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A feasibility study examining the utility of sacral dermatomal evoked potentials in assessing urogenital dysfunction

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Declaration

I, Anjaneya Malladi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources; I confirm that this has been indicated in the thesis.

Abstract

Background: Tarlov cysts are cerebrospinal fluid-filled sacs that form in multiple numbers at the location of dorsal root ganglia in the sacral spinal cord region. Tarlov cysts have been known for over seventy years and are often considered benign findings in MRI reports.

A group of predominantly female patients suffer from one or more symptoms, such as lower back pain, lower limb pain, sensory disturbance in the perineum, urinary incontinence, constipation, and sexual dysfunction, for no apparent reasons. All these patients have one common feature - Tarlov cysts in their sacral spinal segment. Most of the traditional diagnostic tests are normal in this group.

Since all patients with Tarlov cysts do not suffer from these symptoms, traditionally, their presence is often ignored, and patients with urogenital symptoms are investigated for urological, gynaecological, gastroenterological, or spinal causes. Many tests cause more delays in treatment and create economic and psychological burdens on these patients.

Studies have shown that patients can get relief from their symptoms after removing Tarlov cysts, which spurred interest in understanding symptomatic Tarlov cysts. It was hypothesised that some Tarlov cysts can interfere with sacral nerve root functions, causing urogenital dysfunction.

Aim:

To provide objective evidence for sacral root dysfunction in patients with symptomatic Tarlov cysts.

Methods:

Prospective, cross-sectional observational studies were conducted in three cohorts.
In a healthy group (cohort1) study, 20 healthy volunteers (14 women and 6 men) whose age $\pm$ SD (women: 39$\pm$16.6, men:35$\pm$10.6), height in cm (women: 162$\pm$8.8, men:176$\pm$8.1) and BMI (women: 25.9$\pm$6.6, men:24.5$\pm$5.5) were recruited to generate normative values for the sacral S2, S3 and S4 dermatomal Somatosensory Evoked Potential (dSEP). Regression

equations were generated for the cortical latency, amplitude and inter-side differences using independent age, height and BMI parameters.

In the spinal cord injury (cohort 2) study, 20 volunteers (13 women and 7 men) had cauda equina-level lesions (18) or thoracic-level lesions (2) confirmed by MRI. Three of the volunteers had an acute onset of symptoms, and the rest had an onset of symptoms ranging from less than a year to over a decade. All volunteers had sensory deficits on their buttocks, the back of their thighs, or in their perineum. The S2, S3 and S4 dSEPs were tested in this group, and the sensitivity and specificity of the sacral dSEPs were established using the Receiver Operating Curve.

In the symptomatic Tarlov cyst (cohort 3) study, 20 volunteers (18 women and 2 men) with one or more Tarlov cysts at their sacral spinal cord segment shown in their MRI were recruited. These volunteers were suffering from lower urinary tract symptoms (70%), perineal pain (65%), Persistent Genital Arousal Disorder - PGAD (20%) and paraesthesia in the perineum (15%).

Tibial Somatosensory Evoked Potentials (SEP) and Pudendal SEP were also recorded on all volunteers in all three cohorts.

The study was approved by the Manchester Metropolitan University Research Ethics and Governance Team (EthOS Reference Number: 46173). Volunteers in all three cohorts were compensated according to the Health Research Authority recommendations (21/NE/0194).

Results:

Inter-side cortical latency difference is the most useful parameter when considering sacral root dysfunctions. S2 dSEPs have 75% / 70%, S3 dSEPs have 85% / 85%, and S4 dSEPs have 90% / 85% sensitivity/specificity in detecting unilateral sacral root abnormalities.

Discussion:

The cohort 1 study showed that S2, S3, and S4 dSEPs can be recorded in all healthy subjects without any discomfort to participants. They are reliable, reproducible and easy to perform in a routine neurophysiology department with no additional investment. dSEP's cortical latencies were rapidly decreased after two times and plateaued after three times the stimulus threshold. Similarly, there was no improvement in the cortical amplitude after three times the stimulus threshold. Similar findings were also seen in S3 and S4 dSEPs. Unlike Tibial SEP, the subject's height did not significantly influence the S3 and S4 dSEP cortical latencies. Sacral dSEP latencies were similar to the Pudendal SEP latency but significantly (approximately 5 ms) shorter than the Tibial SEP latency.

The cohort 2 study showed that dSEPs are more sensitive in identifying abnormalities than Tibial SEP and Pudendal SEPs in spinal cord injuries. dSEP identified abnormalities in 85% of volunteers in this group compared to 40% and 69% in Tibial SEP and the Pudendal SEP, respectively. In this group, the Tibial latency asymmetry criteria showed 55%/70% sensitivity/specificity with an AUC of 0.717 (p-value:0.019), and the Pudendal SEP showed 84.6%/78.6% sensitivity/specificity with an AUC of 0.871 (p-value:0.001). However, the S4 dSEP showed 90%/85% sensitivity/specificity with an AUC of 0.910 (p-value:0.000).

The cohort 3 study showed that sacral root dysfunctions can occur in symptomatic Tarlov cysts, and the degree of dysfunction can be measured objectively with the help of dSEPs. In this group, the Tibial SEP and Pudendal SEP abnormalities were seen in 7 volunteers (35%), whereas the S2, S3 and S4 dSEP abnormalities were seen in 6 (30%), 9 (45%) and 13 (65%) volunteers, respectively.

Conclusion:

dSEPs are reliable testing tools that can be used to assess symptomatic Tarlov cysts and sacral root dysfunction.

Significance:

All Tarlov cysts are not benign; some can cause neuronal damage, resulting in urogenital dysfunction.

Publications arising from this thesis

Papers

Malladi, P., Simeoni, S. and Panicker, J.N., 2020. The role of pelvic neurophysiology testing in the assessment of patients with voiding dysfunction. *Current Bladder Dysfunction Reports*, *15*, pp.229-239.Available at: https://link.springer.com/article/10.1007/s11884-020-00613-0

Li, V., **Malladi, P**., Simeoni, S., Pakzad, M., Everett, R., Satukijchai, C., Leite, M.I., Palace, J. and Panicker, J.N., 2020. A clinico-neurophysiological study of urogenital dysfunction in MOG-antibody transverse myelitis. *Neurology*, *95*(21), pp.e2924-e2934. Available at : https://n.neurology.org/content/95/21/e2924

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List of Abbreviations

Ach	Acetylcholine
ACNS	American Clinical Neurophysiology Society
AUDIT	Alcohol Use Disorder Identification Test
BCR	Bulbocavernosus Reflex
BMI	Body Mass Index
CES	Cauda Equina Syndrome
CHEPS	Contact Heat Evoked Potentials studies
CMS	Conus medullaris syndrome
CSF	Cerebrospinal fluid
DRG	Dorsal Root ganglion
dSEP	Dermatomal Somatosensory Evoked Potentials
EMG	Electromyography
EP	Evoked Potentials
HRQoL	Health-Related Quality of Life
ISCEV	International Society for Clinical Electrophysiology of Vision
IOM	Intraoperative monitoring
IFCN	The International Federation of Clinical Neurophysiology
ISNCSCI	International Standards for the Neurological Classification of Spinal Cord Injury
NCS	Nerve conduction study
PMC	Pontine Micturition Center
PSC	Pontine storage Center
PSEP	Pudendal Somatosensory Evoked Potential
QALY	Quality-Adjusted Life Years
ROC	Receiver operating characteristic
SEP	Somatosensory evoked potentials
TSEP	Tibial Somatosensory Evoked Potentials
VPLT	Ventral posterior lateral thalamic

Introduction

Sacral nerves play a significant role in supporting pelvic organ functions. They relay sensory signals from the genitalia to the brain and carry motor commands from the spinal cord to the pelvic muscles. In addition, autonomic fibres also travel along with sacral somatic nerves, taking impulses responsible for erection, ejaculation, and pelvic pain. The sacral nerves are responsible for urinary and bowel continence, sexual function, and pain pathways in the pelvic area. Unfortunately, partial or complete damage to any of these sacral nerves can cause significant damage to the quality of life or even death to patients. Sacral nerves can be affected due to a variety of reasons, such as infectious diseases (Amarenco et al., 1991), ischemia (Polyzois, Tsitskaris and Oussedik, 2013), degenerative diseases (Todisco et al., 2022), perineural cysts (Kuhn et al., 2017), nerve entrapment (Luther and Castellanos, 2019) and damage during labour (Sultan, Kamm and Hudson, 1994).

Sacral nerve damage due to perineal cysts has debilitating consequences when not treated in time. Herniated perineal cysts can cause a cauda equina syndrome, resulting in voiding dysfunction (Baker, Wilson and Wallach, 2018), bowel dysfunction and erosion in the sacral bone (Ahn et al., 2000). Even though the presence of perineal cysts can be easily identified in MRI scans (O'Neill et al., 2019), finding symptomatic cysts that cause damage to sacral nerves remains an overlooked clinical problem (Murphy et al., 2011).

Chapter 1 describes sacral nerve anatomy and physiology with consideration of the surrounding structures and further explores the pathophysiology of Tarlov cysts and their variances. This chapter explores the findings of the literature review on Tarlov cysts and analyses the current difficulties in identifying and treating symptomatic Tarlov cysts. Additionally, the perception of Tarlov cyst illness among patients and medical teams and its impact on the healthcare system are explored, and potential solutions are explored using neurophysiology studies. The chapter concludes by setting aims to develop new dermatomal evoked potentials in assessing symptomatic Tarlov cysts.

Chapter 2 aims to develop S2, S3 and S4 sacral dSEPs in healthy adults. Current practices and limitations of dermatomal evoked potential studies in assessing symptomatic Tarlov cysts are explored. Posterior Tibial Somatosensory Evoked Potentials (TSEP) and Pudendal Somatosensory Evoked Potential (PSEP) studies share some common sacral nerve roots.

Studies have shown the relevance of TSEPs and dSEPs in diagnosing lumbosacral lesions (Hakatifi, 1986; Restuccia et al., 2000a). Similarly, studies have demonstrated the relevance of PSEPs in diagnosing lumbosacral lesions and sacral nerve dysfunctions (M. L. Delodovici and C. J. Fowler, 1995; Loening-Baucke, 1994). A few studies have examined the correlation between TSEP and PSEP in sacral root lesions (M. L. Delodovici and C. J. Fowler, 1995; Sultan, Kamm and Hudson, 1994). However, no studies on normative values for all evoked potentials in a healthy group were conducted. This chapter explores the importance of comprehensive normative data for S2, S3 and S4 sacral dermatomal evoked potentials and conventional TSEP and PSEP in diagnosing sacral nerve lesions.

Chapter 3 builds upon the normative values generated in Chapter 2 and aims to validate these in patients with known spinal root injuries. Evoked potential studies are sensitive to picking up unilateral abnormalities and helping localise lesions (Ferri et al., 2001; Wong and Chung, 2011). Some studies have shown that the dermatomal evoked potential studies are reliable and sensitive tests in picking up unilateral sacral root abnormalities (Hakatifi, 1987; Katifi and Sedgwick, 1986; Storm and Kraft, 2004), while some studies have shown a poor correlation with other evoked potential studies (Daniel Dumitru, 1996). The present study compares dSEPs TSEP and PSEP values and validated the results against published values (Dikmen and Emre Oge, 2013; Essa, Al-Hashimi and Nema, 2018). This chapter explores the discrepancies in the literature on the clinical utility of dermatomal evoked potential studies and supplies solutions while reporting dSEPs.

Chapter 4 deals with the neurophysiological evaluation of symptomatic Tarlov cysts. This work expands upon the findings of Chapters 2 and 3 and other established neurophysiological studies. Bulbocavernosus reflex study (BCR) is a known neurophysiology study to evaluate the sensory and motor pathways integrity in cauda equina lesions (Soler, Navaux and Previnaire, 2018; Tubaro et al., 2013). Needle Electromyography (EMG) is one of the well-established neurophysiological studies to assess the motor pathways dysfunction in the pelvic area (Huang et al., 2018; Podnar, Vodušek and Stålberg, 2000). Needle EMG helps differentiate chronic denervation from ongoing active denervation changes (Preston and Shapiro, 2012). Studies have shown that combining various neurophysiological studies in the pelvic area can increase the yield of diagnosing cauda equina and conus lesions (Zhang et al., 2022). The dorsal nerve of the penis is a valuable nerve conduction study that evaluates peripheral sensory nerve function in the pudendal nerve (Clawson and Cardenas, 1991). The

chapter explores the yield of dSEPs in the evaluation of symptomatic Tarlov cysts along with other established studies such as TSEP, PSEP, BCR and needle EMG studies.

Chapter 5 summarises the findings of this thesis in context with the wider literature and explores the possibilities for future work to assess Tarlov cysts and sacral root function. This chapter outlines diagnostic pathways for patients with symptomatic pathways for patients with symptomatic Tarlov cysts and other neurological disorders affecting pelvic organ functions. Finally, the chapter explores the possibility of setting up dedicated comprehensive neurophysiology referral centres to speed up diagnosing and monitoring patients with Tarlov cysts.

Chapter 1: Tarlov cysts

1.1 Background

Tarlov cysts are non-malignant Cerebrospinal fluid (CSF) - filled sacs that form at the bottom of the spinal cord, attached to spinal roots that supply sensory and motor function to the pelvic region. The presence of Tarlov cysts was initially reported by a neurosurgeon in 1938 in cadaver studies and following successful treatment on a patient (Tarlov, 1948). Tarlov cysts can damage the spinal nerves, resulting in severe lower back pain (Hasoon et al., 2020; Hulens et al., 2018; Nadler et al., 2001; Ostojic, 2015; I. M. Tarlov, 1948), bladder dysfunction (Baker, Wilson and Wallach, 2018; Marino et al., 2013; Yates et al., 2017), bowel dysfunction (Acosta et al., 2003; Boukobza et al., 2018; Shimauchi-Ohtaki et al., 2022), sexual dysfunction, and lower limb weakness (Baek and Rezania, 2006; Hiers et al., 2010; Nicpoń, Lasek and Chyczewska, 2002).

1.2 Prevalence of Tarlov cysts

The prevalence of Tarlov cysts in the European population is approximately 7.9% (Burdan et al., 2013; Gleeson et al., 2005; Larsen, Smith and Fossan, 1980) against the global prevalence of 5.4% (Klepinowski, Orbik and Sagan, 2021a). However, there was a significant variation in the prevalence among European studies. Gleeson et al. (2005) reported the prevalence as 0.4%, whereas a similar European survey by Larsen, Smith and Fossan (1980) and a French study by Kuhn et al. (2017) showed 17.7 % and 12%, respectively. Similar variations in the prevalence numbers are also seen in global studies, such as 0.5% in an Asian survey (Zeitoun and Mohieddin, 2019) and 16.1 % in a North American study (Lim and Selbi, 2023). The variation in the prevalence number could be due to the underreporting of Tarlov cysts on MRI scans. The prevailing notion among healthcare professionals is that Tarlov cysts are incidental findings and do not have any clinical significance (Hulens et al., 2019). Hence, they often neglect to mention them in MRI reports (Murphy et al., 2011). In addition, routine MRI scans for neurological diseases cover the brain and spinal cord up to L5 and S1 sacral roots. However, sacral Tarlov cysts form much below the S1 sacral root

levels and hence have a greater chance of missing them on regular MRI studies (Klepinowski, Orbik and Sagan, 2021a).

Tarlov cysts were reported across Europe, North America, Asia, and Africa, and after reviewing 13,266 subjects with Tarlov cysts, Klepinowski, Orbik and Sagan (2021a) observed no statistically significant difference in the incidence of Tarlov cysts among the above four regions. There were no publications available from Australia and South America regions on the incidence of Tarlov cysts in their respective areas. Still, the presence of self-help groups such as the Tarlov Cyst Disease Society of Australia (TCDF, 2023) suggests the presence of patients with Tarlov cysts in these unreported regions.

1.3 Disease Burden

No prospective or retrospective studies are available on the Tarlov cyst disease burden. No studies are available looking into either patient-rated Health-Related Quality of Life (HRQoL) or Annual socio-economic costs per year related to the Tarlov cyst disease. No studies exist on Quality-Adjusted Life Years (QALYs) on Tarlov cyst disease. However, studies have shown that patients continue to suffer from one or more symptoms, including severe back pain, urogenital pain, bowel and bladder incontinence and lower limb weakness, for 1 to 4 years with a mean duration of 40 months before Tarlov cyst diagnosis is made (Acosta et al., 2003; Kameda-Smith et al., 2021; Nabors et al., 1988). Following symptom onset, symptoms either worsen or become plateaued, incapacitating the patient if medically not intervened (Sahin, Lee and Eun, 2020; Tarlov, 1948). Tarlov cyst patients continue to take pain medication, such as non-steroidal anti-inflammatory agents. In moderate conditions, they need to take nerve pain blockers such as anti-epileptic medications and anti-depressants. In severe cases, they need periodic epidural steroid injections to reduce the inflammation. In addition, Tarlov cyst patients develop additional symptoms such as urinary incontinence, faecal incontinence or constipation, and sexual dysfunction. In some cases, their mobility will be compromised and need physical care. At all these stages, the Tarlov cyst causes a significant socio-economic impact on the patient and the NHS.

1.4 Age

Tarlov cysts can affect both genders, but females are preferentially affected by two-thirds of the majority (Klepinowski, Orbik and Sagan, 2021b). Tarlov cysts are rarely reported in children, and no studies were available on symptomatic Tarlov cysts in paediatric cases. Children, too, suffer from bladder and bowel dysfunction due to symptomatic Tarlov cysts, but they do get better after the excision of their Tarlov cysts (Mijalcic et al., 2019; Shimauchi-Ohtaki et al., 2022).

1.5 Overview of Pathophysiology

1.5.1Cerebrospinal fluid (CSF)

Cerebrospinal fluid (CSF) is a clear fluid formed between the brain and spinal cord and bony structures around them. It acts as a shock absorber, protecting the brain and spinal cord from hitting the bony structures around them during movement, coughing, or lying on one side (Standring, 2016). CSF contains mostly water but a small amount of glucose, minerals, and traces of proteins. In addition to providing natural buoyancy to the central nervous system, CSF also subserves other functions such as regulating temperature around the central nervous system, regulating electrolytes and removing metabolic waste products from the brain (Darby and Frysztak, 2014).

CSF is produced by specialised cells that form the Choroid plexus in the lateral ventricle, third ventricle and, to a lesser extent, the fourth ventricle. CSF produced in the lateral ventricle flows through the third ventricle, which then passes to the fourth ventricle through a narrow passage called the Cerebral aqueduct, as shown in Figure 1. CSF from the fourth ventricle passes to the Cerebral subarachnoid space through a narrow path called the Median aperture of the fourth ventricle. Nearly half of CSF produced passes through spinal subarachnoid space and reaches the cauda equina, encapsulating the entire spinal cord.

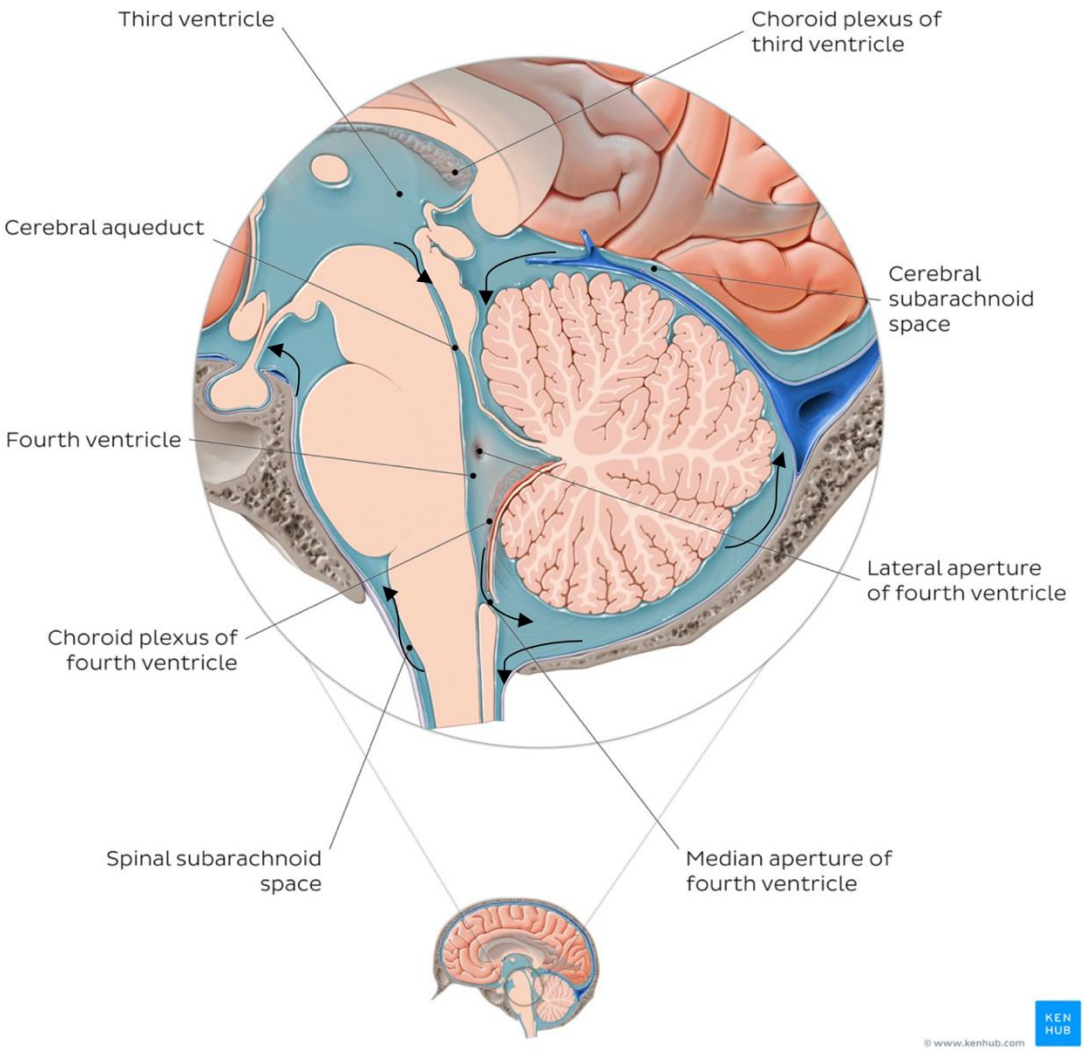


Figure 1: Arrows show the direction of the CSF flow in the brain and spinal cord (Image adapted with permission from Kenhub (https://www.kenhub.com/en/dashboard); Appendix: 7.1)

The brain and spinal cord are protected by three layers of connective tissue collectively referred to as the Meninges. The outer layer is a tough and avascular connective tissue called the Dura mater. The meninges' middle layer that forms like a spider web is called the Arachnoid mater. The meninges' innermost layer, the pia mater, hugs and protects the brain and spinal cord. The space between the Arachnoid and the pia mater is called Subarachnoid space. The subarachnoid space is filled with CSF, pushing the arachnoid mater against the dura mater, forming a combined thick layer around the spinal cord. The pia mater in the spinal cord, which closely attaches to the white matter, forms a ligament that attaches to

the arachnoid mater called the Denticulate ligament (Türkoğlu, Sehlikoğlu and Tokdemir, 2019) that helps to stabilise the spinal cord by restricting the movement of the Dural sac. Spinal rootlets emerge from the spinal cord anteriorly and posteriorly on both sides. As the rootlets emerge, they are individually wrapped by pia mater, buoyance in the CSF and emerge as dorsal and ventral roots by piercing through the Dura mater. Both dorsal and ventral roots carry the dura covering until past the dorsal root ganglion, slightly beyond the intervertebral foramina, at which point the dura mater merges into the epineurium (Cramer and Darby, 2013). However, the arachnoid layer does not follow the dura mater. It terminates at the level of dorsal root ganglia (Figure 2), where it merges into the perineurium and allows the CSF in the subarachnoid space to reach up to the dorsal root ganglia but not leak into the peripheral nerves. The presence of CSF in the proximal part of the spinal nerve is helpful in MRI imaging to identify healthy spinal nerve roots in the intervertebral space, as the lack of CSF suggests compression of spinal nerve roots.
Dorsal Root ganglia (DRG) consists of a group of nerve cell bodies that carry sensory information from the periphery to the central nervous system. The location of DRGs in the spinal cord varies from region to region. DRG's location is primarily extraforaminal, while it lies mainly within the foramen in the lumbar region. DRG's location shifts towards the intraspinal from the S1 sacral root and progressively increases as sacral roots travel down caudally (Kikuchi et al., 1994). The shift towards the intraspinal is more pronounced in females (Moon et al., 2010). Due to the pressure gradient, CSF is reabsorbed in the brain through the dura mater into the venous sinus. At the spinal level, CSF is reabsorbed through dura matter into spinal veins at the DRGs (Darby and Frysztak, 2014). Studies have shown that one-fourth of CSF is reabsorbed through the spinal arachnoid villi at the DRG level (Pollay, 2010).

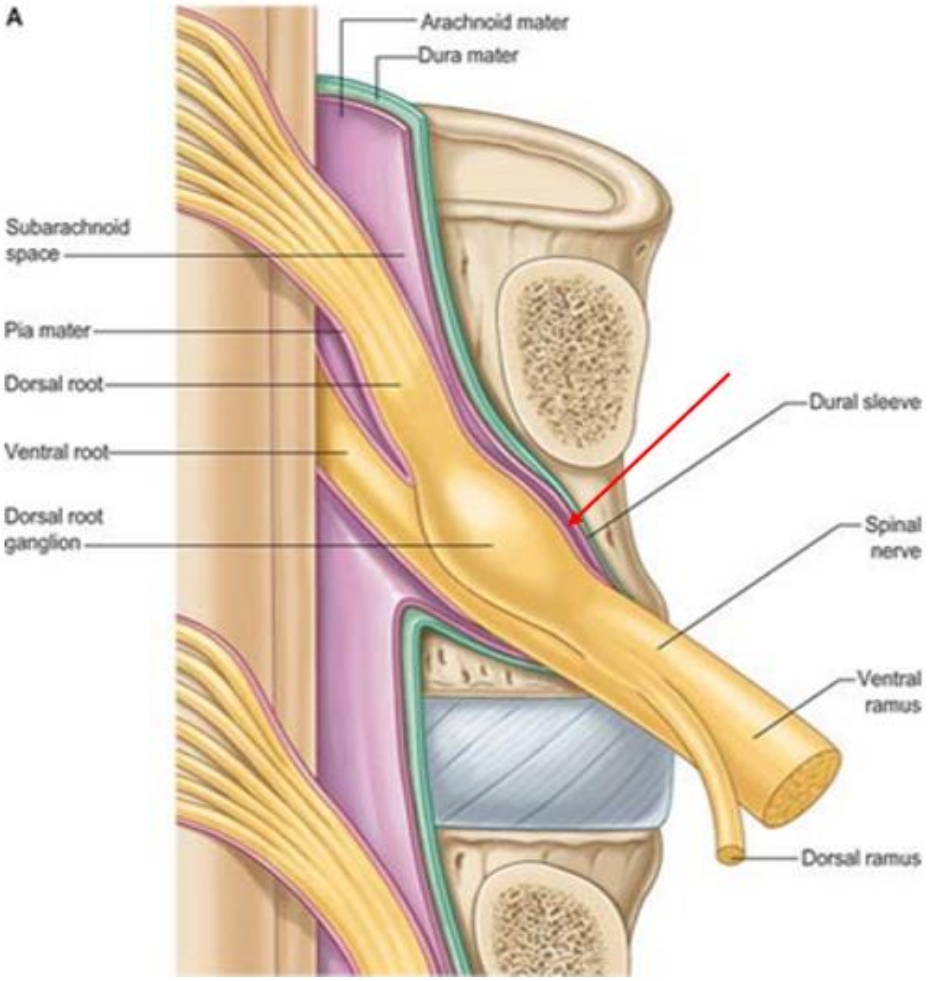


Figure 2: Subarachnoid space ends at the level of DRG (Red arrow); Image adapted with permission from Clinicalgate (https://clinicalgate.com/); Appendix: 7.2)

Since this is a unidirectional flow of CSF, any obstruction of CSF absorption can create a high-pressure gradient across the DRGs. Several studies showed there was no naturally forming subarachnoid space at the sacral dorsal root level, but a rupture of the dura mater due to reasons such as external pressure or trauma or connective tissue disorder (Henderson et al., 2017; Hoshino et al., 2005) can create an artificial subarachnoid space at the DRG level (Frederickson, 1991; Haines, 1991; Reina et al., 2002) that CSF can fill.

1.5.2 Formation of Tarlov Cysts

Dr Tarlov, a neurosurgeon, identified and first reported extradural cysts located at the sacral and coccygeal posterior nerve roots during filum terminale autopsy examinations. He had noticed similar findings in 5 out of 30 adult autopsy procedures (Tarlov, 1938). Dr Tarlov successfully treated a patient who presented with an acute symptomatic extradural cyst by

deflating the cyst during a neurosurgery procedure. His histopathology report revealed that part of the Tarlov cyst wall consisted of nerve cells and other substances of the dorsal root ganglia, suggesting that the Tarlov cysts formed adjacent to the dorsal root ganglia and intruded into it and, at times, compressed the neighbouring sacral roots, as shown Figure 2b.

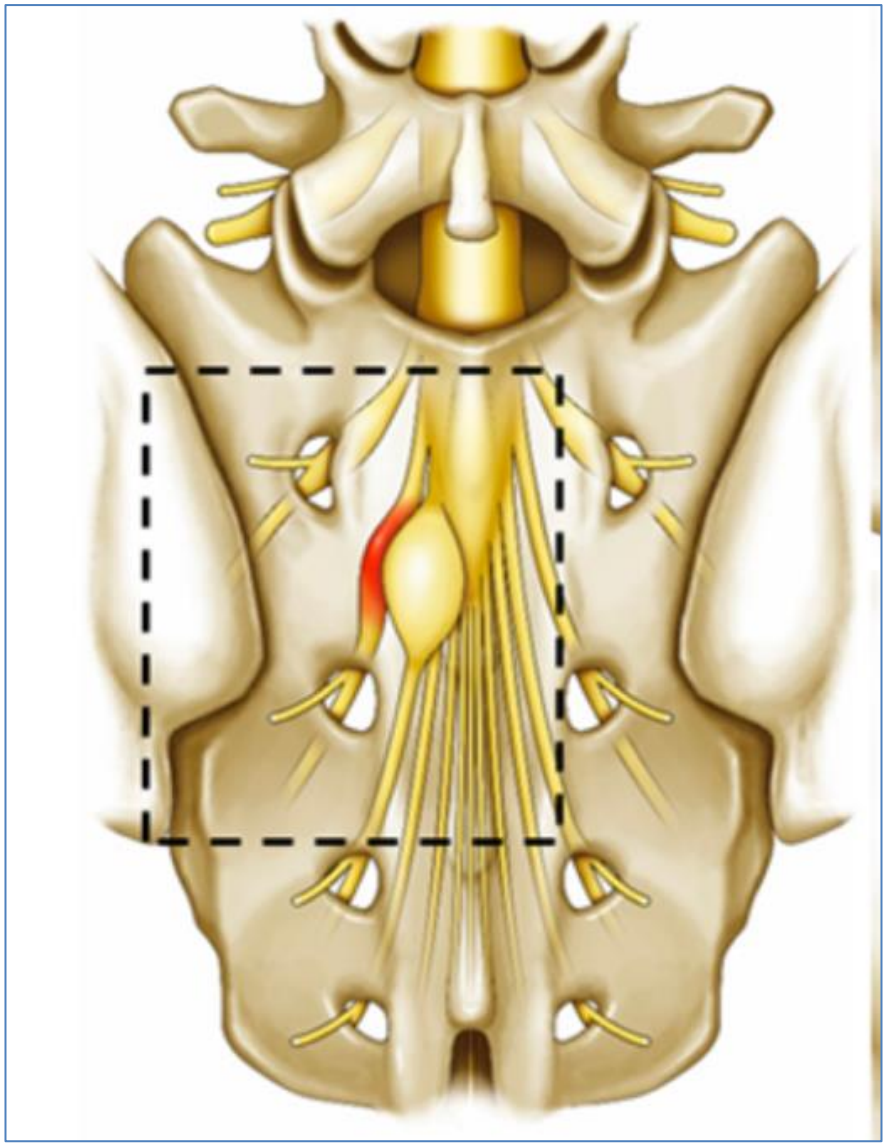


Figure 2b:
Compression of sacral roots by the Tarlov cyst. (Source: Sugawara et al., 2022).

These histopathological findings were later confirmed by several studies (Voyadzis, Bhargava and Henderson, 2001), suggesting Tarlov cysts contain some part of underlying nerve fibres. Dr Tarlov further noticed that the cyst did not communicate with the subarachnoid space (Tarlov, 1948), hence, these cysts cannot be easily compressed

intraoperatively. In addition, tilting the surgical table did not dilate or decrease its size, suggesting no direct connection between the subarachnoid space and the CSF in the cyst. However, several subsequent studies have shown a free flow of CSF from subarachnoid space to the cyst, similar to meningeal diverticula (Bartels and van Overbeeke, 1997; Rodrigues et al., 2018; Shams et al., 2005).

Meningeal diverticula form proximal to the dorsal root ganglia and directly connect with the subarachnoid space. Some cysts have diverticulum presentation, whereas some cysts have cell bodies of DRGs. In contrast, a few have cysts containing posterior nerve fibres, speculating that all three have a common origin and could be part of the disease evolution (Voyadzis, Bhargava and Henderson, 2001). Several theories were postulated about the formation of Tarlov cysts, but three stand out. The first is the blood-nerve barrier theory, suggesting the endoneurium and perineurial microvascular environment permeability dysfunction (Mizisin and Weerasuriya, 2011) at the DRG site. Consequently, any excessive pressure on the CSF in the cauda equina pushes the CSF into the endoneurium, causing a one-way flow to the cyst (Godel et al., 2016; Mizisin and Weerasuriya, 2011). Another critical theory proposed for the formation of the Tarlov cyst is due to a genetic cause. Soft tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome weaken the epineurium and perineurium, thereby giving way to the formation of Tarlov cysts (Henderson Sr. et al., 2017; Marathe, Lohkamp and Fehlings, 2022). Another theory proposed based on the calcification within the cyst wall suggests local trauma to the nerve root due to a sudden fall or impact injury to the spinal cord where CSF leaks into the endoneurium layer, forming Tarlov cysts (Nabors et al., 1988; Nishiura, Koyama and Handa, 1985; Rexed and Wennstrom, 1959). Spinal meningeal cysts were classified based on MRI and Computerised tomographic myelography into three main categories (Nabors et al., 1988). Type 1 consists of extradural meningeal cysts without spinal nerve root fibres. Type 1 was further divided into non-sacral (Type-A) and sacral (Type-B) categories. Tarlov cysts were categorised Type II as extradural meningeal cysts with spinal nerve root fibres. Type III categories were spinal intradural meningeal cysts. Tarlov cysts were not unique to humans but were also observed in animals. Sacral Tarlov cyst symptoms in dogs were similar to those in humans, and the painful chronic progressive neurological deficit was compatible with the lesions on their MRIs (Lowrie, Platt and Garosi, 2014).

1.5.3 Symptomatology

Tarlov cysts can cause debilitating pain and changing bowel, bladder, and sexual functions. They can cause physical damage to sacral nerve roots and cause sacral bone erosions. The initial presentation of the Tarlov cyst may be one or more of these symptoms, but most patients have debilitating back pain that radiates to the back of the thigh or the perineum (Ostojic, 2015; Singh et al., 2009; Sun et al., 2013). Hulens et al. (2019)reviewed 565 patients affected by symptomatic Tarlov cysts and found thirty different symptoms patients had experienced across the population.

Most (35%) suffered from leg pain. The symptoms can severely impact social, economic, and psychological well-being. Many studies have suggested these symptoms have a causative relation with the Tarlov cyst, but there was no direct evidence of nerve damage due to cyst compression (Davis et al., 1987; Kageyama et al., 1998; Strully, 1956; Strully and Heiser, 1954).

1.6 Surgical management of Tarlov cysts

Since the initial description of a surgical solution for symptomatic cysts, neurosurgeons have attempted to provide a consistent neurosurgical solution for this disease. However, even after more than seven decades, a consensus has yet to be reached on treating these cysts surgically (Kameda-Smith et al., 2021). There was a persistent dilemma on the aetiology of Tarlov cyst formation and the underlying pathophysiology of the disease. It was unclear which onset of symptoms among the thirty-odd presentations of Tarlov cyst symptoms should be a red flag for surgery (Murphy et al., 2011). A systematic review of post-surgical complications revealed rates as high as 21 % (Patel, Louie and Rachlin, 1997), which was far less than complications related to non-operative Tarlov cyst cases.

Post-operative complications such as spontaneous intracranial hypertension (Pross et al., 2017), aseptic meningitis (Patel, Louie and Rachlin, 1997), CSF leakage (Kadian et al., 2022), infection (Mohamed, 2016), chronic pain, haemorrhage (Tanaka et al., 2006), and neurological deficit (Voyadzis, Bhargava and Henderson, 2001) deterred less experienced institutions from attempting surgical remedies in this condition. However, several institutions introduced novel techniques to mitigate complications inherited in Tarlov cyst surgeries. Cyst fenestration is an elaborate procedure where the Tarlov cyst is opened and

drained, its contents filled with fibrin glue, and sutured to avoid the refilling of the CSF. Patients showed marked improvement after the procedure, with relatively fewer complications (Medani et al., 2019; Smith et al., 2011). Imbrication of the Tarlov cyst is another surgical procedure where the nerve root is repaired by reducing the tension from the cyst, which showed good improvement of symptoms and had less post-surgical complication than the fenestration procedure (Medani et al., 2019; Nkwerem et al., 2018). Clipping the Tarlov cyst is another well-described procedure. Since the cyst is clipped, there is a reduced chance of CSF leaking during the procedure and less possibility of the cyst growing. There are a few other surgical procedures, such as surgical excision (Mohamed, 2016), cyst remodelling (Cantore et al., 2013), microsurgical treatment (Caspar et al., 2003), percutaneous aspiration (Lee et al., 2004), Intraluminal epidural steroid injection (Mitra, Kirpalani and Wedemeyer, 2008), sacral laminectomy (Mummaneni et al., 2000) and novel wrapping technique (Sugawara et al., 2022).

1.7 Limitations in the current surgical approach to Tarlov cysts

Sacral Tarlov cysts form in a complex area where several important nerve roots responsible for bladder, bowel and sexual function are present. As the aetiology of Tarlov cysts is yet to be understood clearly, various surgical procedures are in practice to minimise the risk to patients. Several Neurosurgical centres proposed surgical management algorithms for Tarlov cysts based on their past clinical experiences (Cantore et al., 2013; Fletcher-Sandersjöö et al., 2019; Kameda-Smith et al., 2021). These treatment algorithms are proposed based on patients' symptoms and MRI findings, as shown in Figure 3. However, there are some inherent limitations to current practice, as the severity of symptoms would not necessarily correlate to the degree of compression of nerves. Slight irritation of nerves can cause persistent pain in the lower limbs (Lim and Selbi, 2023). Also, the size of the Tarlov cyst does not directly correlate to the symptoms, as many large Tarlov cysts can stay asymptomatic for many years. Consequently, no method or tool is currently available to assess the degree of neuronal damage in Tarlov cyst cases (Hulens et al., 2019).

Timing for the neurosurgical intervention is crucial as in other instances, such as lumbosacral radiculopathies (Tsao, Levin and Bodner, 2003) and meningiomas (Goldbrunner et al., 2021) before it becomes too late to reverse the damage.

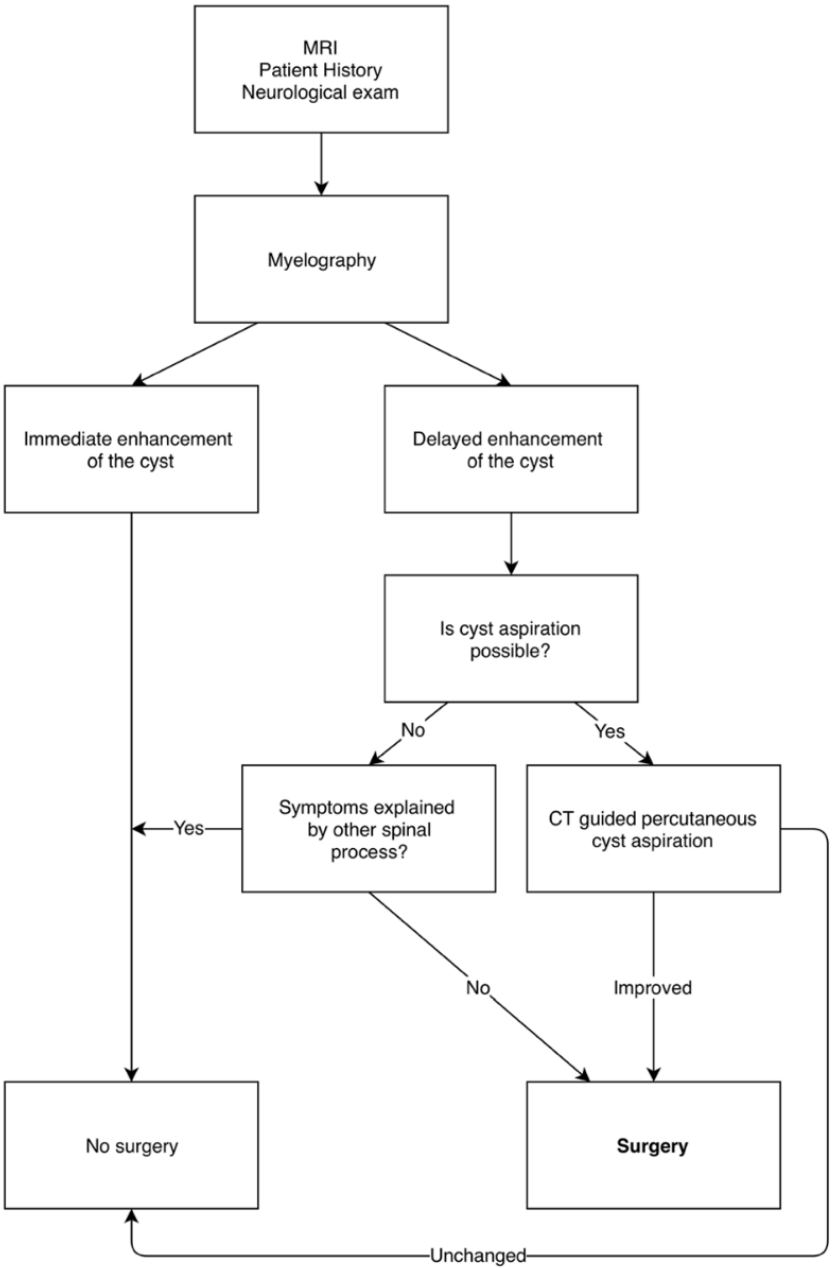


Figure 3: Current practice in the treatment of Tarlov cysts based on the symptomatology and imaging techniques. Image source: (Fletcher-Sandersjöö et al., 2019).

1.8 Role of Neurophysiology in Tarlov cyst disease

Nerve conduction studies (NCS) are well-established tests extensively used to assess distal motor and sensory axons and their myelin sheaths. Even though NCS show a significant

amplitude asymmetry in either sural or superficial nerve conduction studies on the symptomatic side of the Tarlov cyst (Cattaneo, Pavesi and Mancia, 2001), they are rarely used in routine clinical practice as normal NCS locate individual sensory root dysfunction. Sensory conduction studies could be abnormal due to underlying peripheral neuropathy, clouding interpretation. In addition, many neurophysiologists and neurologists would not deal with this condition, hence, they are less experienced in looking for abnormalities in the NCS.

Motor nerve conduction studies are a subdomain of NCS investigating efferent pathway function. Reduction in motor nerve conduction velocity or amplitude is a good indicator of loss of sacral motor nerve axons. Unfortunately, most of the Tarlov cysts form at the level of DRGs. Hence, a motor nerve conduction study is unlikely to be helpful. F-wave and H-wave reflex studies assess the integrity of sensory and motor pathways, but they are insufficient to identify dorsal root lesions. TSEP study is another essential tool in assessing afferent sacral innervations. TSEP is routinely used to evaluate demyelinating features in the central nervous system (Kanbayashi et al., 2023). The posterior tibial nerve contains nerve fibres from lumbosacral roots L5 to S3. Fast-conducting fibres of any of these roots can contribute to cortical potentials, which means abnormalities in even one or two sacral roots can be easily masked by normally conducting sensory fibres. Tarlov cysts compress individual sacral roots. Hence, abnormalities in single root function cannot be identified with certainty with TSEP.

Needle EMG is the most valued test in neurophysiology, providing objective evidence for ongoing active or chronic denervation changes in the muscle. By carefully selecting muscles, one can assess individual myotomes and, thereby, individual nerve root function. However, needle EMG only provides information regarding efferent pathway function. Motor pathway abnormalities are usually seen at the later stages of Tarlov cysts. In addition, there are no specific myotomes to assess S3 and S4 root function, hence, the role of needle EMG in the Tarlov cyst assessment is minimal until a severe and advanced stage.

Intraoperative monitoring (IOM) is a critical neurophysiology tool for assessing sensory or motor pathway dysfunction during Tarlov cyst resection surgeries (Medani et al., 2019). However, it cannot be used in the routine baseline assessment of Tarlov cysts.

Contact Heat Evoked Potential Studies (CHEPS) is a neurophysiology tool that assesses Ad and C-fibres that convey pain and cold and warm sensations to the brain. CHEPS is an

excellent tool to evaluate small fibre nerve functions primarily affected by Tarlov cysts. However, specialised equipment is not routinely available in Neurophysiology departments. In addition, some laser CHEPS are costly and bulky and cannot be afforded by routine Neurophysiology departments.

dSEPs are helpful neurophysiology tools, specifically assessing individual dermatomal pathways, thereby assessing the integrity of individual dorsal roots. Since Tarlov cysts compress individual dorsal roots, this tool should be ideal for determining S2, S3 and S4 sacral root functions. Unfortunately, dSEP is not developed in sacral dermatomal regions, and no published normative values exist.

1.9 Chapter 1: Summary

Tarlov cysts are relatively rare and not well-known among patients and healthcare providers. The condition is not fully understood, affecting approximately 5.4% of the global population but causing a significant burden on the patient's quality of life. Even though there are no research studies available on the cost implications of Tarlov cyst on the NHS and patients, the number of diagnostic tests required, cost of medical treatment and loss of productivity hours due to Tarlov cyst together coupled with the prevalence of Tarlov cyst in the UK will reveal the gravity of the situation and burden on the NHS.

Tarlov cysts are CSF-filled cysts that usually form multiple numbers at the sacral spinal location, affecting the DRGs of sacral roots. Persistent compression on sacral roots damages nerve fibres, resulting in constant pain in the lower limbs and pelvic area. In addition, these patients develop various symptoms affecting the bladder, bowel, sexual, sensory, and motor function.

Given the lack of clarity on the aetiology and pathophysiology of the Tarlov cysts, symptomatic treatment with analgesic medication and occasionally surgical intervention are the only options for these patients. Current NICE guidelines also endorse these options due to insufficient scientific information (NICE, 2006). There is no consensus on the correct surgical procedure for Tarlov cyst decompression. Every surgical institution adopts its method based on its skill set and experiences. No diagnostic tools are available for surgeons to decide when to intervene in Tarlov cyst surgery. Neurophysiology diagnostic tools provide objective evidence for sensory and motor functions. They provide the exact location, type of

dysfunction and severity of the disease. Current neurophysiology diagnostic tools are not sufficient to examine individual sacral dorsal roots.

1.10 Rationale and justification for the research

Since established tests like EMG, NCS, TSEP, and PSEP are not suitable for evaluating individual sacral root functions, dSEPs may be suitable for providing objective evidence for the degree of neuronal damage. This study will determine if it is feasible to use dSEPs to assess individual S2, S3 and S4 sacral root functions. The output of this thesis will improve our understanding of the impact of Tarlov cysts on individual sacral root function. The overall findings from individual dSEPs will directly impact the current practice of evaluating and treating symptomatic Tarlov cysts.

1.11 Study design

The overall aim of this thesis is to assess the suitability of dSEPs in the evaluation of sacral root dysfunction in symptomatic Tarlov cysts.

