2 statistic 86.48%).

The SSEP study characteristic's support the finding with under reporting of technical parameters the amount of heterogeneity can't reliably be assessed and remains largely unexplained. The SSEP recording parameters that are reported show variability in the filter bandwidths used and the number of averages contributing to methodological heterogeneity. One of the largest sources of variation and not reported was electrode impedance, high unequal impedances are at risk of variation and artefact contamination.

The large heterogeneous variation in the combined effect size which remains in the subgroup analysis implies that the synthesised combined effect size would not be a useful measure for the interpretation of percentage pain relief with tonic stimulation and shouldn't be meta-analysed as one single group or population. Percentage pain relief with neurophysiological measures currently need to be reported as individual values and therefore the prediction interval may be a better estimate currently under this circumstance. The meta-analysis was limited by the small number of primary research studies available and represents a significant gap in the literature.

The moderator effect on percentage pain relief was investigated using the included studies with variables EEG theta power decrease, SSEP P39 amplitude reduction and SSEP central conduction (CCT). When the moderator effect (x-axis) was plotted against effect size (y axis)

a negative correlation was noted on a scatter plot (Figure 2.8). Higher effect sizes were associated with a decrease in the moderator effect and as the moderator effect increased the effect size decreased. This would suggest that EEG theta power reduction, SSEP P39 amplitude reduction and SSEP CCT has a negative effect on percentage pain relief. This observed relationship was most obvious from the SSEP P39 amplitude reduction subgroup due to the size of the subgroup. The R^2 value was 17%, a low value suggesting that the decrease in pain relief (effect size) is not totally explained by the three variables. This finding confirms that the moderator effect was influenced by inter-study heterogeneity and a low number of studies included in the meta-analysis. Therefore, due to the low number of studies included in the moderator analysis there is insufficient primary research studies available to accurately determine the effect of neurophysiology moderators on percentage pain relief with tonic stimulation (effect size).

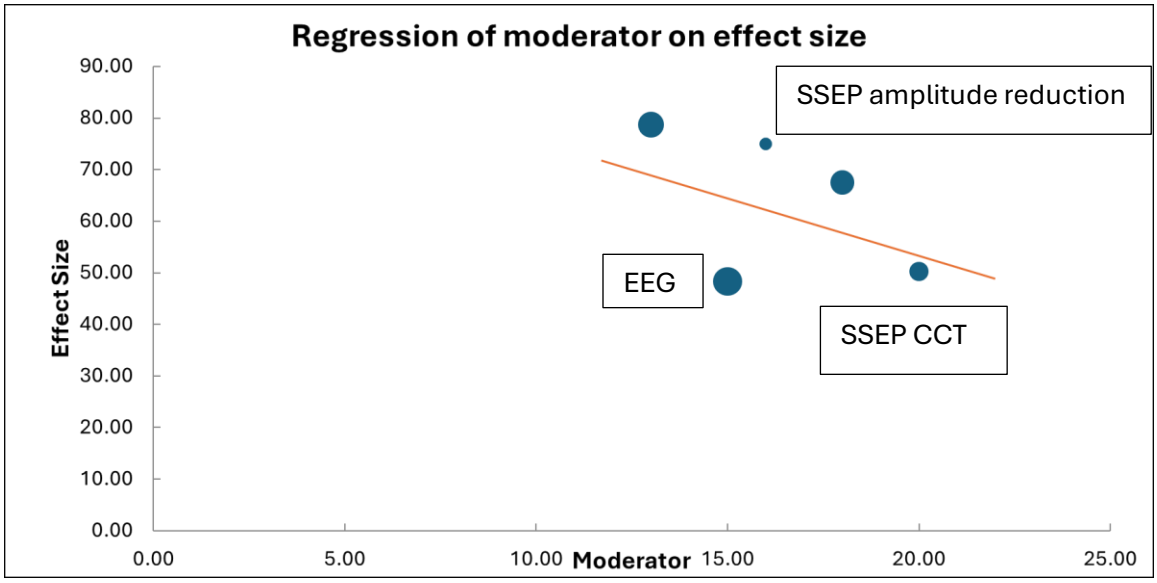
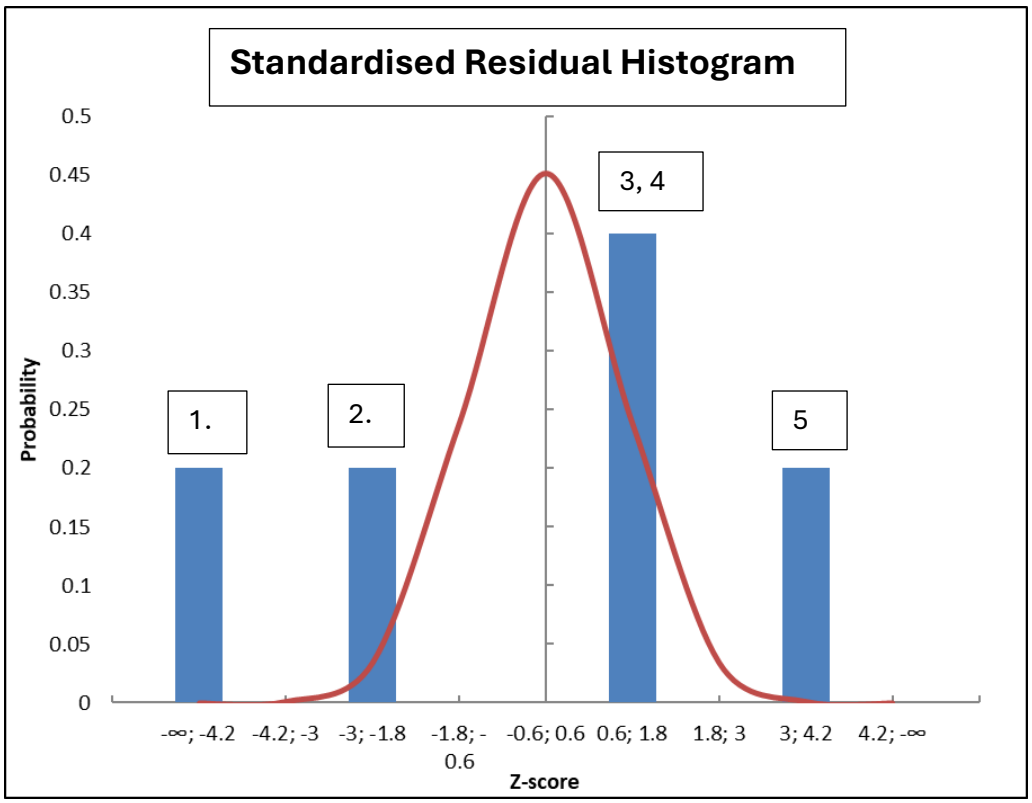


Figure 2.8. Moderator effect on percentage pain relief, The R^2 value was 17% and slope -2.2 suggesting negative correlation pattern. The regression line showed a negative correlation (-2.2) between pain relief and moderator effects with moderator effects seen with SSEP P39 amplitude reduction QEEG and SSEP CCT impacting on pain relief.

A standardised residual histogram was used to assess if there were any outliers from the combined effect size when plotted against a normal distribution. Standardised residuals were expected to follow a normal distribution around the combined effect size.

Poláček et al., (2007) and Sindou et al., (2003) both had residual values that fell within the normal distribution range and outliers, Poláček et al., (2007) standardised residual values were the closest to the combined effect size. Studies from Goudman et al., (2020) and De Andrade et al., (2010) standardised residual values were significant outliers from the combined effect size and contributed to the greatest variation (Figure 2.9).



1. Goudman et al., (2020)
2. Wolter et al., (2013)
3. Poláček et al., (2007)
4. Sindou et al., (2003)
5. De Andrade et al., (2010)

Figure: 2.9: Standardised residual histogram for the assessment of outliers

Publication bias could not be assessed accurately with a funnel plot due to the low number of included studies preventing funnel plot asymmetry to be visualised accurately. There was a slight asymmetry on the funnel plot towards the right, however due to the low number of studies included this may be due to chance. The funnel plot highlighted that two of the SSEP studies report higher effect size estimates with relatively high precision despite high levels of

heterogeneity this may represent exaggerated effect size estimates due to poor methodological quality. The three SSEP P39 amplitude studies scored between 8 and 13 in the case series quality assessment favouring a poorer methodological quality in these studies. Such an exaggerated effect can create subtle asymmetry on the funnel plot towards higher effect sizes.

The scoping review identified 14 primary research studies however only a very small number allowed percentage pain relief to be calculated. This may represent non-reporting bias where small study sizes create subsequent small not significant effect sizes, these are not reported as they may not be significant. The lack of under reporting of the methodological study characteristics would support this argument.

Instead, the funnel plot was used to assess precision of the estimated effect size (Figure 2.10). In the absence of both bias and heterogeneity, 95% of studies should lie between the 95% confidence interval diagonal lines (red). The power of the funnel plot was low because only five studies were included in the analysis, this meant that the precision of each study could only be evaluated. Studies with greater precision were displayed at the top of the funnel plot and studies of low precision at the bottom of the funnel plot. Studies that fall outside the funnel plot showed significant heterogeneity, these were Goudman et al., (2020) EEG study and De Andrade et al., (2010) SSEP P39 amplitude reduction measure.

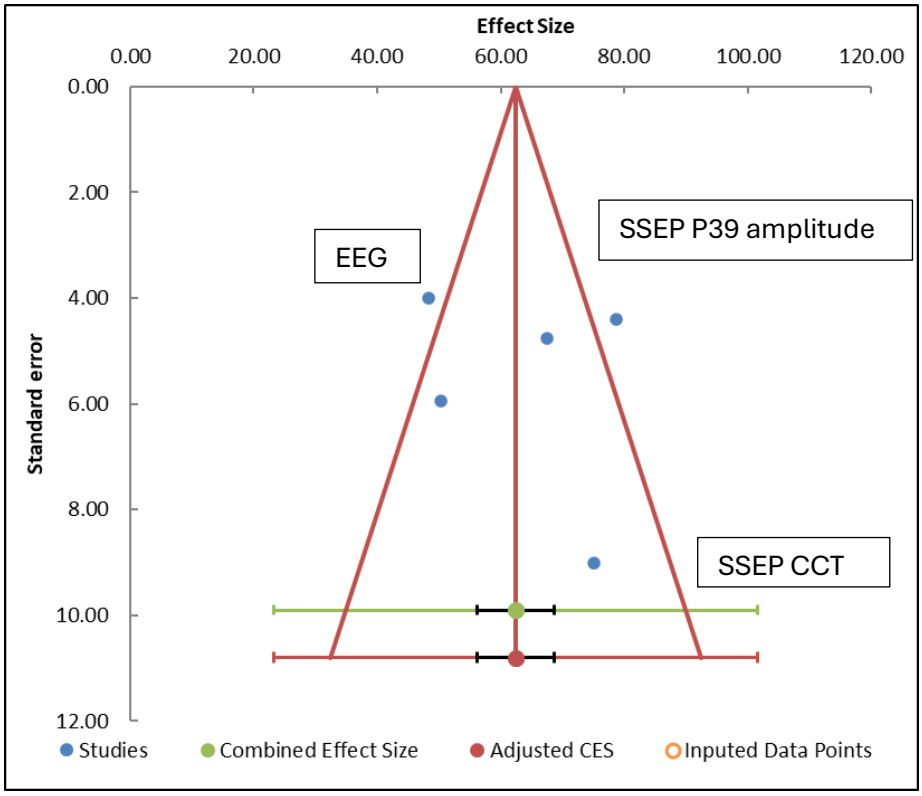


Figure 2.10: Funnel plot used to explore study precision. The least precise measure was SSEP CCT although this was estimated from one study (Sindou et al., 2003). The study closest to the mean effect size was Poláček et al., (2007) representing the most precise.

The EEG study from Goudman et al., (2020) had the smallest standard error value but fell outside the 95% confidence interval suggesting heterogeneity. A Galbraith plot was also used to visualise the outliers in the effect sizes (Figure 2.11).

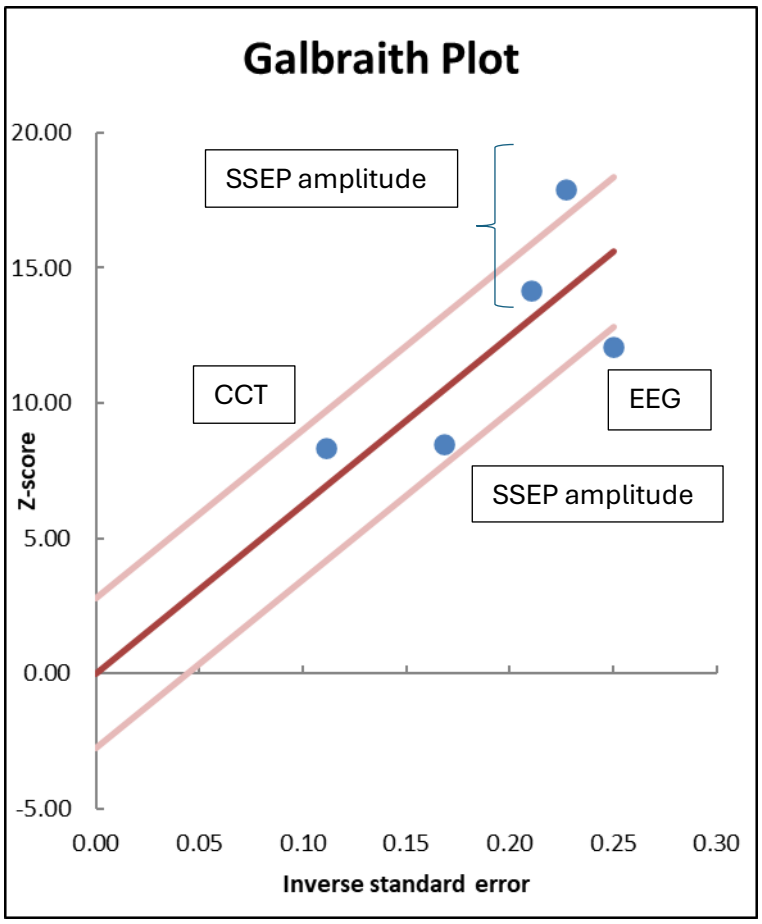


Figure 2.11 Galbraith plot showing Pain relief effect size outliers. The two outliers in the effect sizes were De Andrade et al., (2010) and Goudman et al., (2020). Poláček et al., (2007) was closest to the combined effect size and Sindou et al., (2003) the least precise with the largest standard error.

There was insufficient numerical data to calculate a theta power ratio as an effect size measure. Out of the five EEG studies included in the scoping review only one study allowed for the calculation of this ratio (Goudman et al., 2020).

2.3.6. SSEP P39 Amplitude Effect Size

P39 amplitude reduction was the most common neurophysiology measure used in reported studies. By comparing the amplitude after SCS to the baseline amplitude an effect size measure was created to evaluate the degree of P39 amplitude reduction in SCS responders, this was displayed as an amplitude ratio percentage decrease.

Four studies reported individual P39 amplitude numerical data that allowed the calculation of an average P39 SSEP amplitude ratio percentage decrease with tonic stimulation. There

was insufficient numerical data to calculate mean P39 amplitude ratios for high frequency or burst stimulation.

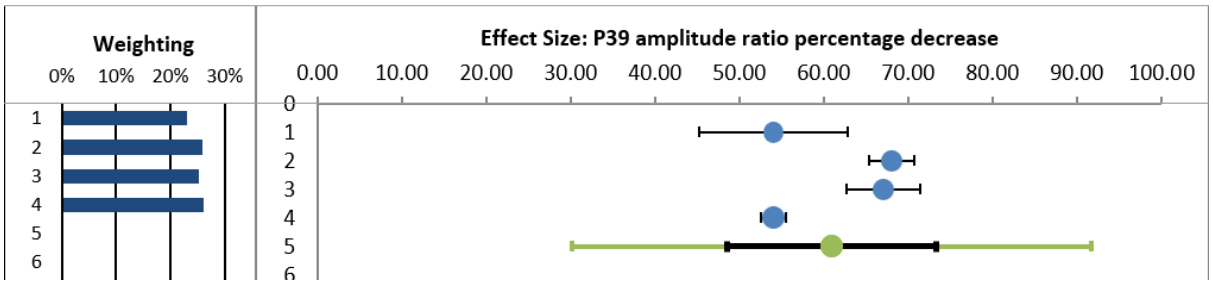


Figure 2.12: Forest plot showing the P39 amplitude ratio percentage decrease for each study and the combined P39 amplitude ratio percentage decrease.

A randomised effect model was used to visualise the four studies on a forest plot (figure 2.12). The combined P39 amplitude ratio reduction percentage was 60.8% with a confidence interval range of 48.45% - 73.30% and standard error of 3.90. The standard error was less than the standard error for percentage pain relief. This is likely the result of the same modality and method being used in calculating the effect size.

There were no subgroups within P39 amplitude ratio percentage decrease effect measure. The moderator effect on SSEP P39 amplitude ratio percentage decrease was investigated using the included studies (Figure 2.13).

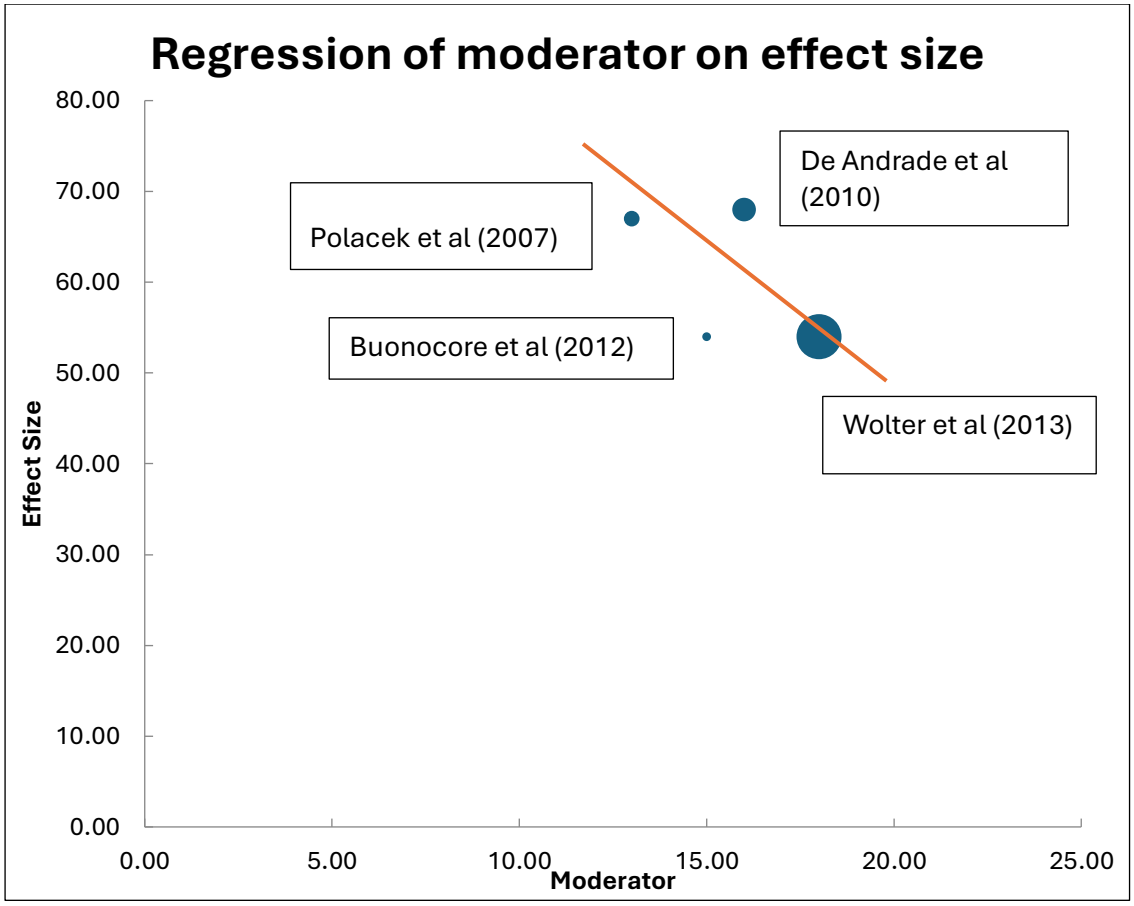


Figure 2.13. Moderator effects on the SSEP P39 amplitude ratio percentage decrease. A negative correlation (-3.22) was observed between SSEP P39 amplitude reduction and moderator effects. The R^2 value was high at 64.4%, a high value favours the moderator effect not being influenced by moderator heterogeneity.

There was no clear pattern with any of the technical parameters reported except for stimulation frequency, decreasing the stimulation frequency from 5 Hz (Wolter et al., 2013) to 2 Hz (De Andrade et al., 2010) increased the SSEP P39 amplitude ratio percentage reduction this may reflect a more stable SSEP response to measure the amplitude reduction from and not a true moderator effect. The study from De Andrade et al., (2010) was twice the size of the study from Wolter et al., (2013) with greater variability (larger standard error).

The study by Wolter et al., (2013) showed the greatest moderator effect with the smallest P39 amplitude reduction. The standard error for this study was very low at 0.66 if this value is true as suggested by the low standard error value then it would suggest that the true mean SSEP P39 amplitude ratio percentage decrease would be closer to 50%.

The moderator analysis favours no moderator effects on the combined data sets due to methodological heterogeneity. A standardised residual histogram was used to explore the distribution of values recorded for each study in relation to the combined effect size (Figure 2.14).

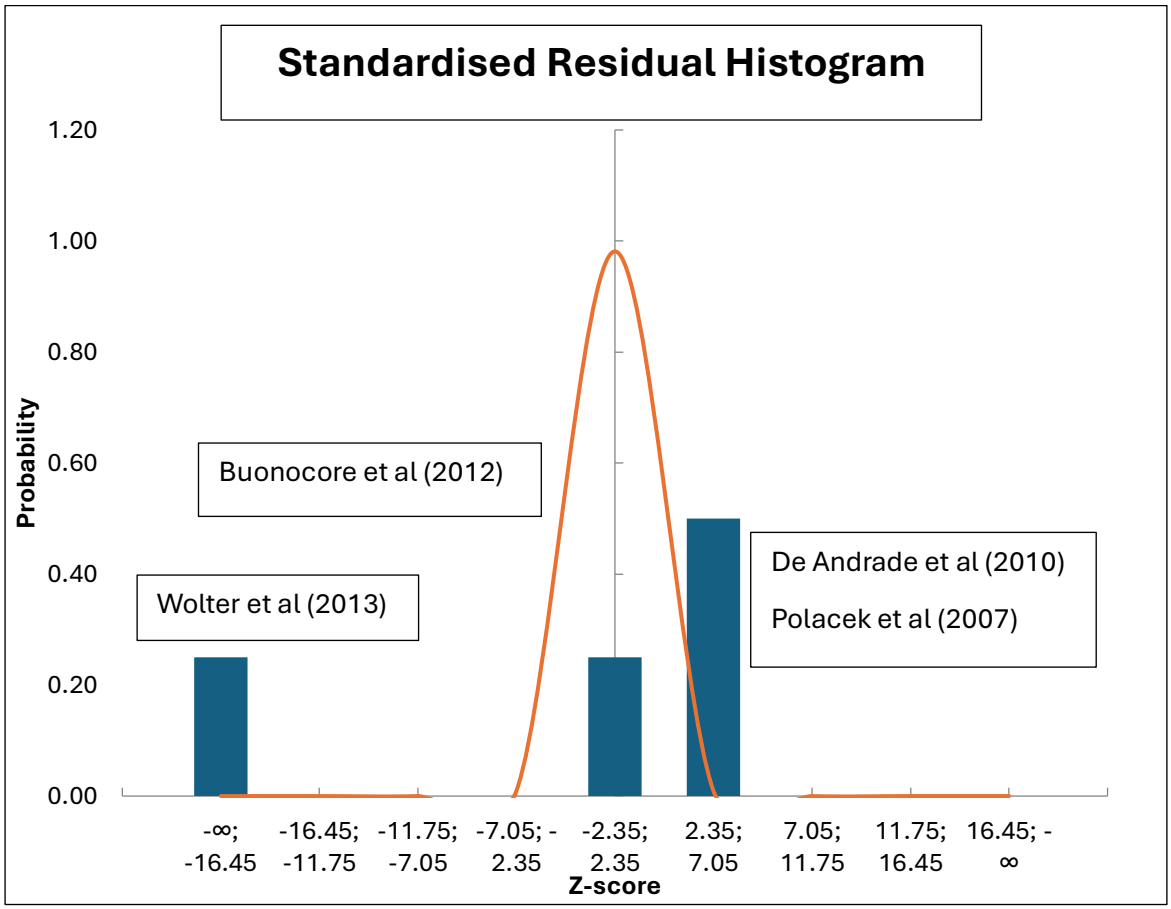


Figure 2.14: Standardised residual histogram for the assessment of outliers for SSEP amplitude limited by a low number of included studies. Wolter et al., (2013) falls significantly outside the normal distribution and significantly differs from the other three studies, this would favour increased heterogeneity from the other three studies.

The standardised residual plot assumes the combined data effects follow a normal distribution. However, the low number of studies included in the analysis makes deviation from normality difficult to interpret.

In contrast the study from Buonocore et al., (2012) had a data set whose standardised residual values fell within the normal distribution model predicted for the combined studies; despite having the largest standard error, this would favour the sample effect size being

inaccurate. The two remaining studies (Poláček et al., 2007; De Andrade et al., 2010), the residual values fell outside of the predicted normal distribution favouring heterogeneity.

A funnel plot was used to evaluate the study in terms of publication bias. However, Publication bias could not be assessed accurately with a funnel plot due to the low number of included studies preventing funnel plot asymmetry to be visualised accurately (Figure 2.15).

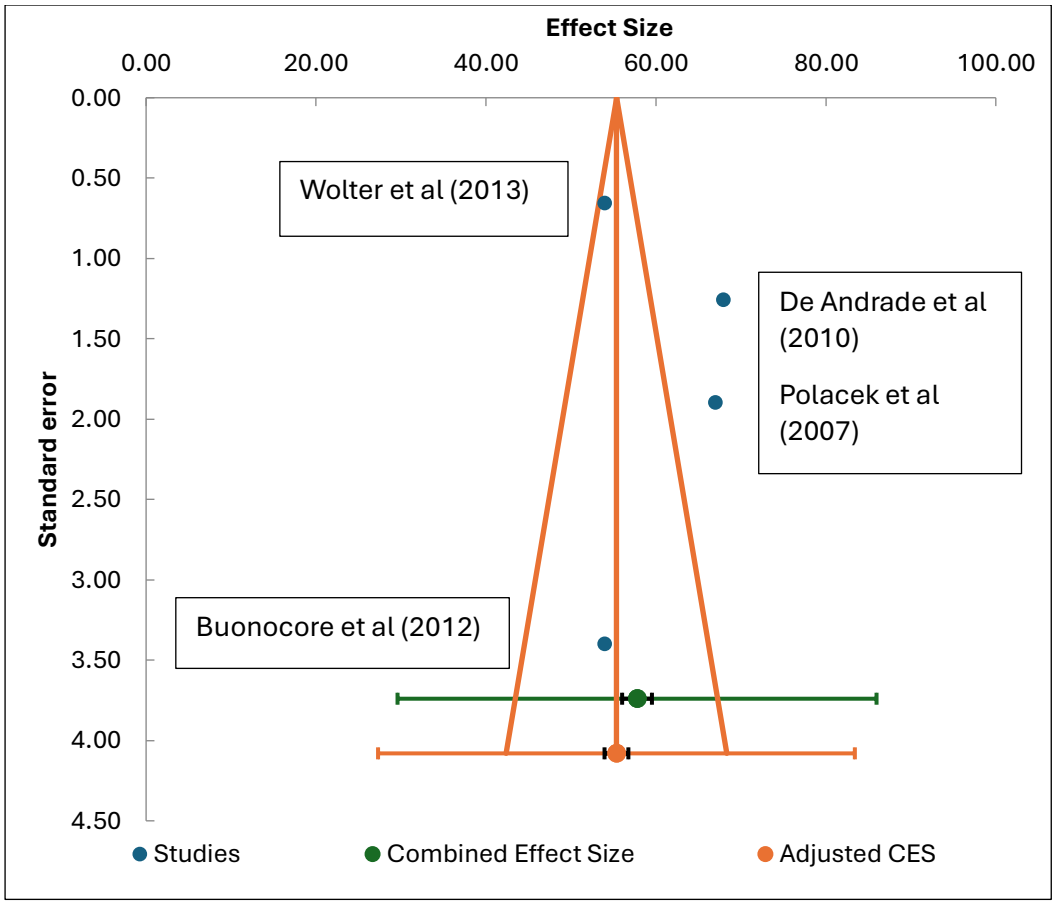
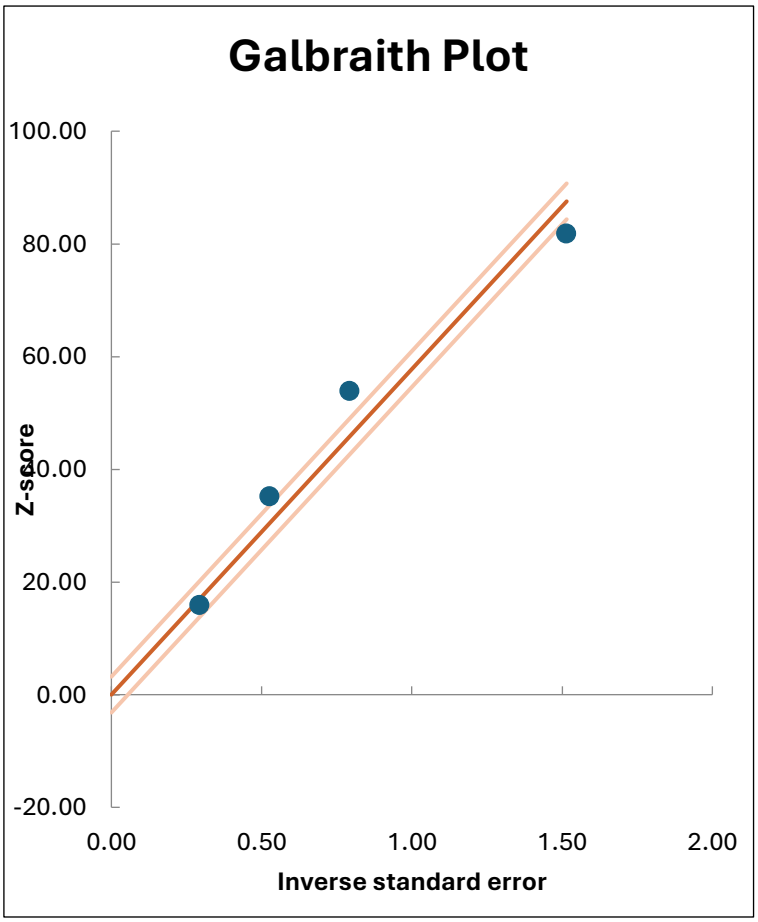


Figure 2.15: Funnel plot used to explore study precision with SSEP amplitude reduction and shows no clear asymmetry, the two studies lying outside the 95% confidence intervals (Poláček et al., 2007; De Andrade et al., 2010) favour large amounts of heterogeneity likely due to methodological bias which exaggerates and elevates the estimated effect size creating subtle asymmetry on the funnel plot towards a higher P39 amplitude ratio percentage decrease.

The other two studies (Buonocore et al., 2012; Wolter et al., 2013) were aligned close to the central line, slightly to the left. Given the small number of studies included in the meta-analysis this is likely due to chance.

The studies outside the 95% confidence intervals lines (Poláček et al., 2007; De Andrade et al., 2010) favour a larger effect size that is significantly different from the combined estimated sample mean effect size and more likely to be an inaccurate estimate for the true population mean.



The study from Wolter et al., (2013) occupied the top of the funnel plot close to the central estimated effect size. This finding would favour high precision, the low standard error is in keeping with the individual SSEP amplitude values being tightly clustered around the sample mean SSEP amplitude reduction ratio value and an indicator of the true population mean. In contrast the study from Buonocore et al., (2012) occupied the lower portion of the funnel plot indicating low precision, with individual amplitude values being far more spread out around the sample mean.

A Galbraith plot was used to look for outliers in the combined effect size (Figure 2.16). Like the funnel plot only the study from Buonocore et al., (2012) fell between the 95% interval lines and this study had the greatest standard error. The most precise study from Wolter et al., (2013) fell outside the 95% interval lines suggesting that the study values were different than over 95% of studies. The study from De Andrade et al., (2010) showed a lower standard error and fell outside 95% of predicted studies as did the study from Poláček et al., (2007).

Wolter et al (2013)

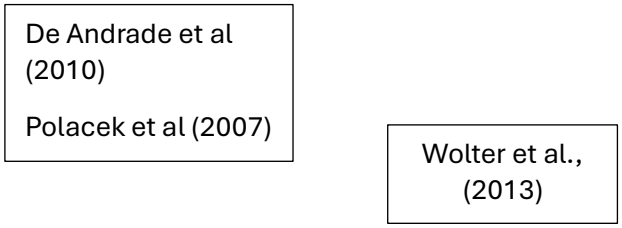


Figure 2.16: Galbraith plot showing SSEP amplitude reduction effect size outliers. The study from Wolter et al., (2013) was significantly different from the other studies included in the group with the smallest standard error. The study from Buonocore et al., (2012) had the greatest standard error and was the smallest study.

2.4. Discussion:

This scoping review identified fourteen primary prospective case series or cases studies. The studies included were of a poor to moderate study design and at risk of moderate to high levels of bias. The Research and planning Consultants, (2022) group reported similar quality issue in the literature for SCS, arguing that there is insufficient high-quality evidence to recommend SCS in patients who have not had lower back surgery prior to the onset of their pain. They cite moderate to high-risk bias as reasons for not recommending SCS with a lack of control data for comparison and studies tending to be short term case series, consisting of small sample sizes, without any long-term follow up. The fourteen studies showed heterogeneity in both clinical and methodological study characteristics, with many study characteristics not reported making comparison between studies and synthesis difficult.

2.4.1 Subjective measures of pain

The meta-analysis and scoping review identified three subjective measures for pain that showed sufficient evidence in the literature to support using them in the assessment of chronic lower back pain and SCS. These were VAS, Pain Detect and ODI.

The VAS is a unidimensional measure of pain intensity and consists of a numeric scale usually from 0-10 with 0 being no pain and 10 being the worst pain imaginable. Patients assign a grade to their perception of pain experienced using this scale. VAS and other numeric pain scales are the "gold standard" in pain related research (Aicher et al., 2012; Begum et al., 2019; Bendinger and Plunkett, 2016; De Andrade et al., 2010; Goudman et al., 2020; Niso et al., 2021; Poláček et al., 2007; Telkes et al., 2020 and Wolter et al., 2013). The VAS design is to measure pain intensity in acute nociceptive pain with greater sensitivity than other numeric scales for analysing treatment effects (Aicher et al., 2012; Begum et al., 2019). The limitation to the VAS is that 7%-11% of people have been reported to have trouble scoring their pain using VAS (Aicher et al., 2012; Begum et al., 2019). This may be due to the challenge of understanding, particularly in the elderly, patients in impaired comprehension post-anaesthesia, or those with language barriers, or poor verbal fluency and cognition. VAS is poor at comparing changes in pain over time, especially small changes, or differentiating between multiple painful regions unless there are multiple VAS scores reported (Aicher et al., 2012; Begum et al., 2019 and Goudman et al., 2020). When patients report multiple regions

of pain, patients may continue to score pain high on VAS despite pain relief in another area or that changes in pain are so small that it is hard to differentiate. This means VAS may have low sensitivity to small changes or multi-regional pain and the development of more sensitive and nuanced tools may be useful in these patients. FBSS patients frequently present with both lower back pain and lower limb leg pain. In SCS trials VAS scores are further complicated by post-operative implantation pain that can take several days or even weeks to subside giving a false representation of therapeutic effects experienced. There is a need in SCS trials to differentiate between back and leg pain in determining therapeutic effects. Goudman et al., (2020) were the only authors to report two VAS scores differentiating between back and leg pain. This raises questions about reliability of VAS scores being reported by groups not differentiating between back or leg pain. The evaluation of therapeutic effects on symptomatic leg pain would be more beneficial in a SCS trial clinically due to post implantation effects and this is an area that needs to be developed.

Despite these limitations, VAS has good test-retest reliability and validity over other numeric pain scales used in pain management. VAS have been reported to have moderate to strong correlation with pain intensity (Aicher et al., 2012; Begum et al., 2019 and Goudman et al., 2020). In chronic pain studies numeric scales of 10 points have been shown to provide sufficient level of discrimination for pain severity.

Begum et al., (2019) recommends VAS to be reported as a ratio scale when used to assess treatments, allowing the calculation of percentage pain relief. VAS scores after treatment can be compared to VAS scores at baseline. VAS ratios that show >50% pain relief can be classified as responders and those with <50% pain relief as non-responders. The studies reviewed tended to favour reporting VAS as responders (De Andrade et al., 2010; Goudman et al., 2020; Niso et al., 2021; Poláček et al., 2007; Sindou et al., 2003).

Significant VAS score reduction was associated with the inhibition of cortical activity in both EEG and SSEP studies (De Andrade et al., 2010; Goudman et al., 2020 Poláček et al., 2007). The single EEG study (Goudman et al., 2020), observed cortical theta power inhibition across all electrodes with a reduction in VAS leg scores. No spatial patterns were discussed as to the regions associated with greatest theta power inhibition. The SSEP studies favour inhibition over the somatosensory cortex relating to the legs (De Andrade et al., 2010; Poláček et al., 2007). This is evidence of a bottom-up mechanism in support of increased lateral

spinothalamic afferent activation with chronic pain and subsequent inhibition with tonic stimulation. Significant VAS score reduction was associated with more pronounced SSEP P39 amplitude reduction in patients with a mixed pain profile observed in FBSS patients than typical neuropathic pain or mechanical related lower back pain profiles (De Andrade et al., 2010). The evidence presented suggests that VAS is an adequate subjective measure for measuring FBSS chronic leg pain intensity and lateral spinothalamic pain processing.

The Pain Detect questionnaire is a more accurate measure of acute post-surgical neuropathic lower back pain (Bendinger and Plunkett, 2016; Freynhagen et al., 2006). The original intended use for the Pain Detect questionnaire was to differentiate neuropathic lower back pain from mechanical nociceptive lower back pain (Freynhagen et al., 2006). The Pain Detect questionnaire is a simple and reliable screening tool designed to predict the likelihood of a neuropathic pain component in chronic pain (Bendinger and Plunkett, 2016; Freynhagen et al., 2006) and may be more suitable for evaluating chronic pain in conditions like FBSS. The Pain Detect questionnaire has a high sensitivity (84%) and high specificity (84%), indicating that this test was good at identifying people with neuropathic pain and those without neuropathic pain (Freynhagen et al., 2006; Bendinger and Plunkett, (2016). Pain Detect shows good sensitivity to treatment effects and measures severity of neuropathic pain allowing for small and large changes in pain to be more easily assessed than the VAS. A lower specificity of 55% has been reported in one study by Timmerman et al., (2018) who advises caution when only using Pain Detect in chronic pain patients and this may be one reason for the low number of studies identified in the scoping review using Pain Detect.

The Pain Detect questionnaire generates Pain Detect scores that are classified into nociceptive pain (0-12), associated with average VAS scores of ≤5 and neuropathic pain scores >19 associated with mean VAS scores of ≥6. Higher Pain Detect scores are associated with higher VAS scores and neuropathic pain. Lower Pain Detect scores were associated with lower VAS scores and nociceptive pain. This would suggest that responders with VAS scores ≤5 are associated with nociceptive pain and that pain relief because of SCS results in a transition from neuropathic pain to nociceptive pain. Despite Pain Detect appearing to be better suited to study chronic pain in FBSS only one study used Pain Detect to quantify pain (Hewitt et al., 2023).

