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An investigation of somatosensory evoked potential responses during brain tumour surgery

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That the contributions of others to the project are as follows:

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ABSTRACT

Introduction: Intra-operative neurophysiological monitoring (IONM) is the use of electrophysiological tools to evaluate and monitor the functional status of the nervous system during surgery. The main aim of IONM is to mitigate the risk of damage to nervous tissue during neurological surgery, such as brain tumour resection surgery, and to reduce the incidence of postoperative neurological complications.

The IONM techniques commonly employed include somatosensory evoked potentials (SSEPs). The main use of SSEPs is the indirect warning of possible sensory nervous pathway injury. Intraoperative SSEP monitoring requires adroit coordination by healthcare professionals. Despite progression in this field, there is rather limited research comparing responses in the cortical, sub-cortical contralateral, and ipsilateral SSEP responses.

Aim: This study aimed to evaluate the use of continuous SSEP monitoring during resection of intracranial brain tumours to provide an ongoing functional assessment of the somatosensory pathway.

Methods: This retrospective study was conducted using data from patients who underwent continuous somatosensory evoked potential (SSEP)monitoring during brain tumour reresection surgery between January 2019 and December 2021 at Steve Biko Academic Hospital (SBAH). The data was compiled electronically and then subjected to statistical analysis as per the study the objectives.

Results: Contralateral latencies showed consistently higher values than ipsilateral readings across all the cortical measurements. In addition, the cortical latencies consistently exceeded the subcortical latencies. Particularly, the latencies prior to brain tumour resection tended to exhibit greater values than those recorded during and after the resection process.

Conclusion: The data suggests that latency tends to decrease over the course of surgery, reflecting improvements in sensory pathways following tumour removal. This pattern suggests a dynamic relationship between the timing of the surgical intervention and the somatosensory evoked potential latencies.

Keywords: Intra-operative neurophysiological monitoring, somatosensory evoked potentials, brain tumour resection surgery

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LIST OF ABBREVIATIONS

BAEP	Brainstem auditory evoked potentials
CNS	Central Nervous System
CST	Corticospinal tract
EEG	Electroencephalography
EMG	Electromyography
EP	Evoked potentials
IQR	Interquartile range
IONM	Intra-operative Neurophysiological Monitoring
MR	Median Raphe
MEP	Motor evoked potential
NHRD	National Health Research Database
ROC	Receiver operating characteristic
SSEP	Somatosensory evoked potentials
SD	Standard Deviation
SBAH	Steve Biko Academic Hospital

CHAPTER 1: INTRODUCTION

1.1 CHAPTER OBJECTIVE

In this chapter, the background, problem statement and background literature pertaining to this study will be discussed.

1.2 BACKGROUND

Intra-operative neurophysiological monitoring (IONM) is commonly used in a variety of adult and paediatric surgical procedures.[1] Intraoperative neuromonitoring is defined as “electrophysiological methodology to evaluate functional status of the nervous system during surgery”.[2] Although ‘monitoring’ is part of the function, the process does not solely ‘monitor’ but also assists in mapping.[2] Monitoring refers to the continuous receiving of neural signals in order to assess the nervous system, whereas mapping identifies and reveals the neural structures within the area of operation or surgery to aid in minimising neural damage.[2] Intraoperative neuromonitoring is an alternative to testing patients while they are awake in order to monitor neurological injury.[2]

1.3 PROBLEM STATEMENT

Brain tumour surgery is a high-risk procedure that can lead to postoperative functional impairment owing to neural damage. The use of IONM during neurological surgery aims in mitigating this risk or to reduce the incidence of postoperative neurological complications. However, SSEPs can be a complex neuromonitoring tool. For this reason, the study assessed the impact of SSEPs on brain tumour resection.

1.4 LITERATURE REVIEW

1.4.1 Midline vs hemispheric brain tumours

Midline brain tumours

Midline brain tumours are typically defined by their location within the central part of the brain, which is neither on the left nor on the right side. This central region includes structures such as the thalamus, hypothalamus, pineal gland, and structures surrounding the third ventricle. Tumours that develop within or around these central structures are considered to be midline brain tumours.[3]

Midline brain tumours can cause a range of neurological symptoms and can be challenging to treat owing to their location and potential impact on critical brain functions. Treatment options may include surgery, radiation therapy, chemotherapy, or a combination of these approaches, depending on the type, size, and grade of the tumour. The specific treatment plan is determined by the patient's medical team, based on a thorough evaluation of the tumour and its effects on brain function.[4-5]

Hemispheric brain tumours

Hemispheric brain tumours are those that are located in areas of the brain that can be categorised either as left-sided or right-sided tumours. These tumours typically occur in the cerebral hemispheres, which make up the largest part of the brain and are divided into a left hemisphere and a right hemisphere. The cerebral hemispheres are responsible for functions such as motor control, sensory perception, language processing, and higher cognitive functions.[4]

When a brain tumour is described as hemispheric, it means that it is situated within one of the cerebral hemispheres. For example:

1. Left brain tumour: A tumour located in the left cerebral hemisphere can affect functions related to language, speech, and right-sided motor control. Depending on its precise location within the left hemisphere, it may impact specific cognitive functions.

2. Right brain tumour: A tumour in the right cerebral hemisphere can affect functions related to spatial perception, creativity, and left-sided motor control. Again, the impact depends on the tumour's exact location.

Brain tumours in the cerebral hemispheres may vary in size, type, and grade, which can influence their symptoms and treatment options. Treatment may involve surgery, radiation therapy, chemotherapy, or a combination of these therapies, depending on the characteristics of the tumour and the patient's overall health.[3,6]

1.4.2 Motor evoked potential (MEP)

Motor evoked potentials involve directly activating and monitoring motor pathways.[2] The most common IONM technique of MEP during surgery is to stimulate the corticospinal tract (CST) and to record the responses at the spinal cord or relative muscles.[7] Stimulation is conducted by transcranial electrical stimulation via subdermal

or surface needle electrodes on the scalp. The stimulation elicits an excited response in corticospinal projections at various levels, just beneath the motor cortex, the internal capsule, or at the pyramidal decussation.[8] Figure 1 illustrates the generation of motor evoked potentials at different levels of the brain. To isolate the side of interest, the stimulation parameters can be adjusted to avoid deeper structures.[2,8]

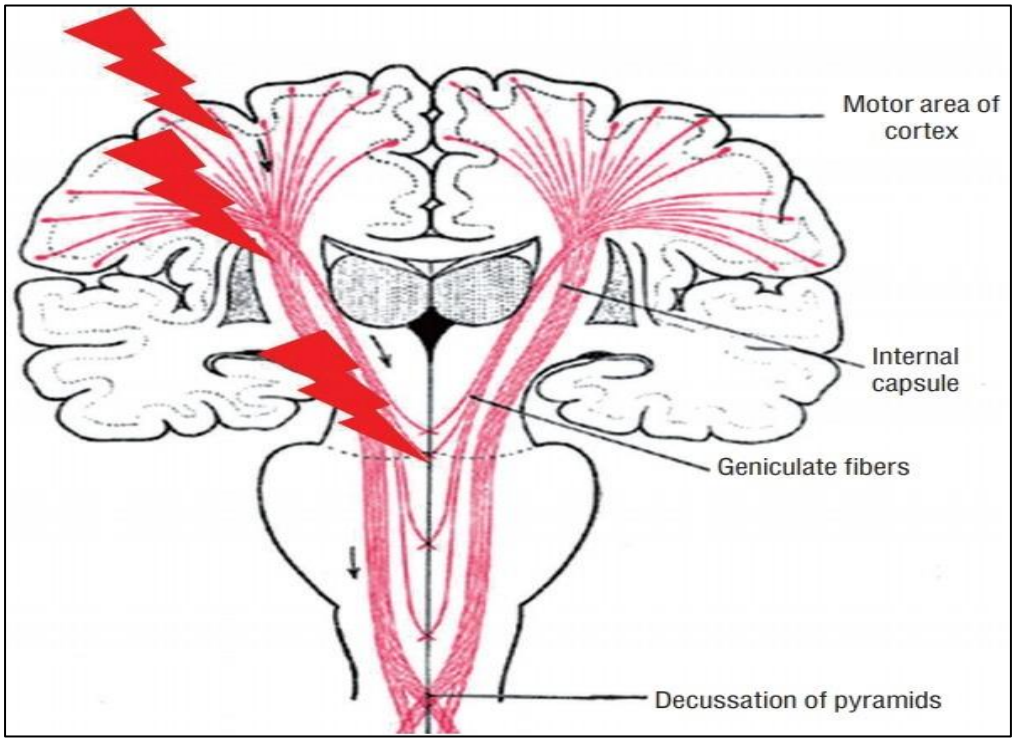

Figure 1. Generation of motor evoked potentials at different levels of brain [2]