The thesis presents data from three distinct but related studies.

1. The first study develops technical parameters for the sacral dSEPs and evaluates S2, S3 and S4 dSEPs in twenty healthy adults. The outcome of this study will reveal the feasibility and reproducibility of dSEPs and provide normative data for S2, S3 and S4 dSEPs.
2. The second study evaluates the utility of dSEPs in known neurological conditions by recruiting twenty adults with spinal cord injuries. The study also assesses the usefulness of dSEPs by comparing them with established studies such as PSEP and TSEP. The outcome of this study will reveal the sensitivity and specificity of dSEPs and the most useful criteria for dSEP abnormalities.
3. The third study evaluates S2, S3 and S4 dSEPs in twenty Tarlov cyst patients. The outcome of this study will reveal the extent of sacral root dysfunction

caused by Tarlov cysts. This study also introduces a classification based on the degree of dSEP abnormalities.

1.12 Ethics

The Joint Research Office of the University College London (UCL) and University College London Hospital (UCLH) NHS Trust approved this research work. Patient representative group member, Patient advice and liaison service member, nursing staff member, Neurosurgeon group member, Neurologist and clinical scientists were involved while developing patient leaflets and study design. A prospective observational study entitled "Neurophysiology assessment in symptomatic sacral Tarlov cysts "was performed, sponsored by University College London Hospitals NHS Trust (Sponsor reference number: 140504) and approved by the Health Research Authority and Healthy and Care Research Wales (IRAS Project ID:287553), Appendix 7.3. This research study adhered to the trust policies on gender equality, age, ethnicity, and disabilities. Call for volunteers was advertised on the UCL and UCLH websites, the Uro-Neurology department, and the Pain Management Centre at UCLH.

The study was approved by the Manchester Metropolitan University Research Ethics and Governance Team (EthOS Reference Number: 46173), Appendix 7.4. Volunteers in all three Studies were compensated according to the Health Research Authority recommendations (21/NE/0194).

Chapter 2: Development of S2, S3 and S4 sacral dSEPs

2.1 Introduction

Sensory information such as vibration, light touch, pain, temperature, two-point discrimination, pressure, and joint position sensation from the periphery to the brain is conveyed through specific tracts in the spinal cord called ascending pathways. Peripheral receptors such as thermoreceptors, nociceptors and mechanoreceptors recognise muscle stretch (Darby and Frysztak, 2014) and transduce sensations into action potentials. These action potentials are conveyed to the brain through specific ascending pathways. The dorsal column-medial lemniscus pathway takes information such as vibration, two-point discrimination, light touch, and joint position from peripheral receptors in the skin and muscles to the brain. In contrast, anterolateral ascending tracts convey temperature and pain sensations to the brain. Even though both pathways have all three groups of neurons, i.e. first, second and third-order neurones, the conduction velocity in these two pathways is significantly different. Somatosensory evoked potential responses primarily travel through the dorsal column-medial lemniscus pathway to the brain.

2.2 Dorsal column-medial lemniscus (DC-ML) system

Sensory information from periphery is perceived by pseudounipolar neurons whose cell bodies are located at DRGs. These first-order neurons sense sensory input through their dendrites and convey it through their axons either at the spinal cord level or at the medial lemniscus level unidirectionally, from the periphery to the central nervous system. Large diameter, heavily myelinated Aα neurons are rapidly adopting mechanoreceptors, and myelinated Aβ neurons are slowly adopting mechanoreceptors to relay information such as fine touch, vibration, and joint positioning sensation to the central nervous system. First-order neurons enter the spinal cord through the dorsal horn, branching into smaller-length axons that descend and synapse in the grey matter of the lower spinal cord segment to generate reflex motor responses. In contrast, the longer branch of the axon ascends to the medulla. Sensory information derived from the sacral and lumbar segment travel in the dorsal column white matter more medially forming a bundle of axons called medial fasciculus gracilis, whereas the sensory axons from the mid-thoracic and above form a

bundle of axons called lateral fasciculus cuneatus. The superficial layer of the white matter dorsal column contains fibres carrying tactile information, whereas deeper layers convey vibration (Gray et al., 2008). These two independent bundles continue to travel and synapse with the second-order neurons at the medulla. Axons coming from the first-order neurons in the fasciculus gracilis synapse with the second-order nuclei called Gracile nucleus, and fasciculus cuneatus axons synapse with the second-order nuclei Cuneatus nucleus. Axons from these two nuclei decussate and form a bundle on the contralateral side - the medial lemniscus. The second-order axons continue to ascend and synapse with the third-order nuclei in the ventral posterior lateral thalamic (VPLT) nucleus, as shown in Figure 4. Axons from the VPLT travel through the posterior limb of the internal capsule and corona radiata and reach the somatosensory cortex to process sensory information.

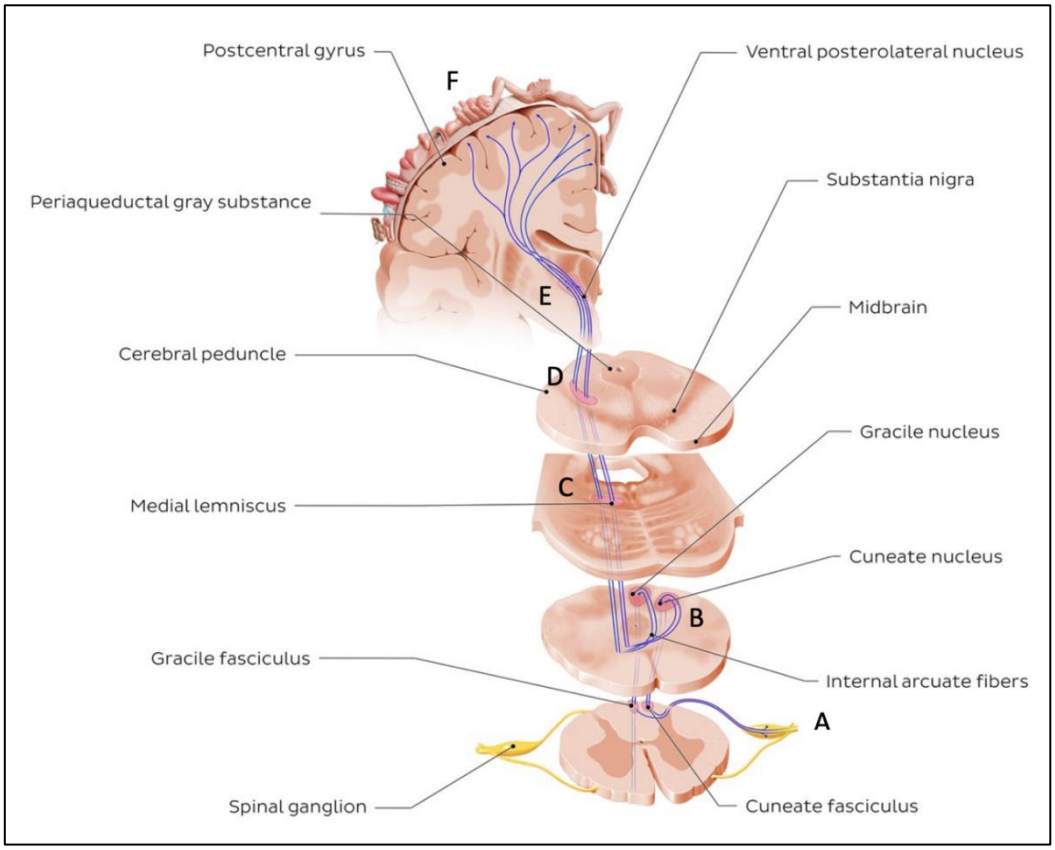


Figure 4: DC-ML system – Sensory information conveyed from the periphery (A) to the medulla oblongata (B) through the first-order neurons. The medial lemniscus pathway (B to E) is supplied by second-order neurons. Third-order neurons located at E convey the sensory information to the somatosensory cortex (F). (Image adapted with permission from Kenhub (https://www.kenhub.com/en/dashboard); Appendix: 7.1)

2.3 Sensory distribution in lower limbs and the genitalia

Understanding sensory nerve territory and dermatomal distribution is essential for diagnosing neurological diseases and localising lesions. Nerve roots from the lumbar anterior rami L1-L4 and sacral anterior rami S1-S4 combine to form the lumbosacral plexus. The lateral femoral cutaneous nerve originates in the pelvic cavity and is combined with the anterior rami's L2 and L3 posterior division. The nerve descends to the iliac ligament, passes through it, and distributes the sensation over the lateral aspect of the thigh. The femoral nerve originates from L2 to L4 anterior rami, descends to the iliac ligament and divides into anterior and posterior divisions. From the anterior division, two cutaneous branches emerge that supply the anterior and medial aspects of the thigh. From the posterior division, the saphenous nerve supplies sensation over the medial aspect of the leg, ankle, and portion of the medial foot. The sciatic nerve is the longest in the posterior aspect of the thigh and divides into the common peroneal and tibial nerves. The common peroneal nerve, through its superficial and deep branches, supplies sensation over the lateral aspect of the leg and dorsum of the foot. The tibial nerve supplies sensation to the rest of the leg and foot through the sural, medial, and lateral plantar nerves (Gray et al., 2008). The posterior femoral cutaneous nerve supplies the posterior part of the thigh and the gluteal area (Leis and Schenk, 2013). Sensation over the anterior aspect of the perineum is mainly supplied by the pudendal nerve and perineal branch of the posterior femoral cutaneous nerve (Mills, 2017; Saba, 2022). The Ilioinguinal, genitofemoral, and obturator nerves supply a small area over the proximal part of the anterior thigh, as shown in Figure 5.

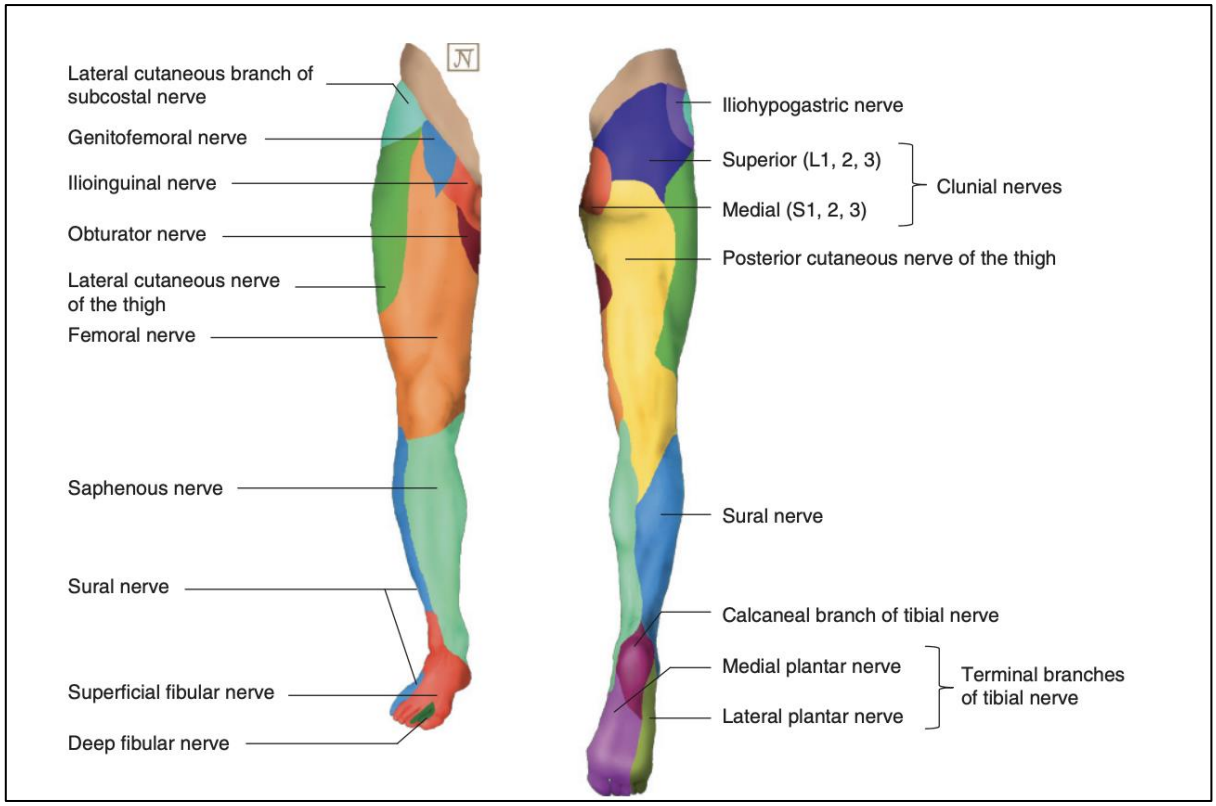


Figure 5: Sensory distribution of Ilioinguinal nerve (L1) overlaps with the posterior femoral cutaneous nerve (S2-S3), making clinical examination difficult to differentiate nerve lesion from sacral root lesion (Image adapted from Georgious, Thompson and Nickells 2014)

2.4 Dermatomal distribution in lower limbs and the genitalia

A lesion at a single spinal segment usually affects a single dermatome, whereas a nerve lesion affects multiple dermatomes. Hence, loss of sensation differentiates nerve lesions from sacral root lesions. Dermatomes do not have a strict boundary of a single sensory root level. Each dermatome can be divided into autonomous areas and overlapping areas. The area on the skin supplied by a single root level comes under the autonomous area. In contrast, neighbouring dermatomes contribute some of the sensation in the overlapping area. Hence, the loss of sensation progressively fades away when the examination goes into the normal dermatome. Therefore, a neurological exam with a pinprick should first start from the loss of sensation area to the normal area, thereby, the boundaries between the autonomous area, overlapping area, and the normal areas can be delineated.

Evaluation of normal sensory function is valuable in understanding radicular level abnormalities in some neurological conditions. However, mapping dermatomal areas in humans is still a work in progress. Initial descriptions of the dermatomes in humans were

given by (Herringham, 1887) and later by (Sherrington, 1898) provided detailed pictures of overlapping dermatomes. However, Sherrington's studies were mostly performed on primates and explained as far as thoracic and post-thoracic segments. Most dermatome mapping was done by understanding traumatic spinal cord lesions, selective rhizotomy, or observing herpes zoster infection distribution. Interestingly, herpes zoster infection affects more than two dermatomes in the sacral distribution, which would not clarify individual sacral dermatomal distribution (Acheson and Mudd, 2004). One study based on evidence-based literature (Lee, McPhee and Stringer, 2008) found inconsistencies in the earlier experimental studies. Studies in macaque showed that the dermatomal distribution increased to double its original area when dorsal roots were severed below or above the area. The expanded dermatomal area showed hypersensitivity to pinprick examination in monkeys, suggesting dermatomal distribution is not static but depends on the spinal cord distribution (Denny-Brown, Kirk and Yanagisawa, 1973). Dermatomal distribution becomes complicated to understand due to the overlap of neighbouring dermatomes and overlapping neighbouring sensory nerve distributions. However, this neuronal overlap was not seen at all dermatomal borders but in some areas such as supraclavicular nerves (C3, C4) and T2 spinal nerve distribution, Ilioinguinal nerve (L1) and posterior femoral cutaneous nerve (S2-S3) (Ladak, Tubbs and Spinner, 2014).

2.5 Mixed, Segmental and Dermatomal somatosensory evoked potentials

Peripheral nerve fibres are classified based on size, diameter, afferent or efferent pathway, excitability, and function. Erlanger (1924) classified peripheral nerve fibres into A, B and C groups based on their myelination and somatic and autonomic function (Whitwam, 1976). Gasser (1950) refined this classification and subdivided it into a, b, c, and d fibres. Lloyd and Chang (1948) introduced the term afferent fibres based on nerve fibre size, which includes muscle spindles and tendon organs (Schalow, Zäch and Warzok, 1995). Peripheral nerve fibres act like electric conductors due to the potential difference between extracellular and intracellular ion concentration, separated by a non-conducting myelin sheet, which acts like a capacitor. According to Lloyd's classification, heavily myelinated large-diameter nerve fibres should conduct faster than small-diameter myelinated fibres. Several studies have

shown a direct relation between fibre diameter and its conduction velocity (Hursh, 1939; McLeod and Wray, 1967; Skoglund and Romero, 1965). Caton (1887) successfully recorded the first somatosensory evoked potential after stimulating the limb by exploiting the electrically excitable feature of peripheral nerve fibres. By 1958, with the advent of digital averaging, somatosensory evoked potentials (SEP) became a routine diagnostic tool in clinical neurophysiology. Since electrical stimulation is an artificial way of sending sensory responses to the brain, the type of fibres and pathways involved in SEPs need to be clarified. According to the numerical classification of nerve fibres, 1.5 to 2 times the threshold of 1a fibres are accountable for SEPs in cats (Appelberg et al., 1983). If we translate into humans, a minimal twitch of the toe or finger will selectively activate 1a nerve fibres (Burke, Skuse and Lethlean, 1981). Stimulating 1.5 to 2 times the sensory threshold in humans predominantly involves 1a fibres and minimal involvement of group II fibres (Burke et al., 1982; Hunt, 1954). Group IV nociceptive fibres are small-diameter unmyelinated fibres that cannot be activated at these stimulation levels. Hence, in routine SEP studies, nerve fibres responsible for conveying sensation for vibration, tactile, muscle spindles and Golgi tendon organs carry the electrically stimulated somatosensory evoked potentials. However, SEP abnormalities did not always correlate with clinical loss of sensation in patients. Extensive studies with proprioception and vibration sensation loss showed an abnormal SEP study. However, patients with loss pain showed normal SEP values, suggesting SEP travel through the DC-ML system (Halliday and Wakefield, 1963; Spudis et al., 1980). Studies have shown that specific loss of sensation did not correlate with SEP abnormalities (Dimitrijevic, Prevec and Sherwood, 1983; Schiff et al., 1984).

2.5.1 Mixed nerve somatosensory evoked potentials

Mixed nerves, such as the posterior tibial nerve and median nerve, are commonly used to record somatosensory evoked potentials from the cortex, known as tibial SEPs and median SEPs. Tibial SEPs travel through dorsal roots, the DC-ML system and reach the somatosensory cortex. SEPs are excellent tools in diagnosing Multiple Sclerosis and Neuromyelitis Optica spectrum disorders (Kanbayashi et al., 2023) and spinal cord injuries (Chabot et al., 1985). Median SEPs are not only used in traditional areas of demyelinating disease, cervical stenosis and brachial plexus lesions but also used in the prediction of ischemic diseases, functional neuroplasticity and critically ill patients (Azabou et al., 2017;

Ferri et al., 2001; Maudrich et al., 2021). There are a few limitations with mixed somatosensory evoked potential studies. The tibial nerve consists of various roots from L4 to S3, and the median nerve consists of cervical roots supplying from C6 to T1. Single root level abnormalities can be easily masked by normally conducting neighbouring roots and poor correlation with radiological findings (Yu and Jones, 1985). In addition, peripheral nerves, such as the tibial nerve, are the first to be affected by underlying peripheral neuropathy. The tibial nerve can only be stimulated at the ankle as this is where the nerve is superficial. However, patients usually find the test painful when stimulated more than 2.5 times their threshold. In addition, any oedema over the ankles impedes recording. Mixed nerve somatosensory evoked potential studies are relatively insensitive in diagnosing lumbosacral radiculopathies.

2.5.2 Segmental somatosensory evoked potentials

Segmental evoked potentials are the cortical evoked potential responses when stimulated by a pure peripheral sensory nerve such as the sural nerve, superficial sensory peroneal nerve, or saphenous nerve. These evoked potential studies are easy to record from the mid-cortex region, similar to mixed evoked potential studies. Normative values were generated for the sural nerves (Chiappa and Ropper, 1982; Perlik et al., 1986; Smith, 1988), superficial radial nerve (Grisolia and Wiederholt, 1980; Smith, 1988; Yiannikas, Shahani and Young, 1986) and other sensory nerves, such as the superficial sensory peroneal nerve and the saphenous nerve. Segmental evoked potential studies were developed primarily to assess radiculopathies. However, in most radiculopathies, pain fibres in the dorsal root and motor fibres in the anterior roots are involved and segmental evoked potentials cannot pick them up. In addition, sensory nerves are supplied by multiple dorsal roots. The S1 and S2 sacral roots supply the Sural nerve; the superficial radial nerve is contributed by the cervical roots from C7 to T1 and the Saphenous nerve from L3 and L4 lumbar dorsal roots. A single dorsal root or adjacent dorsal root compression can be easily masked by usually conducting the rest of the dorsal roots, thereby proceeding with standard segmental evoked potentials. In addition, segmental evoked potentials have several other disadvantages. Pure sensory branches are anatomically inaccessible for testing for all dorsal nerve roots. C5 radiculopathy produces a small patch of numberless over the deltoid muscle, which a segmental evoked potential study cannot test. Silent peripheral neuropathies can affect the

outcome of segmental evoked potentials. It is technically challenging to stimulate sensory nerves such as saphenous nerves, and there are no easy ways to confirm the proper stimulation of the nerves.

2.5.3 Dermatomal somatosensory evoked potentials (dSEP)

Dermatomal evoked potentials are obtained by stimulating the cutaneous nerve fibres in each dermatome's autonomous nerve zone of a particular nerve root. The cutaneous nerve fibres send afferent signals through a single dorsal nerve root, ascend through the DC-ML system, and reach the somatosensory cortex, producing cortical evoked potential with a similar waveform of any mixed nerve somatosensory evoked potential. Normative values of dSEPs in L5 and S1 dermatomes have been reported and used in lumbosacral radiculopathies (Aminoff et al., 1985; H. A. Katifi and E. M. Sedgwick, 1986; Rodriquez et al., 1987). Normative values were also generated in the cervical area (Kramer et al., 2010) and were used in cervical spinal cord injury evaluations. Dermatomal evoked potential studies showed excellent results in diagnosing lumbar canal stenosis (Snowden et al., 1992). Dermatomal evoked potential studies evaluate dorsal root compressions. Traditional tests like mixed somatosensory evoked potential studies or radiology imaging techniques cannot detect such microscopic posterior column dysfunctions. Hence, dSEP uniquely evaluates the spinal cord stenosis (Zhang et al., 2022). The superiority of dSEPs over MRI and mixed somatosensory evoked potential studies was observed by Kraft (2003), suggesting multiple rootlets will be involved in neurodegenerative conditions and nerve fibres travel at different speeds in the cauda equina and hence recording multiple dermatomal evoked potential at the same time will give a better picture in identifying spinal stenosis. S2, S3 and S4 sacral dermatomal evoked potentials will be the most suitable for evaluating Tarlov cysts as they test individual dorsal roots where potential Tarlov cysts form in the spinal cord.

To date, little work has been reported for sacral dSEPs. In developing this literature review, several databases were searched for sacral dermatomal recording techniques and normative values. Cochrane Database of Systematic Reviews, National Library of Medicine and Science Direct databases were searched with the terms "Dermatomal somatosensory evoked potentials" or "Dermatomal evoked potentials", which showed 1432 results. Duplications, short abstracts, animal studies, editorials, short communications, and

Intraoperative monitoring-related results were removed. A total of 821 records were reviewed. A total of 456 full articles were available for review. Most of the articles were related to the utility of dSEPs in evaluating lumbosacral radiculopathy or cervical radiculopathy. However, normative values were found in 43 records; 11 showed normative values for S1 sacral dermatome (Zhang et al., 2022). No records were found for techniques or normative values in the S2, S3 or S4 sacral dermatomes.

Mixed SEPs and dSEPs are not good at identifying anterior horn compression abnormalities like lumbosacral or cervical radiculopathies, where motor fibres are often compressed. Due to relatively low amplitude cortical responses in the dermatomal responses, dSEPs are particularly discouraged (Eisen, Hoirch and Moll, 1983; Owen, Bridwell and Lenke, 1993; Rodriquez et al., 1987; Seyal, Emerson and Pedley, 1983; Tokuhashi et al., 1989; Walk et al., 1992). In many papers, the word dermatomal stimulation was intermixed with the segmental technique (Katifi and Sedgwick, 1986). Hence, the disadvantages of the segmental technique were mistakenly attributed to dSEPs. Mixed SEPs are suitable for diagnosing demyelinating lesions in the central nervous system but not for identifying dorsal root lesions, such as Tarlov cysts. There is a need to develop a sacral dermatomal evoked potential technique to improve the amplitude responses. dSEPs did not find their place in routine practice due to their low amplitude, even though their value was recognised in lumbar or cervical stenosis and myelopathy conditions (Cakmur et al., 1998; Slimp, 2008). Dermatomal evoked potentials can be used to identify sacral sensory roots while implanting neuromodulators. The current intraoperative monitoring technique must be improved in dermatomal evoked potential tools.

Knowledge gained in the last seven decades from surgical procedures and histopathology reports showed that the Tarlov cyst forms at the level of DRGs and compresses the dorsal nerve root fibres. Established knowledge of mixed nerves, such as the posterior tibial nerve, shows that they send sensory impulses to the somatosensory cortex through DRGs. Mixed nerve-evoked potential studies are not a good tool for identifying individual sensory root abnormalities. Despite solid evidence for neuronal compression at the individual dorsal root level, no sacral dermatomal evoked potential studies have been developed and validated.

2.6 Identifying the research question for Study 1.

Informed by the preceding literature review, I hypothesised that S2, S3, and S4 sacral dSEPs are suitable tools to assess symptomatic Tarlov cysts. I also hypothesised that surface electrode stimulation can record S2, S3 and S4 sacral dermatomal evoked potentials. I also hypothesise that normative values generated for posterior tibial nerve SEPs in the conventional recording method are unsuitable for comparative studies with the dermatomal evoked potentials due to selective stimulation of nerve fibres in dermatomal studies. I aimed to generate normative values for all evoked potentials with the same technical parameters as all three tests assess the same DC-ML system. I intended to do this by developing mixed evoked potentials from the posterior tibial nerve and segmental evoked potential studies from the pudendal nerve and comparing these results with the published data in healthy volunteers. This was hypothesised to provide an evidence base for the subsequent studies.

2.6.1 Study 1 aims.

The specific aims for Chapter 2 were to:

1. Develop uniform technical parameters for mixed, segmental, and dermatomal somatosensory evoked potentials.

2. Develop S2, S3 and S4 dermatomal evoked potentials in healthy volunteers.

2.6.2 Study 1 objectives

Specific objectives for Chapter 2 were to:

1. Generate normative values for the posterior tibial nerve as an example of mixed nerve somatosensory evoked potentials in healthy volunteers.

2. Generate normative data for S2, S3 and S4 dermatomal evoked potentials in healthy volunteers.

3. Generate normative values for pudendal nerve as an example of segmental evoked potentials in healthy volunteers.

4. Investigate the relation between S2, S3 and S4 dermatomal evoked potential studies. Investigate the relationship between posterior tibial latencies and sacral dermatomal evoked potential latencies.

5. Investigate the relationship between sacral dermatomal and pudendal nerve evoked potential studies.

2.7 Materials and methods

American Clinical Neurophysiology Society guidelines (ACNS, 2006) were followed throughout this research while recording all short latency somatosensory evoked potentials. Electrode nomenclature, waveform peak identification and latency and amplitude measurement methods were followed according to the ACNS guidelines and British Society of Clinical Neurophysiology guidelines.

2.7.1 Equipment and recording settings

Single Cadwell Sierra Summit EMG/EP equipment was used throughout the study. High and low-frequency filters of 1Hz and 3kHz were used (Acns, 2006; Mauguière, Desmedt and Courjon, 1983). One hundred milliseconds of analysis time was used with ten milliseconds /division screen duration. Sensitivity was set at 2mV/Division.

2.7.2 Recording montage

A three-channel evoked potential montage was used. C3'-Fz, Cz'-Fz and C4'-Fz channels were used. Even though the Cz'-Fz channel was used to measure latency and amplitude, additional C3'-Fz and C4'-Fz were used to identify the field of central peaks. C3'-Fz and C4'-Fz were used to help differentiate noise from the absence of actual responses (Daniel Dumitru, 1996).

2.7.3 Recording electrodes

Five standard EEG electrodes with 10-millimetre diameter Ag/AgCl discs were used to record evoked potential responses from the cortex. Cortical recording electrodes were placed according to the standard international 10-20 EEG measurement system (Jasper, 1958). The mid-central electrode Cz, mid-frontal electrode Fz, and right and left central electrodes C4 and C3 were identified according to the 10-20 system. Cz', C4' and C3' were identified as 2 cm posterior to Cz, C4 and C3 respectively. A ground electrode was placed at the mid-point between Cz' and Fz. Subcortical electrodes were not used in this research work as the primary purpose was not to measure the central conduction times.

2.7.4 Stimulating electrodes.

Mixed somatosensory evoked potentials can be achieved by stimulating mixed nerves, such as the posterior tibial nerve, with a hand-held stimulator (Yu and Jones, 1985).
Segmental evoked potentials can be achieved by stimulating the dorsal penile or dorsal clitoris nerve with small surface electrodes (Scott Haldeman, 1982). Dermatomal evoked potentials can be recorded after stimulating the respective dermatome (Slimp, 2008). One current research aim is to bring uniform technical parameters among all three evoked potential modalities. dSEPs will help in comparative studies between all evoked potentials and determine cut-off values in normal subjects.
Consequently, 5x5cm square stickers were used to stimulate the posterior tibial nerve, S2 dermatome and S3 dermatome. Due to the small distribution area of the S4 dermatome, two circular stickers with a 3.2 cm diameter were used to stimulate the S4 dermatome. Standard 28x22mm stickers were used to stimulate the pudendal nerve for the pudendal somatosensory evoked potentials, as shown in Figure 6.

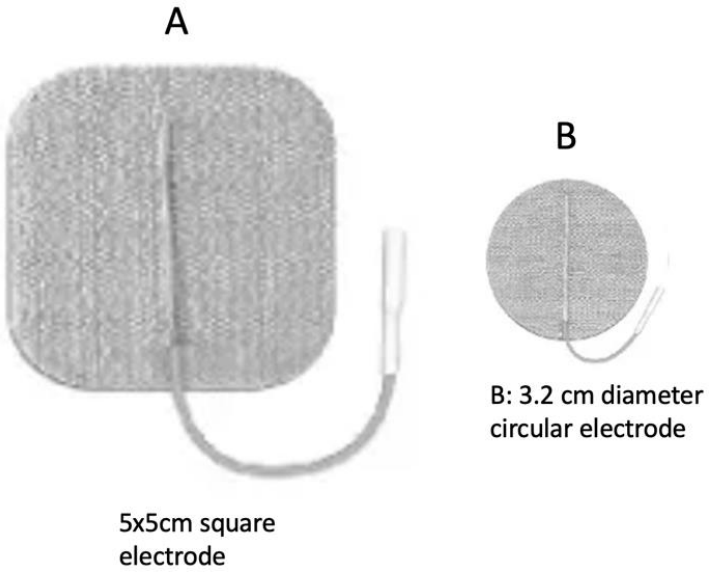


Figure 6: Electrode A was used for S2 and S3 dSEPs, and electrode B was used for S4 dSEP (image source: open access image adapted from www.healthcarehk.com).

The placement of stimulating electrodes is vital in dermatomal evoked potential studies. Foerster's tactile dermatome map (Foerster, 1933) was used to identify the S2 autonomous zone. The S2 dermatome area is a wide strip extending from the popliteal fossa to the mid-gluteal area. S2 dermatomal distribution gets thinner while reaching the popliteal fossa as

the posterior femoral cutaneous distribution reduces and overlaps the L3 distribution. The S2 distribution is the widest at the level of the gluteal fold. Connecting the stimulating electrodes at a consistent position is essential to make a meaningful comparison possible when analysing left and right side differences. Since identifying the gluteal fold is easy, a standard electrode placement technique is proposed. The cathode electrode is placed 2 centimetres distal to the gluteal fold on a virtual line connecting the gluteal fold's mid-point to the popliteal fossa's mid. The anode electrode was placed 2 centimetres distal to the cathode electrode. Foerster's dermatomal map did not reveal the exact distribution of the S3 and S4 dermatomes. Keegan and Garrett provided dermatomal distribution based on intervertebral disc prolapse symptoms (Keegan, 1947), but S3 and S4 dermatomal distribution were reported. Electrode placement for the S3 dermatome was chosen based on the International Standards for Neurological Classification of Spinal Cord Injury Scale-2019 (Roberts, Leonard and Cepela, 2017) and the distribution of the perineal branch of the posterior femoral cutaneous distribution (Dellon, 2015). The cathode electrode for the S3 dermatome was placed 2 centimetres proximal to the gluteal fold, as shown in Figure 7A. At the midpoint between the S2 imaginary line on the gluteal muscle and the midpoint of the anal orifice, the anode electrode was placed 2 centimetres proximal to the cathode electrode. S4 and S5 dermatomes overlap and are difficult to differentiate with electrophysiological testing. The landmark for the S4 dermatome used the mucocutaneous junction of the anus, as shown in Figure 7B. The cutaneous area immediately lateral to the mucocutaneous junction is supplied by the haemorrhoidal branch of the pudendal nerve that contains S4 sensory fibres (Cramer and Darby, 2013; Kirshblum and Eren, 2020; Sagar and Pemberton, 2007). Two 3.2-centimetre disc electrodes were placed ipsilaterally around the anal orifice, but the stimulating wires were placed lateral to the mucocutaneous junction.

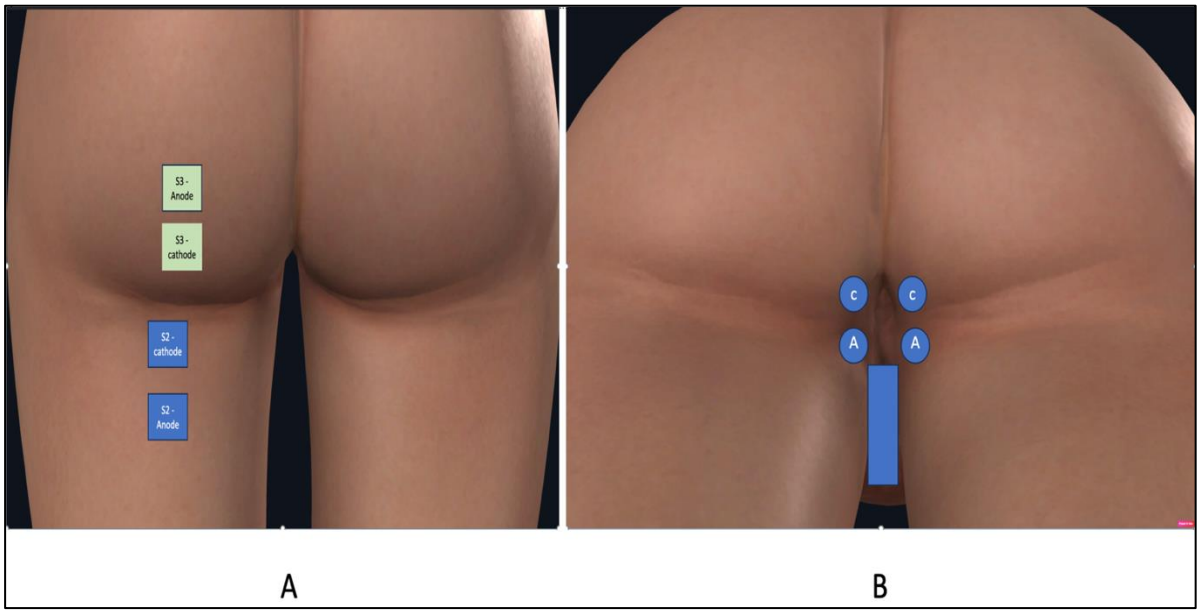


Figure 7: A – Electrode placement for S2 and S3 dSEPs where the cathode was proximal to the gluteal fold. B – Electrodes were at the mucocutaneous junction for S4 dSEP (image source: adapted and edited using 3D4 anatomy software with permission from 3D4Medical; appendix 7.5)

2.7.5 Evoked potentials nomenclature and measurements

American Clinical Neurophysiology Society guideline 9D was followed while identifying and designating waveforms and peaks (Cruccu et al., 2008). Peaks were marked with N, which went up from the baseline, and P, which went down from the baseline.

There was a considerable discrepancy in the nomenclature of N and P peaks between the International Society for Clinical Electrophysiology of Vision (ISCEV) and the International Federation of Clinical Neurophysiology (IFCN), as shown in Figure 8. Discrepancies are also seen in the measurement of latency and amplitudes. ISCEV suggests the latency to be taken from the highest upward peak and amplitude from the preceding downward peak (Odom et al., 2016). However, the IFCN suggests latency and amplitude from the first downward to the next upward deflection. On close observation, the real discrepancy comes from comparing these two dissimilar evoked potential studies. In VEPs, all potentials have cortical origins and are attention-dependent, whereas in SEP, popliteal and lumbar responses have extracortical generators. In VEPs, the P100 peak is more stable, whereas in SEPs, the P37 is more stable. In SEPs, baseline distortion is more common due to very low amplitudes and hence, IFCN suggested taking amplitude measurements from P37 to N45 peaks (Nuwer et al., 1994). Since dSEPs are more related to SEPs, IFCN nomenclature

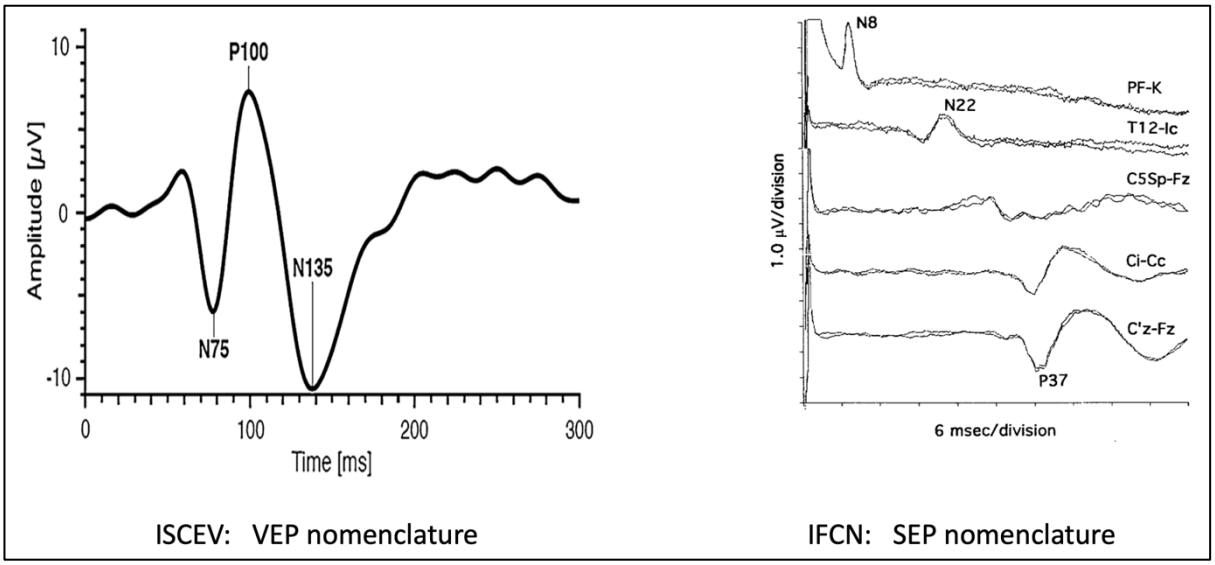


Figure 8: The ISCEV guideline suggests the peak that went up from the baseline to be called P, whereas the IFCN suggests it as N.

was followed through the studies. The cortical latency and amplitude were measured as per IFCN guidelines, i.e., latency was the time taken from the stimulus artifact to the first downward peak. The amplitude was measured from the downward peak to the following upward peak.

2.6 Recruitment

The sample size was considered to be twenty in all three studies. Since this is a pilot study in sacral dSEPs, a pragmatic approach was taken while considering the sample size. Since there were no suitable studies to compare mean cortical latencies in the sacral dermatomes, owing to the difficulties of recruiting volunteers to be investigated in the genital areas, the plausible number of volunteers who can be recruited in two years' time was 20. Even though there were no studies in the sacral dSEPs, a few studies were available in the TSEPs. The tibial latency variance among the population was 11.5 ms (Vogel, Rüber and Klein, 1986). To find a unilateral abnormality, the latency difference of 3.6 ms is clinically significant in the TSEPs (Chu, 1986). Using these numbers, the required sample size for TSEPs was calculated using the formula.

$$N = (Z_{\alpha/2} + Z_{\beta})^2 * 2 * \sigma^2 / d^2$$

Where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$, Z_{β} is the critical value of the Normal distribution at β. σ^2 is the population variance, and d is the difference likely to be detected (Rosner, 2015). The minimum required same size was 18 for a population variance of 11 ms, hypothesised difference of 3.6, power of 90% and confidence interval of 95%. Based on the sample size calculation, the first study aimed to generate normative values for the S2, S3 and S4 dermatomes of twenty healthy adults. Eleven participants responded to the current research study advertisement and volunteered to participate. In addition, nine patients who attended the Uro-Neurology department also volunteered to participate in this study. These nine patients were people with non-neurogenic voiding dysfunction. The HSST trainee Clinical Scientist (Mr Anjaneya Malladi) contacted them and assessed their suitability before giving mutually suitable appointments for the study. All volunteers were given a patient information leaflet (Appendix 7.6) approximately a week in advance and given sufficient time to clarify their doubts. On the assessment day, the clinical scientist received the volunteers, explained the procedure, and obtained informed consent. The participants who agreed to the test were screened for alcohol dependency using the Alcohol Use Disorder Identification Test (AUDIT) shown in Appendix 7.7. Those who scored less than 15 points were selected for clinical assessment. Those volunteers who provided written consent and cleared the AUDIT test were clinically examined by Prof. Jalesh Panicer, Dr Sara Simeoni, or Dr Sarah Wright, consultant neurologists, for their suitability to participate in the study. All volunteers were compensated per the ethics committee recommendations for their time and effort to participate in this study.

2.7 Demographic data

Background data was collected regarding date of birth, sex, height in centimeters and weight in kilograms. Between February 2022 and August 2023, 29 volunteers expressed their willingness to participate in Study 1. The reasons for volunteers who did not participate in Study 1 are given in Figure 9. A total of 20 participants were eligible to participate in Study 1. Out of 20 participants, 14 were female (70%), and 6 (30%) were male. The participants' mean height, age and BMI are given in Table 1.

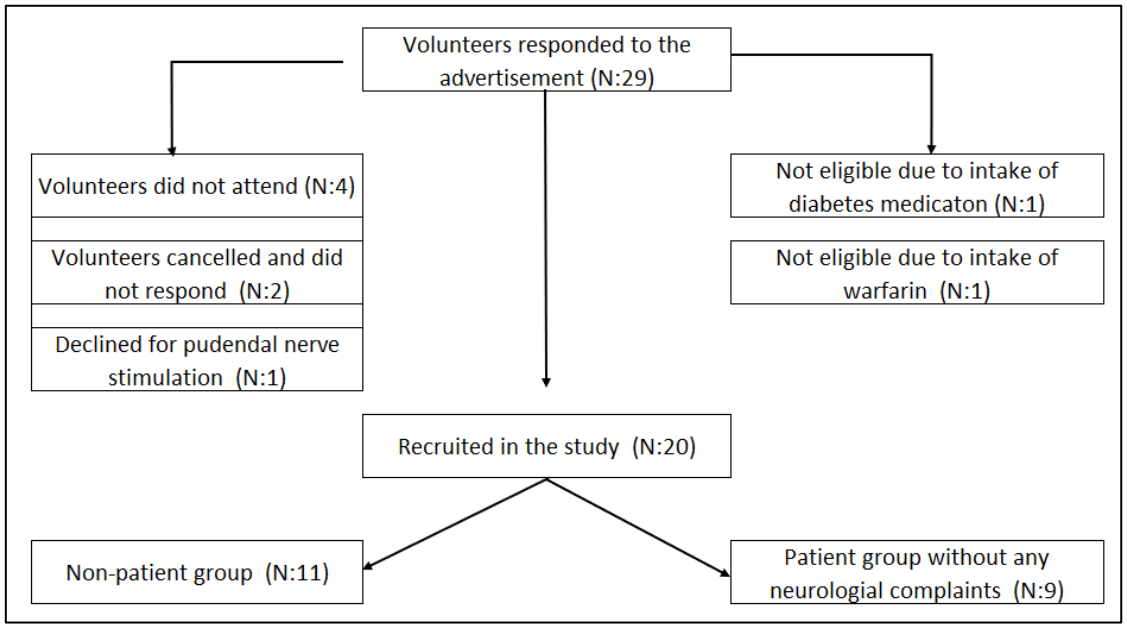


Figure 9: Details of volunteers who responded to the advertisement and the actual number of volunteers recruited in Study 1.

Table 1: Mean height, age and BMI of Study 1 participants.

	Male (N=6) ±SD	Female (N=14) ±SD
Mean height (cm)	176 (168-190) ±8.1	162(150-183) ±8.8
Mean age (years)	35 (26-49) ±10.6	39 (20-75) ±16.6
Mean BMI (kg/m^2)	24.5 (19.3-31.9) ±5.5	25.9(17.7-39.9) ±6.6

2.8 Inclusion and exclusion criteria

All volunteers were considered for the test if they met the inclusion criteria and did not have any of the exclusion criteria, Table 2

Table 2: Inclusion and exclusion criteria for Study 1 participants

Inclusion Criteria	Exclusion Criteria
Age over 18 years	Language barrier requiring an interpreter.
Written informed consent	Incapacity to consent
Received Information Leaflet one week prior	Known neurological disorders.

	Had a history of spinal or brain surgeries.
	Had a history of peripheral neuropathy.
	Having diabetes
	Neurological examination susceptive or suggestive of central or peripheral sensory or motor pathway abnormalities
	Had a history of prolonged or traumatic deliveries.
	Had history taking medication for chronic conditions.

2.9 Performing Evoked Potential Studies

All volunteers who consented to the tests and completed satisfactory clinical examinations were asked to change into a hospital gown and were accompanied by a chaperone throughout the study. Their standing height and weight were measured to calculate BMI. All subjects lay supine on a softly padded couch with a pillow under the head. The room was fully lit, and subjects were asked to remain awake but close their eyes to avoid muscle and blink artifacts. The test started with the posterior tibial SEP and then proceeded with the S2, S3, and S4 dermatomal SEP and Pudendal SEP studies in the same order. After cleaning the skin thoroughly, a 5x5cm cathode electrode was attached below the medial malleolus for the Posterior tibial SEP. The anode electrode was connected 2 cm proximal to the cathode. To identify the electrical perception threshold, 0.2 milliseconds duration square wave pulse electrical stimulation at a 3.1 Hz rate was given, starting with 0 milliamperes and gradually increasing until the subject started appreciating the tapping sensation. The procedure was repeated, identifying the mean electrical perception threshold for the study. Electrical stimulations for all evoked potentials were aimed at three times that of the mean electrical perception threshold. However, if the subject complained of pain or muscle twitching under the electrodes, the stimulus current was lowered to minimise the pain and avoid the muscle twitching under the electrodes. Two runs of a minimum of 200 averages were taken to assess the consistency and reproducibility of the signals. Latency and amplitude

measurements were taken from the grand average run. Notch filters or signal smoothing were not used throughout the recording.

2.10 Statistical Analysis

2.10.1 Sample size and statistical tests

The number of data points from 20 volunteers in the study 1 was 40. Even though cortical latencies and amplitudes can be produced from both the left and right sides, only the mean of left and right cortical latencies and amplitudes were taken for all comparative analyses. The Shapiro-Wilk test was performed to assess data normality. A one-sample t-test compared the tibial SEP mean values with the published mean values. The current study's mean latency and SD were compared with the average mean and SD values of ten published studies. Abnormally prolonged cortical latencies have a detrimental effect on the final diagnosis, but short latency responses do not have this issue. Consequently, a one-tailed t-test was conducted. The linear regression analysis of cortical latencies on independent parameters of height and age was calculated for all dermatomal evoked potentials. Limits of normality were proposed for all dermatomal evoked potentials based on regression formulae.

SPSS software (version 28.0.1.1) was used for all statistical analyses throughout the studies. Previous studies have shown a positive correlation between height and cortical latency (Chu, 1986; Miura, Sonoo and Shimizu, 2003), and hence, regression analysis was selected to assess the impact of height on the latency in Study 1. In addition, I aim to determine the impact of other independent factors, such as BMI and age, on the latencies and amplitudes. Also, multivariant analysis was done to assess various combinations of height, age and BMI and their impact on the cortical latencies and amplitudes.