Hewitt et al., (2023) used this as a neuropathy pain scale and observed a significant reduction in neuropathic pain with tonic SCS related suppression of Aβ fibres. They observed raised theta EEG power over the somatosensory, prefrontal and anterior cingulate brain regions at baseline in association with raised neuropathic pain scores. Tonic SCS was observed to reduce theta power over the somatosensory cortex with a reduction of somatosensory tactile processing with paraesthesia. This evidence favours a bottom-up mechanism involving the lateral spinothalamic pathway and supports the Gate Controlled Theory for tonic SCS. The baseline profiles reported in this study are particularly interesting and may suggest a potential signature for neuropathic pain in the theta frequency band and warrant further study.

The Oswestry disability index (ODI) is the most common outcome measure for post operative lower back pain assessing the quality of daily living and offering an indication of disability. ODI scores are displayed as a percentage with higher scores, indicating more severe disability. In the surgical community ODI is the gold standard for measuring disability in chronic lower back pain and is considered to be an easy, reliable tool for assessing lower back pain related disability for patient management (Mehra et al., 2008; Telkes et al., 2020 and Yates and Shastri-Hurst, 2017). The ODI is used to assess both acute and chronic lower back pain conditions with high test-retest reliability to assess intervention effectiveness by comparing ODI scores after intervention to baseline ODI scores. The ODI assessment consists of 10 domains which include pain intensity, personal care, lifting, working, sitting, standing, sleeping, sex life, social life and travelling. In the reviewed FBSS studies only one group used ODI scores (Telkes et al., 2020) in their evaluation. Telkes et al., (2020) consisted of a neurosurgical team carrying out their study under intra-operative conditions and likely use ODI in their clinical practice. They reported significant reduction in ODI scores with an increase in alpha EEG power over the primary somatosensory cortex and prefrontal regions with both tonic and high frequency SCS. This finding also favours bottom-up mechanism involving the lateral spinothalamic pathway and is in keeping with using ODI scores as a subjective measure in FBSS studies.

Other subjective pain measures identified in the scoping review were the McGill Pain questionnaire, pain catastrophising questionnaire and central sensitisation inventory. These

subjective measures had limited use and were not associated with significant changes with pain relief (Goudman et al., 2020; Telkes et al., 2020).

The McGill Pain questionnaire is a self-reported questionnaire that assesses the quality and intensity of pain being experienced using 78 words in 20 sections. The questionnaire aims at assessing the sensory, cognitive and emotional components of pain. The McGill Pain questionnaire has been used in lower back pain research and in the evaluation of different pain treatments, despite this their remains insufficient evidence to determine its role in assessing lower back pain in FBSS patients receiving SCS. The McGill Pain questionnaire provides a single measure of both neuropathic pain and non-neuropathic pain, and fails to differentiate between nociceptive, mixed and neuropathic pain. Furthermore, the McGill Pain questionnaire fails to consider some of the classical neuropathic pain features reported in FBSS patients and therefore has a role in SCS evaluation like the preferred VAS used in most studies found in the scoping review. Only one study was identified as using the McGill Pain questionnaire (Telkes et al., 2020) as a part of a battery of tests.

The pain catastrophizing questionnaire characterises how individuals experience pain and assesses catastrophic thinking towards pain. The intended use for this questionnaire is general pain in adults. The central sensitisation inventory assessors' symptoms of central sensitisation and has been primarily used in chronic pain central sensitisation syndromes such as fibromyalgia, neck injury and migraine. The pain catastrophizing questionnaire and the central sensitisation inventory favour group analysis, focusing on psychological factors associated with a fear of movements their precision on an individual level is poorly understood making clinical decision making on an individual level difficult. Only two studies used either of these questionnaires in the scoping review to evaluate SCS (Goudman et al., 2020 and Telkes et al., 2020). Both reported medium scores for catastrophising pain and central sensitisation that failed to reduce with pain relief. Both the pain catastrophizing questionnaire and the central sensitisation inventory were of little clinical use in these studies and evidence for the persistence of clinical symptoms associated with central sensitisation.

The scoping review revealed that VAS is the most popular method used in SCS evaluation studies using neurophysiological techniques, largely due to being quick to implement in an evaluation trial allowing pain relief to be calculated. VAS lacks the ability to differentiate between nociceptive, mixed and neuropathic pain, and essential feature for SCS evaluation

and depends upon the pain region being evaluated. The Pain Detect questionnaire in contrast offers a better alternative for SCS trials using numerical scale that differentiates between nociceptive, mixed and neuropathic pain. Pain Detect considers the different pain characteristics of neuropathic pain, pain patterns and location often under reported, an advantage over the more common VAS. Another subjective measure identified as being potentially beneficial in FBSS SCS evaluation was the ODI a common post operative outcome measure used to evaluate lower back surgery. This questionnaire evaluates an individual's quality of life beneficial for clinical decision making in therapeutic evaluation. Combining this triad of subjective questionnaires may prove beneficial in SCS for FBSS patients, allowing pain relief, pain type and therapeutic effect to be evaluated in FBSS patients receiving SCS. The other questionnaires reviewed either lacked individual precision or were comparable to the more favoured VAS which was quicker and easier to implement in clinical practice or SCS evaluation trials.

2.4.2. QEEG power

The scoping review revealed five primary research studies using QEEG absolute power spectral density (absolute power) to evaluate tonic stimulation (Svoboda et al., 2007; Goudman et al., 2020; Telkes et al., 2020; Berwal et al., 2023; Hewitt et al., 2023). In the identified studies absolute power represents the total energy intensity at a certain frequency band with absolute theta power being most often investigated. All five studies used changes in QEEG absolute power to evaluate tonic SCS with significant pain relief in SCS responders. No study compared SCS to non-responders.

In four of the five studies absolute theta power was elevated with chronic pain (Sarnthein et al., 2006; Goudman et al., 2020; Telkes et al., 2020; Berwal et al., 2023) over the prefrontal, somatosensory and parietal cortical areas. This cortical pattern corresponds to primary cortical areas and precuneus of the lateral spinothalamic pathway and surrogate cortical areas relating to the medial spinothalamic pathway (prefrontal cortical regions). This type of pattern would be expected with a bottom-up chronic pain mechanism with activation of both spinothalamic pathways and subsequent thalamocortical dysrhythmia. The baseline patterns reported in all four studies are compelling for a potential baseline signature for chronic pain and are concordant with pain studies for chronic neuropathic lower leg and back pain. It remains unclear whether these spatial patterns in absolute theta power vary

over time, pain severity or pain progression or if they could be used in patient SCS responder selection. None of the studies reviewed commented on baseline patterns or their future utility as a spectral signature.

Two differences were noted in the baseline patterns from the four studies, the magnitude of measurable absolute theta power and their spectral appearance following FFT. Baseline absolute theta power either presented as individual spectral peaks (Telkes et al., 2020; Berwal et al., 2023) or as raised absolute theta power spread across the entire theta band, (Sarnthein et al., 2006; Goudman et al., 2020). The studies with clear individual spectral peaks were undertaken during intraoperative monitoring conditions and may represent anaesthetic effects on the thalamus synchronising the cortex to specific theta frequencies. The studies showing raised absolute theta power spread across the entire theta band (Sarnthein et al., 2006; Goudman et al., 2020) occurred in studies with awake patients. This spectral appearance can be explained by the interaction between low threshold spike (LTS) inhibitory interneurons and excitatory pyramidal neurones during thalamocortical dysrhythmia. These interactions lead to transient synaptic plasticity changes in the network influencing synchronisation (Hayut et al., 2011). There are several activated thalamocortical networks (thalamo-cortico-thalamic, thalamo-reticulo-thalamic and cortico-reticulo-thalamic) that could directly influence the magnitude of absolute theta power measured under this circumstance. It remains unclear which thalamocortical network contributes the most to this spectral appearance. In both studies alpha power was the dominant spectral peak, this can be explained by the patients being awake with their eyes closed.

All five studies reported EEG absolute power changes with significant pain relief with tonic SCS. Three studies described a bottom-up mechanism involving the lateral spinothalamic pathway with subsequent theta absolute power reduction over the somatosensory and parietal cortical network. This was observed in the studies by Goudman et al., (2020) and Berwal et al., (2023) and indirectly by Svoboda et al., (2007). The study by Svoboda et al., (2007) failed to report on the lower frequency spectrum range where theta frequencies are found. However, reviewing the data presented in the paper distinct peak frequencies were noted in the upper portion of the beta bandwidth corresponding to frontal and vertex brain regions. Frequencies analysed started at 20 Hz, preventing analysis of both theta and alpha frequency bands. Absolute beta power (13-25 Hz) changes have been observed in frontal

brain regions in the pain literature due to cortico-cortical inhibition from GABAergic interneurons leading to collateral inhibition of neighbouring cortical areas. Cortical neurones in these areas become over-active firing at the beta range. This mechanism may explain why beta frequencies were found frontally in this study representing an edge effect from the dysfunctional somatosensory cortex. This finding compliment both Goudman et al., (2020) and Berwal et al., (2023) who observed theta power reduction over the somatosensory and parietal cortical network. In all three studies tonic SCS effects can be explained by activated supraspinal circuity in the spinal cord exerting segmental effects on the spinal gate. A bottom-up effect was induced from the spinal level activating the lateral spinothalamic pathway and inhibiting the thalamus, reversing the effects thalamocortical dysrhythmia on the cortex.

In contrast to these findings Telkes et al., (2020) reported that theta absolute power remained unchanged over the somatosensory region. Both Telkes et al., (2020) and Berwal et al., (2023) used intra-operative EEG recordings with patients under general anaesthesia. The impact of anaesthesia induced theta frequencies on either study remains unclear. Anaesthesia induced theta power may have masked any effects on thalamocortical dysrhythmia observed due to SCS in the study by Telkes et al., (2020). The type of anaesthesia used was not reported neither was the depth in either study. The thalamus is a common site for anaesthetic modulation disrupting the thalamocortical network it remains unclear what bias effect this had on either study, however, may explain the lack of responsive absolute theta power observed by Telkes et al., (2020) to tonic SCS.

Telkes et al., (2020) observed in their study an increase in the dominant alpha frequency rather than a decrease in relative theta power. Telkes et al., (2020) used an alpha/theta peak power ratio in their study under intra-operative condition. One criticism of this index in awake patients would be related to the magnitude difference between the dominant alpha peak power and excess relative theta power. Absolute alpha power would mask the smaller absolute theta power changes. Furthermore, log10 scales used to report absolute theta power in the two awake studies would make this index confusing without transformation.

A more reliable index in awake conditions would be a relative theta power ratio which compared absolute theta power at SCS to baseline power. Only one study provided data that allowed a relative theta power ratio to be calculated from their published results (Goudman

et al., 2020). A relative theta power ratio of 0.96 was calculated suggesting only a minimal theta power reduction from baseline. The significance of such a small reduction on pain relief is unclear based on a single study.

The studies reviewed were biased towards tonic SCS a limited number investigated high frequency or burst SCS. In one study (Telkes et al., 2020) high frequency SCS decreased absolute theta power over the central and parietal areas like tonic SCS effects reported in other studies. Telkes et al., (2020) observed in their data absolute theta power reduction to be greater than with tonic SCS. This finding suggests that high frequency SCS may also induce a bottom-up effect activating the lateral spinothalamic pathway and inhibiting the thalamus, reversing the effects thalamocortical dysrhythmia on the cortex. As this is only one study and under intra-operative conditions this evidence is insufficient to confirm this observation and requires further study.

Hewitt et al., (2023) found that burst and tonic stimulation modulated the processing of tactile stimulation. Hewitt et al., (2023) concluded that processing tactile inputs differed between the two stimulation programmes due to the stronger stimulation effects on the dorsal column with tonic stimulation. The effects of burst SCS on absolute theta power and chronic pain remains insufficient.

Percentage pain relief is the most common effect size reported in the literature for SCS studies. However, none of the studies reported the effect size due to SCS as percentage pain relief. Only one study presented raw data that allowed percentage pain relief to be calculated (Goudman et al., 2020). The mean percentage pain relief for Goudman et al., (2020) was calculated to 48.3% and was associated with only a minimum decrease in absolute theta power. Goudman et al., (2020) compared tonic SCS to high dose tonic SCS (500 Hz, 0.5 ms) and found that percentage pain relief with high dose tonic stimulation was 57.8%, showing improved pain relief with tonic SCS delivered at a frequency higher than conventional tonic stimulation. Goudman et al., (2020) was the only study to report VAS scores for both lower back and leg pain in FBSS patients. They found that pain relief changes were significant in the legs and not significant in the lower back for either tonic stimulation programmes.

In summary, absolute theta power was used to investigate chronic pain. Relative theta power ratios were used to evaluate absolute theta power changes from baseline. Despite this there

remains insufficient primary research evidence to support the argument that percentage pain relief was moderated by EEG theta power reduction. There was insufficient primary research evidence to observe the percentage pain relief effects for high frequency and burst SCS. There was insufficient primary research evidence to determine if relative theta power could differentiate between responders and non-responders during SCS.

2.4.3. Clinical bias impact on QEEG power measures

This meta-analysis revealed that the included studies were heterogenous with moderate to high levels of clinical and methodological heterogeneity and bias. QEEG theta and alpha power as a measure of pain were at high risk of clinical bias from both sleepiness, anxiety, depression and medication effects.

2.4.3.1 Sleepiness

In spinal cord injury patients, chronic neuropathic pain disrupts sleep patterns and other homeostatic mechanisms. Patients suffering from chronic pain are at risk of experiencing drowsiness during a daytime eyes closed EEG assessment (Jensen and Finnerup, 2014 and Sarnthein et al., 2006). Drowsiness has several effects on the EEG including alpha frequency attenuation, appearance of slow waves which includes theta activity and an anterior frontal alpha frequency shift (Jensen and Finnerup, 2014 and Sarnthein et al., 2006). Sleepiness was poorly reported in the scoping review. Future recommendations include evaluating sleep quality and undertaking trials in the morning to standardise bias from circadian rhythms (Sarnthein et al., 2006). Similar sleep bias has been found in neurogenic pain patients thalamotomy patients (Sarnthein et al., 2006). Drowsiness was evaluated using vigilance testing and lateral eye movements monitored in the live EEG, they also excluded patients with a known sleep disorder. These are sensible recommendations for future FBSS studies.

In the present scoping review, no QEEG study evaluated sleep quality as a bias effect on theta and alpha relative power. The Epworth sleepiness scale evaluates the degree of excessive sleepiness and is a short questionnaire that is inexpensive, widely available and commonly used and would be ideal for evaluating sleep quality in chronic pain patients undergoing SCS assessment trials that use QEEG measures. The questionnaire scores range from 0 indicating no sleepiness to 24 indicating a high level of sleepiness (Scharf, 2022). The questionnaire has been validated in a range of sleep disorders. In healthy controls the

Epworth scale has good test-retest reliability. The test-retest reliability decreases with worsening levels of sleepiness. Scharf, (2022) recommends for clinical practice a cut off ≥11 as normal to account for the increasing test-retest variability with excessive sleepiness. Implementation in future studies is recommended.

2.4.3.2 Anxiety and depression

Anxiety and depression are also associated with chronic pain and associated with an anterior shift in alpha activity over the frontal regions (de Aguiar Neto and Rosa, 2019). Anxiety EEG signatures are associated with a decrease in alpha power and an increase in beta power over the frontal areas and can take on a similar appearance to the frontal asymmetrical EEG signature associated with depression. Frontal alpha power asymmetry with increased alpha over the left hemisphere is a strong candidate for an EEG biomarker for depression and is associated with a lack of approach behaviour (approach-withdraw model). Both anxiety and depression appear to show gender differences, with frontal alpha asymmetries being more prominent in female patients. De Aguiar Neto and Rosa, (2019) acknowledge that patients displaying EEG biomarkers associated with anxiety or depression may also have disrupted sleep patterns, especially if related to chronic pain where frontal alpha power and alpha power attenuation signatures may be present and related to sleepiness and not anxiety or depression.

This would imply out of the two main EEG signatures for chronic pain identified in the scoping review, alpha power is at greater risk of bias from sleepiness, anxiety and depression. In the present scoping review, no studies evaluated anxiety and only one study used the Becks depression inventory to evaluate depression (Telkes et al., 2020) and this score was not commented on in the results or discussion.

2.4.3.3 Medication

Medication can influence theta and alpha power values. A limited number of studies included reported medication as a part of the study characteristics. Studies that included medication reported patients using opioids, non-opioids, tricyclic anti-depressants as a co-analgesic medication and antiepileptic medications. Sindou et al., (2003) listed a range of medications used in the treatment of chronic lower back pain. These included anticonvulsant drugs (i.e., clonazepam, carbamazepine, gabapentin), tricyclic antidepressants (i.e.,

clomipramine, amitriptyline), weak opioids and nonopioids (i.e. paracetamol, propoxyphene, codeine).

Opioids tend to increase alpha activity over the frontal and central regions (Thürauf et al., 1996; Lelic et al., 2021). Thürauf et al., (1996) reported that tramadol, a common opioid used to treat neuropathic pain, increased alpha power over the frontal regions and decreased alpha power over the vertex and parietal areas. Lelic et al., (2021) showed that the changes in alpha power for morphine occurred more centrally. Lelic et al., (2021) observed morphine specific changes over the right side of the brain, leading to frontal alpha asymmetry, the explanation for this asymmetry is unknown. Lelic et al., (2021) considers these to be QEEG biomarkers for opioid related analgesia. They added that gender differences for mechanisms in analgesia and pain are poorly understood, suggesting that different opioids may be more effective in one gender than another. Individual variation has been linked to genetic variation and sexual dimorphism (Lelic et al., 2021; Packiasabapathy and Sadhasivam, 2018). Sex hormones are a strong candidate testosterone decreases pain sensitivity whilst oestrogen and progesterone have been shown to increase and decrease pain sensitivity. The stage of the menstrual cycle is also considered to be a factor with females in the post ovulatory luteal phase showing a greater sensitivity to pain than in the follicular phase (Packiasabapathy and Sadhasivam, 2018). Furthermore, sexual dimorphism has been demonstrated in the descending pain modulating system through opioid MOR+ receptors expression and binding at the PAG (Lelic et al., 2021; Loyd and Murphy, 2014; Mallampalli and Carter, 2014; Packiasabapathy and Sadhasivam, 2018). Variability in both opioid and pain sensitivity makes individual therapeutic pain relief challenging in clinical practice and will contribute to individual varying responses seen with SCS. This may be one explanation for suboptimal non-responders. Drowsiness for example is a common side effect in both males and females with opioid use however the potency of drowsiness may vary between genders. Sleep potency has been shown in women to vary with menses, pregnancy, lactation and menopause (Mallampalli and Carter, 2014) all of which have been shown to be associated with variability in opioid and pain sensitivity (Packiasabapathy and Sadhasivam, 2018). Opioids in some individuals can induce excess theta and delta activity particularly patients taking tramadol (Thürauf et al., 1996).

Tricyclic Antidepressants, when used as co-analgesic medication, can augment both theta and beta activity whilst anticonvulsant medications can slow dominant alpha peak frequencies and increase theta relative power. Pregabalin, gabapentin and carbamazepine when used to treat chronic pain, slow the EEG most marked over the theta frequency band due to reduced NMDA receptor activation (Graversen et al., 2012; Höller et al., 2018). This in turn dampens the excitatory effects of glutamate. Slowing of the peak alpha frequency on QEEG can also accompany changes in theta power. This pharmacological EEG bias may obscure the treatment effects of SCS when using theta power as an EEG biomarker. Non-opioids show less effects from this list however propoxyphene a non-opioid also lists drowsiness as a possible side effect.

In the scoping review on two identified EEG studies (Goudman et al., 2020 and Svoboda et al., 2007) included medication in their study characteristics. Neither study discussed medication effects on their data.

2.4.4. Lower limb SSEP studies.

This scoping review identified nine primary research studies that used lower limb SSEP short or long latency responses with tonic SCS (Theuvenet et al., 1999; Sindou et al., 2003; Poláček et al., 2007; De Andrade et al., 2010; Buonocore et al., 2012; Wolter et al., 2013; Buonocore and DeMartini, 2016; Falowski, 2019; Niso et al., 2021).

Six of the nine studies investigated lower limb SSEP P39 amplitudes in the evaluation of SCS, Poláček et al., (2007); De Andrade et al., (2010); Buonocore et al., (2012); Wolter et al., (2013); Buonocore and DeMartini, (2016) and Falowski, (2019) all observed SSEP P39 amplitude reduction from baseline with tonic SCS. There was good agreement between studies for SSEP stimulation methodology with all six studies stimulating the posterior tibial nerve. The recording methodology was under reported and likely the source of heterogeneity observed between study groups in the meta-analysis.

Two competing hypotheses have been suggested to explain the observed SSEP amplitude reduction with tonic SCS. The first hypothesis is based on intra-operative mapping evidence (Buonocore et al., 2012; Roth et al., 2015). This hypothesis assumes that SSEP amplitude reduction is a product of collision between the ascending orthodromic SSEP volley and descending antidromic tonic stimulation volley. Collision between these two volleys results in

interference and cancellation of some of the stimulation effects. Such collisions have been shown to manifest as a reduction in ipsilateral SSEP amplitude. Further antidromic evidence from Buonocore et al., (2008) supports this hypothesis in their study antidromic sensory nerve action potentials (SNAP) were from the sural nerve when two contacts of a spinal cord stimulator were used to stimulate the dorsal columns of the spinal cord. Tonic SCS at 10 Hz was used. They found that antidromic stimulation through the implanted spinal cord stimulator activated dorsal column neurones of different sizes and conduction velocities. The SNAP responses were of low amplitude due to the number of activated fibres and distance travelled by the SNAP responses. SSEP P39 amplitude reduction with tonic stimulation was reported as temporary by Buonocore et al., (2012) and Buonocore and DeMartini, (2016) when tonic SCS was turned off.

The second hypothesis is based on a decrease in cortical processing in the primary somatosensory cortex as a direct result of a reduction in somatosensory afferent input at the segmental level, reducing the P39 amplitude (Poláček et al., 2007; De Andrade et al., 2010). Somatosensory modulation has also been demonstrated in the secondary somatosensory cortex (De Andrade et al., 2010) and at the sensory thalamus (Poláček et al., 2007) which has been shown to significantly reduce pain when stimulated directly in FBSS patients. Somatosensory processing during tonic SCS may be responsible for the reduction in allodynia seen in a minority of FBSS patients (De Andrade et al., 2010). Further evidence to support altered somatosensory cortical processing have been observed with the prolonged effects of tonic SCS outlasting the stimulator when turned off. A dose dependent relationship was observed by Wolter et al., (2013) when compared to the transient effects of a TENs machine.

I suspect that both hypothesise are correct with volley cancellation representing the initial effects of tonic stimulation and alterations in somatosensory cortical processing more prolonged effects. The dose dependent relationship suggests that tonic stimulation has a wash in / wash out period beyond that of simply stopping stimulation. This should be included in future study designs for investigating tonic stimulation.

Four studies allowed percentage pain relief to be calculated for tonic stimulation with P39 amplitude reduction resulting in a synthesised pain relief of 60%. However, due to the heterogeneity observed between study groups this synthesised value is likely unreliable. No

study reviewed reported a correlation between pain relief and SSEP amplitude reduction with studies biased to reporting responders.

Long latency SSEP responses were studied by Theuvenet et al., (1999); Poláček et al., (2007) and Niso et al., (2021). In the three studies reviewed there was no agreement on which components to use in SCS evaluation. All three studies agree that SSEP long latency responses show amplitude reduction with tonic stimulation and pain relief. The evidence from the reviewed studies suggests that reduction in long latency SSEP studies is related to somatosensory cortical processing across distant networks.

SSEP amplitude reduction was observed by Poláček et al., (2007) to be greater in short latency responses when compared to long latency SSEP responses. This finding suggests that long latency SSEP responses represent altered cortical processing at more distant cortical regions. Using source localisation and dipole analysis Poláček et al., (2007) identified long latency SSEP responses associated with the contralateral secondary somatosensory cortex, ipsilateral secondary somatosensory cortex and mid-cingulate cortex. Poláček et al., (2007) concluded that tonic stimulation decreases heightened somatosensory cortical processing across the entire somatosensory network (primary and secondary somatosensory cortices and mid-cingulate cortex).

This scoping review revealed that high frequency and burst SCS with SSEP amplitude reduction is under studied.

Only one study explored High frequency SCS, Buonocore and DeMartini, (2016) who in a single case study reported that high frequency sub threshold stimulation (10 kHz, 0.2 ms) inhibited lower limb SSEP early responses to the same degree as tonic stimulation at 60 Hz, 200 Hz and 500 Hz. In all stimulation conditions SSEPs were completely inhibited. Buonocore and DeMartini, (2016) argue that a conduction block was created which suppressed the SSEP response with high frequency SCS. This was reversible when the stimulator was turned off. In the tonic stimulation 60 Hz condition the intensity was set below the paraesthesia threshold suggesting that the conduction block due to orthodromic/antidromic collision occurred at a dorsal column level close to stimulation.

Burst stimulation was explored by Niso et al., (2021) using long latency SSEP responses. They found that both tonic and burst SCS stimulation long latency responses at 300 ms reduced in amplitude when participants were instructed to not pay attention to the stimulus.

Only one study evaluated all three SCS programmes with SSEPs (Falowski, 2019) however this evaluation was observational didn't compare all three stimulation programmes during a single trial. Instead, different stimulators were evaluated, the types of stimulation used varied with a bias towards tonic and burst stimulation and stimulator sales and added little evidence to SCS scientific literature.

One study used a different SSEP measure, (Sindou et al., 2003), central conduction time. Sindou et al., (2003) followed 95 patients with chronic pain who received tonic SCS of these, 24 patients had FBSS. From the group of 95 patients, 26 patients with poor pain relief (VAS score <50% pain reduction) at 18.8 months had abnormal central conduction times and subsequent delayed early response (P39) latencies prior to tonic SCS. In patients with normal central conduction times and normal early response (P39) latencies, 75.4% had successful pain relief with tonic SCS. Sindou et al., (2003) concluded that patients with either a delayed central conduction time or delayed P39 latency should not be considered for tonic SCS. Although not directly implied this group of patients would represent tonic SCS non-responder. The implied result here is that patients with normal central conduction time and normal P39 latency have a good chance of being tonic stimulation responders. Here Sindou et al., (2003) has used central conduction time to select tonic SCS responders and argues that this group to not require a percutaneous trial before permanent implantation.

The main criticism of the study by Sindou et al., (2003) is that the patients included were heterogeneous consisting of a mixture of different chronic pain disorders many of which had severe peripheral nerve damage which included nerve trauma, amputation and spinal root avulsions. Twenty-four (25%) of the patients included in the study were FBSS patients with lumbosacral rhizopathies representing the most severe FBSS patients and atypical. Patients either had complete or incomplete peripheral nerve, dorsal root or spinal cord damage. Furthermore, it was unclear what latency value was considered as pathologically abnormal by Sindou et al., (2003) as latencies were dichotomised into normal and abnormal in the study without a clear definition of the cut off latency. Patients with lumbosacral rhizopathy would likely have grossly delayed SSEPs, pathologically reduced amplitudes or absent cortical

waveforms. Given the severity of somatosensory pathway damage in this FBSS subgroup I agree this group of patients would not be suitable for SCS and be non-responders. However typical FBSS patients with mild to moderate somatosensory pathology may well show a different result. Further study to confirm whether SSEP latency can predict SCS responders and non-responders in FBSS patients with mild to moderate pathology is recommended.

2.4.5. Other Neurophysiology objective measures

Only one study in the scoping by De Andrade et al., (2010) reviewed other neurophysiology objective measures. They studied the plantar sympathetic skin response (SSR), F-waves, soleus H-reflex, quantitative sensory testing (QST) and the nociceptive flexor reflex. The SSR increased in amplitude and shortened in latency. In contrast, the Soleus H-reflex reduced in amplitude and F-wave studies were variable showing a variety of changes which included reduction in amplitude, shortening of F-wave latency and increased F-wave persistence. The nociceptive flexor reflex attenuated and increased the reflex threshold. De Andrade et al., (2010) suggested that the effects seen on soleus H-reflex and nociceptive flexor reflex were inhibitory effects on the spinal cord due to tonic SCS. The observations from F-wave studies would imply that inhibition is at a segmental level, presynaptic to the motor neurones. Whilst the SSR findings were in keeping with sympathetic cholinergic mechanisms (sweat glands) being facilitated rather adrenergic pathways which are inhibited. They suggest that this is likely to be a compensatory mechanism. Quantitative sensory testing increased in sensory (temperature and pressure) and pain tolerance thresholds primarily with dorsal root ganglion stimulation (De Andrade et al., 2010; Sankarasubramanian et al., 2021; Plantaz et al., 2022). In chronic pain patients the reduction of chronic pain due to an increase in pain tolerance is thought to represent an inhibition of Aδ and C-fibres.

There remains insufficient evidence available to evaluate the role of plantar SSR, F-waves, soleus H-reflex, quantitative sensory testing (QST) and the nociceptive flexor reflex as neurophysiology biomarkers in SCS for lower back pain and the identification of responders from non-responders across the different SCS programmes.

2.5. Meta-analysis summary of findings

The studies included in the meta-synthesis (Sindou et al., 2003; Poláček et al., 2007; De Andrade et al., 2010; Wolter et al., 2013; Goudman et al., 2020) were heterogeneous in both

clinical and methodological heterogeneity with a large proportion of unexplained heterogeneity between studies (88%). The combined moderator effect of the neurophysiological measures on the effect size showed a negative correlation limited by inter-study heterogeneity. There was no significant moderator effects noted from the technical characteristics.

The standardised residual plot, funnel plot and Galbraith plot all agreed that there was significant heterogeneity that was at risk of publication bias however the low study sample size prevented an accurate analysis with effects at risk of occurring by chance. The individual studies differed significantly in terms of standard error, effect size, and accuracy, and residual values for most studies failed to follow a normal distribution. The least precise neurophysiology measure was SSEP central conduction time and most precise the SSEP amplitude measure. Only one study included used QEEG theta power, this study fell outside the normal distribution.

The meta-analysis was used to synthesise a combined percentage pain relief from QEEG and SSEP studies included in the scoping review. Five studies were used in the meta-synthesis producing a synthesised pain relief of 64% for tonic stimulation with the prediction interval much larger than the confidence interval. The meta-analysis revealed extensive heterogeneity existed between each study. In summary there was insufficient primary research evidence to evaluate percentage pain relief using both QEEG power and SSEP amplitude as an accurate effect size measure for tonic SCS in the treatment of lower back pain. The limited studies available were subject to large amounts of inter-study clinical, methodological and unexplained heterogeneity.

There was insufficient primary research numerical data available in the literature to evaluate percentage pain relief using both QEEG power and SSEP amplitude as an effect size measure for high frequency or burst SCS in the treatment of lower back pain. There was insufficient primary research numerical data available in the literature to evaluate theta power ratio as an effect size measure for tonic, high frequency or burst SCS in the treatment of lower back pain.

The meta-analysis indicated that QEEG theta and alpha power measures may be promising biomarkers for chronic pain, currently there remains insufficient evidence to determine their

usefulness in the evaluation of different spinal cord stimulator programmes (tonic, high frequency and burst) or their ability to differentiate between responders and non-responders. This warrants further study to evaluate how useful these biomarkers are in clinical practice.

There is insufficient evidence on how anxiety, depression, medication and sleepiness effect QEEG power biomarkers in the evaluation of chronic pain and spinal cord stimulator therapy in clinical practice. It would appear from the literature that alpha power is at a greater risk of bias from sleepiness and medication than theta power.

There is limited evidence to support using lower limb SSEP early response (P37, P39 or P40) amplitude as a biomarker in tonic stimulation evaluation. SSEP early response amplitudes reduce in varying degrees with tonic stimulation, and it remains unclear if this is related to volley collision or changes in thalamocortical physiology at the somatosensory cortex. The mechanism responsible is thought to be either supraspinal or segmental. The available evidence favours a collision between the inhibitory antidromic conduction block caused by tonic stimulation and the ascending orthodromic SSEP volley. The pain relief that follows may lead to transient plasticity changes reducing thalamocortical dysrhythmia and cortical plasticity at the somatosensory cortex. Tonic stimulation may have dose dependent relationship with stimulation up to 60 Hz resulting in transient plasticity changes at the cortex that might outlast the stimulus and result in a prolonged wash in and wash out period. Future prospective studies should consider the wash in/out periods and the effects on long term follow up. There is insufficient evidence available to evaluate the role of SSEP short latency (P39) responses in evaluating high frequency and burst stimulation.

There remains limited evidence for the role of long latency SSEP responses in measuring chronic pain relief, however the studies reviewed favoured long latency SSEP responses being used in dipole exploration and source modelling of the wider somatosensory cortical and subcortical network in chronic pain studies and not in the selection of individual responders. There was insufficient evidence to evaluate the effects on chronic pain phenotypes before and after tonic, high frequency and burst stimulation.

2.5.1 Recommendations for future studies

This scoping review has highlighted the heterogeneity that exists in the current literature due to study design quality. Absolute theta power, relative theta power and SSEP amplitude objective neurophysiological measures warrant further study as candidates for patient selection in SCS clinical practice. Future studies need to address these quality issues before a decision can be made on the role these measures play on current clinical practice. Using the lessons learned from this scoping review the following recommendations were proposed for future study design in this field when evaluating for application to clinical practice.

Table 2.15 Quality improvement areas identified in the scoping review recommended for future study designs

(study characteristics)

Factor	**Recommendation for future study design**
Patient selection varied between studies	MDT approach using ICD-11 framework for FBSS, patients selected consecutively with radicular neuropathic pain, to standardise patient selection in line with clinical recommendations
Subjective pain measures varied with a bias towards pain intensity (VAS), pain characteristic	Consider a triad battery approach to subjective pain evaluation using VAS (pain intensity), Pain Detect (pain characteristics) and ODI (quality of life) to evaluate pain relief.
VAS non-specific, lower back pain may be persistent due to post surgical implant pain	VAS matched to symptomatic leg (painful area).
Pain relief was not expressed as a percentage	Percentage pain relief used as the main effect size measure in evaluating SCS clinical effectiveness
Anxiety and depression not evaluated	Evaluate anxiety and depression using Hospital Anxiety and Depression index to screen for bias and to evaluate SCS therapeutic effects.
Medication often not included in study characteristics	List medication as part of the study characteristics, to screen for any medication bias.
Study designs only included tonic stimulation with either high frequency or burst stimulation never both	Study protocol to include high frequency, tonic and burst stimulation
Tonic stimulation protocols failed to consider wash in/wash out effects due to dose dependency	Study designs to include adequate wash in/wash out period for tonic stimulation a minimum of 3 days between trials is recommended.

Table 2.16: Quality improvement areas identified in the scoping review recommended for future study designs.

(Neurophysiology characteristic)

Factor	**Recommendation for future study design**
EEG methodology varied between studies, number of electrodes, standardised head measurement system, electrode impedance and recording characteristics	EEGs performed to IFCN standards for EEG clinical practice (Nuwer et al., 1999): Minimum of 19 electrodes, electrodes placed using Ten-Twenty measuring system, electrode impedances <5 KΩ and equal, minimum Nyquist rate 250 Hz, Filter bandwidth 0.5 – 70 Hz
A lack of standardised EEG recording protocol	Minimum 5 minutes artefact free eyes closed EEG, artefacts removed in MATLAB, minimum epoch size for data analysis 60 seconds.
Lower limb SSEP methodology varied between studies, number of electrodes, standardised head measurement system, electrode impedance and recording characteristics	SSEPs performed to IFCN standards for SSEP clinical practice (Cruccu et al., 2008). Cortical recordings: Electrodes placed at CPz (2 cm posterior from Cz ten-twenty position), reference placed at Fz ten twenty position, ground placed between the active and reference electrodes. electrode impedances <5 KΩ and equal, Filter bandwidth 3 Hz to 2 kHz, minimum 500 averages
Lower limb SSEP stimulation characteristics	Posterior tibial nerve stimulation, monophasic square wave pulse, stimulation frequency 3-5 Hz and 2-3x sensory threshold with a visible motor twitch
Sleepiness bias not evaluated may contaminate theta power evaluation	Evaluate all EEG trials with Epworth sleepiness scale.
Studies only reported responders	Study designs to include a comparison between SCS responders and non-responders.
Studies only reported responders	Study designs to include a comparison between SCS responders and non-responders.
Studies failed to classify pain characteristics	Study designs to include individual pain characteristics and compare at baseline to post SCS and responders to non-responders.
Studies failed to consider baseline profiles for EEG or SSEP.	Study designs to explore baseline spatial profiles for EEG (theta power) and SSEP amplitudes and whether these change with SCS.

2.5.2. Conclusion

The scoping review identified absolute theta power, relative theta power and SSEP amplitude as suitable objective neurophysiological measures for clinical practice application. Tonic SCS effects in these three measures have been studied with reduction in absolute theta power, relative theta power and SSEP amplitude all representing potential clinical indictors of SCS responders. Baseline profiles for these measures have not been investigated in terms of SCS patient selection. There was limited evidence available in the literature on the effects with high frequency and burst SCS requiring further study before clinical application.

To better understand the potential clinical role of absolute theta power, relative theta power and SSEP amplitude in SCS responder selection a prospective study was designed based on the recommendations from the scoping review.

3. PROSPECTIVE STUDY

3.1. Introduction

SCS is a widely used and an FDA approved treatment for managing chronic and neuropathic pain in FBSS patients. Despite this there is a sizeable portion of patients that receive either suboptimal or inadequate pain suppression placing considerable costs on healthcare services. SCS is beneficial in 50%-60% of patients, who are describe as responders (Hayek et al., 2015; Thomson et al., 2017; Duarte and Thomson, 2019). Available evidence in the literature suggests that current therapies may not be optimised for individual neural and/or spinal segmental features of pain (Telkes et al., 2020).

Absolute theta power is a promising biomarker that has been used to evaluate the effects of SCS in patients receiving tonic stimulation. There is growing evidence to support that absolute theta power increases over the somatosensory cortex and associated parietal cortical areas with thalamocortical dysrhythmia. There is emerging evidence from De Ridder and Vanneste, (2016); Vanneste and De Ridder, (2021) that coupling between the lateral and medial spinothalamic pathways with the default network drives thalamocortical dysrhythmia and inhibits the descending pain modulating system responsible for supressing on-going pain. Tonic SCS is thought to inhibit the ascending nociceptive signals at the spinal segmental level, reversing thalamocortical effects. The reduction of absolute theta power is considered by Goudman et al., (2020; Telkes et al., (2020); Goudman et al., (2021) and others to indicate reduced thalamocortical effects at the cortex.

There is insufficient evidence on how anxiety, depression, medication and sleepiness effect absolute theta power as a biomarker in the evaluation of chronic pain and SCS therapy in clinical practice.

Lower limb SSEP P39 amplitude reduction with tonic SCS is another potential and has been used to evaluate somatosensory cortex processing with tonic SCS. There is limited evidence available whether either of these two neurophysiological measures correlate with pain relief or their role evaluating high frequency and burst SCS. Chronic pain baseline profiles and

their role with patient SCS responder selection is unclear for either of these two measures and this study aims to evaluate their future role in clinical practice.

3.1.1 Aim of prospective study

A prospective study to investigate whether baseline patterns of brain activity measured by QEEG and SSEPs can predict the therapeutic response to SCS in FBSS patients with chronic neuropathic pain.

3.1.2. Objectives

Objective 1: To explore spatial profiles of baseline QEEG and SSEP amplitudes in FBSS patients alongside clinical characteristics to determine their usefulness in responder selection for SCS for a given patient.

Objective 2: To explore the changes in absolute theta power with SCS to a given modality during the trial.

Objective 3: To explore the changes in SSEP amplitude reduction with SCS to a given modality during the trial

Objective 4: To explore clinical characteristics to determine usefulness in responder selection for SCS

Objective 5: To explore the ability to predict a sustained response at 6 months post implantation

3.1.3. Hypothesis

EEG theta power increases with chronic pain and SSEP amplitudes become enhanced due to cortical plasticity and excitability.