A hurdle when performing MEPs is that a stable and effective response is not readily achieved when strong currents alone are applied. This hurdle is even bigger when dealing with paediatric patients.[9]

This can be overcome by applying additional stimulation techniques to optimise MEP monitoring.[2] There are two techniques:

1. Spatial facilitation – Applying peripheral tetanic stimulation before MEP.[10]
2. Temporal facilitation – Applying multi-pulse train stimulations, usually composed of four to five pulses.[9]

A combination of temporal and spatial facilitation may induce more reliable MEPs. However, a study conducted in 2017 stated that temporal stimulation alone was as

effective as the combination technique.[2] It is also more readily available and requires no additional equipment.

Obtaining stable MEP waveforms is more difficult in paediatric patients as their nervous system is not fully developed, depending on their age. Myelination and synaptogenesis may not be completed efficiently, making the patient's electrophysiological responses more sensitive to anaesthesia.[2] Another limiting factor is the size of the patient's body. This can create difficulty when placing stimulators, recording electrodes, and grounds, which could trigger large stimulation artifacts that obscure the signal of interest.[11] Owing to these challenges, MEP in paediatric patients frequently requires more pulses and different train profiles. [12]

An MEP can be recorded at the muscles of interest, in which case it is called a myogenic MEP, or they can also be recorded at the spinal cord level, by recording in D-waves or I-waves.[2] Myogenic MEP responses are partly non-linear and can be interpreted qualitatively, in many circumstances per the rule of "all or none".[12]

1.4.3 Electromyography (EMG)

Electromyography is used as a standard test for neuropathy and myopathy in IONM.[2] Free-running EMG is the standard technique to monitor cranial motor nerves, roots, or peripheral nerves during surgery. Intraoperative EMG signals are activated immediately after cranial motor nerves are damaged or irritated.

Abnormal EMG signals may develop days to weeks after nerve injury.[2] The persistence, morphology, and duration of EMG reflects the severity of neural injury. The longer the EMG train signal persists, the more likely it is that neural deficits in the patient will follow after surgery.[13] A high frequency of sinusoidal, symmetric sequence of EMG discharges implies that there is a possible neural injury.[14] However, it should be noted that injuries from sharp transection or gradual ischemia may not revoke any EMG signal at all.[2] Figure 2 illustrates some EMG setups.

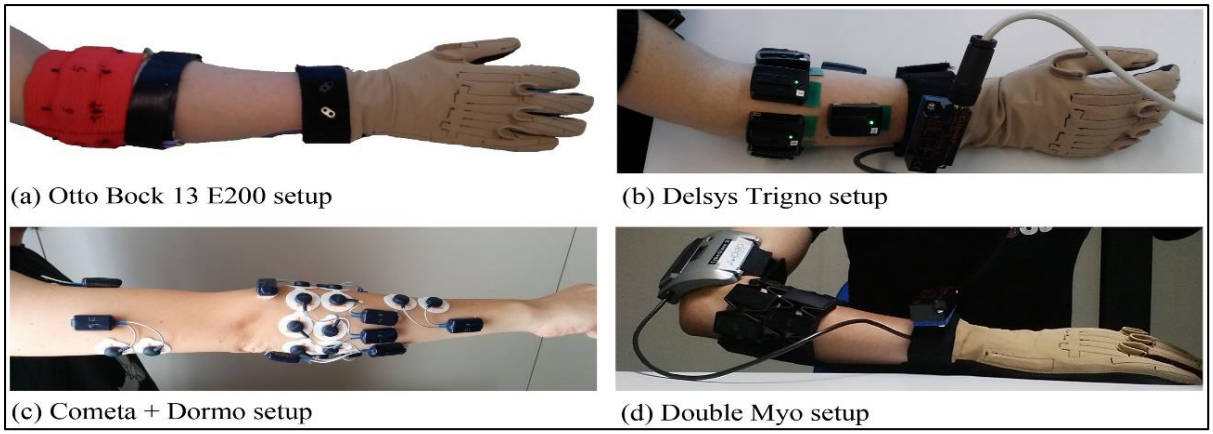

Figure 2. Acquisition setups for EMG[15]Figure 2a) Otto Bock 13 E200 setup, 2b) Delsys Trigno setup, 2c) Cometa and Dormo setup, 2d) Double Myo setup

1.4.4 Electroencephalography

Electroencephalography (EEG) is a valuable tool used in neurological assessments and has become the standard of care in practice because it demonstrates uniform electrophysiological changes across different varieties of surgeries. After all, neurological sequelae from cord injury are grievous in their functional aspects.[2,16-17] Electroencephalography studies are usually conducted before and after the surgeries since the scalp is usually inaccessible for electrode placement during brain tumour removal surgery.[18]

The purpose of performing the EEG is to make sure the patient has healthy overall brain activity and that any abnormalities can be observed easily after surgery to alert medical staff of possible damage or seizure warnings.[18] Signs of seizures include generalised spike-wave discharges at 3/s or faster; and evolving discharges of any type that reach a frequency > 4/s, whether focal or generalised. These would still be referred to as electrographic seizures.[19] The duration, prevalence, and frequencies of these spikes should be noted for further observation about the stimulation.[19] Sometimes EEGs are performed pre-surgery to evaluate any abnormal brain activity as a prognostic tool.[18]

Figure 3 illustrates the possible EEG electrode placements that are used when performing an EEG.

Figure 4 shows an example of an EEG electrode placement on a patient at the Steve Biko Academic Hospital (SBAH).