2.11 Results

2.11.1 Pain tolerance score

Tibial SEP data was generated in 20 healthy adults from 40 lower limbs after stimulation with sticker electrodes. Tibial SEPs were elicitable in all 20 subjects with this new stimulation technique. All subjects well tolerated the new technique. All participants were asked to fill out a numerical pain rate scale between 0 and 10, where 0 means no pain, and 10 is the worst possible pain (Jensen, Karoly and Braver, 1986). All subjects scored no more than one after the test, suggesting all participants well tolerated the test. The pain score data is given in Table 3

Table 3: Tibial SEP data along with independent parameters

No.	Gender	Height	Age	BMI	Pain score due to the test (0-10)	R_Tib_Lat	L_Tib_Lat	Mean latency	R_Tib_Amp	L_Tib_Amp
1	Female	150	30	17.5	1	34.7	34.7	34.7	1.9	2.6
2	Female	165	37	33.1	1	45.8	44.5	45.2	1.5	1.9
3	Female	160	20	19.5	1	43.1	45.5	44.3	2.6	2.0
4	Female	165	22	26.4	1	43.3	41.3	42.3	1.8	2.2
5	Female	165	69	33.1	1	42.8	42.7	42.8	2.4	3.4
6	Female	170	27	20.8	0	38.0	39.2	38.6	2.0	1.9
7	Female	163	24	28.2	1	40.6	36.6	38.6	2.9	2.0
8	Male	168	47	31.9	1	43.1	40.2	41.7	1.0	0.6
9	Male	175	27	19.6	0	39.2	41.9	40.6	1.4	1.4
10	Male	178	49	24.4	0	41.6	42.7	42.2	4.1	5.3
11	Male	190	27	19.3	0	41.3	43.9	42.6	0.5	1.0
12	Female	160	36	28.9	0	39.5	42.0	40.8	2.0	1.5
13	Female	152	42	39.9	0	46.4	48.6	47.5	2.3	2.1

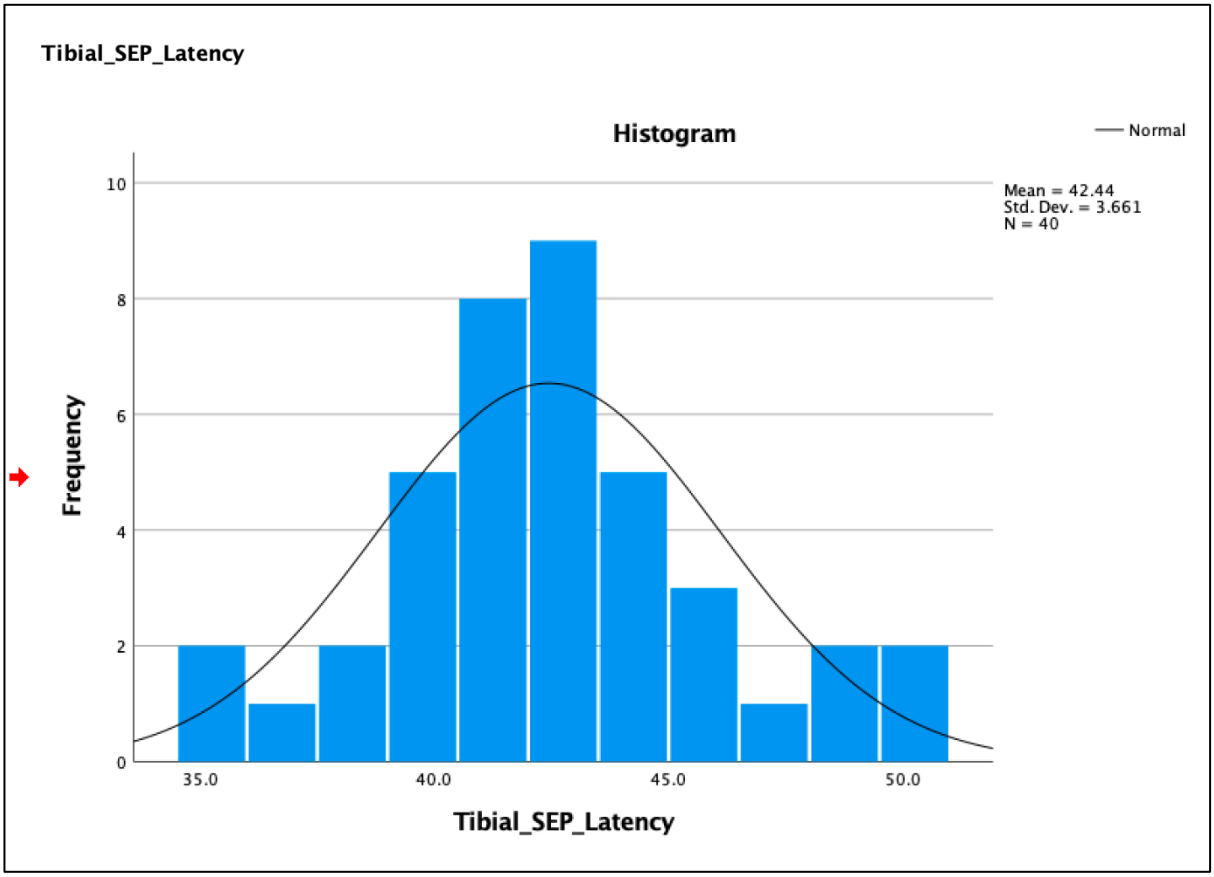
14	Female	183	32	19.4	1	47.0	49.7	48.4	2.2	1.5
15	Male	168	31	21.3	1	43.6	43.6	43.6	2.8	3.1
16	Female	160	49	25.0	0	42.5	44.8	43.7	1.7	1.4
17	Female	150	49	29.0	0	40.2	38.0	39.1	3.0	3.3
18	Female	160	75	17.9	1	50.5	49.2	49.9	1.6	1.1
19	Female	170	40	23.8	1	40.8	40.6	40.7	1.4	1.8
20	Male	177	26	30.3	1	41.3	42.7	42.0	2.5	2.0

R_Tib_Lat: Right Tibial Latency, L_Tib_Lat: Left Tibial Latency, R_Tib_Amp: Right Tibial amplitude, L_Tib_Amp: Left Tibial amplitude. Pain score 0 No pain, 10: worst possible pain.

2.11.2 One-sample T-test for Tibial SEP latency

A one-sample t-test was done on the tibial SEP data to assess whether any statistical difference exists between the mean tibial latency in study 1 and the published mean values. To facilitate a one-sample t-test, a normality test was done on the tibial SEP data. A total of 40 data points were collected for the tibial SEP after stimulating both lower limbs in twenty healthy subjects. The histogram for the tibial SEP latency showed a normal distribution, and there was no positive or negative skewness, as shown in Figure 10a.

Figure 10a: Histogram for tibial SEP latency confirms normal distribution.



The Quantile-Quantile plot (Q-Q plot) shown in Figure 10b also visually confirms the alignment of all data points near the central line, confirming two quantiles drawn from the same normally distributed data set.

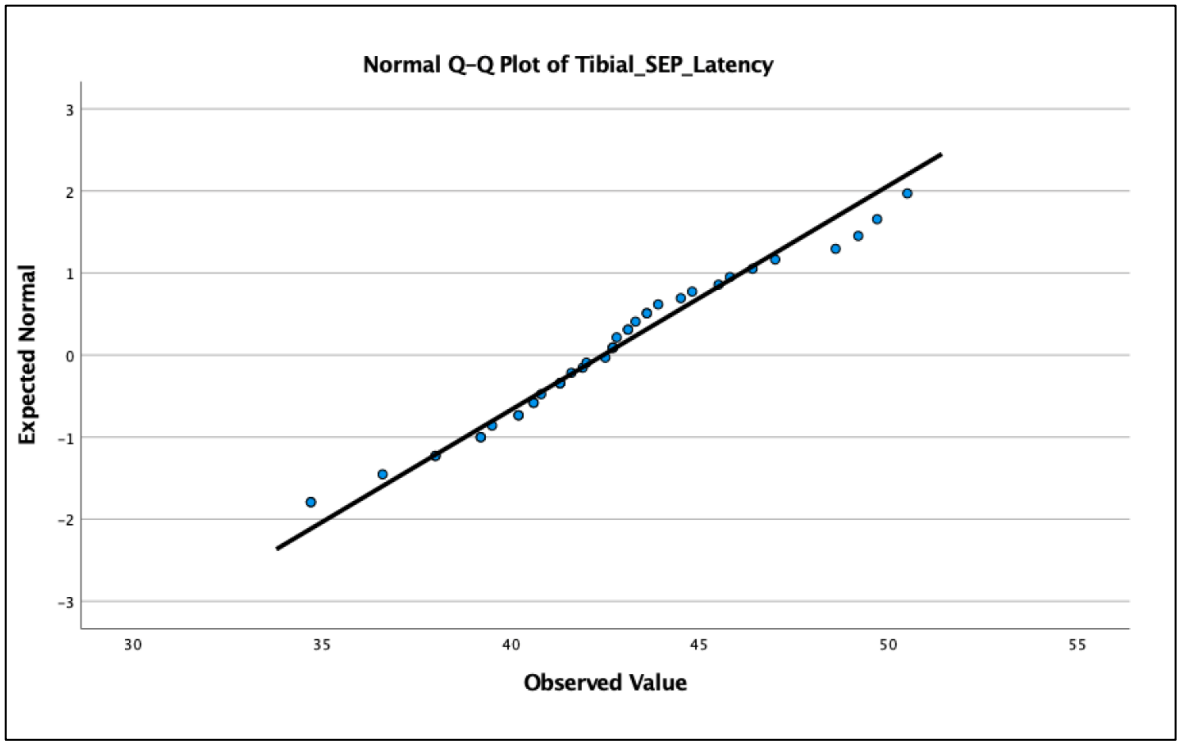


Figure 10b: Q-Q plot suggests a normal distribution of tibial SEP latencies in Study 1.

The box plot for the tibial SEP is shown in Figure 10c. The median line is approximately in the middle of the box, and the whiskers are about the same on both sides, suggesting the tibial SEP latency data was similar to normally distributed data. The mean value for the tibial SEP latency with outliers was 42.6 ms. Without outliers, it was 42.4, suggesting no significant effect of outliers on the mean tibial SEP latency.

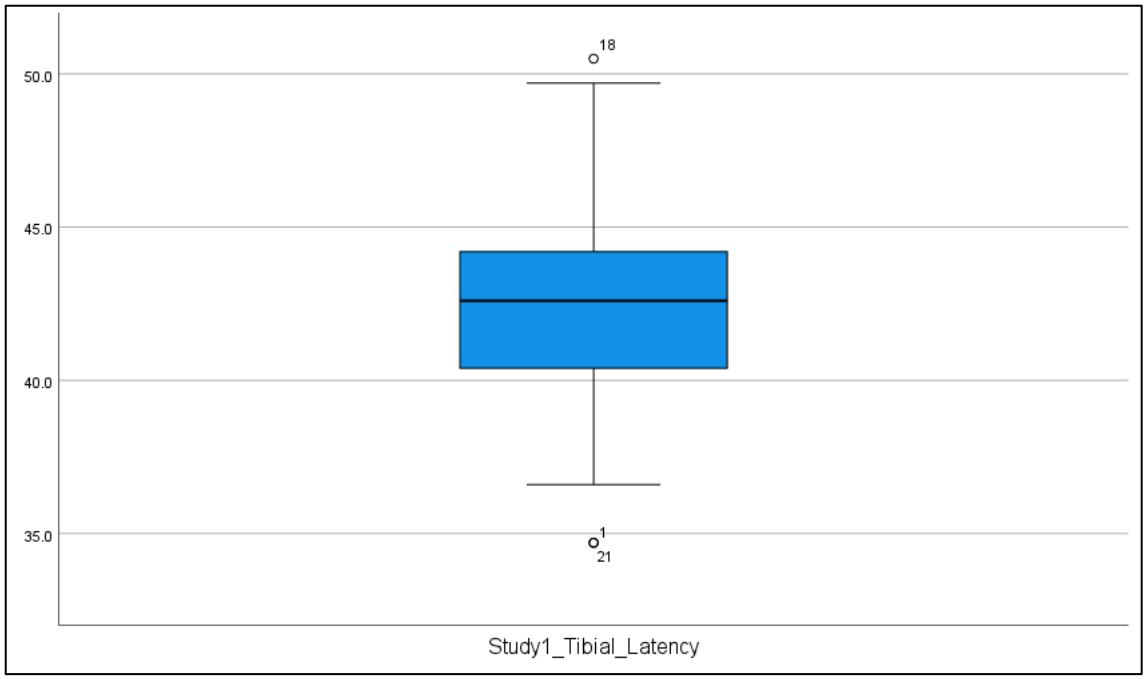


Figure 10c: Boxplot for tibial SEP confirms normal distribution in Study 1.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis test also confirm the tibial SEP latency data was normally distributed, as shown in Table 4.

Table 4: Different statistical tests showed the tibial SEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.200	>0.005	Suggests normal distribution
Shapiro-Wilk	0.555	>0.005	Suggests normal distribution
Skewness	0.379	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	0.338	(-1.96 <z<1.96)	Suggests normal distribution

2.11.3 Published normative value for tibial SEP.

Ten published studies were selected to facilitate the t-test for the tibial SEP, and their sample size, mean latencies and SD are shown in Table 5.

Table 5: Published normative values for the Tibial SEP cortical latencies.

Study Number	Name	N	Mean latency	SD
1	(Misra and Kalita, 1996)	32	41.1	4.6
2	(Hakatifi, 1986)	54	39.8	2.3
3	(Dolu et al., 2004)	30	38.3	1.59
4	(Shaw and Synek, 1985)	38	38.9	2.2
5	(Restuccia et al., 2000b)	35	38.0	2.7
6	(Zhang et al., 2011)	25	41.5	6.2
7	(Eltantawi et al., 2012)	20	38.6	1.9
8	(Miura, Sonoo and Shimizu, 2003)	65	37.8	2.6
9	(Chabot et al., 1985)	27	43.4	4
10	(Chu, 1986)	160	39.3	1.8
	Published mean		*39.7*	*3*
	Current study	*20*	*42.4*	*3.7*

The current study showed a mean latency of 42.4 ms, 2.7 ms more than the average mean latency of 39.7 ms. A list of all tibial SEP data points was given in Appendix 7.8. When comparing the current value with a similar size study (7), the latency difference was 3.8 ms. Table 3 shows that the current study latency is greater than any of the ten studies except study 9. One sample t-test was used to assess the statistical significance of the observed mean latency difference of 2.7 ms.

2.11.4 One sample t-test for tibial SEP in Study 1

Tibial SEP data satisfied all the pre-requisitions for the t-test, such as homogeneous and continuous parameters with no selection bias. One sample t-test was done using SPSS software with the following hypotheses, and the test results are shown in Table 5.

Null hypothesis (H_0)**:** No difference exists between the study 1 tibial SEP latency and the published tibial mean SEP latency.

Alternative hypothesis (H_1)**:** A statistically significant difference exists between the study 1 tibial SEP latency and the published tibial mean SEP latency.

One sample t-test with and without outliers showed a significant p-value and hence could not reject the alternative hypothesis. These results suggest that the tibial SEP data generated using sticker electrodes should not be compared directly with the SEP data generated using conventional handheld stimulators. Since dSEPs and PSEPs are also generated using sticker electrodes, these findings suggest that conventional tibial SEP data may not be suitable for comparing dSEP or PSEP abnormalities.

2.11.5 Linear regression analysis for tibial SEP latency

Studies have shown tibial SEP latencies are influenced by independent parameters such as height and age (Acns, 2006; Chu, 1986; Miura, Sonoo and Shimizu, 2003). Linear regression analysis was done using SPSS software on current tibial SEP data to understand the influence of independent parameters on the tibial SEP latency. The results of the linear regression analysis are shown in Table 6.

Table 6: Linear regression analysis results for tibial SEP

Hypothesis	Regression weights	Beta Coefficient	R^2	F	t-value	ANOVA Sig. p-value	Hypotheses Supported
H_1	Age →Latency	0.357	0.127	5.534	2.353	0.024	Yes
H_1	Height →Latency	0.161	0.026	1.014		0.320	No
H_1	BMI →Latency	0.103	0.11	0.408		0.527	No
H1	Age + Height →Latency	0.266	0.193	4.438	A: 2.772 H:1.745	0.019	Yes
H1	Age + BMI →Latency	0.087	0.128	2.710		0.08	No

A: Age, H: Height

The ANOVA test results in Table 6 showed a significant p-value of 0.024 ($p<0.05$) for the age parameter, suggesting it significantly influences the latency. The R^2 = 0.127 shows that the model explains 12.7% of the variance in latency with the given age. Similarly, the combination of age and height contributes 19.3% of the variance in the latency. The rest of the independent parameters in Table 6 did not significantly influence the latency, and hence, the regression equation for the tibia latency is 22.9+ (0.105) x (Age)+ (0.094) x (Height).

The observed power of the study was calculated based on the p-value of 0.05, and the results are shown in Table 7. This observed power value does not give additional information about the study's merit, as observed power varies depending on the chosen alpha value (Hoenig and Heisey, 2001). However, it helps design future studies with the right sample size and higher power requirements. The optimum sample size for future studies was calculated by measuring effective size. The effective size was calculated in the study by subtracting the current tibial SEP mean from the published mean value and dividing it by the SD of the published value (Sullivan and Feinn, 2012). The sample size for future studies is 23 for a power of 0.9, as shown in Table 7.

Table7: Observed power based on assumed p-value of 0.05 and optimal sample size based on expected power of 0.9.

Effect	Value		Sig	Noncent Parameter	Observed Power
Pillai's Trace	0.156		0.010	7.232	0.746
Wilks'Lambda	0.844		0.010	7.232	0.746
Hotelling'sTrace	0.185		0.010	7.232	0.746
Roy's Largest Root	0.185		0.010	7.232	0.746
Test for Mean	Sample size (N)	Actual Power	Expected Power	Effect size	Sig
	23	0.902	0.9	0.71	0.05

a.Two-sided test
b. Based on noncentral t-distribution.

2.11.6 Impact of Stimulus Strength on dSEPs latencies and amplitudes

One of the aims of Study 1 is to generate normative values for all three sacral dermatomes. Knowing the optimum stimulus strength for dSEPs before recruiting healthy subjects is essential. The impact of stimulus strength on cortical latency was assessed on a small number of healthy volunteers (n=1) owing to the difficulty of maintaining volunteer cooperation for several hours. The electrical stimulation perception threshold was defined as the first sensation of electrical stimulation perceived by the volunteers when the electrical stimulation was gradually increased by 0.5 mA in each incremental step. Two runs of 200 averages were recorded for each stimulus strength. The grand average of two runs was recorded, and P1 latency, N1 latency and amplitude were measured. The effect of increased stimulus strength on the S2, S3 and S4 dSEP latencies and amplitudes are shown in Figure 11a-13b. S2 dSEP latency rapidly decreased to 2.5 times the current perception threshold and plateaued after three times the threshold. No clinically significant latency asymmetry was seen between 2.5 and 3 times the threshold, as shown in Figure 11a.

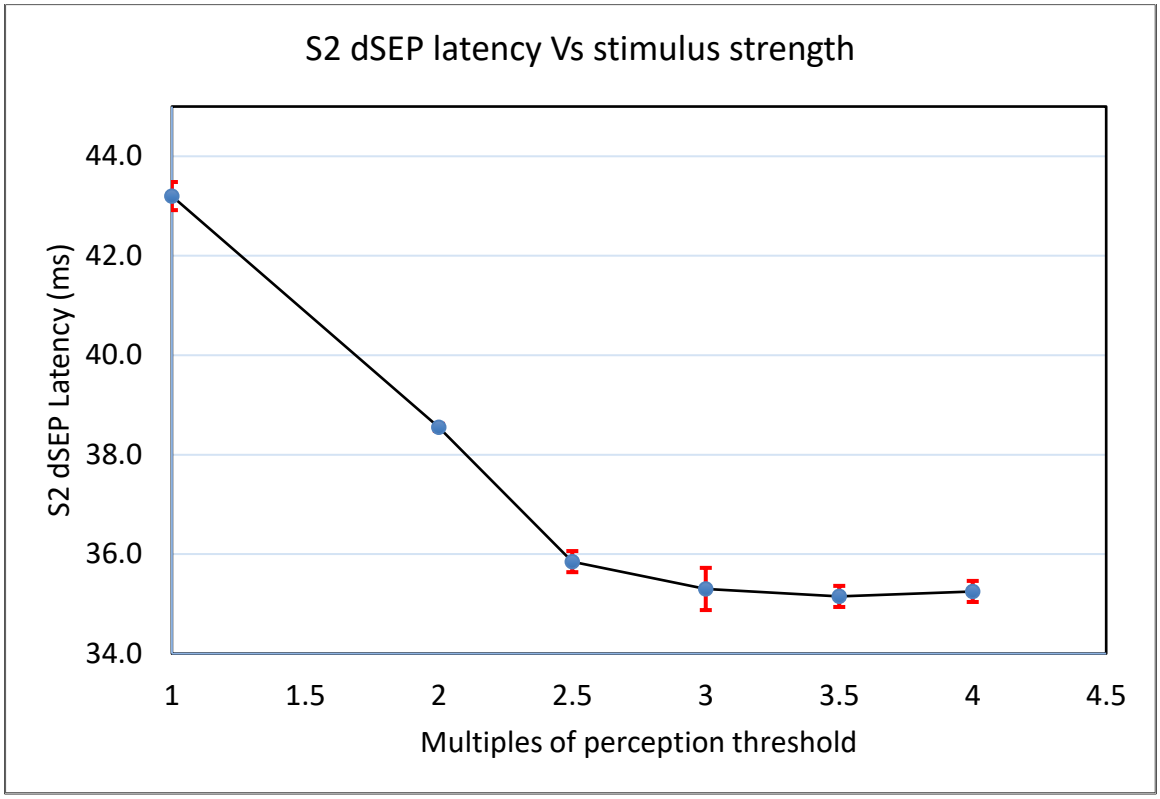


Figure 11a: Stimulus strength has negligible influence on S2 latency after 3 times the stimulus perception threshold.

S2 dSEP change in amplitude with increased stimulus strength was analysed, and the results are shown in Figure 11b. S2 dSEP amplitudes were plateaued after 2.5 times the perception threshold.

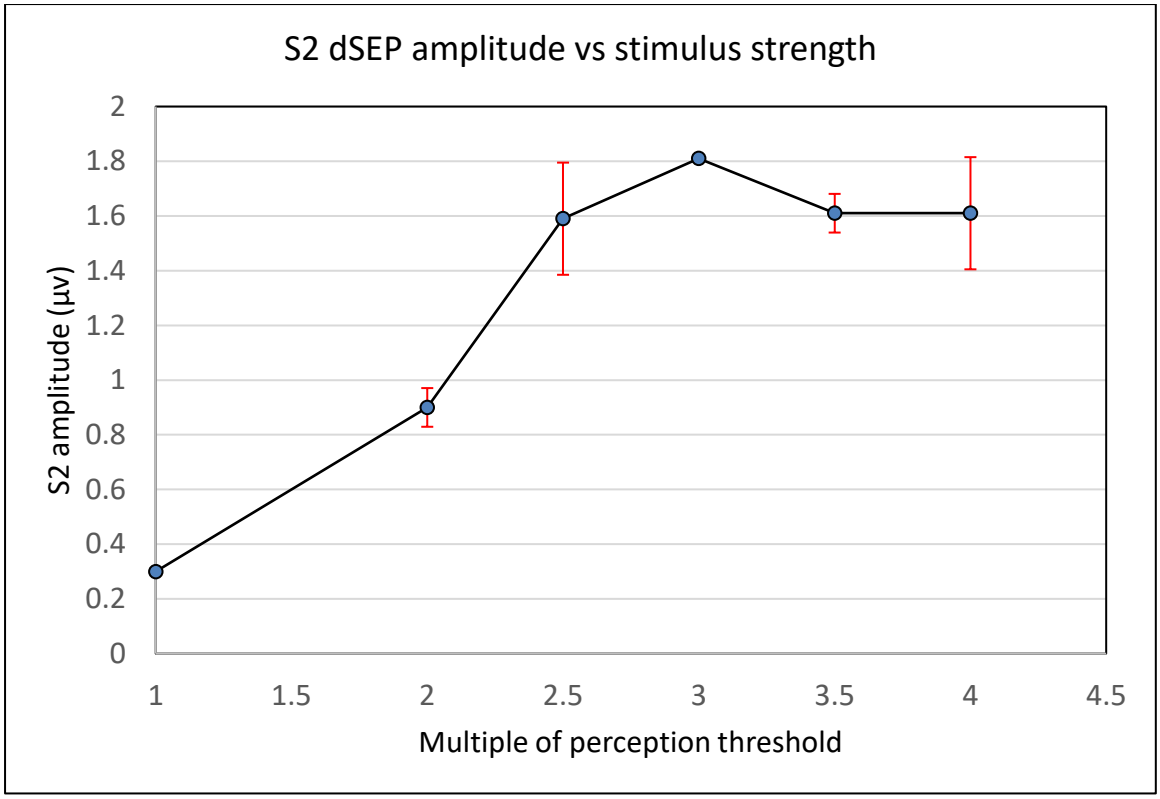


Figure 11b: Stimulus strength has negligible influence on S2 dSEP amplitude after 2.5 times the perception threshold.

S3 dSEP latency rapidly decreased to 2.5 times the current perception threshold and plateaued after three times the threshold. The latency difference between 3 and 4 stimulus strengths was only 0.4ms, suggesting that latency did not change significantly after three times the threshold stimulation, as shown in Figure 12a. Similarly, S3 dSEP amplitude was relatively plateaued after three times the threshold. The amplitude difference between 3 and 4 stimulus strength was 0.3 μV, suggesting that amplitude did not change significantly after three times the threshold stimulation, as shown in Figure 12b.

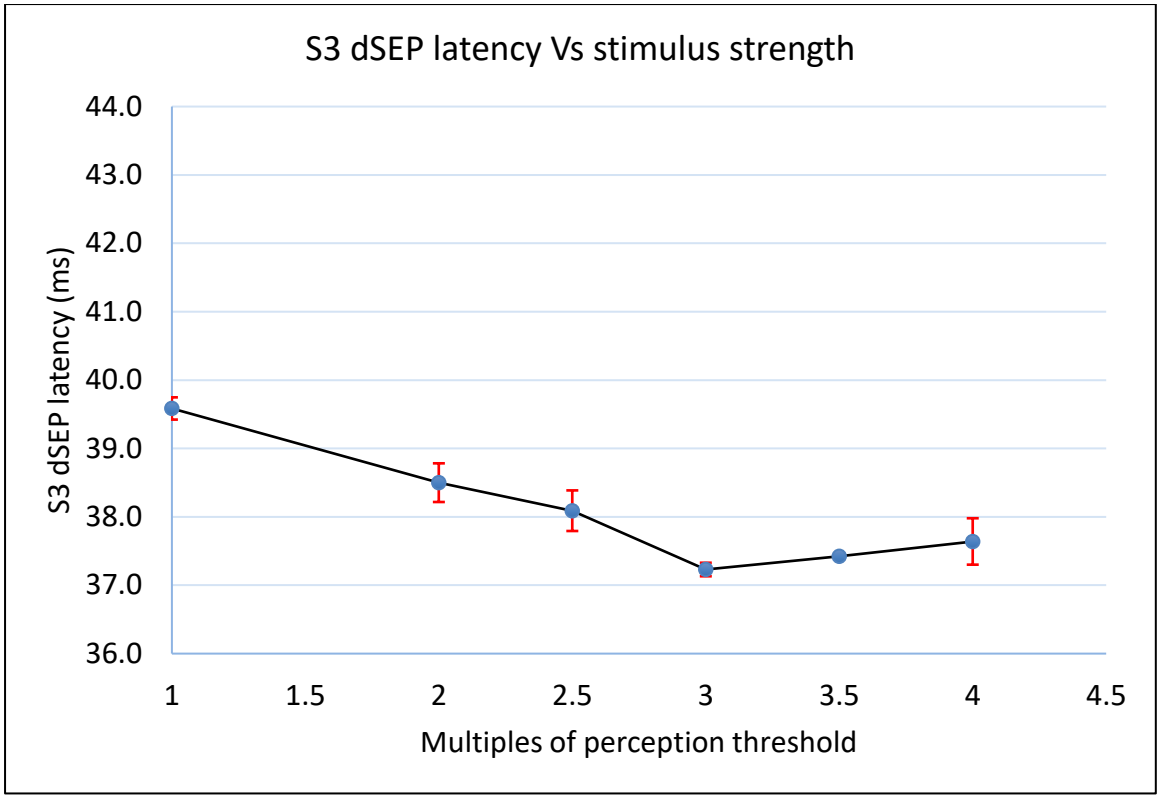


Figure 12a: Stimulus strength has negligible influence on S3 latency after 3 times the stimulus perception threshold.

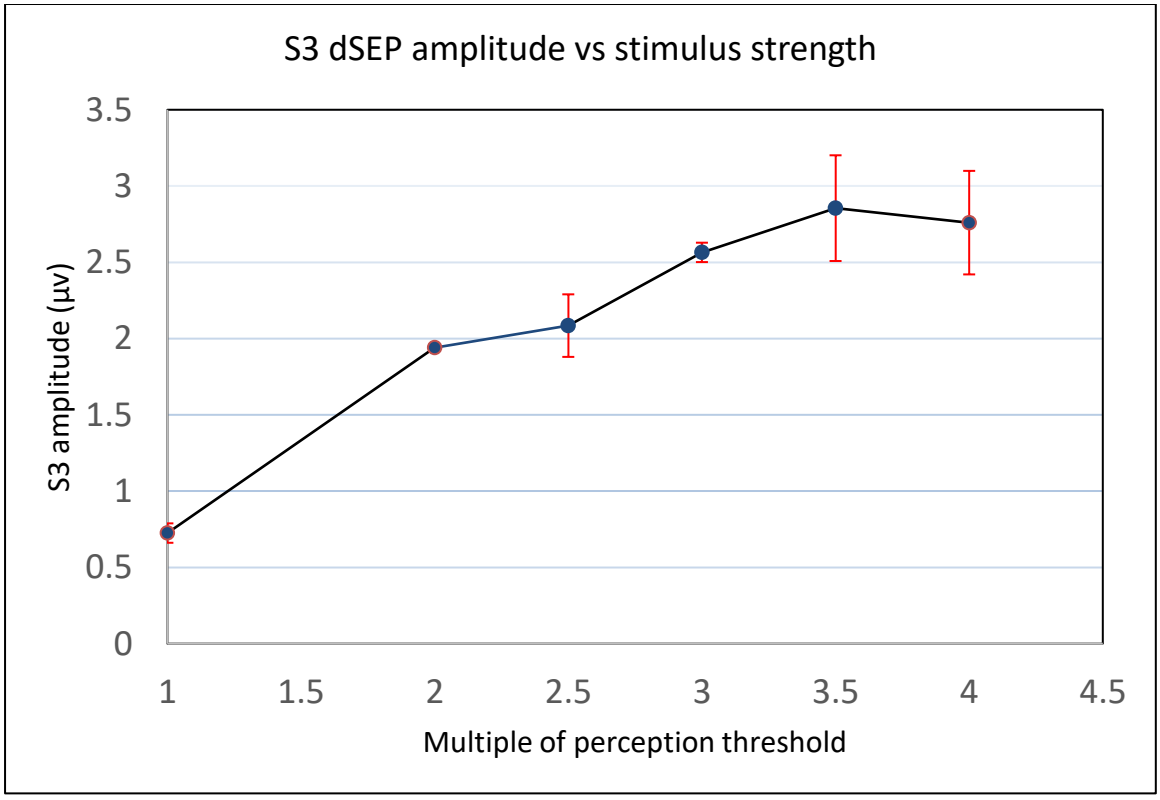


Figure 12b: Higher strength stimulus has negligible influence on S3 dSEP amplitude after 3 times the stimulus perception threshold.

S4 dSEP latency was relatively plateaued after 2.5 times the stimulus strength, as shown in Figure 13a. There was a mild (0.8 ms) increase at 3 times the stimulus strength, but the latency returned to the 2.5 times value at 3.5 times the stimulus strength, suggesting that the 0.8 ms increase in latency is not strictly physiological.

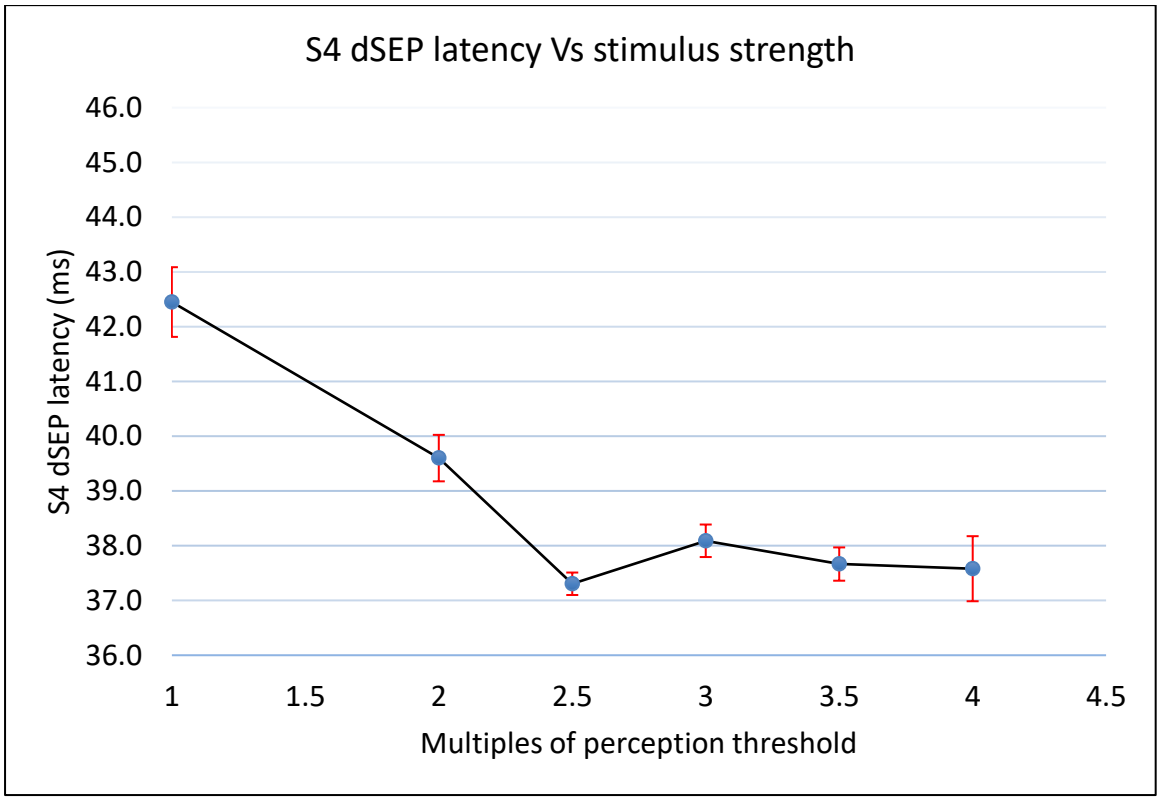


Figure 13a: Stimulus strength has negligible influence on S4 latency after 2.5 times the stimulus perception threshold.

S4 dSEP amplitude was relatively plateaued after two times the stimulus strength but mildly increased between 2.5 and 3. Further to this, there was no significant increase in amplitude. The increase in amplitude between 2 and 3 times the perception threshold was 0.3, which is clinically not significant. These findings suggest that the S4 dSEP amplitudes were relatively plateaued after two times the perception threshold, as shown in Figure 13b.

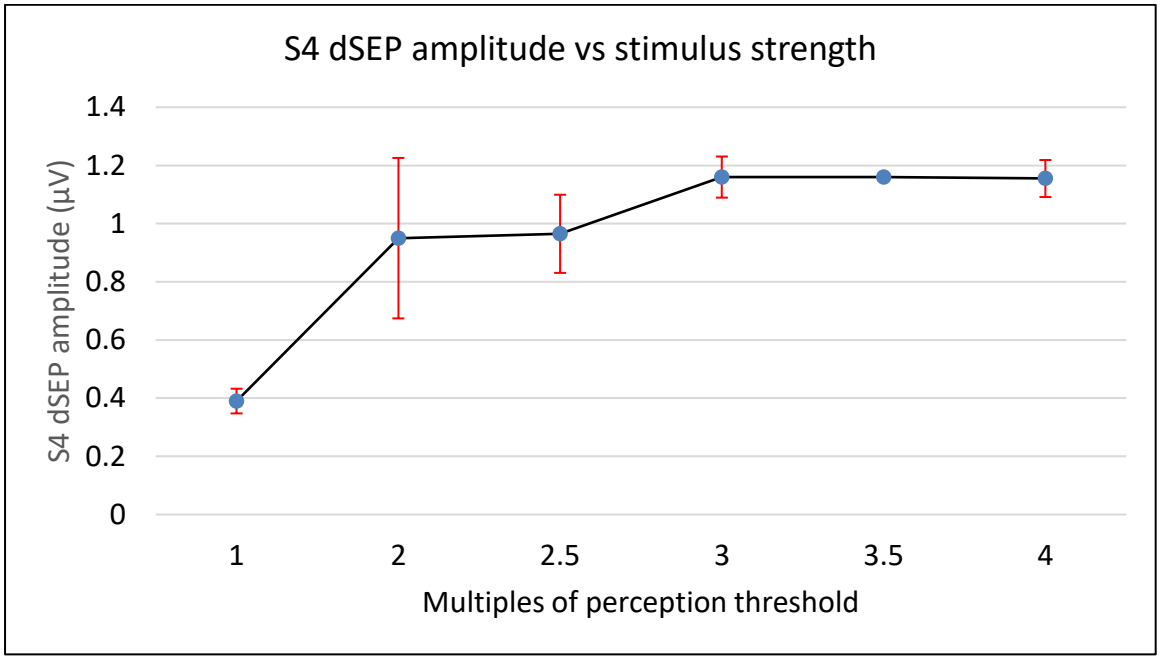


Figure 13b: Higher strength stimulus has negligible influence on S4 dSEP amplitude after 2 times the stimulus perception threshold.

Latency and amplitude characteristics of S2, S3 and S4 dSEPs showed no clinically significant variations after 2.5 to 3 times the stimulus perception threshold. Based on these findings, the stimulus strength was maintained three times the electrical perception threshold in the rest of the studies.

2.12 Sacral S2 dSEP data analysis

S2 dSEPs were recorded on twenty healthy volunteers. Cortical latencies and amplitudes were measured after grand averaging two runs, each with 200 averages.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis were calculated using the SPSS software to assess the normality of the S2 dSEP data, and the outcome was shown in Table 8. Significant values in Kolmogorov-Smirnov and Shapiro-Wilk tests were more than 0.05, suggesting that the data was normally distributed.

Table 8: Different statistical tests showed the S2 dSEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.200	>0.05	Suggests normal distribution
Shapiro-Wilk	0.440	>0.05	Suggests normal distribution
Skewness	-0.986	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	- 0.637	(-1.96 <z<1.96)	Suggests normal distribution

S2 dSEP latency histogram, Q-Q plot and the box plot shows the data is normally distributed as shown in Figures 14a -14c.

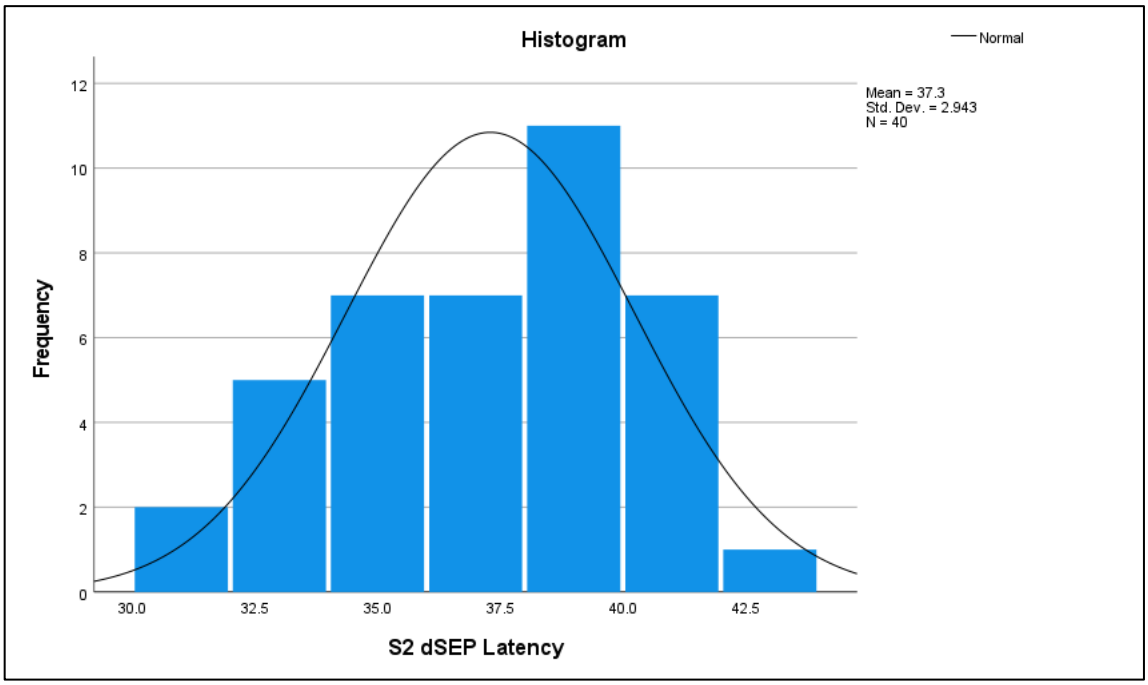


Figure 14a: S2 dSEP latency shows a normal distribution with no significant positive or negative skewness. Kurtosis for the distribution was -0.637 (-1.96 <z<1.96).

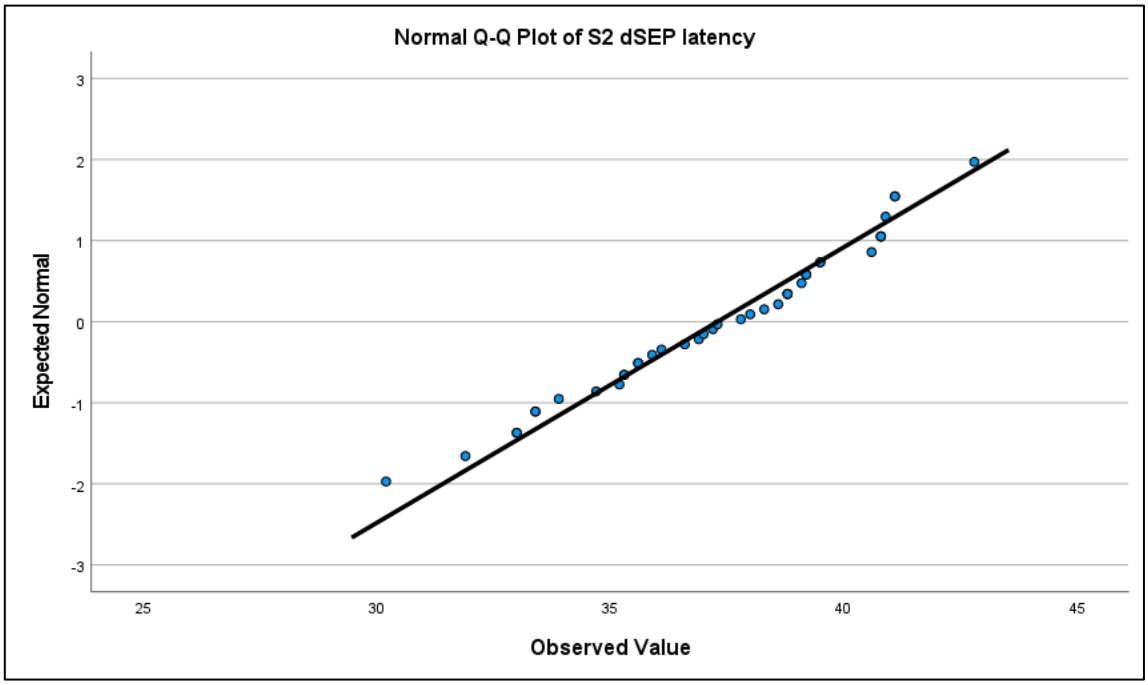


Figure 14b: S2 dSEP latency Q-Q plot shows good adherence to the central line, suggesting a normal distribution.

The box plot did not show any outliers (Figure 14c). The median line is approximately in the middle of the box, and the whiskers are about the same on both sides, suggesting the S2 latency data is similar to normally distributed data.

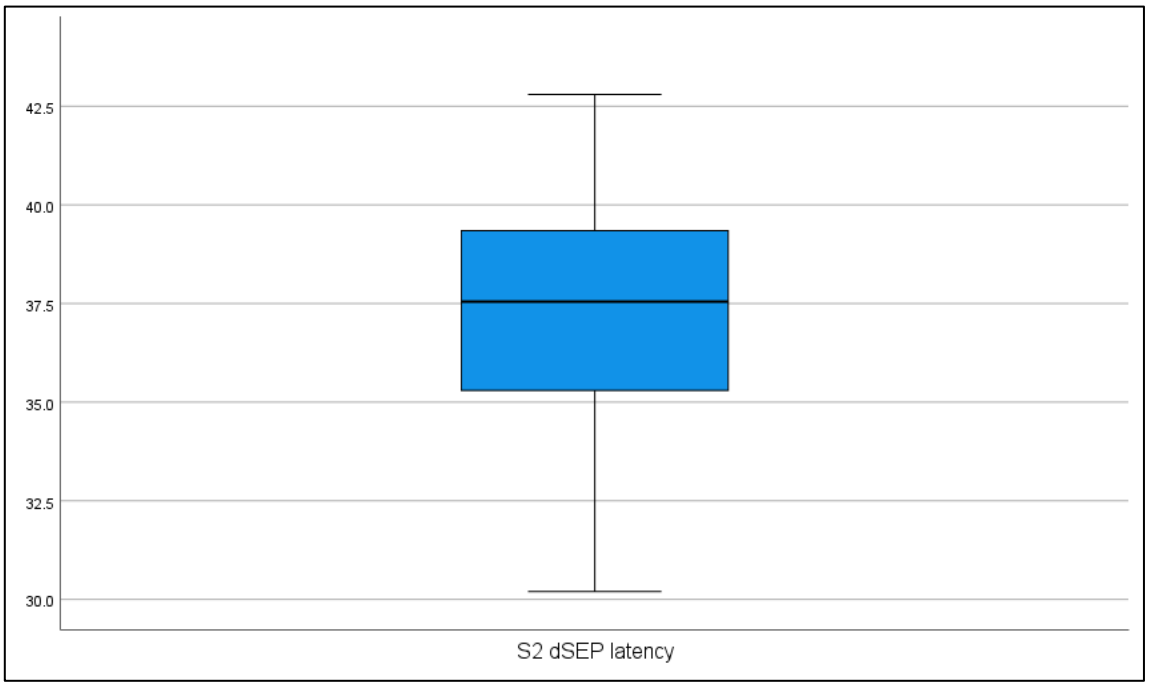


Figure 14c: Box plot for S2 dSEP latency shows a normal distribution with a median line approximately in the middle of the box.

Linear regression analysis was done using SPSS software on the S2 dSEP data to understand the influence of independent parameters on the S2 dSEP latency and amplitude. Since the S2 dSEP latency was a continuous parameter and the data was normally distributed, linear regression analysis was done with independent parameters of age, height, and BMI, and the outcome is shown in Table 9.