Effective SCS (responders) reduce EEG theta power and SSEP enhanced amplitudes when using either high frequency, tonic, or burst stimulation and this may aid in patient selection.

Baseline pain characteristics may change with pain duration and intensity in FBSS leading to changes in baseline EEG theta spatial patterns or enhanced SSEP amplitude profiles. These signatures may be useful in predicting SCS responders and non-responders at baseline.

3.2. Method

3.2.1. Patient selection

Patients were recruited consecutively from the FBSS chronic pain service at the Walton Centre NHS Foundation Trust. All patients recruited were evaluated prior to recruitment by a MDT evaluation group blinded to the study and consisting of pain clinicians, surgeons, specialist nurses, physiotherapists and neuropsychologists (Figure 3.1).

Patients were evaluated for SCS suitability using a three-tiered traffic light system. Requirements for MDT patient selection was chronic pain as a primary symptom that meets the criteria set out in NICE TAG 159 (NICE committee reviewed 2014, 2008) and ICD-11 classification for chronic pain (Treede et al., 2015). Chronic pain was classified as moderate to severe chronic pain for at least 6 months with a VAS score >5 due to either FBSS, complex regional pain syndrome, post-surgical or traumatic neuropathic pain (Figure 3.1).

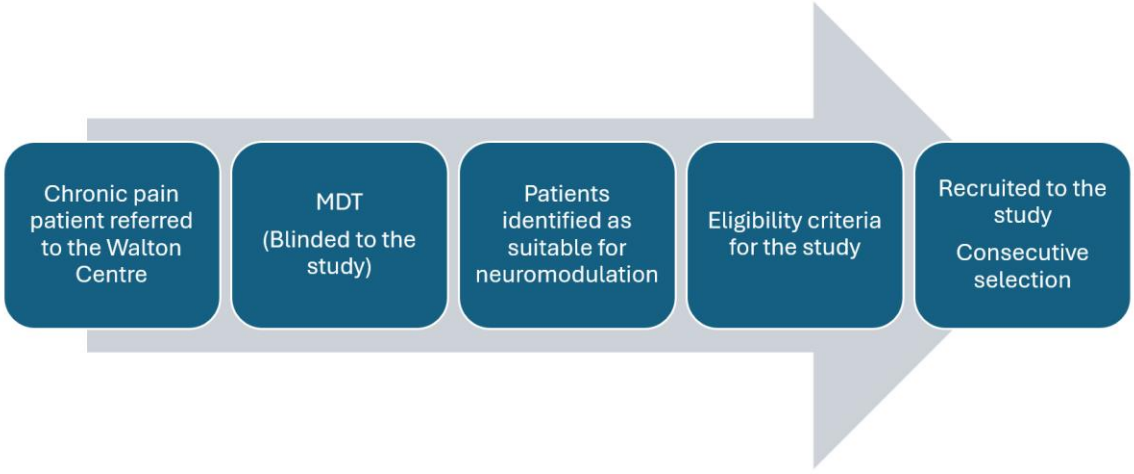


Figure 3.1: Process chart of the recruitment process. Chronic pain patients are referred to the Walton Centre NHS Trust and reviewed by a Consultant Pain Clinician. Patients are reviewed for eligibility for SCS at the Pain neuromodulation MDT. The MDT classified patients as either not suitable, borderline or suitable for SCS, Patients identified as suitable for SCS are reviewed against the study eligibility criteria and invited to participate in the study.

Table 3.1 outlines the criteria used by the MDT to evaluate suitability for SCS and Table 2 the eligibility criteria used for patient selection.

Table 3.1: MDT three-tiered evaluation criteria for spinal cord stimulation (Walton Centre NHS Foundation Trust)

Red **(Not currently suitable)**	**Amber** **(Borderline suitability)**	**Green** **(Suitable)**
Active infective illness.	Significant pain that will not benefit e.g. arthritis pain or spinal instability. Refer for spine surgery opinion	Diagnosis of chronic neuropathic pain (NICE TAG 159, ICD-11)
Severe debilitating uncontrolled chronic medical illnesses, for example severe respiratory disease.	Significant pain beyond the area that a spinal cord stimulation system can cover (widespread pain distribution/multisite pain)	Tried and not responded to conservative treatments
Confirmed allergy to nickel or any other components of the implantable device.	Anatomical problems leading to technical challenges implanting e.g. major spinal deformity, extensive spinal metalwork or extensive spinal scar tissue in the epidural space at the site of SCS lead insertion. Discuss with Functional Neurosurgical team	Willing to stop or reduce excessive medication and use pain management strategies
Coagulopathy	Spinal stenosis (with effacement of CSF, cord compression, or both) at the site of lead placement: Refer to spinal surgery opinion MDT	Able to manage the technical demands of the equipment
Active severe mental health disorder e.g. unstable psychosis	Very high or very low body mass index	Appropriate motivation
Active substance misuse and alcohol dependence, Severe/moderate learning disability (intellectual disability)	No definite diagnoses or identifiable generator for pain. Failed trial of SCS from our or other centres	Good understanding of procedure and outcomes. Appropriate expectations of pain relief
Severe/moderate cognitive impairment e.g. dementia, learning disability (intellectual disability)	History of poor wound healing or previous post-operative wound infection, Significant mental health / psychiatric disorder history, History of misuse of alcohol or drugs, including prescription drugs, Mild learning disability / intellectual disability, dementia diagnosis Concerns of secondary gain (e.g. ongoing litigation)	Insight into Chronic Pain diagnosis & limitations of medical science.
	Self-harm in past 12 months, Poor motivation, unrealistic expectations. Inadequate insight,	Proven adherence to treatment
	Poor adherence to previous advice and Treatment and/or Non-attendance	Failed back surgery syndrome

Table 3.2: Eligibility criteria used for patient selection.

Inclusion criteria	**Exclusion criteria**
Adult patients ≥ 18 years of age	Children and adolescence < 18 years of age
Patients of any gender	Patients with new onset pain of < 6 months
Patients if any ethnicity	Patients with pain scores that measure <5 on the VAS pain rating scale.
Failed back surgery syndrome	History of sleep disorder or poor sleep hygiene
Lumbar sacral disc prolapses	History of epilepsy
Chronic neuropathic lower back and / or leg pain (ICD-11)	Patients presenting with any other type of chronic pain – e.g. in the face, abdomen, bone etc.
Chronic neuropathic pain for at least 6 months that measures ≥5 on the VAS pain rating scale	Patients deemed not suitable or borderline suitability for spinal cord stimulation via the MDT at the Walton Centre NHS Foundation Trust – traffic light tiers – red and amber
Deemed suitable for spinal cord stimulation via the MDT at the Walton Centre NHS Foundation Trust – traffic light tier - green	-

FBSS was defined using the definition used by De Andrade et al., (2010) as persistent neuropathic pain symptoms despite more than two surgical interventions.

All patients identified as eligible for the study gave their informed consent. Informed consent was undertaken at least 3 days before the baseline trial to allow them time to fully consider participating in the study. Consent for the use of photographs and images were taken as a part of the informed consent process.

3.2.2. Sample size

Sample size was determined *a priori* using G*power program for repeated measures ANOVA with 4 groups (alpha = 0.05, power = 0.95 and effect size = 0.25), Standard settings for medical literature were used for the significance level (alpha = 0.05) and power (power = 0.8, 80% – 0.95, 95% β = 0.1-0.2). A sample size of 36 patients was calculated.

The significance level (alpha) refers to the probability of a type I error, when there is a significant difference that does not actually exist (false positive rate) and power, the probability that a difference exists (1-β, where β is the risk of a type II error or false negative rate). The effect size refers to the magnitude of the effect being measured. This was estimated (effect size = 0.25, medium effect size) due to the lack of similar studies in the literature or preliminary trial data identified from the scoping review.

Four repeated measurements were used in the calculation. The G*power program for repeated measures ANOVA determined for statistical power thirty-six patients were needed.

3.2.3. Spinal cord stimulator percutaneous implantation

Each patient underwent a percutaneous implantation of a Nevro HF10 stimulator for the study. The choice of stimulator was agreed in the MDT and was a part of the clinical pathway of the patient and was not changed by the study protocol. Nevro HF10 stimulators have the capability to delivering tonic, high frequency and burst stimulation through HFX IQ programming interface.

For implantation patients were in a prone position. The incision site was determined by X-ray imaging and the entry site used was the L1-L2 interspace marked on the patients back using a surgical pen (Figure 3.2).

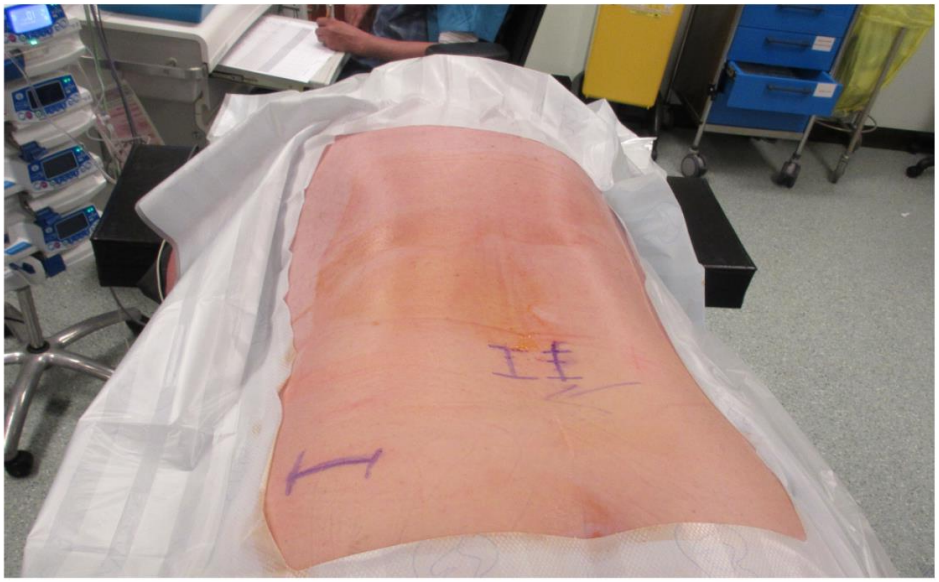


Figure 3.2: Implantation pre-operative planning using X-ray guided imaging with L1-L2 interspace marked.

A 14-gauge Tuohy needle was used to guide the entry into the epidural space under X-ray guidance (Figure 3.3).

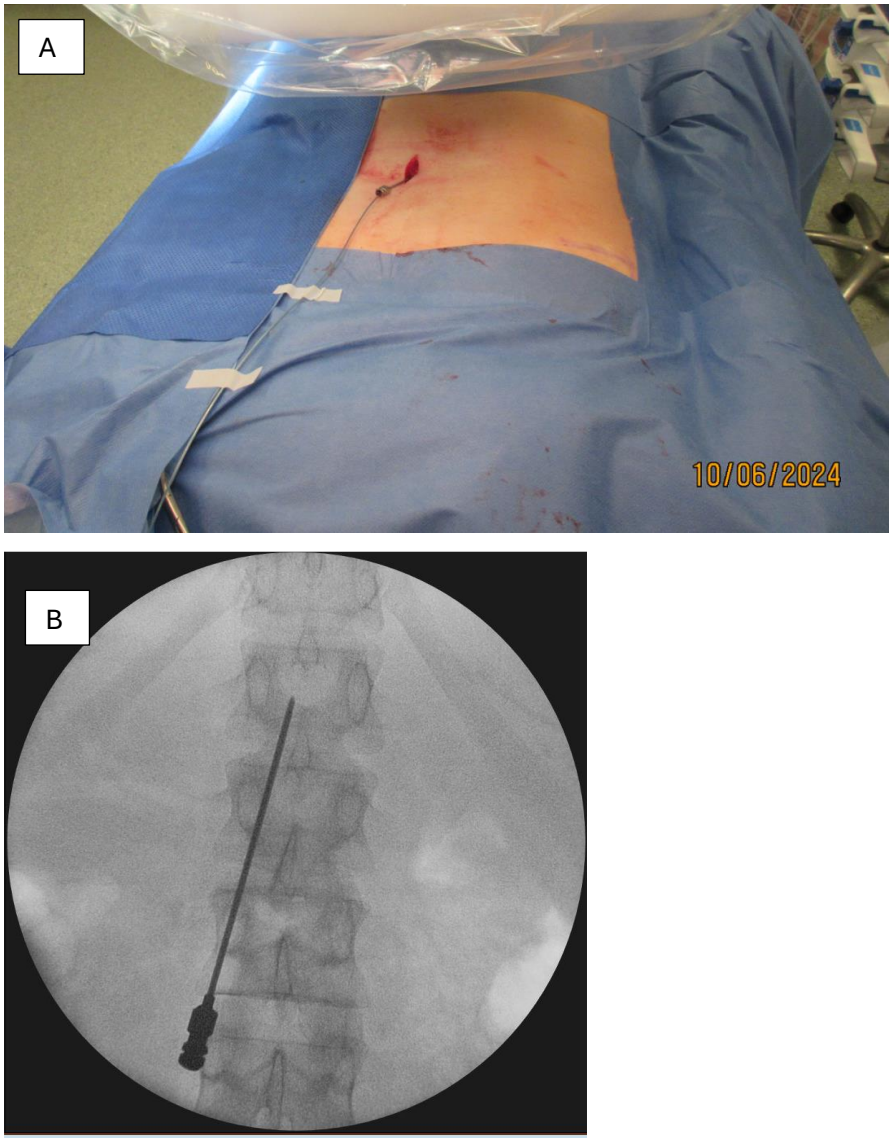


Figure 3.3: Tuohy needle placed in the epidural space and placed at the intended target using L1-L2 entry site. A. Tuohy needle in situ, B X-ray imaging guiding entry.

The Tuohy needle was guided to the target site using a combination of X-ray and tactile feedback. The epidural space was identified using a loss of resistance to saline. Once in position a soft guide wire was passed through the Tuohy needle and the electrode placed on the contralateral paramedian area of the dorsal spinal canal (Figure 3.4).

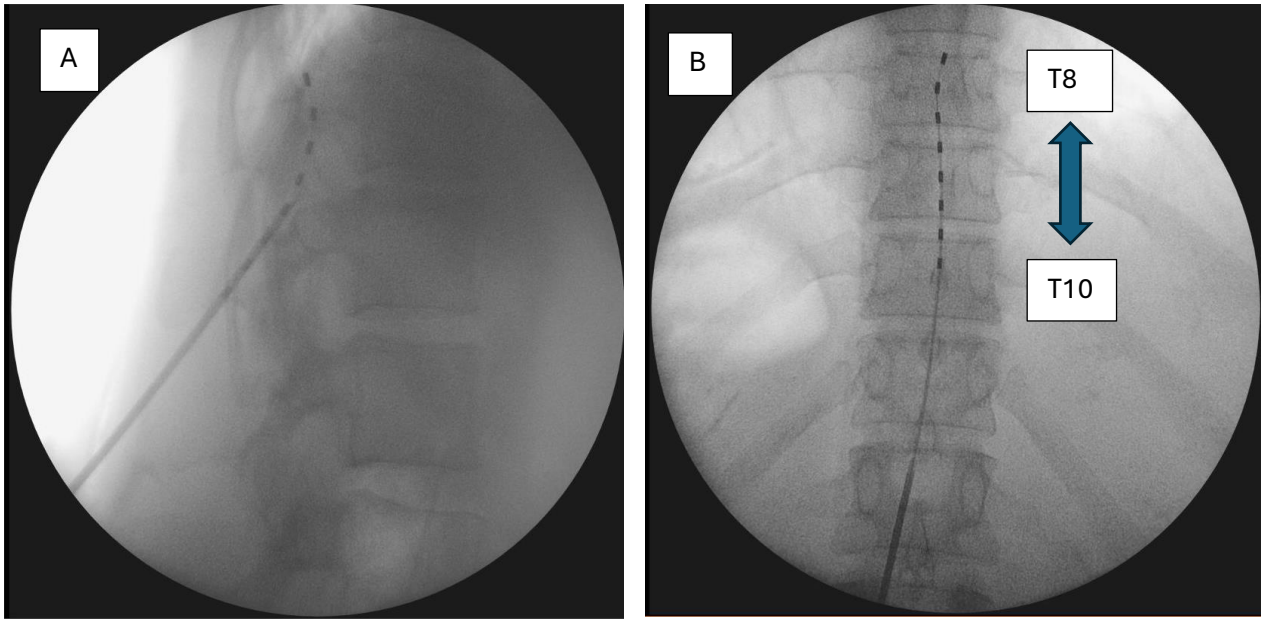


Figure 3.4 Image A positioning of the percutaneous electrode from the soft guide wire at T8. Image B The percutaneous electrode in-situ with tip placed at T8 providing a T8-T10 coverage from the 1st electrode.

The second electrode was placed using the same technique lateral to the first electrode with tip at T9 providing T9-T11 coverage (Figure 3.5 and Figure 3.6).

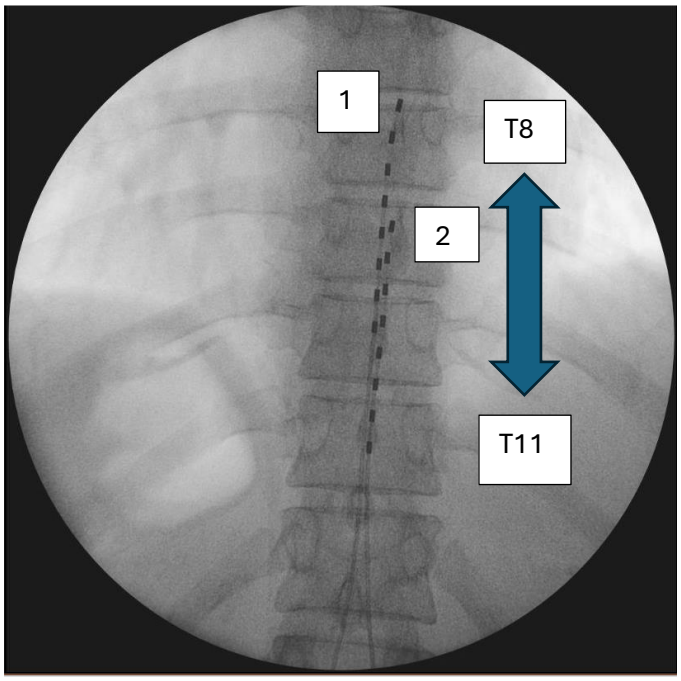


Figure 3.5: The two electrodes in-situ providing a combined T8-T11 coverage for stimulation.

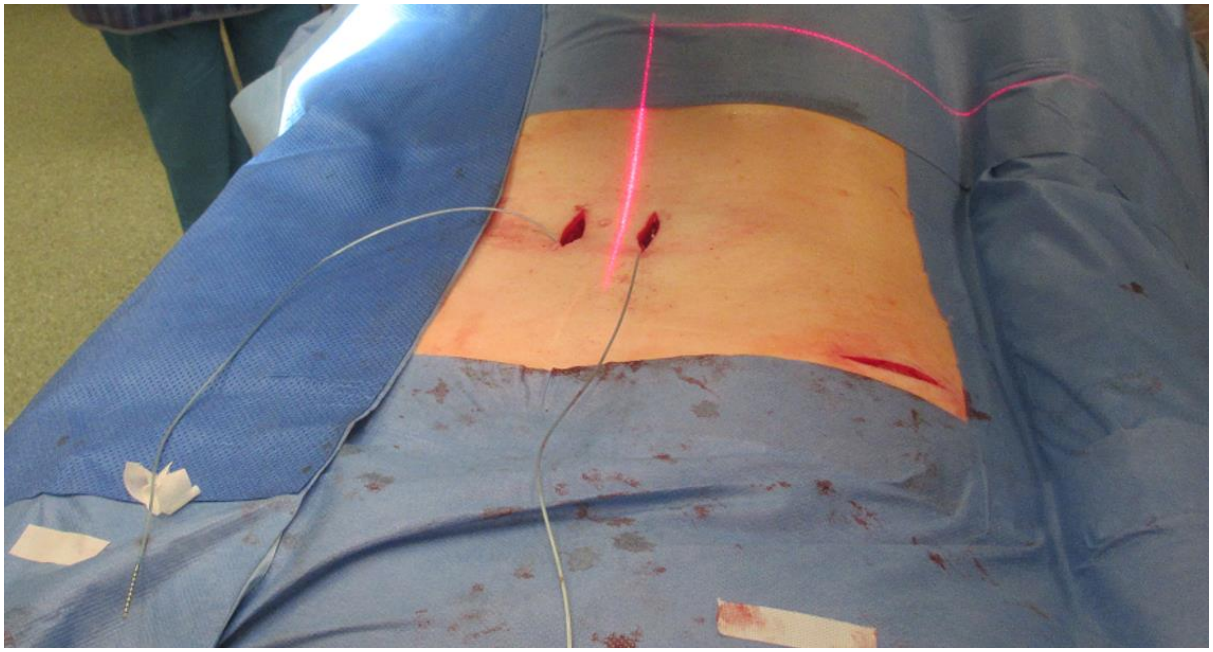


Figure 3.6: A minimal invasive view of the two electrodes under percutaneous implantation.

The electrode leads were anchored to fascia and tunnelled to the right gluteal subcutaneous pocket and connected to extensions and then tunnelled out (Figure 3.7).

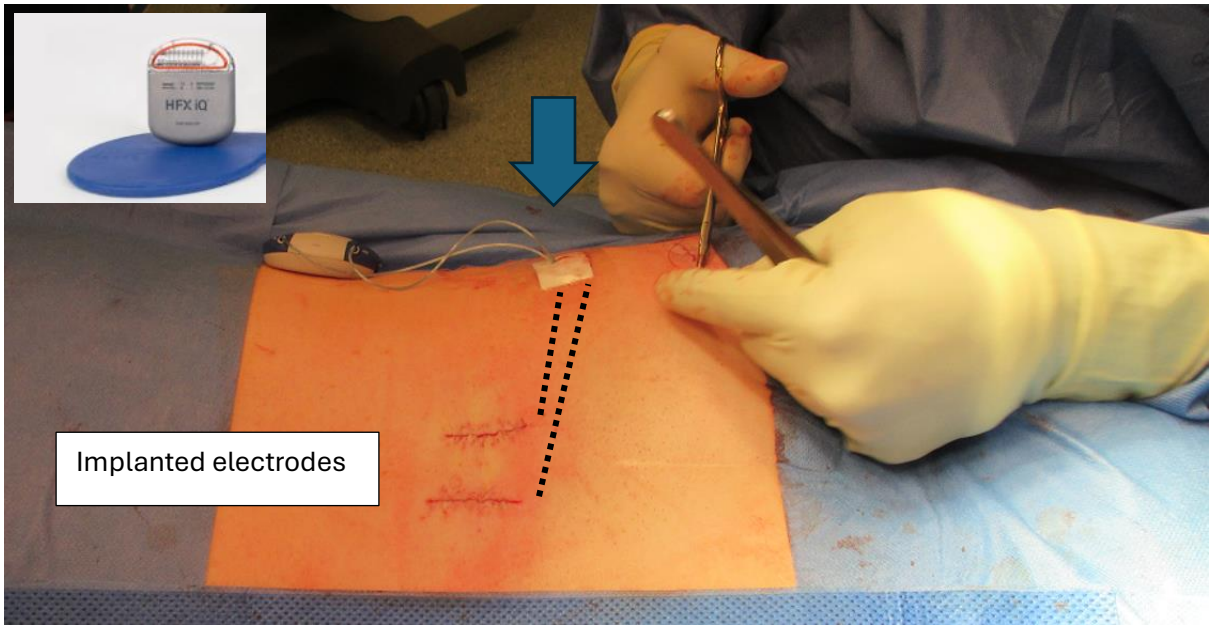


Figure 3.7: Electrode leads connected to extension and tunnelled to the right gluteal subcutaneous pocket and connected to Nevro HF10 (IQ).

Once connected the electrode impedances were checked to ensure that they meet therapeutic specification.

One patient had the percutaneous electrodes placed using an endoscopic approach.

3.2.4. Stimulator programming.

Stimulator programming was undertaken the same day as the surgery by the neuromodulation team led by two specialist nurses who were blinded to the study.

Three programmes were set up for each patient that could be manually changed using the programme selector remote. Table 3.3 outlines the three stimulator programmes.

Table 3.3: Stimulator programmes used in the study.

Programme	**Stimulation paradigm**	**Stimulation settings**
1	High frequency	10 k Hz, 0.2 ms
2	Tonic	60 Hz, 0.25 ms
3	Burst	Train of 5 pulses at 500 Hz, 1.0 ms delivered at 40 Hz

The intensity of each programme was manually set by the patient for comfort using the stimulator remote control.

Tonic stimulation required paraesthesia mapping to ensure adequate paraesthesia coverage overlapping the painful area. Pulse duration was adjusted to allow optimum coverage and in most cases this was 0.25 ms. The frequency used for tonic stimulation was kept constant at 60 Hz.

3.2.5. Study design

The study consisted of a baseline trial followed by three separate trials over a 2-week period. The baseline trial was undertaken on admission (day 1) prior to stimulator implantation.

The remaining three trials were designed around tonic stimulation having a 4-day wash in / washout period. High frequency and burst stimulation wash in / wash out periods were considered within the effects of the stimulator being on or off (Figure 3.8).

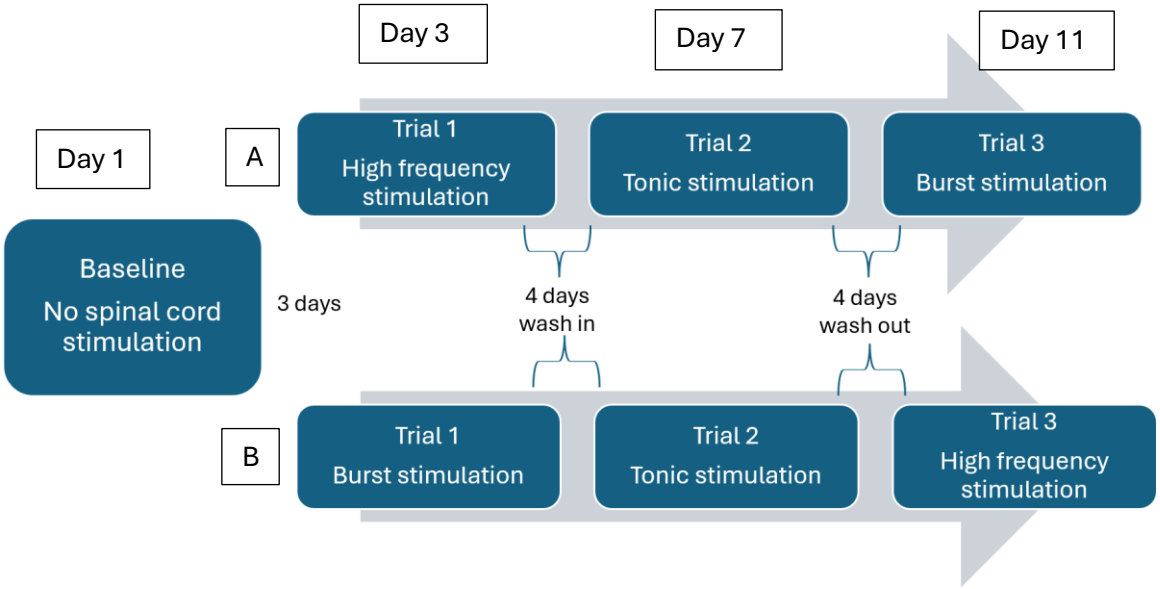


Figure 3.8: Process chart showing the trial design based on a 4-day wash in / wash out model for tonic stimulation, with high frequency and burst stimulation at either day 3 or day 11 (protocol A or protocol B).

The first trial was undertaken 3 days after implantation to minimise any surgical pain bias from the implantation and to allow initial healing. Protocol A consisted of Trial 1 high frequency stimulation, 3 days after the baseline trial. Trial 2 was undertaken 4 days later (day 7) and was tonic stimulation. The final trial was 4 days later (day 11) and was burst stimulation. Protocol B consisted of Trial 1 burst stimulation, 3 days after the baseline trial. Trial 2 was undertaken 4 days later (day 7) and was tonic stimulation. The final trial was 4 days later (day 11) and was high frequency stimulation. Stimulator programmes were changed at the end of each trial after EEG and SSEP studies.

Patients were allocated to either protocol consecutively with the first half of the recruited patients receiving protocol A and the second half receiving protocol B.

SCS (high frequency or burst SCS) for trial 1 was set to on for 3 days and trial 2 (tonic SCS) 4 days and trial 3 (high frequency or burst SCS) for 4 days, to allow wash in and wash out effects of tonic SCS. Each trial lasted 1 hour consisting of a 10-minute EEG and set up and bilateral lower limb SSEP studies with set up. During each trial prior to any neurophysiological testing consent was checked and patients completed an Epworth Sleepiness scale, Pain Detect questionnaire, Hospital Anxiety and Depression scale (HADS), Oswestry Disability Index and Visual analogue scale (VAS).

Patients were asked about adverse events or side effects. On the last trial (day 11) patients were asked to complete a patient satisfaction survey that would be used to monitor patient experience during the study. The survey also asked whether they would be interested in attending a follow up appointment and a patient centred day where the results of the study would be fed back to participants.

This was followed by two neurophysiology tests, A 10-minute EEG followed by lower limb SSEP studies. The study design is outlined as a schematic in figure 3.9.

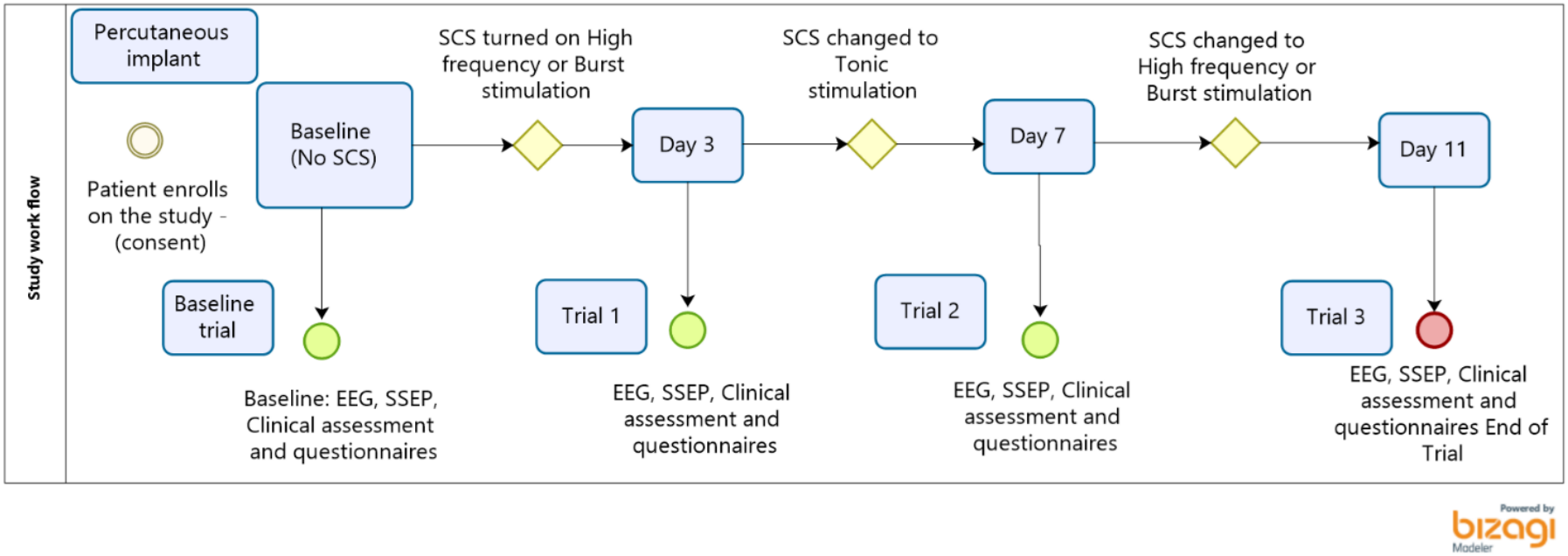


Figure 3.9: Study design schematic with patients either following protocol A or protocol B.

3.2.6. Neurophysiological testing

Neurophysiological testing was undertaken by either the principal investigator (Trainee Consultant Clinical Scientist in Neurophysiology), or one of three clinical physiologists. All involved in data collection were competent in all aspects of EEG and SSEP recordings and were working in neurophysiology clinical practice for more than five years at the Walton Centre NHS Foundation Trust. All three were trained to check consent as part of their routine clinical practice and have participated in data collection for other research studies that the department of neurophysiology have been involved in. The principal investigator took over all responsibility for data collection ensuring that protocols were followed correctly. All three clinical physiologists were blinded to the study.

3.2.6.1. EEG study

During each trial patients underwent a ten-minute EEG recording consisting of five minutes eyes closed and five minutes eyes open. EEG studies were conducted in accordance with IFCN standards. Nineteen silver/silver chloride cup electrodes (Ambu Neuroline) were placed on the scalp at electrode positions Fp1, Fp2, Fz, F7, F3, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 according to the international ten-twenty electrode placement system (Figure 3.10.). Electrode locations were measured using a tape measure and chinagraph pencil. Electrode sites were prepped with NuPrep abrasive gel and electrodes secured with ten-twenty electrode paste. Electrodes FP1, FP2, F7 and F8 were secured with transpore patient tape. An additional common reference electrode was placed between Cz and Pz and a ground electrode between Fz and Cz.

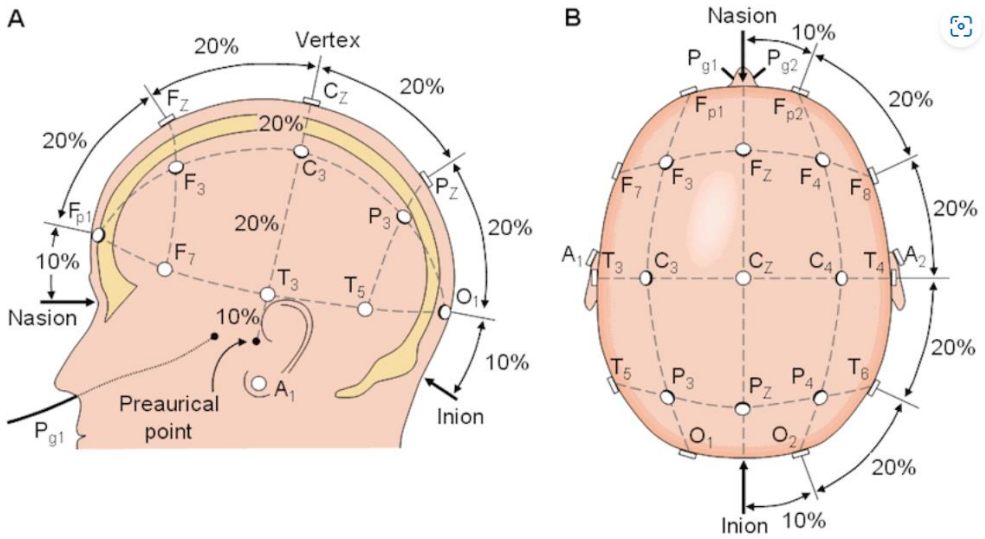


Figure 3.10: International Ten-Twenty EEG electrode placement system taken from Shriram et al., 2018. The electrode locations are marked in 10% and 20% quadrants and labelled F (frontal), C (central), T (temporal), P (parietal) and O (occipital). Even numbers represent right sided electrodes and odd numbers left sided electrodes. Image A is a sagittal view and image B horizontal view. The nasion, preauricular point and inion are anatomical landmarks used for measuring.

Electrode impedance measurements were all <5 KΩ as per neurophysiology EEG standard operating procedure and protocol. EEG recordings were undertaken on a Deymed Tru Scan EEG portable lap top system with a battery powered headbox (Figure 3.11.).

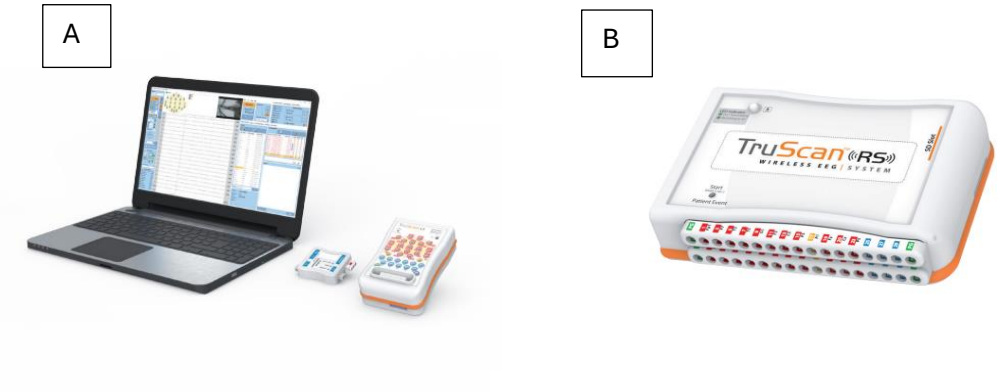


Figure 3.11: Deymed Tru Scan EEG portable lap top system (A) and a battery powered headbox (B) (Neurogen, UK).

EEG recordings were undertaken using a sampling rate of 250 Hz, filter bandwidth of 0.5 Hz – 70 Hz, sensitivity of 10 μV/division and a time base of 30 mm/s. EEG recording were visualised using a bipolar montage and saved using a common average reference montage (Figure 3.12).

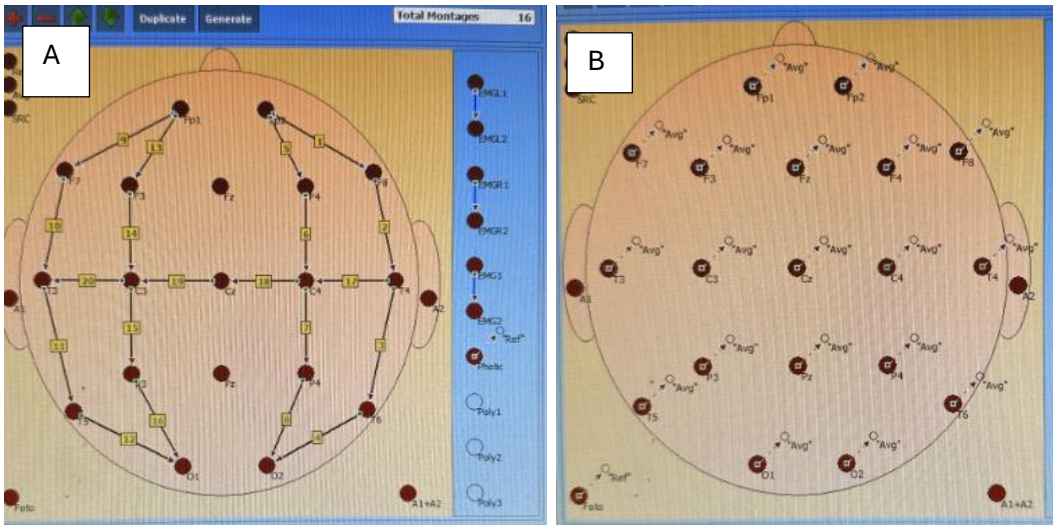


Figure 3.12: (A) Bipolar EEG montage used to visualise the EEG when recording and (B) Common average reference used to save the EEG.

The EEG recording protocol was 10 minutes of artefact free EEG, 5 minutes eyes closed, 5 minutes eyes open. Patients were seated in a supine position and asked to relax their head and neck and maintain a slightly opened mouth to relax jaw muscle tension. When the patients' eyes were open they were asked to fixate on an object ahead of them, keeping their eyes still and trying not to blink excessively. The EEG was monitored in real-time by the clinical physiologist for lateral eye movements, muscle artefact, sweat artefact, ECG artefact and eye blinks. Amplifier desaturations or electrode artefacts resulted in electrodes either being checked, reapplied or replaced and EEG recording times were extended accordingly. An electric fan was used to reduce sweat artefact. All identified artefacts were annotated.