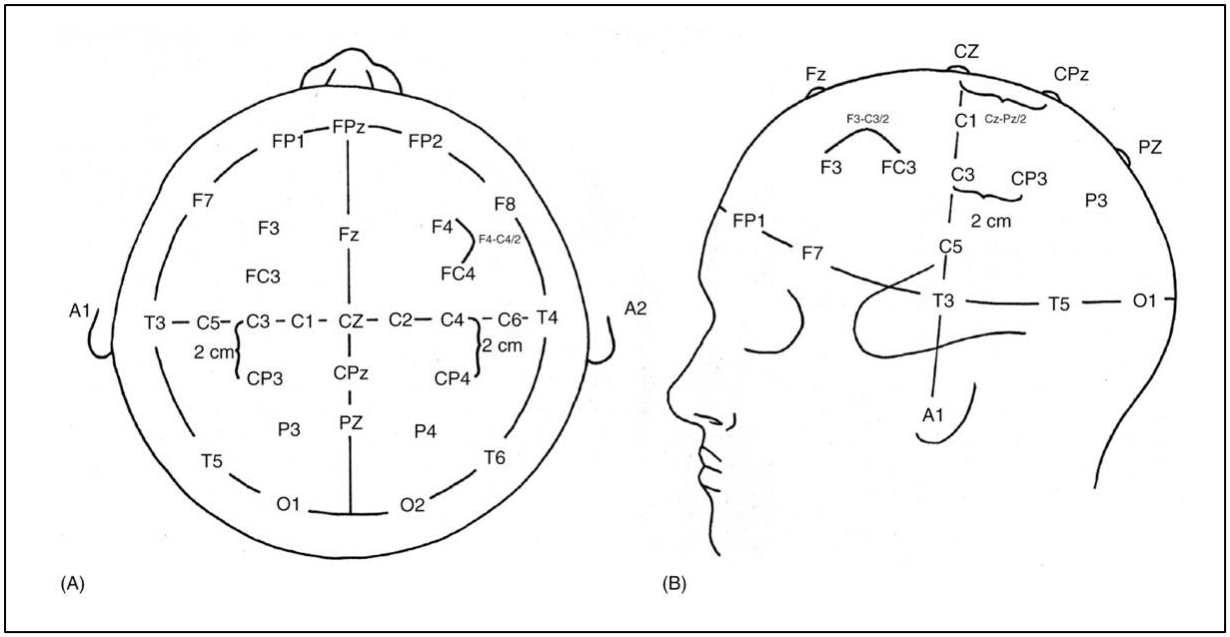

Figure 3. EEG electrode placements. (A): Head in vertex view, nose above, left ear to left. (B): Head in side-profile view. EEG electrodes: Z: Midline: FZ: Midline Frontal; CZ: Midline Central; PZ: Midline Parietal; OZ: Midline Occipital. Even numbers, right hemisphere locations; odd numbers, left hemisphere locations: Fp: Frontopolar; F: Frontal; C: Central; T: Temporal; P: Parietal; O: Occipital.

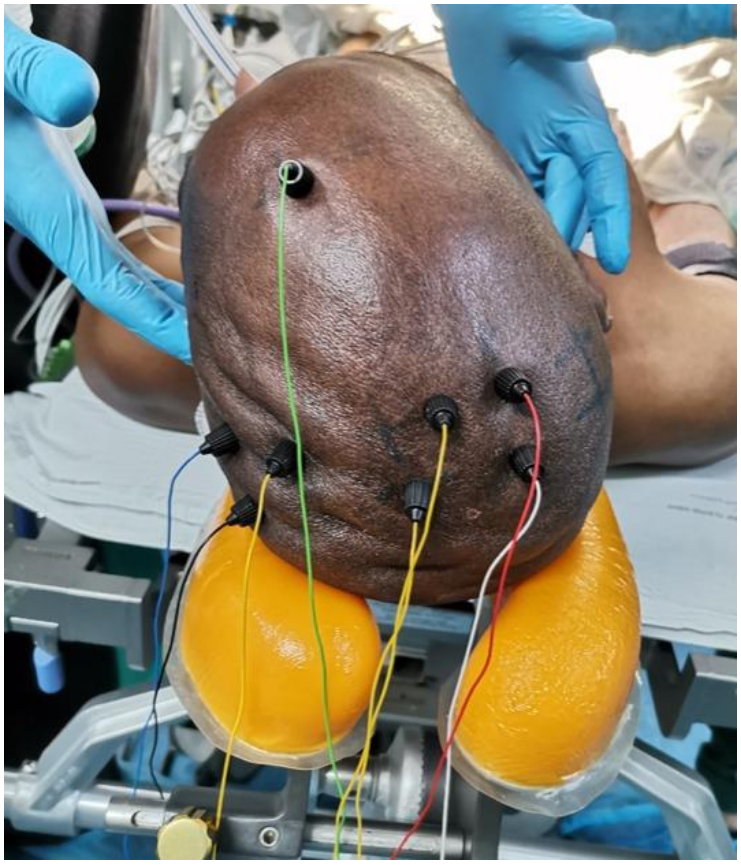

Figure 4. EEG electrode placement on a patient at SBAH. Electrode placement with wires colours as reference as follows: Green: FPz; Yellow: (left to right) C1, CPz, C2; Blue: C3; Black: CP3; Red: C4; White: CP4.

1.4.5 Brainstem auditory evoked potentials (BAEP)

Brainstem auditory evoked potentials are integrated into IONM to monitor the auditory pathway from the periphery to the auditory cortex, especially for infratentorial lesions.[20] Brainstem auditory evoked potentials provide information about the functional integrity of neural structures that can otherwise be obtained only by clinical assessment of unanaesthetised patients. These potentials offer promise as a means of monitoring the auditory nerve and brain stem during neurosurgical operations that place these structures at risk.[21,22] Figure 5 below illustrates how the BAEP is set up at the Steve Biko Academic Hospital as well as the type of ear inserts used.

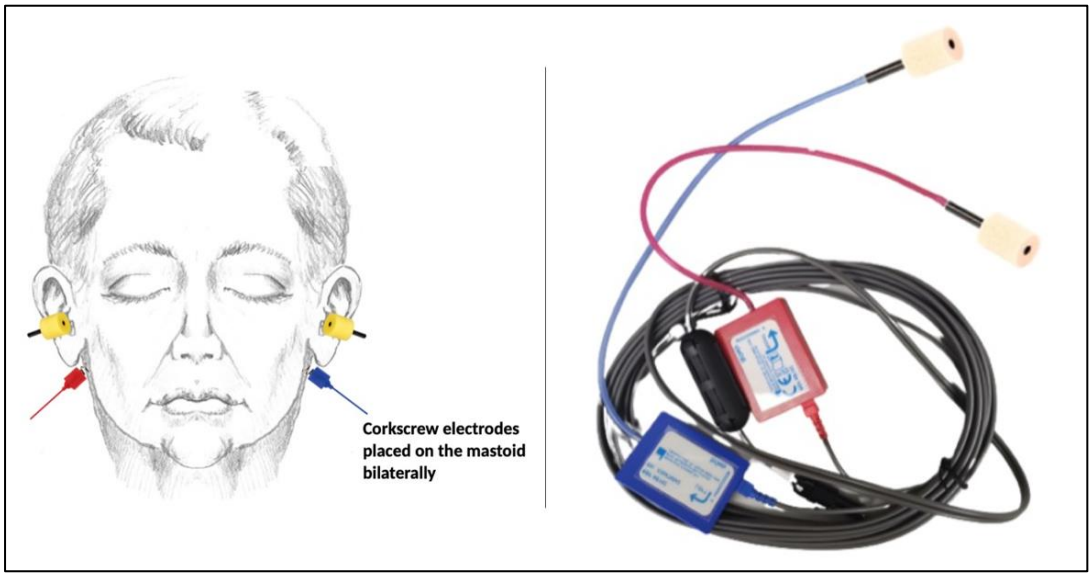

Figure 5. BAEP set-up. Figure 5 (left) indicates the placement of the BAEP ear inserts and electrodes. Figure 5 (right) shows the type of ear inserts that can be used for BAEP.

1.4.6 Somatosensory evoked potentials

What it is used for

Somatosensory evoked potentials (SSEP) have been employed as an intraoperative monitoring tool for more than three decades, which is the most commonly used technique.[2,23-24] Presently, they serve two primary purposes: first, to evaluate the operational condition of somatosensory pathways during various surgical procedures that could impact peripheral nerves, spinal cord functions (such as deformity correction, repairing traumatic spinal fractures, or removing tumours),[25-27] brainstem functions (particularly during posterior fossa tumour removal), and brain functions (e.g., carotid endarterectomy and aneurysm repair);[28-29] and second, to pinpoint the

sensory aspect of the sensorimotor cortex, aiding in tasks like identifying the central sulcus or conducting cortical mapping.[30-36]

When assessing function, SSEP responses are typically triggered through peripheral stimulation distal to the at-risk structure and recorded at one or more proximal sites as well as at a distal site.[37] The distal recording site ensures effective stimulation, while the proximal recording sites monitor changes that might occur in cases of functional compromise in the structure under consideration.[24]

Multiple factors can influence the responses recorded at the proximal recording sites, including technical, physiological, anaesthetic, or surgical factors. Surgically induced alterations can result from either mechanical or ischemic causes. The somatosensory evoked potential is used both for monitoring and for mapping during neurological surgery.