Table 9: Linear regression analysis results for the S2dSEP latency

Hypothesis	Regression weights	Beta Coefficient	R^2	F	p-value	t-value	Hypotheses Supported
H_1	Height →Latency	0.354	0.125	5.427	0.025		Yes
H_1	Age →S2Latency	0.141	0.020	0.774	0.384		No
H_1	BMI →S2Latency	-0.212	0.045	1.793	0.188		No
H_1	Height + Age →S2Latency	A:0.049 H: 0.117	0.181	4.083	0.025	A:1.588 H:2.695	Yes

H_1	Height + BMI →S2Latency		0.137	2.941	0.065		No

The ANOVA test results in Table 8 showed a significant p-value of 0.025 ($p<0.05$) for the height parameter, suggesting it significantly influences the latency. The R^2 = 0.125 shows that the model explains 12.5% of the variance in latency with the given height. Similarly, the influence of age and BMI on the S2 cortical latency was assessed, which did not show any significant impact. However, the combination of height and age showed an 18.1% variance in the S2 dSEP latency. Linear regression analysis showed the equation for the S2 latency as 15.9+ (0.049) *(Age)+ (0.117) *(Height). A similar linear regression analysis was done on S2 dSEP amplitude for independent parameters, which did not show any significant effect, as shown in Table 10.

Table 10: Linear regression analysis results for the S2dSEP amplitude

Regression model	Regression weights	Beta Coefficient	R^2	F	p-value	Hypotheses Supported
H_1	Age →S2 amplitude	0.118	0.041	0.255	0.619	No
H_1	Height →S2 amplitude	-0.146	0.021	0.391	0.540	No
H_1	BMI →S2 amplitude	0.130	0.017	0.311	0.584	No
H_1	Age and Height →S2 amplitude	0.88 -Age 0.124 -BMI	0.028	0.249	0.782	No

2.13 Sacral S3 dSEP data analysis

S3 dSEPs were recorded on twenty healthy volunteers. Cortical latencies and amplitudes were measured after grand averaging two runs, each with 200 averages. Linear regression analysis was done using SPSS software on the S3 dSEP data to understand the influence of independent parameters on the S3 dSEP latency and amplitude.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis were calculated using the SPSS software to assess the normality of the S3 dSEP data, and the outcome was shown in Table 11. Significant values in Kolmogorov-Smirnov and Shapiro-Wilk tests were more than 0.05, suggesting that the data was normally distributed.

Table 11: Different statistical tests showed the S3 dSEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.190	>0.05	Suggests normal distribution
Shapiro-Wilk	0.200	>0.05	Suggests normal distribution
Skewness	-0.324	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	- 0.455	(-1.96 <z<1.96)	Suggests normal distribution

S3 dSEP latency histogram, Q-Q plot and the box plot shows the data is normally distributed as shown in Figures 15a -15c.

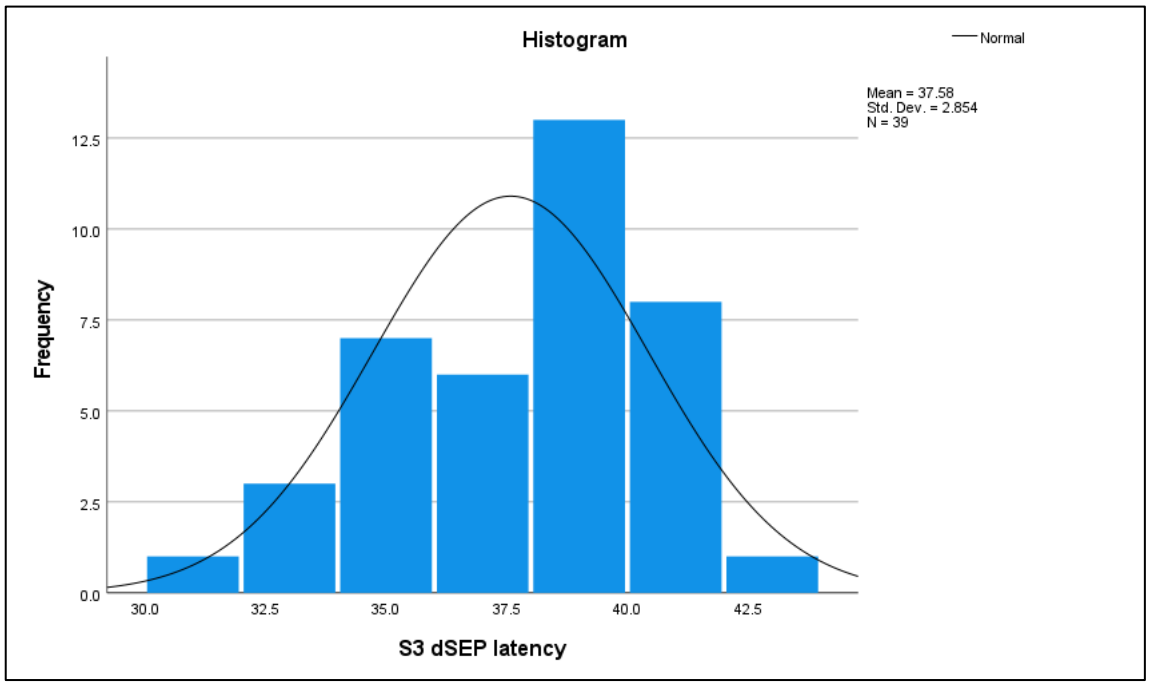


Figure 15a: S3 dSEP latency shows a normal distribution with no significant positive or negative skewness. Kurtosis for the distribution was -0.455 (-1.96 <z<1.96).

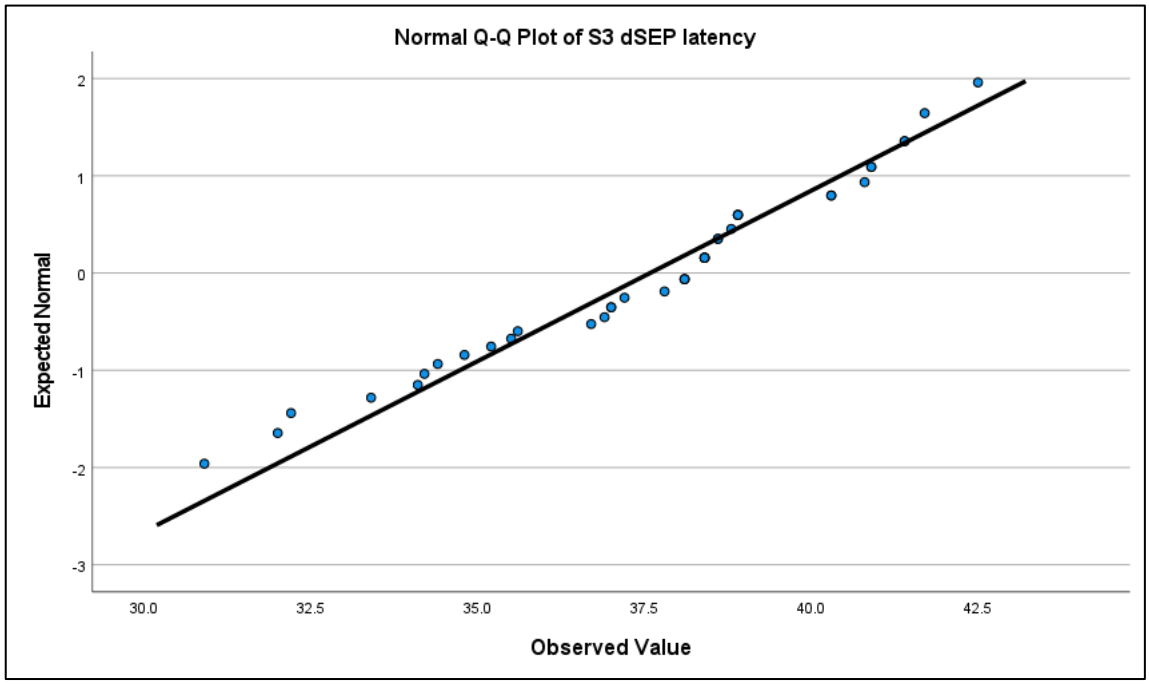


Figure 15b: S3 dSEP latency Q-Q plot shows good adherence to the central line, suggesting a normal distribution.

The box plot did not show any outliers (Figure 15c). The whiskers are about the same on both sides, suggesting the S3 latency data is similar to normally distributed data.

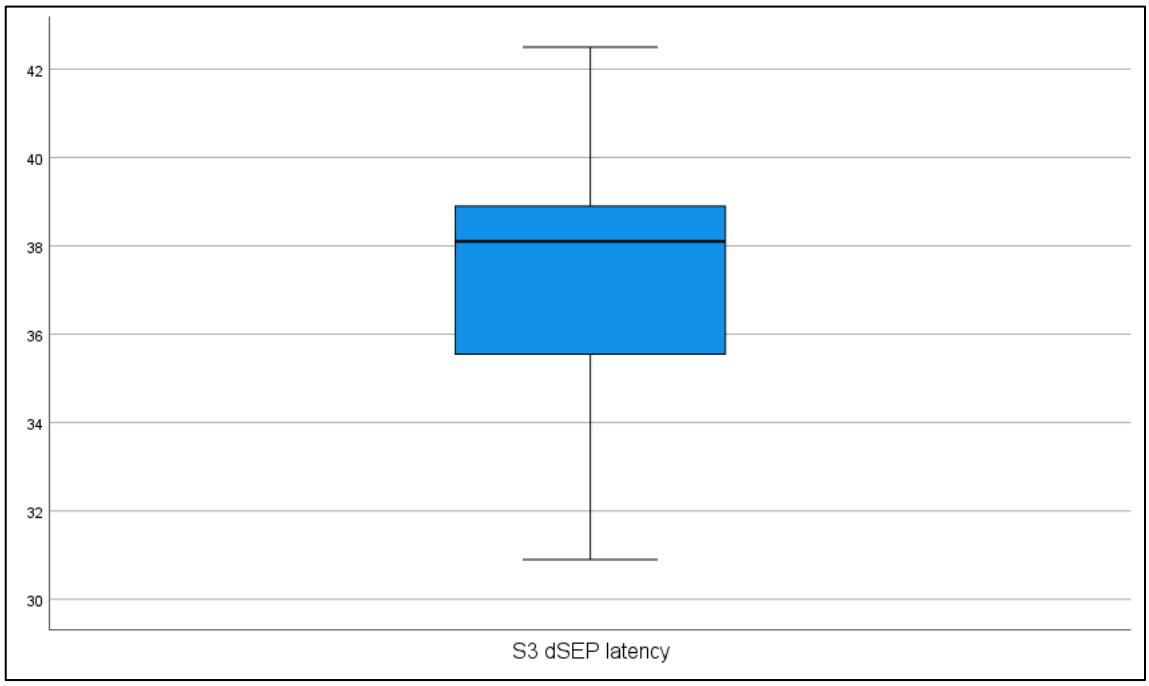


Figure 15c: Box plot for S3 dSEP latency shows a normal distribution with no outliers.

Since the S3 dSEP latency was a continuous parameter and the data was normally distributed, linear regression analysis was done with independent parameters of age, height and BMI and the outcome is shown in Table 12.

Table 12: Linear regression analysis results for the S3 dSEP latency

Hypothesis	Regression weights	Beta Coefficient	R^2	F	p-value	t-value	Hypotheses Supported
H_1	Height →S3 Latency	0.224	0.050	2.006	0.165		Yes
H_1	Age →S3 Latency	0.034	0.01	0.45	0.833		No
H_1	BMI →S3 Latency	-0.216	0.046	1.853	0.182		No
H_1	Height + Age →S3Latency	Height:0.068 Age: 0.18	0.059	1.155	t-value: Height: 1.504 Age: 0.582	A:1.588 H:2.695	No

The ANOVA test results in Table 12 did not show any significant p-values for independent parameters, suggesting that the S3 dSEPs latencies are unaffected by an individual's age, height, or BMI. A similar linear regression analysis was done on S3 dSEP amplitude for independent parameters, which did not show any significant effect, as shown in Table 13.

Table 13: Regression analysis for S3 cortical amplitudes.

Regression model	Regression weights	Beta Coefficient	R^2	F	p-value	Hypotheses Supported
H_1	Age →S3 amplitude	-0.135	0.018	0.703	0.407	No
H_1	Height →S3 amplitude	-0.090	0.008	0.313	0.579	No
H_1	BMI →S3 amplitude	0.002	0.000	0.000	0.991	No

2.14 Sacral S4 dSEP data analysis

S4 dSEPs were recorded on twenty healthy volunteers. Cortical latencies and amplitudes were measured after grand averaging two runs, each with 200 averages. Linear regression analysis was done using SPSS software on the S4 dSEP data to understand the influence of independent parameters on the S4 dSEP latency and amplitude.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis were calculated using the SPSS software to assess the normality of the S4 dSEP data, and the outcome was shown in Table 14. Significant values in Kolmogorov-Smirnov and Shapiro-Wilk tests were more than 0.05, suggesting that the data was normally distributed.

Table 14: Different statistical tests showed the S4 dSEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.200	>0.05	Suggests normal distribution
Shapiro-Wilk	0.319	>0.05	Suggests normal distribution
Skewness	-1.03	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	- 0.821	(-1.96 <z<1.96)	Suggests normal distribution

S4 dSEP latency histogram, Q-Q plot and the box plot shows the data is normally distributed as shown in Figures 16a -16c.

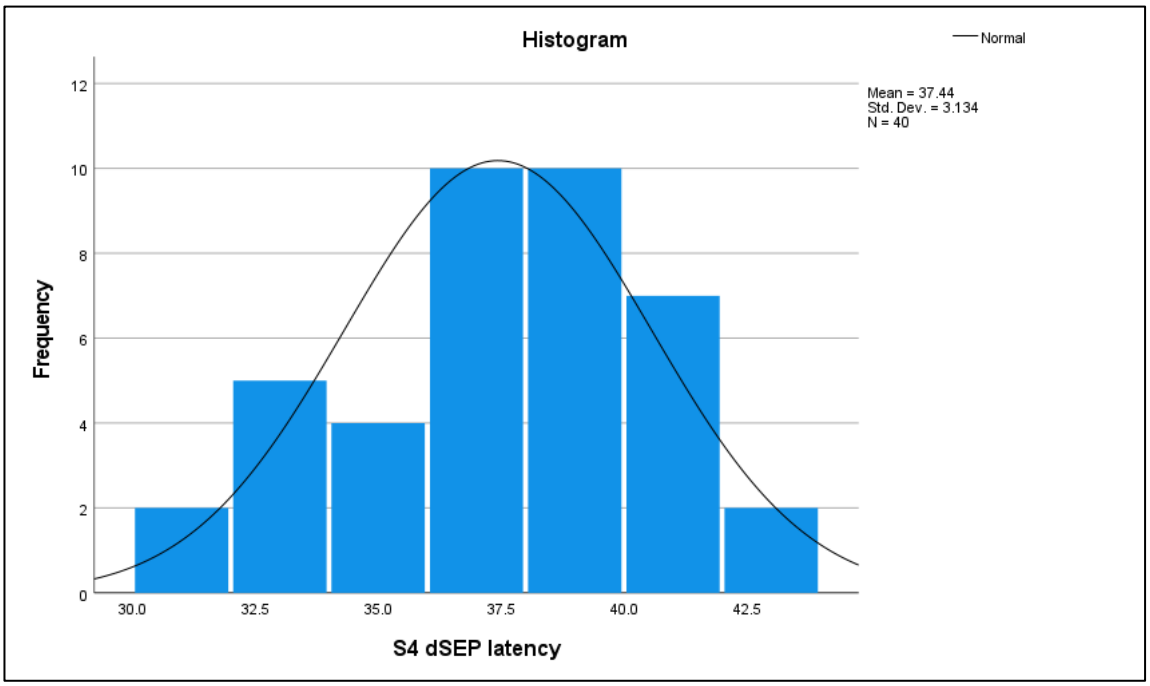


Figure 16a: S4 dSEP latency shows a normal distribution with no significant positive or negative skewness. Kurtosis for the distribution was -0.821 (-1.96 <z<1.96).

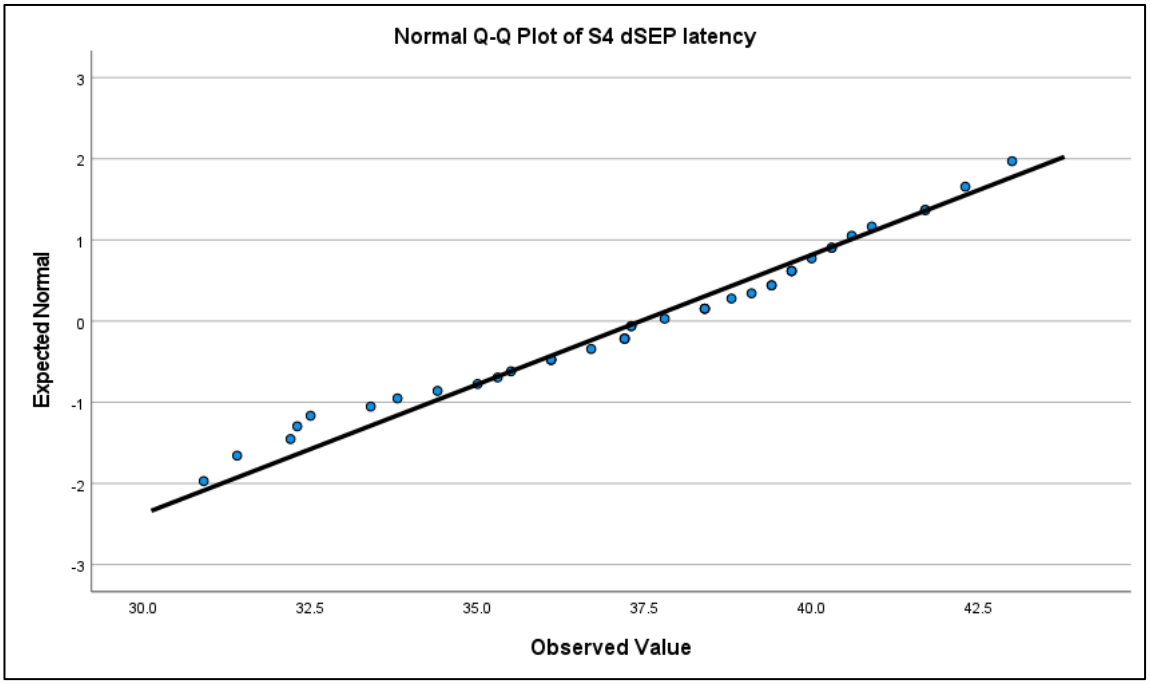


Figure 16b: S4 dSEP latency Q-Q plot shows good adherence to the central line, suggesting a normal distribution.

The box plot did not show any outliers (Figure 16c). The median line is approximately in the middle of the box, and the whiskers are about the same on both sides, suggesting the S4 latency data is similar to normally distributed data.

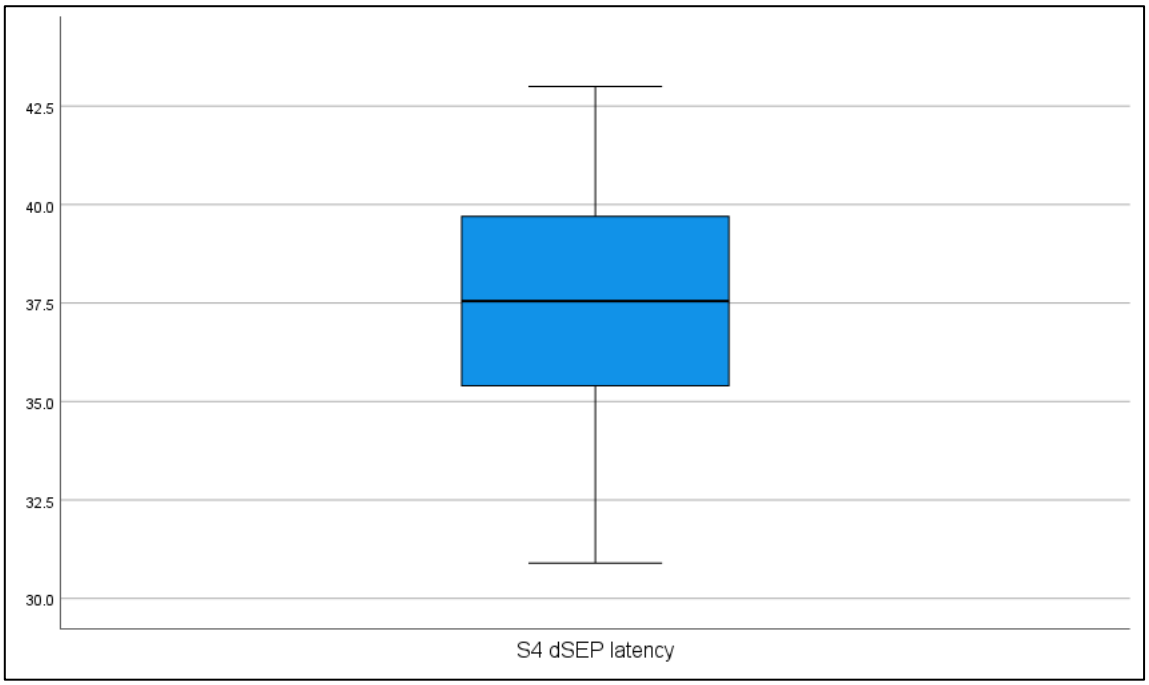


Figure 16c: Box plot for S4 dSEP latency shows a normal distribution with a median line approximately in the middle of the box.

Since the S4 dSEP latency was a continuous parameter and the data was normally distributed, linear regression analysis was done with independent parameters of age, height and BMI and the outcome was shown in Table 15

Table 15: Linear regression analysis results for the S4dSEP latency

Hypothesis	Regression weights	Beta Coefficient	R^2	F	p-value	t-value	Hypotheses Supported
H_1	Height →S4 Latency	0.222	0.049	1.972	0.168		No
H_1	Age →S4 Latency	-0.068	0.005	0.178	0.676		No
H_1	BMI →S4 Latency	-0.366	0.134	5.864	0.02		Yes
H_1	Age + BMI →S4Latency	Age: -0.368 BMI: 0.013	0.134	2.859	0.070		No
H_1	Height + BMI →S4Latency	Height: -0.328 BMI: 0.123	0.147	3.196	0.052		No

The alpha value for the age and height regression analysis did not show any significant value. However, for the BMI, the p-value was 0.02, which was statistically significant, indicating that the BMI can play a significant role in shaping S4 cortical latency. $R^2 = 0.134$ shows that the model explains 13.4% of the variance in the S4 latency as S4 cortical latency = 42.2 + (-0.187) *BMI. A similar linear regression analysis was done on S4 dSEP amplitude for independent parameters, which did not show any significant effect, as shown in Table 16. The findings in Table 16 suggest independent variables do not have any predictive value for the S4 dermatomal amplitudes.

Table 16: Regression analysis for S4 dermatomal amplitudes

Regression model	Regression weights	Beta Coefficient	R^2	F	p-value	Hypotheses Supported
H_1	Age →S4 amplitude	-0.063	0.004	0.152	0.699	No
H_1	Height →S4 amplitude	0.013	0.000	0.006	0.938	No
H_1	BMI →S4 amplitude	-0.013	0.000	0.006	0.936	No

2.15 Normality test for Pudendal SEP

Studies have shown a significant cortical latency difference between the male and female populations (Haldeman et al., 1982; Pelliccioni et al., 2014). In addition, most volunteers (70%) in Study 1 are female. Hence, normality test and regression analyses were done on the female group data. Pudendal PSEPs were recorded on 14 healthy volunteers. Cortical latencies and amplitudes were measured after grand averaging two runs, each with 200 averages. Linear regression analysis was done on the PSEP data using SPSS software to understand the influence of independent parameters on the PSEP latency and amplitude.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis were calculated using the SPSS software to assess the normality of the PSEP data, and the outcome was shown in Table 17. Significant values in Kolmogorov-Smirnov and Shapiro-Wilk tests were more than 0.05, suggesting that the data was normally distributed.

Table 17: Different statistical tests showed the PSEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.055	>0.05	Suggests normal distribution
Shapiro-Wilk	0.145	>0.05	Suggests normal distribution
Skewness	-0.535	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	- 0.582	(-1.96 <z<1.96)	Suggests normal distribution

Female pudendal SEP latency histogram, Q-Q plot and box plot show the data is normally distributed, as shown in Figures 17a -17c.

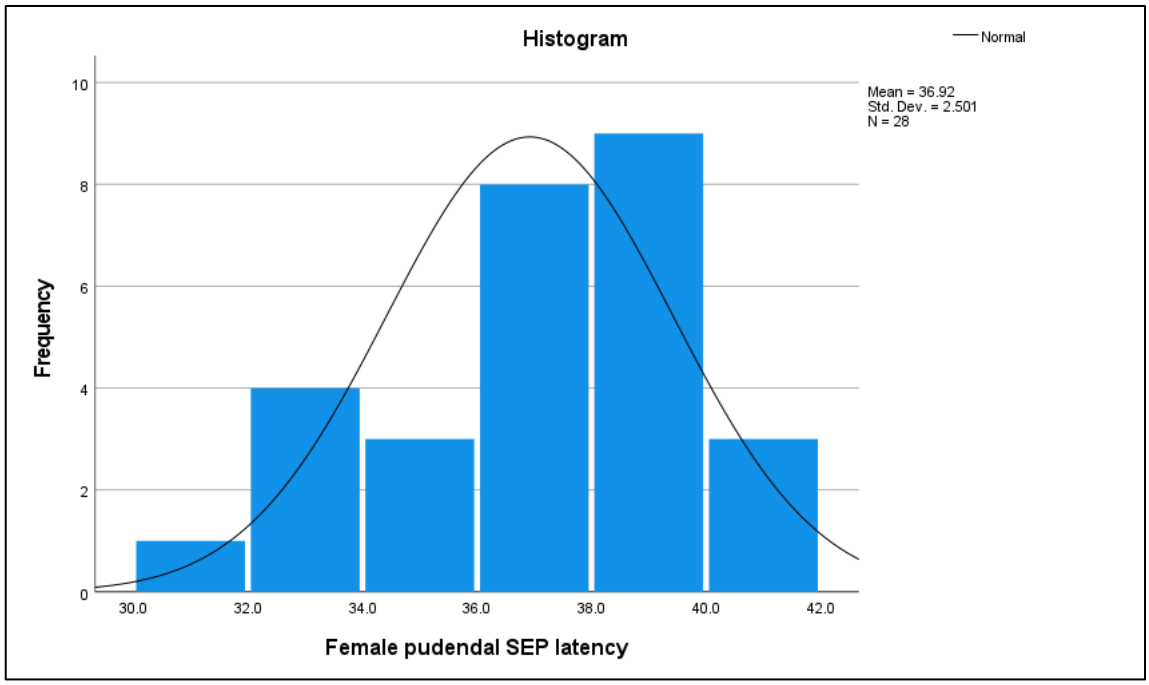


Figure 17a: PSEP latency shows a normal distribution with no significant positive or negative skewness. Kurtosis for the distribution was -0.582 (-1.96 <z<1.96).

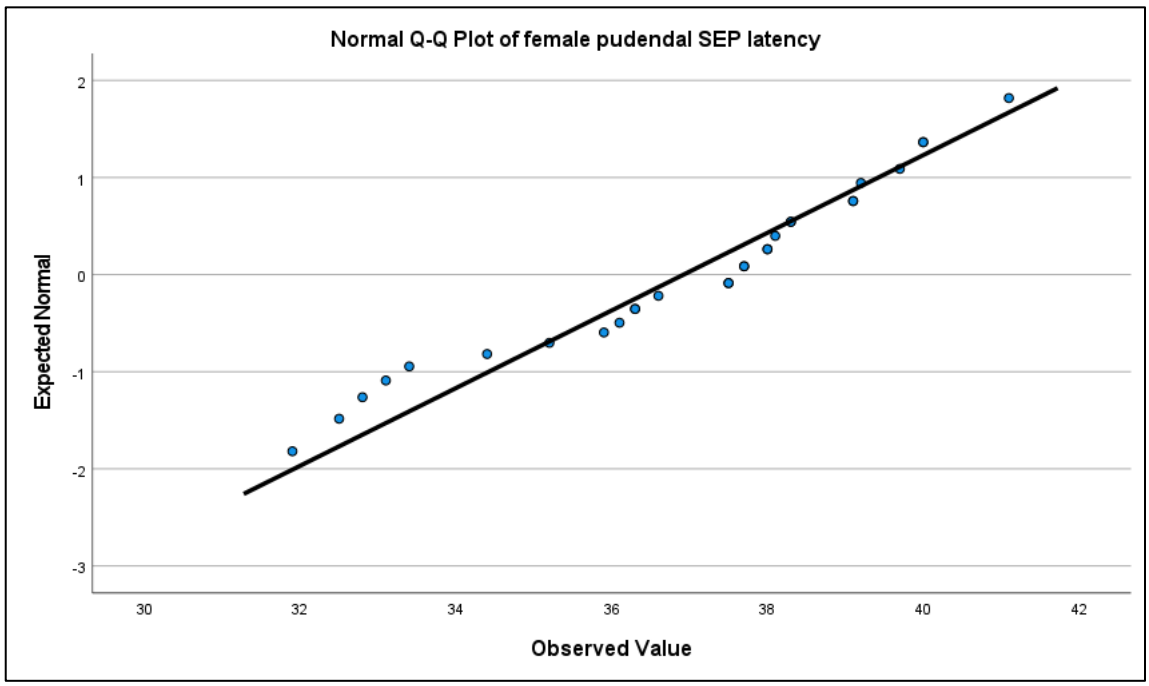


Figure 17b: PSEP latency Q-Q plot shows good adherence to the central line, suggesting a normal distribution.

The box plot did not show any outliers (Figure 17c). The whiskers are about the same on both sides, suggesting the PSEP latency data is similar to normally distributed data.

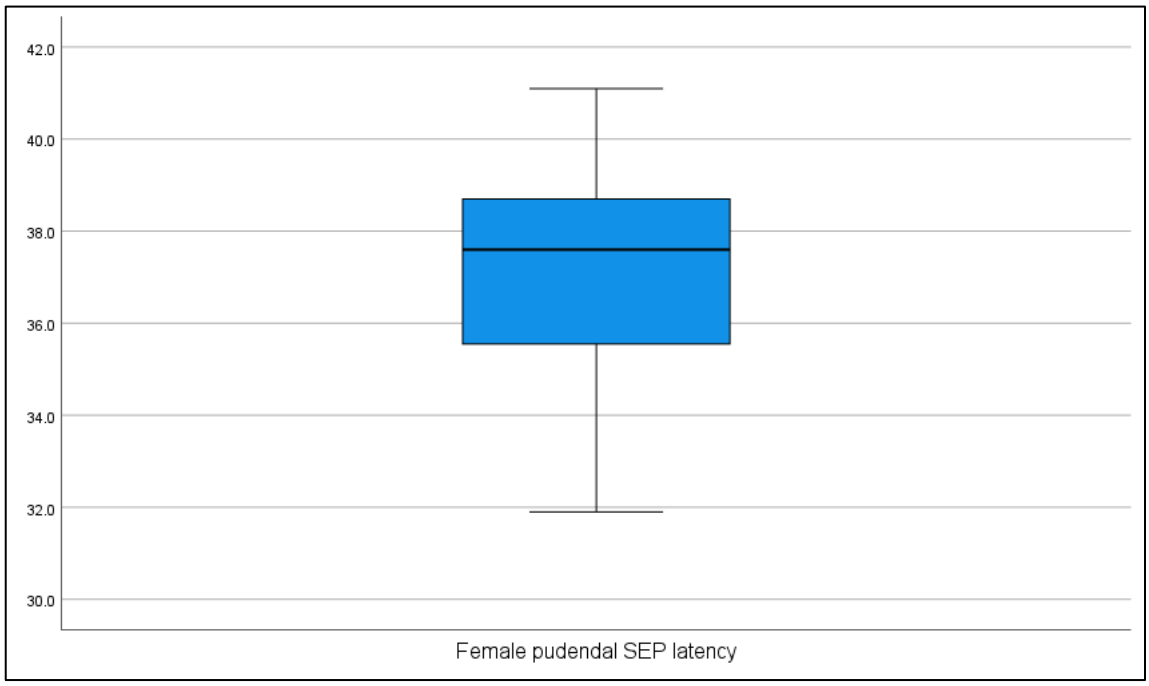


Figure 17c: Box plot for PSEP latency shows a normal distribution with no outliers.

Since the PSEP latency was a continuous parameter and the data was normally distributed, linear regression analysis was done with independent parameters of age, height, and BMI, and the outcome is shown in Table 18.

Table 18: Linear regression analysis results for the PSEP latency

Regression model	Regression weights	Beta Coefficient	R^2	F	p-value	Hypotheses Supported
H_1	Height →Pudendal SEP latency	0.054	0.003	0.075	0.786	No
H_1	Age→ Pudendal SEP latency	0.052	0.003	0.071	0.792	No
H_1	BMI→ Pudendal SEP latency	-0.349	0.122	3.598	0.069	No
H_1	Age→ Pudendal amplitude	0.251	0.063	1.750	0.197	No

H_1	Height →Pudendal amplitude	0.181	0.033	0.879	0.357	No
H_1	BMI→ Pudendal amplitude	0.074	0.005	0.143	0.708	No

The ANOVA test results in Table 15 did not show any significant p-values for independent parameters, suggesting that the PSEP latencies are unaffected by an individual's age, height, or BMI. A similar linear regression analysis was done on PSEP amplitude for independent parameters, which did not show any significant effect, as shown in Table 15.

2.15.1 Comparison of the Pudendal SEP with the published data.

Five published studies were selected to facilitate the t-test for the PSEP, and their sample size, mean latencies and SD are shown in Table 19.

Table 19: Published data for the PSEPs in healthy female subjects.

Authors	N	Latency	SD
(Geraldo A. Cavalcanti and Giuliano, 2007)	11	35.7	2.4
(Pelliccioni et al., 2014)	44	36.4	3.2
(Opsomer et al., 1986)	10	39.9	1.63
(Vodusek, 1996)	12	40.2	2.2
(Haldeman et al., 1982)	7	39.8	1.3
Published mean		*38.4*	*2.1*
Current study	*13*	*36.9*	*2.5*

The current study showed a mean latency of 36.9 ms, 1.5 ms less than the average mean latency of 38.4 ms. One sample t-test was used to assess the statistical significance of the observed mean latency difference of 1.5 ms.

2.15.2 One Sample t-Test for Pudendal SEP

One Sample t-test assesses whether the current study's calculated Pudendal cortical latency mean is statistically different from the published mean value. From the Pudendal SEP study characteristics, it is clear that the Pudendal SEP latencies are continuous, and the participants in this study are randomly selected. The data collected showed that they follow a normal distribution. In addition, the same criteria were used while selecting participants and recording Pudendal SEPs; thereby, homogeneity was maintained across the study sample and the published values.

Null hypothesis (H0): No difference exists between the current posterior Pudendal SEP latency and the established normative values.
Alternative hypothesis (H1): A statistically significant difference exists between the Pudendal SEP latencies produced in the current research and the established normative values.

Table 20: t-test results with and without outliers for PSEP latency

One-sample t-test	N	t-value	Significance (p)		Outcome
			One-sided	Two-sided	
Including outliers	40	4.738	0.482	0.964	Null hypothesis accepted

The one-sample t-test showed p-values more than 0.05 for one-sided and two-sided tests, indicating no statistically significant difference exists between the published normative values and the Pudendal SEP values in study 1, as shown in Table 20.

2.16 Comparative study of all evoked potentials

Tibial SEP, S2, S3 and S4 dSEPs and pudendal SEPs were recorded with the same technical stands. A single operator performed all studies under the same recording settings. Since only 14 mean pudendal SEP values are available, a comparative study was done comparing pudendal SEP with the other evoked potential studies on the same 14 subjects, and the results are shown in Table 21a and Figure 18.

Table 21a: Comparative study of Pudendal SEP (n=14) vs S2, S3 and S4 (n=14)

Parameters	Tibial SEP (n= 14)±SD	S2 SEP (n =14) ±SD	S3 SEP (n =14) ±SD	S4 SEP (n =14) ±SD	Pudendal SEP (n =14) ±SD
Latency	42.6 ±4.3	37±3.2	37.3±3.2	37.5±3.1	36.9±2.5
Amplitude	2.1±0.6	1.11±0.57	1.11±0.56	1.13±0.59	1.7±1.2
Threshold	10.5±2.3	9±2	10±2.5	9.3±2.5	7.5±1.5

Table 26a shows the pudendal SEP latency is comparable with the rest of S2, S3 and S4 latencies but significantly shorter than the tibial SEP. A second comparison was made comparing the female Pudendal SEP latencies with the rest of all evoked potentials, including all subjects shown in Table 21b.

Table 21b: Comparative study of Pudendal SEP (N=14) with entire study 1 group (N=20)

Parameters	Tibial SEP (n = 20) ±SD	S2 SEP (n =20) ±SD	S3 SEP (n =20) ±SD	S4 SEP (n =20) ±SD	Pudendal SEP (n =14) ±SD
Latency	42.4±3.6	37.1±3.1	37.4±2.7	37.4±3	36.9±2.5
Amplitude	2.1±0.9	1.1±0.5	1.2±0.7	1±0.5	1.7±1.2
Threshold	11±2	9.8±3.3	10.7±3.1	9.7±2.2	7.5±1.5

The second comparative study shows the pudendal SEP latencies are comparable with the S2, S3 and S4 dSEPs even after including the entire group. These findings suggest female PSEP latencies can be compared with dSEPs of any gender group but should not be compared with the tibial SEP.

A third comparison was made that includes male and female pudendal latencies with the entire study 1 group, and the results are shown in Table 21c. The findings in Table 26c showed a significant increase in the PSEP latency, which was significantly higher than the rest of the dSEPs. These findings suggest male PSEP latencies are significantly prolonged compared to the female group, and hence, male and female PSEPs should be reported separately.

Table 21c: Comparison of Pudendal SEP (N=20) with the entire study 1 group (N=20)

Parameters	Tibial SEP (n = 20) ±SD	S2 SEP (n =20) ±SD	S3 SEP (n =20) ±SD	S4 SEP (n =20) ±SD	Pudendal SEP (n =20) ±SD
Latency	42.4±3.6	37.1±3.1	37.4±2.7	37.4±3	39.6±2.6
Amplitude	2.1±0.9	1.1±0.5	1.2±0.7	1±0.5	2.4±1.5
Threshold	11±2	9.8±3.3	10.7±3.1	9.7±2.2	7.1±1.5

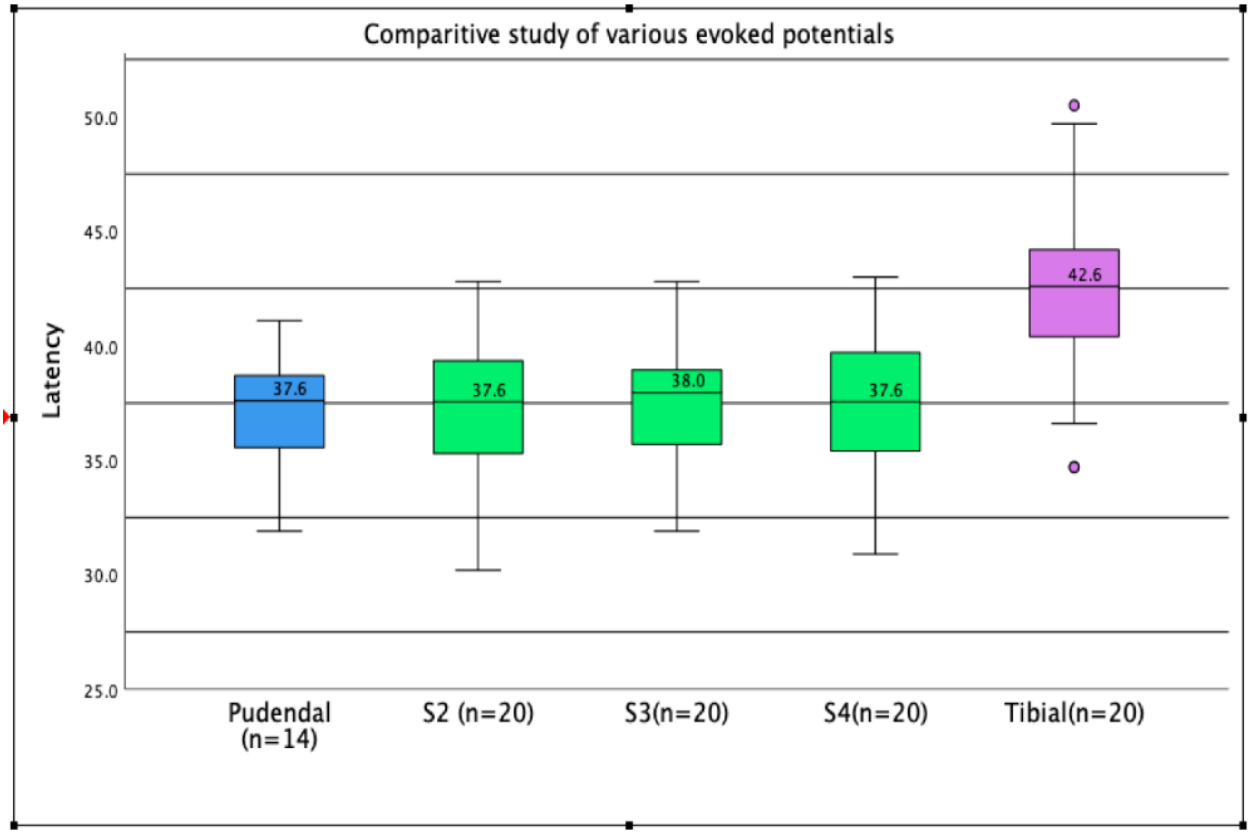


Figure 18: The S2, S3 and S4 dSEPs, PSEP and TSEPs are normally distributed and the mean latencies of S2, S3 and S4 dSEP latencies are comparable with the female PSEP latency.

2.17 Discussion

This chapter has demonstrated evidence for S2, S3 and S4 dSEPs in healthy subjects. In addition, the study also compared various sacral dSEP parameters with the conventional tibial and pudendal SEPs, which helped to assess the relevance of dSEPs in the clinical context. This is the first study to evaluate sacral dSEPs in healthy subjects and comprehensively analyse the impact of independent parameters such as height, age and BMI on their latency and amplitude characteristics. The current study also addressed the common source of errors while acquiring the normative data, such as electrode size, stimulating site, and operator variability.

The utility of dSEPs has been identified in spinal stenosis (Dikmen and Oge, 2013). Normative data for dSEPs was available for L3, L4, L5 and S1 dermatomes (Essa, Al-Hashimi and Nema, 2018), but it was confined to one side and compared with the affected side. Slimp (1992) compared dSEP responses from C4 to S1 dermatomes with the conventional

tibial SEP responses. Katifi and Sedgwick (1986) recorded L5 dSEP responses with needle stimulation and found an 8.6 ms latency prolongation compared to the traditional tibial SEP latency. A comparative study was available between tibial and pudendal SEPs in the patient group (Delodovici and Fowler, 1995).

In routine clinical practice, tibial SEPs are recorded by stimulating the tibial nerve at the medial malleolus with a hand-held stimulator. Conventional hand-held stimulators contain point-like anodes and cathodes with a diameter of 7 to 10 mm and are usually separated by a fixed distance of 25 to 30 mm. When placed near the medial malleolus, these stimulators stimulate the entire tibial nerve trunk, causing a rhythmic foot twitch during stimulations. The fast-conducting group Ia muscle afferents and group II cutaneous afferents are also stimulated at the supramaximal stimulation, producing the shortest latency.

During the tibial SEP recording, the examiner needs to hold or strap the stimulator at the ankle. Due to constant pressure on the tibial nerve, the pain and pressure-sensing fibres also get activated during the test, resulting in discomfort or pain to a patient. In addition, inappropriate holding of the stimulator or orientation towards the bone can stimulate the bone, resulting in more pain in patients. These technical difficulties may not be a considerable issue in an ideal recording condition. Still, in routine clinical practice, many patients would not tolerate supramaximal stimulations at their medial malleolus. It is not uncommon in clinical practice to see patients referred for a tibial SEP also suffer from other medical conditions such as fibromyalgia, arthritis, poor tolerance to pain and swelling at their ankles, and poorly tolerate the supramaximal stimulations. Submaximal stimulations can partially recruit fast-conducting fibres in the posterior tibial nerve (Preston and Shapiro, 2013), resulting in prolonged cortical latency than standard values, making the interpretation challenging.

dSEP studies can overcome these technical difficulties. Uniform electrode size was used in the tibial, S2 and S3 dSEPs, and a single operator performed all evoked potentials on healthy adults in a routine clinical neurophysiology setting. dSEPs are formed after stimulating cutaneous afferent fibres that are group II myelinated fibres (Hakatifi, 1986; Ulrich et al., 2013). These fibres conduct relatively at a low speed compared to Ia fibres and send afferent signals through the DC-ML pathways similar to SEPs. dSPEs were recorded in all participants, irrespective of their BMI. Studies have shown tibial nerve stimulations with stickers were well tolerated even after continuous stimulation over 30 minutes (Ammi et al.,

2014; Booth et al., 2018; de Seze et al., 2011). Several studies have shown the influence of individual parameters on the tibial SEP latency (Cruccu et al., 2008; H. A. Katifi and E. M. Sedgwick, 1986), and a few studies have shown the influence of multiple parameters on the tibial SEP latency (Katifi and Sedgwick, 1986).

The linear regression analysis showed age as a predictive value of 12.7% on tibial latency. These findings are similar to the observations made by Katifi and Sedgwick (1986), which were 12.4%. In the present dataset, volunteer number 1 in Table 8 showed 34.7 ms tibial latency for a height of 150 cm. In contrast, volunteer 14 showed a 48.4 ms latency for a height of 183 cm for a similar age of 30, exemplifying that height influences tibial latency. Similarly, volunteers 3 and 18 were of the same height of 160 cm but were aged 20 and 75 years, and their tibial SEP latencies were 44.3 and 49.8 ms, respectively, showing that age also significantly affects tibial SEP latency. These results indicate that individual parameters such as age or height alone cannot fully explain the tibial SEP latency changes. The combined parameters model would give better predictive latency values. The current study showed a combination of age and height parameters would explain 19.3% changes in tibial SEP latency.

The current study demonstrated that volunteers' BMI has no detectable impact on tibial latency. The present study did not analyse the influence of gender on the tibial SEP latency due to fewer male volunteers, but Miura, Sonoo and Shimizu (2003) found no impact of gender on tibial latency. Tibial SEP amplitude findings in the current study are congruent with the knowledge that tibial SEP amplitudes would not be affected by independent parameters (Chu, 1986; Rappaport, Portillo and Leonard, 1992; Ziegler et al., 1993).

S2, S3 and S4 dSEP latency data were normally distributed, with no outliers. These findings suggest that the extreme height variations do not affect the latency in dSEPs. Since S2, S3 and S4 dermatomal stimulating electrodes are less distal to sacral spinal roots, one can hypothesise that the dSEPs latency's primary component is the time the signal travels in the central nervous system. If confirmed, dSEPs are a suitable test for diagnosing multiple sclerosis (MS), where the lower spinal cord is involved in the presentation. The linear regression analysis of S2 dermatomal data showed that height has a 12.5 % effect on the latency. When the age parameter was also included, the combined impact on the S2 dSEP latency increased to 18%, suggesting age and height both should be considered while performing S2 dSEPs. In S3 dermatomes, as the stimulating electrodes were much closer to

the spinal roots, the effect of height and age on the S3 dSEP latency vanished, suggesting no independent parameter has any detrimental impact on the S3 latency. The S4 dSEP study showed that only the BMI had a 13.4% effect on the S4 cortical latency. Since the S2 and S3 fibres send afferent signals through the posterior femoral cutaneous nerve and some S4 sensory fibres send through an inferior rectal nerve (Dupont et al., 2019), different pathways exist between S4 and the rest of the sacral S2 and S3 sensory roots. The influence of high BMI on the S4 latency could be due to the increased length of the inferior rectal nerve with increased BMI (Maldonado et al., 2015).

The linear regression analysis of the pudendal SEP latency did not correlate positively with individual age, height, or BMI parameters. These findings were consistent with the published data (Cavalcanti et al., 2007). The mild influence of BMI on the S4 dSEP latency was not seen in the pudendal SEP, which could be due to the different paths of the dorsal clitoral nerve and inferior rectal nerve before they join at the pudendal canal (Kinter and Newton, 2023).

A comparative study between dSEPs, pudendal SEPs and the tibial SEP studies showed that the dSEP latencies were resistant to an individual's height, and they are always comparable with the female pudendal SEP latency, as shown in Figure 18. This observation helps us to formulate cut-off values for dSEPs.