3.2.6.2. Lower limb SSEP studies

During each trial following the EEG study, each patient underwent bilateral lower limb SSEP studies in accordance with IFCN standards (Cruccu et al., 2008). Cortical SSEPs were recorded from two silver/silver chloride cup electrodes (Ambu Neuroline) placed on the scalp. The active electrode CPz was placed 2 cm posterior to the ten-twenty Cz electrode position and

the reference electrode Fpz was placed at the Fz ten-twenty electrode position. A ground electrode was placed between Fz and Cz ten twenty electrode positions.

Electrode locations were measured using a tape measure and chinagraph pencil. Electrode sites were prepped with NuPrep abrasive gel and electrodes secured with ten-twenty electrode paste. Electrode impedance measurements were <5 KΩ as per neurophysiology SSEP standard operating procedure and protocol.

SSEP recordings were undertaken on a Deymed Tru Trace EP/EMG portable lap top system with a Tru Trace traveller keyboard, battery powered headbox and stimulator box (Figure 3.13). Lower limb SSEP recordings were undertaken using a sampling rate of 250 Hz, filter bandwidth of 30 Hz – 1 kHz, sensitivity of 1.0 μV/ division or less and time base of 10 ms/division. Two runs of 500 averages were recorded each side and combined as a grand average.

Posterior tibial nerve stimulation was undertaken using self-adhesive surface electrodes (Ambu Neuroline 715) placed on the medial surface of the ankle behind the medial malleolus 2 cm apart stimulating the posterior tibial nerve. Electrodes were placed in a way that followed the path of the nerve around the medial malleolus with the cathode placed proximal in comparison to the anode electrode. Electrode stimulation sites were prepped with NuPrep abrasive gel prior to electrode application to ensure low output contact impedance and then secured with transpore tape.

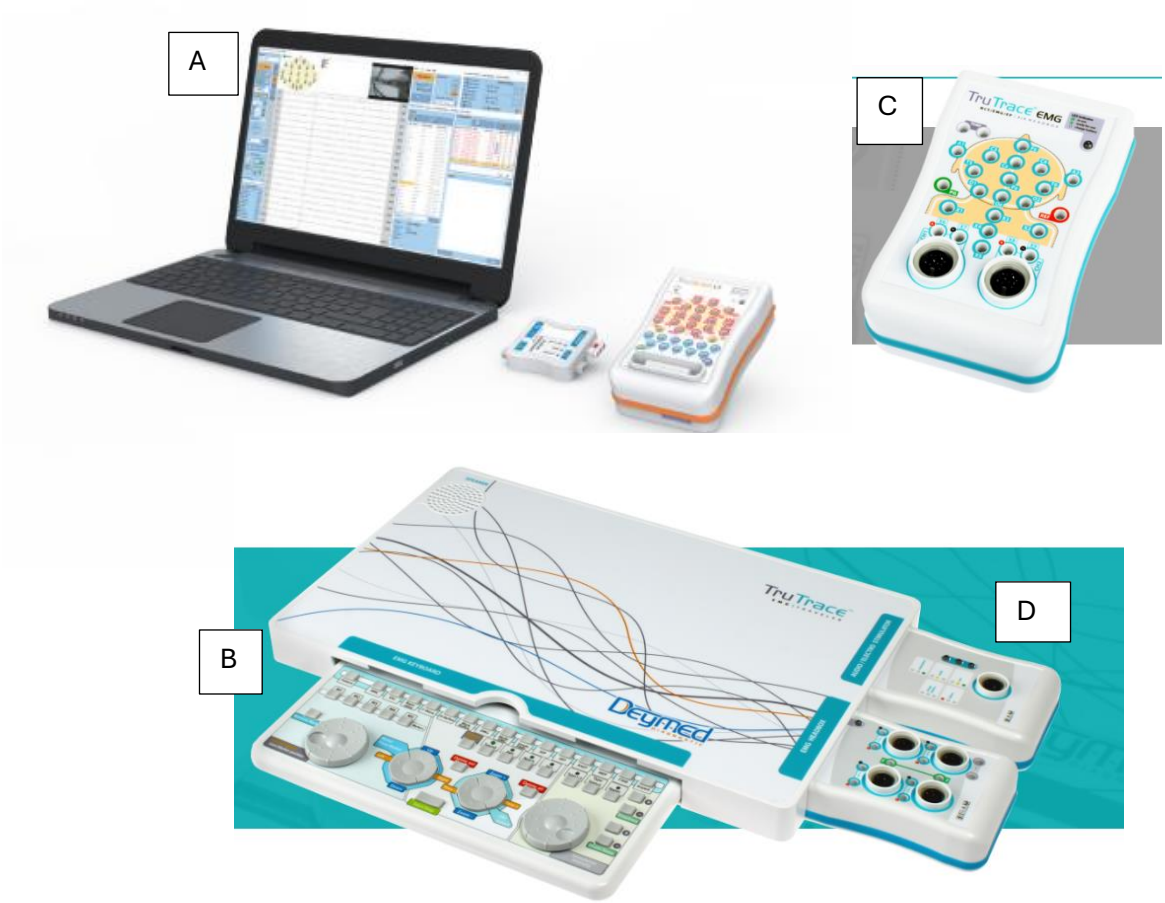


Figure 3.13: Deymed Tru Trace EP/EMG portable lap top system (A) with a Tru Trace traveller keyboard (B), battery powered headbox (C) and stimulator box (D) supplied in the UK by Neurogen.

SSEP stimulation was undertaken with a square-wave repetitive pulse. The stimulation delivered was current (mA) with a stimulation frequency of 4.7 Hz and pulse width of 0.5 ms.

Stimulation was increased in 0.1 mA increments until the patient became aware of the stimulus (sensory threshold). The stimulus was then increased until a visible motor twitch was observed from the big toe (digit I, great toe, hallux). This is the motor threshold; stimulation was performed at a level above the motor threshold that the patient could tolerate. If no visible toe twitch was identified, stimulation was performed at an intensity 3x the sensory threshold at an intensity the patient could tolerate. If the patient had a low tolerance to stimulation the intensity used for stimulation was either at sensory threshold or twice sensory threshold. Patients unable to tolerate the stimulus resulted in SSEP studies being abandoned.

Both lower limbs were tested consecutively with a minimum of two runs (500 averages) per limb. SSEPs were displayed as a grand average and the primary response latency and amplitude marked up. A P39 cursor was placed at the primary response onset for latency (ms) and a second marker placed at the peak of the response used to calculate the amplitude of the primary response.

3.2.7. Data management.

Patients were pseudonymised and identifiable with a unique research number prior to their baseline study. Patients could withdraw from the study at any point up until their data was anonymised following analysis. Once the data was anonymised at this point patients could no longer width draw from the study. The data management workflow is summarised in figure 3.14.

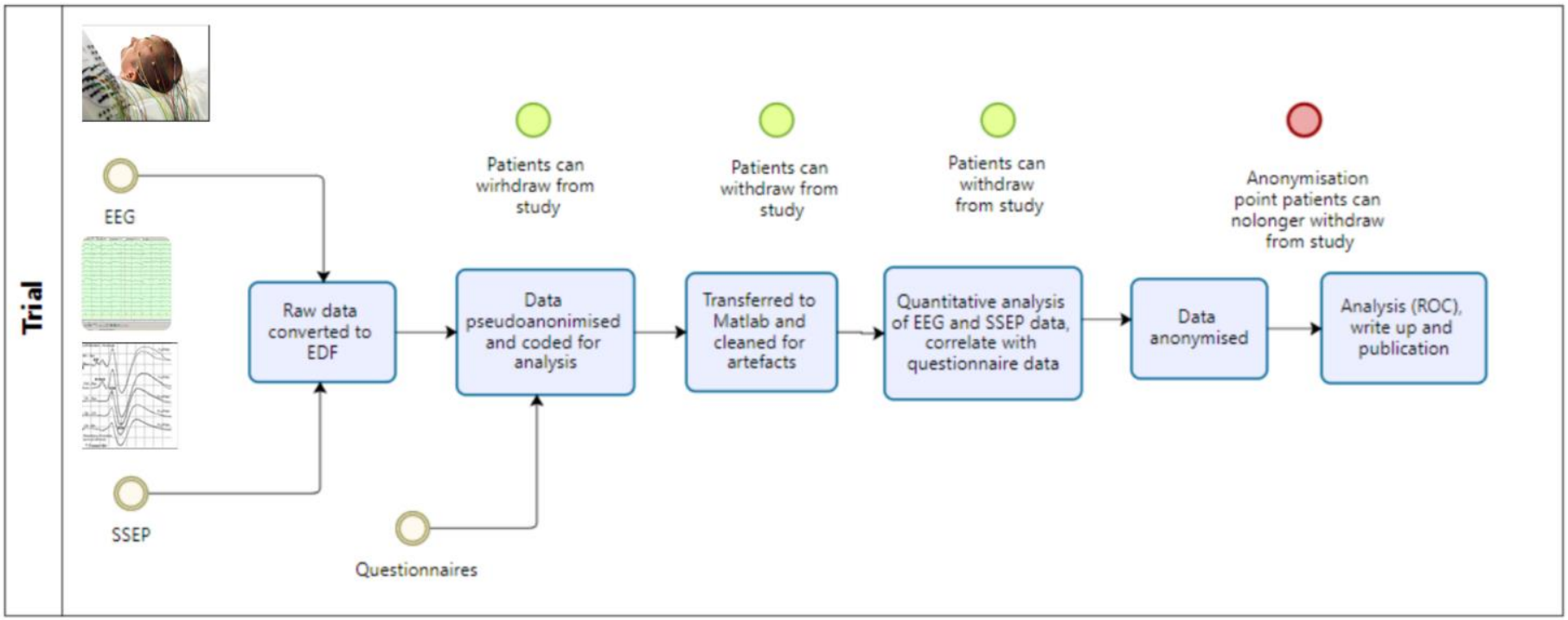


Figure 3.14: Data management workflow showing pseudo-anonymised data and anonymised data

Raw EEG and SSEP data were stored on an encrypted and password protected server used for the storage of clinical data at the Walton Centre NHS Foundation trust.

EEG and SSEP raw data were transformed into an EDF for data analysis.

3.2.8. EEG data analysis

Each EEG patient trial was clipped into two 5-minute studies, creating an eyes closed clip and eyes open clip. Each clip was transformed into an EDF+ file and pseudonymised and assigned a unique code that comprised of the patient's individual pseudonymised number, the trial type (BL, HF, LF or Bu) and the test condition (EC or EO). The individual EDF+ files were exported to MATLAB R2022B for data analysis using a secured and encrypted patient export system used within the hospital to export patient files.

MATLAB scripts were written by Dr Andrej Stancak. He wrote edf2SEPs in February 2022 (Stancak, 2022a), edf2Set in February 2022 (Stancak, 2022b) and updated Set2Spa in November 2022 (Stancak, 2022c).

EEG data analysis was undertaken using MATLAB R2022B using EEGLAB toolbox. MATLAB script edf2Set (Stancak, 2022b) converted EDF+ files to a 19 channel Set file for viewing EEG data in EEGLAB, artefact correction and rejection.

Each EDF+ file attached to an EEG trial was converted into a Set file and visually inspected in EEGLAB. EMG lateral eye movements, muscle artefact, sweat artefact and ECG artefact were removed from each data set by highlighting the relevant sections and rejecting them in EEGLAB. Electrical contamination was removed using a notch filter at 48-52 Hz. Eye blinks were removed using independent component analysis. Figure 3.15 is an example of a Set file used in EEGLAB.

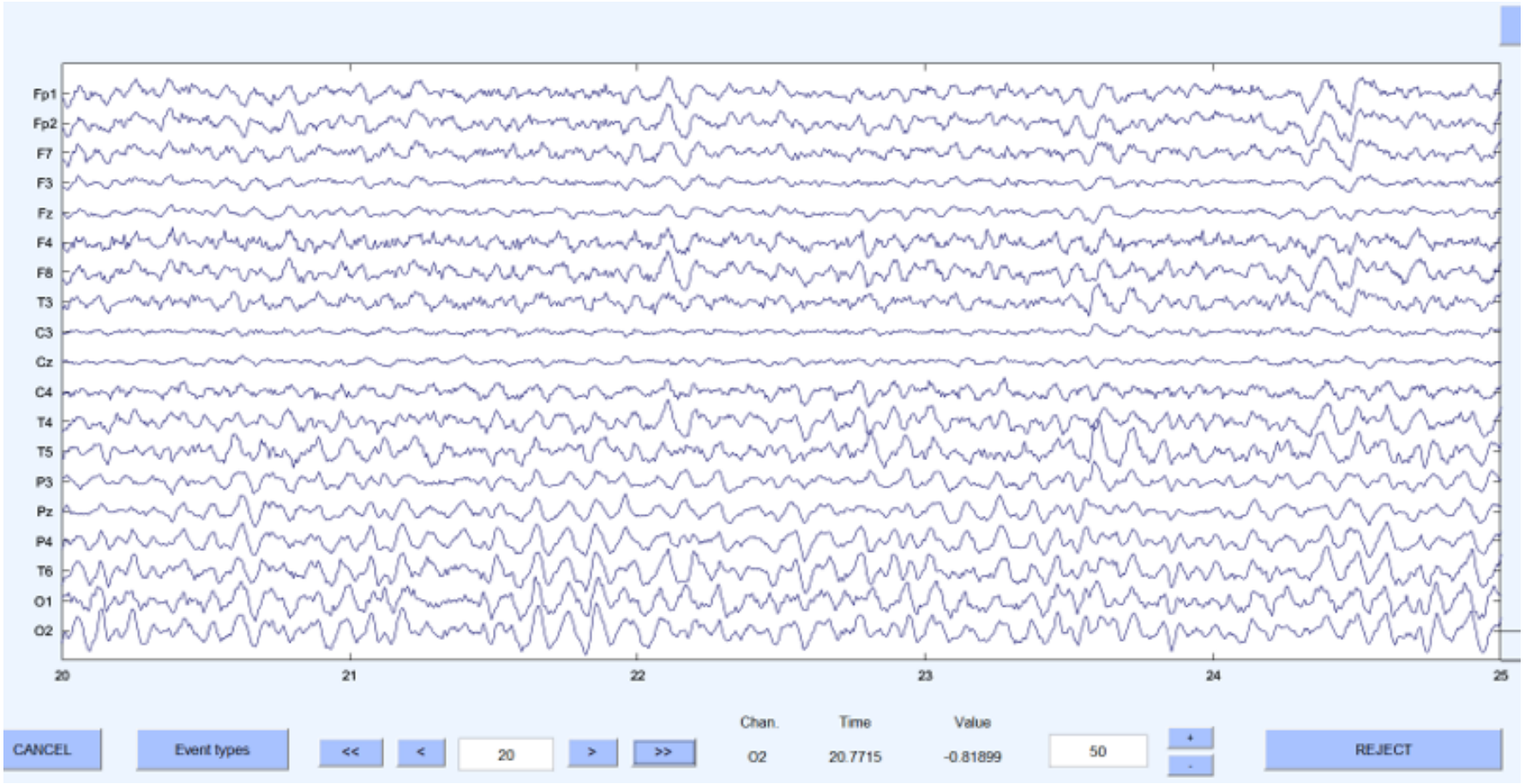


Figure 3.15: EEG EDF+ Set file for a baseline eyes closed study reviewed in EEGLAB.

MATLAB script Set2Spa (Stancak, 2022c) was used to compute absolute power spectral densities in 4 second segments using a FFT algorithm from artefact free EEG Set files. The script used integrated field trip functions in EEGLAB to compute absolute power density using the Welch periodogram method. Absolute power spectral density was computed using a one-second Hanning window and the window was shifted with 50% overlap.

The absolute power spectral density computed referred to the total energy intensity of an electrode at different frequency bands from 0-60 Hz and measured in $\mu V^2/Hz^{-1}$. The absolute power spectral density was calculated from the Pz electrode. The output graphs computed displayed the power spectral density ($\mu V^2/Hz^{-1}$) on a logarithmic scale.

The Set2Spa program (Stancak, 2022c) also computed and plotted for each trial individual power spectral density maps for the theta sub band 4-7 Hz relative to the Pz electrode. This allowed theta absolute power spectral density to be visualised across all electrodes relative to the chosen Pz electrode.

The absolute theta spectral density values were extracted from the spectral density output graphs for each trial. The output absolute power spectral density values were logarithmic and were converted back to their original value by taking the antilog and then used to calculate the relative theta power ratio for the theta frequency band. This allowed the absolute theta power spectral density for each trial to be compared relative to the baseline power values (Equation 3.1).

$$Relative\ theta\ power\ ratio\ = Absolute\ theta\ power\ \div Absolute\ theta\ power\ at\ baseline$$

Trial = high frequency, tonic or burst stimulation

Equation 3.1: Relative theta power ratio

3.2.9. SSEP data analysis.

For each trial lower limb SSEP data sets were converted to an EDF+ and all patient identifiers removed. Patients were allocated a code that comprised of the patient's individual pseudonymised number, the trial type (BL, HF, LF or Bu) and the SSEP side (RT SSEP or LT SSEP). The individual EDF+ files were exported to MATLAB R2022B for data analysis using a secured and encrypted patient export system used within the hospital to export patient files.

SSEP data artefact was removed using MATLAB R2022B using EEGLAB toolbox. MATLAB script edf2SEPs (Stancak, 2022a) was used initially to create Set files. SSEP sets contaminated by artefact can be reviewed. Large deviations in data due to artefact contamination can be rejected. Electrical contamination was removed using a notch filter at 48-52 Hz. The MATLAB script edf2SEPs (Stancak, 2022a) can be run a second time changing code line 19 from EDF to set and lines 20 and 21 to 0 will generate the SSEP responses as an output graph allowing latency and amplitude to be measured for the early P39 response.

The P39 amplitude ratio was then calculated (equation 3.2) for each trial in the symptomatic leg.

$$SSEP\ P39\ Amplitude\ ratio\ = SSEP\ amplitude\ \div SSEP\ amplitude\ at\ baseline$$

Trial = high frequency, tonic or burst stimulation

Equation 3.2: P37 amplitude ratio.

3.2.10 Trial questionnaire data analysis

3.2.10.1 Epworth sleepiness scale

Patients scored their current level of sleepiness against eight likelihood of sleep scenarios, scores of 0 = never, 1 = slight chance, 2 = moderate chance and 3 = high chance. All eight scores were added together, and the Epworth score expressed out of 24, with scores 0-10 classed as normal, 11-14 mild sleepiness, 15-17 moderate sleepiness and 18-24 severe sleepiness.

3.2.10.2 Pain Detect questionnaire

Patients scored their pain using three categories, category one related to their pain pattern and options included persistent pain with slight fluctuation, persistent pain with pain attacks, isolated pain attacks and fluctuating levels of pain. Category two considered if their pain experienced was radiating into the lower limb. Category three related to the grade of pain (phenotype), patients graded their pain against seven items scoring each out of 5. An interpretation algorithm was used to interpret the three sections with a total score out of 38. Scores between 0-12 were classed as nociceptive pain, with neuropathic pain being likely in 15% of patients and unlikely. Scores 13-18 were classed as unclear containing traits of both

nociceptive pain and neuropathic pain and scores 19-38 were classed as neuropathic pain, with neuropathic pain being likely in >90% of patients.

3.2.10.3 Hospital Anxiety and Depression scale (HADS)

Patients were presented with 14 items relating to either depression or anxiety, 7 linked to anxiety symptoms and 7 linked to depression symptoms. Patients scored their agreement with each item using a scale from 0-3. Anxiety and depression were interpreted separately. Scores between 0-7 were classed as normal, scores 8-10 classed as borderline and scores between 11-21 as abnormal and evidence of anxiety or depression.

3.2.10.4 Oswestry Disability Index

Patients scored their chronic lower back pain against sixteen sections (pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sexual activity, social life, travelling, mobility, self-care, usual activity, pain and anxiety and depression). The total score multiplied by 100 and expressed as a percentage. Scores between 0%-20% were classed as minimal disability and able to cope with most daily living activities, scores 21%-40% were classed as a moderate disability with patient management by conservative treatment. Pain impacts on sitting, lifting and standing. Travel and social life may also be impacted by pain with the patient being unfit to work. Personal care, sex life and sleep are not grossly affected. Scores of 41%-60% were classed as a severe disability with pain impacting on most daily living activities. Scores of 61%-80% were classed as crippled with pain impacting on all aspects of the patient's life. Scores of 81%-100% these patients are either bed -bound or are exaggerating symptoms.

3.2.10.5 VAS

Patients were asked to grade their current lower back and leg pain from 0-10 with 10 being their worst pain. VAS scores were used to calculate their percentage pain relief (equation 3.3).

$$Percentage\ pain\ relief\ = VAS\ at\ baseline - VAS\ at\ trial\ \div VAS\ at\ baseline$$

Trial = high frequency, tonic or burst stimulation

Equation 3.3: Percentage pain relief.

3.2.11 Adverse events or side effects

Patients were asked about any adverse events or side effects these were noted down.

3.2.12 Statistical method

A Shapiro-Wilk test was used to check whether data was normally distributed. A Shapiro-Wilk test was chosen due to the sample size of the present study (<50 subjects) and divided up into smaller subgroups. The hypothesis that was used to test for a normal distribution assumed that subgroup data was different and not normally distributed. The null hypothesis assumed that the data was taken from a normal distributed population.

Subgroups that were found not to be of a normal distribution were common log-transformed for parametric analysis. The data was analysed using parametric statistics due to the greater statistical power of parametric testing. A significant effect is more likely to be detected when one truly exists.

A one-way analysis of variance (ANOVA) was used to compare mean Epworth scores at baseline and at subsequent trials. A Tukey Honestly Significant Differences (HSD) post hoc pair wise comparison test was used to compare mean Epworth scores at baseline and at subsequent trials.

Paired data from the study was collected from the same subject either at baseline or at each trial. Data was compared using means in either data normally distributed or log transformed. A paired student t-test was used to compare data within the same subject and was independent consisting of continuous data (absolute theta power, relative theta power ratio and SSEP amplitude).

Responder and non-responder data from the study were from unrelated groups, with different people providing data for each group. An independent t-test was used to determine if the responder group was different from the non-responder group for each neurophysiological measure. Effect sizes were compared with the Cohen's d-statistic and displayed with either the paired t-test (within-subjects) or independent t-test (between subjects). Pain relief was correlated with relative theta power ratio and SSEP amplitude ratio using a Pearson correlation coefficient to determine the strength and direction of any relationship.

A series of receiver operator characteristic curves were created for relative theta power ratio, SSEP amplitude ratio and baseline absolute theta power maps for each stimulation programme in-order to evaluate over all diagnostic performance of the chosen neurophysiological measures at identifying responders. The area under the curve (AUC) was used to compare each ROC model produced and compared to random prediction (ROC = 0.5). The AUC scale used to compare each neurophysiology measure (Table 3.4) was adapted from Mandrekar, (2010) and consisted of a scale from 0 = a perfect inaccurate score to 1 = a perfect accurate score allowing for model quality as a diagnostic test to be evaluated.

Table 3.4: AUC scores used for the ROC evaluation

AUC score	**Model quality**
≥ 0.9	Outstanding
0.9	Excellent
0.8	Good
0.7	Acceptable
0.6	Better than random prediction
≤ 0.5	No better than random prediction

Models chosen for further analysis required a 95% confidence interval lower boundary to be better than random prediction with an AUC score that was good or higher and significantly different from random prediction ($P<0.05$).

Candidates identified from the ROC analysis had sensitivity, specificity and accuracy calculated from the study data. Data was categorised into true positive, false positive, true negative and false negative values.

Models identified were evaluated in terms of usefulness in clinical practice by combining sensitivity and specificity and compared to a scale between 1 = useless and 2 = perfect (Power et al., 2013) with tests scoring ≥1.5 being considered as useful for clinical practice.

3.2.13 Follow up method

At 6-months the patients were contacted to evaluate sustained clinical usefulness of the stimulation programmes used and whether this correlated to the neurophysiological

measures evaluated in the study. This involved checking their VAS and reviewing which stimulation programme they were using with pain relief.

3.2.14 Ethical approval

The study protocol was approved by the Walton Centre Clinical Governance group for research, Health Research Authority and Health and Care Research Wales (IRAS 283335) and Manchester Metropolitan University (EthOS 49167) available in the appendix.

3.2.15 Competing interests and sources of support

There were no competing interests for this study and no affiliations to be declared. The study was completed as a part of a Doctorate in Clinical Science at Manchester Metropolitan University.

Sponsorship was obtained from the Pain Relief Foundation receiving £21,400 to cover acquisition, operator, consumables, data analysis and publication costs. The project cost per patient for five trials which included a follow up trial was £338.70. The total cost of the study for 36 patients was £12,193.20 which was fully funded by the Pain Relief Foundation grant.

The Pain Relief Foundation is a registered charity (Registered Charity No 1156227) and provides sponsorship for research into chronic pain and treatments in humans. The Pain Relief Foundation is closely associated with the chronic pain service at the Walton Centre NHS Foundation Trust.

3.3 Results:

Thirty-seven patients were recruited from the MDT and consented. Ten patients withdrew from the study at the baseline appointment without data collection. Nine patients were unable to commit to the trial dates due to the distance they would need to travel to attend each trial. One patient decided to withdraw participation from the research study due to anxiety. No neurophysiological testing was undertaken on these patients, and they were removed from the study.

Twenty-seven patients received trial 1 either high frequency or burst stimulation. Four patients had the project terminate prematurely after trial 1. Of these patients, three were due to inadequate therapeutic paraesthesia mapping preventing the programming of tonic

stimulation (trial 2). Post implantation imaging revealed that in all three patients the percutaneous lead had migrated leading to suboptimal stimulation. One patient found tonic stimulation uncomfortable and refused to change the programme from high frequency stimulation. All four patients agreed to have trial 1 data included in the study.

In summary, a total of 27 patients were included in the study and 23 patients completed all three trials, all undergoing EEG recordings. Two patients had absent SSEPs at intensity levels 3x their sensory threshold and 1 patient found SSEPs too painful to participate in that portion of the trial.

Patient recruitment was limited by several different factors. Recruitment was initially impacted by winter related pressures which included COVID. Spinal cord stimulation implantation was classified as low clinical priority by the surgery list planning team and was often the first type of procedure to be cancelled due to winter pressures.

Patient participation following MDT recruitment was another limiting factor. As a specialist centre and tertiary hospital many patients travel from within the Cheshire and Merseyside region and for some patients even further from North Wales. The impact here was that nine patients were unable to travel to the Walton Centre for the additional trials due to distance and withdrew from the study, one patient withdrew due to anxiety a loss of 27% from MDT recruitment. One solution to this problem was to offer patients an in-patient option and a place on one of the wards. Three patients included in the study remained as in-patients on the ward but due to bed-pressures this was stopped for subsequent patients enrolled on the study.

The recruitment process was also impacted by neuromodulation nurse work force capacity issues. The SCS service was briefly suspended for 6 months to allow recruitment and training of specialist nurses, two nurses were successfully recruited and joined the team. Further delays in recruitment have been experienced due to a twelve-month theatre refurbishment project that has significantly reduced theatre activity and directly impacting on available lists for implantation.

Due to the difficulties in recruiting, 36 patients a second sample size was calculated using data from the meta-analysis which included the incidence of patients with FBSS following back surgery, 40% (Chan and Peng, 2011; Christelis et al., 2021, Chan and Peng, 2011;

Christelis et al., 2021) and the incidence of effective pain relief following SCS at 6 months follow up, 70% (Hayek et al., 2015; Thomson et al., 2017). The alpha level was set to 0.05 and power reduced to 80% the minimum power required for a study. The primary end point was classified as binomial, two possible outcomes, either a responder or non-responder to spinal cord treatment. The minimum sample size at 80% power was calculated to 20 patients.

The final decision was made to end recruitment based on the observed power being greater than 80% indicating that the observed sample size (27 patients) was sufficient for statistical analysis and justified ending the study.

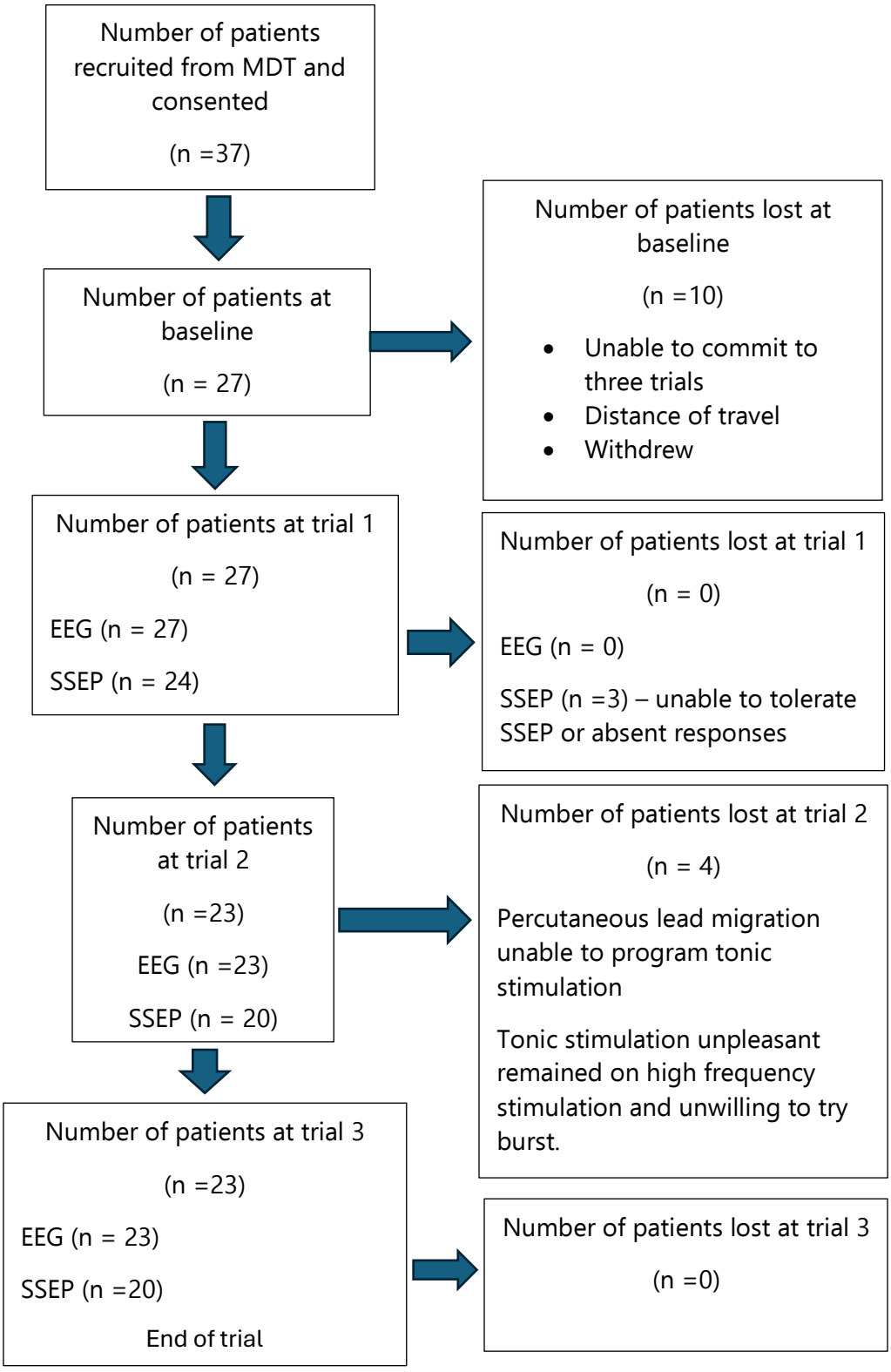


Figure 3.16: Recruitment workflow, layout modelled on the PRISMA flowchart (Liberati et al., 2009)

3.3.1 Adverse events

No patients reported any serious adverse events. Four patients reported minor adverse events with SCS during the study. One patient reported a transient burning sensation in the dorsal surface of digit 1 on his left foot, asymptomatic to the side of his pain, this persisted 24 hours and had resolved by trial 1. Two patients experienced unpleasant sensations in the thorax and chest wall when raising their arms with tonic stimulation, one of these patients developed an accompanying spontaneous myoclonus resulting in a minor leg jerk. The unpleasant sensations in the thorax are a recognised side effect of tonic SCS at levels T8-T12 and the motor component represented corticospinal tract activation due to stimulation spread. In this patient the percutaneous lead had migrated slightly during the study on post-trial imaging.

One patient reported a burning sensation over the implant area, headache and nausea with high frequency stimulation and this same patient reported hyperalgesia with tonic stimulation. The burning sensation and hyperalgesia experienced likely represented altered pain signalling in the sensing pain pathway due to SCS. His tonic and high frequency inter trial intervals were shortened to one day due to discomfort.

3.3.2 Study characteristics:

Patients included in the study had a mean age of 53 years (27 years – 71 years), twelve patients were female, and fifteen patients were male. The study characteristics for the study are included in Table 3.5. The mean pain duration for patients entering the study was 14 years ranging from 2 years to 44 years (standard error 1.90). Pain duration was skewed with a median age of 10 years. There was considerable variability between individual patient's pain duration with a variance of 98.3. The high degree of variability was biased by three patients having very long pain durations before being recruited for the trial, these outliers had pain durations of 31 years, 35 years and 44 years. Despite this huge variation in pain duration patients recruited had a mean VAS score for pain of 9 (7-10) with a standard error of the mean of 0.17, standard deviation of 0.89 and a low variance of 0.79. Despite patients entering the study with vastly different pain durations based on their VAS score patients entered the study with similar levels of pain severity.

Using the Pain Detect questionnaire to classify their pain mechanism, nineteen patients presented with a neuropathic pain mechanism, six patients with a mixed pain mechanism showing both neuropathic and nociceptive components and two patients presented with a nociceptive mechanism. All patients presented with lower back pain with pain radiating into one leg eighteen patients had pain radiating into the right leg and nine patients had pain radiating into their left leg.

Pain distribution patterns involving the lower limbs, sixteen patients had pain patterns extending to L5-S1**,** six patients L4-S1**,** three patients confined to L4 and L5 and two patients whose pain was localised to L4.

All patients presented with lumbar spine degeneration with varying degrees of foraminal stenosis in five patients this was associated with lumbar disc prolapse. The most common precipitating surgical factors were following spinal fusion with instrumentation, spinal decompression, discectomy or microdiscectomy or a combination of these. Four patients had scar tissue surrounding or compressing the S1 spinal nerve and one patient with scar tissue compressing their L5 spinal nerve with fibrosis around L4, one patient had an arachnoid cyst develop over L4-S1 levels following spinal fusion and instrumentation. Three patients presented with cauda equina syndrome with S1 rootlet compression with foot drop, two patients experienced injury to the lumbar spine following a road traffic accident and one patient following a hip replacement.

All included patients had spinal cord stimulator lead tips placed at either T8 or T9 with coverage down to T10 or T11.Twenty-two patients had the spinal cord stimulator placed at T8 to T11**.** One patient from this group had the percutaneous lead placed under endoscopy. Two patients had stimulator leads placed at T9-T11, one patient T8-T10 and two patients at T9-T10.

Table 3.5: Study characteristics patients 1-14.

No.	Sex	Age in years	Pain duration in years	Pain intensity at baseline (VAS score)	Surgery	Pain distribution
1.	F	55	4	10	Right disc prolapse L4	Lower back and right leg L4
2.	F	47	7	8	Left discectomy L3/L4	Lower back and left leg L4
3.	M	56	7	8	Right L4/S1 fusion with foraminal stenosis and decompression	Lower back and right leg L4-S1
4.	M	58	12	10	Interlaminar lumbar decompression	Lower back and left leg L4-L5
5.	F	39	9	8	Microdiscectomy L5-S1, scar tissue S1	Lower back and left leg L5-S1
6.	M	37	5	7	Cauda equina syndrome, S1 foot drop and bladder dysfunction	Lower back and right leg L5-S1
7.	F	48	9	10	Disc prolapses at L4/L5, L5/S1, fenestration and microdiscectomy	Lower back and right leg L4-L5
8.	M	27	2	9	L4/L5 discectomy	Lower back and right leg L4-S1
9.	M	48	15	9	L4-S1 spinal fusion with decompression, arachnoid cyst at L4-S1	Lower back and right leg L4-S1
10.	M	71	15	8	Multilevel degeneration, lumbar discectomy L5-S1, scar tissue S1	Lower back and right leg L5-S1
11.	M	66	8	9	Road traffic accident, lower back and left leg injury	Lower back and left leg L5-S1
12	F	45	31	9	L5-S1 spinal fusion, L4/L5 disc replacement	Lower back and right leg L4-S1
13.	M	66	10	10	Degenerative lumbar spine	Lower back and right leg L5-S1
14.	F	55	35	10	Degenerative lumbar spine, disc replacement L4-S1	Lower back and right leg L5-S1

Table 3.6: Study characteristics patients 15-25.

No.	Sex	Age in years	Pain duration in years	Pain intensity at baseline (VAS score)	Surgery	Pain distribution
15.	F	58	10	10	Spinal fusion L5-S1	Lower back and right leg L5-S1
16.	M	66	14	9	Discectomy L5/S1, scar tissue around right S1	Lower back and right leg L5-S1
17.	M	60	10	9	Hip replacement	Lower back and left leg L5-S1
18.	M	45	6	8	Cauda equina syndrome post road traffic accident, discectomy L5-S1	Lower back and left leg L5-S1
19.	M	71	44	9	Scoliosis fixation T9-T10, thoracic myelopathy T9-L1, scar tissue T9, spondylolisthesis L4-L5, foraminal stenosis L4-S1	Lower back and left leg L5-S1
20.	F	36	7	10	Spinal fusion with microdiscectomy L4-L5, disc prolapse L5-S1	Lower back and right leg L4-S1
21.	F	52	9	9	Microdiscectomy and discectomy L5-S1	Lower back and right leg L5-S1
22.	F	44	6	10	Microdiscectomy L5-S1, scarring compressing S1, incontinence	Lower back and left leg L5-S1
23.	F	64	24	10	Spinal fusion L5-S1, decompression L5-S1, swelling S1, epidural scar S1	Lower back and left leg L5-S1
24.	M	65	19	10	Cauda equina syndrome, discectomy L5-S1, disc prolapse L5-S1, left lateral recess stenosis, left foraminal stenosis L5-S1	Lower back and right leg L5-S1
25.	F	41	16	10	Discs prolapse, microdiscectomy L4-L5, L5-S1	Lower back and right leg L4-S1

Table 3.7: Study characteristics patients 26-27.

No.	Sex	Age in years	Pain duration in years	Pain intensity at baseline (VAS score)	Surgery	Pain distribution
26.	M	62	20	9	Spinal fusion L4-S1, instrumentation loose L3-L4 repeat	Lower back and right leg L4-S1
27	M	49	15	8	Repeated spinal decompression surgery (x5) at L4/L5 scar tissue at L5 and fibrotic tissue at L4, stenosis at L4/L5 with L5 root impingement	Lower back and right leg pain at L5, left leg paraesthesia at L5 without pain.

3.3.3 Analgesic medication

Most patients included in the study were receiving a polypharmacy of pain medication which included anti-convulsant drugs (n = 20), opiates (n = 26), non-opiates (n = 17), tricyclic antidepressants and other antidepressants (n =14).

Anti-convulsant used were gabapentin (n=9), pregabalin (n=10) and lamotrigine (n=1) Opiates used were morphine (n = 7), buprenorphine patch (n = 3), oxycodone hydrochloride (n = 4), tramadol (n = 5), codeine/co-codamol (n=5), tapentadol (n= 2) and Fentanyl (n=1). Non opiates used were paracetamol (n = 10), naproxen (n = 5), aspirin (n=1), ibuprofen (n = 1). Tricyclic antidepressants and other antidepressants used were amitriptyline (n=4), duloxetine (n=5), citalopram (n=2), sertraline (n=1), nortriptyline (n=1) and mirtazapine (n=1).