Anatomy of Somatosensory evoked potentials

SSEPs are generated by stimulating a peripheral nerve at a distant location, typically the median or ulnar nerves at the wrist for obtaining upper extremity SSEPs and the posterior tibial nerve at the ankle or the peroneal nerve at the fibular head for lower extremity SSEPs.[38-39] In some cases the ulnar nerve can be used instead of the median nerve, to examine the brain, cervical spine, or the upper limbs.[40-41] Figure 6 shows the pathway from the somatosensory periphery to the cortex.

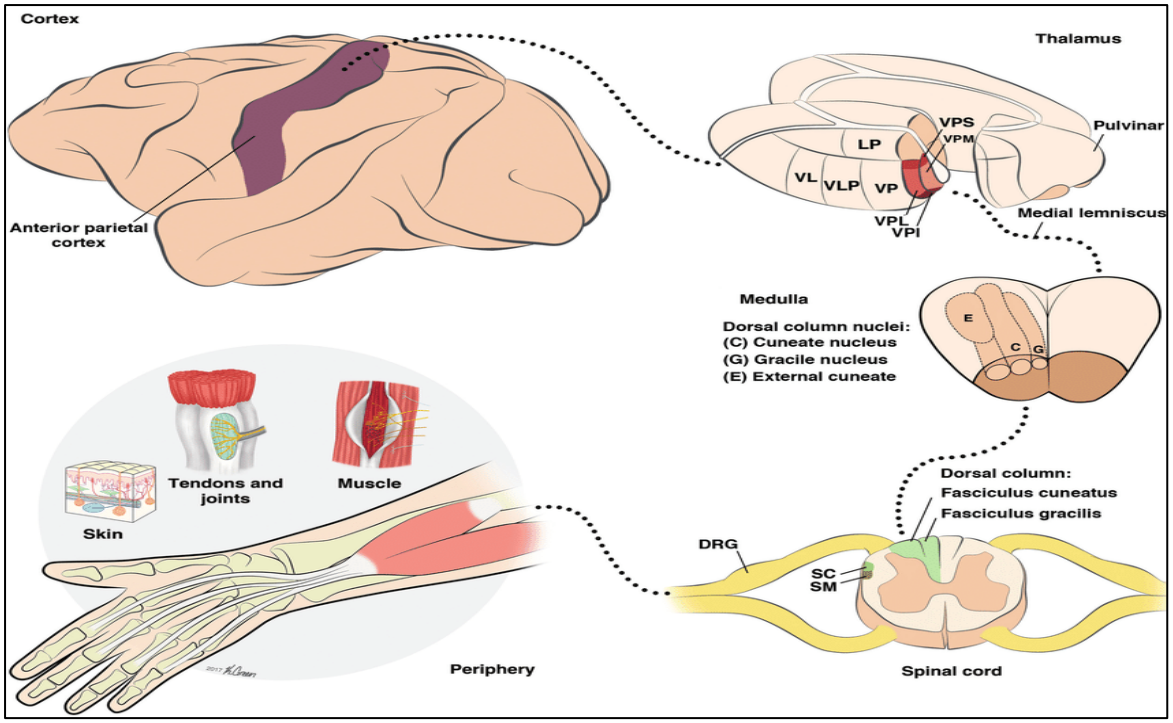

Figure 6. Pathways from somatosensory periphery to cortex.[42] This image illustrates the sensory pathway known as the dorsal column-medial lemniscus pathway, which is responsible for transmitting fine touch, vibration, and proprioceptive (position) information from the peripheral nervous system through the spinal column to the brain.

The sensory signals contributing to SSEPs enter the spinal cord through dorsal nerve roots at various segmental levels and can travel through multiple pathways within the spinal cord.[26,43-45] Generally, it is agreed that SSEPs are mainly mediated by the dorsal or posterior column spinal pathways. However, other pathways like the dorsal spinocerebellar tracts and anterolateral columns might also play a role in the early SSEP responses used for monitoring.[46-47] Notably, no synapses occur between the peripheral stimulation sites and the medullary nuclei (nucleus cuneatus and nucleus gracilis) where the responses arrive after traversing the posterior column of the spinal cord. These initial responses primarily reflect the integrity of the white matter of the spinal cord and offer limited direct information about the state of the gray matter of the spinal cord.[48-49] Consequently, the ascending SSEP responses up to the level of the medullary nuclei are only minimally influenced by general anaesthetics. After reaching and synapsing at the medullary nuclei, the responses cross and ascend through the medial lemniscal pathways to thalamic nuclei, where they once again synapse with other neurons. These neurons then project to the sensorimotor cortex, where additional synaptic interactions may occur. Notably, synapses are critical sites of

action for inhalational anaesthetic agents commonly used during surgery.[50] Therefore, managing[51] anaesthesia is a crucial consideration when attempting to record cortical SSEPs.

The posterior column pathways, which primarily mediate SSEPs, are generally believed to be nourished by the posterior spinal arteries. Conversely, the anterior spinal artery is thought to supply blood primarily to the anterior and anterolateral parts of the spinal cord, constituting the remaining two-thirds of the spinal cord. Motor function pathways are dependent on spinal cord sections that receive their blood supply from the anterior spinal artery. Consequently, a loss of motor function owing to a compromised blood supply to the anterior spinal artery may not necessarily result in a significant loss of sensory function mediated by the dorsal column pathways (referred to as anterior cord syndrome). However, the extent to which this holds true can vary among individuals.[52]

Once the SSEP signals have traversed the spinal cord, the functional state of the brain regions responsible for processing these signals depends on the blood supply to the brain and brainstem, provided by specific arterial branches. Perforating branches of the basilar and vertebral arteries supply the brainstem. Meanwhile, the middle cerebral artery provides blood to the brain region responsible for upper extremity SSEPs, and the anterior cerebral artery supplies the region responsible for lower extremity SSEPs. Reduced blood pressure can impact cerebral perfusion significantly. In a normothermic individual, when cerebral perfusion drops to about 18 cc/min/100 grams of tissue, brain electrical activity decreases, and SSEPs start to diminish in amplitude. If perfusion drops to 15 cc/min/100 grams of tissue, brain electrical activity further decreases, and SSEPs are generally not detectable. Subsequent reductions in blood flow to the brain, especially if sustained, can result in cellular damage and irreversible alterations in electrical activity.[51,53-55]

Triggered proprioceptive sensory signals are the fastest and most potent signals, thus reflecting the integrity of the posterior column of the spinal cord when monitored by SSEPs.[56] Epidural electrodes at the spinal cord can also record SSEPs, and epidural or subdural SSEPs are performed by placing electrodes directly on the posterior column.[57] It should be noted that sensory modalities other than proprioception (pain, touch, temperature) are not readily assessed by SSEP.[58]

1.4.7 SSEP waveforms, generators, and recording sites

SSEPs are generated through the application of mechanical or thermal stimuli to somatic sensory nerves, with the most common stimulus being an electrical pulse. The resultant waveform, reflecting nerve stimulation, is visually represented as a graph plotting voltage against time. This waveform is characterized by measurements of post-stimulus latencies (measured in milliseconds) and amplitudes (measured in microvolts) of specific peaks. As per convention, deflections below the baseline are denoted as positive (P), while those above are labelled negative (N). The standard identification of these waveforms involves a letter indicating the direction of deflection, followed by a number representing the latency of the waveform, for example, N9.[59]

Peaks vs waveforms

In SSEP terminology, "N9", “N20”, “P37” and “N45” are typically referred to as "peaks" rather than "waveforms." Peaks represent specific points of interest on the waveform, indicating a distinctive event in the neural response. Each peak is associated with a specific latency and amplitude, providing valuable information about the sensory pathway.[60]

Post-stimulus latency

The post-stimulus latency of an SSEP peak indicates the duration needed for the transmission of impulses from the location of sensory stimulation to the neurophysiological generator associated with that peak. Consequently, the latency is influenced by both the length of the sensory pathway and the velocity of neural conduction.[59]

Generators of the somatosensory evoked potentials after median nerve stimulation

1. N9 peak:

Generator: Brachial plexus.