Many discrepancies were noted in the literature regarding either establishing the cut-off value for the pudendal SEP or comparing the pudendal SEP with the tibial SEP. Haldeman et al. (1982) observed no latency difference between the pudendal and tibial SEP latencies in a sample size of 7. Opsomer et al. (1986) found no pudendal latency difference between genders for a sample size of 10, suggesting the mean latency for the pudendal SEP was 35.1ms for both genders. Pelliccioni et al. (2014) showed a significant pudendal latency difference between genders in a sample size 40. Based on Opsomer et al. (1986) study and Haldeman et al. (1982) study, Delodovici and Fowler (1995) suggested the abnormal criterion for the pudendal SEP as either prolongation of the pudendal SEP more than 47.8 ms or the latency difference between the tibial SEP and the pudendal SEP more than 7 ms. Since 2SD covers 95% of the population in all neurophysiology observations (Preston and Shapiro, 2012), normative values for S2, S3 and S4 dSEPs are provided in Table 22 based on mean + 2SD. The current study showed a significant pudendal SEP latency difference

between genders (Female: 36.9 ms, male: 42.3 ms) similar to the observation made by Pelliccioni et al. (2014).

Table 22: Normative values for tibial SEP, pudendal SEP and S2, S3 and S4 dSEPs.

Tibial SEP	Mean	SD	Cut-off value (Mean +2SD)
Latency (ms)	42.5	3.7	22.9+ (0.105) *(Age)+ (0.094)*(Height) +7.4
Latency side-to-side difference	0.9	0.6	2.1
Amplitude side-to-side difference in percentage (%)	22	13	48 %
S2 dermatome Parameters			
Latency (ms)	37.3	2.95	15.9+ (0.049) *(Age)+ (0.117) *(Height)+5.9
Latency side-to-side difference	1.6	1	3.6
Amplitude side-to-side difference in percentage (%)	23.4	15.8	55%
S3 dermatome Parameters			
Latency (ms)	37.4	2.7	42.8
Latency side-to-side difference	1.3	1.1	3.5
Amplitude side-to-side difference in percentage (%)	20	15	50%
S4 dermatome Parameters			
Latency (ms)	37.4	3	42+(-0.187) *BMI
Latency side-to-side difference	1.6	0.8	3.2

Amplitude side-to-side difference in percentage (%)	22	10	42%
Pudendal SEP			
Latency (ms)	36.9	2.5	41.9
Latency side-to-side difference	1.3	0.8	2.9
Amplitude side-to-side difference in percentage (%)	17.3	14.2	45.7 %

Table 27: Normative values for Tibial SEP, S2, S3 and S4 dSEPs and Pudendal SEPs.

2.17.1 Strengths

The present study had several advantages over many other pelvic neurophysiology studies. Uniform technical standards were used across the tibial SEP, S2, S3, and S4 dSEPs, and the pudendal SEPs. This enabled us to compare dSEPs with the rest of EPs. Even though it was a pilot study, care was taken while taking sample size, stimulus strength, stimulus threshold and volunteer selection. This helped to compare the data collected with previously published values. In this chapter, normative values were generated in a routine clinical neurophysiology step-up by a single operator in healthy adults, and hence, the cut-off values can be used in clinical interpretations in the future.

2.17.2 Limitations

A minimal but statistically acceptable sample size was taken to generate normal values owing to the difficulty of recruiting a large number of healthy volunteers. However, the calculated sample size was 23, close to the current sample size. A single operator generated data in a single neurophysiology department, and hence, inter-operator variability is unknown. Normative values for the pudendal SEP are applicable to female subjects only, as there were very few male subjects (n=6) in the study. Future work should focus on generating pudendal SEP values in male subjects along with dSEPs. All values in the current

study were generated in the adult population, and hence, normative values in Study 1 cannot be extrapolated to the paediatric population.

2.17.3 Future work

In the current study, S2, S3 and S4 dermatomal evoked potentials were elicited in all healthy subjects, and dSEP latencies and inter-peak latency differences were calculated. The influence of independent parameters on the latencies and amplitudes was analysed. However, S2, S3 and S4 dSEPs should be investigated in known pathologies to assess their sensitivity and specificities. Study 1 showed the dSEPs are ideal for comparison with pudendal SEPs. However, pudendal SEPs are to be done in the patient's genital area. Many patients may not appreciate testing in their intimate areas when they do not have symptoms in that region. Hence, developing an alternative strategy, such as L2 /L3 dSEPs, is helpful. Since L2/L3 dermatomes are anatomically the same distance from the spine as S2/S3 dermatomes, they stand as promising alternative tools to pudendal SEPs.

2.18 Conclusions for Chapter 2

This chapter dealt with a significant clinical need for developing S2, S3 and S4 dSEPs as a tool for neurophysiological evaluation of sacral root function. If dSEP values were validated in known neurological conditions, they would be ideal for investigating sacral root pathologies. Sacral dSEPs are easily recordable on existing neurophysiological equipment, requiring little further training. The dSEPs are reproducible and well-tolerated by all healthy subjects. Sacral dSEP latencies are not variable with height or age but are mildly affected by high BMI. Hence, they are excellent tools for comparison and follow-up studies. Tibial SEP recorded with surface sticker electrodes showed a mild latency prolongation compared to the conventional tibial SEP latencies. However, this mild latency asymmetry is statistically significant. Hence, while performing dSEPs, recording tibial SEP with the same dSEP recording settings would be helpful. Sacral dSEPs are comparable with female pudendal SEP latencies to tibial SEPs, and hence, recording pudendal SEPs wherever possible would be ideal in comparative studies. There is a need to develop alternative dSEPs, such as L2/L3, to substitute pudendal SEPs in comparative studies with sacral dSEPs.

In conclusion, S2, S3, and S4 sacral dermatomal evoked potential studies that are easily elicitable in healthy subjects. dSEPs are reliable, reproducible, well-tolerated and valuable tools in evaluating S2, S3 and S4 sacral dorsal root functions.

Chapter 3: Evaluation of sacral dSEPs in spinal cord injury patients

3.1 Introduction

Spinal cord injury (SCI) is one of the most frequent referral conditions to orthopaedics and neurology departments, accounting for 19 new confirmed cases of SCI per million population in the UK (Patek and Stewart, 2023). The estimated economic impact of SCI on a single patient over a life period was approximately 1.12 million pounds in the UK (McDaid et al., 2019). The costs incurred in diagnosing the true SCI, the costs due to misdiagnosed SCI, and the costs due to medicolegal cases are equally enormous (Ma, Chan and Carruthers, 2014). SCI is commonly seen in two distinctive groups. One with the young group, predominantly male, is affected by high-impact injuries such as road traffic accidents. In contrast, low-impact injuries are seen in elderly patients due to falls and fragile bony conditions. Even a small amount of low-impact injury can be sufficient to cause significant damage to the spinal cord. Most SCI occurs in the cervical region, accounting for more than 50% due to the relatively fixed thoracic and highly mobile cranio-cervical regions. Since it is an urgent condition, the NICE guideline suggests that an assessment by a consultant and imaging should be done within 4 hours of the onset of symptoms (Mony and Gilbert, 2022). Even though MRI is an excellent tool to assess ongoing compression in the spinal cord, all patients' symptoms may not be explained by imaging technique alone. In addition, it is often challenging to differentiate old lesions in the MRI from the current onset of symptoms. Neurophysiology tools complement neuroradiological findings to understand the new onset of symptoms. Assessment of anterior roots can be done with certainty from lower limb NCS studies and EMG studies (Preston and Shapiro, 2012). Dorsal column lesions from L5 or above can be assessed with lower and upper limb SEPs (Restuccia et al., 2000a).

Since all spinal cord injuries are not similar, SCI onset, progression, and recovery depend on the nature of the injury. In addition, the recovery of axons in the peripheral nerve differs from axonal recovery in the central nervous system. Schwan cells support peripheral nerve recovery, whereas the Oligodendrocytes support the central nervous system (Huebner and Strittmatter, 2009). Axonal regeneration in the central nervous system is extremely slow.

Peripheral nerves regenerate at a rate of 1 inch per month. Neurons in the central nervous system regenerate more slowly than peripheral nerves (Huebner and Strittmatter, 2009). Peripheral muscles can survive only up to 2 to 3 years, and without proper motor signals from the brain, the muscle fibres will be replaced entirely by fibrotic tissues, and chances of functional recovery of peripheral muscles would be impossible after three years (Menorca, Fussell and Elfar, 2013).

3.2 Types of Spinal Cord Injuries

Conus medullaris syndrome (CMS) constitutes 2 to 3 % of all SCIs. The spinal cord ends approximately at T12/L1 vertebral bodies in the adult population. Conus can be affected due to a variety of reasons, such as herniated disc at T12 or L1, mechanical trauma at the disc level, breaking of the bone fragmentation due to spondylolysis or slip disc in T12/L1 in spondylolisthesis condition. Formation of tumours or vascular changes can also affect the conus acutely or progressively, resulting in severe pain and symmetric numbness in the perineum (Howard and Barrow, 2017). Conus lesions present with both upper and lower motor signs (Brouwers et al., 2017). Bowel and bladder signs are always present in CMS. Urinary retention is the red flag in conus medullaris syndrome, which should be addressed immediately (Rider and Marra, 2023). Conventional neurophysiology studies would not be helpful in the suspected CMS lesions. S2, S3 and S4 dermatomal evoked potentials should provide valuable information in this condition as they send afferent signals through this region. Also, the Bulbocavernosus reflex (BCR) helps differentiate upper motor neuron lesions from lower motor neuron lesions. In conjunction with the peripheral conduction study, BCR would be helpful in differentiating CMS lesions from upper motor neuron lesions. Cauda Equina Syndrome (CES) may not strictly come under spinal cord injury as the spinal cord ends at T12/L1. However, spinal roots travel in the spinal column until sacral and coccygeal foramen. Disc herniation is unlikely to cause full cauda equina compression as there is enough space for at least some spinal nerve to move away from the protruding disc (Kuris et al., 2021). Nevertheless, CES is the most common referral condition in SCI cases. Partial or complete CES is often seen due to lumbar or lumbosacral disc bulging. Epidural injection, epidural haematoma, and tumours in that area can cause CES (Kuris et al., 2021). Due to partial compression of nerves, patients experience asymmetric sensory and motor symptoms. If pain is present, it will be asymmetric, and bladder complaints are the most

common symptom (Nas et al., 2015). Tibial SEPs and dSEP studies should be helpful to either establish or differentiate CES lesions from supraconal lesions.

Brown-Sequard syndrome is a type of SCI that can be treated therapeutically or surgically, depending on the underlying cause. Since one side of the spinal level is affected in this condition, patients will experience loss of sensation and muscle power on the ipsilateral side and loss of temperature and pain on the contralateral side (Shams and Arain, 2023). Traumatic injuries and non-traumatic conditions such as tumours, infectious diseases, and spinal ischemia can cause this condition (Shams and Arain, 2023). Neurophysiology tests, including CHEPs, have a role in diagnosing the condition.

Posterior cord syndrome is also one of the SCI types affecting the posterior column of the spinal cord, resulting in loss of sensation, proprioception and vibration sensation (McKinley, Hills and Sima, 2021). Muscle strength would not be affected in this condition due to the sparing of the anterior horn cells. Still, patients experience ataxia due to disturbance of the muscle spindle's afferent pathways' function. This syndrome is often seen in demyelinating conditions (Valsasina et al., 2022), but traumatic injuries can also cause this condition.

Delayed post-traumatic spinal cord syndromes are a group of conditions where patients develop neurological deficits several months to years after the initial insult to the spinal cord (Dubey et al., 2018; Gupta et al., 2011). Syringomyelia, microcystic myelomalacia and arachnoiditis are some of the few conditions in this category where fluid-filled cysts form gradually in the middle of the spinal cord (Yuan, Guan and Jian, 2022). These cysts often lie silent, but at times, they get bigger and compress surrounding neuronal structures, resulting in motor and sensory deficits and bowel and bladder dysfunctions. Dermatomal evoked potentials, in conjunction with other neurophysiology studies, will diagnose the affected nerve roots and the level of lesions.

Spinal shock is a medical emergency that briefly affects the temporary loss of complete motor, sensory and autonomic function (Hall, 1840). The duration of spinal shock depends on the injury’s severity and the location in the spinal cord. Clinically, often, it is challenging to differentiate loss of motor and autonomic reflexes due to spinal shock from actual damage to the upper motor neurons (Smith and Jeffery, 2005). Neurophysiological tests such as BCR and SEPs are excellent tools to differentiate spinal shock from structural damage to spinal roots (Ji et al., 2013).

3.3 Complications from the Spinal Cord Injury

3.3.1 Bladder dysfunction

Bladder dysfunction is one of the prime complications of SCI (Benevento and Sipski, 2002; Tate et al., 2020). Uninterrupted communication between the brain and the bladder is essential for normal bladder function. Any interruption in the spinal neuronal pathways due to SCI has devasting and often irreversible consequences (Samson and Cardenas, 2007). Given bladder function, the SCI can divided into two groups, i.e sacral and supra-sacral spinal cord lesions. Supra-sacral spinal cord lesions cause detrusor sphincter dyssynergia (DSD), where the external urethral sphincter does not relax when the detrusor muscle wants to contract. If DSD is not adequately managed, it can cause frequent urinary tract infections and hydronephrosis (Taweel and Seyam, 2015). Sacral spinal cord lesions cause flaccid bladder where the bladder continues to fill but fails to empty fully due to impairment of sensory and motor signalling pathways to the bladder. If the flaccid bladder is not adequately managed, it can lead to overflow incontinence, bladder pain, UTIs and chronic urinary retention. Neurophysiological testing is crucial in understanding the level and severity of spinal cord injuries (Abdel-Azim, Sullivan and Yalla, 1991; Clarke and Thomas, 1981).

3.3.2 Bowel dysfunction

Spinal cord dysfunction causes substantial socio-economic and physical health burdens due to bowel dysfunction in patients. Over two-thirds of all SCI patients develop faecal incontinence, severe chronic constipation, or both (Glickman and Kamm, 1996). The smooth flow of liquids and faeces is possible due to the synchronised flow of autonomic, somatic sensory signals, and motor signals from the spinal cord to the large and small intestines. In healthy adults, the puborectalis muscle, supplied by the pudendal nerve, wraps around the rectum, resulting in an acute angle between the rectum and anus when it contracts. The Puborectalis muscle is always in tonic mode due to the continuous firing of neurons in the sacral spinal cord. Supra-sacral spinal cord lesion results in a hyper-reflexic bowel (Glickman and Kamm, 1996) due to uncoordinated external anal sphincter contraction, resulting in severe constipation in SCI patients. SCI at the sacral level affects somatic and parasympathetic input to the rectum and the muscles surrounding it. Loss of

parasympathetic input to the rectum causes slow transit of faeces. With increased time in the rectum, the faeces become dryer and rounded, causing constipation. On the other hand, loss of somatic input to the external anal sphincter muscles causes incontinence. Hence, sacral spinal cord injury is the most devasting condition, causing constipation and bowel and bladder incontinence (Han, Kim and Kwon, 1998).

3.3.3 Sexual dysfunction

A coordinated sympathetic, parasympathetic and somatosensory input to the genitalia is essential for normal sexual function. Sympathetic innervation provides initial erection through the hypogastric plexus. For the erection to be sustained, somatosensory input to the sacral spinal cord and parasympathetic reflexes through the pudendal nerve to the genitalia are needed (Benevento and Sipski, 2002).

For normal ejaculation function, well-coordinated parasympathetic reflexes, rhythmic contraction of bulbocavernosus muscles and sympathetic outflow are needed.

Patients with complete SCI above the thoracic level lead to loss of erection, whereas sacral spinal cord damage leads to loss of ability to ejaculate (Monga, Bernie and Rajasekaran, 1999). Sexual dysfunction differs in male and female patients with SCI (Benevento and Sipski, 2002). Hence, neurophysiological assessment would be beneficial to understand the level and severity of SCI before planning for any therapy.

3.4 Identifying the research question for study 2

Spinal cord injury is a significant neurological condition continuously affecting millions worldwide annually. Considerable improvement has been achieved through introducing seat belts, imposing speed limits, changing workplace practices and improving recreational activities and care for older adults (Biering-Sørensen, Pedersen and Clausen, 1990). Advancements in the diagnosis of SCI and early intervention also significantly improved the survival rate in SCI patients (Snyder, Verla and Ropper, 2020). Neurophysiology testing plays a significant role in identifying SCI and assessing the severity and prognosis in these patients (Dimitrijevic, Hsu and McKay, 1992). Tibial and median nerve SEPs will provide information about the DML pathways' function above the sacral roots level, whereas a motor-evoked potential study from the tibial nerve will assess central motor pathways from the brain up to the lumbosacral level. Since current neurophysiology testing tools are inadequate in

assessing S2, S3 and S4 sacral root functions, I hypothesise that the dSEP in the sacral roots should help identify sacral-level spinal cord injuries and the tibial SEPs in conjunction with sacral dSEPs should identify supra-sacral spinal cord injuries.

I intend to test this hypothesis by recruiting patients with SCI who continue to have neurological deficits affecting their sensation in the perineum and bladder, bowel, or sexual functions.

3.4.1 Study 2 aims

The specific aims for study 2 are to:

1. Evaluate the role of S2, S3 and S4 dermatomal evoked potential studies in SCI patients.
2. Evaluate the sensitivity and specificity of dermatomal evoked potentials.
3. Evaluate the reproducibility of dermatomal evoked potentials.

3.4.2 Study 2 study objectives

Specific objectives for study 2 are to

1. Generate dermatomal evoked potentials.
2. Generate tibial SEP and pudendal SEPs.
3. Investigate the relation between S2, S3 and S4 dSEPs.
4. Investigate the relationship between dSEPs and other studies.
5. Repeat dSEPs after 24 hours to assess the reproducibility of dSEPs.

3.5 Materials and Methods

American Clinical Neurophysiology Society guidelines (Acns, 2006) were followed throughout this chapter to place scalp electrodes, perform studies, and identify waveforms. The equipment and electrodes used were similar to those in Chapter 2.

3.6 Recruitment

The sample size is twenty, following the same rationale used in Chapter 2. I aimed to recruit 20 volunteers with a history of SCI that resulted in loss of sensation over the back of their legs, buttocks, or genital area. The cause and the level of SCI should be known before joining the study. Twenty-five volunteers responded to the advertisement and participated in this chapter. The HSST trainee clinical scientist (Mr Anjaneya Malladi) contacted them and

assessed their suitability before giving mutually suitable appointments for the study. All volunteers were given a patient information leaflet (Appendix 7.6) approximately a week in advance and given sufficient time to clarify their doubts. All volunteers gave written consent to access their relevant medical records to know more about their SCI. On the day of the assessment, the clinical scientist received the volunteers, explained the procedure, and obtained informed consent. Those volunteers who provided written consent were clinically examined by Prof. Jalesh Panicker, Dr Sara Simeoni, or Dr Sarah Wright, consultant neurologists, for their suitability to participate in the study.

3.7 Demographic Data

Background data was collected regarding date of birth, sex, height in centimeters and weight in kilograms. Between February 2022 and August 2023, 25 volunteers expressed their willingness to participate. Three volunteers did not complain of numbness, and two did not have access to their medical records. Hence, all five were excluded from the study, as shown in Figure 19. After recruitment started, it became clear that most volunteers were not interested in attending the follow-up study after 24 hours. Only three volunteers out of 20 attended the follow-up study. The research protocol was amended not to make the follow-up study mandatory. The volunteer's disability and transportation difficulties were two main reasons that influenced the participant's decision not to participate in the follow-up study. Seven out of 20 volunteers were male (35%) and 13 (65%) were female. The participants' mean height, age, and BMI are given in Table 23.

Table 23: Mean height, age and BMI of participants.

	Male (n=6) ±SD	Female (n=14) ±SD
Mean height (cm)	170 (157-188) ±10.7	164(157-175) ±4.9
Mean age (years)	49 (30-65) ±11.6	44 (27-59) ±11
Mean BMI (kg/m^2)	25 (20.3-36.5) ±4.3	28(20.3-44.5) ±8.1

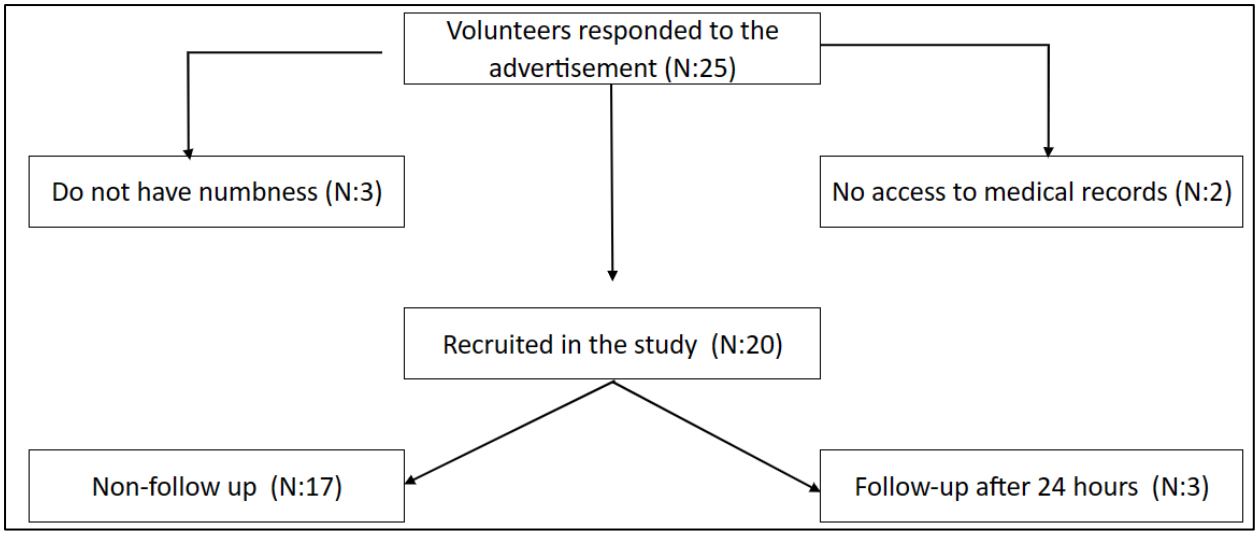


Figure 19: Details of volunteers who responded to the advertisement and the actual number of volunteers recruited in the study.

3.8 Inclusion and exclusion criteria

All volunteers were considered for the test if they met the inclusion criteria and did not have any of the exclusion criteria, Table 24

Table 24: Inclusion and exclusion criteria for the study 2 participants

Inclusion Criteria	Exclusion Criteria
Age over 18 years	Language barrier requiring an interpreter.
Written informed consent	Incapacity to consent
Received Information leaflet one week prior	Having diabetes
History of loss of sensation in at least one area, which includes the back of thighs, buttocks, or genital area due to known spinal cord injury.	Had a history of peripheral neuropathy.
Details of the SCI, including the nature of the injury and the level of the injury, should be known.	Known SCI but currently does not have any sensory complaints.
	Known SCI with transient symptoms
	Known SCI with loss of sensation, but details of the SCI or the level of injury are unknown.
	Known lumbar or sacral surgeries before SCI

3.9 Performing examination studies

Neurologic examination: All volunteers underwent neurological examinations following the protocol of the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI). Accordingly, pinprick examination was quantified as 0,1,2 for absent, impaired, and normal (Kirshblum and Eren, 2020). Light touch classification in the genital area was referred to the right index finger's score. The percentage of loss of sensation was not considered as per ISNCSCI guidelines.

MRI of spinal cord lesion: MRI scans were performed prior to the study. The level of SCI was taken from the MRI report or clinical or surgical notes but not from the image itself. The latest report was analysed to see if the volunteer had multiple MRI scans.

Bladder, bowel and sexual dysfunction: No volunteer was required to undergo urodynamics or gastrointestinal physiology studies to know their bladder and bowel dysfunction. Information on the bladder, bowel and sexual dysfunctions was noted from relevant clinical notes. Volunteers were not requested to complete any questionnaire to reveal their sexual function.

Neurophysiology testing: All eligible volunteers underwent clinical and neurophysiology testing similar to Chapter 2. In the repeat study after 24 hours, only the clinical examination part was omitted, but the rest of the procedure was similar to that in Chapter 2. Tibial SEP, S2, S3 and S4 dSEPs and pudendal SEPs were recorded in all volunteers. All evoked potentials were rated absent if there was no visually detectable P1/N2 peak. All evoked potential studies were reported using normative values generated in Chapter 2.

3.10 Statistical Analysis

All patients in Study 2 had abnormal MRI changes. However, MRI reports did not often explicitly reveal the side of the lesion. Pinprick examination and Von Frey test provided the percentage of loss of sensation but did not provide any unequivocal side of the lesion. Due to the nature of SCI injury, variable pathophysiologic abnormalities, and variable onset of symptoms, bilateral lower limb data was compared with Chapter 2 normative values.

Sensitivity is defined as the ability of a test to identify an individual as diseased, and specificity is defined as the ability of a test to identify an individual as disease-free (Parikh et al., 2008). Sensitivity was defined here as the percentage of patients with at least one abnormality in absolute cortical latency, peak latency difference or amplitude asymmetry between two sides. Receiver operating characteristic (ROC) curve analysis was performed on absolute cortical latency, peak latency difference and amplitude asymmetry for each tibial SEP, S2, S3, and S4 dSEPs and pudendal SEPs to assess the diagnostic test power of dermatomal evoked potential studies in comparison with the established studies of tibial SEP and pudendal SEPs. In addition, individual tests were compared with Chapter 2 to assess the validity of the cut-off values proposed in Chapter 2. The sensitivity of individual evoked potential studies was assessed for the present chapter. Three volunteers were assessed 24 hours after the first visit to assess the reproducibility of dSEPs.

IBM Statistics 28.0 software was used in the Receiver operating curve (ROC) analysis. A non-parametric ROC analysis will be helpful to identify optimum sensitivity and specificity of S2, S3 and S4 dSEPs in SCI cases. The same software was used to calculate the Coefficient of Variation and Intraclass Correlation Coefficient in follow-up studies to assess the reproducibility of the dSEPs.

3.11 Results

3.11.1 MRI level abnormalities

Out of twenty volunteers in Study 2, two presented with thoracic-level lesions. The rest had lumbosacral-level lesions. All participants reported sensory deficits on their buttocks, the back of their thighs, or in their perineum. Volunteer 15 had SCI a year ago, whereas volunteers 4 and 6 had SCI over a decade ago. Volunteers 3, 4, and 10 had acute onsets of symptoms after the injury, and the rest had insidious onsets of symptoms. Demographic information of Study 2 participants was given in Table 25.

Table25: List of volunteers with spinal cord / Cauda equine injuries (CES)

Volunteer Number	Sex	Age	Height	BMI	MRI level	Diagnosis
1	Female	59	168	21.3	CES	S2/S3 roots were damaged during cancer surgery
2	Female	48	167	21.5	CES	S1/S2 Cystic lesion
3	Female	47	165	22.1	CES	Sacral roots damage during impact injury
4	Female	29	160	20.3	CES	Pelvic fracture during road traffic accident
5	Female	52	165	24.6	CES	Central disc protrusion
6	Female	51	158	27.2	CES	L5/S1 disc protrusion
7	Female	50	157	36.5	CES	L5/S1 disc protrusion; microdiscectomy
8	Male	65	177	24.8	CES	Sacral tumour
9	Female	40	160	23.4	CES	L5/S1 disc protrusion
10	Male	35	188	25.8	CES	Impact injury to the sacrum
11	Male	54	187	31.7	CES	L5/S1 disc protrusion
12	Male	65	168	24.8	CES	Congenital tethered cord
13	Male	38	177	22.1	Thoracic lesion	T6-T9 thoracic syrinx
14	Female	57	162	37.3	CES	L5/S1 disc protrusion, decompression done
15	Female	33	162	27.4	CES	Excision of intradural tumour
16	Female	48	175	20.9	CES	Disc protrusion
17	Female	27	167	38	CES	Disc protrusion, decompression done
18	Female	28	167	44.5	CES	Spinal detethering was attempted thrice
19	Male	30	177	25.2	Thoracic lesion	Spinal TB, T1-T9 vertebral level meningitis
20	Male	58	187	27.5	CES	L4/5 decompression done

3.11.2 Bladder and bowel abnormalities

The prevalence of bladder and bowel complaints was determined by gathering basic information through volunteers' history and medical records. Eight volunteers (40%) have urinary retention symptoms, and 11 (55%) suffer from urinary urgency. Thirteen volunteers (65%) suffer from bowel-related symptoms. Details of bladder and bowel symptoms are given in Appendix (7.1). A consultant neurologist clinically examined all volunteers for sensory and motor deficits. During the clinical examination, the neurologist examined the quality, nature, and distribution of neuropathic pain. Sexual dysfunction was self-reported by volunteers. The list of all sensory and motor deficits is given in Appendix (7.2).

3.11.3 Comparison of conventional criteria with Study 1 criteria

The conventional criteria, “the pudendal evoked potential was considered abnormal when either absent, prolonged more than 47.8 ms or when its latency exceeded that of tibial evoked potential by more than 7 msec” (M. L. Delodovici and C. J. Fowler, 1995), was applied to the case 7 who presented with CES due to L5/S1 disc protrusion. The participant is a 50-year-old female patient who suffered from L5/S1 disc protrusion, lost bladder sensation and is currently performing intermittent self-catheterisation. A comparison was made between Study 1 cut-off criteria and the conventional criteria to understand their relative merits in identifying lesions in known SCI patients, and the results are shown in Table 30.

Conventional criteria: The test should be considered abnormal if the pudendal SEP latency exceeds 47.8 ms or the pudendal SEP latency is 7 ms more than the tibial SEP latency.

Study 1 criteria: The test should be considered abnormal if the pudendal SEP latency exceeds 41.9 ms or the pudendal SEP latency asymmetry is more than 2.9 ms.

Table 26: Comparison of conventional criteria with Study 1 criteria in case 7

	Latency (ms)	**Conventional criteria**	**Study 1 criteria**
Pudendal SEP	Rt.31.4 Lt.38.6	Normal study	Abnormal study
Tibial SEP	Rt.37.7 Lt.41.6	Normal study	Abnormal study
S2 dSEP	31.3 37.2	n/a	Abnormal study
S3 dSEP	31.1 35.3	n/a	Abnormal study
S4 dSEP	31.9 37.8	n/a	Abnormal study

The comparison in Table 26 showed that the current criteria are inadequate in identifying CES lesions.

Case 12 in Study 2 is a 65-year-old gentleman who underwent detethering surgery twice in the last two decades. He continues to have bladder and bowel symptoms. His bladder symptoms include a high-pressure bladder volume of over 100 cm of water with difficulty voiding. He requires regular self-catheterisation but finds it challenging to introduce the catheter. He has ongoing evacuation difficulty and fragmented stool with recurrent visits to the toilet. He suffers from sexual dysfunction. He had biofeedback and rectal irrigation, which has not helped. His MRI showed a low-lying conus at S2, separated from the lumbar theca by a CSF cleft. There was T1 shortening associated with the conus medullaris and cauda equina filaments at S2-S3, suggesting a residual fatty filum. There was also evidence of shallow broad-based disc protrusion at L2-3 and L3-L4 but no appreciable lumbar foraminal narrowing, as shown in Figure 20.

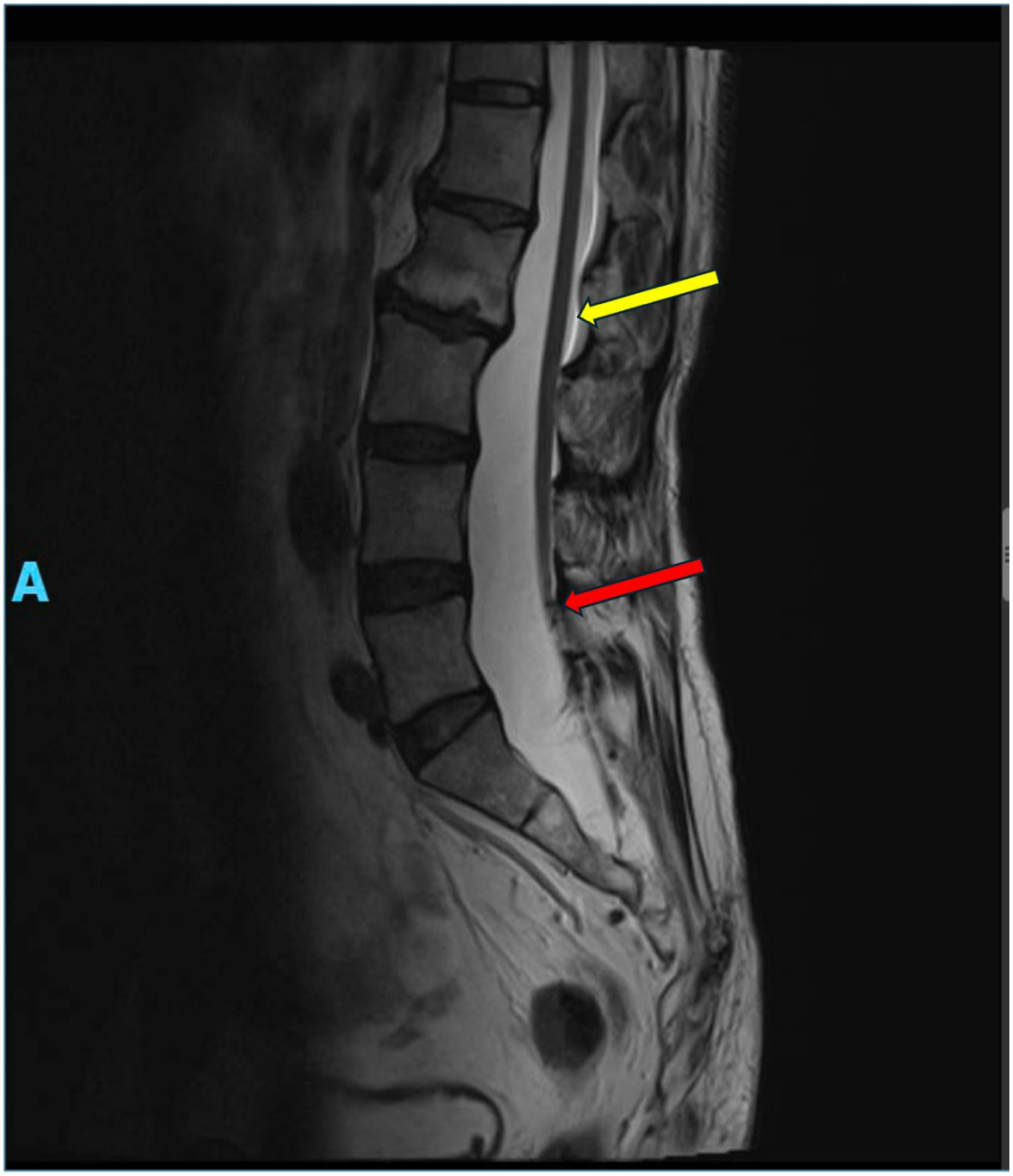


Figure 20: The distal spinal cord is abnormally low, terminating at L4-5 level due to tethering of the cord (Red arrow). In normal adults, it usually terminates at L1-L2 (Yellow arrow). (Image used with consent from the participant).

Nerve conduction studies were normal, including tibial, peroneal, sural, and superficial peroneal nerves. Needle EMG examination was normal. His clinical examination showed normal sensory findings up to L5/S1 dermatomes but reduced sensation in S2-S3 dermatomes bilaterally. His anal tone was reduced, and the bulbocavernosus reflex was absent. His pelvic neurophysiology findings are given in Table 27.

Table 27: Pelvic neurophysiology findings in a detethered cord condition.

Test	Right	Left
Tibial SEP latency (ms)	51.9	50
Tibial SEP amplitude (uv)	1.94	2.46
S2 dSEP latency (ms)	38.8	41.3
S2 dSEP amplitude (mv)	1.09	1.04
S3 dSEP latency (ms)	40.8	Absent
S3 dSEP amplitude (mv)	1.94	Absent
S4 dSEP latency (ms)	Absent	Absent
S4 dSEP amplitude (mv)	Absent	Absent
Pudendal SEP latency (ms)	45.2	
Pudendal amplitude (mv)	0.88	

As per the conventional criteria, case 12 should be considered normal. However, when Study 1 criteria are applied, the study becomes abnormal. dSEP studies suggest the lesson affects left S3 and bilateral S4 sacral roots. These pelvic neurophysiological findings were compatible with his bladder symptoms, such as high bladder tone and voiding dysfunction. These dSEP findings were also concurrent with his bowel symptoms, such as constipation, faecal urgency, and sexual dysfunction (DeLong, Polissar and Neradilek, 2008; Gardner, Gardner and Morley, 2011; Garfin, Rydevik and Brown, 1991; Podnar, Oblak and Vodušek, 2002). The current study showed that dSEPs can identify S3 and S4 sacral root abnormalities not diagnosed by conventional neurophysiology tools.

3.12 Receiver Operating Curve for Latency Abnormalities

ROC analysis was used to assess the power of absolute cortical latency as a diagnostic tool in discriminating known SCI groups from known healthy subjects. A non-parametric ROC was used based on the observations to decide the optimum sensitivity and specificity in the clinical context. ROC curves are widely used in the healthcare sector when determining the sensitivity and specificity of a diagnostic test.

(Nahm, 2022). All cortical latencies are continuous parameters, and the tibial SEP is a widely used diagnostic tool in assessing central demyelination conditions. Hence, assessing tibial SEP with the ROC curve analysis is reasonable. dSEPs follow the same DC-ML pathways as the tibial SEP, and therefore, ROC analysis was also applied to all dSEPs. The ROC curve near the diagonal line represents a 50% chance of recognising the disease and, hence, no discriminating value. In contrast, the curve close to the top and Y-axis represents a high diagnostic yield. The area under the ROC curve (AUC) gives the power for the given diagnostic tool. According to Hosmer (2013), an AUC value near 0.5 is not helpful for a diagnostic test, 0.7 to 0.8 is acceptable, 0.8 to 0.9 is excellent, and more than 0.9 is considered outstanding.

3.12.1 ROC analysis for latency differences for all EPs

ROC curves for the tibial SEP, S2, S3 and S4 dSEPs and pudendal SEP latency differences between sides were analysed, as shown in Figure 21. The AUC values for the tibial and S2 dSEPs were between 0.7 and 0.8, suggesting acceptable for diagnostic use. But, for the S3 and S4 studies, the AUC values were above 0.9, indicating outstanding power for diagnostic use, as shown in Table 28.

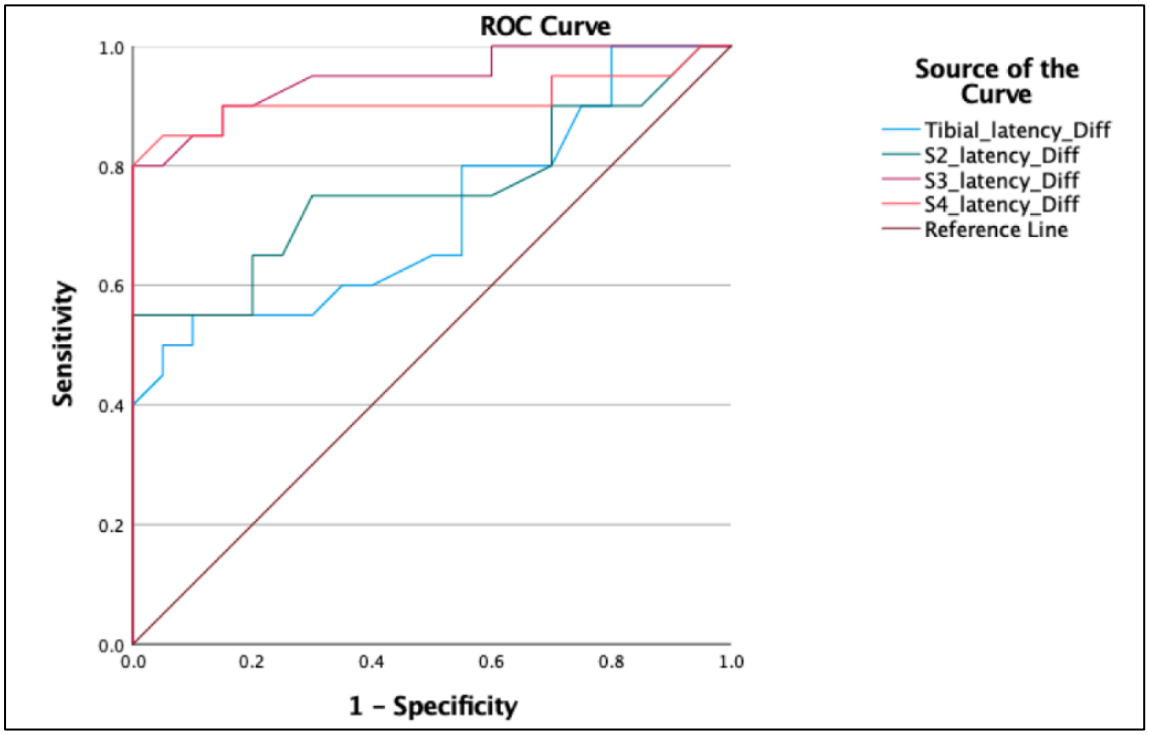


Figure 21: ROC curves for latency differences in tibial and S2, S3 and S4 dSEPs. The latency differences show the outstanding power of S3 and S4 dSEPs for diagnostic use.

Table 28: ROC analysis results for latency differences between the right and left sides.

Test	Sensitivity	Specificity	AUC	p-value
Tibial SEP latency asymmetry	55%	70%	0.717	0.019
S2 dSEP latency asymmetry	75%	70%	0.760	0.005
S3 dSEP latency asymmetry	85%	85%	0.946	0.000
S4 dSEP latency asymmetry	90%	85%	0.910	0.000
Pudendal SEP latency asymmetry	85%	79%	0.871	0.001

3.12.2 ROC analysis for absolute latencies for all EPs

ROC curves for the tibial SEP, S2, S3 and S4 dSEPs and pudendal SEP latencies were analysed, as shown in Figure 22. The AUC values for absolute latencies for the tibial, S3, and S4 were approximately 0.7, suggesting the latency parameter is acceptable for diagnostic use. But, for the S2 and pudendal SEP studies, the AUC values were around 0.6, indicating poor indicators for diagnostic use, as shown in Table 29.

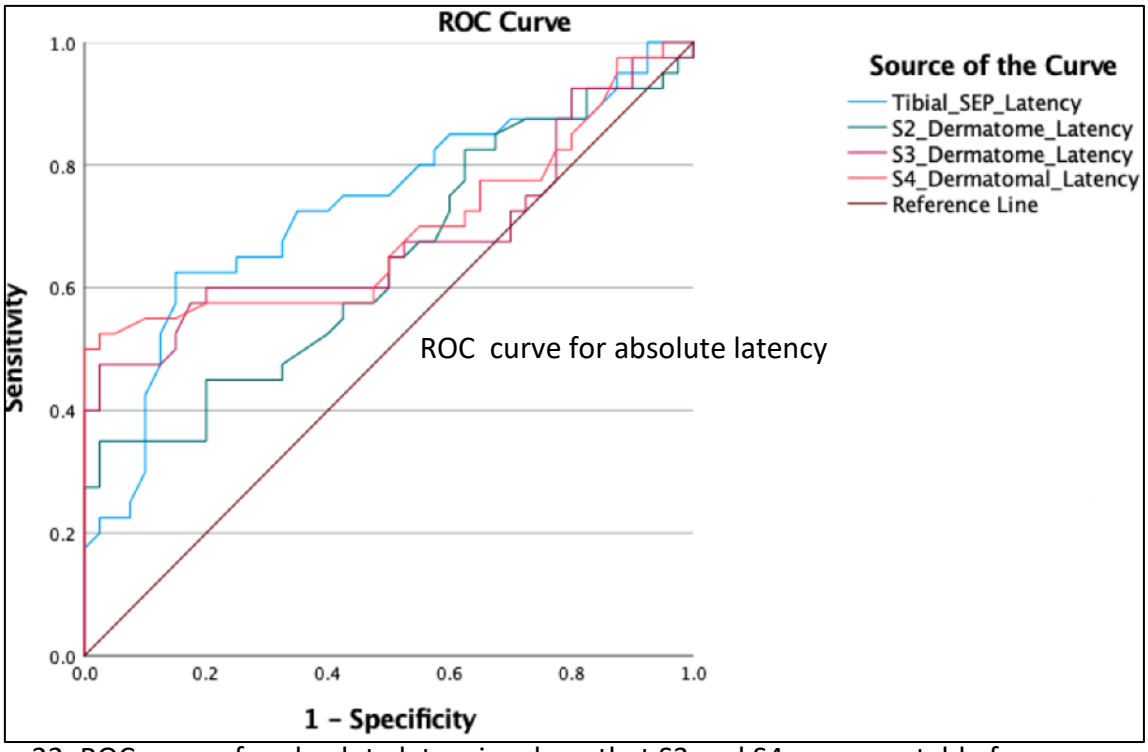


Figure 22: ROC curves for absolute latencies show that S3 and S4 are acceptable for diagnostic use.

Table 29: ROC analysis results for latency as a parameter.

Test	Sensitivity	Specificity	AUC	p-value
Tibial SEP latency	63%	88%	0.729	0.000
S2 dSEP latency	45%	68%	0.641	0.030
S3 dSEP latency	60%	50%	0.680	0.006
S4 dSEP latency	58%	52%	0.694	0.003
Pudendal SEP latency	50%	65%	0.635	0.090

3.12.3 ROC analysis for amplitude difference for all EPs

ROC curves for the tibial SEP, S2, S3 and S4 dSEPs and pudendal SEP amplitude differences were analysed, as shown in Figure 23. The AUC values for the S2, S3, and S4 amplitude asymmetries were shown to have significant AUC values, with S3 as the highest sensitivity and specificity values, as shown in Table 30. The tibial SEP study showed insignificant ACU value, suggesting tibial SEP amplitude differences should not be used.

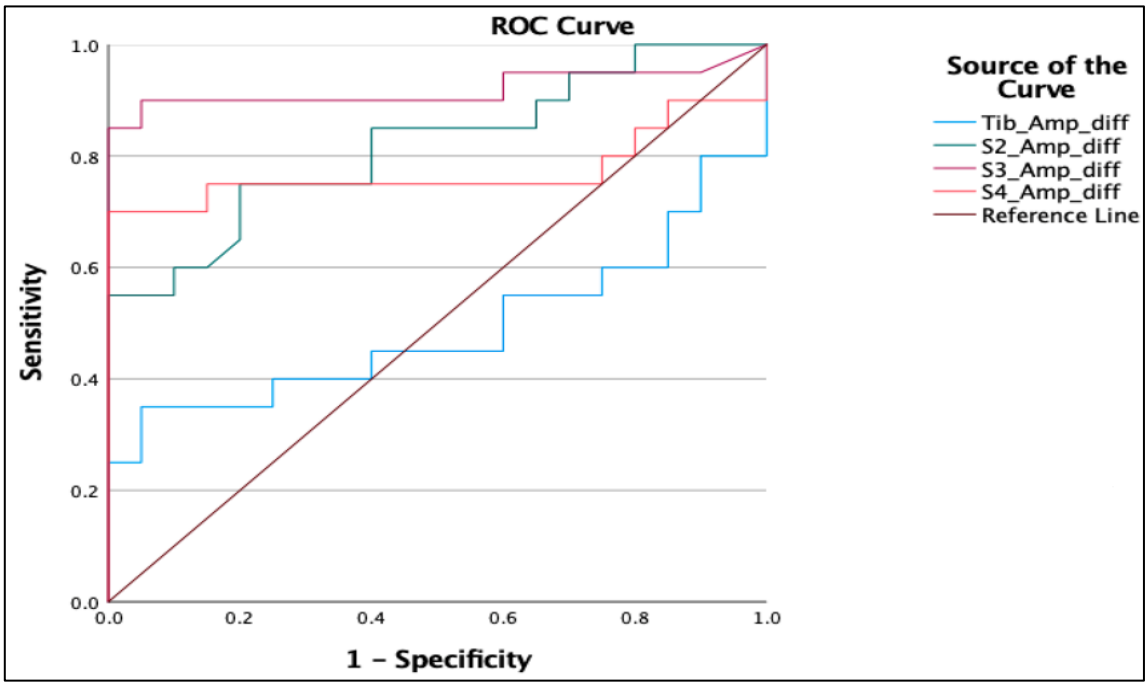


Figure 23: The ROC curve for amplitude difference in the tibial SEP was insignificant for clinical evaluation consistent with the ACNS recommendations. It shows the dSEP amplitude difference is also a good criterion for clinical evaluation.