The different combinations of analgesic polypharmacy medications used during the study is summarised in table 3.8. Medication was not, reduced or stopped for the trial.

Table 3.8: Medication and implantation level

No.	Pain mechanism (Pain detect)	Medication for pain relief	SCS electrode tip and coverage
1.	Neuropathic	Paracetamol, amitriptyline	T8-T11
2.	Mixed	Gabapentin, paracetamol, duloxetine	T9-T11
3.	Mixed	Paracetamol, Gabapentin, Morphine, amitriptyline	T8-T11
4.	Neuropathic	Paracetamol	T8-T11
5.	Neuropathic	Paracetamol, Buprenorphine	T8-T11
6.	Neuropathic	Oxycodone hydrochloride, pregabalin, citalopram, morphine	T8-T11
7.	Neuropathic	Gabapentin, duloxetine, buprenorphine	T8-T11
8.	Nociceptive	Pregabalin, duloxetine, co-codamol	T8-T11
9.	Neuropathic	Gabapentin, morphine	T8-T11
10.	Nociceptive	Gabapentin, paracetamol, Citalopram	T8-T11
11.	Neuropathic	Pregabalin, naproxen, tramadol, sertraline, mirtazapine	T8-T11
12.	Mixed	Paracetamol, Neproxen, pregabalin, oxycodone hydrochloride, amitriptyline	T8-T11
13.	Neuropathic	Pregabalin, co-codamol	T8-T11
14.	Neuropathic	co-codamol	T8-T11
15.	Neuropathic	Oxycodone hydrochloride	T8-T11
16.	Mixed	Oxycodone hydrochloride, Gabapentin	T9-T10
17.	Mixed	Buprenorphine, codeine, duloxetine	T8-T11
18.	Neuropathic	Fentanyl, paracetamol, nortriptyline	T8-T11
19.	Mixed	Paracetamol, Naproxen, Pregabalin, codeine phosphate, aspirin	T8-T11
20.	Neuropathic	Paracetamol, morphine, tapentadol	T8-T11
21.	Neuropathic	Gabapentin, ibuprofen	T8-T10
22.	Neuropathic	Gabapentin, morphine	T9-T11
23.	Neuropathic	Pregabalin, morphine, tapentadol	T8-T11
24.	Neuropathic	Gabapentin, naproxen, duloxetine	T8-T11
25.	Neuropathic	Pregabalin, tramadol, amitriptyline	T8-T11
26.	Neuropathic	Pregabalin, lamotrigine, morphine, naproxen	T8-T9
27.	Neuropathic	Tramadol and pregabalin	T9-T10

3.3.4 Assessment of sleepiness

Sleepiness was assessed with the Epworth sleepiness scale at baseline and each subsequent trial and compared using a one -way analysis of variance (ANOVA).

The hypothesis used in the analysis was the mean Epworth scores at baseline and subsequent trials were different and the null hypothesis that mean Epworth scores were equal between the baseline and subsequent trials.

There were no statistically significant differences between group means determined by one-way ANOVA F (3,96) = 0.70, p = 0.55, Eta squared = 0.022.

A Tukey HSD post hoc test revealed that there were no paired differences between mean Epworth scores at baseline and subsequent trials (p = 0.810 to 0.99). Epworth sleepiness mean scores at baseline and subsequent trials (high frequency, tonic and burst stimulation) were normal showing average amounts of daytime sleepiness across the study (Table 3.9).

Table 3.9: Statistical comparison of sleepiness in high frequency, tonic and burst stimulation (0-7 no sleepiness, 8-9 average amounts of daytime sleepiness, 10-15 excessive daytime sleepiness, 16-24 excessive daytime sleepiness requiring medical intervention)

Trial	**Mean**	**95% confidence interval**	**Variance**	**Shapiro-wilk**	**Skew**	**Median**
Baseline (n=27)	8.7	6.9-10.4	19.5	0.92 P = 0.039 Not normal distribution	-0.5	7.0
High frequency trial (n = 27)	7.8	5.6-9.9	29.3	0.88 P = 0.08 Normal distribution	0.81	6.0
Tonic stimulation trial (n = 23)	7.4	5.3-9.5	23.4	0.92 P = 0.06 Normal distribution	0.87	6.0
Burst stimulation trial (n=23)	8.0	5.6 – 10.3	28.8	0.88 P = 0.01 Not normal distribution	0.74	6.0

At baseline and subsequent trials outliers were noted with Epworth sleepiness scores showing mild levels of excessive daytime sleepiness.

3.3.5 VAS Scores

Patients were dichotomised into two subgroups based on VAS score. VAS score reduction ≥50% from baseline VAS scores were categorised as responders and those with VAS scores <50% reduction from baseline as non-responders (Table 3.10).

Table 3.10: Subgroups categorised into responders and non-responders.

Responder or non-responder category	**Stimulation subgroup**		
	High frequency stimulation	**Tonic stimulation**	**Burst stimulation**
Responder	16	14	15
Non-responder	11	9	8

Nine patients responded to all three stimulation programmes (high frequency, tonic and burst stimulation), six patients responded to at least two SCS programmes and five patients to at least one SCS programme. Seven patients failed to respond to any of the three SCS programmes.

3.3.6 Percentage pain relief

Percentage pain relief for responders and non-responders for each trial were compared using an independent t-test. Descriptive statistics for responders and non-responders are summarised in Tables 3.11 and 3.12.

Table 3.11: Pain relief responders' descriptive statistics

Trial	Mean pain relief percentage	Standard error	95% confidence interval	Variance	Shapiro-wilk
High frequency trial (n =16)	63	3.96	55-70	220.0	P = 0.03 Not normal distribution
Tonic stimulation trial (n = 14)	68	3.90	60-75	217.3	P = 0.33 Normal distribution
Burst stimulation trial (n= 15)	69	3.97	50-100	236.9	P = 0.08 Normal distribution

Table 3.12: Pain relief non-responders' descriptive statistics

Trial	Mean pain relief percentage	Standard error	95% confidence interval	Variance	Shapiro-wilk
High frequency trial (n =11)	24	4.27	15-34	200.8	P = 0.70 Normal distribution
Tonic stimulation trial (n = 9)	24	4.79	12-35	206.7	P = 0.41 Normal distribution
Burst stimulation trial (n= 8)	16	5.77	2-29	267.0	P = 0.28 Normal distribution

For high frequency stimulation a statistically significant difference between responder and non-responders group means was determined by an independent t-test, $t(24) = 6.149$, $p = <0.001$ and $d = 0.16$. One responder patient experienced 100% pain relief, and one non-responder patient experienced no pain relief.

For tonic stimulation a statistically significant difference between responder and non-responders group means was determined by an independent t-test, $t(21) = 7.040$, $p = <0.001$, $d = 14.6$. One responder patient experienced 100% pain relief, and one non-responder patient experienced no pain relief.

For burst stimulation a statistically significant difference between responder and non-responders group means was determined by an independent t-test, $t(21) = 7.677$, $p = <0.001$, $d = 15.7$. Two responder patients experienced 100% pain relief, and three non-responder patients had no pain relief.

In all three trials non-responders experienced suboptimal pain relief.

3.3.7 Pain characteristics

Pain was categorised into either nociceptive, mixed or neuropathic pain using the Pain Detect scoring system. Pain Detect scores at baseline and at each trial were compared using a paired t-test. Descriptive statistics for responders and non-responders are summarised in Tables 3.13 and 3.14.

Responder patients presented on average with strong to very strong burning, prickling/crawling and electric shock sensations. Associated numbness and pain in response to temperature tended to be classed as moderate with outliers classifying as strong to very strong. Allodynia at baseline was rarely experienced across all three responder groups however when experienced allodynia was classed as moderate to very strong. Pain was isolated to the lower back with radicular pain spreading into either leg.

Table 3.13: Pain Detect responders' descriptive statistics (0-12 = nociceptive, 13-18 mixed, 19-38 = neuropathic)

Trial	**Mean Pain Detect score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	21	1.48	18-24	35.2	0.88 Normal distribution
High frequency stimulation (n =16)	14	1.48	10-17	35.4	0.63 Normal distribution
Tonic stimulation baseline (n=14)	20	1.70	16-23	41.9	0.67 Normal distribution
Tonic stimulation (n=16)	12	1.34	9-14	25.1	0.28 Normal distribution
Burst stimulation baseline (n=15)	20	1.61	16-23	39.0	0.66 Normal distribution
Burst stimulation (n=15)	12	1.71	8-16	43.4	0.86 Normal distribution

Table 3.14: Pain Detect non responders' descriptive statistics (0-12 = nociceptive, 13-18 mixed, 19-38 = neuropathic)

Trial	**Mean Pain Detect score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	20	1.6	16-23	28.6	0.07 Normal distribution
High frequency stimulation (n =11)	17	1.2	14-19	15.6	0.03 Not normal distribution
Tonic stimulation baseline (n=9)	21	1.1	18-23	11.0	0.12 Normal distribution
Tonic stimulation (n=9)	18	1.5	15-22	19.3	0.02 Not normal distribution
Burst stimulation baseline (n=8)	21	1.2	18-24	11.1	0.35 Normal distribution
Burst stimulation (n=8)	18	2.1	12-23	38.6	0.58 Normal distribution

In the responder subgroup for high frequency stimulation a statistically significant difference between baseline and high frequency stimulation was determined by a paired t-test, $t(15) = 2.975$, $p = 0.009$, $d = 9.49$. High frequency stimulation reduced mean neuropathic Pain Detect scores at baseline to a mean mixed pain score. Patients reported a reduction in strong to very strong burning, prickling/crawling and electric shock sensations and associated numbness. Pain patterns shifted from persistent pain with pain attacks to persistent pain with slight fluctuation in pain and corresponded to the marked reduction in strong to very strong electric shock sensations as a part of their pain profile. However, electric shock sensations persisted at moderate to strong intensities in eight patients, over 50% of the subgroup, in three patients this was accompanied by allodynia.

In the non-responder subgroup for high frequency stimulation a statistically significant difference between baseline and high frequency stimulation was determined by a paired t-test, $t(10) = 3.034$, $p = 0.013$. High frequency stimulation reduced baseline mean neuropathic Pain Detect scores to mean mixed Pain Detect scores. Patients reported a reduction in the moderate burning and prickling sensations, numbness and pain to light pressure. However moderate electric shock sensations persisted in five patients and strong in two patients with patients reporting a mixed pain profile. One patient reported a nociceptive pain profile at baseline (Pain detect = 7) which remained unchanged with high frequency stimulation. On average pain patterns shifted from persistent pain with pain attacks to isolated pain attacks characterised by moderate to strong electric shock sensations which persisted despite high frequency stimulation.

No statistically significant difference between responder and non-responder subgroup means was determined by an independent t-test, $t(24) = 0.926$, $p = 0.363$, $d = 5.2$.

In the responder subgroup for tonic stimulation a statistically significant difference between baseline and tonic stimulation was determined by a paired t-test, $t(13) = 4.063$, $p = 0.001$. Tonic stimulation reduced mean neuropathic Pain Detect scores at baseline to a mean nociceptive Pain Detect score. Patients reported reduced strong to very strong burning, prickling/crawling sensations, pain with light pressure and electric shock sensations and associated numbness. Pain with light touch (allodynia) was completely abolished in the minority of patients experiencing this symptom at baseline (n=2). On average pain patterns shifted from persistent pain with pain attacks to either persistent pain with slight fluctuation

in pain or isolated pain attacks. A minority of patients still reported moderate burning and prickling/crawling sensations (n = 3) and moderate electric shock sensations (n = 2).

In the non-responder subgroup for tonic stimulation no statistically significant difference between baseline and tonic stimulation was determined by a paired t-test, $t(8) = 1.54$, $p = 0.162$. Tonic stimulation reduced baseline neuropathic Pain Detect scores to mixed Pain Detect scores. In contrast to the responder subgroup, no patients from this subgroup reported nociceptive Pain Detect scores. Patient pain profiles remained dominated by moderate to very strong burning sensations, moderate to strong prickling, moderate to very strong electric shock sensations and moderate to very strong paraesthesia.

A statistically significant difference between responder and non-responder's subgroup means was determined by an independent t-test, $t(21) = -3.136$, $p = 0.005$, $d = 0.17$.

In the responder subgroup for burst stimulation a statistically significant difference between baseline and burst stimulation was determined by a paired t-test, $t(14) = 3.081$, $p = 0.008$. Burst stimulation reduced mean neuropathic Pain Detect scores at baseline to a mean nociceptive Pain Detect score. Patients reported reduction in moderate burning and crawling sensation with electric shock sensations persisting. Pain patterns shifted from persistent pain with pain attacks to persistent pain with slight fluctuations, this was to a lesser extent than high frequency or tonic stimulation.

In the non-responder subgroup for burst stimulation no statistically significant difference between baseline and burst stimulation was determined by a paired t-test, $t(7) = 1.739$, $p = 0.126$. Burst stimulation reduced baseline neuropathic Pain Detect scores to mixed Pain Detect scores. Patients report reduction in very strong burning sensations, moderate to strong prickling sensations, strong to very strong electric shock sensations, moderate to strong numbness and strong pain to light pressure. Moderate burning sensations, very strong allodynia, moderate pain to temperature and very strong numbness all increased in intensity from baseline. Burst stimulation reduced the number of patients reporting pain patterns described as persistent pain with pain attacks or persistent pain with slight fluctuation in pain with two patients reporting pain attacks with pain between them.

No statistically significant difference between responder and non-responder's subgroup means was determined by an independent t-test, $t(21) = -1.998$, $p = 0.059$, $d = 6.46$. The

critical t-value = 2.080 was larger than the absolute t-value 1.998 and failed to reject the null hypothesis. In the burst stimulation responder subgroup, the electric shock sensation component of the pain profile remained unchanged decreasing any significant difference between responder and non-responders.

3.3.8 Quality of life and disability

The patient's quality of life and level of disability was assessed using the ODI. ODI scores at baseline and at each trial were compared using a paired t-test. Descriptive statistics for responders and non-responders are summarised in Tables 3.15 and 3.16.

At baseline most patients reported their physical disability due to chronic pain on the ODI as either a severe disability or as crippled with their back and leg pain impacting on most aspects of their life indicating that they required therapeutic intervention to control their pain. Patients typically struggled with personal care, walking, sitting, standing, sleeping, they described impacts on their sex and social life with many patients struggling to travel anywhere. Pain was found to have significant impacts on work, home and family life. Many patient goals were around interacting with their family.

Table 3.15: ODI responders' descriptive statistics (0-20 minimal disability, 21-40 moderate disability, 41-60 severe disability, 61-80 crippled, 81-100 bed bound or exaggerating symptoms)

Trial	**Mean ODI score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	62	2.47	56-67	97.6	0.51 Normal distribution
High frequency stimulation (n =16)	52	3.89	44-60	243.0	0.37 Normal distribution
Tonic stimulation baseline (n=14)	59	2.74	53-65	105.4	0.11 Normal distribution
Tonic stimulation (n=16)	44	4.5	34-54	288.3	0.08 Normal distribution
Burst stimulation baseline (n=15)	57	2.6	51-62	101.0	0.14 Normal distribution
Burst stimulation (n=15)	44	4.7	34-54	335.0	0.33 Normal distribution

Table 3.16: ODI non-responders' descriptive statistics (0-20 minimal disability, 21-40 moderate disability, 41-60 severe disability, 61-80 crippled, 81-100 bed bound or exaggerating symptoms)

Trial	**Mean ODI score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	59	3.3	51-66	123.8	0.07 Normal distribution
High frequency stimulation (n =11)	58	3.9	51-66	134.5	0.29 Normal distribution
Tonic stimulation baseline (n=9)	60	3.6	51-68	121.6	0.11 Normal distribution
Tonic stimulation (n=9)	60	3.9	51-69	138.0	0.52 Normal distribution
Burst stimulation baseline (n=8)	64	3.4	55-72	97.8	0.06 Normal distribution
Burst stimulation (n=8)	63	3.6	54-72	108.5	0.01 Not normal distribution

All three SCS programmes elicited significant reductions in ODI scores in responder subgroups, with a paired t-test. High frequency stimulation elicited a $t(15) = 2.993$, $p = 0.009$, $d = 12.7$, tonic stimulation a $t(13) = 3.486$, $p = 0.004$, $d = 16.4$ and burst stimulation $t(14) = 2.805$, $p = 0.014$, $d = 17.9$ with large effect sizes. Disability was improved from patients presenting as crippled to severe disability. Pain remained their main problem despite significant pain relief however improvements were noted in activities of daily living which included walking, standing, sitting and self-care. The high frequency responder subgroup was biased by a higher proportion of patients scoring as crippled (10 out of 16 patients) in comparison to the other responder subgroups. In both high frequency and tonic responder subgroups SCS reduced ODI scores into the minimal disability range allowing patients to cope with most daily living activities, these patients were associated with 100% pain relief.

In contrast non-responders from all three stimulation programs showed no statistically significant difference between baseline and SCS. High frequency stimulation, $t(10) = 0.327$, $p = 0.751$, $d = 4.33$, tonic stimulation $t(8) = -0.169$, $p = 0.870$, $d = 4.92$ and burst stimulation $t(7) = 1.027$, $p = 0.339$, $d = 0.01$. All three SCS programmes had minimal effects on ODI scores with burst stimulation the least. Patients remained within baseline ODI score ranges with most patients classified as severely disabled due to their chronic pain.

In the high frequency stimulation group responders and non-responders were not statistically significantly different when using an independent t-test, $t(25) = 1.121$, $p = 0.273$, $d = 14.1$. In this group the higher proportion of chronic disability patients in the responder subgroup that reduced to a severe disability range was offset by the non-responders that failed to change from baseline ODI scores also in the severe disability range masking any significant differences between these two groups.

Tonic and burst stimulation were found to be significantly different for responders and non-responders. Tonic stimulation independent t-test, $t(21) = 2.463$, $p = 0.022$, $d = 15.2$ and burst stimulation independent t-test, $t(21) = 2.323$, $p = 0.030$, $d = 0.19$ significant differences were associated with improvements in disability in responders and minimal changes in the non-responder subgroups.

In summary all three SCS programmes improved disability and quality of life in responder subgroups. Suboptimal effects on pain relief experienced by non-responders failed to improve disability.

3.3.9 Anxiety and Depression

Anxiety and depression were measured on the Hospital Anxiety and Depression scale. Anxiety and depression scores at baseline and at each trial were compared using a paired t-test.

Baseline anxiety scores ranged from normal to borderline with outliers in the abnormal range (Table 3.17 and Table 3.18), a surprise finding for patients presenting with chronic pain and ODI scores in the severe disability to chronic range. Chronic pain often creates a fear of movement due to triggering painful episode and with this increased anxiety. I was expected a higher proportion of patients with abnormal levels of anxiety. In this study patients presented with normal to borderline levels for anxiety.

In the high frequency responder subgroup 5 out of 16 patients scored as abnormal for anxiety and a similar pattern was observed for tonic stimulation (3 out of 14) and burst stimulation (4 out of 15) far lower than expected. Patients tended to be either functioning in the normal range for anxiety or lower boundary of borderline with fewer patients presenting with abnormal anxiety who were outliers. The same pattern was observed in the baseline non-responder subgroup.

Table 3.17: Anxiety scores for responders' descriptive statistics (0-7 normal, 8-10 borderline, 11-21 abnormal).

Trial	**Mean anxiety score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	9	1.0	6-11	16.6	0.02 Not normal distribution
High frequency stimulation (n =16)	7	0.82	4-8	10.8	0.87 Normal distribution
Tonic stimulation baseline (n=14)	8	1.0	5-10	15.6	0.13 Normal distribution
Tonic stimulation (n=16)	5	0.84	3-7	10.0	0.14 Normal distribution
Burst stimulation baseline (n=15)	7	0.96	5-9	13.9	0.14 Normal distribution
Burst stimulation (n=15)	5	0.90	3-7	12.4	0.13 Normal distribution

Table 3.18: Anxiety scores for non-responders' descriptive statistics (0-7 normal, 8-10 borderline, 11-21 abnormal).

Trial	**Mean anxiety score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	7	1.0	5-10	12.2	0.46 Normal distribution
High frequency stimulation (n =11)	8	0.9	5-10	9.0	0.96 Normal distribution
Tonic stimulation baseline (n=9)	8	1.1	5-10	12.6	0.19 Normal distribution
Tonic stimulation (n=9)	7	1.1	4-9	10.9	0.73 Normal distribution
Burst stimulation baseline (n=8)	9	1.3	5-11	13.5	0.21 Normal distribution
Burst stimulation (n=8)	8	1.3	4-11	14.5	0.48 Normal distribution

All three SCS programmes showed significant reductions with mild anxiety scores at baseline. In both responder and non-responder subgroups mean anxiety scores were either normal or borderline at baseline and following SCS anxiety scores reduced to normal anxiety levels or remained within borderline anxiety levels. Anxiety score reduction was observed to be significant in the responder subgroup in patients with either borderline upper boundary anxiety scores or outlier abnormal anxiety scores at baseline.

In the responder subgroup for high frequency stimulation a statistically significant difference between baseline and high frequency stimulation was determined by a paired t-test, $t(15) = 2.250$, $p = 0.040$, $d = 0.2$. The effect size although small suggests that high frequency stimulation significantly improved anxiety within this patient subgroup. This finding may be linked to reduced fear of movement often seen with chronic pain due to the significant pain relief experienced by high frequency stimulation. In contrast the non-responder subgroup for high frequency stimulation found no statistically significant difference between baseline and high frequency stimulation when determined by a paired t-test, $t(10) = -0.431$, $p = 0.683$, $d = 2.1$. Non-responders showed minimal changes between their normal to borderline anxiety scores.

In contrast both tonic and burst stimulation found statistically significant differences between baseline and SCS stimulation with a paired t-test, tonic stimulation found a $t(13) = 2.619$, $p = 0.021$, $d = 3.67$ and burst stimulation $t(14) = 3.359$, $p = 0.005$, $d = 2.69$. Both stimulation programs elicited no statistically significant differences in the non-responder anxiety scores for tonic stimulation $t(8) = 0.758$, $p = 0.470$, $d = 3.51$ and burst stimulation $t(8) = 0.758$, $p = 0.470$, $d = 3.91$ with similar effect sizes. Both effect sizes were significantly larger than the high frequency stimulation responder subgroup. All three stimulation programmes had minimal effects on anxiety with suboptimal pain relief seen in all three non-responder subgroups. No significant differences were found between responders and non-responders for high frequency stimulation $t(25) = 1.13$, $p = 0.269$, $d = 3.18$, tonic stimulation $t(21) = -1.405$, $p = 0.175$, $d = 3.22$ or burst stimulation $t(21) = -1.571$, $p = 0.131$, $d = 3.62$.

This group of FBSS patients were more affected by depression than anxiety with mean baseline scores in the responder subgroups being abnormal in the high frequency subgroup and borderline in the tonic and burst stimulation subgroups (Table 3.19).

Table 3.19: Depression scores for responders' descriptive statistics (0-7 normal, 8-10 borderline, 11-21 abnormal).

Trial	**Mean depression score**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	11	0.78	9-12	9.8	0.80 Normal distribution
High frequency stimulation (n =16)	8	0.92	6-10	13.6	0.52 Normal distribution
Tonic stimulation baseline (n=14)	10	0.96	7-11	12.9	0.17 Normal distribution
Tonic stimulation (n=16)	7	0.96	4-9	13.0	0.13 Normal distribution
Burst stimulation baseline (n=15)	10	0.92	7-11	12.8	0.12 Normal distribution
Burst stimulation (n=15)	7	1.0	4-9	16.28	0.24 Normal distribution

Table 3.20: Depression scores for non-responders' descriptive statistics (0-7 normal, 8-10 borderline, 11-21 abnormal).

Trial	Mean depression score	Standard error	95% confidence interval	Variance	Shapiro-wilk (p-value)
High frequency baseline (n =11)	8	1.0	5-10	12.4	0.18 Normal distribution
High frequency stimulation (n =11)	8	1.0	5-10	13.2	0.95 Normal distribution
Tonic stimulation baseline (n=9)	9	1.0	6-11	10.2	0.32 Normal distribution
Tonic stimulation (n=9)	7	1.22	4-10	13.5	0.15 Normal distribution
Burst stimulation baseline (n=8)	9	1.1	5-11	10.5	0.33 Normal distribution
Burst stimulation (n=8)	8	1.5	4-11	19.3	0.32 Normal distribution

High frequency, tonic and burst stimulation significantly reduced depression scores from borderline (upper boundary)/abnormal to normal/borderline (lower boundary). A paired t test found for high frequency stimulation t (15) = 4.502, p = <0.001, d = 2.22 tonic stimulation t (13) = 4.545, p = <0.001, d = 2.29 and burst stimulation t (14) = 3.205, p = 0.006, d = 3.22 with large effect sizes. Three patients remained depressed with high frequency stimulation, two patients with tonic stimulation and one patient with burst stimulation despite having good pain relief.

In contrast high frequency and burst stimulation showed minimal effects on depression in the non-responder subgroups (Table 3.20). No significant differences from baseline were found with a paired t-test for high frequency stimulation, t (10) = 0.00, p = 1.0, d = 2.04 and burst stimulation t (7) = 0.397, p = 0.703, d = 2.66. Depression scores remained within baseline values.

A significant difference was found in the non-responder tonic stimulation subgroup using a paired t-test, (), t (8) = 2.626, p = 0.030, d = 1.26, depression scores reduced from border to normal with a large effect size.

No significant differences were found using an independent t-test between responders and non-responders, with high frequency stimulation, t (25) = 0.059, p = 0.953, d = 3.66, tonic stimulation, t (21) = 0.286, p = 0.778, d = 3.63 and burst stimulation t (21) = 0.686, p = 0.500, d = 4.16. In both responder and non-responder subgroups mean depression scores were borderline/abnormal at baseline except for the responder subgroup for high frequency stimulation. During SCS mean depression scores were either from the upper boundary of normal or borderline in both responder and non-responder subgroups. Significant differences in depression scores were observed in the responder subgroups from all stimulation programs and most evident in patients with depression scores from the upper boundary of borderline or abnormal outliers. This pattern was also observed in the tonic stimulation non-responders.

In summary, high frequency, tonic and burst stimulation significantly reduced depression in SCS responders. In non-responders these effects were suboptimal with depression being like baseline. The difference in depression observed in responders and non-responders was not significant. Both anxiety and depression scores at baseline were borderline abnormal a

finding that was not expected. This finding may indicate in this group of patients reduced connectivity between the lateral spinothalamic tract and default network as described by the triple network model for pain and optimal pain conditions for SCS.

3.3.10 Absolute theta power

Absolute theta power was measured in $\mu V^2/Hz$ at baseline and from each trial of SCS (high frequency, tonic and burst stimulation. A reoccurring baseline absolute theta power pattern was seen in twelve out of sixteen high frequency responders, ten out of fourteen tonic responders and eleven out of fifteen burst responders. In total sixteen patients out of twenty-seven patients included presented with this pattern at baseline. In non-responder patients the pattern was absent in 7 out of 11 patients with high frequency stimulation, 5 out of 9 patients with tonic stimulation and 5 out of 9 patients with burst stimulation.

The pattern consisted of concentric rings of elevated absolute theta power over the dorsolateral prefrontal electrodes (F7, F3, Fz, F4 and F8), electrodes C3 and C4 and parietal electrodes Pz, P3 and P4 forming a ring. Theta power was seen to reduce within concentric rings towards the vertex at Cz. Variations to this pattern included asymmetry over the vertex offset towards either C3 or C4 or P3 or P4. The size of the field relating to absolute theta power reduction over the vertex region was seen to vary and was always lower than the surrounding ring.

Throughout this study this pattern will be referred to as the absolute theta power concentric pattern (Figure 3.17).

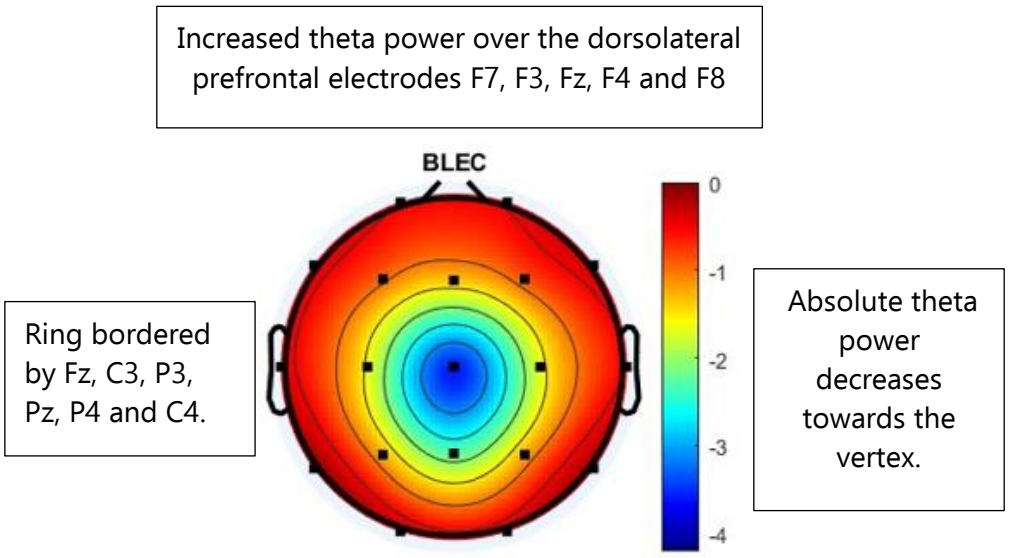


Figure 3.17: Absolute theta power concentric pattern seen in most responders to high frequency, tonic and burst stimulation. Absolute theta power forms as concentric rings with inhibition over the vertex electrode at Cz.

The sixteen patients presenting with the absolute theta power concentric pattern at baseline (Figure 3.18), five patients presented with minor variations to this pattern. Variations in the absolute theta power concentric pattern included asymmetries noted over the C3, C4 or towards Pz electrode. All baseline concentric patterns were associated with inhibition over the vertex at Cz at varying intensities, the least being patients 13 and 22. Thirteen patients had Pain Detect scores for neuropathic pain and three patients had Pain Detect scores that were for a mixed pain profile.

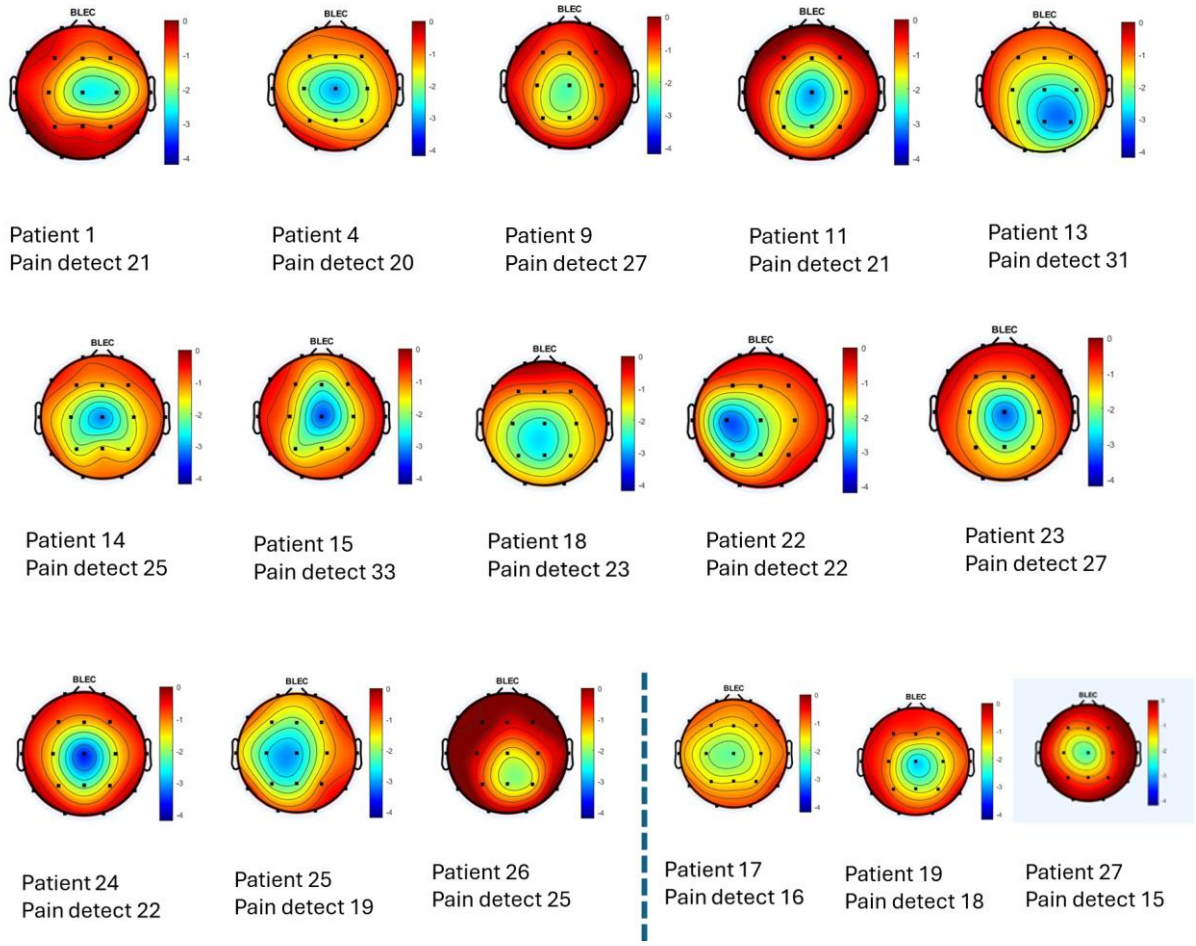
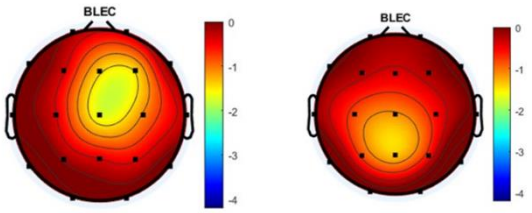


Figure 3.18: Baseline absolute theta power concentric baseline maps for all sixteen patients characterised by varying degree of concentric inhibition over vertex. Absolute theta power remained elevated over the prefrontal electrodes in all sixteen patients and parietal over P3, P4 and Pz. Patients 17, 19 and 27 presented with nociceptive pain profiles, the other patients had neuropathic pain profiles on Pain Detect.

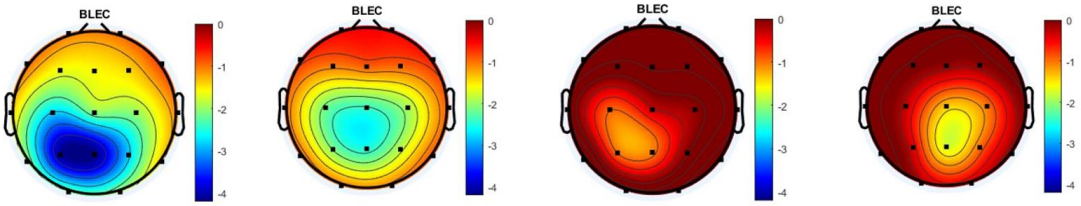
The remaining eleven patients included in the study had baseline patterns that were either unclear or absent of a concentric baseline pattern. This group consisted of patients with either a nociceptive pain profile (Figure 3.19), mixed pain profile (Figure 3.20) or neuropathic pain profile (Figure 3.21).



Patient 8
Pain detect 7

Patient 10
Pain detect 10

Figure 3.19: Absolute theta power baseline power maps absent or not clear of the concentric pattern and nociceptive pain detect scores. Minimal inhibition is either anterior or posterior to the vertex. Both patients presented with a nociceptive pain profile.



Patient 2
Pain detect 18

Patient 3
Pain detect 18

Patient 12
Pain detect 16

Patient 16
Pain detect 18

Figure 3.20: Absolute theta power baseline power maps absent or not clear of the concentric pattern and mixed pain detect scores. Absolute theta power inhibition was diffuse over the parietal regions with varying levels of intensity. Patient 16 absent of the absolute theta power concentric pattern was a non-responder to all three stimulation programs tested.

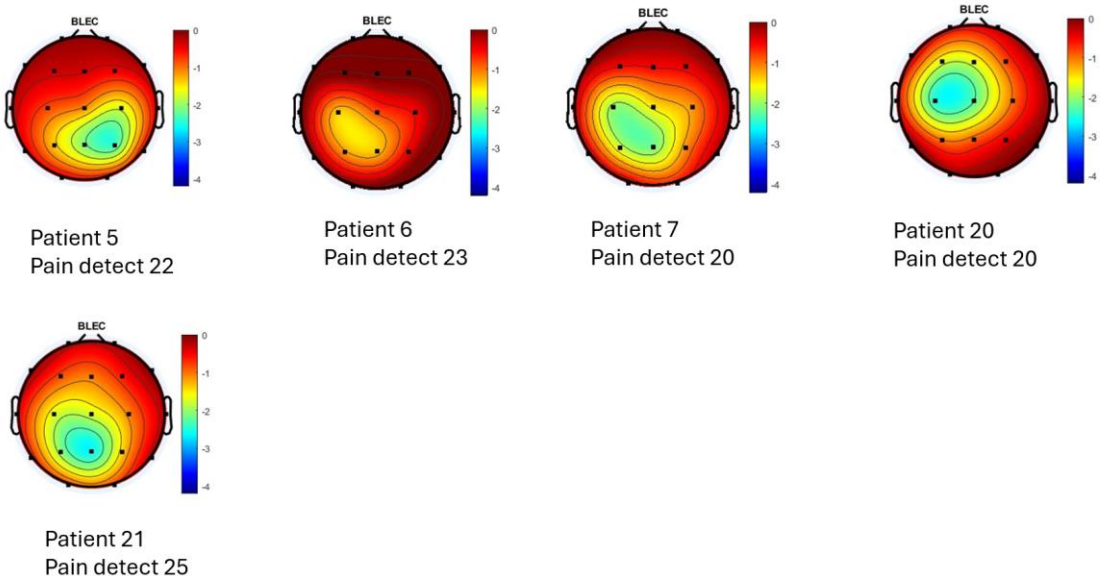


Figure 3.21: Absolute theta power baseline power maps absent or not clear of the concentric pattern and neuropathic pain detect scores. Absolute theta power inhibition was either anterior or posterior to Cz at the vertex and of varying intensities. Patients 6, 7 and 21 were non-responders to all three stimulation programmes tested and patient 20 a non-responder to high frequency stimulation. Patient 5 was a responder to all three stimulation programmes.

Absolute theta power was either displayed as an absolute theta power map with absolute theta power for each electrode relative to the Pz electrode or as a single value from the Pz electrode.

In the responder subgroups (Table 3.21) high frequency and tonic stimulation significantly reduced absolute theta power at Pz from baseline values. A paired t-test found for high frequency stimulation t (15) 2.86, p = 0.012, d = 0.32 and for tonic stimulation t (13) 3.30, p = 0.006, d = 0.40. In high frequency stimulation responder patients when the baseline absolute theta power concentric pattern was present, absolute theta power inhibition was observed to move posteriorly away from the vertex at Cz towards the parietal regions covering electrodes P3, Pz and P4. (figure 3.22). In tonic stimulation responders the inhibitory field that formed with SCS was asymmetrical and contralateral to the painful lower limb (figure 3.23).

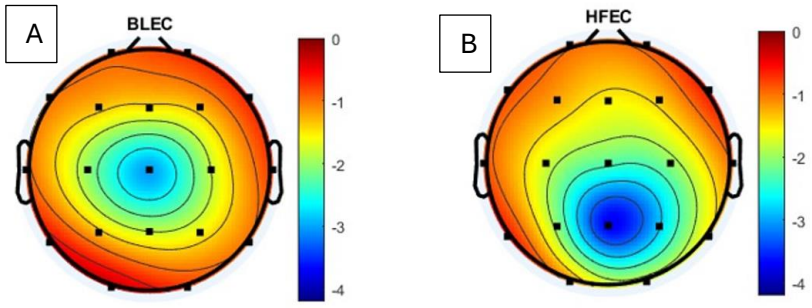


Figure 3.22: High frequency stimulation responder profile. Image A shows the absolute theta power concentric pattern at Baseline. Image B. High frequency stimulation drives absolute theta power reduction posteriorly over Pz away from electrode Cz where absolute theta power levels rise.