Recording site: Erb’s point

Function: N9 records the initial sensory input from the peripheral nerve, which is then transmitted to the central nervous system. This is the starting point for SSEP monitoring.[61]

2. N20 peak:

Generator: Somatosensory cortex.

Recording site: Scalp.

Function: N20 represents the first major cortical response in SSEPs. It reflects the arrival of sensory information at the contralateral somatosensory cortex, specifically in the postcentral gyrus. N20 is a key component of SSEP waveforms.[61]

3. P37 peak:

Generator: Somatosensory cortex.

Recording site: Scalp.

Function: P37 represents a later cortical response in SSEPs. It is often associated with the processing of sensory information in the somatosensory cortex.[61]

4. N45 peak:

Generator: Somatosensory cortex.

Recording site: Scalp.

Function: N45 is another component of SSEP waveforms, reflecting the processing of sensory information in the contralateral somatosensory cortex.[61]

During SSEP monitoring, electrical impulses generated by the peripheral nerve stimulation travel through the nervous system, reaching the contralateral somatosensory cortex, and sometimes also the ipsilateral cortex. The latencies and amplitudes of these responses are measured and analysed. Any changes in these parameters can indicate abnormalities in the sensory pathways, helping medical professionals to assess the integrity of the nervous system during surgery.[62]

The specific electrodes and recording sites may vary depending on the clinical protocol and the type of surgery being performed. SSEP monitoring is a valuable tool for preventing damage to sensory pathways during procedures that pose a risk to these neural structures.[63]

1.4.8 Stimulation

Stimulation electrodes

The effectiveness of SSEP monitoring relies on factors such as the size, type, and placement of the stimulating electrode. Achieving consistent and dependable stimulation at the designated sites throughout the surgical procedure is crucial. Various types of electrodes can serve this purpose, including bar electrodes, EEG metal disc electrodes, adhesive surface electrodes, and subdermal needle electrodes, both disposable and non-disposable. Each type has its own set of advantages and disadvantages.[55]

Bar electrodes and metal disc electrodes are used in conjunction with electrode paste and can be reused. Adhesive surface electrodes, on the other hand, require a conductive gel. While electrode paste and adhesive gels may experience drying or changes in their electrical conductance characteristics during extended surgeries, using a constant current stimulus can compensate for these variations as long as the electrodes remain securely in place.[55,64]

Non-disposable bar electrodes can be susceptible to displacement, potentially leading to inconsistent responses in the operating room unless they are well secured. EEG metal disc electrodes, when secured with collodion, are more stable but can be more challenging to secure compared to subdermal or adhesive surface electrodes. The stability of SSEP responses hinges on firmly anchoring the stimulation electrodes throughout the surgical procedure. When properly secured, responses obtained using subdermal or adhesive surface electrodes tend to remain stable.[65]

Subdermal electrodes may or may not be reusable but come with concerns related to their invasive nature, including the risk of infection or bleeding. Handling them with care is essential to prevent accidental needle sticks. Despite these concerns, they are commonly used for recording purposes. In contrast, adhesive surface electrodes do not carry these concerns, but they are more expensive compared to some other electrode options that are not reusable.[66]

Stimulation sites

While SSEPs can be triggered by any form of tactile stimulus, they are typically generated through electrical stimulation applied to major nerve trunks or dermatomes.

The responses originating from the stimulation of major nerve trunks are commonly known as mixed nerve or major nerve SSEPs, often simply referred to as SSEPs. In contrast, responses elicited by stimulating dermatomes are termed dermatomal SSEPs (DSSEPs).[67]

For dermatomal responses (DSSEPs), it is recommended to use surface electrodes instead of subdermal needle electrodes. Surface electrodes are better suited to stimulate the sensory fibres that innervate the surface of the skin, whereas needle electrodes tend primarily to stimulate the underlying muscle tissue. In theory, the correct placement of stimulating electrodes should result in responses mediated by a single nerve root. However, owing to the overlap between dermatomes and individual variations, the responses may sometimes be mediated by more than one nerve root or by an unexpected nerve root, potentially compromising their reliability. Published dermatomal maps and guidelines for optimal stimulation sites have been made available. Other factors, such as the relative intensity of stimulation from side to side, can also affect the usefulness of DSSEPs.[68]

Mixed or major nerve SSEPs are typically induced by stimulating nerves like the median or ulnar nerves in the upper limbs, or the posterior tibial or peroneal nerves in the lower limbs. Stimulation sites are selected based on easily identifiable anatomical landmarks and the convenience of placing stimulating electrodes near the target nerve. In the upper limbs, unless these sites are inaccessible, electrodes for stimulation are usually positioned near the wrist. [69]

To stimulate the median nerve, the cathode of the electrode pair should be positioned approximately two to four centimetres proximal to the wrist crease, between the tendons of the palmaris longus and flexor carpi radialis muscles. The anode electrode should be placed two to three centimetres distal to the cathode to avoid what is known as an anodal block. Similarly, for ulnar nerve stimulation, the cathodal electrode should be placed two to four centimetres proximal to the wrist crease on either side of the tendon of the flexor carpi ulnaris muscle, with the anode placed two to three centimetres distal to the cathode.[70-71] Other effective stimulation sites in the upper limbs include the superficial radial nerve at the wrist and the ulnar nerve at the elbow.[69]

For obtaining SSEP responses from the lower limbs, stimulation of the posterior tibial nerve is performed typically near the ankle, while stimulation of the peroneal nerve is

done slightly distal to the knee near the head of the fibula. To stimulate the posterior tibial nerve, the cathode should be placed between the medial malleolus of the ankle and the Achilles tendon, just proximal to the malleolus, with the anode electrode positioned two to three centimetres distal to the cathode. This placement aligns with the path of the nerve around the malleolus. For peroneal nerve stimulation, the cathode should be placed distal to the lateral aspect of the knee, slightly medial to the head of the fibula, and the anode electrode should be positioned two to three centimetres distal to the cathode. [69-71]

Stimulation technique

Because a dermatome pertains to a specific skin area innervated by a single nerve root, it is advisable to employ surface electrodes rather than needle electrodes to elicit DSSEP responses.[55,64,72] Surface electrodes can be either EEG-type disc electrodes or adhesive electrodes. However, when it comes to eliciting SSEP responses, both surface and subdermal needle electrodes can be utilised to deliver the stimuli. While each method has its advantages, none of them appear to offer a significant advantage over the others, and all tend to be similarly effective. The crucial element for effective stimulation is the spread of current to the underlying nerves, and the use of constant current stimulation is designed to compensate for changes in contact resistance. Nevertheless, the intensity of the constant current stimulus and its ability to compensate for contact resistance changes are constrained by the maximum output voltage of the stimulator. When contact resistance becomes excessively high, the stimulator's current output will be limited. Most machines designed for evoked potential acquisition will provide a warning in such cases. Consequently, the use of constant current stimulation is the recommended approach.[70,73]

Typically, an electrical stimulus is delivered in the form of a series of rectangular pulses with specific pulse duration and presentation frequency. The stimulus intensity depends on its amplitude, pulse duration, and frequency. An increase in any of these parameters generally results in higher stimulus intensity owing to increased current flow. However, the response of underlying nerves or tissue to the stimulus is not reliant solely on stimulus intensity; it also depends on the positioning of the stimulation electrodes concerning the intended neural structures to be stimulated. In certain cases, particularly with patients having large or swollen extremities, the current spread

resulting from surface electrodes may not excite the intended underlying neural structures effectively. In such instances, subdermal needle electrodes may prove more effective, as they can be positioned closer to the underlying nerves, requiring lower stimulation intensities to produce excitation compared to surface electrodes. It is recommended to use a pulse duration of 200 to 300 microseconds for eliciting both SSEPs and DSSEPs.[70,73] Controlling the stimulus rate is crucial for obtaining high-quality evoked responses.[69,74] The key factor in acquiring evoked responses is ensuring that the response and underlying noise are not synchronised. Therefore, to reduce noise amplitude with averaging, the stimulus rate should not be a submultiple of any noise frequency. Since the most common noise frequency is 60 Hz, it is essential to avoid using stimulation rates like 5.0, 4.0, or 10.0 Hz. [70,73] Sometimes, other noise sources can affect the evoked response, and even minor adjustments in the stimulus rate (e.g., from 4.7 to 4.9 Hz) may impact the quality of recorded evoked potentials in the presence of high-amplitude rhythmic noise.[65] Stimulation rates between 2 and 5 Hz are recommended.[70,73] However, lower stimulation rates (between 1.5 and 3 Hz) can sometimes improve lower extremity responses, especially when neurological function is compromised. In contrast, upper extremity SSEPs may not show significant changes at stimulation rates as high as 9 Hz. Beyond 9 Hz for upper extremity SSEPs and 5 Hz for lower extremity SSEPs, increasing the stimulus rate generally leads to substantial degradation of SSEPs, particularly cortical responses.[70,73,75]