Table 30: ROC analysis results for amplitude asymmetry between right and left sides.

Test	Sensitivity	Specificity	AUC	p-value
Tibial SEP amplitude asymmetry	40%	60%	0.490	0.914
S2 dSEP amplitude asymmetry	75%	80%	0.819	0.001
S3 dSEP amplitude asymmetry	90%	80%	0.920	0.000
S4 dSEP amplitude asymmetry	75%	80%	0.773	0.003
Pudendal SEP amplitude asymmetry	69%	71%	0.830	0.004

3.12.4 ROC curve for pudendal SEP parameters

Pudendal SEP values were analysed by comparing female pudendal SEP data from this chapter (n=13) with those from chapter 2 (n=14), and the results are shown in Table 31. The AUC value for the pudendal SEP latency asymmetry was 0.5, suggesting it is not acceptable for diagnostic use. The pudendal amplitude asymmetry shows an AUC value of 0.8, suggesting it is a good predictor for diagnostic use in SCI.

Table 31: ROC analysis results for pudendal SEP parameters

Test	Sensitivity	Specificity	AUC	p-value
Pudendal SEP latency asymmetry	40%	60%	0.490	0.001
Pudendal SEP absolute latency	42%	75%	0.635	0.090
Pudendal SEP amplitude asymmetry	69%	71%	0.830	0.004

3.13 Latency differences in Study 1 vs Study 2

Comparative studies were done between the healthy and SCI groups to assess the extent of overlap of latency asymmetry between the right and left sides. This comparison should reveal the sensitivity of the test in assessing unilateral abnormalities. The mean + 2SD of latency asymmetry was shown as a red line. Latency asymmetry comparison between tibial SEPs in Study 1 and Study 2 are shown in Figure 24a. From the comparison, it is clear that the cut-off value for the tibial latency proposed in Study 1 as 2.1 ms would not be sufficient to identify unilateral abnormality as it overlaps with healthy adults. These findings agree with ROC data, where the tibial SEP has 40% sensitivity and 60% specificity.

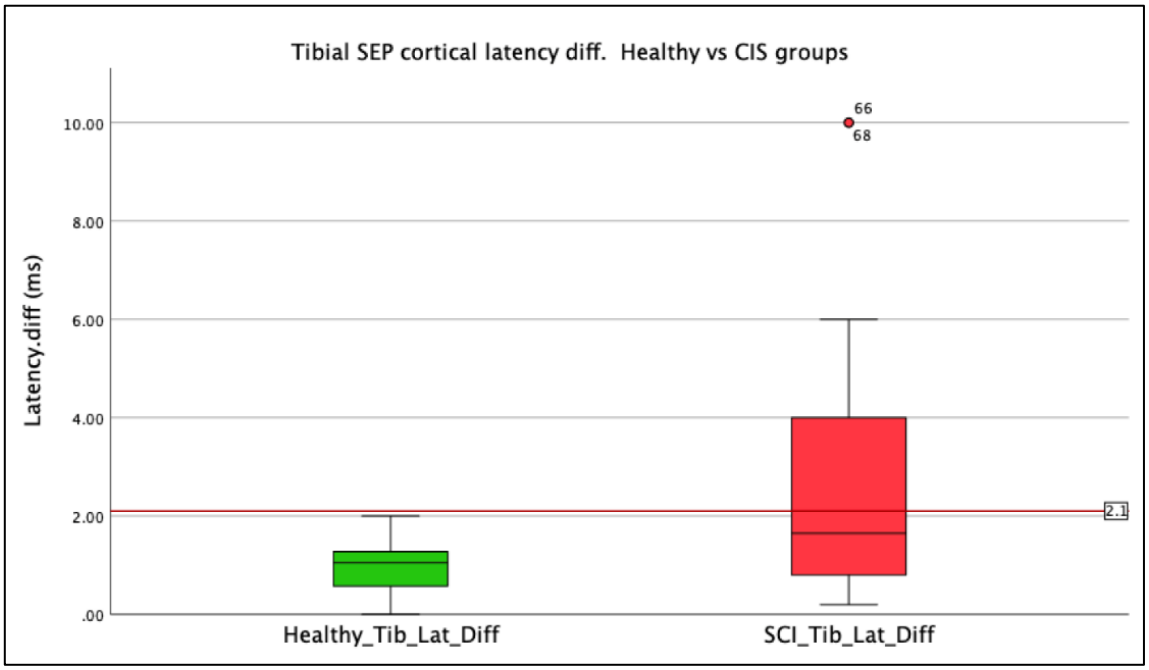


Figure 24a: Tibial SEP latency asymmetries in SCI groups show a significant overlap with the healthy group, suggesting 2SD would not be sufficient to differentiate abnormalities.

A comparative study of S2 dSEP latency differences between Study 1 and 2 shows that the proposed cut-off value of 3.6 would be sufficient to identify unilateral abnormalities even though there was a minimal overlap at 2 ms, as shown in Figure 24b. The sensitivity/specificity for S2 dSEP latency asymmetry was 75% / 70%.

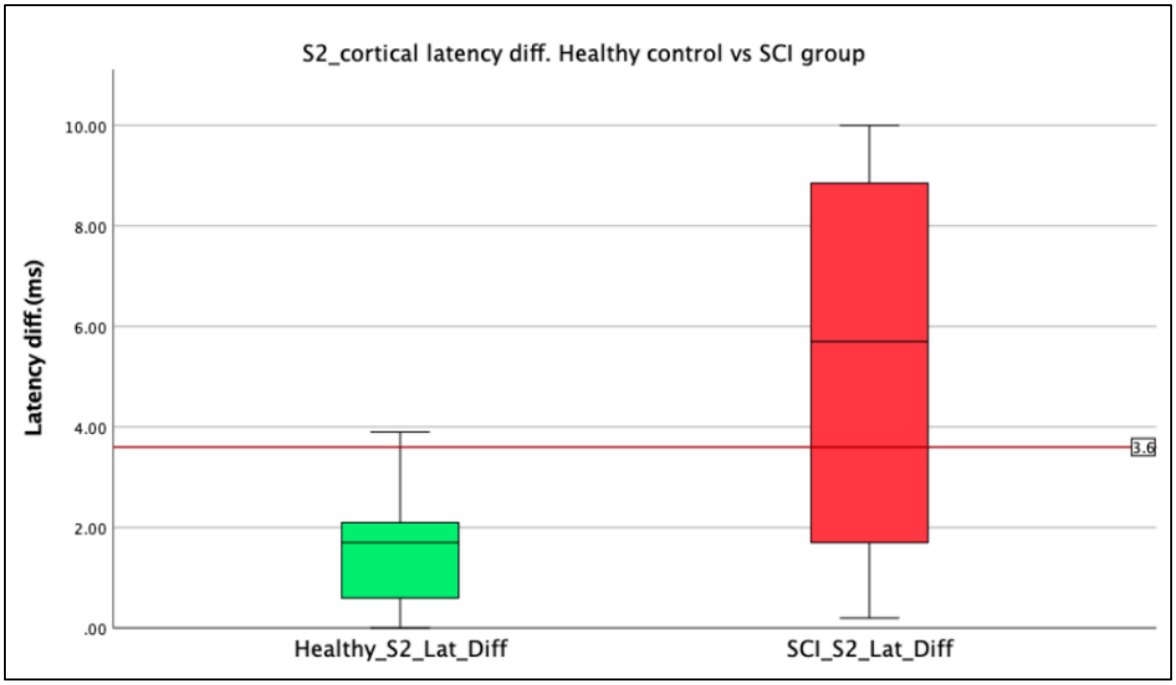


Figure 24b: S2 dSEP latency difference shows that 3.6 ms would be sufficient to differentiate abnormalities in the SCI group.

A comparative study of S3 dSEP latency differences between Study 1 and 2 shows that the proposed cut-off value of 3.5 would be sufficient to identify unilateral abnormalities, as shown in Figure 24c. The sensitivity/specificity for S3 dSEP latency asymmetry was 85% / 85%.

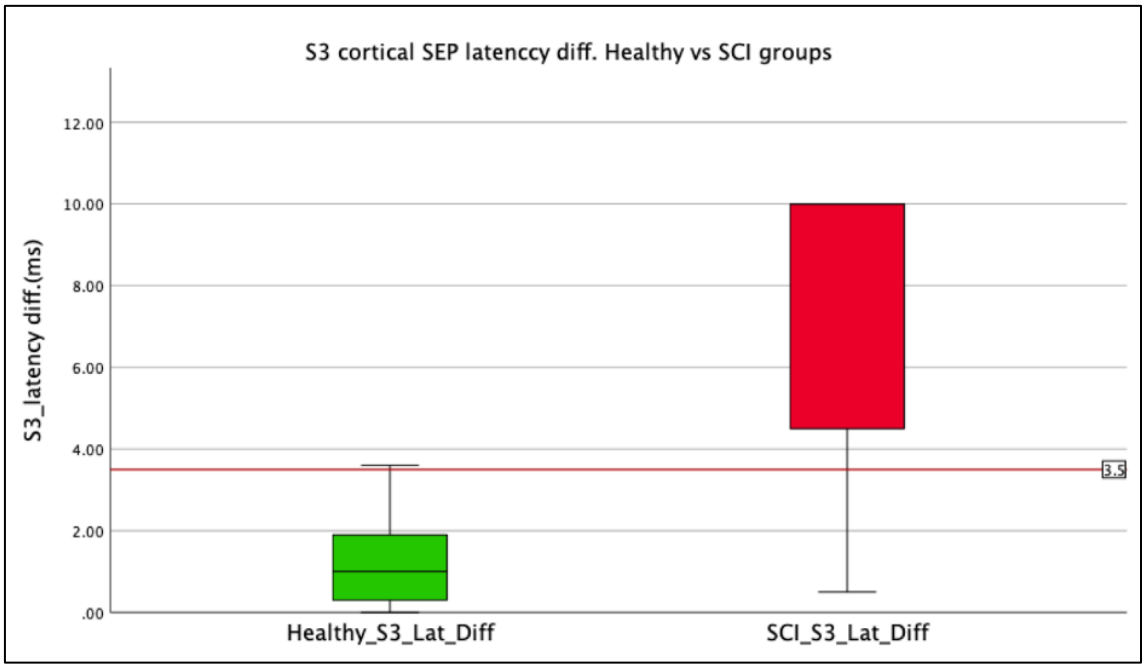


Figure 24c: S3 dSEP latency difference shows that 3.5 ms would be sufficient to differentiate abnormalities in the SCI group.

A comparative study of S4 dSEP latency differences between Study 1 and 2 shows that the proposed cut-off value of 3.2 would be sufficient to identify unilateral abnormalities, as shown in Figure 24d. The sensitivity/specificity for S2 dSEP latency asymmetry was 90% / 85%.

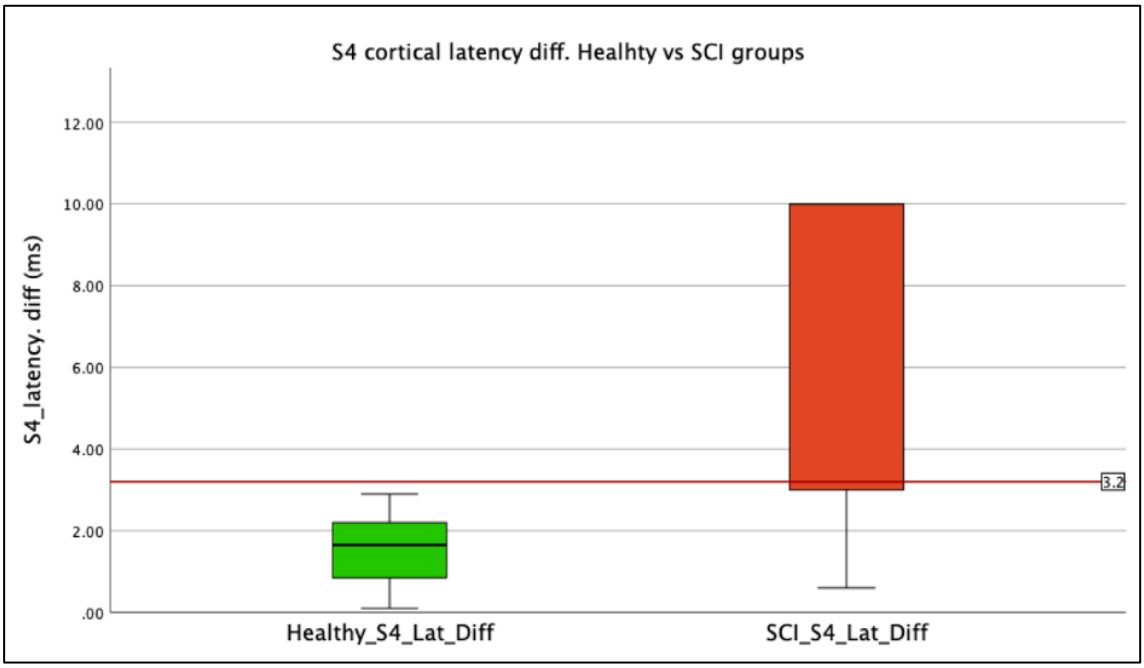


Figure 24d: S4 dSEP latency difference shows that 3.2 ms would be sufficient to differentiate abnormalities in the SCI group.

3.14 Follow-up Studies in Study 2

Three volunteers attended the follow-up study 24 hours after the initial visit. One volunteer's neurophysiology findings were severely affected due to a pelvic fracture. Hence, there was not much data to compare as many findings were absent or severely reduced. The neurophysiology data of the two remaining volunteers is shown in Table 29. The data in Table 32 showed that the values are similar, and no statistical or clinically significant difference exists between the two visits. The comparison suggests that dSEPs are reliable and reproducible even after 24 hours.

Table 32: Follow-up studies shows no difference in two visits of Study 2

Case 1	Right		Left	
	Visit 1	Visit 2	Visit 1	Visit 2
Tibial latency (ms)	48	48.6	48.6	48.3
Tibial amplitude (mv)	0.97	0.64	0.34	0.45
S2 latency	40	40.5	Absent	Absent
S2 amplitude	0.23	0.35	Absent	Absent
S3 latency	35.5	35.8	Absent	Absent
S3 amplitude	0.7	0.53	Absent	Absent
S4 latency	Absent	Absent	Absent	Absent
S4 amplitude	Absent	Absent	Absent	Absent
Pudendal latency	Absent	Absent	Absent	Absent
Pudendal amplitude	Absent	Absent	Absent	Absent

Case 2	Right		Left	
	Visit 1	Visit 2	Visit 1	Visit 2
Tibial latency	46.6	47.5	48.6	48
Tibial amplitude (mv)	0.94	1	0.74	1.15
S2 latency (ms)	40.2	39.4	38.9	39.2
S2 amplitude(mv)	0.98	1.36	1.14	1.34
S3 latency (ms)	40.6	39.4	Absent	Absent
S3 amplitude(mv)	1.29	1.77	Absent	Absent
S4 latency (ms)	43.9	43.2	Absent	Absent
S4 amplitude(mv)	0.48	0.47	Absent	Absent
Pudendal latency (ms)	41.3	41.3	42.3	42
Pudendal amplitude(mv)	0.9	1.1	0.32	0.41

The Coefficient of Variation (CV) was calculated by dividing the SD by the mean value for the follow-up studies, as shown in Table 33. Since mean values are widely varied in the follow-up studies between dSEP latencies and their amplitudes, it would be more beneficial to study CV than mean values (Botta-Dukát, 2023). CV values for all dSEPs are not more than 1.5% in all follow-up studies, suggesting latencies or their asymmetries are the most robust criteria in the diagnostic workup compared to dSEP amplitudes, where CV values reach up to 21%. Intraclass Correlation Coefficient (ICC) was calculated to assess the reliability of dSEP latency and amplitude parameters from the follow-up studies, and the results are shown in Table 34. A two-way mixed effects model with an absolute agreement type of relationship and mean of raters unit was used while calculating ICC values. ICC value for mean amplitudes was 0.800, indicating good reliability, and 0.999, indicating excellent reliability (Koo and Li, 2016).

Table 33: Calculation of CV in Study 2 follow-up studies.

	Visit 1	Visit 2	SD	Mean	CV	
Tibial latency (ms)	48.0	48.1	0.424	48.0	0.9	%
S2 latency (ms)	39.7	39.7	0.377	39.7	0.9	%
S3 latency (ms)	38.1	37.6	0.530	37.8	1.4	%
S4 latency (ms)	Absent	Absent				
Tibial amplitude (µs)	0.7	0.8	0.161	0.8	20.9	%
S2 dSEP amplitude (µs)	0.8	1.0	0.165	0.9	21.2	%
S3 dSEP amplitude (µs)	1.0	1.2	0.230	1.1	20.9	%
S4 dSEP amplitude (µs)	Absent	Absent				

SD: Standard Deviation, CV: Coefficient of variation

Table 34: Calculation of ICC in Study 2 follow-up studies.

Average measures	Intraclass correlation	Cronbach's alpha	Sig
EP Latencies	0.999	0.999	<0.001
EP amplitudes	0.800	0.973	0.026

3.15 Discussion

Study 1 has provided normative values for S2, S3 and S4 dSEPs, whereas Study 2 tested these dSEPs in known SCI subjects. In addition, Study 2 also assessed the yield of dSEPs with routine evoked potentials such as tibial and pudendal SEPs. dSEPs were recorded in all twenty SCI volunteers along with the tibial SEP and the pudendal SEP studies without technical difficulties. Study 2 shows that sacral dSEPs are helpful in clinical use. Most volunteers (90%) in Study 2 suffered from CES injury. The tibial SEP study did not help in Study 2 in diagnosing the lesion. The tibial nerve consists of nerve fibres originating from lumbosacral roots from L4 to S3. Selecting such a wide range of nerve fibres defeats the purpose of identifying lesions in the cauda equina. Any normally functioning nerve root is sufficient to send afferent signals to the brain. Hence, tibial SEP is not helpful in CES cases. Study 2 showed only three abnormal findings (15%) in the tibial SEP latencies. These findings are consistent with the published data (Matsukura et al., 2023; Restuccia et al., 2000a).
The pudendal SEP also suffers from the same disadvantage of the wide distribution of sacral root inputs from S2-S4 in the pudendal nerve. Unless the damage to the sacral roots is substantial, pudendal SEP will not yield much information in isolation (M. L. Delodovici and C. J. Fowler, 1995). Current neurophysiology tools, such as NCS and F-waves studies, would not be sufficient to identify and quantify the sacral root damage (Wilbourn and Aminoff, 1998).
AUC values in the current study were 0.95 and 0.91 for S3 and S4 dSEPs, respectively. These findings were similar to dSEPs in myelopathies, where AUC values were 0.89 and 0.87, respectively (Ulrich et al., 2013). dSEPs were done in several spinal conditions (Aminoff et al., 1985; Katifi and Sedgwick, 1986; Righetti, Tosi and Zanette, 1996), but no standard technique was used across these publications. Some publications used disc electrodes for

stimulation (Aminoff and Eisen, 1998; J.C. Slimp, 1992), and some used subcutaneous needles (Daniel Dumitru, 1996). The current study used standard electrodes with standard distance across all EP studies. Thereby, the comparison will be possible across all EPs. dSEPs were extensively studied for L5/S1 radiculopathies but achieved mixed results (Daniel Dumitru, 1996; Jo et al., 2021; Righetti, Tosi and Zanette, 1996). In these studies, dSEPs were studied on patients with unilateral motor abnormalities confirmed by well-defined MRI changes. dSEP were produced by stimulating either sural or superficial peroneal territories with NCS stimulators. A comparison was made between dSEP abnormalities and EMG abnormalities, and concluded that dSEPs were not helpful in clinical use. One limitation of this approach in these publications was assuming both dorsal and ventral roots would be affected in all radiculopathies. But there was no reason to suspect both roots would be involved simultaneously. It would be prudent to claim that dSEPs may not be helpful in lumbosacral motor radiculopathies or that dSEP should be used in suspected sensory radiculopathies (Albeck et al., 2000; Dumitru and Dreyfuss, 1996). Dikmen and Emre Oge (2013) suggested that selecting the right patient group is essential for better results in dSEPs. They indicated that dSEPs help diagnose SCI with multiple roots affected. Studies have shown that dSEPs are helpful in a variety of conditions such as lumbosacral spinal stenosis (Essa, Al-Hashimi and Nema, 2018), multiple root compressions (Hakatifi, 1987), cervical and thoracic level compression (Pop et al., 1988), the assessment of congenital scoliosis (Zhang et al., 2022), cervical medullary injury (Kramer et al., 2010) and cervical spondylosis and lumbar spondylosis (Storm and Kraft, 2004).

The sensory nerve fibres in S2, S3 and S4 dermatomal evoked potential studies through the branches of the posterior femoral cutaneous nerve. However, S2 and S3 sensory fibres also supply the pudendal nerve. If pudendal SEP studies were abnormal on one side, but S2, S3 and S4 dSEP studies were normal on that side, it suggests a pudendal nerve lesion. If all dSEPs were abnormal on one side, but the pudendal SEP was normal, it means more of a posterior femoral cutaneous nerve lesion than a plexus lesion. A combination of S2, S3, and S4 dSEP abnormalities and an abnormal pudendal SEP suggests a root-level lesion. Additional tests like NCS and EMG will differentiate plexus lesions from root-level lesions. The comparison study between the conventional criteria and the criteria proposed in Study 1 shows latency asymmetry is a suitable parameter while assessing abnormalities, which will

complement the traditional diagnostic criteria. In addition, 7 ms latency between the pudendal SEP and the tibial SEP may produce false negative results.

3.16 Strengths and limitations

Study 2 used a new technique of obtaining dSEPs and obtained relatively better amplitudes than the published studies (Dumitru and Dreyfuss, 1996; Slimp et al., 1992). Hence, additional criteria, such as amplitude asymmetry or a combination of latency and amplitude asymmetries, can be considered while interpreting dSEP abnormalities. Additional amplitude criteria will increase the sensitivity and specificity of dSEPs in the sacral spinal disorders. Study 2 included several pathologies, and dSEPs showed robustness in identifying abnormalities in various pathologies. In the absence of standard neurophysiology testing tools available in assessing S3 and S4 sacral root functions, the sacral dSEPs can be used as a 'gold standard test' in future use.

Study 2 has only two follow-up cases. Even though the reproducibility of dSEPs is substantial in the current study supported by CV and ICC values, some of S3 and S4 values were completely absent due to severe damage to sacral roots. The reliability of the dSEPs was demonstrated in these two severe cases, but the percentage of reproducibility cannot be commented on either mildly or partially damaged nerve roots. A large sample is required with varying degrees of sacral root involvement in future studies.

This pilot study assessed the feasibility of sacral dSEPs in healthy adults and known SCI cases. Several sacral dSEP studies with larger sample sizes in different neurological conditions are needed before establishing dSEP in routine clinical use. Study 2 did not include other diagnostic tests such as urodynamic studies, gastroenterology physiology studies and sexual function questionnaires to correlate dSEP findings with other tests in SCI patients. The comparative studies between neurophysiology and non-neurophysiology studies will reveal the superiority of dSEPs over other tests. Future studies should include non-neurophysiological studies while assessing the efficacy of dSEPs in CES condition.

3.17 Future work

Even though it is a pilot study, it fulfilled some requirements for successfully recording dSEPs in the SCI group. Since tibial SEP and dSEP parameters in the current study are similar to those in Study 1, the optimum sample size should also be the same in Study 2. The

present study has only two follow-up studies. Future studies should focus on achieving 23 follow-up studies to assess the reproducibility of dSEPs in the SCI group. Study 2 is a single-centre study with a single operator performing all steps. Future studies should also focus on conducting trials in a multicentered setup to assess inter-operator variability and robustness of dSEPs. Several such studies are needed before being recommended to NICE guidelines.

3.18 Study 2: Conclusion

Chapter 3 dealt with a critical clinical need of validating sacral dSEPs in known neurological conditions. dSEPs have been known for over three decades, but the current study filled the knowledge gap by providing a robust, reliable, reproducible technique to record sacral S2, S3 and S4 dSEPs. Study 2 also validated dSEP results in known SCI cases. Chapter 3 also speculated on the potential use of dSEPs in the other neurological disorders that present or mimic similar symptoms of CES. Finally, Chapter 3 also provided a road map to take these dSEPs into routine clinical practice through NICE guidelines and establish this technique as a gold standard in pelvic neurophysiology testing.

Chapter 4: Evaluation of dSEPs in Symptomatic Tarlov Cysts

4.1 Anatomy of Sacral somatic and autonomic innervation

Symptomatic Tarlov cysts can affect bladder, bowel, and sexual functions. In addition, Tarlov cysts can cause motor deficits and produce debilitating pain in the pelvic area and lower limbs. Reviewing the basic anatomy and physiology of sacral root functions is essential to understanding the Tarlov cyst's pathophysiology. Sacral dorsal roots are the information highways, constantly conveying the status of the bladder and bowel functions to the brain. Large diameter thickly myelinated Aα sensory fibres, stretch receptors of group Ia, group II afferent fibres, thinly myelinated Aδ and unmyelinated C fibres send afferent signals through the dorsal root. Any disturbance to the sacral sensory pathways can adversely affect bowel, bladder, and sexual function (Kanai and Andersson, 2010).

Pre-ganglionic sympathetic neurons originate at the thoracolumbar region T11-L2 of the spinal cord. Some of these fibres descend through the sympathetic chain and exit at the S2 and S3 sacral roots level, forming sacral splanchnic nerves and joining the inferior hypogastric plexus. The rest of the fibres exit the sympathetic chain at the T11-L2 and synapse at the inferior mesenteric ganglion. Post-ganglionic sympathetic neurons from the mesenteric ganglion travel through the superior hypogastric plexus, descend through either the right or left hypogastric nerves and reach the inferior hypogastric plexus (Sam, Jiang and LaGrange, 2018). Cell bodies of the pre-ganglionic motor neurons of the parasympathetic nervous system lie within the lateral grey horn of the S2, S3 and S4 sacral spinal segments. First-order parasympathetic fibres exit through the S2, S3 and S4 ventral branches and descend through the sacral roots. These pre-ganglionic parasympathetic nerve fibres continue to travel through the sacral roots but deviate from the primary roots and form pelvic splanchnic nerves, as shown in Figure 25 and join the inferior hypogastric plexus. The Inferior hypogastric plexus is a mesh-like structure that contains predominantly pre-ganglionic sympathetic and parasympathetic fibres that innervate to the minor plexus, such as

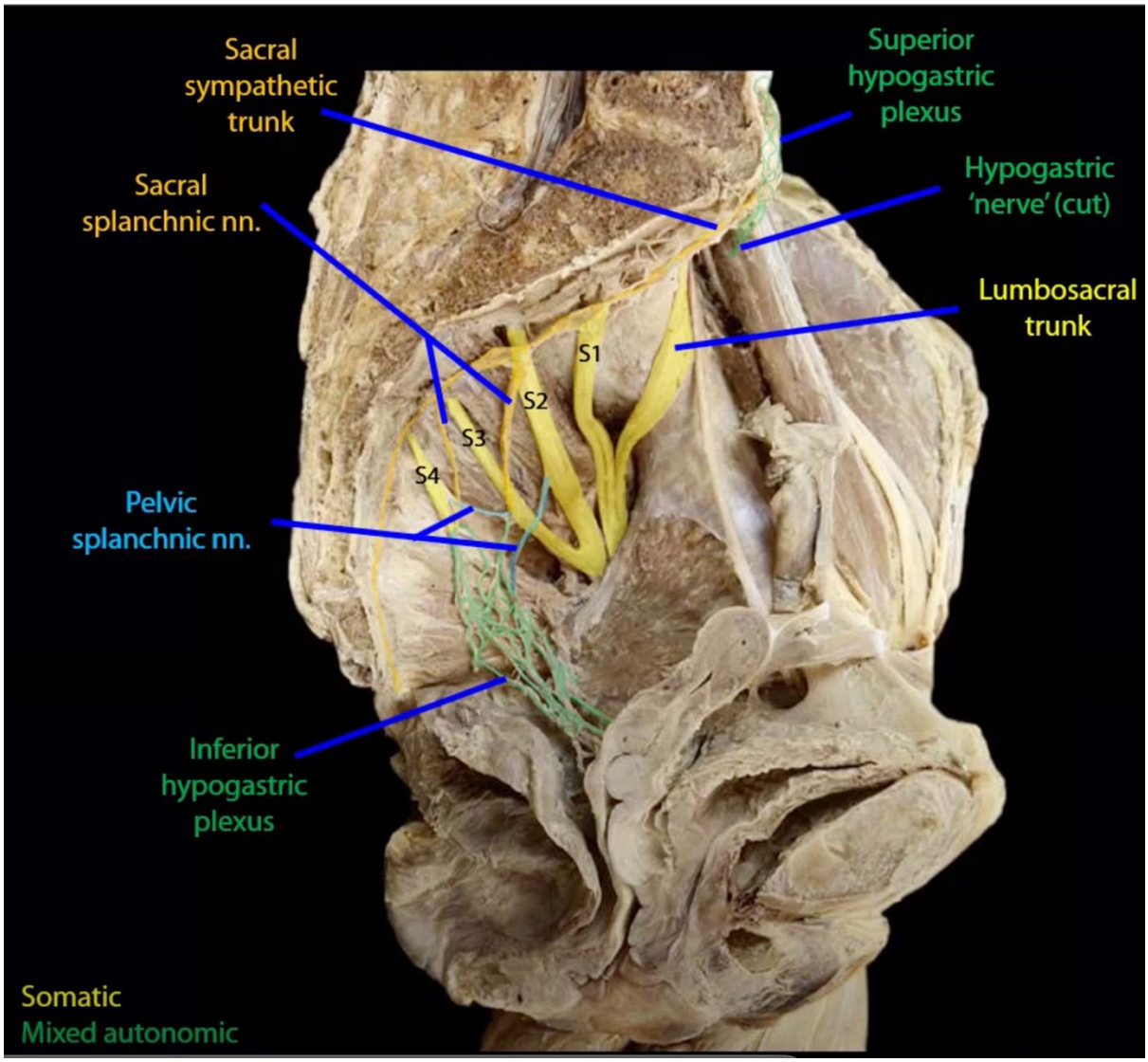


Figure 25: Pelvic splanchnic nerves exiting from S2, S3 and S4 sacral roots (Image source : Blue link: University of Michigan Anatomy, permission to use for non-commercial purposes, Appendix:7.11)

vesical plexus, prostatic plexus, rectal plexus and uterovaginal plexus on the walls of the end organs (Standring, 2016). Sacral roots S2, S3 and S4 mainly supply somatic innervation to pelvic organs and the perineum. The anterior rami of S2, S3 and S4 sacral roots, as they descend further, divide into anterior and posterior divisions. The posterior branches of S2, S3 and S4 sacral divisions form the posterior femoral cutaneous nerve, which travels under the piriformis muscle, descend medially to the sciatic nerve and supply the sensation to the posterior part of the thigh. The anterior branches of the S2, S3, and S4 sacral divisions form the pudendal nerve, which travels through the pudendal canal on both sides. In the one-third of the pudendal canal, the pudendal nerve divides into the inferior rectal and distal pudendal nerve. The distal pudendal nerve further divides into a pure sensory nerve branch

called the dorsal nerve of the penis/clitoris, the motor branch to the bulbocavernosus muscle and the sensory branch to the perineum (Netter, 2014).

4.2 Micturition Reflex

Bladder dysfunction is one of the main complaints in Tarlov cyst patients. Tarlov cysts do not directly affect the bladder or kidneys but interfere with the communication pathways from the bladder to the spine. Hence, it is essential to understand the sensory and motor pathways from the sacral spinal segment to the bladder. The bladder is a muscular sac holding the urine until a signal comes from the central nervous system to release it. The bladder consists of four layers of Lining epithelium, Lamina propria, Muscularis propria, and Serosa/Adventitia. The Lining epithelium is the innermost layer of the bladder. Muscularis propria, also called the detrusor muscle, consists of three layers where smooth muscles are arranged longitudinally in the inner layer, in a circular fashion in the middle layer and longitudinally in the outer layer (Bolla et al., 2023).

During the filling phase, the detrusor muscle sends afferent sensory signals continuously to the brain. The afferent signals are low frequency and low amplitude signals compared to somatic afferent signals, conveying bladder-filling sensation through sympathetic and parasympathetic afferent fibres.

Sympathetic afferent fibres convey bladder filling through the hypogastric nerve and sacral splanchnic nerve that supplies through the sympathetic chain to the pre-ganglionic sympathetic neurons located at the thoracolumbar region at T11-L2 (de Groat and Wickens, 2013). The parasympathetic afferent fibres that travel through the anterior roots also convey information about bladder filling. In the spinal cord, these parasympathetic afferent signals travel through Lissauer's tract and synapse with pre-ganglionic neurons at T11-L2 segments (Thor et al., 1989).

Sensory information from the urethra and external urethral sphincter muscle is conveyed through afferent fibres in the pudendal nerve that passes through the dorsal column and project to the thalamus (Fowler, Griffiths and de Groat, 2008). During the normal filling phase, afferent signals are conveyed through the thinly myelinated Aδ fibres, forming a feedback reflex at the inferior mesenteric ganglia located at the origin of the Inferior mesenteric artery. Until the bladder volume is more than 300 to 400 ml, sympathetic

efferent fibres are continuously activated through the hypogastric nerve, inhibiting the detrusor muscle's contraction and activating the internal urethral sphincter muscle that helps the bladder expand.

Simultaneous inhibition of the detrusor muscle and contraction of the internal urethral sphincter muscle is possible due to different locations of alpha-adrenergic receptors and beta-3 adrenergic receptors. Alpha-adrenergic receptors contract the muscle, whereas the beta-3 adrenergic receptors are inhibited by noradrenaline (Schena and Caplan, 2019).

During the filling phase, afferent signals travel in the dorsal column and Lissauer's tract and reach the cerebral cortex. During the filling phase, the Pontine storage Center (PSC) is activated, and the PSC is inhibited by the continue commands of the cerebral cortex (Rahman and Siddik, 2020)

As long as the PSC gets activated, it continues to send signals to the pre-ganglionic sympathetic neurons at T11-L2 segments to activate them. In addition, these descending signals from the PSC reach the sacral segment and inhibit the pre-ganglionic parasympathetic fibres located at the lateral grey horn of the S2, S3 and S4 sacral spinal segments. The pre-ganglionic parasympathetic neurons release Acetylcholine (Ach) at M3 receptors in the detrusor muscle. Hence, inhibiting the pre-ganglionic parasympathetic fibres reduces the release of Ach, and interns facilitate the expansion of the detrusor muscle. As the bladder filling reaches the critical volume, the rate of firing of stretch receptors in the detrusor muscle increases. These fast-firing sensory signals are transmitted through the pudendal nerve sensory fibres. The fast-firing somatosensory fibres convey the bladder-filling sensory input to the cerebral cortex through the dorsal column without synapsing with the pre-ganglionic sympathetic or parasympathetic fibres at the thoracolumbar region.

At this level, the person is consciously aware of a filled bladder. If the person consciously decides to void, a signal goes to the Pontine Micturition Center (PMC) and stimulates the nuclei there. A parallel command also goes to PSC and inhibits the nuclei. Inhibition of PSC causes a cascading effect on the pre-ganglionic sympathetic fibres at the T11-L2, reducing the commands to Alpha-adrenergic receptors, which relaxes the internal urethral sphincter. In addition, PMC also sends signals to the sacral segment to act on the pre-ganglionic parasympathetic neurons and motor neurons in the anterior horn, which in turn act on the M3-Cholinergic receptors to contract the detrusor muscle (Chess-Williams, 2002) and inhibit

the nicotinic type 1 receptor to relax the external urethral sphincter. As the urine starts to flow through the urethra, sensory input will be conveyed to the cerebral cortex, and the PSC will be reset when the bladder is emptied to start storing the urine again.

4.3 Bowel and sexual dysfunction

In addition to bladder dysfunction, Tarlov cyst patients often suffer from bowel and sexual dysfunction (Almansa et al., 2023). Even though the underlying mechanism is not precisely the same as the bladder function, the sympathetic, parasympathetic, somatosensory, and motor pathways and their central connections to the spine remain the same. Any disturbance in the dorsal root ganglia or their projections due to the presence of Tarlov cysts affects bowel and/or sexual function.

4.4 Identifying the research question for Study 3

Symptomatic Tarlov cysts can cause debilitating radicular pain, bladder, bowel and sexual dysfunctions (Almansa et al., 2023). The presence of Tarlov cysts and their prevalence is well known, but the impact of symptomatic Tarlov cysts on patient's health and social and psychological well-being is not well understood (Hulens et al., 2019). Similarly, surgical management of symptomatic Tarlov cysts is also not well known, and there is no consensus on treatment pathways. The heart of the problem lies in the lack of objective evidence for the damage caused by Tarlov cysts to sacral roots. Unless this is addressed, the ambiguity continues to exist. In addition, surgeons need objective evidence for the precise location of the sacral roots that have been impinged by Tarlov cysts before they contemplate any surgical intervention—this knowledge gap is to be filled before taking Tarlov cysts into mainstream clinical and surgical practices. The current study is aiming to fill this knowledge gap through neurophysiology studies.

4.4.1 Study 3 study aims.

1. To provide objective evidence for the location and the degree of neurophysiological damage caused by symptomatic Tarlov cysts to sacral nerve roots.

4.4.2 Study 3 Study Objectives

1. To compare S2, S3 and S4 dermatomal evoked potential data in symptomatic Tarlov cysts with healthy volunteers.

2. To translate neurophysiological abnormalities into easily understandable abnormal categories.

4.5 Materials and Methods

American Clinical Neurophysiology Society guidelines (Acns, 2006) were followed throughout Study 3 to place scalp electrodes, perform studies, and identify waveforms. The equipment and electrodes used in Study 3 were similar to those in Study 1.

4.6 Recruitment

The sample size was twenty in Study 3, following the same rationale used in previous chapters. I aimed to recruit 20 volunteers with a history of sacral Tarlov cysts that resulted in loss of sensation over the back of their legs, buttocks, or genital area. The presence of a sacral Tarlov cyst was known before joining the study. Twenty-three volunteers responded to the advertisement and participated in the research study. The HSST trainee Clinical Scientist (Mr Anjaneya Malladi) contacted them and assessed their suitability before giving mutually suitable appointments for the study. All volunteers were given a patient information leaflet (Appendix 7.6) approximately a week in advance and given sufficient time to clarify their doubts. All volunteers gave written consent to access their relevant medical records to know more about their Tarlov cysts and their effects on their health condition. Minimal details were accessed from the volunteers about their bladder, bowel, sexual and pain-related difficulties. The clinical scientist received the volunteers on the assessment day, explained the procedure, and obtained informed consent. Those volunteers who provided written consent were clinically examined by Prof. Jalesh Panicer, Dr Sara Simeoni, or Dr Sarah Wright, Consultant Neurologists, for their suitability to participate in the study.

4.7 Demographic Data

Background data was collected regarding date of birth, sex, height in centimeters and weight in kilograms. Between February 2022 and August 2023, 23 volunteers expressed their willingness to participate in Study 3. Three volunteers did not have access to their imaging and, hence, were excluded from the study. The remaining volunteers gave written consent to participate. Of 20 volunteers, two were male (10%) and 18 (90%) were female. The mean onset of symptoms was two years, ranging from 9 months to 8 years. The participants' mean height, age, and BMI are given in Table 35.

Table 35: Mean height, age and BMI of study 3 participants.

	Male (n=2) ±SD	Female (n=18) ±SD
Mean height (cm)	181 (173-188) ±11	166(152-183) ±8.8
Mean age (years)	47 (45-48) ±2	53 (32-77) ±14
Mean BMI (kg/m^2)	25 (23-27) ±3	23(18.9-32.2) ±4.3

4.8 Inclusion and exclusion criteria

All volunteers were considered for the test if they met the inclusion criteria and did not have any of the exclusion criteria shown in Table 36.

Table 36: Inclusion and exclusion criteria for Study 3

Inclusion Criteria	Exclusion Criteria
Age over 18 years	Language barrier requiring an interpreter.
Written informed consent	Incapacity to consent
Received Information Leaflet one week prior	Had a history of peripheral neuropathy
A known Tarlov cyst in the sacral spinal cord segment was confirmed by MRI	Having diabetes
	Known Lumbar or Lumbosacral radiculopathy confirmed by MRI.

	Known demyelinating diseases.
	Known pudendal nerve interventional procedures such as pudendal nerve block, etc.

4.9 Performing examination studies.

A neurological examination was done in a manner similar to the previous chapters. While collecting data related to MRI, bladder, bowel and sexual dysfunction, a similar protocol was used as mentioned in Study 2. The protocol for tibial SEP, S2, S3 and S4 dSEP and pudendal SEP recordings were similar to Study 2. In addition, tests related to BCR and EMG were also collected whenever the data was available for comparison studies.

4.10 Statistical Analysis

Study 3 consisted of 20 volunteers. Hence, 20 data points were collected from each side and compared with healthy volunteers in Study 1. An absent cortical amplitude was taken as zero. Study 3 values were tested for normal distribution and compared with Study 1. The dSEPs were considered abnormal if their values exceeded the mean +2 SD of their corresponding values in Study 1. An independent sample t-test was used to assess any significant influence of Tarlov cysts on tibial SEP latencies. A comparative study was done to assess the overlap of dSEP latencies with Study 1 findings. The comparison will test the utility of cut-off values proposed in Study 1. In addition, unique abnormalities across all dSEPs were assessed to identify the most useful diagnostic parameter in the Tarlov cyst patient group. All statistics were performed with IBM SPSS Statistics 28.0 software. An alpha value < 0.05 was considered statistically significant.

4.11 Results

4.11.1 MRI, Clinical and dSEP findings

MRI findings showed a single Tarlov cyst in 5 cases (25%). In 8 cases (40%), MRI reports indicated the presence of multiple Tarlov cysts. In seven volunteers (35%), the MRI report only confirmed the presence of Tarlov cysts but did not elaborate on the number of cysts.

Thirteen volunteers (65%) complained of severe perineal pain and pain over the posterior part of the thigh. Fourteen volunteers (70%) complained of lower urinary tract symptoms. Three volunteers (15%) complained of bowel symptoms. No volunteer reported any sexual dysfunction.

Three volunteers (15%) presented with a primary complaint of paraesthesia in the perineum. Four volunteers (20%) presented with a primary complaint of Persistent Genital Arousal Disorder (PGAD). One volunteer (5%) presented with a non-specific complaint of abdominal ± pelvic pain, as shown in Table 37.

Four cases (20%) showed normal neurophysiological findings, and the rest were abnormal.

Table 37: MRI, neurophysiology, bladder, and bowel function findings in Study 3

No.	Gender	MRI findings -Location of Tarlov cysts	dSEP findings	Perineal & Thigh Pain	Voiding dysfunction	Bowel dysfunction	Additional symptoms
1	Male	S1-Left S2 - Bilateral	Lt. S3 -abnormal Lt. S4 -absent	Yes	No	No	
2	Male	Extensive sacral Tarlov cyst	Lt. S2-abnormal	Yes	No	No	
3	Female	Considerable size Sacral Tarlov cysts	Lt. S2-abnormal Lt. S3-absent Lt. S4-absent	Yes	No	No	
4	Female	Tarlov cyst at S1 and S2	Lt. S2-absent Lt. S3-absent Lt. S4-abnormal	Yes	Yes	No	
5	Female	Tarlov cyst at S2 and S3 Nerve sheath enlargement at Left S4	S2, S3 and S4 normal dSEPs on both sides	No	No	No	Paraesthesia over the perineum
6	Female	Tarlov cyst at Left S2 and S3	S3 and S4 dSEPs were absent on the left.	Yes	Yes	No	
7	Female	Tarlov cyst at bilateral S1 and right S2	S3 -Abnormal on the right S4 – Absent on the right side.	Yes	Yes	Yes	
8	Female	Sacral Tarlov cysts	S3 – left side abnormal S4 – left side absent	Yes	Yes	Yes	Perineal sensory impairment
9	Female	Small sacral Tarlov cyst, Right -S3 root	Left S2 &S3 abnormal Left S4 - Absent	No	Yes	No	PGAD

10	Female	S1 & S2 bilaterally, left S3 & S4	S2, S3 and S4 left dSEPs are absent	No	Yes	No	PGAD
11	Female	Sacral Tarlov cyst	S2, S3 and S4 - Normal	No	No	No	Pain and paraesthesia over perineum
12	Female	Sacral Tarlov cyst	Right S3 – Abnormal S2, S4 – Normal	Yes	Yes	No	PGAD
13	Female	Large Tarlov cyst at S2-S3 level resulting in bony remodelling of the spinal canal.	S2 – Normal B/L S3- Right side absent S4- bilateral absent	Yes	Yes	No	PGAD
14	Female	Sacral Tarlov cyst	S2 & S3 – Normal S4 – Left absent	Yes	Yes	No	
15	Female	S3- Sacral Tarlov cyst	S2 – Left absent. S3- Left abnormal. S4- Left abnormal	Yes	Yes	No	
16	Female	Sacral Tarlov cyst	S2, S3 and S4 - Normal	No	No	No	Abdominal/ pelvic pain
17	Female	Sacral Tarlov cyst	S2, S3 and S4 - Normal	No	Yes	No	
18	Female	S2- Sacral Tarlov cyst	S2, S3 and S4 - Normal	No	Yes	No	
19	Female	Sacral Tarlov cyst	S2, S3 – Normal S4 -absent	Yes	Yes	No	
20	Female	Large sacral cyst at S2	S2- Normal S3 – Right abnormal S4 -right side -Absent	Yes	Yes	Yes	

4.11.2 An Independent sample t-test for tibial SEP latency

An Independent sample t-test was done on the tibial SEP data to assess whether any statistical difference exists between the mean tibial latency in Study 3 and Study 1. A normality test was done on the tibial SEP data to facilitate the independent test. A total of 40 data points were collected for the tibial SEP after stimulating both lower limbs in Study 3 subjects.

Kolmogorov-Smirnov test, Shapiro-Wilk test, Skewness and Kurtosis were calculated using the SPSS software to assess the normality of the tibial SEP latency data, and the outcome was shown in Table 38. Significant values in Kolmogorov-Smirnov and Shapiro-Wilk tests were more than 0.05, suggesting that the data was normally distributed.

Table 38: Different statistical tests showed the tibial SEP data was normally distributed.

Test	p-value	Limits	Outcome
Kolmogorov-Smirnov	0.200	>0.005	Suggests normal distribution
Shapiro-Wilk	0.192	>0.005	Suggests normal distribution
Skewness	1.640	(-1.96 <z<1.96)	Suggests normal distribution
Kurtosis	1.140	(-1.96 <z<1.96)	Suggests normal distribution

Tibial SEP latency histogram, Q-Q plot and box plot show the data is normally distributed, as shown in Figures 26a -26c.