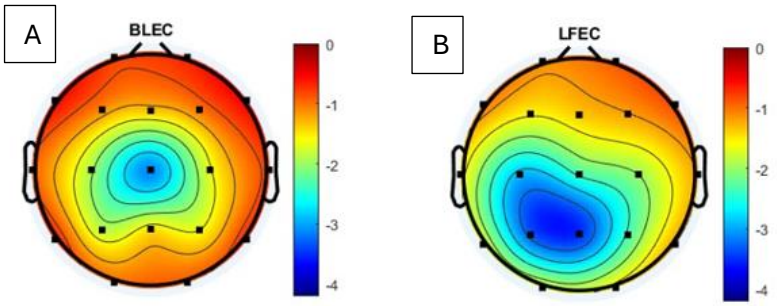


Figure 3.23: Tonic stimulation responder profile. Image A shows the absolute theta power concentric pattern at Baseline. Image B. Tonic stimulation drives absolute theta power inhibition posteriorly over Pz and contralateral to the painful side. Absolute theta power levels rise at electrode Cz.

In burst stimulation responders mean absolute theta power remained within baseline levels. No significant differences were found from baseline with a paired t-test, t (14) 1.08, p = 0.296, d = 0.39. Absolute theta power inhibitory changes occurred anterior to the Pz electrode with burst stimulation enlarging the inhibitory field over the central electrodes C3, C4 and Cz with an asymmetry contralateral to the painful side (Figure 3.24).

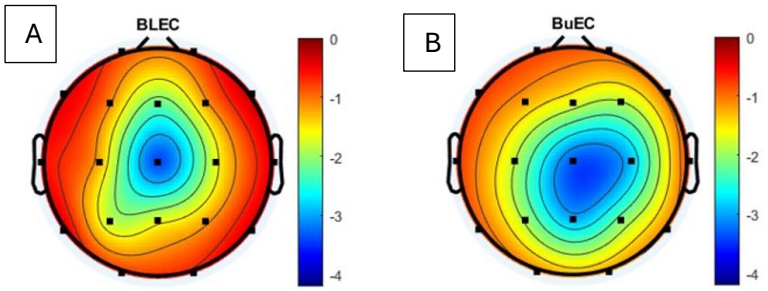


Figure 3.24: Burst stimulation responder profile. Image A shows the absolute theta power concentric pattern at Baseline. Image B. Burst stimulation expands the inhibitory field over C4 and contralateral to the painful side. Absolute theta power shows minimal changes at Pz that were not statistically significant (P>0.05).

In the high frequency stimulation non-responder subgroup, the baseline absolute theta power concentric pattern was seen in four out of the eleven non-responders (36%). The seven patients without the absolute theta power concentric pattern, one patient was from the nociceptive pain subgroup (patient 8), two patients were from the mixed pain subgroup (patients 3 and 16) and four were from the neuropathic pain subgroup (patients 6, 7, 8 and 20). In the tonic stimulation non-responder subgroup, the baseline absolute theta power concentric pattern was seen in three out of the eight non-responders (37%). The five patients without the absolute theta power concentric pattern, two patients were from the mixed pain subgroup (patients 3 and 16) and four were from the neuropathic pain subgroup (patients 6, 7, 16 and 21).

High frequency, tonic and burst stimulation elicited minimal changes in absolute theta power (Table 3.22), either as a minimal increase or minimal decrease in absolute theta power. No significant differences from mean baseline absolute theta power were found with a paired t-test for high frequency stimulation t (10) 1.325, p = 0.215, d = 0.60 tonic stimulation t (8) 0.242, p = 0.815, d = 0.43 and burst stimulation t (7) 0.099, p = 0.924, d = 0.23 with the smallest effect size observed with burst stimulation.

Table 3.21: Absolute theta power recorded at Pz in the responder subgroup. Significant reduction in absolute theta power from baseline (p=<0.05) observed with high frequency and tonic stimulation.

Trial	**Mean absolute theta power / $\mu V^2/Hz$**	**Standard error**	**95% confidence interval / $\mu V^2/Hz$**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	**0.21**	0.03	0.14-0.28	0.02	0.004 Not normal distribution
High frequency stimulation (n =16)	**0.14**	0.03	0.07-0.21	0.02	0.002 Not normal distribution
Tonic stimulation baseline (n=14)	**0.23**	0.04	0.06 – 0.60	0.02	0.07 Normal distribution
Tonic stimulation (n=16)	**0.13**	0.03	0.06 – 0.20	0.01	0.02 Not normal distribution
Burst stimulation baseline (n=15)	0.29	0.05	0.08 – 0.67	0.04	0.03 Not normal distribution
Burst stimulation (n=15)	0.29	0.07	0.03 – 1.10	0.08	0.008 Not normal distribution

Table 3.22: Absolute theta power recorded at Pz in the non-responder subgroup

Trial	**Mean absolute theta power / $\mu V^2/Hz$**	**Standard error**	**95% confidence interval / $\mu V^2/Hz$**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	0.39	0.12	0.12 – 0.66	0.16	0.01 Not normal distribution
High frequency stimulation (n =11)	0.62	0.14	0.29 – 0.94	0.23	0.35 Normal distribution
Tonic stimulation baseline (n=9)	0.54	0.24	0.025 – 1.11	0.55	0.001 Not normal distribution
Tonic stimulation (n=9)	0.38	0.09	0.16 – 0.60	0.08	0.15 Normal distribution
Burst stimulation baseline (n=8)	0.34	0.02	0.02 – 0.70	0.19	0.001 Not normal distribution
Burst stimulation (n=8)	0.32	0.13	0.04 – 0.63	0.14	0.005 Not normal distribution

Absolute theta power showed suboptimal inhibitory changes with high frequency, tonic and burst. In the high frequency stimulation non-responder subgroup absolute theta power remained elevated over the pre-frontal electrodes. Absolute theta power inhibition was minimal over the Pz electrode (Figure 3.25).

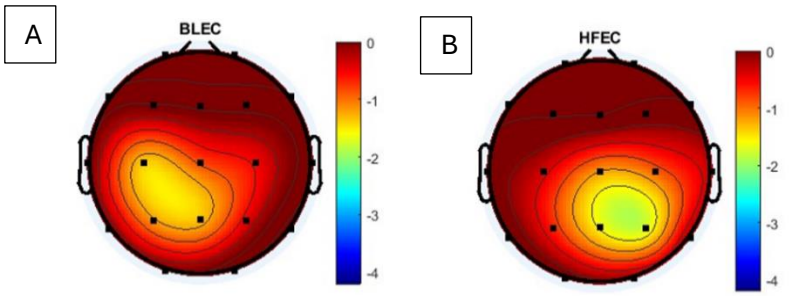


Figure 3.25: High frequency stimulation non-responder profile. Image A shows raised absolute theta power across all electrodes with minimal inhibition over P3, Pz and C3 at Baseline. Image B. High frequency stimulation failed to drive absolute theta power inhibition posteriorly over Pz absolute theta power levels were observed to rise.

In contrast tonic stimulation non-responders showed on average a suboptimal reduction in absolute theta power over the parietal regions which was not statistically significant (Figure 3.26).

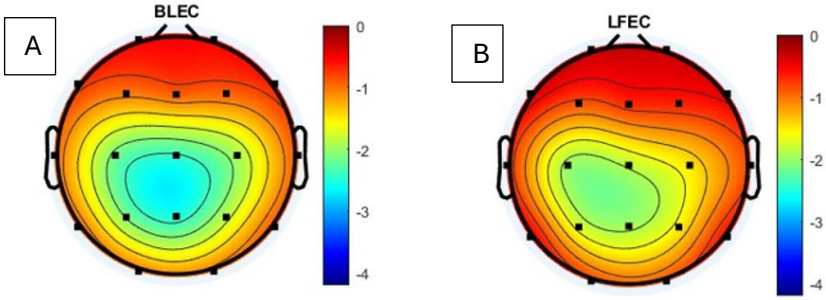


Figure 3.26. Tonic stimulation non-responder profile. Image A shows minimal diffuse absolute theta power inhibition over Cz and Pz at baseline. raised absolute. Image B. Absolute theta power levels remained; in this example a slight elevation was noted.

In burst stimulation minimal changes in absolute theta power were noted with suboptimal inhibition over the central regions (Figure 3.27).

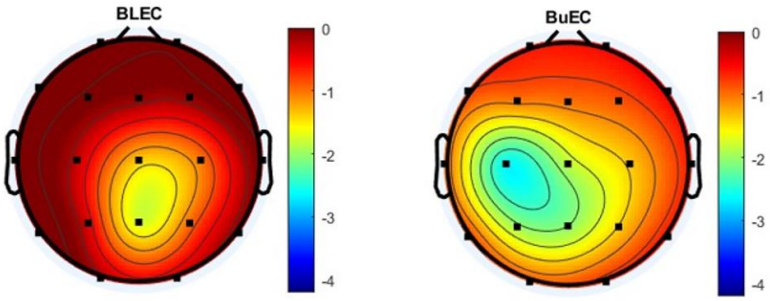


Figure 3.27: Burst stimulation non-responder with no significant difference between baseline and burst stimulation absolute theta power at Pz.

3.3.11 Relative theta power ratio

The relative theta power ratio was calculated comparing absolute theta power at each trial to their corresponding baseline. The relative theta power ratio in the high frequency and tonic stimulation subgroups were both <1.0 in comparison to the burst stimulation responder subgroup (Table 3.23). This finding reflects the significant differences found for absolute theta power from baseline in both high frequency and tonic stimulation. The 95% confidence limit upper boundary is also <1.0 in both high frequency and tonic stimulation in keeping with 95% of patients showing absolute theta power reduction at Pz.

In the high frequency responder subgroup, there was a single outlier (patient 1) that differed from the rest of the group. This outlier had a relative theta power ratio of 1.80, inhibition was not observed over Pz. Patient 1 reported 50% pain relief a borderline result. In this outlier at baseline the absolute theta power concentric pattern that was present had an inhibitory field that was oval shaped over Pz and C4. High frequency stimulation restricted the inhibitory field over Cz. Absolute theta power remained high over the frontal and parietal electrodes and was seen to increase from baseline forming a concentric ring around Cz with restricted absolute theta power inhibition over this region. Absolute theta power was seen to increase at Pz (Figure 3.28).

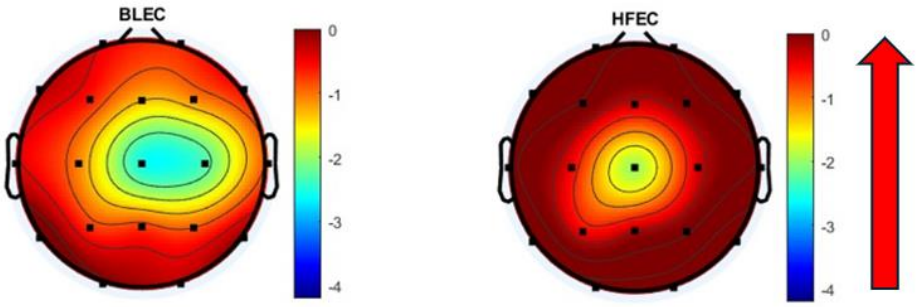


Figure 3.28: High frequency stimulation responder outlier showing theta absolute power increase over the frontal and parietal areas with minimal inhibition remaining over Cz. A relative theta power ratio of 1.8 was observed with increased absolute theta power over Pz. The baseline pattern shows inhibition at Cz and resembles the absolute theta power concentric pattern which with visual analysis is subjective.

The mean relative theta power ratio for burst stimulation responders was 1.0 in keeping with absolute theta power levels remaining within baseline values of which there was no statistical difference.

Mean relative theta power ratios for high frequency, tonic and burst stimulation non-responders were all >1.0 (Table 3.24) with larger variation in relative theta power ratios for high frequency and tonic stimulation when compared to the responder subgroups. Burst stimulation mean relative theta power ratio showed smaller variance indicating that inhibitory changes in absolute theta power were minimal at Pz with little variation within the subgroup.

A statistically significant difference was found using an independent t-test between responders and non-responders for high frequency stimulation, $t(25) = 2.24$, $p = 0.033$, $d = 0.79$ and tonic stimulation $t(21) = 2.185$, $p = 0.04$, $d = 0.41$ both showing large effect sizes. No statistical difference was found between burst stimulation responders and non-responders $t(23) = 0.106$, $p = 0.916$, $d = 0.69$ and evidence of absolute theta modulation occurring anterior to the Pz electrode in responders.

Table 3.23: Relative theta power ratio in the responder subgroup. Significant reduction in absolute theta power from baseline (p=<0.05) observed with high frequency and tonic stimulation and corresponds to the low relative theta power ratio

Trial	**Mean relative theta power ratio**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency stimulation (n =16)	**0.61**	0.10	0.39-0.84	0.17	0.02 Not normal distribution
Tonic stimulation (n=16)	**0.63**	0.16	0.29-0.98	0.37	0.001 Not normal distribution
Burst stimulation baseline (n=15)	1.00	0.20	0.6 – 1.4	0.60	0.23 Normal distribution

Table 3.24: Relative theta power ratio in the non-responder subgroup.

Trial	**Mean relative theta power ratio**	**Standard error**	**95% confidence interval**	**Variance**	**Shapiro-wilk (p-value)**
High frequency stimulation (n =11)	1.61	0.51	0.95 – 2.62	2.96	0.02 Not normal distribution
Tonic stimulation (n=9)	1.66	0.58	0.30 – 3.00	3.05	0.01 Not normal distribution
Burst stimulation (n=8)	1.09	0.17	0.67 – 1.50	0.24	0.68 Normal distribution

A Pearson product-moment correlation was used to determine the relationship between relative theta power ratio and percentage pain relief. High frequency and tonic stimulation showed a weak negative correlation with pain relief (high frequency stimulation r = -0.251, n = 27, P = 0.206 and tonic stimulation r = -0.398, n = 23, P = 0.06) that was not statistically significant (Figures 3.29 and 3.30). The increased variability in the non-responder subgroup for the relative theta power ratio diluted the statistical relationship observed.

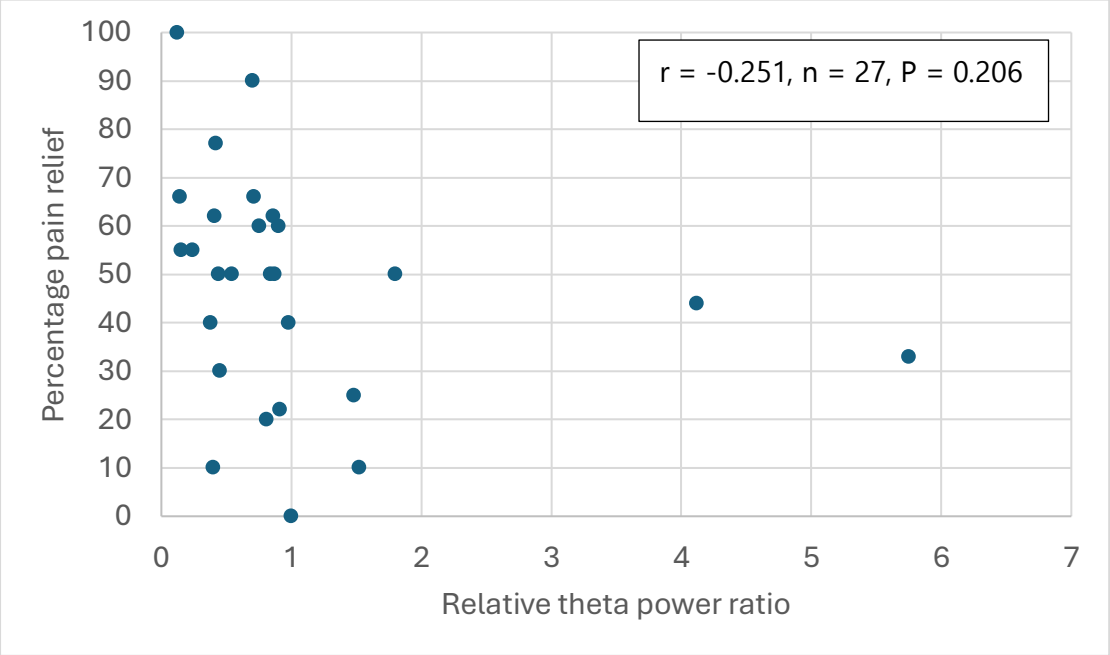


Figure: 3.29: Scatterplot correlation between relative theta power ratio and percentage pain relief for high frequency stimulation. Twenty-one patients out of twenty-seven had relative theta power ratios <1.0 with increased variability in patients that were non-responders. A weak negative correlation was observed that was not statistically significant.

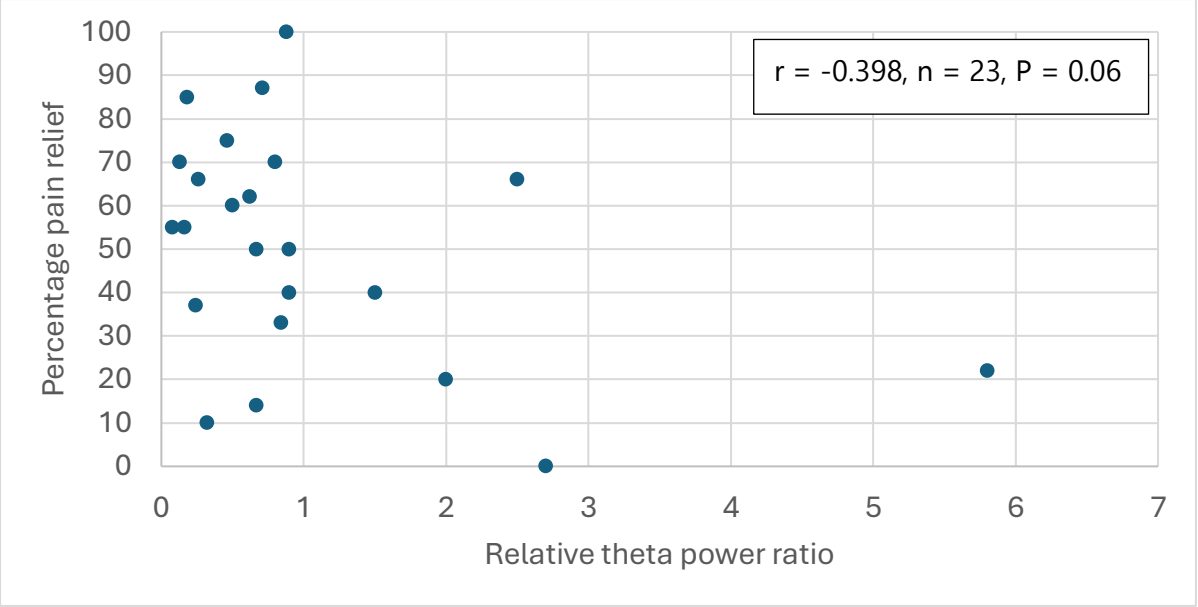


Figure 3.30: Scatterplot correlation between relative theta power ratio and percentage pain relief for tonic stimulation. Seventeen patients out of twenty-two had relative theta power ratios <1.0 with increased variability in patients that were non-responders. A weak negative correlation was observed that was not statistically significant.

In contrast for burst stimulation no correlation was observed (Figure 3.31) using a Pearson product-moment correlation between relative theta power ratio and pain relief (r = -0.054, n = 23, P = 0.808).

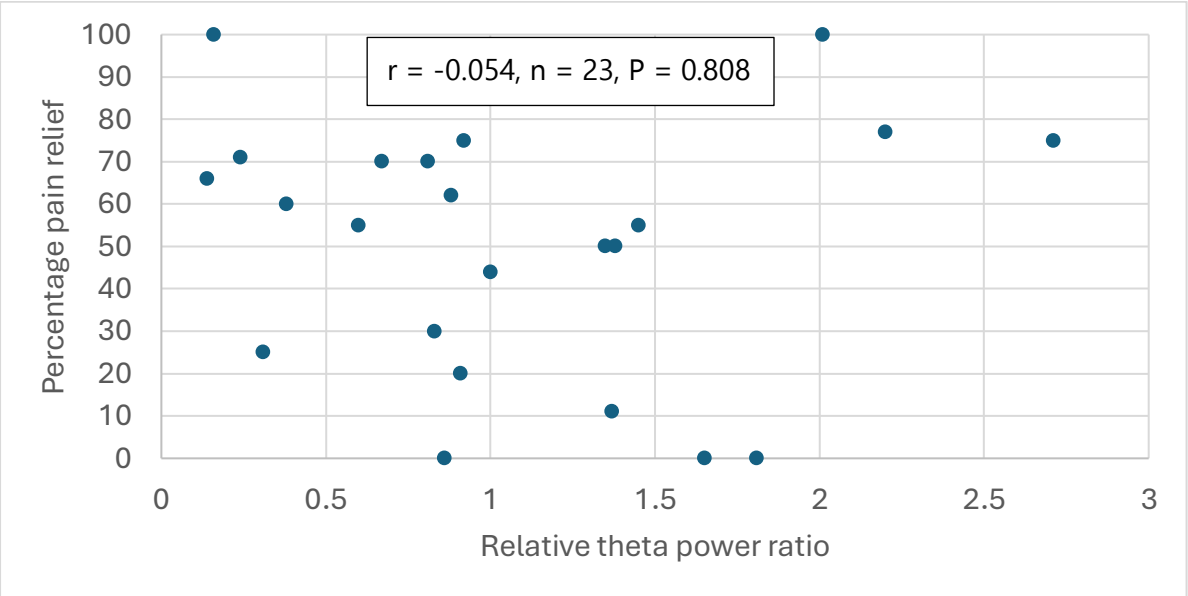


Figure 3.31: Scatterplot correlation between relative theta power ratio and percentage pain relief for burst stimulation. No correlation was observed between relative theta power ratio and pain relief. Relative theta power ratios were observed to be <1.0 and >1.0 throughout the subgroup.

3.3.12 Dominant frequency profiles

In twenty-three of the twenty-seven patients included in the study the dominant frequency in the absolute power spectral density profile was in the alpha frequency band when the eyes were closed. Four patients had dominant frequencies in the upper boundary (7Hz) of the theta frequency band. High frequency, tonic and burst stimulation responders the mean dominant frequency at baseline was in the alpha frequency range with eyes closed (Table 3.25). No significant differences were found with a paired t-test between dominant frequency at baseline with high frequency, t (15) 0, p = 1, d = 0.344, tonic stimulation t (13), 0.893, p = 0.38, d = 0.253 or burst stimulation t (14) 0.893, p = 0.38, d = 0.342. The mean dominant frequency was the same at baseline and with each stimulation program occupying the lower alpha frequency range (8-11 Hz).

In the non-responder subgroups, the mean dominant frequency was in the lower alpha frequency range (Table 3.26). No significant differences were found with a paired t-test between dominant frequency at baseline with high frequency, t (10), 0.303, p = 0.767, d = 0.147, tonic, t (8), -0.394, p = 0.703, d = 0.129 or burst, t (7), -0.235, p = 0.820, d = 0.036 stimulation.

There were no significant differences found with an independent t-test between responders and non-responders for high frequency t (27) = -0.273, p = 0.786, d = 0.114, tonic, t (23) = 0.855, p = 0.401, d = 0.370 or burst t (23) = -0.074, p = 0.941, d = 0.033 stimulation.

In this study the dominant frequency showed no significant changes in frequency for any of the stimulation programs investigated and is of little use for SCS patient responder selection.

Table 3.25: Dominant frequency profiles for SCS responders at baseline and at each SCS trial (Theta frequency = 4-7 Hz and alpha frequency 8-12 Hz)

Trial	**Mean dominant frequency with eyes closed / Hz**	**Standard error**	**95% confidence interval / Hz**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	8.9	0.28	7.3-11.4	1.29	0.72 Normal distribution
High frequency stimulation (n =16)	9.3	0.29	7.8-11.9	1.42	0.03 Not normal distribution
Tonic stimulation baseline (n=14)	9.3	0.30	7.3-11.47	1.29	0.79 Normal distribution
Tonic stimulation (n=16)	9.6	0.31	7.5-12.2	1.34	0.47 Normal distribution
Burst stimulation baseline (n=15)	9.1	0.25	7.3-10.4	0.96	0.31 Normal distribution
Burst stimulation (n=15)	9.5	0.28	7.8-11.9	1.23	0.62 Normal distribution

Table 3.26: Dominant frequency profiles for SCS non-responders at baseline and at each SCS trial (Theta frequency = 4-7 Hz and alpha frequency 8-12 Hz)

Trial	**Mean dominant frequency with eyes closed / Hz**	**Standard error**	**95% confidence interval Hz**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	9.3	0.24	7.5 -10.2	0.67	0.06 Normal distribution
High frequency stimulation (n =11)	9.5	0.19	8.7 -10.9	0.43	0.31 Normal distribution
Tonic stimulation baseline (n=9)	9.3	0.21	8.3-10.2	0.43	0.15 Normal distribution
Tonic stimulation (n=9)	9.2	0.29	8.0-10.4	0.76	0.72 Normal distribution
Burst stimulation baseline (n=8)	9.6	0.31	8.3-11.4	0.80	0.13 Normal distribution
Burst stimulation (n=8)	9.5	0.44	8.0-11.9	1.56	0.53 Normal distribution

3.3.13 SSEP amplitude

SSEP amplitudes were measured for the P39 early component of lower limb SSEPs recorded in the symptomatic leg. In the present study tonic stimulation was the only stimulation programme to show marginal evidence of a significant SSEP P39 amplitude reduction in SCS responders (Table 3.27). This was only apparent on non-parametric testing with a Wilcoxon signed rank test (n=14, Z = -1.977, p = 0.048). Statistically, no significant differences were found between baseline SSEP P39 amplitude in the responder subgroups at high frequency stimulation t (14) 0.497, p = 0.627, d = 0.15, tonic stimulation t (13) 1.529, p = 0.150, d = 0.35 and burst stimulation t (15) 1.152, p = 0.269 using a paired t-test. The marginal result for tonic stimulation is borderline and given the p = 0.048 and effect size is small (d=0.35) this result likely represents a marginally non-significant result.

Non-responders (Table 3.28) showed minimal amplitude reduction with all three stimulation programs that were not statistically different from SSEP P39 baseline amplitudes. Statistically, no significant differences were found between baseline SSEP P39 amplitude in the non-responder subgroup at high frequency stimulation t (9) 0.354, p = 0.732, d = 0.40, tonic stimulation, t (6) 1.56, p = 0.169, d = 0.48, and burst stimulation t (5) 1.472, p = 0.201, d = 0.22.

Table 3.27: SSEP amplitudes for SCS responders at baseline and at each SCS trial.

Trial	**Mean SSEP P39 amplitude / µV**	**Standard error**	**95% confidence interval / µV**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =16)	1.18	0.20	0.75-1.61	0.61	0.04 Not normal distribution
High frequency stimulation (n =16)	1.14	0.20	0.29-2.09	0.65	0.07 Normal distribution
Tonic stimulation baseline (n=14)	1.32	0.30	0.65-1.98	1.32	0.56 Normal distribution
Tonic stimulation (n=16)	0.78	1.11	0.53-1.02	0.18	0.02 Not normal distribution
Burst stimulation baseline (n=15)	1.16	0.20	0.71-1.61	0.65	0.07 Normal distribution
Burst stimulation (n=15)	1.28	0.23	0.79-1.78	0.80	0.07 Normal distribution

Table 3.28: SSEP amplitudes for SCS non-responders at baseline and at each SCS trial

Trial	**Mean SSEP P39 amplitude / µV**	**Standard error**	**95% confidence interval / µV**	**Variance**	**Shapiro-wilk (p-value)**
High frequency baseline (n =11)	0.76	0.14	0.44-1.08	0.20	0.09 Normal distribution
High frequency stimulation (n =11)	0.71	0.12	0.43-0.99	0.15	0.69 Normal distribution
Tonic stimulation baseline (n=9)	0.79	0.20	0.29-1.30	0.29	0.22 Normal distribution
Tonic stimulation (n=9)	0.51	0.08	0.31-0.71	0.04	0.11 Normal distribution
Burst stimulation baseline (n=8)	0.70	0.22	0.13-1.27	0.30	0.01 Not normal distribution
Burst stimulation (n=8)	0.47	0.10	0.20-0.74	0.06	0.15 Normal distribution

3.3.14 SSEP amplitude ratio

An SSEP amplitude ratio was calculated to better understand changes in SSEP amplitude relative to baseline.

The SSEP amplitude ratios for high frequency and tonic stimulation responders were <1.0 (0.99, 0.98) showing evidence of marginal SSEP amplitude reduction and similar in both responder subgroups (Table 3.29). This is further evidence to support the marginal finding for tonic stimulation being non-significant. The SSEP amplitude ratio for burst stimulation was >1.0 suggesting an increase in amplitude from baseline which was found not to be statistically significant with the paired t-test. The SSEP amplitude ratios for high frequency and tonic SCS stimulation non-responders were >1.0 (1.10 and 1.17) and <1.0 (0.80) in the burst SCS non-responder subgroup (Table 3.30).

No significant differences were found between responders and non-responders for SSEP ratio with high frequency stimulation $t(23) = 0.540$, $p = 0.594$, $d = 0.49$, tonic stimulation, $t(19) = 0.315$, $p = 0.756$, $d = 0.36$ and burst stimulation, $t(19) = 1.472$, $p = 0.157$, $d = 0.24$.

Table 3.29: SSEP amplitude ratio in SCS responders

Trial	Mean SSEP amplitude ratio	Standard error	95% confidence interval	Variance	Shapiro-wilk (p-value)
High frequency stimulation (n =16)	0.99	0.08	0.82-1.17	0.09	0.64 Normal distribution
Tonic stimulation (n=16)	0.98	0.23	0.46-1.53	0.79	0.003 Not normally distributed
Burst stimulation baseline (n=15)	1.30	0.22	0.81-1.78	0.77	0.003 Not normally distributed

Table 3.30: SSEP amplitude ratio in SCS non-responders

Trial	Mean SSEP amplitude ratio	Standard error	95% confidence interval	Variance	Shapiro-wilk (p-value)
High frequency stimulation (n =11)	1.10	0.99	0.61-1.59	0.46	0.56 Normal distribution
Tonic stimulation (n=9)	1.17	0.44	0.08-2.27	1.40	0.017 Not normal distribution
Burst stimulation (n=8)	0.80	0.14	0.43-1.17	0.12	0.93 Normal distribution

A Pearson product-moment correlation was used to determine any relationship between SSEP amplitude ratio in the symptomatic leg and percentage pain relief. High frequency, tonic and burst stimulation showed no evidence of statistical correlation between SSEP amplitude reduction and pain relief (high frequency stimulation, r = -0.002, n = 25, P = 0.992, tonic stimulation r = -0.274, n = 21, P = 0.230 and burst stimulation r = 0.243, n = 21, P = 0.289). There was no statistical evidence of correlation with SSEP amplitude ratio and pain relief (Figures 3.32, 3.33 and 3.34).

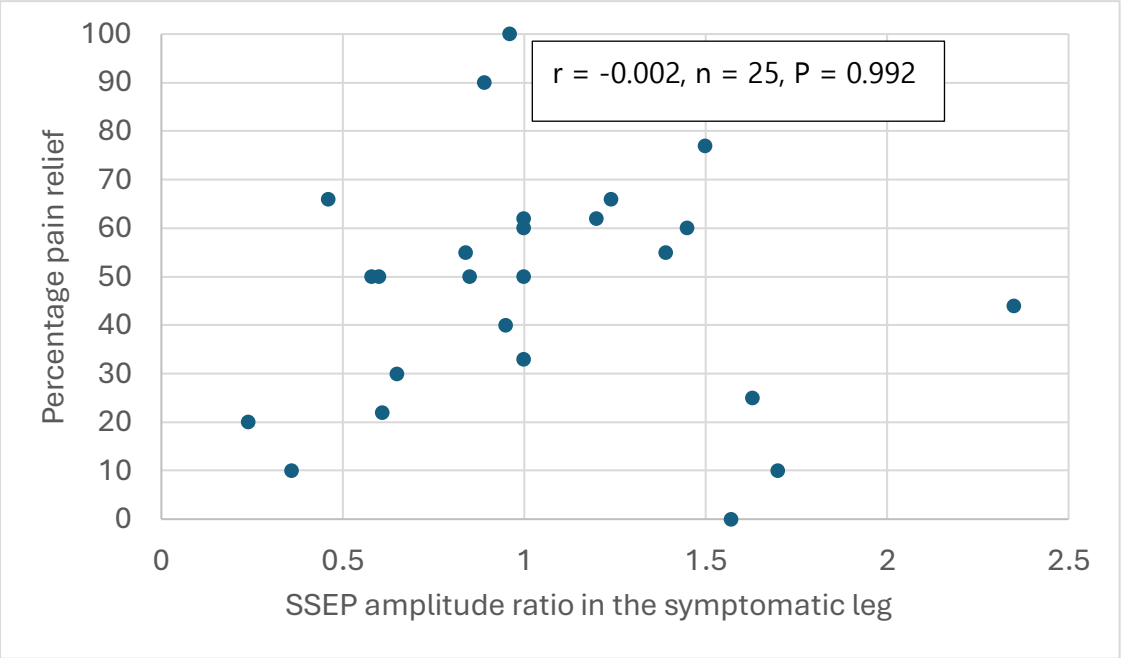


Figure 3.32: Scatterplot correlation between SSEP amplitude ratio and percentage pain relief for high frequency stimulation, no correlation was observed with pain relief.

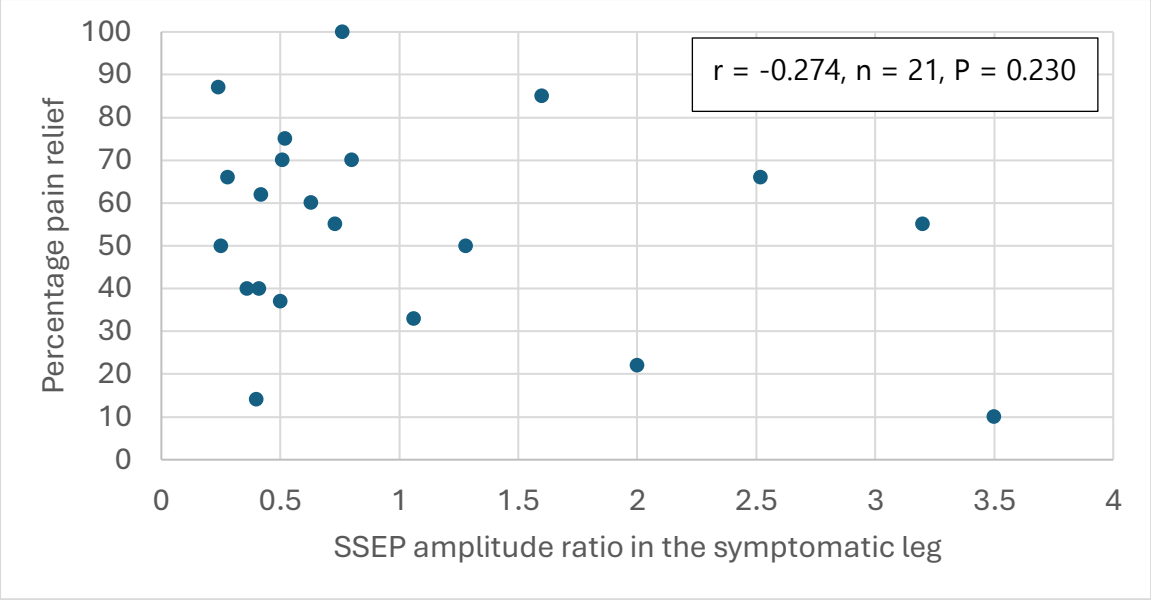


Figure 3.33: Scatterplot correlation between SSEP amplitude ratio and percentage pain relief for tonic stimulation showing no clear association.

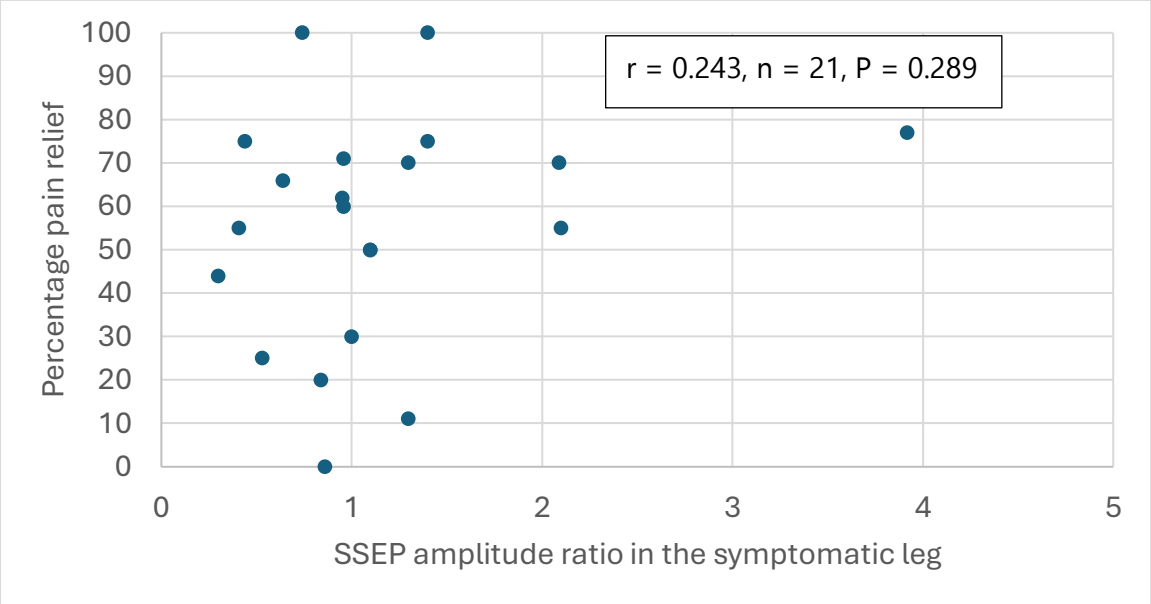


Figure 3.34: Scatterplot correlation between SSEP amplitude ratio and percentage pain relief for burst stimulation showing no clear association.

3.3.15 Receiver operating characteristic curve (ROC)

A ROC evaluation of all the possible decision thresholds for high frequency, tonic and burst stimulation was undertaken for relative theta power ratio, SSEP amplitude ratio in the symptomatic leg and baseline absolute theta power concentric pattern using relative theta power ratio.

Each neurophysiology value or baseline pattern was categorised as either a responder or non-responder. The ROC graph generated in SPSS represented the decision made on whether the test result was a responder. The graph plotted sensitivity against 1- specificity.

3.3.15.1 Relative theta power ratio ROC evaluation

Both high frequency and tonic stimulation produced ROC models that were significantly better than random prediction at identifying responders when using the relative theta power ratio. Both models were good. In contrast the burst stimulation subgroup, the AUC was as good as random prediction at identifying responders, this finding was not statistically significant in keeping with the null hypothesis that the AUC = 0.5 and no better than random prediction (Table 3.31 and Figure 3.35).

Table 3.31: A summary of the ROC evaluation for the relative theta power ratio. Good models for patient selection were identified for high frequency and tonic stimulation with AUC of 0.75.