For reliable SSEP and DSSEP elicitation, it is important to use supramaximal stimulation intensities that produce consistent responses and ensure that variations in response amplitudes are not due to differences in effective stimulation intensities. Generally, it is usually unnecessary to employ stimulation intensities exceeding 50 mA to elicit reliable SSEPs or DSSEPs and for effective monitoring.[69] While commercial stimulators typically offer stimulation intensities greater than 50 mA, it is uncommon for such high-intensity stimuli to be ineffective in eliciting SSEP responses unless there is an underlying pathology or the current from the stimulation electrode is not reaching the underlying neural tissue with sufficient intensity for excitation, which can occur in patients with large or swollen extremities. Concerns about potential tissue damage resulting from high current densities at the stimulation sites appear unfounded, as

there is no evidence in the literature or otherwise to support this when using the stimulus parameters available on commercially available devices.

Different considerations apply when acquiring DSSEP responses. High stimulation intensities in this case may lead to current spread and contamination of the desired DSSEP responses from a single dermatome with responses from adjacent dermatomes or neural structures beneath the skin surface, such as muscle stretch receptors. Additionally, the latencies of DSSEP responses are related to stimulus intensities.[72] Therefore, careful attention must be paid to stimulation intensities. It is advisable to use minimal effective stimulation intensities to elicit DSSEP responses and to avoid elevated stimulation intensities.

There are various methods for delivering electrical stimuli to elicit SSEPs. Earlier monitoring equipment allowed responses to be recorded from stimulation at one site, which was then repeated for validation to ensure response replication. A similar set of responses was then acquired from the opposite extremity, typically with several minutes between obtaining new responses from the first stimulation site. This data acquisition format could delay the detection of a unilateral SSEP change significantly. Consequently, advancements in data acquisition equipment enabled interleaved stimulation between pairs of extremities, essentially recording responses from each extremity simultaneously. This improvement has been widely adopted, resulting in faster data acquisition and allowing for the rapid identification of SSEP changes and side-to-side differences. [66,70,73,75] Another method to elicit SSEPs is the simultaneous stimulation of a pair of extremities. Historically, this approach was discouraged owing to concerns that the resulting responses could mask significant unilateral functional changes. However, for patients with minor or no neurological deficits and well-defined responses, bilateral stimulation seems to provide no substantial advantage over interleaved unilateral stimulation. There is no published evidence indicating that bilateral stimulation is better, compared to interleaved unilateral stimulation, at detecting functional changes. Nevertheless, bilateral stimulation may be valuable when the responses resulting from the stimulation of a single extremity are too small or variable for monitoring purposes. Therefore, unless otherwise indicated, interleaved unilateral stimulation is recommended rather than simultaneous bilateral stimulation for monitoring.

The choice of which nerves to stimulate depends largely on the location of the surgical site. It is crucial for monitoring to select nerves whose responses are mediated by neural tissue at risk during surgery. Thus, when the thoracic region of the spinal cord is at risk, monitoring median nerve responses to detect a spinal cord insult would be ineffective, whereas monitoring posterior tibial nerve responses would be appropriate. When nerve roots are at risk, DSSEPs are sensitive to changes in nerve root function.[64,76] Occasionally, the responses of a nerve may be influenced by tissue both above and below the at-risk site. In such cases, the response mediated by the tissue above the at-risk site could potentially overshadow an abnormal response from tissue at the site of risk, resulting in recorded responses that show little or no change despite the presence of a neurological deficit. Therefore, it is best to choose to monitor nerves whose responses are entirely mediated by tissue located below the at-risk area.[5.6] Additionally, the choice of which nerves to stimulate may be influenced by other factors, such as the neurological structures at risk owing to positioning, accessibility of nerves, or to which nerves yield the best responses upon stimulation. For instance, changes in brachial plexus function owing to positioning are typically better detected by monitoring ulnar rather than median nerve function. In patients with swollen legs, peroneal nerve stimulation might offer better responses than posterior tibial nerve stimulation.[66]

Somatosensory evoked potentials are semi-quantitative measures, which means that their interpretation of warning criteria is more specific than that of other IONM techniques.[57] In general, a 50% decrease in amplitude or a 10% delay in latency is regarded as a critical change.[57-58] SSEPs are used both for monitoring and mapping during surgeries.

Median SSEP phase reversal is a procedure used to determine the physiological location of the central sulcus.[77] It is a mapping technique in which a strip electrode is placed perpendicularly across the approximate sulcus. The median nerve is then stimulated to generate a near-field response at the sensory cortex.[78] Evoked potentials (EPs) recorded at each electrode of the strip electrode will demonstrate different waveforms according to their relative location to an SSEP dipole in the post-central gyrus. Owing to the sensory stimulation, the directionality of the dipole changes across the motor cortex, thus reversing the phase of waveforms, creating the flipped waveform witnessed in the SSEP.[16] The method is illustrated in Figure 7.

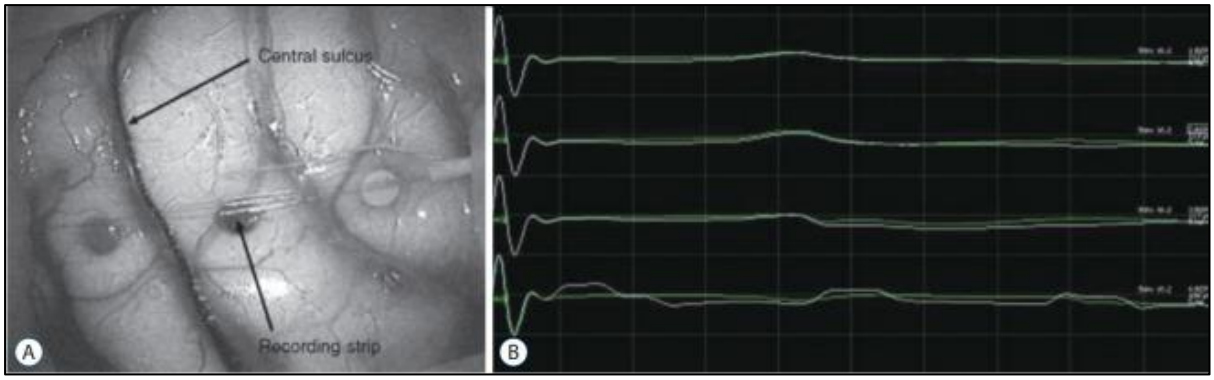

Figure 7. Median sensory evoked potential phase reversal.[2] Figure 7(A) indicates the placement of the somatosensory evoked potential dipole in the post-central gyrus, Figure 7(B) shows an example of the somatosensory evoked potential waveforms.