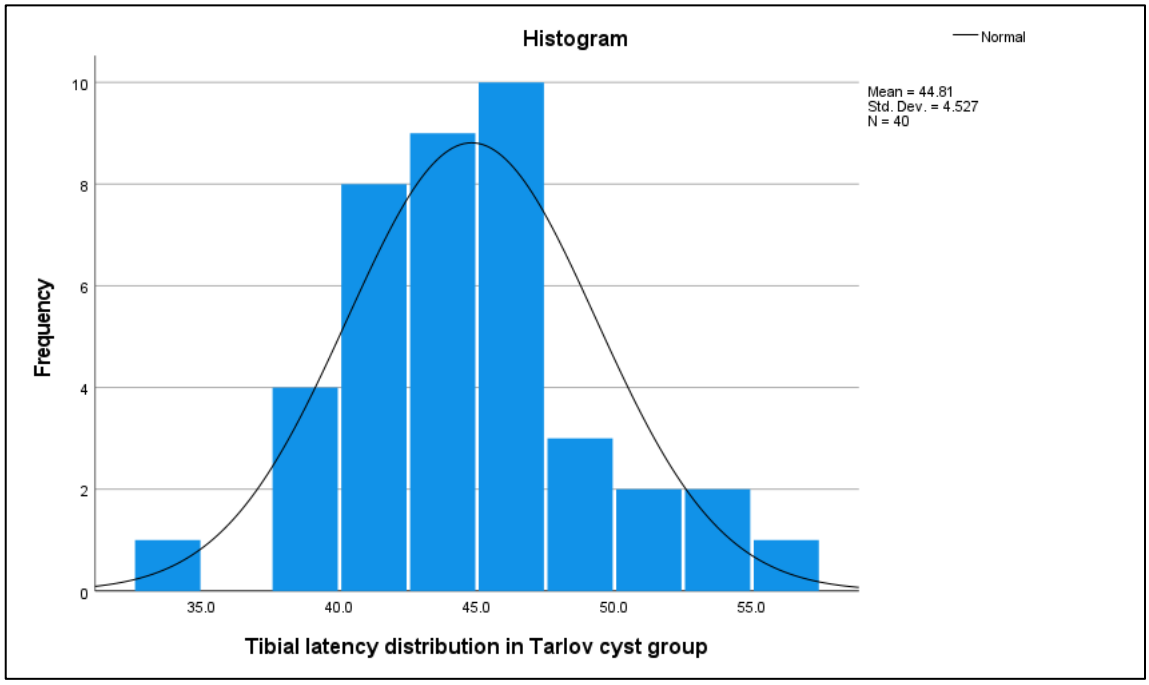


Figure 26a: Tibial SEP latency shows a normal distribution with no significant positive or negative skewness. Kurtosis for the distribution was 1.14 (-1.96 <z<1.96).

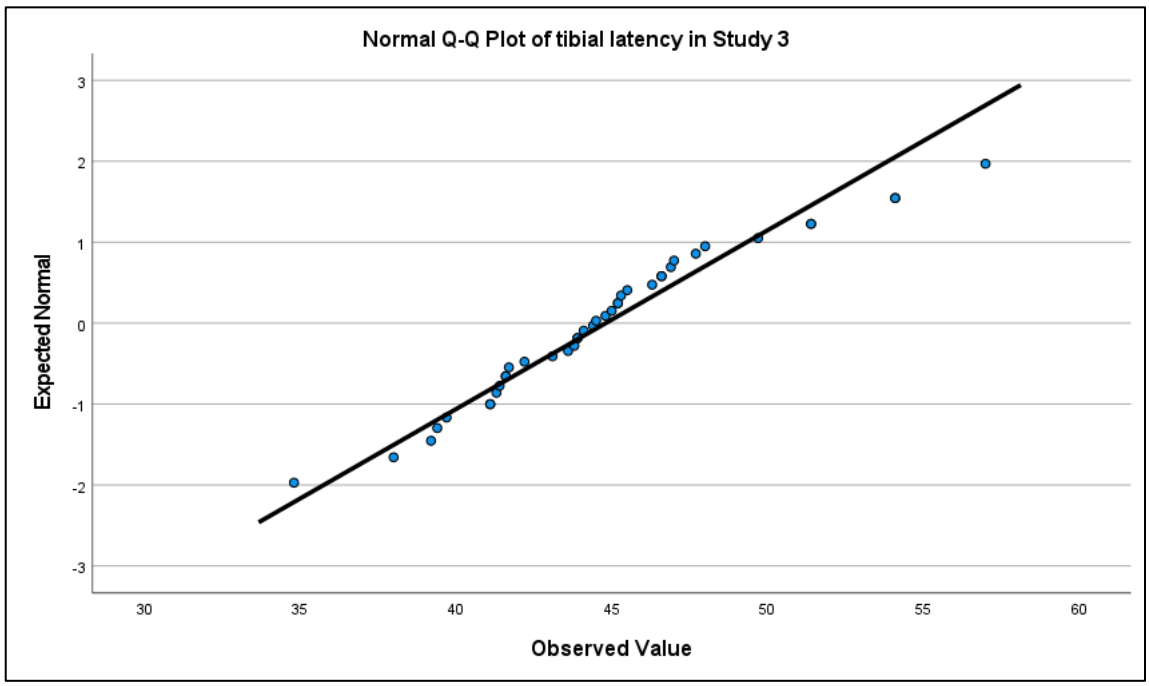


Figure 26b: Quantile-Quantile plot (Q-Q plot) visually confirms the alignment of all data points near the central line, confirming two quantiles drawn from the same normally distributed data set.

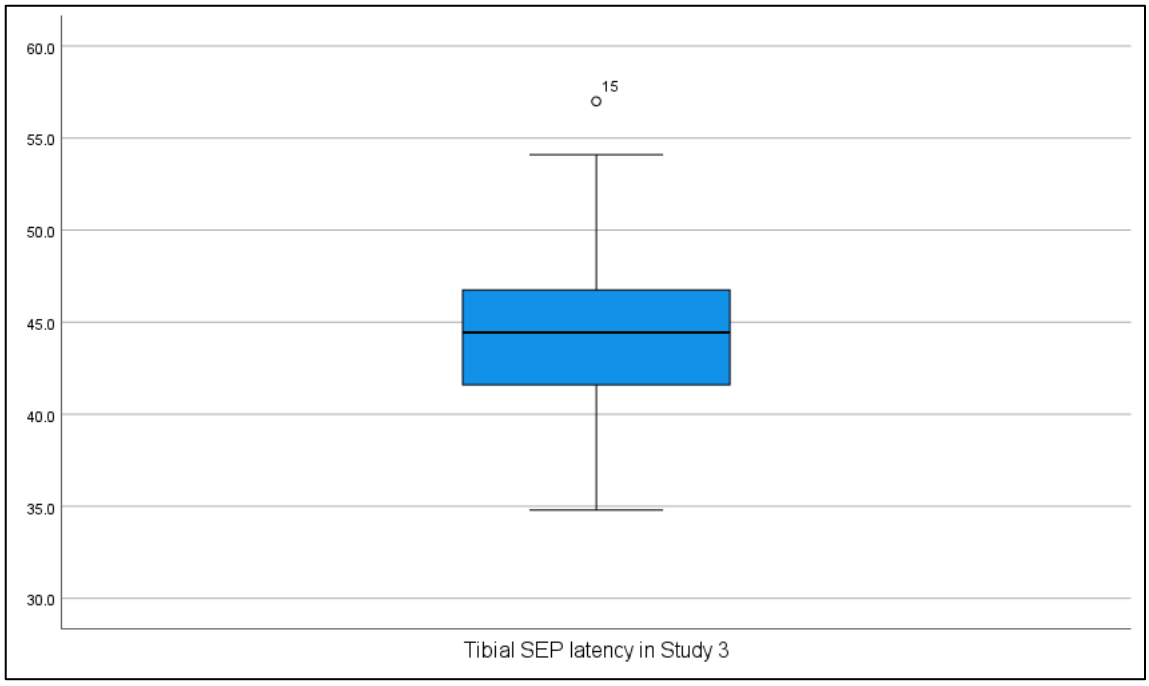


Figure 26c: The box plot for tibial SEP showed no outliers. The whiskers are about the same on both sides, suggesting the tibial latency data is similar to normally distributed data.

4.11.3 Independent samples t-test for tibial latency in Study 3

Tibial SEP data satisfied all the pre-requisitions for the t-test, such as homogeneous and continuous parameters with no selection bias. Independent samples t-test was done using SPSS software with the following hypotheses, and the test results are shown in Table 39.

Null hypothesis (H0): No difference exists between mean tibial latency in Study 3 and 1.

Alternative hypothesis (H1): A statistically significant difference exists between mean tibial latency in Study 3 and 1.

Table 39: t-test results for tibial SEP latency in Study 3

Independent samples t-test	df	t-value	Significance (p)		Outcome
			One-sided	Two-sided	
Equal variances assumed	78	-2.567	0.006	0.012	Alternative hypothesis accepted

Independent samples t-test showed a significant p-value and hence could not reject the alternative hypothesis, concluding that a statistically significant difference exists between Study 3's and 1's tibial latency values, as shown in Table 39. In the absence of any other known underlying pathologies, these findings suggest that patients with symptomatic Tarlov cysts have significantly different tibial latencies compared to the healthy group.

4.11.4 Comparison of tibial SEPs in Study 3 and 1

Tibial SEPs were elicitable in all volunteers on both sides in Study 3. Nine volunteers (45%) showed unilateral abnormal tibial SEPs; none had bilateral tibial SEP abnormalities. Most (7 out of 9) abnormalities in Study 3 were seen in the tibial latency asymmetry parameter. Since the posterior tibial nerve is a mixed nerve, any single sacral root abnormality can be masked by fast-conducting healthy fibres from L4 to S4 roots (Haanpää et al., 2011; Preston and Shapiro, 2012). Study 3 showed three abnormally prolonged tibial latencies, as shown in Figure 27a-27b. Of the three records, one volunteer had bilaterally prolonged tibial latency of 54.1 ms, and another had unilateral tibial SEP latency abnormality (57 ms). In the

volunteer with bilaterally prolonged tibial SEP latency, it is difficult to rule out any underlying silent peripheral neuropathy or bilateral radiculopathy. Additional NCS and needle EMG studies are required to rule out peripheral neuropathy and lumbosacral radiculopathy in this case.

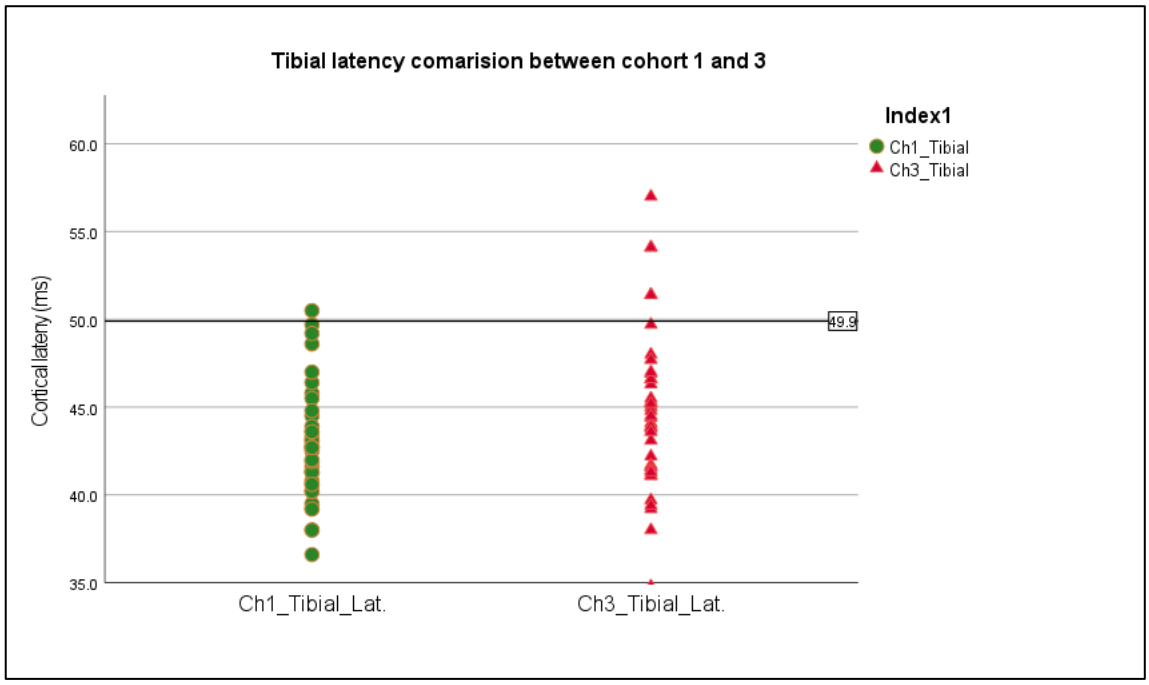


Figure 27a: Comparison of Tibial latencies in Study 1 and Study 3.
Ch1_Tibial_Lat = Study 1 tibial latency and Ch2_Tibial_Lat = Study 3 Tibial latency

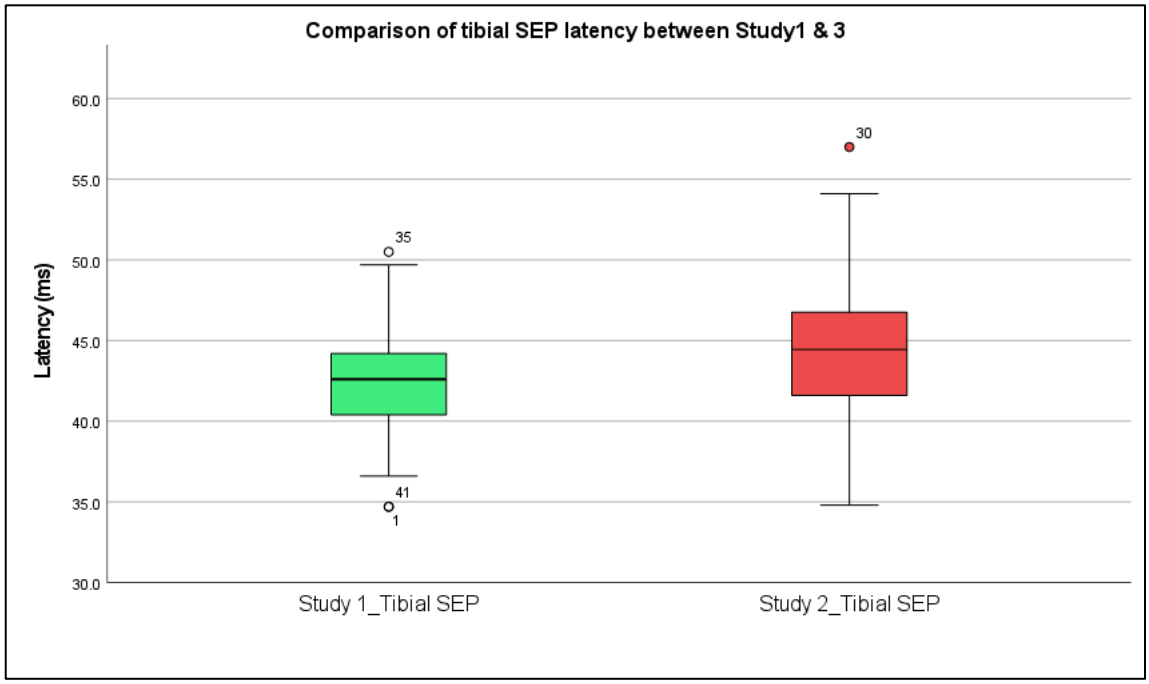


Figure 27b: Box plot comparison shows Study 3 tibial SEP latencies significantly overlap with Study 1, suggesting less utility of tibial SEP in Tarlov cyst diagnostic workup.

Study 3 showed seven abnormal cases with latency asymmetry parameters, one each with amplitude asymmetry and absolute latency parameters, as shown in Figure 28. The American Clinical Neurophysiology Society cautioned while taking absolute amplitude cut-off value or asymmetry in amplitude as an abnormal criterion while reporting Tibial SEPs. It suggests that the most reliable criteria for abnormality are either absolute cut-off value for the cortical latency or asymmetry in cortical latencies between sides (Acns, 2006).

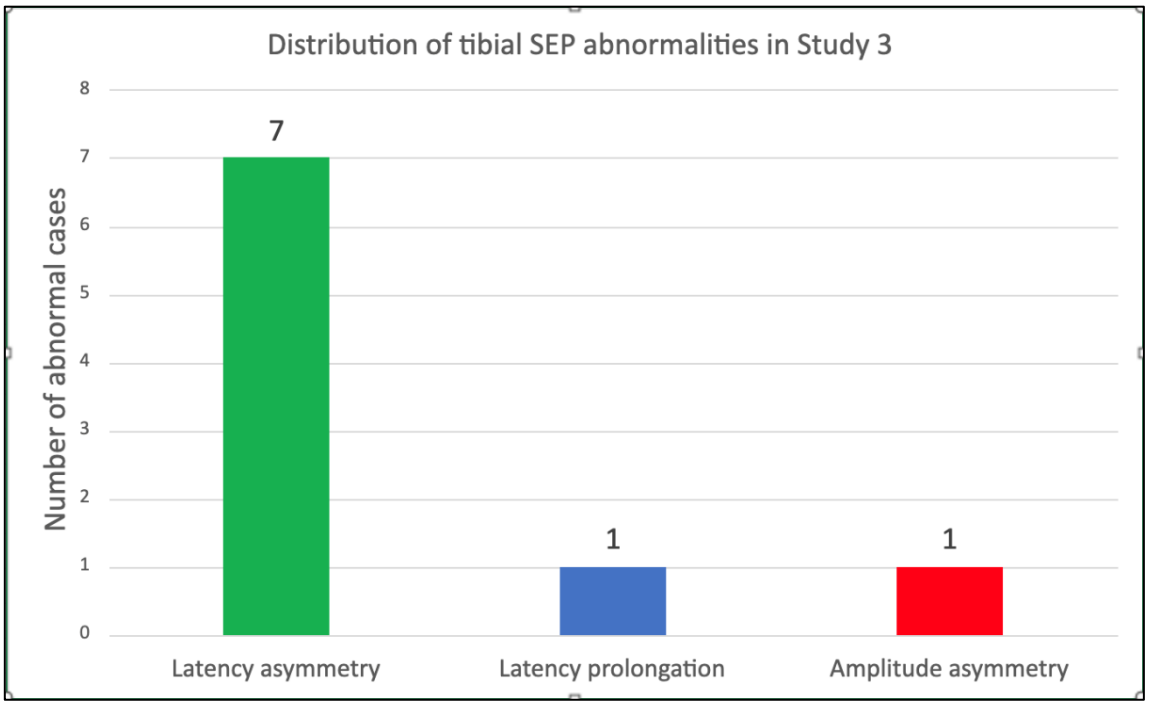


Figure 28: Tibial SEP abnormalities were often seen in the latency asymmetry parameter in Study 3.

Similarly, S2, S3 and S4 dSEPs were analysed based on absolute latencies, latency asymmetries between sides and amplitude asymmetries and the results are shown in Table 40a. The findings in Table 37a were further analysed to look for duplicate results. S2 latency asymmetry abnormalities were seen in 6 cases. However, the same six abnormalities were also seen in amplitude asymmetries, and hence, amplitude asymmetry criteria did not add to the total number of abnormalities in the S2 test. Similarly, 3 cases showed absolute latency abnormalities, but these three were also seen in the latency asymmetries, and hence, absolute latency abnormalities did not add any additional information. A similar analysis was also done on the data of tibial SEP, S3 dSEP and S4 dSEPs, and the results are shown in Table 40b and Figure 29.

Table 40a: Total number of abnormal cases in Study 3

Study 3 group	S2 latency (n=20)	S3 latency (n=20)	S4 latency (n=20)	Tibial (n=20)
Latency asymmetry abnormalities	6	9	13	7
Absolute latency abnormalities	3	4	7	2
Amplitude asymmetry abnormalities	6	9	12	3

Table 40b: Total number of unique abnormal cases in Study 3

Study 3 group	S2 latency (n=20)	S3 latency (n=20)	S4 latency (n=20)	Tibial (n=20)
Latency asymmetry abnormalities	6	9	13	7
Absolute latency abnormalities	0	0	0	1
Amplitude asymmetry abnormalities	0	1	0	1
	6/20 (30%)	9/20(45%)	13/20(65%)	7/20 (35%)

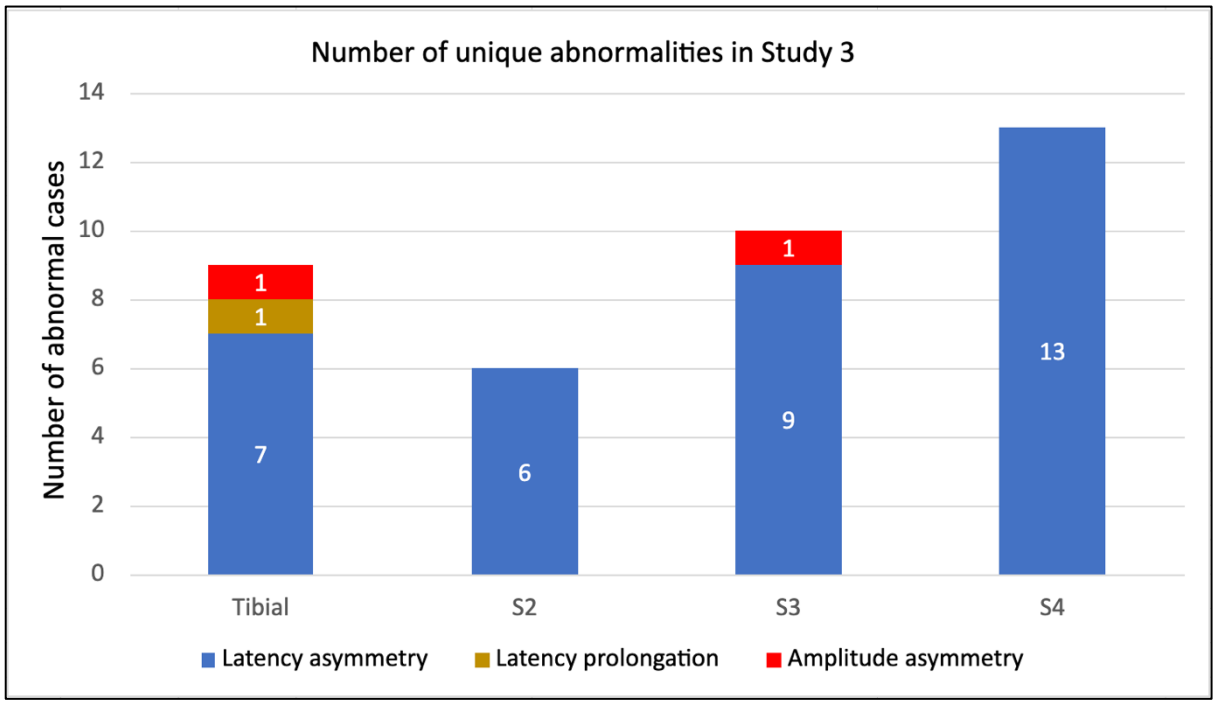


Figure 29: Most abnormalities were seen in latency differences (blue colour) across all Eps.

From Figure 29, it is clear that most abnormalities were identified in latency asymmetry parameters across all EPs. These findings are concurrent with the guidelines given by the ACNS that latency asymmetry is the most reliable abnormal criterion while reporting evoked potentials. The S4 dSEP study showed the highest number of abnormalities (65%) followed by S3 dSEP (45%), suggesting Tarlov cysts affect more S4 and S3 sacral roots than the rest. These electrophysiological findings agree with the clinical findings in the symptomatic Tarlov cysts (Hulens et al., 2019).

4.12 Supplementary studies in Study 3

Patient records showed that volunteers also had other neurophysiology tests such as PSEP, BCR and anal sphincter EMG as a part of their routine clinical examination. All available neurophysiology test results were compiled for analysis. Female pudendal SEP values were compared with Study 1, as shown in Figure 30a-30b. There were two male volunteers in Study 3 whose pudendal SEP values cannot be compared with Study 1. Hence, male pudendal SEP values were compared with the published data. The cut-off value for the male pudendal SEP was taken as 47.6 ms (Maria Luisa Delodovici, 1995).

Anal sphincter EMG is to assess efferent pathways function of sacral nerve roots. Anal sphincter EMG abnormalities could be seen in a variety of conditions, such as motor pathways dysfunction involving sacral nerve roots, local trauma to the anal sphincter muscle and central motor pathways dysfunction. The current study showed abnormal anal sphincter EMG findings in 7 volunteers (35%), as shown in Table 41. None of the 7 EMG studies showed any active denervation changes. Unlike Pudendal SEPs, BCR and Anal sphincter EMG tests do not have normal values from Study 1, and hence local values were taken for interpretation.

Table 41: Supplementary neurophysiology findings in Study 3

Study 3	Pudendal SEP	BCR	Anal sphincter EMG
Absolute latency abnormalities	6	8 (1- Prolonged unilaterally; 5- unilateral absent; 2- bilateral absent)	7
Latency asymmetry abnormalities	6		
Amplitude asymmetry abnormalities	7		
Total	7/20(35%)	8/20(40%)	7/20(35%)

When comparing Tables 40a and 40b, it is clear that the most abnormal findings are seen in the S4 dSEPs (65%) followed by S3 dSEPs (45%). A clear mean latency difference exists between Study 1 and 3 dSEPs, as shown in Figure 31. These findings suggest symptomatic Tarlov cysts can affect S4 and S3 sacral roots to a greater extent and S2 sacral roots to a lesser degree, and these abnormal changes can be diagnosed with dSEPs. Pudendal SEP was abnormal only in 35% of cases, significantly lower than sacral dSEPs. These findings are consistent with the earlier observation in Study 1, as mixed EPs, such as tibial and pudendal SEPs, are less sensitive to single root-level lesions. BCR abnormalities were seen in 8 volunteers (40%), and five (25%) had unilateral absent responses. The low yield in the BCR abnormalities could be due to the polysynaptic nature of BCR responses.

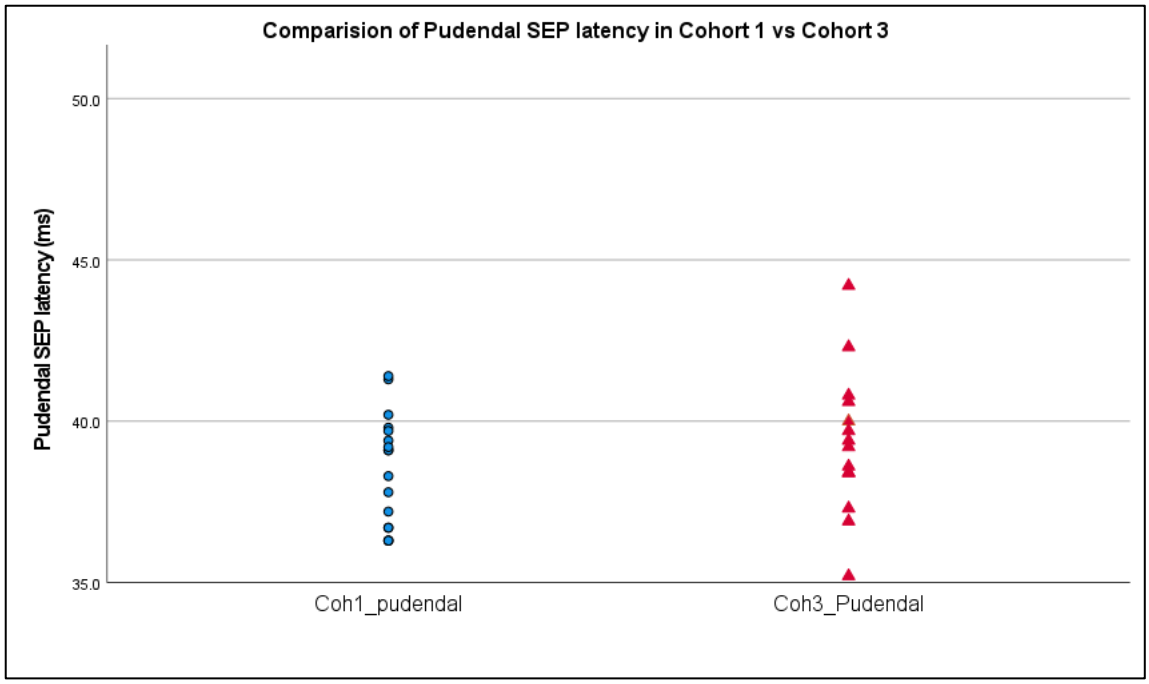


Figure 30a: Study 3 pudendal SEP latency findings show a greater overlap with Study 1, suggesting it is a less reliable parameter in Tarlov cyst diagnostic workup.

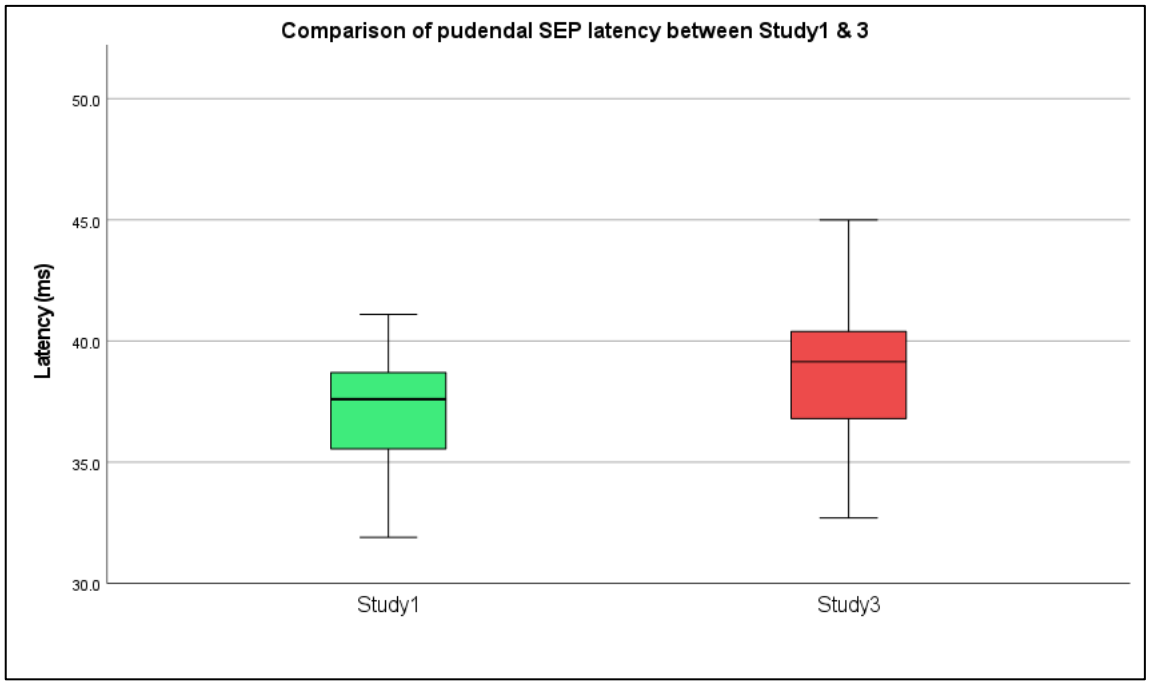


Figure 30b: Box plot of pudendal SEP latency in Study 3 shows a greater overlap with Study 1, suggesting 2 SD for pudendal SEP would not be sufficient to differentiate abnormalities.

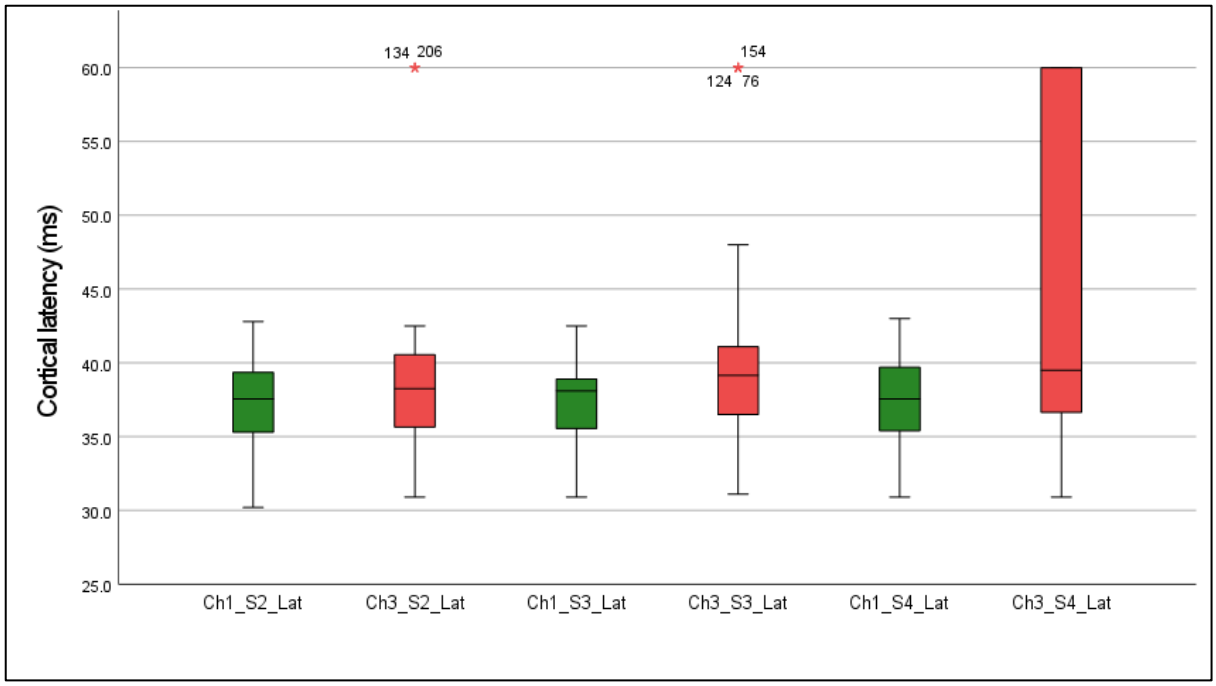


Figure 31: S4 dSEPs are the most affected, followed by the S3 dSEP in Tarlov cysts cases. Ch1_S2_Lat: S2 dSEP latency in Study 1, Ch3_S2_Lat: S2 dSEP latency in Study 3, Ch1_S3_Lat: S3 dSEP latency in Study 1, Ch3_S3_Lat: S3 dSEP latency in Study 3, Ch1_S4_Lat: S4 dSEP latency in Study 1 and Ch3_S4_Lat: S4 dSEP latency in Study 3

Neurophysiology findings were compared with the clinical and MRI findings to assess the role of dSEPs in Tarlov cyst patients. Case 4 in Study 3 is a 38-year-old female participant who presented with insidious onset of impaired sensation of bladder fullness and incontinence for the last eight years. She developed dull aches at the base of her spine and paraesthesia over the legs and in the perineum for the last five years. After thoroughly ruling out any urological and gynaecological causes, she was referred to a pain clinic for pain management. She had an MRI scan to rule out any demyelinating lesions in the central nervous system. MRI report showed no significant abnormalities except incidental S2 level Tarlov cyst, as shown in Figure 32. The patient was referred from the pain clinic to a neurosurgeon to assess the relevance of the Tarlov cyst in the context of her urinary symptoms and pain. The neurosurgeon did not feel her symptoms were relevant to the cyst but referred her to a uro-neurologist for an opinion. During the consultation, the neurologist did not feel her symptoms were typical for a symptomatic Tarlov cyst but referred her to the pelvic Neurophysiology department to rule out any sacral root dysfunction. She was clinically examined by a neurologist who did not find any deficits. However, the pelvic neurophysiology test found significant abnormalities, as shown in Figure 33a-c.

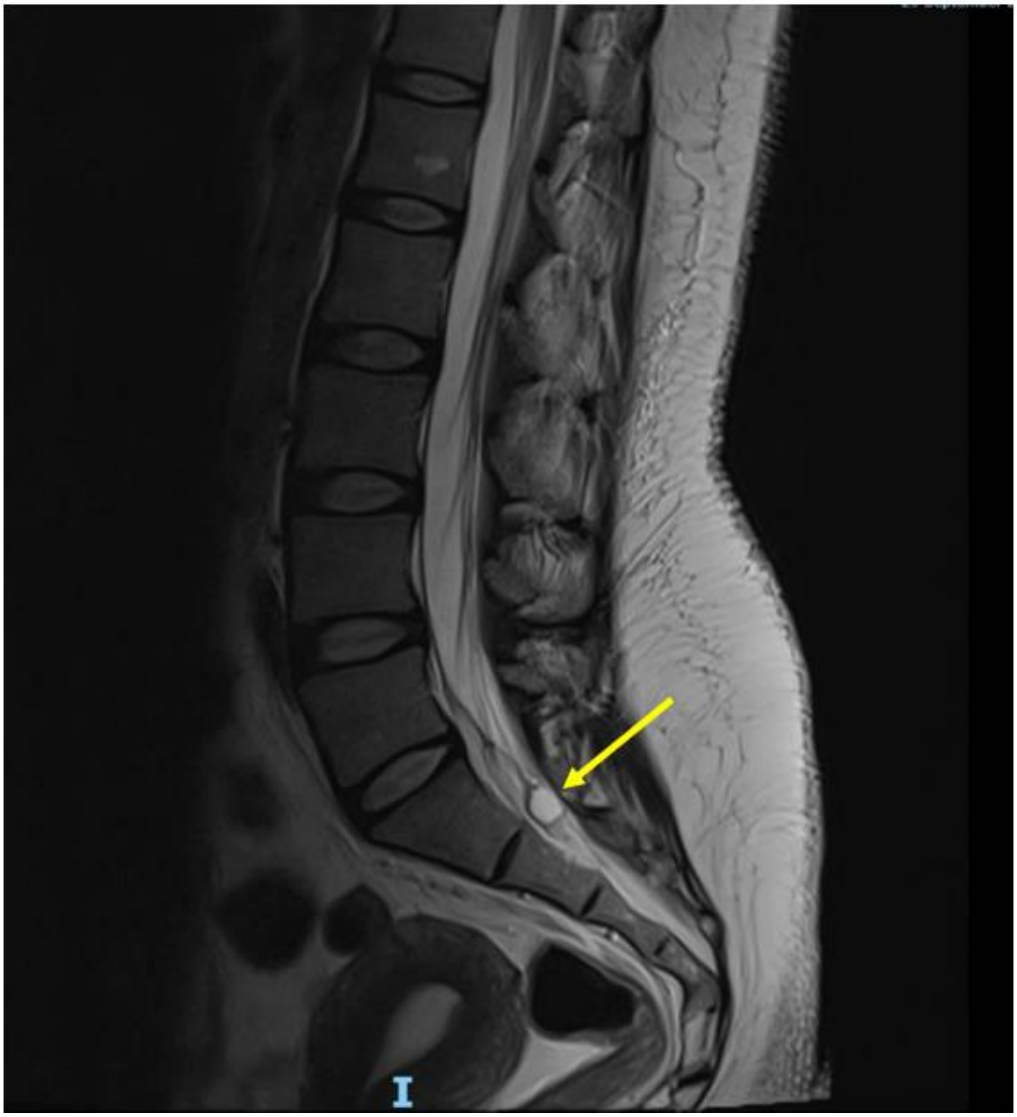


Figure 31: Sagittal T2-weighted MRI lumbosacral spine revealing Tarlov cyst (Yellow arrow) at the level of S1/S2.

Table 42: Neurophysiology findings in symptomatic S2 Tarlov cyst

	Tibial SEP	S2 dSEP	S3 dSEP	S4 dSEP	Pudendal SEP	BCR	Anal sphincter EMG
Right	Normal (45ms)	Normal (39.2)	Normal (38.3)	Abnormal Lat.diff (4.1 ms)	Abnormal Lat.diff (2.9 ms)	Normal	Normal
Left	Normal (45ms)	Absent	Absent			Absent	Abnormal

Lat.diff = Latency difference

The neurophysiology findings in Table 42 and Figures 33a-33c show that the tibial SEP findings were within normal limits, whereas the S2 and S3 dSEPs were absent on the left

side. The S4 dSEP and the pudendal SEP were prolonged on the right and left sides respectively. BCR and EMG studies were abnormal on the left side.

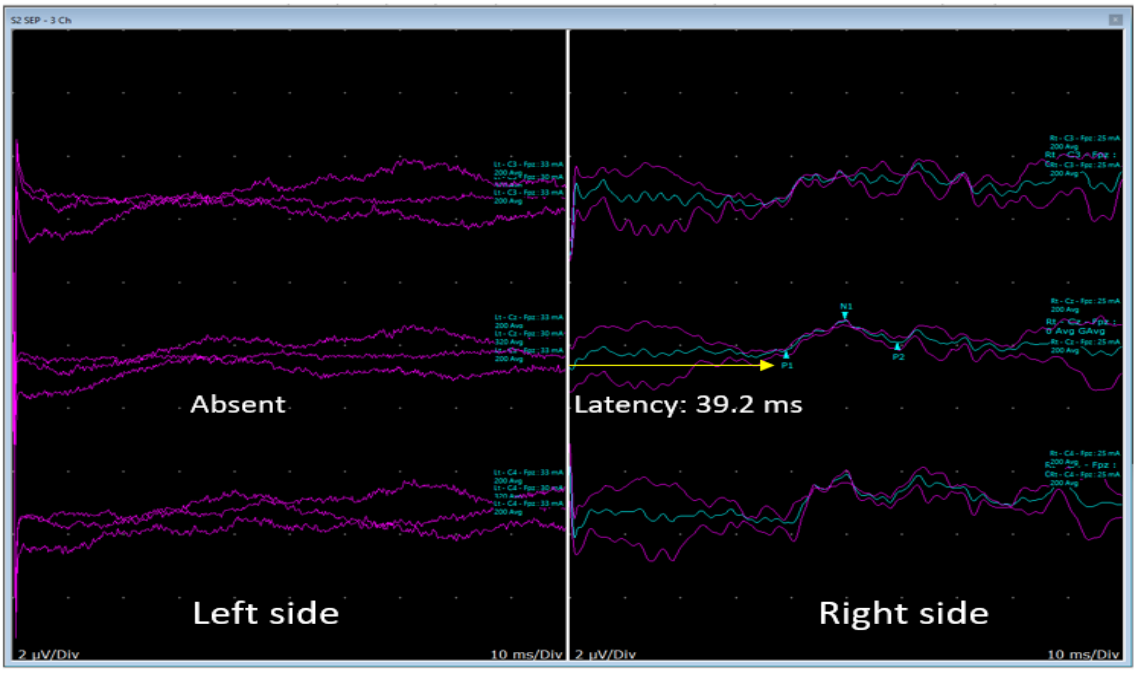


Figure 33a: S2 dSEP cortical evoked potential responses were normal on the right side but absent on the left.

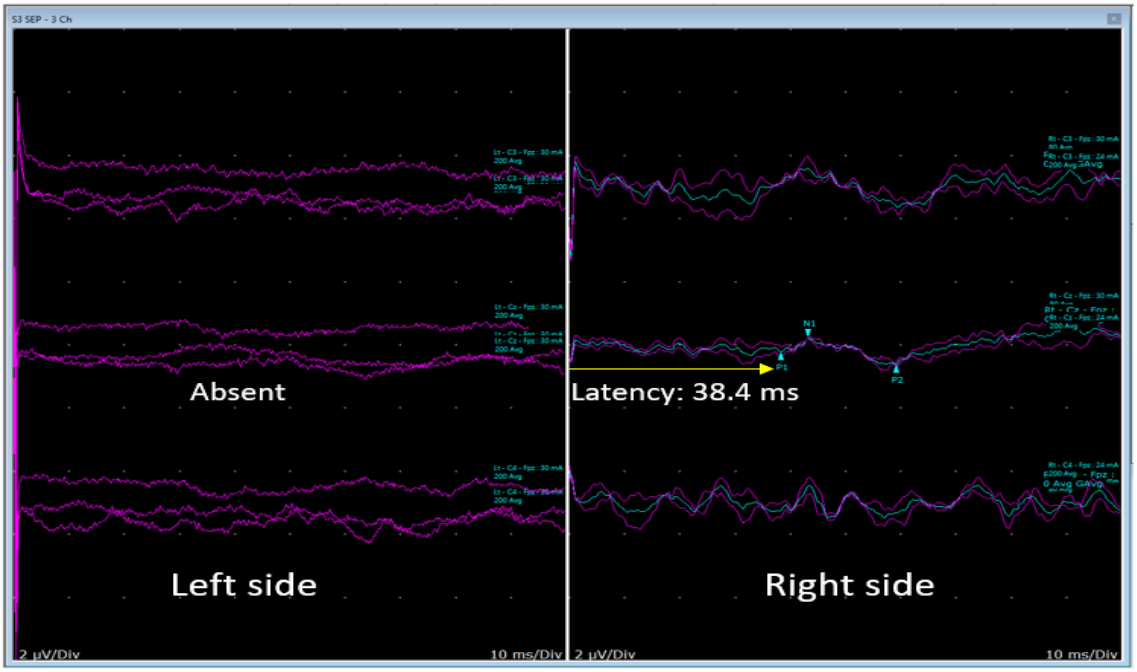


Figure 33b: S3 dSEP cortical evoked potential responses were normal on the right side but absent on the left.

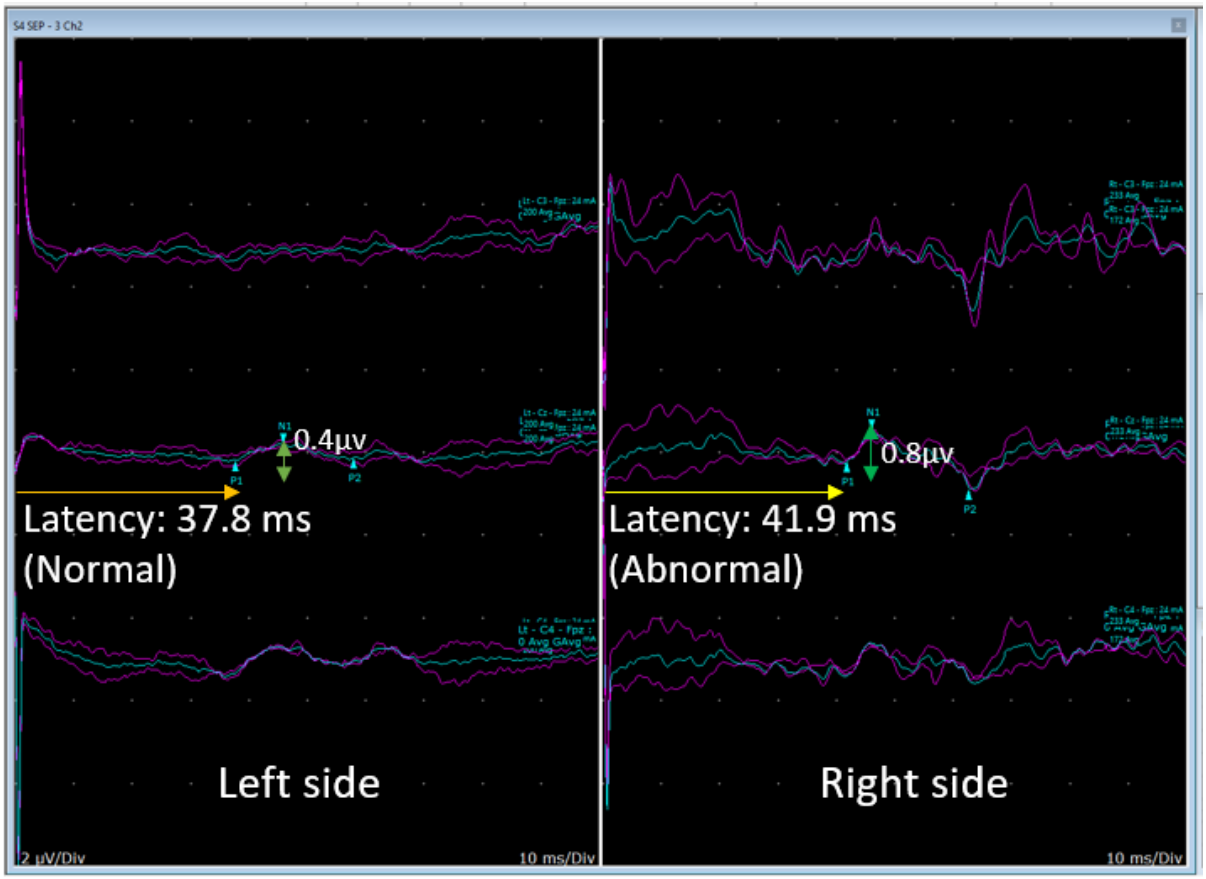


Figure 33c: S4 dSEP cortical evoked potential study showed 4.1 ms latency asymmetry on the right side and 50% reduction in amplitude on the left side.

The MRI report confirmed the presence of a Tarlov cyst at the S2 level but did not elaborate on the lateralisation. Clinical examination findings may not be concurrent with MRI findings in all cases. In radiculopathies, only 29% of clinical examination findings were concurrent with the lesion level on the MRI (Redebrandt et al., 2022). In addition, inter-examiner variability in neurological clinical examination is as much as 50 % with varying expertise (Araújo et al., 2015; Redebrandt et al., 2022). As per MRI reports, EP abnormalities should be seen only at S2. However, the current study showed abnormalities extending from S2 to S4, which suggests that the Tarlov cyst affects not only the sacral roots where it lies but also its adjacent sacral roots. This assumption is further confirmed by the mildly abnormal S4 dSEP, which is far from the S2 sacral root. These findings favour Sugawara et al. (2022)'s hypothesis that the Tarlov cyst exerts mechanical pressure on its neighbouring sacral roots.