Relative theta power ratio	**Trial**		
	High frequency stimulation	**Tonic stimulation**	**Burst stimulation**
AUC	0.75	0.75	0.56
Standard error	0.10	0.10	0.12
P-value (P = 0.05)	0.01	0.01	0.57
95% confidence interval	0.55 to 0.95	0.54 to 0.96	0.33 to 0.80
Model	Acceptable to outstanding	Acceptable to outstanding	Random prediction to good

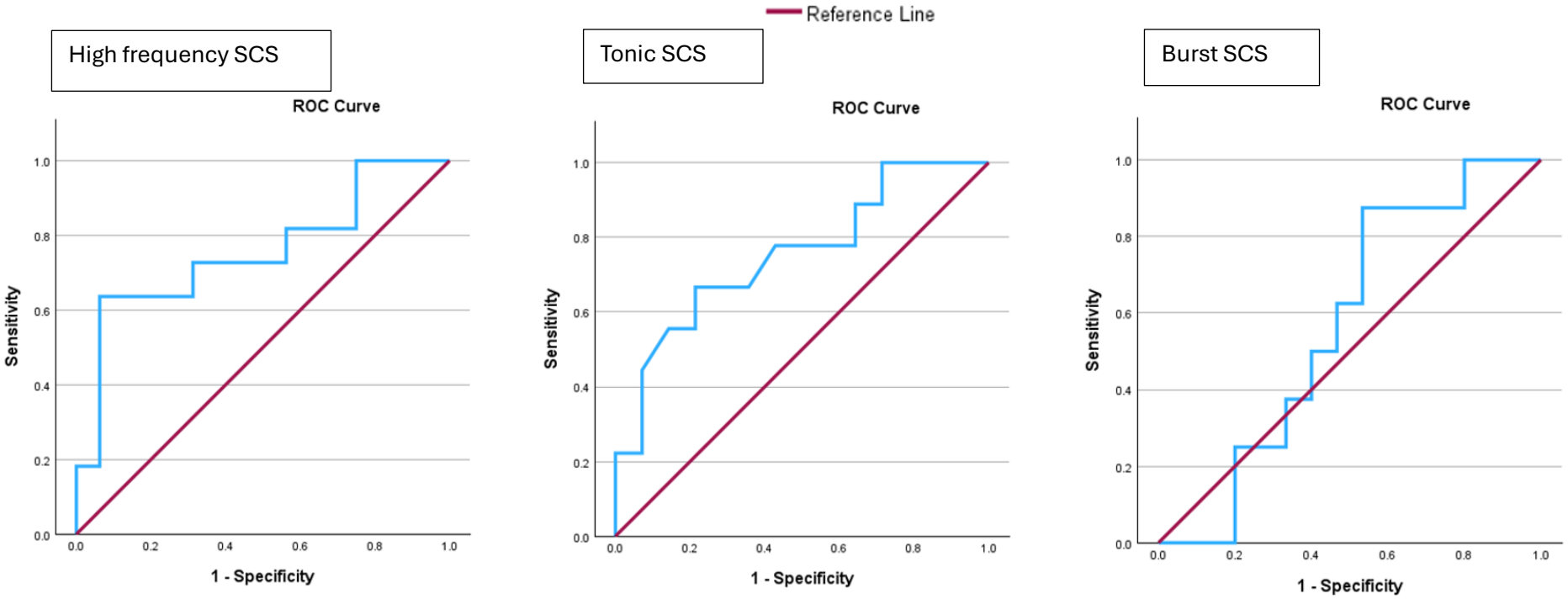


Figure 3.35: ROC curves for high frequency, tonic and burst stimulation for the relative theta power ratio. The AUC for high frequency stimulation was 0.756 (good), for tonic stimulation 0.754 (good) both of which were significantly different from random prediction. Burst stimulation AUC 0.56 was not significantly different from random prediction.

3.3.15.2 SSEP amplitude ratio ROC evaluation

High frequency and burst stimulation produced ROC with AUC that were no better than random prediction at differentiating responders from non-responders. Both stimulation modalities were not significantly different from random prediction.
In contrast tonic stimulation produced a ROC model that was acceptable, however not statistically different from random prediction (Table 3.32 and Figure 3.6).

Table 3.32: A summary of the ROC evaluation for the SSEP amplitude ratio in the symptomatic leg. ROC models for SSEP amplitude ratio were no better than random prediction for selecting responders. The model for tonic stimulation was acceptable but not statistically significant.

SSEP amplitude ratio in the symptomatic leg	**Trial**		
	High frequency stimulation	**Tonic stimulation**	**Burst stimulation**
AUC	0.53	0.73	0.29
Standard error	0.13	0.13	0.11
P-value (P = 0.05)	0.78	0.07	0.08
95% confidence interval	0.26 to 0.80	0.47 to 0.99	0.06 to 0.52
Model	No better than random prediction	Acceptable model	No better than random prediction

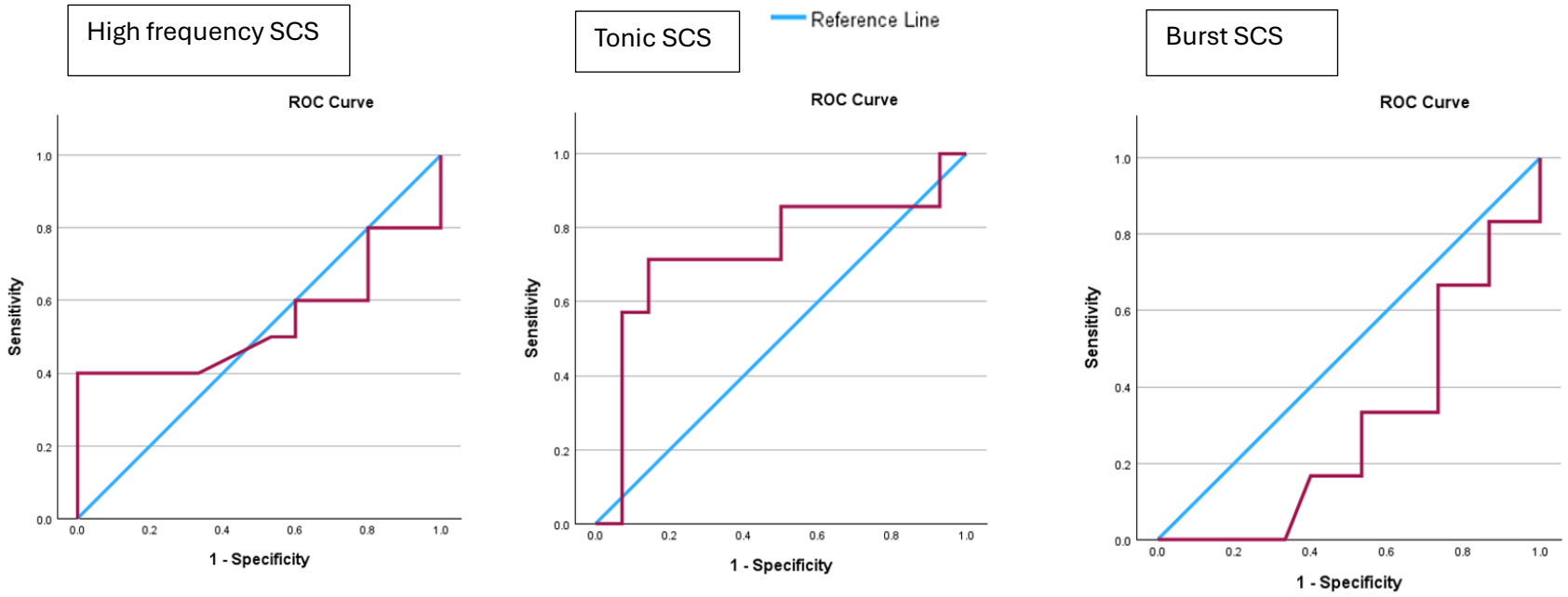


Figure 3.36: ROC curves for high frequency, tonic and burst stimulation for the SSEP amplitude ratio in the symptomatic leg. The AUC for high frequency stimulation was 0.537 and for burst stimulation 0.294 both no better than random prediction at differentiating responders from non-responders. For tonic stimulation the AUC was 0.735 and acceptable however not statistically different from random prediction ($P<0.05$).

3.3.15.3 Baseline absolute theta power concentric pattern ROC evaluation

The absolute theta power concentric pattern was evaluated with relative theta power ratio. For high frequency stimulation, the ROC model produced was good and was significantly different from random prediction. Tonic stimulation and burst stimulation using relative theta power ratio were not statistically different from random prediction (Table 3.33 and Figure 3.37).

Table 3.33: A summary of the ROC evaluation for the absolute theta power concentric pattern with relative theta power.

Baseline theta absolute power spectral concentric pattern	**Trial**		
	High frequency stimulation	**Tonic stimulation**	**Burst stimulation**
AUC	0.750	0.660	0.545
Standard error	0.121	0.154	0.146
P-value (P = 0.05)	0.039	0.300	0.756
95% confidence interval	0.512 to 0.988	0.358 to 0.962	0.259 to 0.832
Model	Good	No better than random prediction	No better than random prediction

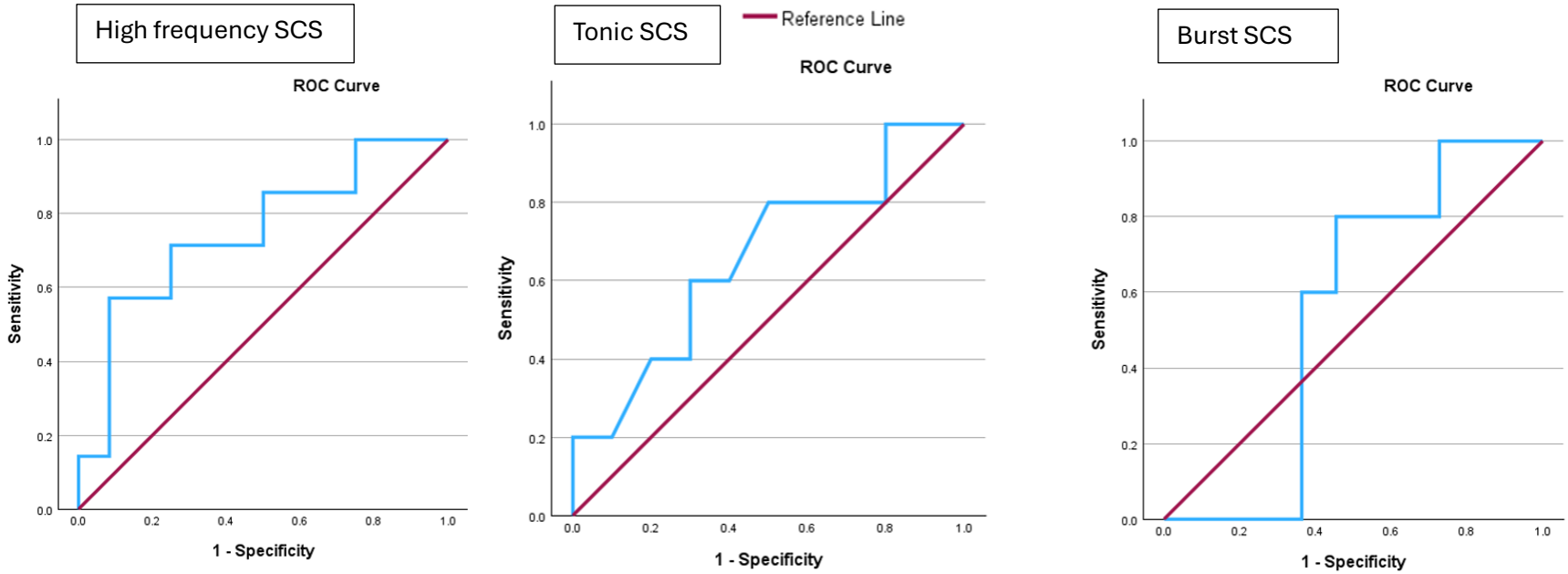


Figure 3.37: ROC curves for high frequency, tonic and burst stimulation for the absolute theta power concentric pattern and relative theta ratio. The AUC for high frequency stimulation was 0.750 and statistically different from random prediction at differentiating between responders and non-responders. Tonic stimulation produced an AUC of 0.660 that was not statistically significant from random prediction. Burst stimulation was 0.545 no better than random prediction at differentiating responders from non-responder

3.3.15.4 Baseline absolute theta power concentric pattern at identifying a responder in either high frequency, tonic or burst stimulation ROC evaluation

The absolute theta power concentric pattern at identifying a responder in either high frequency, tonic or burst stimulation (Figure 3.38) had an AUC of 0.79 (good), with a standard error of 0.100, P-value of 0.003 which was significantly different from random prediction. The 95% confidence interval was between 0.59 (above random prediction) to 0.99 (outstanding).

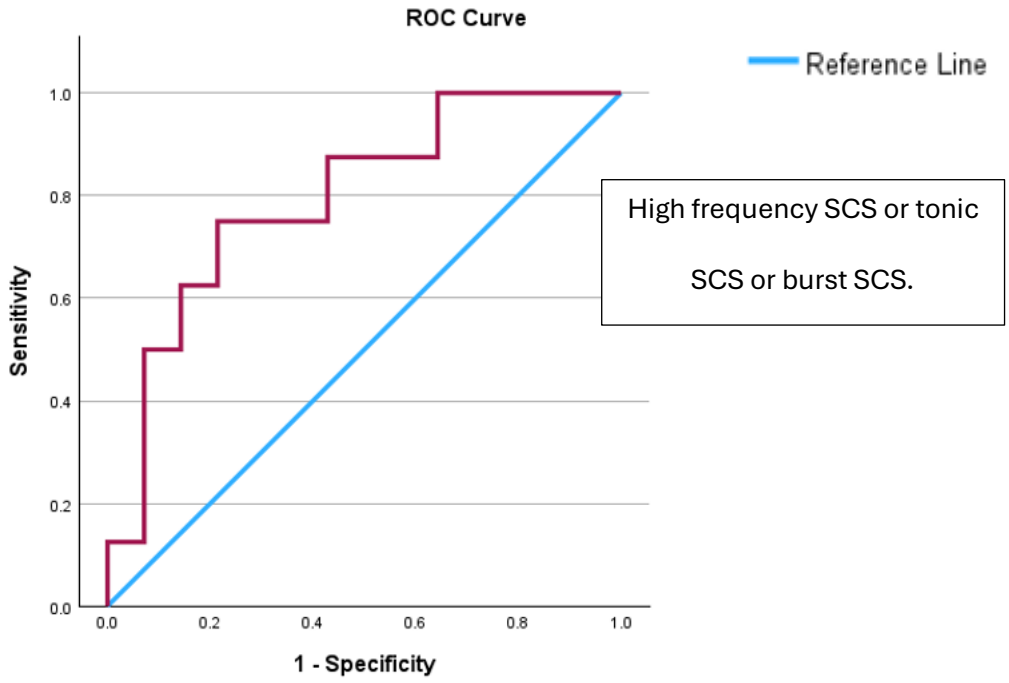


Figure 3.38: ROC curve for the baseline absolute theta power using relative theta power ratio to select SCS responders that were either high frequency, tonic or burst stimulation.

3.3.16 Sensitivity and specificity of the absolute theta power concentric pattern at identifying responders

The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and accuracy for the absolute theta power concentric pattern was calculated. Power et al., (2013) considered a useful diagnostic screening test to have a combined sensitivity + specificity score ≥ 1.5 on a scale of 1 = useless and 2 = perfect (Power et al., 2013). This rule was used in the evaluation of the baseline absolute theta power concentric pattern as a test to detect responders and to differentiate non-responders.

For high frequency responders the baseline absolute theta power concentric pattern had a sensitivity of 75% (0.75) and specificity of 64% (0.64). The false negative rate was 25% (0.25) and false positive rate 36% (0.36). The baseline theta absolute power concentric pattern for high frequency stimulation had a combined sensitivity and specificity score of 1.38 and was below the 1.5 cut off for usefulness. The false positive rate reduced the specificity making the likelihood of identifying non-responders less reliable. However, the negative likelihood ratio was 0.39 and less than 1.0 suggesting that absent concentric baseline patterns were likely to be non-responders. The positive likelihood ratio was 2.06 and in keeping with the high sensitivity (75%) and over all accuracy of 70%.

The baseline absolute theta power concentric pattern correctly identified twelve high frequency stimulation responder patients and seven non-responders. Eight patients were incorrectly classified of these four were due to having baseline patterns that were concentric with minimal pain relief that was <50% from baseline (false positive) and four whose baseline patterns were absent of a concentric pattern but experienced pain relief >50% (false negative) and were responders.

For the tonic stimulation responders, the baseline absolute theta power concentric pattern had a sensitivity of 71% (0.71) and specificity 60% (0.6). The false negative rate was 29% (0.29) and false positive rate was 40% (0.40). The combined sensitivity and specificity score was 1.3 and was below the 1.5 cut off for usefulness. However, the negative likelihood ratio was 0.47 and less than 1.0 suggesting that absent concentric baseline patterns were likely to be non-responders. The positive likelihood ratio was 1.78 and in keeping with the high sensitivity (71%) and over all accuracy of 67%.

The baseline absolute theta power concentric pattern correctly identified ten tonic stimulation responder patients and six non-responders. Eight patients were incorrectly classified of these four were due to having baseline patterns that were concentric with minimal pain relief that was <50% from baseline (false positive) and four whose baseline patterns were absent of a concentric pattern but experienced pain relief >50% (false negative) and were responders.

For the burst stimulation responders, the baseline theta absolute power concentric pattern had a sensitivity of 80% (0.80) and specificity of 62.5% (0.62). The false negative rate was 20%

(0.20) and false positive rate was 38% (0.38). The combined sensitivity and specificity score was 1.42 and was below the 1.5 cut off for usefulness. However, the negative likelihood ratio was 0.32 and less than 1.0 suggesting that absent concentric baseline patterns were likely to be non-responders. The positive likelihood ratio was 2.1 and in keeping with the high sensitivity (80%) and over all accuracy of 74%.

The baseline absolute theta power concentric pattern correctly identified twelve burst stimulation responder patients and five non-responders. Six patients were incorrectly classified of these three were due to having baseline patterns that were concentric with minimal pain relief that was <50% from baseline (false positive) and three whose baseline patterns were absent of a concentric pattern but experienced pain relief >50% (false negative) and were responders.

The baseline absolute theta power spectral concentric pattern's ability to detect a responder, either a high frequency, tonic or burst stimulation responder had a sensitivity of 85% (0.85) and a specificity of 67% (0.67). The false negative rate was 15% (0.15) and false positive rate 33% (0.33). The combined sensitivity and specificity score was 1.51 and considered useful in identifying both responders and non-responders. The positive likelihood ratio was 2.55, >1 and strong evidence that the baseline theta absolute power concentric pattern had a high likelihood at indicating a true responder. The negative likelihood ratio was 0.225 and <1 and evidence that an absent baseline theta absolute power concentric pattern was likely to indicate a true non-responder with an accuracy of 81%.

The baseline absolute theta power concentric pattern correctly identified seventeen responder patients and four non-responders. Five patients were incorrectly classified of these two were due to having baseline patterns that were concentric with minimal pain relief that was <50% from baseline (false positive) and three whose baseline patterns were absent of a concentric pattern but experienced pain relief >50% (false negative) and were responders.

In summary the baseline absolute theta power spectral concentric pattern is a good model for identifying responders and non-responders with an accuracy of 81% for identifying responders (high frequency, tonic or burst stimulation). The model's ability to differentiate between high frequency, tonic and burst stimulation was found to be acceptable and is biased by the false positive rate.

3.3.17 Preliminary Follow up results:

Patients were followed up after 6 months, post permanent SCS implantation. Fourteen participants of the study remain on the permanent SCS implant waiting list and were lost at follow up (51%).

Twelve patients went onto have permanent implants. One patient following the trial decided not to proceed with a permanent implant, she was a non-responder to all three stimulation programmes (Table 3.34).

Table 3.34: Follow up at 6-months (HF High frequency, TC Tonic stimulation, Bu Burst stimulation, PR Pain relief, R Responder, NR Non-responder

Number	Trial results	Baseline absolute theta power pattern	6 month follow up
1	HF R 50% PR, TC NR 0% PR, Bu NR 0% PR	Concentric pattern	HF R with 80% PR. Residual burning sensations
2	HF R 50% PR, TC R 62% PR, Bu NR 25% PR	Absent concentric pattern	HF R with 50% PR, TC uncomfortable
3.	HF NR 25% PR, TC NR 37% PR, Bu R 50% PR	Absent concentric pattern	Bu R 80% PR
4.	HF R 60% PR, TC R 70% PR, Bu R 50% PR	Concentric pattern	HF R 80% PR, TC uncomfortable
5.	HF R 62% PR, TC R 87% PR, Bu R 75% PR	Absent concentric pattern	HF R 90% PR, TC uncomfortable
6.	HF NR 0% PR, TC NR 14% PR, Bu NR 0% PR	Absent concentric pattern	HF NR 30% PR, Depressed
7	HF NR 20% PR, TC NR 40% PR, Bu NR 20% PR	Absent concentric pattern	Waiting list for implant
8.	HF NR 22% PR, TC R 55% PR, Bu R 55% PR	Absent concentric pattern	Waiting list for implant
9.	HF R 77% PR	Concentric pattern	Waiting list for implant
10.	HF R 50% PR, TC R 50% PR, Bu R 75% PR	Concentric pattern	Waiting list for implant
11.	HF NR 44% PR, TC R 55% PR, Bu R 66% PR	Concentric pattern	Bu R 80% PR
12.	HF R 55% PR	Absent concentric pattern	HF NR 30% PR. Silastic allergy
13.	HF R 100% PR	Concentric pattern	HF R 100% PR
14.	HF NR 40% PR, TC R 85% PR, Bu R 71% PR	Concentric pattern	Bu NR 40% PR, TC uncomfortable
15.	HF R 90% PR, TC R 100% PR, Bu R 100% PR	Concentric pattern	HF R 40% PR, Sleep has improved, TC uncomfortable
16.	HF NR 10% PR, TC NR 33% PR, Bu NR 44% PR	Absent concentric pattern	Lead migration during trial, Awaiting second trial
17.	HF R 55% PR, TC NR 10% PR, Bu R 55% PR	Concentric pattern	Waiting list for implant
18.	HF R 66% PR, TC R 66% PR, Bu R 100% PR	Concentric pattern	HF R 70% PR, Bu R 70% PR, TC uncomfortable
19.	HF R 50% PR	Absent concentric pattern	Waiting list for implant
20.	HF NR 30% PR, TC R 70% PR, Bu R 70% PR	Absent concentric pattern	Waiting list for implant
21.	HF NR 33% PR, TC NR 22% PR, Bu NR 11% PR	Absent concentric pattern	Waiting list for implant
22.	HF R 50% PR, TC R 60% PR, Bu R 60% PR	Concentric pattern	Waiting list for implant
23.	HF NR 40% PR, TC NR 40% PR, Bu NR 0% PR	Concentric pattern	Waiting list for implant
24.	HF R 60% PR, TC R 50% PR, Bu R 70% PR	Concentric pattern	Waiting list for implant
25.	HF NR 10% PR, TC NR 20% PR, Bu NR 30% PR	Concentric pattern	Decided not to proceed with permanent implant
26.	HF R 66% PR, TC R 66% PR, Bu R 77% PR	Concentric pattern	Waiting list for implant
27.	HF R 62% PR, TC R 75% PR, Bu R 62% PR	Concentric pattern	Waiting list for implant

3.4 Discussion:

In current UK clinical practice, the identification of spinal cord stimulation responders from non-responders in FBSS patients is reliant on an expensive screening trial before permanent implantation in patients identified as responders (NICE, 2014; Duarte and Thomson, 2019). In addition to cost spinal cord stimulator trials expose the patient to an increased risk of infection and further surgical complication that may make their chronic pain worse (Duarte and Thomson, 2019). Furthermore, the psychological effects on non-responders whose trials fail in a group of patients already affected by anxiety and depression is of considerable concern.

Several neurophysiological objective measures have been used in the literature to evaluate SCS during a screening trial to aid in the identification of responders as a part of the growing field of personalised medicine in clinical practice. Studies have primarily used tonic stimulation, the effects of high frequency and burst stimulation on these neurophysiological measures remains largely unknown.

This study aimed to explore two of the most common neurophysiological measures used in the literature for SCS chronic pain evaluation in FBSS patients. The two neurophysiological objective measures investigated were absolute theta power and SSEP amplitude. Baseline patterns in each measure were reviewed to identify candidates for patient responder selection without the need for a SCS trial.

In this study a cortical signature for chronic neuropathic pain was identified at baseline in 12 out of 16 high frequency stimulation responders, 10 out of 14 tonic stimulation and with burst stimulation in 11 out of 15 responders. In contrast in the non-responder subgroup only two patients presented with the absolute theta power concentric pattern and failed to respond to any of the stimulation programmes tested. This finding strongly suggests that the absolute theta power concentric pattern was associated with SCS responders.

The absolute theta power concentric pattern was characterised by elevated absolute theta power in a concentric ring pattern over the frontal, central and parietal regions with increasing inhibition towards the vertex. Raised absolute theta power at F7, F3, F4, Fz and F8 relate to the dorsolateral frontal and prefrontal cortex a primary node for the descending

pain modulating system involved with suppressing ongoing pain. (Vanneste and De Ridder, 2021; De Ridder et al., 2022). Electrodes C3 and C4 with the post central gyrus in 85% of people (Scrivener and Reader, 2022) and location of the primary somatosensory cortex for the upper limbs. The Pz electrode with the precuneus cortex which borders the somatosensory cortex and plays a crucial role in pain processing (Mayr et al., 2022) and electrodes P3 and P4 to the lateral occipital cortex (Scrivener and Reader, 2022) a region that has been linked to encoding pain intensity in chronic lower back pain patients (Mayr et al., 2022) and becomes coupled to the default network in chronic pain (Karten et al., 2013).

In this baseline pattern absolute theta power was observed to decrease in concentric regions towards the vertex at electrode Cz the site of the precentral gyrus in 87% of people and the post central gyrus specifically the region of the somatosensory cortex relating to the trunk and lower limbs in 13% of people (Scrivener and Reader, 2022). This finding implies that the SCS responders in FBSS patients in this study were associated with absolute theta power reduction over the primary motor cortex and the region of the somatosensory cortex relating to the lower back and legs.

In acute experimental pain research Mercier & Léonard, (2011) observed an inhibitory effect on the motor cortex and argued that in chronic pain the motor cortex becomes inhibited. Chang et al., (2018) adds that in acute muscle pain motor cortex inhibition represents an adaptive mechanism to prevent further injury. Experimental models have suggested that motor cortex inhibition occurs with sustained muscle pain (Chang et al., 2018) and that motor cortex plasticity alters when pain becomes chronic. Chang et al., (2018) argues that experimental evidence suggests that motor cortex inhibition is associated with chronic neuropathic pain and not chronic nociceptive pain. Corti et al., (2022) agrees and adds that in chronic lower back pain, cortical plasticity changes result in the reduction of intracortical excitability over the motor cortex. Motor thresholds have been observed to be higher than control subjects in lower back pain patients with evidence of decreased corticospinal excitability which Corti et al., (2022) attributes to motor cortex inhibition. Corti et al., (2022) considers altered motor cortex excitability to be the most common feature of chronic neuropathic pain. There is convincing evidence to support this statement primarily relating to neuropathic pain onset and motor cortex inhibition representing an adaptive mechanism to prevent further injury. Chang et al., (2018) agrees adding that patients with chronic lower

back pain typically present with abnormalities of movement effecting gait, standing and sitting reducing movement and risk of further injury. In this study at baseline patients presented with ODI scores for severe to chronic disability scoring highly for daily living activities that require motor cortex function. This finding supports the hypothesis that the motor cortex is inhibited in patients with the baseline concentric pattern.

The role of motor cortex inhibition and its effects on the somatosensory cortex however remains poorly understood. Berwal et al., (2023) suggests that both somatosensory and motor cortex are likely influenced by other neural circuits during SCS due to plasticity changes at the cortex.

Protachevicz et al., (2023) reported that cortical plasticity changes can result in transmission delays within the same subnetwork when the network becomes desynchronised due to neural excitation and inhibition. Transmission delays have been reported as a signature of other brain networks involved in a larger more complex interconnecting network. Protachevicz et al., (2023) explains that transmission delays in networks effected by plasticity changes can show latency transmission delays independent from initial demyelination due to injury and that latency delays may be several milliseconds long. It is unclear if significant axonal signalling delays are true for plasticity changes at the motor and somatosensory cortex with chronic lower back pain.

In the current study seventeen patients at baseline were found to have lower limb SSEP P37 latencies in the symptomatic leg of >42 ms and associated with the absolute theta power concentric pattern. This incidental finding may represent transmission delays related to motor and somatosensory cortex inhibition.

FBSS patients in this study presented mainly with lumbosacral degenerative related spinal issues or disc prolapse requiring surgical intervention which included discectomy, microdiscectomy and decompression surgical procedures. In the study group the most common post operative complications included entrapment of spinal nerves S1, L4 and L5 by scar tissue or foraminal stenosis and in one patient an arachnoid cyst formed around the scar tissue leading to further compression. The assumption here is that the patients in the study were at an increased risk of spinal nerve compression subsequent Aβ and Aδ fibre injury.

There is good consensus in the literature that compression of a spinal nerve or root beyond several hours leads to demyelination of Aβ and Aδ fibres at the nodes of Ranvier leading to myelin retraction and subsequent exposure of underlying Aβ and Aδ axons. Dodson et al., (2003) and Zhang et al., (2021) have both proposed that potassium channel impairment leads to the onset and maintenance of neuropathic pain when axons are exposed due to prolonged demyelination. Zhang et al., (2021) investigated in rats a subclass of voltage gated potassium channel, KV1.2 located in the juxtaparanode domain of axons in contact with the node of Ranvier internode. Here voltage gated KV1 potassium channels cluster and modulate presynaptic function by suppressing terminal hyperexcitability. Zhang et al., (2021) found that impairment of KV1.2 potassium channels participated in the development of axon hyperexcitability and was crucial in the maintenance of neuropathic pain and continued hyperexcitability beyond the initial effects of demyelination. This may account for the unusually high number of patients in the study group presenting with SSEP pathway dysfunction at baseline which may represent a combination of signalling delay and demyelination.

Further evidence was observed in the patient pain characteristics associated with the absolute theta power concentric pattern which were biased towards neuropathic symptoms linked to hyperexcitability in the literature. The common symptoms included moderate to very strong burning, prickling and crawling sensations. The most common symptom experienced by all patients included in the study was spontaneous "electric shock" sensations. These unpleasant ectopic sharp sensations were seen to dominate patients lower back pain profiles and the most resistant pain characteristic to SCS. The most frequent back pain pattern reported by patients was persistent pain with sudden pain attacks these sudden pain episodes were described as strong to very strong electric shock sensations and evidence of peripheral excitability.

Prickling and crawling sensations with sudden sharp "electric shock" sensations are considered by Finnerup et al., (2021) and Choi, (2019) as clinical indicators for somatosensory pathway dysfunction and evidence of hyperexcitability which would fit with the observed pain characteristics of this study group. Aβ and Aδ hyperexcitability have been linked to nerve root entrapment and are considered as one of the major causes of painful electric shock sensations in FBSS patients. Paraesthesia often accompanies these unpleasant

sensations which is evidence for larger Aβ fibre involvement and was observed in patients included in the study. Choi, (2019) cites paraesthesia and tingling with radicular pain radiating down the leg as a clinical indicator of spinal root entrapment.

The findings from this study imply that the presence of the absolute theta concentric pattern may represent a cortical signature for neuropathic pain with intracortical inhibition of the motor cortex and a biomarker for SCS responders. This pattern was associated with neuropathic pain on the Pain Detect scale in twenty-two of the twenty-seven patients. The proposed signature represents absolute theta power elevation in combination with motor cortex inhibition (Figure 3.39)

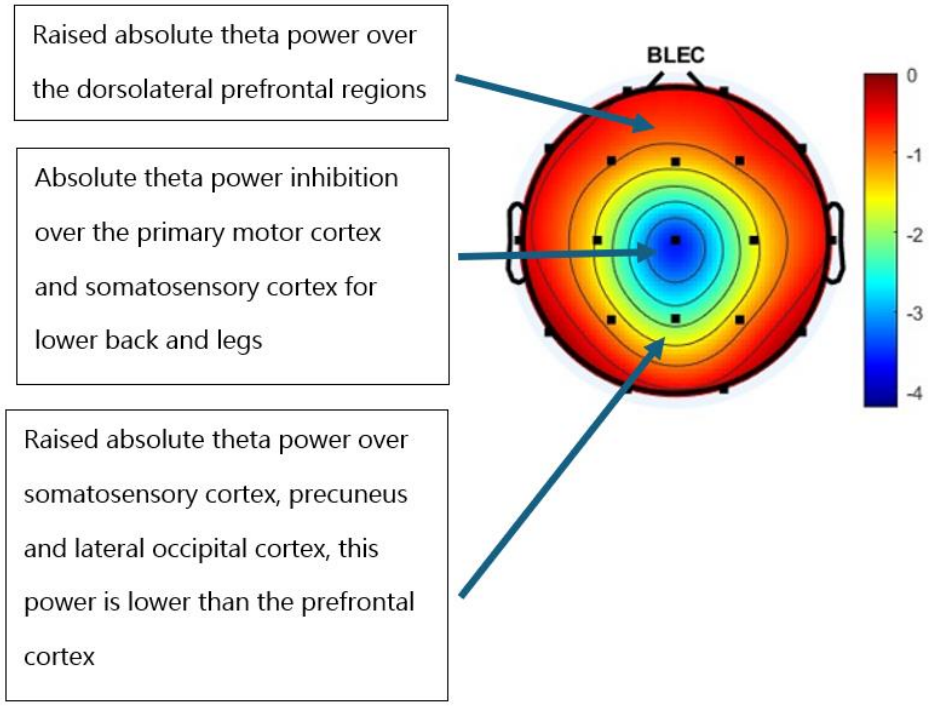


Figure 3.39: Absolute theta power concentric pattern and typical pain signature for lower back neuropathic pain with motor cortex inhibition. Characterised by raised absolute theta power over the dorsolateral prefrontal cortex, precuneus cortex and lateral occipital cortices.

In this study patients either presented with nociceptive, mixed or neuropathic pain profiles. Patients with either nociceptive or mixed pain profiles presented with symptoms that were dominated by moderate burning, prickling/crawling and electric shock sensations evidence of nociceptive Aδ and C-fibre irritation. This patient subgroup had normal lower limb SSEP latencies. This finding favours a milder entrapment, with the somatosensory pathway

functioning normally, with pain primarily nociceptive, and the motor cortex not inhibited. In this subgroup of patients, the absolute theta power concentric pattern was absent, and motor cortex not inhibited. The mechanism here is a combination of peripheral sensitisation and spinal cord central sensitisation. Thalamocortical dysrhythmia effects are very weak, and the motor cortex is not inhibited (Chang et al., 2018).

In the neuropathic patient group absent of the concentric pattern burning, prickling/crawling and electric shock sensations remained strong to very strong and baseline lower limb SSEPs had primarily abnormal P37 latencies and in keeping with somatosensory pathway dysfunction. One explanation for the difference between the patients with the absolute theta power concentric pattern and neuropathic patients without the pattern is the strength of the moderator effect created by thalamocortical dysrhythmia. Thalamocortical dysrhythmia progressively becomes dominant with the development of chronic pain driven by cortical plasticity. Intracortical plasticity changes lead to raised absolute theta power across the pain network and inhibition of the motor cortex and central somatosensory regions associated with the trunk and legs. When thalamocortical dysrhythmia becomes the dominant component of this mechanism absolute theta power rises across the motor and somatosensory cortices and the absolute theta power concentric pattern is lost. Walton & Linas, (2010) refer to this pattern as increased coupled thalamocortical physiology which Schulman et al., (2005) classifies as thalamocortical dysrhythmia pain. This is marked by increased coupling between the two ascending pain pathways with the default network and inhibition of the descending pain pathway as explained by the triple network model (Vanneste and De Ridder, 2021; De Ridder et al., 2022).

Therefore, evidence from the current study favours intracortical inhibition at the motor cortex as the driving mechanism for the appearance of the absolute theta power concentric pattern.

Therefore, three groups of spectral patterns were present in the study group which represent three stages of chronic pain in FBSS patients (Figure 3.40) with the absolute theta power concentric pattern representing the optimum physiological conditions for SCS responders.

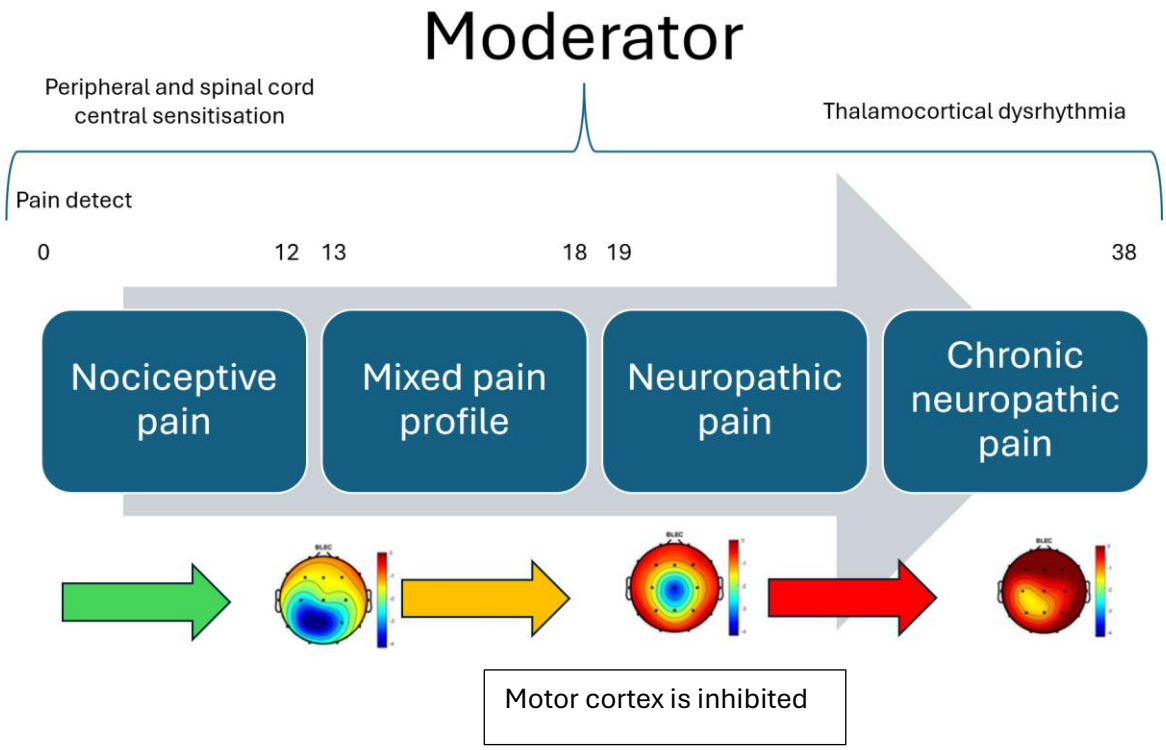


Figure 3.40: Pain model of baseline theta absolute power profiles showing the progression of chronic pain in FBSS patients with motor cortex inhibition being the signature for optimum SCS responders.

The absolute theta power concentric pattern was found to have a high accuracy in all three stimulation programmes for identifying responders. This represents for the first time a potential screening tool for identifying SCS responder candidates without the need of a trial.

In the high frequency stimulation group the accuracy was 70% in tonic stimulation the accuracy was lower at 67% and for burst stimulation accuracy was 74%. Sensitivity in three stimulation programmes was high with high frequency stimulation sensitivity at 75%, tonic stimulation at 71% and burst stimulation at 80% suggesting that the absolute theta power concentric pattern was very good at identifying responder patients from their baseline absolute theta power profile. This finding confirms that the appearance of the concentric pattern represents a goldilocks zone of potential SCS responders driven by motor cortex inhibition and intracortical plasticity changes with chronic neuropathic pain.

Specificity however was lower for all three stimulation programmes. High frequency stimulation had a specificity of 64%, tonic stimulation 60% and burst stimulation 62.5%.

Therefore, relying on visual inspection alone would be far too unreliable and would benefit combing with a neurophysiological measure.