Cortical and subcortical SSEPs can be used to locate the Rolandic cortex reliably and quickly as well as subcortical fibre tracts.[79] Cortical SSEP mapping is used for locating the eloquent cortex during operations. Stimulation mapping helps to balance the benefits of maximal tumour resection and the risks of damaging the eloquent cortex or subcortical fibre tracts. Mapping techniques, such as cortical stimulation and sensory mapping, require the patient to be awake and cooperative and require specific anaesthetic considerations when performing mapping or evoked potential monitoring.[79]

Somatosensory evoked potential analysis is also useful when attempting to identify the dorsal median raphe of the spinal cord. This is an important technique of dorsal column mapping during myelotomy, to preserve proprioception of each side.[80] There are three different approaches to localise the dorsal median raphe (dorsal MR) in IONM. First, making use of personal communication techniques by stimulation of the spinal cord at fine intervals and recording retrograde sensory conduction at bilateral peripheral nerves. Second, stimulation of the peripheral nerves and recording of orthograde sensory conduction on the spinal cord using a strip electrode.[80] And lastly, stimulation of the spinal cord at fine intervals and recording SSEPs on the scalp to observe phase reversal.[81] According to studies undertaken in 2014, the third approach is more readily applicable because it does not require a custom set of electrodes and it yields accurate and timely responses.[82] Figure 8 represents the methodology of this third approach applied to a patient.

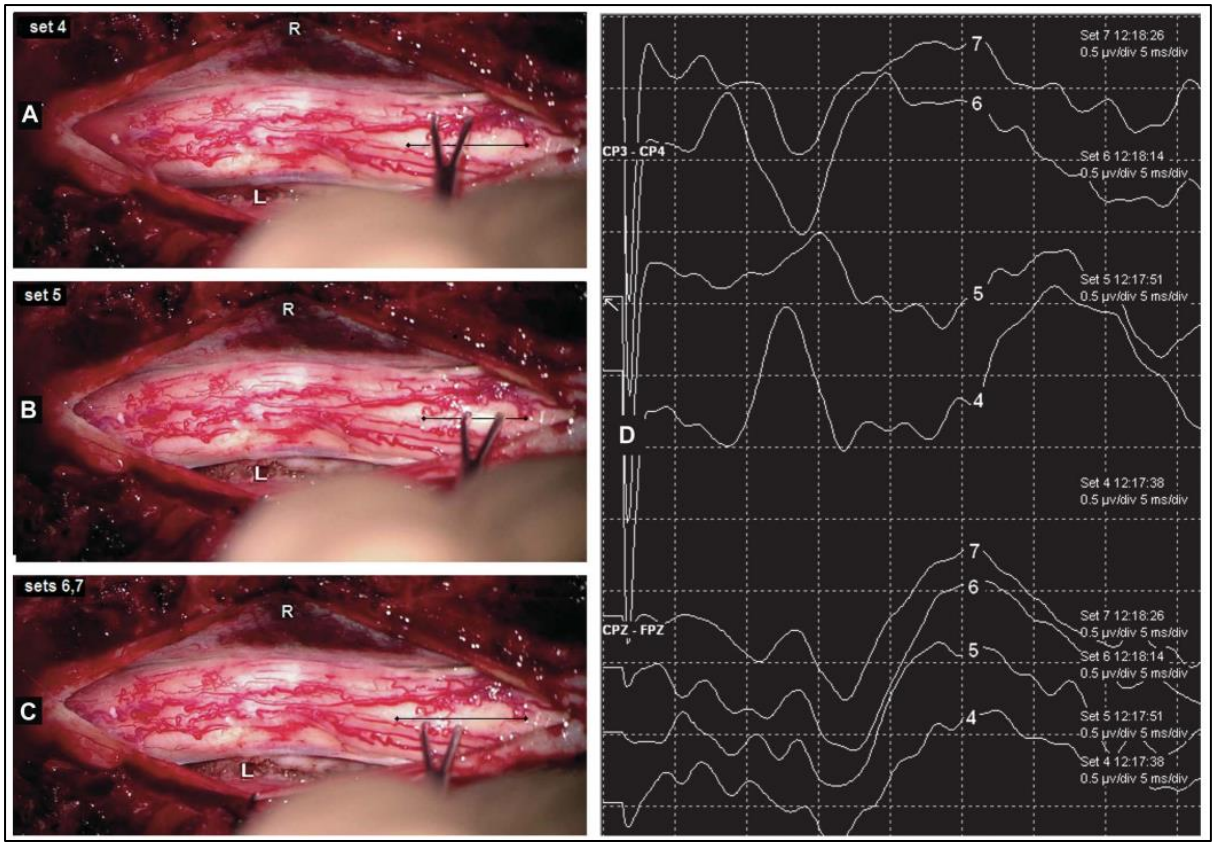

Figure 8. Illustration of the methodology applied for dorsal column mapping in patient.[82] *Figure 8(A-C) show different sets of spinal cord stimulation at different places along the spinal cord, Figure 8(D) shows the somatosensory evoked potential readings from these different sets.*

1.4.9 Recording

Recording electrodes

Just as the stimulation electrodes providing a consistent and safe stimulus is important, it is equally vital for recording electrodes to yield dependable, high-quality recordings while ensuring safety.

For surface recordings, subdermal needle electrodes or metal ‘cup’ surface electrodes (gold, silver, or tin) are commonly employed.[69] Subdermal needle electrodes are convenient for quick placement but can be displaced easily if not secured, often when an anaesthetist reaches under surgical drapes or while preparing for an X-ray. Therefore, when using subdermal needles, placement should be considered carefully to prevent displacement. Alternatively, corkscrew electrodes, which are screwed into the scalp, or surface electrodes filled with conductive gel or paste and secured with collodion or tape, can be used to avoid displacement.

In the case of direct cortical recordings of SSEPs, a ‘strip’ or grid electrode array can be employed, typically used for correlating cortical surface anatomy with function (corticography).[43,45]

Recording sites

The recording montage used for intraoperative monitoring may differ from that used for diagnostic purposes owing to varying concerns and questions. The choice of recording montage depends on the number of available recording channels, the possibility of simultaneous recordings from both sides of the body, and the need for replication. The fundamental principle of mixed-nerve SSEP monitoring involves stimulating distal to the surgical site at risk and recording from site(s) proximal to the surgical site. Typically, recording sites include at least one cortical and one subcortical recording site. An additional recording site placed proximal to the stimulating site but distal to the surgical site, is often used to verify peripheral stimulus status. For upper extremity stimulation, this additional site is usually the ipsilateral Erb’s point, and for lower extremity stimulation, it is the ipsilateral popliteal fossa. Recording cortical responses is valuable since they indicate anaesthetic management and are easily recognisable. However, relying solely on cortical responses can yield false positives owing to the influence of general anaesthesia and blood pressure. Subcortical responses are less affected by anaesthesia owing to fewer synapses, but relying solely on them can also yield false positives. Therefore, it is advisable to use both cortical and subcortical recording sites. In cases where spinal recording sites are unavailable, such as during posterior cervical procedures, subcortical responses can be recorded from one earlobe or linked earlobes.[55]

The cortical recording site captures the SSEP as it reaches the postcentral gyrus of the contralateral somatosensory cortex. For upper extremity stimulation, the cortical recording site is typically at CP3 or CP4, contralateral to the side of stimulation and two centimetres posterior to the C3 and C4 positions of the 10–20 International System of EEG electrode placement. For lower extremity stimulation, the cortical recording site is at CPz, on the midline and two centimetres posterior to the Cz position of the 10–20 system.[45]