4.13 Discussion

In Study 3, Bladder symptoms were noted in 14 (70%) volunteers, lower back pain and pain in the perineum in 13 (65%) cases and bowel dysfunction in 3 (15%) volunteers. In addition, PGAD symptoms were noted in 4 (20%) and perineal paraesthesia in 2 (10%) volunteers. In Study 3, debilitating pain, which was refractory to routine analgesic therapy, and bladder symptoms, such as frequency and urge incontinence, were the two prominent symptoms noticed. These observations were in agreement with Baker, Wilson and Wallach (2018), where lower back pain (83%), lower extremity pain (75%) and urinary urgency and frequency (54%) were the main symptoms. Urinary urge and incontinence in the general population is approximately 1-7%. Study 3 showed urge incontinence is 70%, which cannot be explained other than the presence of Tarlov cysts. Since bladder afferent pathways pass through the dorsal roots, the prevailing understanding is that any compression on these afferent fibres can cause dysfunction in bladder reflex pathways, resulting in frequency and urge incontinence in Tarlov cysts. However, there were several shortcomings in our current understanding of Tarlov cysts. There was no evidence of a correlation between the degree of compression and the severity of bladder symptoms. Also, we do not know the relation between the size of the Tarlov cyst and the degree of voiding difficulties. Table 39 showed no correction between the level of Tarlov cysts and voiding symptoms. Unfortunately, the MRI report did not provide the exact location in the sacral region in 7 volunteers (35%). Table 39 showed voiding dysfunction in Tarlov cysts located at S2 or S3 but not S4. However, 4 (20%) volunteers did not show voiding symptoms even though their Tarlov cysts were present at the S2 or S3 sacral root level, suggesting that the mere presence of Tarlov cyst at S2 or S3 may not lead to voiding dysfunction.

In Study 3, bladder symptoms were noted in 14 (70%) cases, lower back pain and pain in the perineum in 13 (65%) cases and bowel dysfunction in 3 (15%). In addition, PGAD symptoms were noted in 4 (20%) and perineal paraesthesia in 2 (10%). Debilitating pain and urge incontinence were the two prominent symptoms noticed in Study 3. These observations were similar to published values (Baker, Wilson and Wallach, 2018), where lower back pain (83%), lower extremity pain (75%) and urinary urgency and frequency (54%) were noted in patients with symptomatic Tarlov cysts. Urinary urge incontinence in the general population is approximately 1-7% (Ariman, Merder and Çulha, 2021). Study 3 showed urge incontinence

in 70% of cases, which cannot be explained other than due to Tarlov cysts. Since bladder afferent pathways pass through the dorsal roots, the prevailing understanding is that any compression on these afferent fibres can cause dysfunction in bladder reflex pathways, resulting in frequency and urge incontinence in Tarlov cysts. However, there were several shortcomings in our current understanding of Tarlov cysts. There was no evidence of a correlation between the degree of compression and the severity of bladder symptoms. Also, we do not know the relation between the size of the Tarlov cyst and the degree of voiding difficulties. Table 39 showed no correction between the level of Tarlov cysts and voiding symptoms. In Study 3, MRI reports did not provide the exact location of Tarlov cysts in 7 (35%) cases. Table 39 showed voiding dysfunction in Tarlov cysts located at S2 or S3 but not S4 sacral roots. However, 4 (20%) volunteers did not show voiding symptoms even though their Tarlov cysts were present at the S2 or S3 sacral root level, suggesting that the mere presence of Tarlov cyst at S2 or S3 may not lead to voiding dysfunction.

4.13.1 Impact of Tarlov cysts on sacral nerve roots

Study 3 investigated all dSEPs individually, which showed the highest number (65%) of abnormalities in the S4 dSEP test. Still, none of the MRI reports in Study 3 showed any Tarlov cysts at this level. The second-highest number of abnormalities was seen at S3. These observations suggest that Tarlov cysts can cause more damage to adjacent roots than their original roots. Sugawara et al. (2022) hypothesized that sacral symptoms were caused by stimulation of the adjacent nerve roots due to pulsation of Tarlov cysts. Hence, Sugawara and colleagues introduced nerve wrapping surgery to contain the damage to neighbouring roots. Study 3 now gives direct evidence for Sugawara and colleagues' hypothesis. Hulens et al. (2022) hypothesized that compressing Tarlov cysts can cause small and large fibre neuropathies. They observed loss of small fibres in the skin biopsy test on the dorsum of the foot and also noticed a reduction in sural nerve amplitude. Study 3 provides unequivocal evidence for sacral root damage, thereby providing evidence for Hulens and colleagues' small and large fibre focal neuropathy hypothesis in symptomatic Tarlov cysts.

4.13.2 PGAD symptoms in Tarlov cysts

PGAD is a disturbing condition where a patient experiences persistent genital arousal without known sexual triggering. Patients often describe it as a throbbing or pulsating sensation or electric shock-like feeling in the vagina. The sensory branch of the pudendal nerve supplies to the vagina and contains mainly the S3 and S4 sacral nerve roots (Possover and Forman, 2014). Several studies have speculated that PGAD symptoms in Tarlov cyst patients could be due to stimulation or damage to S2, S3 or S4 sacral roots by pulsating Tarlov cysts (Deka et al., 2015; Kim et al., 2022; Komisaruk and Lee, 2012; Moussa, Garcia-Cardenas and Benrimoj, 2019). The current study showed four volunteers (20%) with PGAD complaints and two patients (10%) with paraesthesia in the genital area. All four PGAD volunteers had abnormal S3 dSEP abnormalities, and three had additional S4 abnormalities. These four volunteers had additional symptoms such as back pain, lower limb pain and urinary symptoms. Several observational studies proposed that PGAD could be due to persistent nerve compression (Bedell, Goldstein and Burrows, 2014; Filler, 2009; Rosenbaum, 2010). Based on observations of mild ulnar nerve compression in humans and experimental studies in hyperexcitability of chronic nerve compressions in rats, Klifto and Dellon (2020) proposed that PGAD symptoms could be due to central or peripheral nerve damage. The findings of Study 3 supported Klifto and Dellon's hypothesis by providing evidence for sacral root damage in PGAD patients.

4.14 Classification of sacral roots damage

I propose a neurodiagnostic classification in symptomatic Tarlov cysts based on knowledge gained from nerve conduction studies in Carpal tunnel syndrome (CTS) and other nerve compressive disorders. This classification can be refined in future when more data is available. Also, small fibre neuropathy diagnostic testing such as Contact Heat Evoked potentials and Quantitative Sensory Testing can strengthen this classification in future. Unlike nerve conduction studies in CTS, very mild demyelinating changes in a short segment cannot be detected by dSEPs studies. With increased compression, substantial demyelination can cause dSEPs prolonged latencies. Axonal loss may also occur with severe compression, resulting in absent dSEP responses. Unlike peripheral nerve axonal loss, pre-ganglionic axonal loss has less chance of recovery, resulting in a permanent loss of sensation in the affected area. In addition, afferent signals from the bladder, bowel and sexual organs

pass through this critical pre-ganglionic sensory pathway. Hence, intervention at the earlier stage would help to contain the loss of axonal damage due to the compressive nature of symptomatic Tarlov cysts. A surgical intervention would be helpful before the neurophysiology shows severe abnormal findings. Based on these assumptions, I propose the classification of abnormalities in symptomatic Tarlov cysts, as shown in Table 43.

Table 43: Severity scale for symptomatic Tarlov cysts.

Tests	**Findings**	**Classification**
S2, S3 and S4 dSEPs *(CHEPS, QST, Sural sensory conduction studies to be included in future studies*)	S2, S3 and S4 dSEPs are present but with a significant side-to-side latency asymmetry	Mildly abnormal study (Need to specify which root is affected)
S2, S3 and S4 dSEPs *(CHEPS, QST, Sural sensory conduction studies to be included in future studies*)	S2, S3 and S4 dSEPs are present but with a significant amplitude and latency asymmetry	Moderately abnormal study
S2, S3 and S4 dSEPs *(CHEPS, QST, Sural sensory conduction studies to be included in future studies*)	No recordable S2, S3 and S4 responses	Severely abnormal study

4.15 Limitations of the Study

Study 3 showed evidence of sacral dorsal root dysfunction in symptomatic Tarlov cysts. dSEPs primarily assess somatosensory pathways, which include peripheral nerve and DML pathways. S2, S3, and S4 dSEPs cannot be used to assess small fibre nerve function, which includes Aδ and C-fibres. Hence, pain symptoms in symptomatic Tarlov cysts cannot be assessed using dSEPs, which is a significant limitation in this study. Bladder symptoms such as urinary frequency and urge incontinence were either self-reported or noted from the clinical reports. In future studies, dSEP findings need to be correlated with advanced urological tests such as urodynamics and uroflowmetry. Earlier studies showed no significant correlation between neurophysiological findings and urological studies (Hentzen et al., 2023), but the study did not use prospective controls and advanced neurophysiology

stimulating techniques proposed in the current study. Hence, a fresh approach is needed to assess the correlation between neurophysiology findings and uro-physiology, gastroenterology physiology findings and sexual dysfunction scores. Even though it is a pilot study, it established some of the technical parameters required for a successful recording of dSEPs. However, this is a single-centre study with a single operator performing all dSEPs. Multicentred, large sample studies are required to assess inter-operator variability. Several such studies are needed before being recommended to NICE guidelines.

4.16 Study 3 Conclusion

Study 3 dealt with a significant clinical need to assess sacral nerve roots in symptomatic Tarlov cysts. This study has provided evidence for sacral root damage in patients with symptomatic Tarlov cysts and information on the specific affected sacral roots. Based on neurophysiology findings, the study also provided an easily understandable severity scale, such as mild, moderate, and severe for symptomatic Tarlov cysts. This classification will help gauge the severity of abnormalities while making clinical and surgical decisions. It would be easy to assess the progression of the disease in follow-up studies. It would also be helpful to determine the change in sacral root function in pre- and post-Tarlov cyst surgery cases. The small fibre neuropathy is one of the critical unexplored areas in symptomatic Tarlov cysts. C-fibres are the nociceptive fibres that communicate pain in the perineum, and these fibres take a direct hit from the Tarlov cysts. This chapter speculated on the potential use of small fibre testing to understand the severity of the disease and encouraged future research in this area. Since neurophysiology testing provides laterality information, it would be easy for surgeons to protect the sacral roots with the help of intraoperative monitoring and pre-surgery neurophysiology findings. Lastly, this study also identified its limitations and paved the way for future research.

Chapter 5: General Discussion & Conclusion

Studies have shown that dSEPs can be recordable from the cervical and lumbosacral dermatomes. Still, they are rarely used in clinical practice due to their limited role in diagnosing motor radiculopathies. S2, S3 and S4 sacral dSEPs can provide direct evidence for individual sacral root functions. Study 1 is the first to attempt to generate normative values for sacral S2, S3, and S4 dermatomal evoked potentials by stimulating respective dermatomes with surface electrodes. Study 2 showed a unique, stimulating technique and recruited 20 healthy volunteers to generate normal values for S2, S3 and S4 dermatomes. All volunteers tolerated the test well, and the cortical evoked potential responses were elicitable. Study 1 analysed the data for potential influencing factors such as the subject's height, weight, and age. This study has established a robust method to record reliable and reproducible dermatomal evoked potentials in healthy individuals. The study also provided cut-off values for sacral dSEPs, tibial SEP and pudendal SEP studies. Further studies should focus on healthy male subjects to generate normal values for pudendal SEPs. Future studies can also consider including small fibre neuropathy studies in conjunction with dSEPs to understand the function of dorsal root small fibre pathways.

Study 2 aimed to validate sacral dermatomal evoked potentials in known neurological conditions before being attempted in unknown conditions. Twenty volunteers who had a known history of spinal cord injury that resulted in a loss of sensation in their sacral dermatomes were recruited to understand the value of dSEPs. All volunteers underwent clinical examination by neurologists and had an MRI. All twenty volunteers underwent neurophysiology testing, and their sacral dSEP responses were compared with the standard values generated in Study 1. In Study 2, dSEPs have differentiated the normal and affected sides. The study has demonstrated the reproducibility of dSEPs in three volunteers whose responses were consistent even after a gap of 24 hours. Study 2 revealed the ability of dSEPs to assess spinal cord injuries and their role in predicting the severity of the injury. Future studies can focus on dSEPs in acute spinal cord injury cases and study their variation with follow-up studies.

The prevalence of Tarlov cysts is high worldwide, but it is often underdiagnosed and underreported. It is considered a benign feature and often ignored in MRI reports. Tarlov

cysts can damage sacral nerve roots and cause sacral bone erosion, resulting in bladder, bowel, and sexual dysfunctions. The hallmark of the symptomatic Tarlov cysts is the debilitating persistent back pain that can extend to the pelvic area and lower limbs. These symptoms have life-changing consequences on the patient's psychological, physical, and economic well-being. Even though no formal studies have been done on the disease burden, given the sheer numbers and the variety of ways the disease could impact patients, it is suggested that the unreported economic impact runs in billions of pounds in the UK. A few cases have shown the impact of Tarlov cysts on bladder and bowel dysfunction. However, the medical teams continue to debate the Tarlov cysts due to a lack of neurophysiological evidence for the damage. A few surgical centres attempted to either deflate or resect the cysts but met with mixed results. Another contentious issue is the lack of a direct correlation between the size and location of cysts on the MRI imaging and the degree of expected sacral nerve damage. Until a neurodiagnostic test is available, it will not be possible to show any evidence of sacral root damage due to Tarlov cysts and establish a prevention strategy to alleviate the suffering of patients.

Study 3 showed objective evidence for sacral root dysfunction due to Tarlov cysts. The study has shown that a large number of patients (65%) with symptomatic Tarlov cysts suffer from the S4 sacral root dysfunction. It also showed the location of the Tarlov cyst on MRI did not directly correlate with sacral root dysfunction. The sacral root dysfunction often extends beyond the MRI location. The study has shown comprehensively that sacral root damage due to the Tarlov cyst is genuine and can be measured objectively. The study has highlighted the importance of including a neurophysiology examination in a symptomatic Tarlov cyst evaluation.

5.1 Future research

The current pilot study met all the aims and objectives of all three Studies. The techniques developed in this research work can be used to do large-scale research in future. Care must be taken to record tibial SEP, S2, S3 and S4 dSEPs along with the pudendal SEP to make a meaningful comparison between them. Future research should focus on cutting the diagnostic pathways to a minimum by educating the medical community and bringing broad awareness among patients. It is also equally crucial for the BSCN to encourage and train

clinical scientists and consultant clinical neurophysiologists to test sacral nerve roots and interpret their findings.

5.2 Change in practice

Clinical scientists and clinical neurophysiologists should explore the possibility of setting up dedicated clinics to evaluate sacral root functions. The conventional clinical setup for pelvic neurophysiology evaluation is not feasible in future due to the sheer number of patients referred for suspected CES, pre-surgical evaluations, suspected small fibre neuropathies and other conditions in sacral segments. In the early 1940s, EEGs were recorded exclusively by medical doctors, which is unimaginable in recent days. With the advancement of technology and improved training facilities, clinical scientists should be able to run these advanced neurophysiology centres independently, thereby reducing the pressure on routine clinical practice. In addition, this hybrid model in clinical neurophysiology will immensely help patient care and spur innovations in healthcare.

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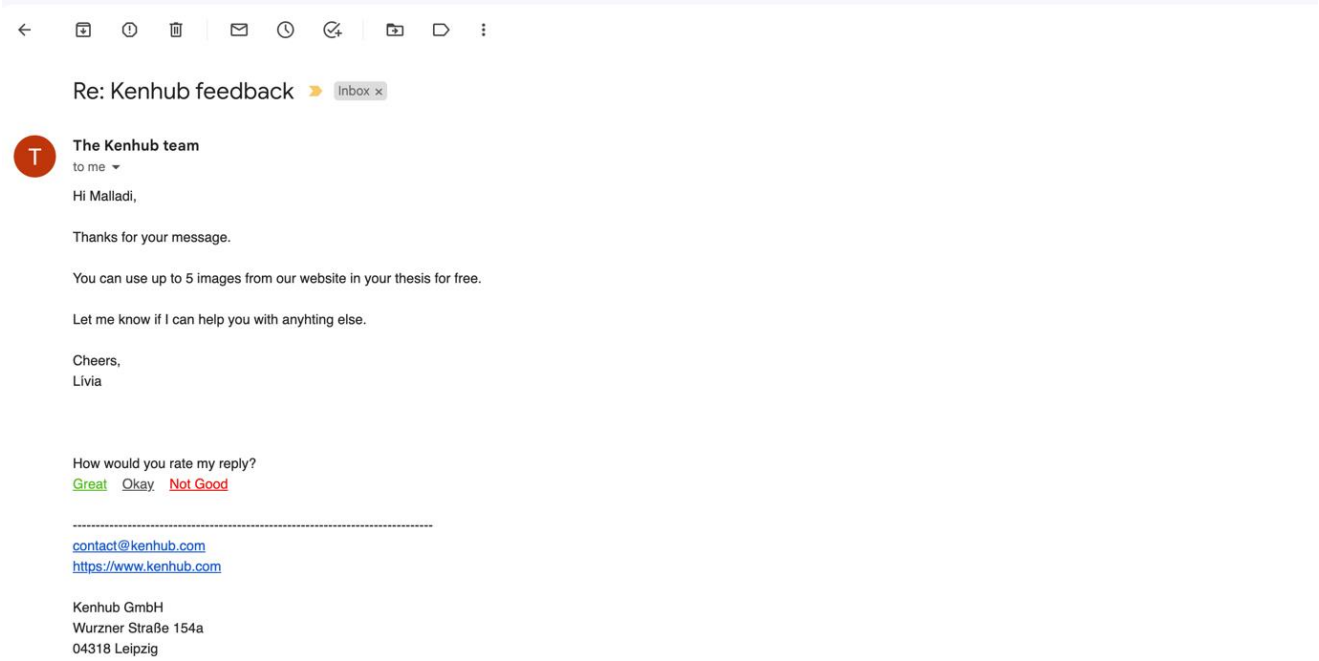
7.Appendices

7.1 Approval to use image from Kenhub.



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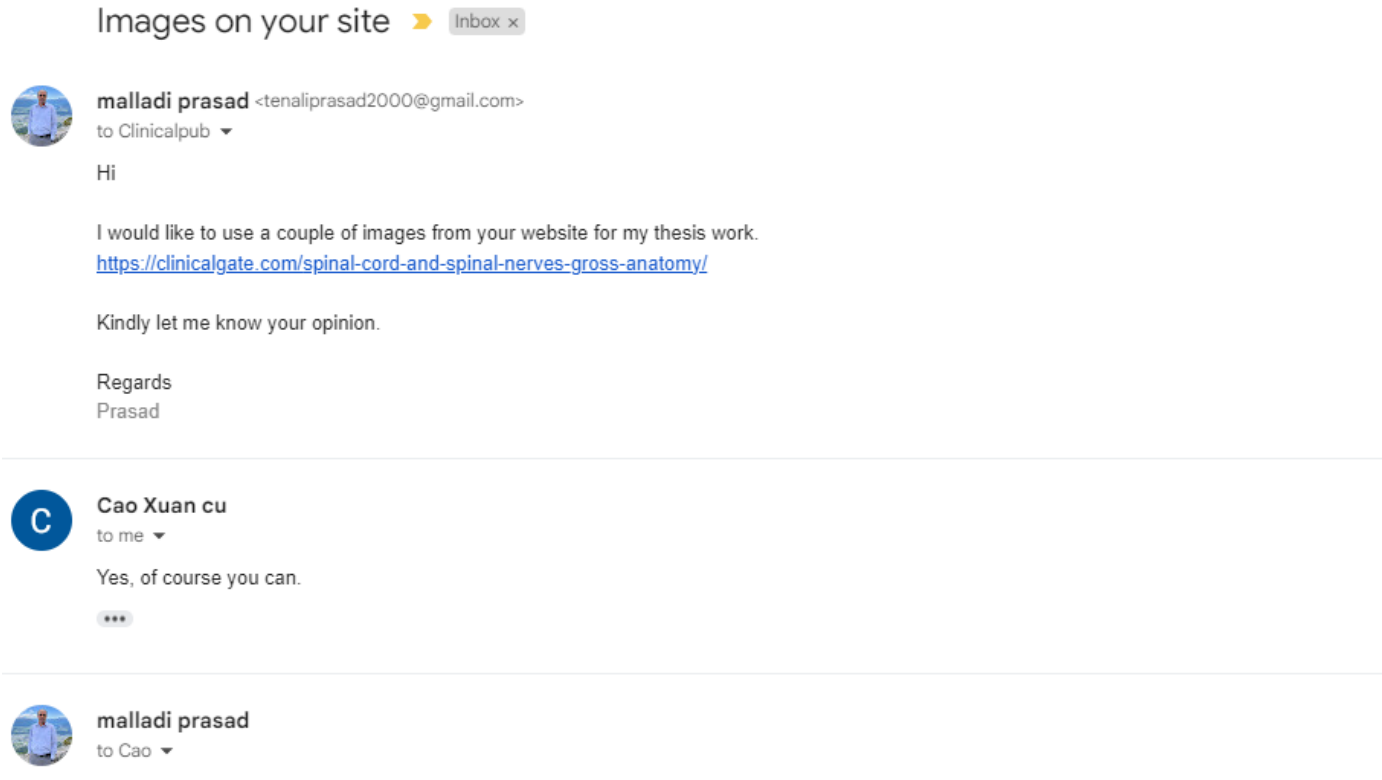

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7.3 Approval from Health Research Authority

Ymchwil Iechyd a Gofal Cymru
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25 January 2022

Dear Mr Malladi,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A comprehensive evaluation of the effects of sacral Tarlov cysts on pelvic neurophysiology and pelvic organ functions**
IRAS project ID:	**287553**
Protocol number:	**V1.0**
REC reference:	**21/NE/0194**
Sponsor	**University College London Hospitals 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

7.4 Approval from MMU Ethics and Governance team

13/09/2022

Manchester Metropolitan University

Project Title: Assessment of Neurophysiology parameters in symptomatic sacral Tarlov cysts

EthOS Reference Number: 46173

Certification

Dear Anjaneya Malladi,

The above application was reviewed by the Research Ethics and Governance Team and on the 13/09/2022, was certified. The certification is in place until the end date of your existing ethical approval and is based on the documentation submitted with your application.

Application Documents

Document Type	File Name	Date	Version
External Approval Supporting Information	Organisation Information Document	07/04/2021	v1.0
External Approval Supporting Information	Supervisor CV	30/05/2021	v1.0
External Approval Supporting Information	Applicant CV	30/05/2021	v1.0
External Approval Supporting Information	Consent form	15/06/2021	V1.0
External Approval Supporting Information	Cost attribution template	13/08/2021	V1.13
External Approval Supporting Information	Study Protocol	30/11/2021	v1.1
External Approval Supporting Information	Approved IRAS Form	12/01/2022	IRAS Version 6.3.2
External Approval Supporting Information	PIS+Version+1.2	12/01/2022	v1.2
External Approval Supporting Information	GP letter template	12/01/2022	v1.1
External Approval Letter	287553 - Letter_of_HRA_Approval	25/01/2022	V.1
External Approval Application Form	REC approval letter	25/01/2022	v1.0
External Approval Supporting Information	EDGE ID: 140504; Final approval from the NHS to start recruiting patients	18/03/2022	v 1.0
External Approval Supporting Information	Advertisement template	15/06/2022	v1.0

Conditions of certification

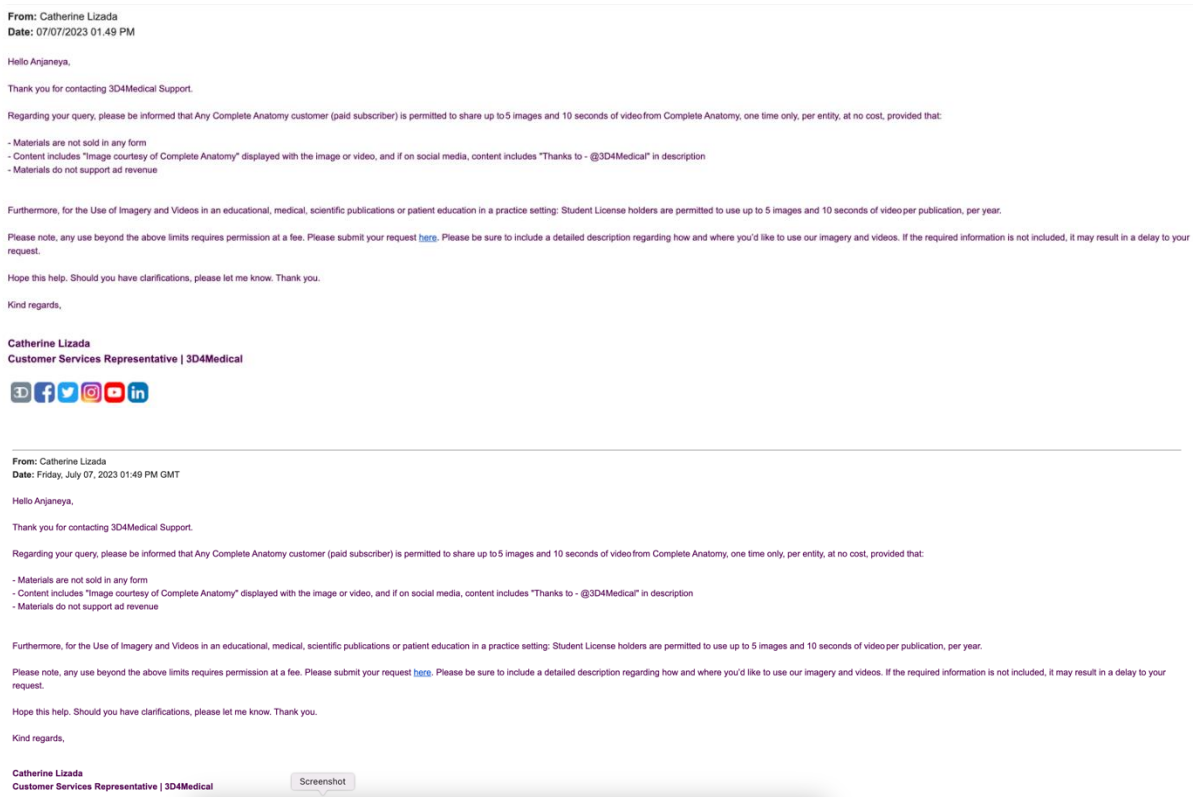
The Research Ethics and Governance Team would like to highlight the following conditions

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.

Page 1 of 2

7.5 Approval to use image from 3DMedical



From: Catherine Lizada
Date: 07/07/2023 01.49 PM

Hello Anjaneya,

Thank you for contacting 3D4Medical Support.

Regarding your query, please be informed that Any Complete Anatomy customer (paid subscriber) is permitted to share up to 5 images and 10 seconds of video from Complete Anatomy, one time only, per entity, at no cost, provided that:

- Materials are not sold in any form
- Content includes "Image courtesy of Complete Anatomy" displayed with the image or video, and if on social media, content includes "Thanks to - @3D4Medical" in description
- Materials do not support ad revenue

Furthermore, for the Use of Imagery and Videos in an educational, medical, scientific publications or patient education in a practice setting: Student License holders are permitted to use up to 5 images and 10 seconds of video per publication, per year.

Please note, any use beyond the above limits requires permission at a fee. Please submit your request here. Please be sure to include a detailed description regarding how and where you'd like to use our imagery and videos. If the required information is not included, it may result in a delay to your request.

Hope this help. Should you have clarifications, please let me know. Thank you.

Kind regards,

Catherine Lizada
Customer Services Representative | 3D4Medical

From: Catherine Lizada
Date: Friday, July 07, 2023 01:49 PM GMT

Hello Anjaneya,

Thank you for contacting 3D4Medical Support.

Regarding your query, please be informed that Any Complete Anatomy customer (paid subscriber) is permitted to share up to 5 images and 10 seconds of video from Complete Anatomy, one time only, per entity, at no cost, provided that:

- Materials are not sold in any form
- Content includes "Image courtesy of Complete Anatomy" displayed with the image or video, and if on social media, content includes "Thanks to - @3D4Medical" in description
- Materials do not support ad revenue

Furthermore, for the Use of Imagery and Videos in an educational, medical, scientific publications or patient education in a practice setting: Student License holders are permitted to use up to 5 images and 10 seconds of video per publication, per year.

Please note, any use beyond the above limits requires permission at a fee. Please submit your request here. Please be sure to include a detailed description regarding how and where you'd like to use our imagery and videos. If the required information is not included, it may result in a delay to your request.

Hope this help. Should you have clarifications, please let me know. Thank you.

Kind regards,

Catherine Lizada
Customer Services Representative | 3D4Medical

Screenshot

7.6 Copy of patient information leaflet

PARTICIPANT INFORMATION SHEET

Development of Dermatomal Evoked Potentials in symptomatic Tarlov cysts

"Development of Dermatomal Evoked Potential (DEP) in normal subjects and to use them in the assessment of Tarlov cysts"

Participation could really make a difference to develop tests to study nerve functions

We would like to invite you to take part in our research study. Before you make a decision, it is important you take the time to understand why we are doing this research and what it would involve. Please read the following information carefully and consider discussing it with friends and relatives.

What is the purpose of this research study?

This research project is a part of a student's academic qualification of The *Doctor of Clinical Science to study nerve functions in individuals with a condition called Tarlov Cysts*.

Tarlov cysts are fluid-filled sacs that generally form around nerve roots at the base of the spinal cord, causing pain below the waist that can spread to the buttocks, legs, and genital areas. Some individuals may also develop bowel and bladder complaints. The exact cause why Tarlov cysts occur is unknown, but they may occur due to variations in the flow of fluid around the nerves. There are no established tests to assess the damage caused to nerves by Tarlov cysts, and hence it is often difficult to make a surgical decision.

In this research study, we would like to develop a series of tests to assess the nerves emerging from the lower part of the spinal cord that is often close to Tarlov cysts. The findings of this research will help considerably to fill a gap in our understanding of how Tarlov cyst affects nerves and thereby help with making a decision about their treatment.

Summary of the study

In this research project, we will be studying how the nerves that arise from the base of the spine function. In this study, we will be studying nerve functions by assessing how

they carry electricity when they are stimulated using small electric pulses. The nerves we will be stimulating are located over your leg, buttock, in the area between the legs (called the perineum) and over the genitalia (penis/clitoris).

There will be three parts to this, and you will be invited to participate in only one of the studies:

In study 1, we would like to recruit healthy adults to understand nerve function when we stimulate their nerves with electrical pulses.

In study 2, we would like to recruit volunteers who have suffered some sort of injury to their lower spinal cord or nerves that affect sensations over their leg, buttock, and genital area and understand nerve functions. The comparison of results between study 1 and study 2 will help us to understand how accurate the tests can identify that nerves have been affected.

In study 3, we would like to recruit volunteers who have been told to be having Tarlov cysts. We would like to understand nerve functions and compare findings with the MRI changes and correlate them with bowel and bladder functions.

This research work will help us to establish new tests to study the function of nerves from the base of the spine, which currently does not exist. The study will lead to designing a diagnostic pathway for assessing individuals with Tarlov cysts.

We plan to share our research knowledge with clinicians and scientists through publications and research meetings.

What are we testing in this research work?

We will stimulate nerves in the lower limbs and genital area with small electrical pulses and record the responses from the head by attaching six small metal discs using a sticky paste. These metal discs are approximately the size of a pea and do not hurt while connecting or removing from the head. We observe how much time it takes for an electrical pulse to travel from the stimulating point to the head.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your decision will not result in any penalty or impact the standard of medical care that you receive in any way. If you do decide to take part after reading this information sheet, you will be given this information sheet to keep (or be sent electronically) and will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason.

Can I take part?

Volunteers who are above the age of 18 are eligible to participate.

If you are joining study 1:

- You should not have any history of sensory loss over your legs, buttock, or genital area.
- We would request that you share with us your medical history. Any information you provide will be kept confidential.
- You would need to visit the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery (part of the University College London Hospitals NHS Foundation Trust) **only once** during the study.

If you are joining study 2:

- You should be having a history of spinal cord injury that caused damage to the base of the spinal cord or nerves and should be experiencing a loss of sensations in the genital area, buttock or back of the leg.
- We would request that you share with us your medical history. Any information you provide will be kept confidential.
- You would need to visit the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery (part of the University College London Hospitals NHS Foundation Trust) **twice** during the study with a minimum interval of 24 hours apart.

If you are joining study 3:

- You should be having Tarlov cysts at the base of your spine that has been confirmed by MRI scan, and you are currently affected by these cysts
- We would request that you share with us your medical history. Any information you provide will be kept confidential.
- You would need to visit the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery (part of the University College London Hospitals NHS Foundation Trust) **only once** during the study.

You will not be able to participate in this study if:

- Have an implanted cardiac device such as a Pacemaker or Implantable cardioverter-defibrillator
- Currently taking anticoagulants, such as Warfarin or Apixaban, Rivaroxaban, Dabigatran or Edoxaban
- Have suspected or known alcohol or drug dependency currently
- Have a known severe and/or uncontrolled cardiovascular disease or neurological illness
- There is a history of allergic disease or a reaction that could be made worse by using micropore tape or non-woven polyester

What will happen if I decide to take part?

If you decide you would like to take part in this research project, you can contact the investigator Mr Prasad Malladi at prasad.malladi@nhs.net to ask any questions and arrange a suitable appointment date for the visit.

On the day of the visit – 2 hours (Listen to a consent presentation, ask any questions, sign a consent form, height and weight check, alcohol dependency check, medical history, physical examination and Evoked Potential Studies).

You will spend some time going through the information leaflet with a member of the investigating team to ensure that you understand what to expect by taking part. You can ask any questions before signing a consent form. If you decide you would like to take part, you will sign a consent form and a neurologist will ask questions about your health and discuss details of your medical history.

You will then change into a hospital gown and be accompanied by a chaperone throughout the test.

A neurologist will perform a physical examination which could involve asking to walk normally or on a line on the floor, maybe instructed to tap your fingers or foot quickly or touch something, such as your nose with eyes closed. You may be tested by having to push and pull against the doctor's hands with your arms and legs. The doctor will also check your sensations over your skin using tuning forks, swabs, or nylon thread. Sensation will be checked in areas that include arms, legs and in the genital area. The entire physical examination should take no more than 20 minutes.

A scientist will take some measurements of your head and attach six small discs onto your head using a sticky paste over your hair and tape them down to hold in place over your scalp. The skin under each disc has to be rubbed gently to ensure the discs have good contact with your skin. The scientist will also attach a couple of small pads and wires and stimulate nerves at your ankle, back of your thigh, on your buttocks and the penis/ clitoris. The scientist will also attach two small sticker electrodes on the skin around your back passage.

The tests may be mildly uncomfortable, but not painful, and the amount of electrical stimulation can be adjusted to accommodate your tolerance levels. Furthermore, you could request taking a break or stop entirely. From our experience, most individuals tolerate these procedures well without any problem.

What are the side effects and risks?

There are no side effects or risks from having a sensory evoked potential study.

What should I avoid before or during the visit?

There are no restrictions on your activity or your current medication

Will I be paid for taking part in this trial?

If you choose to take part in this research study, you will be compensated for your time, the inconvenience of attending and undertaking the procedure, and your travel expenses. The amount compensated will be £100 per visit in the form of a voucher.

What will happen if I don't want to carry on with the research work?

If at any time after agreeing to participate you change your mind, you are free to withdraw without giving a reason. Your decision will not result in any sort of penalty and this will not affect the standard of medical care that you receive.

Complaint's statement

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this research study, please contact the patient advice and liaison service (uclh.complaints@nhs.net or telephone number (02034477413).

Would my taking part in this research work be kept confidential?

All information that is collected about you during the course of this research will be coded with a study number and kept confidential. The information collected will be accessible only to members of the research team.

If you are participating in study 1:

Your GP will not be informed about this study. Your medical records will not be reviewed by any of the investigators.

If you are participating in study 2:

Your GP will not be informed about this study. We will use information from your medical records for this research project and this includes your

- NHS number
- Type of your spinal cord/nerve injury

People will use this information to do the research or to check your records to make sure that the research is being done properly.

If you are participating in study 3:

Your GP will be informed about this study. We will need to use information from your medical records for this research project. This information will include your

- NHS number
- Details of your Tarlov cysts from your MRI scans
- Details of your bowel and bladder functions

People will use this information to do the research or to check your records to make sure that the research is being done properly.

What will happen to the results of the research study?

The results of this research study will be presented at scientific meetings or conferences and published in a scientific medical journal. At no point will the identity of study participants be shared.

Who is sponsoring, organising and funding the research?

The study is organised and sponsored by the University College London Hospitals NHS Trust (UCLH). The study is funded through financial support to the UCLH from Health Education England, which is an executive non-departmental public body, sponsored by the Department of Health and Social Care.

7.7 Alcohol Use Disorder Identification Test (AUDIT) form

Alcohol use disorders identification test (AUDIT)

AUDIT is a comprehensive 10 question alcohol harm screening tool. It was developed by the World Health Organisation (WHO) and modified for use in the UK and has been used in a variety of health and social care settings.

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times per month	2 to 3 times per week	4 times or more per week	
How many units of alcohol do you drink on a typical day when you are drinking?	0 to 2	3 to 4	5 to 6	7 to 9	10 or more	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Total AUDIT score	

7.8 Tibial latency data from Study 1

No.	Gender	Height	Age	BMI	Pain score due to the test (0-10)	R_Tib_Lat	L_Tib_Lat	Mean latency	R_Tib_Amp	L_Tib_Amp
1	Female	150	30	17.5	1	34.7	34.7	34.7	1.9	2.6
2	Female	165	37	33.1	1	45.8	44.5	45.15	1.5	1.9
3	Female	160	20	19.5	1	43.1	45.5	44.3	2.6	2
4	Female	165	22	26.4	1	43.3	41.3	42.3	1.8	2.2
5	Female	165	69	33.1	1	42.8	42.7	42.75	2.4	3.4
6	Female	170	27	20.8	0	38	39.2	38.6	2	1.9
7	Female	163	24	28.2	1	40.6	36.6	38.6	2.9	2
8	Male	168	47	31.9	1	43.1	40.2	41.65	1	0.6
9	Male	175	27	19.6	0	39.2	41.9	40.55	1.4	1.4
10	Male	178	49	24.4	0	41.6	42.7	42.15	4.1	5.3
11	Male	190	27	19.3	0	41.3	43.9	42.6	0.5	1
12	Female	160	36	28.9	0	39.5	42	40.75	2	1.5
13	Female	152	42	39.9	0	46.4	48.6	47.5	2.3	2.1
14	Female	183	32	19.4	1	47	49.7	48.35	2.2	1.5

15	Male	168	31	21.25	1	43.6	43.6	43.6	2.8	3.1
16	Female	160	49	25	0	42.5	44.8	43.65	1.69	1.4
17	Female	150	49	29	0	40.2	38	39.1	3	3.3
18	Female	160	75	17.9	1	50.5	49.2	49.85	1.6	1.1
19	Female	170	40	23.8	1	40.8	40.6	40.7	1.4	1.8
20	Male	177	26	30.3	1	41.3	42.7	42	2.5	2

7.9 Bladder and bowel symptoms reported in Study 2

Table 30: Bladder and bowel symptoms in cohort 2 participants.

No	Bladder retention	Bladder incontinence	ISC	Bladder sensation	urgency	Constipation	Bowel Incontinence	Digital Evacuation	Rectal Sensation
1	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
2	No	No	No	Yes	Yes	No	No	No	Yes
3	No	No	No	Yes	yes	No	No	No	Yes
4	No	No	No	Yes	Yes	Yes	No	No	Yes
5	No	No	No	Yes	yes	No	Yes	No	Yes
6	Yes	No	Yes	Yes	yes	Yes	Yes	No	Yes
7	Yes	No	Yes	No	No	No	No	No	No
8	No	Yes	No	No	No	Yes	No	No	Yes
9	No	No	No	Yes	No	No	No	No	No
10	No	Yes	No	No	Yes	Yes	Yes	No	Yes
11	No	Yes	No	Yes	No	Yes	No	No	Yes
12	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
13	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
14	No	Yes	No	No	No	No	Yes	No	Yes
15	No	Yes	No	No	Yes	No	No	No	Yes
16	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
17	No	No	No	No	Yes	No	No	No	Yes
18	Yes	No	No	No	Yes	Yes	No	No	Yes
19	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
20	Yes	Yes	Yes	No	No	Yes	Yes	No	No

7.10 Sensory and motor deficits reported in Study 2

Table 31a: Distribution of pain and sensory deficits observed in cohort 2.

				Loss of sensation revealed in the clinical examination									
				S2		S3		S4		S1		L5	
	Pelvic Pain	Buttock Pain	Leg Pain	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
1	Yes	Yes	Yes	1	2	1	2	0	1	2	2	2	2
2	Yes	Yes	Yes	2	2	2	2	2	2	2	2	2	2
3	No	No	Yes	1	1	1	1	0	0	2	2	2	2
4	No	No	No	1	2	2	2	1	1	1	2	2	2
5	No	No	No	2	2	2	2	1	1	2	2	2	2
6	No	No	No	2	2	2	2	2	2	2	2	2	2
7	No	No	Yes	2	2	2	2	2	2	2	2	2	2
8	Yes	No	No	2	1	2	1	2	1	2	2	2	2
9	Yes	Yes	No	2	2	2	2	2	2	2	2	2	1
10	No	No	No	1	1	0	0	0	0	1	1	2	2
11	No	No	No	1	1	1	1	1	1	2	2	2	2
12	Yes	Yes	Yes	1	1	1	1	1	1	2	2	2	2
13	No	No	No	2	2	2	2	2	2	1	2	1	2
14	No	No	No	2	2	2	2	2	2	2	2	2	2
15	Yes	Yes	No	2	2	2	2	2	2	2	2	2	2
16	Yes	No	No	2	1	2	1	0	0	2	1	2	2
17	No	Yes	No	2	2	1	2	2	2	2	2	2	2
18	Yes	No	No	2	2	2	2	2	2	2	2	2	2
19	Yes	No	No	1	1	1	1	1	1	0	1	1	1
20	Yes	No	No	2	1	2	1	1	1	2	1	2	2

Sensory deficits were coded according to the International Standards for the Neurological Classification of Spinal Cord Injury guidelines. 0 – Absent, 1- reduced and 2 -normal.

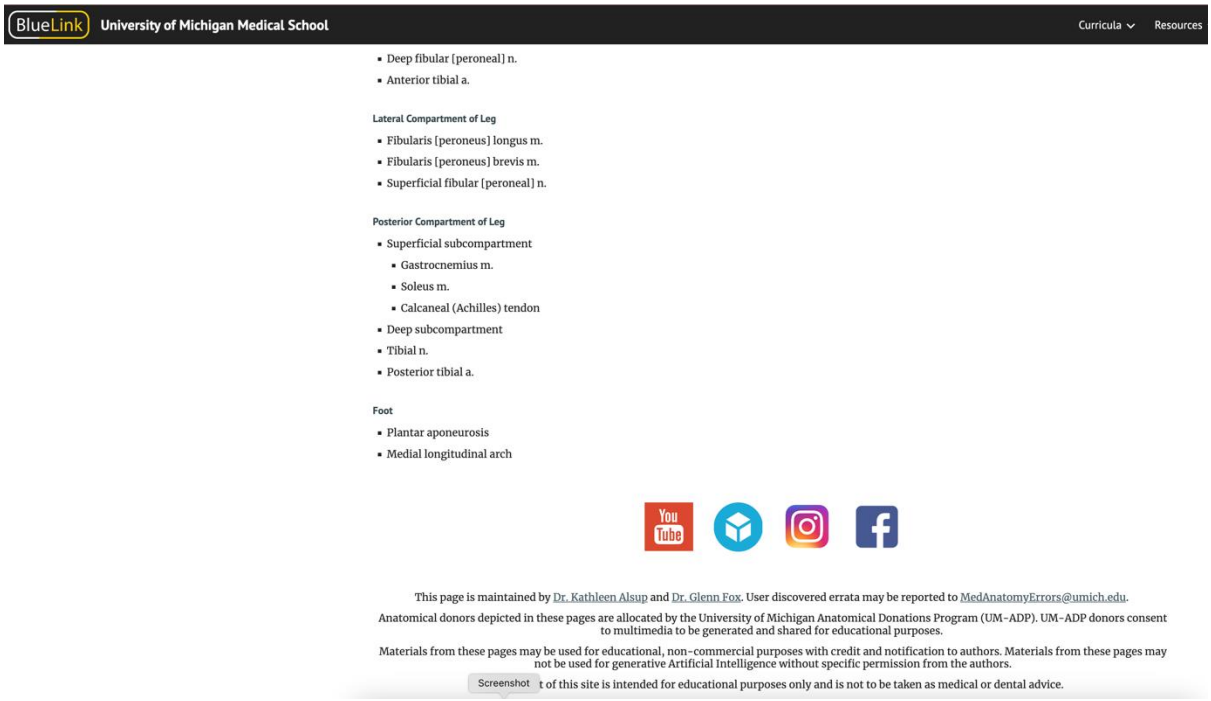
Table 31b: Distribution of motor deficits observed in cohort 2.

Volunteer Number	Anal tone	Anal reflex	S1	L5	Sex Dysfun

1	2	0	2	2	Yes
2	2	2	2	2	No
3	2	2	1	1	Yes
4	1	0	2	2	Yes
5	2	2	2	2	Yes
6	2	2	2	2	No
7	1	1	2	2	Yes
8	2	2	2	2	No
9	2	2	2	2	No
10	1	1	2	2	Yes
11	1	1	2	2	No
12	1	0	2	2	Yes
13	2	2	2	2	No
14	2	2	2	2	No
15	1	2	2	2	No
16	1	1	2	2	Yes
17	2	2	2	2	No
18	1	1	2	2	No
19	1	1	2	2	Yes
20	1	1	2	2	Yes

Motor deficits were coded according to the International Standards for the Neurological Classification of Spinal Cord Injury guidelines. 0 – Absent, 1- reduced and 2 -normal.

7.11 Approval to use the pelvic splanchnic nerves image from the University of Michigan Medical School



BlueLink University of Michigan Medical School Curricula Resources

- Deep fibular [peroneal] n.
- Anterior tibial a.

Lateral Compartment of Leg

- Fibularis [peroneus] longus m.
- Fibularis [peroneus] brevis m.
- Superficial fibular [peroneal] n.

Posterior Compartment of Leg

- Superficial subcompartment
  - Gastrocnemius m.
  - Soleus m.
  - Calcaneal (Achilles) tendon
- Deep subcompartment
- Tibial n.
- Posterior tibial a.

Foot

- Plantar aponeurosis
- Medial longitudinal arch

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7.12 Supplementary data for dSEPs latency vs stimulus strength

Threshold	Number of times	Stimulus strength given (mA)	P1 - Latency (ms)	N1 - Latency (ms)	Amplitude (µV)
6	1	6	43.1	49.1	0.3
6	2	12	38.4	47.7	0.9
6	2.5	15	35.5	45	1.59
6	3	18	35	45	1.81
6	3.5	21	35.3	44	1.61
6	4	24	35.2	44.7	1.61

S3 Dermatome latency vs stimulus strength

Threshold	Number of times	Stimulus strength given	P1 - Latency (ms)	N1 - Latency (ms)	Amplitude (µV)
8	1	8	37.8	47.4	0.47
8	2	16	38.9	49.1	1.66
8	2.5	20	38.8	47.1	1.67
8	3	24	37.8	47.1	1.64
8	3.5	28	37.3	46.8	1.62
8	4	32	36.9	45.9	1.47

2.12.10 S4 Dermatome latency vs stimulus strength

Threshold	Number of times	Stimulus strength given	P1 - Latency (ms)	N1 - Latency (ms)	Amplitude (µV)
5	1	5	Inconsistent		0
5	2	10	39.4	47.1	0.89
5	2.5	12.5	36.4	47.1	0.74
5	3	15	37.8	47.4	0.88
5	3.5	17.5	36.7	47.1	0.80
5	4	20	36.7	47.1	0.95

-