There is convincing evidence in the literature that absolute theta power is sensitive to drowsiness and excessive sleepiness. Multiple publications have reported fractured sleep-wake cycles as a classical feature of chronic pain. Patients included in this study had normal levels of daytime sleepiness at the time of each trial favouring sleepiness not being a biasing factor for these results.

The other baseline profile reviewed in the study was dominant frequency of the absolute power spectral density. This was found to be in the lower alpha range in most patients and was not associated with an increase in alpha frequency with SCS as reported by other authors. In this present study baseline absolute power dominant frequencies could not differentiate between responders and non-responders. The frequency range occupied by the dominant peak was concordant with observations by Telkes et al., (2020).

Most studies in the literature have used absolute theta power and lower limb SSEP amplitude studies to model the effects of tonic SCS. Goudman et al., (2020); Telkes et al., (2020) and Berwal et al., (2023) all reported significant differences in absolute theta power reduction with tonic stimulation in responder patients.

In the current study absolute theta power reduced significantly with both high frequency and tonic stimulation over the precuneus cortex, lateral occipital cortices and somatosensory cortices. This significant decrease in absolute theta power was found to be significant at Pz, the precuneus cortex in both high frequency and tonic stimulation. The mean relative theta power ratio used to measure the change from baseline in both produced mean ratios <1.0.

Significant reduction in absolute theta power was associated with pain relief and a reduction in neuropathic pain characteristics in responders. Pain patterns were altered significantly moving from a neuropathic pain profile to a nociceptive pain profile. Both stimulation modalities were associated with reducing very strong burning, prickling/crawling and electric shock sensations and accompanying numbness pain characteristics associated with chronic hyperexcitability of Aβ and Aδ fibres. The persistence of electric shock sensations at moderate to strong intensities in eight patients, suggested that high frequency stimulation

failed to fully suppress Aδ fibre hyperexcitability in 50% of the subgroup. In three patients this was accompanied by the appearance of allodynia a clinical indicator of C-fibre excitation.

Both stimulation modalities rely on closing the spinal gate to inhibit ascending pain signals, high frequency stimulation relies on opioidergic mechanisms to create analgesia, and tonic stimulation relies on GABA inhibition to create paraesthesia.

High frequency and tonic stimulation created a modulatory effect on the cortex. Absolute theta power reduction moved posterior away from the motor cortex and somatosensory cortex relating to the trunk and lower limbs posteriorly to the precuneus and lateral occipital cortices responsible for encoding and processing pain. The field generated by tonic stimulation tended to show an asymmetrical oval shape appearance favouring the contralateral side to the painful lower limb driven by dorsal column activation. This was less obvious in high frequency stimulation which tended to be more focal over the precuneus cortex due to the direct Aδ modulatory effect on the lateral spinothalamic pathway. In addition to absolute theta power reduction over the precuneus and somatosensory cortices, the motor cortex was observed to be reactivated. An improvement in motor cortex function was seen in both responder subgroups as improvements in ODI scores for walking, sitting, lifting and personal care (washing, dressing) all skills that require normal motor function.

Further evidence of neuromodulator effects on the triple pain network was observed more in depression than anxiety scores. A significant reduction in both anxiety and depression was observed favouring decoupling between the pre-frontal cortex, anterior cingulate of the medial spinothalamic tract and the default network as normal function is restored between the three pain networks

The relationship between an absent absolute theta power concentric pattern and being a non-responder was validated by the absence of any significant changes in absolute theta power from baseline with relative theta power ratio's >1.0 seen in non-responders. In both high frequency and tonic stimulation subgroups absolute theta power tended to remain high over the lateral occipital cortex for encoding pain, the motor cortex and over the somatosensory cortical areas. The current study supports the hypothesis that the absence of motor cortex intracortical inhibition at baseline prior to high frequency or tonic stimulation is associated with suboptimal pain relief and being a non-responder. This finding agrees with

both Chang et al., (2018) and Corti et al., (2022) who both argue that altered motor cortex excitability is the most important feature in chronic pain.

Walton & Linas, (2010) and Schulman et al., (2005) argue that the underlying mechanism driving these changes is thalamocortical dysrhythmia. The absence of motor cortex inhibition may be a cortical signature of increased thalamocortical physiology coupling where thalamocortical dysrhythmia becomes the dominant part of the pain mechanism.

Schulman et al., (2005) reported that absolute theta power increased in non-responders where thalamocortical dysrhythmia prevented any significant inhibitory changes taking place at the cortex with SCS. The observations from this study agreed with Schulman et al., (2005).

Several studies have reported improved pain relief of over 50% with the reduction of absolute theta power and tonic stimulation whether there is a correlation between absolute theta power reduction and pain relief is poorly understood (Goudman et al., 2020; Telkes et al., 2020; Berwal et al., 2023). In this study a weak negative correlation was found between the relative theta power ratio and pain relief for both high frequency and tonic stimulation however this relationship was found not to be statistically significant. This would indicate that the magnitude of absolute theta power reduction was dependant on cortical dysrhythmia influences at the cortex with cortical dysrhythmia behaving as a physiological moderator on the cortex and on pain relief experienced with SCS (Figure 3.41).

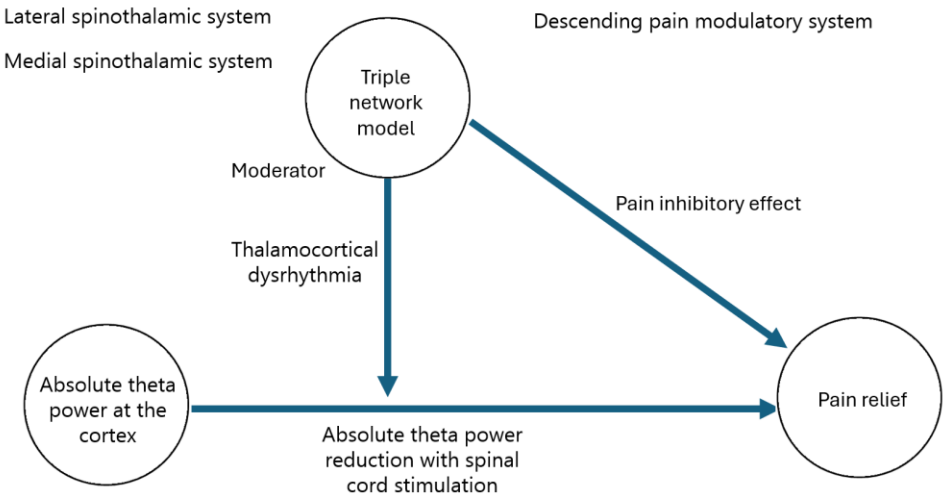


Figure 3.41: A moderator diagram detailing the triple network model moderator effects on absolute theta power and pain relief for high frequency and tonic stimulation. Imbalances between the triple network model determine the strength of the moderator effect on thalamocortical dysrhythmia which moderates the responsiveness of absolute theta power at the cortex to SCS. Pain relief is moderated by the descending pain modulating system at the spinal gate.

Based on this model prolonged high frequency and tonic stimulation would therefore be expected to lead to better pain relief outcomes long term in responders due to decreased thalamocortical dysrhythmia effects and restoration of intracortical excitability of the motor cortex (Vanneste and De Ridder, 2021; Corti et al., 2022; De Ridder et al., 2022).

In this study 6 month follow up data was limited to 12 patients from the original 27 patients largely due to patients waiting for permanent implants. Four high frequency stimulation responders showed an improvement in pain relief at follow up when compared to the study and one high frequency non-responder patient showed improved pain relief at follow up due to prolonged exposure to SCS. In five patients (patients 2, 4, 5, 14 and 15) tonic stimulation gave the best pain relief however at follow up all five were found not to be using tonic stimulation due to unpleasant sensations, these patients preferred paraesthesia free options.

The effects of burst stimulation on absolute theta power and the relative theta power ratio in this study were unclear due to absolute theta power reduction occurring more anterior to the Pz electrode chosen for analysis. No significant differences were observed between baseline and burst stimulation and between responders and non-responders. Reduction in absolute theta power primarily occurred over the inferior parietal area of the primary and secondary somatosensory cortex. Inhibition over the precuneus and lateral occipital cortices was found to be minimal. Minimal theta power reduction was also noted over the frontal and pre-frontal regions.

Multiple studies have demonstrated that burst stimulation modulates absolute theta power in the inferior parietal area of the primary and secondary somatosensory cortex and Para-hippocampus increasing connectivity with the dorsal anterior cingulate cortex agreeing with the observed absolute theta power changes in this study (De Ridder et al., 2013, 2015; De

Vos et al., 2014; De Ridder and Vanneste, 2016; Witjes et al., 2023). Absolute alpha power displaces absolute theta power over the left dorsolateral prefrontal cortex which may account for the minor prefrontal spectral changes observed in the present study (De Ridder and Vanneste, 2016; Witjes et al., 2023).

The motor cortex remained inhibited with low absolute theta power which may account for patient outliers in the burst stimulation responder subgroup with ODI scores remaining as crippled in their disability profile and mean scores decreasing to the severely disability range. However, a statistically significant improvements in ODI scores were found despite continued motor cortex inhibition.

In the present study burst stimulation responders' patients reported reduced moderate to very strong pain due to light pressure, moderate pain sensitivity to temperature and strong allodynia. The reduction of these three pain characteristics according to Finnerup et al., (2021) suggest modulation of central pain within the spinal cord of both Aδ and C-fibres related second order neurones. Pain sensitivity to temperature is a common symptom of post-surgical or post therapeutic treatment involving peripheral nerve or spinal root injury. Cold allodynia is particularly common in central pain mechanisms. Jensen and Finnerup, (2014) and Finnerup et al., (2021) consider reduction of these symptoms to be related to central neuromodulation of neuronal firing rates.

In comparison to high frequency and tonic stimulation responders central pain characteristics at baseline were reported in more patients who responded to burst stimulation suggesting that high frequency and tonic stimulation responders were predominantly patients with peripheral pain and burst stimulation responders' central pain.

In the burst responder subgroup several patients reported persistent strong burning and moderate to very strong prickling/crawling and electric shock sensations pain characteristics associated with peripheral Aβ, Aδ and C-fibre damage. Finnerup et al., (2021) considers the presence of persistent burning sensations to be an indicator of regenerating C-fibres. The prevalence of evoked pain symptoms described in the burst stimulation responder subgroup is highly suggestive of preserved afferent pathways. Strong to very strong numbness was also reduced in this group with burst stimulation indicating Aβ fibre modulation in patients with dysfunctional afferent pathways. In this study burst stimulation reduced mean Pain

Detect scores from 20 (neuropathic) to 12 (nociceptive) in the responder subgroup which was found to be significantly different ($p<0.05$). Pain patterns on average were altered from persistent pain with pain attacks to persistent pain with slight fluctuations in pain evidence of pain modulation. Significant improvements were also reported for both anxiety and depression with burst stimulation showing mean reductions into the normal range evidence of modulation between the medial spinothalamic tract and default network.

In the present study mean pain relief for burst stimulation was 69%, the highest in the entire study when compared to high frequency and tonic stimulation, two patients reported 100% pain relief. It remains unclear from this study whether absolute theta power was correlated with pain relief in burst stimulation. The present study failed to demonstrate statistical correlation with burst stimulation. This was attributed to burst stimulation modulatory effects occurring over the inferior parietal regions at electrodes C3 and C4 anterior to Pz electrode used in the analysis. The degree of thalamocortical dysrhythmia as a moderator of pain relief with burst stimulation could not be evaluated with this current study protocol.

In the current study no significant SSEP amplitude reduction was observed from baseline with high frequency, tonic or burst stimulation. These findings are not surprising for high frequency and burst stimulation which primarily modulate Aδ fibres and not Aβ fibres thought be responsible for SSEP amplitude reduction via antidromic collision with the ascending orthodromic SSEP volley. Furthermore, the absence of any significant amplitude reduction in this study favours SSEP amplitude reduction to be a product of collision rather than a reduction in somatosensory cortical processing as previously proposed by Poláček et al., (2007) and Wolter et al., (2013).

Tonic stimulation however also failed to significantly reduce SSEP amplitudes in SCS responders, a marginal effect was observed but this was too weak to be statistically significant. This finding was surprising and may be linked to suboptimal placement over the dorsal columns at implantation. Given the statistically significant changes in absolute theta power and pain relief this finding may suggest that optimising electrode placement over the dorsal columns may add little benefit to the therapeutic effects experienced with tonic SCS. Electrode positioning on the spinal cord warrants further study.

In the non-responder subgroup not explored by other studies in the literature SSEP amplitudes showed changes in amplitude (increase or decrease) that were not statistically significant.

There is insufficient evidence available in the literature to demonstrate a correlation between pain relief and SSEP amplitude reduction with tonic stimulation. Wolter et al., (2013) failed to demonstrate a correlation in their study of ten patients. In the current study no correlation was found with the SSEP amplitude ratio for high frequency, tonic or burst stimulation.

ROC evaluation of the relative theta power ratio found that relative theta power ratios for high frequency and tonic stimulation were good neurophysiological measures to differentiate between responders and non-responders. Statistically both high frequency and tonic stimulation were different from random prediction. When combined with the presence the absolute theta power concentric ratio accuracy, sensitivity and specificity increased particularly when identifying any SCS responder.

The SSEP amplitude ratio failed to identify responders and was no better than random prediction. Tonic stimulation although produced an acceptable model was statistically no better than random prediction.

The absolute theta power concentric pattern was found to be an accurate predictor of SCS responders and could differentiate between non-responders within the diagnostic standards for clinical practice.

In UK clinical practice NICE, (2014) guidelines recommend a multidisciplinary assessment and a screening trial prior to permanent implantation. Duarte & Thomson, (2019) costed the SCS process for UK NHS clinical practice. They found that the total cost for a successful trial (responder) and non-rechargeable permanent implant was £14,288 per patient. For a rechargeable permanent implant, the total cost increased to £20,429. The cost of a failed trial (non-responder) with the patient requiring removal of a permanent implant was £5,141 (explant).

They compared these costs to an implant only strategy with cost savings of £3,007 per patient for both non-rechargeable implants with an implant cost of £11,281 and rechargeable implants with an implant cost of £17,422.

Duarte & Thomson, (2019) based on a cost savings approach recommended a change in UK clinical practice removing the mandatory screening trial before permanent implantation for chronic neuropathic pain. Duarte & Thomson, (2019) report that service review data for UK practice indicated a trial: Implant ratio of 92% (23:25) and explant rate between 6.7% and 23.9% (Duarte and Thomson, 2019). There is no consensus on whether there is value of a screening trial under this current model.

The present study proposes a new model for SCS clinical practice selection using the absolute theta power concentric baseline pattern to identify responders and non-responders. Identified responders would be given the option to proceed to permanent implant without a screening trial (Figure 3.42).

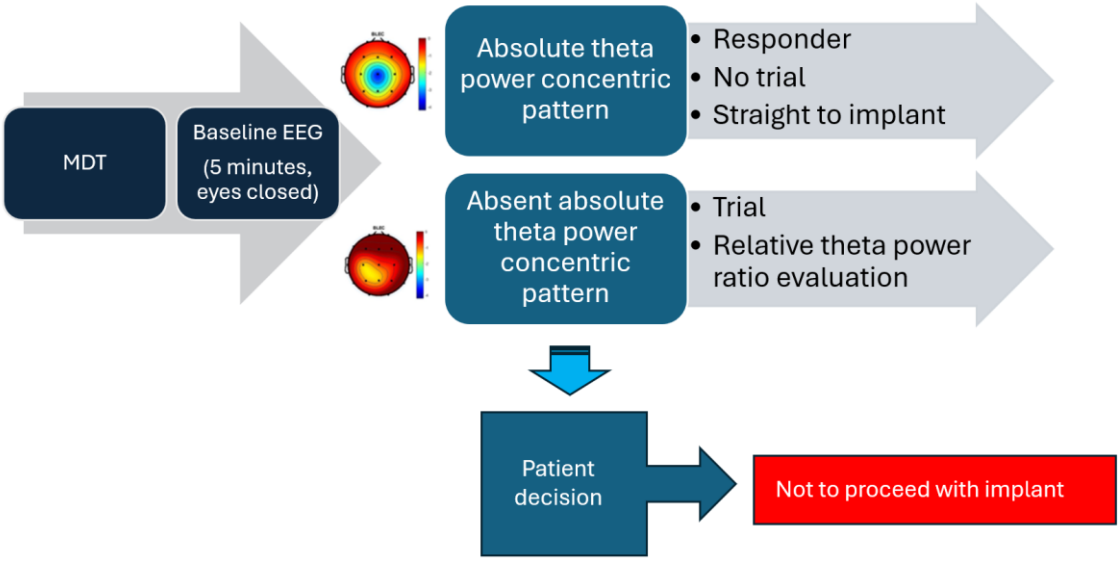


Figure 3.42: A proposed SCS decision making chart using absolute theta power concentric pattern. Patients with the absolute theta power concentric pattern at baseline could go straight for permanent implant without a trial. The patients without this pattern would be offered a trial with EEG theta power evaluation to aid clinical decision making. Patients without the absolute theta power concentric pattern at baseline but showed evidence of

significant theta power reduction would be offered a permanent implant. Patients without significant theta power reduction would not be offered an implant.

In the present study the follow up data was limited to 12 patients with 51% of patients lost due to the long waiting list for a permanent implant. Therefore, it is difficult to make any valid conclusions on clinical benefit without more follow up data. The limited data available indicates that in five patients who received a permanent implant at 6 months continued to use the stimulation programme that gave them maximum benefit at trial of these four patients at trial were classified as having a baseline theta absolute power concentric pattern and represented true responders.

In the present study the permanent effect on cortical plasticity is unknown, future studies would benefit from follow up EEGs to better elucidate these preliminary findings.

3.5. Conclusion

The aim of the study was to investigate whether patterns of brain activity measured at baseline by QEEG and SSEPs could predict the therapeutic response to SCS in FBSS patients with chronic neuropathic pain.

In this study a cortical signature for neuropathic pain was identified in FBSS patients. The spectral pattern identified consisted of a concentric pattern of absolute theta power with theta power reduction over the motor cortex and somatosensory cortex relating to the trunk and lower limbs. Raised absolute theta power was noted over the prefrontal, somatosensory, precuneus and lateral occipital cortical regions forming a ring. This pattern was associated with SCS responders receiving either high frequency, tonic or burst SCS and offers a cheap outpatient alternative to screening trials prior to permanent implantation of SCS devices.

The inhibition of the motor cortex would appear to be the most significant part of this baseline pattern representing intracortical inhibitory plasticity. Mechanisms driving these changes include increasing central sensitisation, thalamocortical dysrhythmia and a physiological imbalance between the two ascending pain pathways and the modulating descending pain pathway leading to increased connectivity especially with the default network.

High frequency and tonic SCS decreased absolute theta power at the cortex over the precuneus, somatosensory and lateral occipital regions with significant pain relief. This was comparable to other studies in the literature for tonic SCS and suggested that both high frequency and tonic SCS activated the ascending lateral spinothalamic pathway.

The current study showed no significant reduction in SSEP amplitude for high frequency, tonic or burst stimulation. This surprising finding for tonic SCS may have been related to suboptimal placement of percutaneous electrodes at the dorsal column.

High frequency and tonic SCS reduced neuropathic pain symptoms associated primarily with Aβ and Aδ fibre hyperexcitability specifically paraesthesia, crawling and electric shock sensations. Neuropathic pain was seen to significantly decrease in both high frequency and tonic stimulation responders and patients with the absolute theta power concentric pattern at baseline.

High frequency and tonic SCS in responder patients reactivated the motor cortex which was observed on the absolute theta power maps generated in this study. This observation may suggest that it is the reactivation of motor cortex function rather than the decrease in absolute theta power that underpins pain relief. ODI scores associated with physical motor disability improved in patients where the motor cortex was reactivated. The high sensitivity observed for the absolute theta power concentric pattern at identifying responders would seem to indicate that the cortical signature of motor cortex inhibition was essential for predicting SCS responders.

However, correlation between relative theta power ratio and pain relief in high frequency, tonic SCS revealed a weak negative correlation that was not statistically significant. This may suggest modulatory effects on the cortex due to varying levels of thalamocortical dysrhythmia. No significant correlation was seen with burst SCS.

In the majority of non-responder patient's, the absolute theta power concentric pattern was absent. The most striking feature being the absence of motor cortex inhibition. The motor cortex under these circumstances was dominated by raised absolute theta power which dominated the profile across frontal, somatosensory and precuneus cortical regions. Absolute theta power inhibition if present was minimal and not significant. Under these circumstances absolute theta power was seen to be statistically unresponsive to high frequency and tonic SCS showing minimal reduction in absolute theta power with suboptimal pain relief.

However, despite not being significant most patients in the non-responder subgroups for high frequency and tonic SCS responded with suboptimal absolute theta power reduction. This may be evidence of strong thalamocortical dysrhythmia a mechanism proposed to underpin chronic pain and motor cortex inhibition.

Therefore, results from the current study indicate that the absolute theta power concentric pattern may represent optimum physiological conditions at the cortex for SCS a potential "goldilocks" cortical signature for determining SCS responders.

Despite a very high sensitivity for identifying burst SCS responders with the absolute theta power concentric pattern, no significant changes in absolute power or relative theta power ratio were observed in burst responders. This finding suggests that the baseline cortical

signature for neuropathic pain identified also applies to burst stimulation. The lack of significant results for absolute theta power reduction and relative theta power ratio was limited by the study design. Burst stimulation primarily modulates the medial spinothalamic tract with changes in absolute theta power occurring more anterior and deeper to the precuneus cortex chosen for absolute theta power analysis. This was a limitation to the EEG study design.

The absolute theta power concentric pattern identified in this research project may offer significant benefits to the FBSS patient population in terms of SCS responder selection with significant cost savings and other patient benefits. More comprehensive follow up data with larger sample sizes for non-responder is required to validate findings. A large multicentre study is recommended to better elucidate the findings from this preliminary study.

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APPENDICES

EthOS approval Manchester Metropolitan University

24/10/2023

Project Title: Can the reversal of QEEG theta band power and SSEP reduction in amplitude be used as objective measures of efficacy of spinal cord stimulation in chronic neuropathic pain?

EthOS Reference Number: 49167

Certification

Dear Michael David Pridgeon,

The above application was reviewed by the Research Ethics and Governance Team and on the 24/10/2023, was certified. The certification is in place until the end of your HRA approval according as declared on the amendment tool and is based on the documentation submitted with your application.

Application Documents

Document Type	File Name	Date	Version
External Approval Supporting Information	2020peer+review+Sheet+A+Marshall	28/04/2020	Final
External Approval Supporting Information	Andy+marshall+small+grant++2020 (1)	22/07/2020	Grant
External Approval Supporting Information	final+protocol+SCS+EEG	28/06/2021	Final
External Approval Supporting Information	Deepti_Curriculum+vitae (1) IRAS Chief investigator	13/07/2021	Final
External Approval Application Form	IRASForm final	20/07/2021	Final
External Approval Supporting Information	IRAS check list summary	21/07/2021	Final
External Approval Supporting Information	REC favourable opinion[31755]	27/07/2021	Final
External Approval Supporting Information	Final+Patient+Consent+form+SCS+EEG+study	20/08/2021	Final (V2)
External Approval Supporting Information	Final+PIS+SCS+EEG+study	20/08/2021	Final (V2)
External Approval Letter	HRA_Approval 26.01.22[31754]	26/01/2022	Approval letter
Additional Documentation	Good_Clinical_Practice	25/11/2022	1
External Approval Supporting Information	NSA1 submitted amendment tool[54263]	14/08/2023	Amendment tool
External Approval Supporting Information	IRAS 283335 completion date amendment	15/09/2023	Email amendment

Conditions of certification

The Research Ethics and Governance Team would like to highlight the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This certification is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment in accordance with **HRA** guidelines. Please contact the Research Ethics and Governance team for advice around how to do this.

We wish you every success with your project.

Research Ethics and Governance Team

HRA and Health and Care Research Wales (HCRW) Approval Letter

Walton Centre for Neurology and Neurosurgery
Miss Deepti Bhargava
Consultant Neurosurgeon

Email: approvals@hra.nhs.uk

Walton Centre

Liverpool

L9 7LJ

26 January 2022

Dear Miss Bhargava

HRA and Health and Care

Study title:	**Reversal of EEG theta rhythm as an objective measure of efficacy of spinal cord stimulation in chronic neuropathic pain- a pilot study**
IRAS project ID:	**283335**
Protocol number:	**RG349-20**
REC reference:	**21/NI/0132**
Sponsor	**Walton Centre NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set, and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation.

The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **283335**. Please quote this on all correspondence.

Yours sincerely,

Natasha Bridgeman

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Debbie Atkinson, Walton Centre for Neurology and Neurosurgery*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_20072021]		20 July 2021
IRAS Checklist XML [Checklist_21072021]		21 July 2021
Letter from funder [Approval of funding]		22 July 2020
Participant consent form [Amended PIS SCS EEG study.docx]	2	20 August 2021
Participant information sheet (PIS) [Amended Patient Consent form SCS EEG study.docx]	2	20 August 2021
Referee's report or other scientific critique report [Peer review]		28 April 2020
Research protocol or project proposal [Protocol]	3	28 June 2021
Summary CV for Chief Investigator (CI) [summary CV]	1	13 July 2021

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they do not intend to apply for inclusion on the NIHR CRN Portfolio

Types of participating NHS organisation	**Expectations related to confirmation of capacity and capability**	**Agreement to be used**	**Funding arrangements**	**Oversight expectations**	**HR Good Practice Resource Pack expectations**

This is a single site study sponsored by the participating NHS organization therefore there is only one site type.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to decide to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study sponsored by the participating NHS organization therefore no agreements are expected.	External study funding has been secured.	A Principal Investigator should be appointed at study sites.	The sponsor has stated that local staff in participating organisations in England who have a contractual relationship with the organisation will undertake the expected activities. Therefore, no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

Business Services Organisation

Office for Research Ethics Committees Northern Ireland (ORECNI)

Customer Care & Performance Directorate
Unit 4, Lissue Industrial Estate West
Rathdown Walk
Moira Road
Lisburn
BT28 2RF
Tel: 028 9536 1400
www.hscbusiness.hscni.net/orecni

Health and Social Care Research Ethics Committee B (HSC REC B)

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

27 July 2021

Miss Deepti Bhargava
Consultant Neurosurgeon

Walton Centre for Neurology and Neurosurgery

Walton Centre

Liverpool

L9 7LJ

Dear Miss Bhargava

Study title:	**Reversal of EEG theta rhythm as an objective measure of efficacy of spinal cord stimulation in chronic neuropathic pain- a pilot study**
REC reference:	**21/NI/0132**
Protocol number:	**RG349-20**
IRAS project ID:	**283335**

The Proportionate Review Sub-committee of the HSC REC B reviewed the above application on 26 July 2021.

Ethical opinion

On behalf of the Research Ethics Committee (REC), the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Providing Support to Health and Social Care

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All research should be registered in a publicly accessible database, and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:

https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registrationhttps://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/applicationhttps://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approvedhttps://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvalshttps://www.hra.nhs.uk/approvals-amendments/managing-your-approval/amendments/managing-your-approval/.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see
"Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_20072021]		20 July 2021
IRAS Checklist XML [Checklist_21072021]		21 July 2021
Letter from funder [Approval of funding]		22 July 2020
Participant consent form [Consent form]	1	28 June 2021
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Referee's report or other scientific critique report [Peer review]		28 April 2020
Research protocol or project proposal [Protocol]	3	28 June 2021
Summary CV for Chief Investigator (CI) [summary CV]	1	13 July 2021

IRAS project ID: 283335	**Please quote this number on all correspondence**

Yours sincerely

HSC REC B

Attendance at PRS Sub-Committee of the REC meeting on 26 July 2021

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr John Edward Mone	Retired (Former Executive Director of Nursing)	Yes	
Dr Anne Moorhead	Senior Lecturer in Health Communication	Yes	Chaired Meeting
Dr Seamus O'Brien	Outcomes Manager, Primary Joint Unit	Yes	Lead Reviewer

Pain Relief Foundation small grant

Pain Relief Foundation

Charitable Incorporated Organisation

RELIEVING CHRONIC & CANCER PAIN THROUGH RESEARCH

Tel: 0151 529 5820 · Fax: 0151 529 5821 · E-mail: Lorraine.roberts.@painrelieffoundation.org.uk.

www.painrelieffoundation.org.uk

Clinical Sciences Centre

University Hospital Aintree

Lower Lane

Liverpool L9 7AL

22nd July 2020

Dr Andrew Marshall
Walton centre Foundation Trust

Dear Dr Marshall

'Reversal of EEG theta band rhythm as an objective measure of efficacy of spinal cord stimulation in chronic neuropathic pain - a pilot study'

I refer to your grant application described as above, and I am pleased to inform you that following the process of Peer Review and discussion regarding the small grant application which you submitted to Pain Relief Foundation, your application was agreed and approved at a meeting of our Trustees this week, for the sum of £21,400.
Please remember that the validity of your application is subject to any ethics approval required being in place and that the project satisfies the requirement of Research

Governance. The awarding of the grant is also subject to written report being submitted to the Foundation on the research project at six months from the commencement of the project and at six monthly intervals thereafter, to evaluate the progress being made.

So that I can prepare the Agreement on the research proposal, would you please let me have details of the person who will sign and process the Agreement and manage the finances and submission of supporting invoices for the period of the grant.

May I offer you every best wish for the future success of your research.

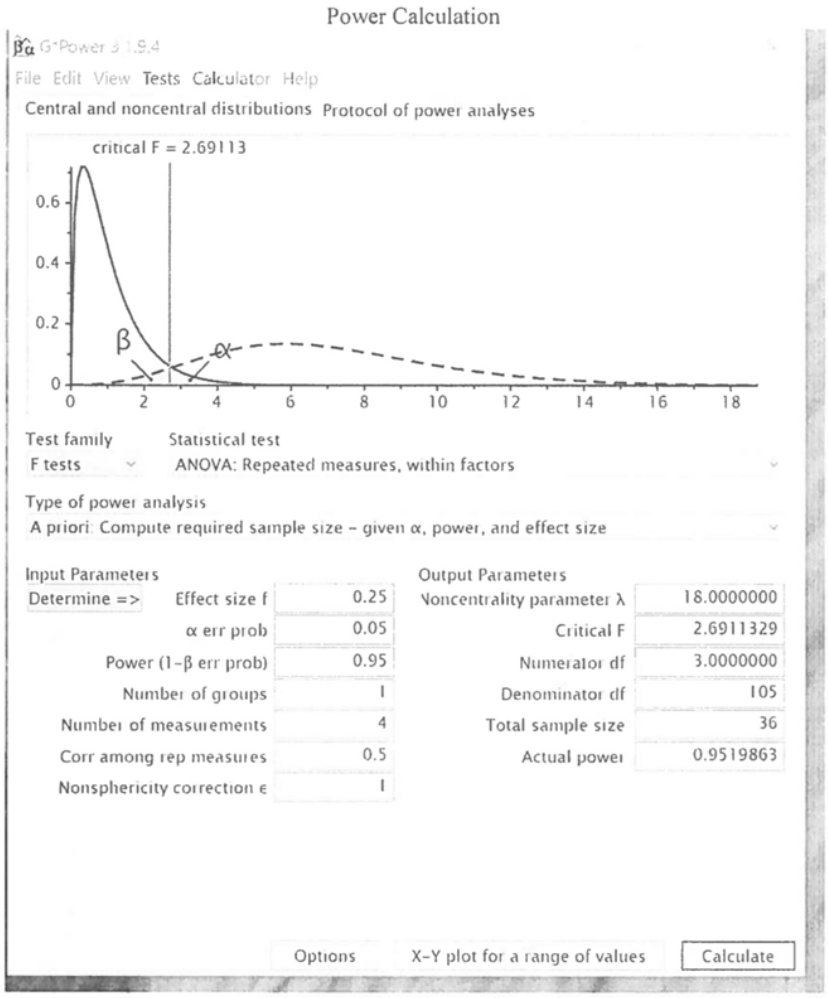
My kind regards.

Yours sincerely

JWilliams

Julie Williams
Charity Manager

G-power calculation for sample size.



Patient experience of participating in the research study

On the completion of 3 trials patients were given a patient experience questionnaire, 22 (81%) patients completed and returned the questionnaire, 5 patients (19%) failed to complete the questionnaire.

All patients classified the patient interaction and quality of care received as good. Most patients classified the patient information leaflet, and the quality of the information received each trial as good. Three patients commented that the patient information leaflet needed more information. This was early in the study and more information was supplied by the researcher at each trial to compensate for this comment. These results are summarised in Figure 3.32.

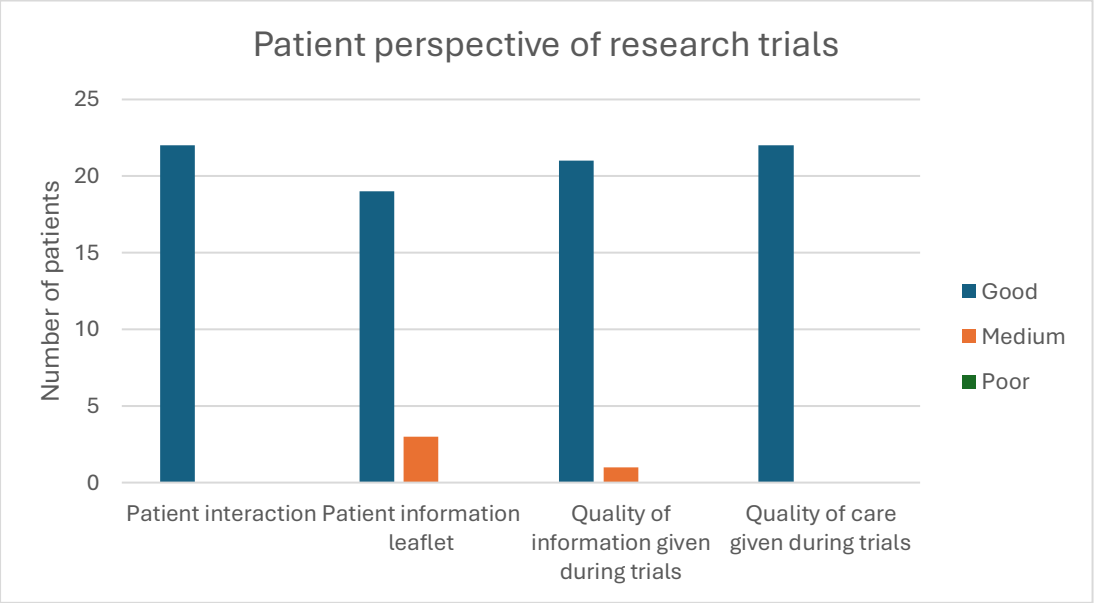


Figure 3.32. A bar chart summarising patient research experience during the project to allow reflection and modification of the study to maximise patient experience

All patients agreed that dignity was maintained during each trial and that appointment times were convenient and flexible.

Patients were asked about their initial expectations of participation in the trial following the consent process. Prior to the first EEG study at baseline 86% of patients were not anxious and 14% were a little anxious in comparison prior to the first SSEP study 63% of patients were not anxious and a higher number of patients, 37% were a little anxious, of this group patients reported being put at ease by the researcher undertaking the test. The main reason

for this reported by patients was that SSEP testing involved electrical stimulation of nerves. No patients were very anxious about participating in both EEG and SSEP studies.

Patients were also asked about their experience of the two tests for the EEG studies 86% of patients found the test not painful and 14% uncomfortable due to persistent lower back pain in a supine sitting position. In contrast for the SSEP studies 63% of patients found the test not to be painful, 32.5% found SSEPs uncomfortable and one patient found SSEPs very painful and was unable to tolerate this part of the study. Two patients had absent SSEP responses at each trial on the symptomatic side. There was no visible toe twitch on stimulation and testing was undertaken up to the intensity they could tolerate without becoming painful. Stimulation electrodes were also adjusted but failed to elicit any viable lower limb SSEP response.

Figure 3.33 summarises patient expectations after the consent process.

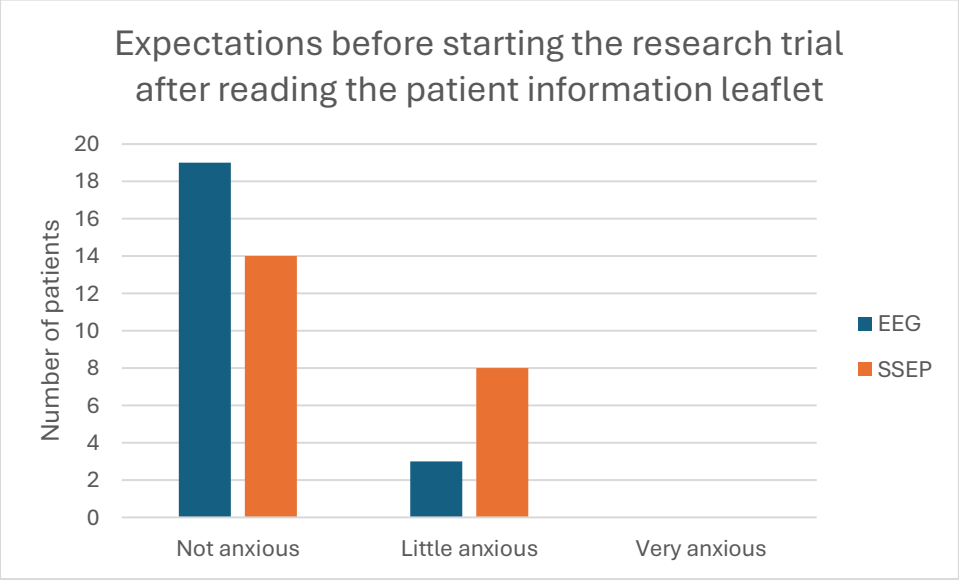
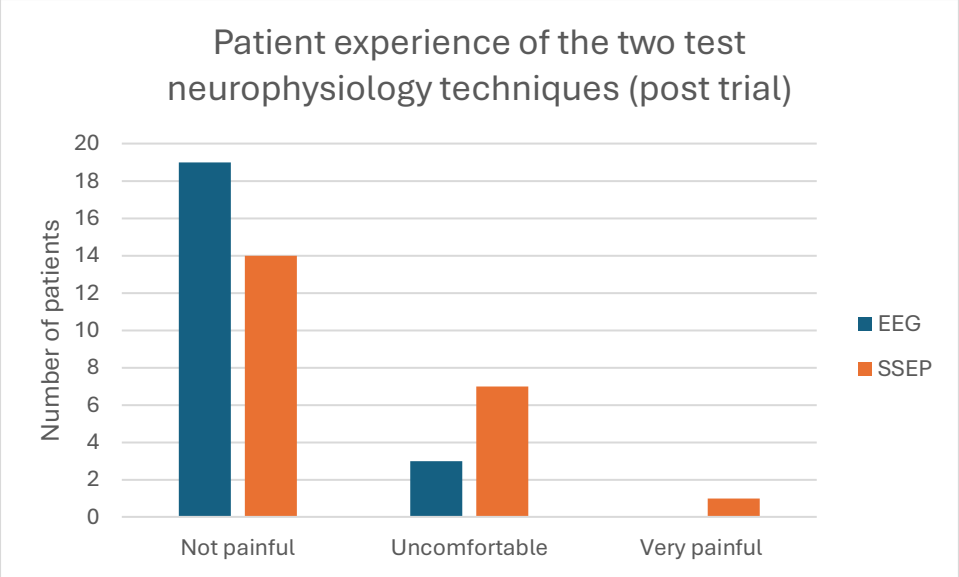


Figure 3.33. Patient expectations of the two tests, EEG and SSEP after the consent process

Figure 3.34 summarises the individual patient experiences of the two neurophysiology tests used (EEG and SSEP).



Graph 3.34: Patient experience of both EEG and SSEP following their participation in the study

The overall experience of the study was rated as excellent and beneficial in 90% of patients the remaining 10% scored their experience as good. No patients described their experience as poor or very poor.