The nomenclature used to label SSEP waveform peaks and valleys employs N and P to denote signal polarity (negative is up, positive is down) and an integer for the

nominal post-stimulus latency in normal adults. Illustrations of sample SSEP waveforms with this nomenclature are available in previously published guidelines.[70] There are different ways to record key cortical and subcortical responses. Typically, two peaks, N20 and P22, resulting from median nerve stimulation, are used to define cortical SSEP response amplitude. These peaks, originating from the thalamus and cortex, can be recorded using derivations like CPc-Fz (cortex contralateral to stimulus) or CPc-CPi (contralateral to ipsilateral). Both are acceptable, but the laboratory should choose the most appropriate. It is crucial to be able to record in either manner, as low-amplitude cortical responses may necessitate using one derivation over the other in certain patients with neurological injuries. The choice of recording derivation should also consider ease of interpretation when interleaved stimulation from both sides is used. For example, CP3-Fz might be inadequate because it yields the N20-P22 response primarily when the right arm is stimulated, so it would be appropriate to record from the single derivation CP3-CP4 or both CP3-Fz and CP4-Fz. Various methods exist to record far-field subcortical potentials. The P14 and N18 potentials, akin to upper extremity N13 peaks, are best recorded using a derivation that involves ipsilateral centro-parietal cortex with a non-cephalic reference, like CP3-right Erb's point for left median nerve stimulation. Another subcortical response, the cervical or N13 response, can be recorded using methods such as a cervical to Fz derivation or Fz or Cz to linked ears. The choice of method depends on the surgical procedure and the response components of interest. Brachial plexus peripheral potentials are best recorded with electrodes over Erb's point, located just two cm above the midpoint of the clavicle and at the angle between the clavicle and the posterior border of the sternocleidomastoid muscle. Ipsilateral responses are referenced to the opposite of Erb's point.[50]

For stimulation and recording, it is advisable to place the ground electrode nearer rather than further from the other recording electrodes to minimise noise. Placing it on a shoulder is generally a good choice. Using multiple reference grounds should be avoided to prevent ground loops that can introduce noise. An earth ground should never be used, for safety reasons, as it can provide an alternate path for electrical current.

To minimise stimulus artifacts and electrical noise in recordings, it is important to keep recording input leads short and electrode impedance values at or below 5 kOhms for

gold disc or subdermal electrodes. However, capturing some stimulus artifacts can be useful for verifying the functionality of stimulators during troubleshooting.

Recording technique

General anaesthetics have minimal impact on subcortical responses but affect cortical responses significantly. Therefore, when using inhalational anaesthetics, it is common to observe a marked reduction in cortical response amplitude during surgery while subcortical responses remain relatively stable. To capture lower extremity cortical SSEP responses effectively, attention should be paid to measures that may improve the recording, such as altering anaesthetic management, optimising or selecting alternative recording sites, and adjusting stimulation intensity or frequency. These changes should be implemented early in surgery, before any neurological function is at risk, to avoid misinterpretation of acquired data. The same caution applies to modifications in stimulation and recording parameters.[55]

1.4.10 Latency

The latency of SSEPs refers to the time it takes for a specific component of the evoked potential waveform to reach its peak after the sensory stimulation. It is an essential parameter because changes in latency can indicate dysfunction or compromise of the sensory pathways.[83-84]

What follows is a simplified explanation of how latency is calculated during SSEP monitoring in brain resection surgery:

1. Stimulation: The process begins with electrical or sensory stimulation applied to a specific peripheral nerve, usually in the arms or legs of the patient. This stimulation generates sensory signals that travel along the peripheral nerves, through the spinal cord, and eventually reach the brain.

2. Recording electrodes: Electrodes are placed strategically on the patient's scalp and along the sensory pathway to record the evoked potentials. These electrodes detect the electrical activity in response to the sensory stimulation.

3. Signal acquisition: The signals detected by the recording electrodes are amplified and filtered to isolate the SSEPs from background electrical noise. The recorded data are typically displayed on a computer monitor.

4. Latency measurement: Latency is calculated by identifying specific points on the evoked potential waveform. The most common points used for latency measurement are the N20 and P37 peaks for upper extremity SSEPs. For lower extremity SSEPs, different peaks may be used, such as N22 and P45. Latency is typically measured from the onset of the stimulus to the peak of the selected component.

N20 (Negative 20): This is the first negative peak in the upper extremity SSEP waveform, occurring at approximately 20 milliseconds after the stimulus.

P37 (Positive 37): This is the first positive peak in the upper extremity SSEP waveform, occurring at approximately 37 milliseconds after the stimulus.

5. Comparison: The calculated latency is then compared to a baseline measurement or normative data. Any significant increase in latency beyond the established baseline may indicate a problem with the sensory pathway. Surgeons and neurophysiologists monitor these changes closely during surgery to ensure the integrity of the neural structures being operated on.

6. Real-time monitoring: SSEP monitoring is typically performed in real-time during the surgery. If there is a significant change in latency, it can alert the surgical team to potential issues, such as compromised blood flow to the brain or direct damage to sensory pathways. In response, adjustments can be made to protect the patient's neurological function.

In summary, latency in SSEP monitoring during brain resection surgery is calculated by measuring the time it takes for specific peaks in the evoked potential waveform to occur after sensory stimulation. Monitoring changes in latency helps to assess the integrity of sensory pathways and allows for immediate intervention if any issues are detected during the surgery.[85-86]

Waveforms of SSEP recordings are denoted as a negative (N) or positive (P) wave polarity and the number represents the expected latency of consecutive waves in milliseconds.[84]

Each spot on the sensory pathway will have a recording value. Direct stimulation of the dorsal cord at the T3 level is performed by the stimulator oriented with the prongs parallel to the longitudinal axis of the cord. Stimulation of the right dorsal column results in a negative upward peak in the CP3-CP4 channel and a positive downward

peak in the CPz-Fz channel. Next, the surgeon performs stimulation closer to the midline, yet still right-sided and slightly more distally, resulting in a smaller negative peak in the CP3-CP4 channel and a positive peak in the CPz-Fz channel. Stimulation of the left dorsal column triggers positive deflections in both channels.[82] SSEPs are generally not the sole method used in IONM. It is recommended to use SSEPs along with motor-evoked potentials (MEPs).

During intraoperative monitoring, baseline SEP waveforms should be recorded for the patient. The surgical team members will be alerted if there are changes in SEP waveforms. The amplitude of a SEP waveform reflects intact axons within the neural pathway. When the amplitude decreases, there is a concern that axons are being compromised or functionally lost.[58] During surgery, there are multiple possible causes for decreased amplitude and/or increased latency of a waveform. These include medication, decreased blood flow, changes in blood pressure, changes in temperature, retraction, local pressure, cautery, and operative techniques, such as surgical dissection.[57]

1.4.11 Anaesthesia

While evoked potential monitoring can provide valuable insights during various surgical procedures, the administration of anaesthesia to facilitate these surgeries has notable effects on evoked responses. These effects are most pronounced in cortically generated responses, where repeatability may be absent, and less significant in subcortical and peripheral responses, where apparent changes may be minimal. Importantly, these effects vary among individuals and are generally dose-dependent. Changes in cortical SSEPs (somatosensory evoked potentials) often mirror alterations in EEG (electroencephalogram). Most used anaesthetic drugs lead to dose-dependent changes in SSEPs, characterised by decreases in amplitude and increases in latency. The extent of change differs among anaesthetic agents, with the dosage required for a 50% decrease in cortical SSEP amplitude correlating with the lipid solubility of the agent and its anaesthetic potency.[87-88] Consequently, when considering anaesthetic techniques, it is crucial to account for the impact of each specific anaesthetic agent on monitoring modalities.[89-91]

Halogenated inhalational agents

Halogenated inhalational agents (e.g., desflurane, enflurane, halothane, isoflurane, sevoflurane) are among the most frequently used anaesthetics. These agents generally lead to dose-dependent increases in SSEP latency and reductions in amplitude in cortically recorded SSEPs. These effects can be particularly detrimental, causing unstable responses over time. However, their impact is less significant on subcortical SSEP responses over the cervical spine and minimal on spinal responses recorded epidurally or on peripherally recorded responses. Studies have indicated variations in the potency of different halogenated agents on cortical SSEPs, with isoflurane being reported as the most potent, followed by enflurane and halothane. Sevoflurane and desflurane show similar potency to isoflurane once they reach a steady state. If it is crucial to monitor cortical SSEPs, especially in combination with motor responses elicited by transcranial stimulation, the use of halogenated inhalational agents might need to be limited or avoided entirely. This is particularly important in patients with conditions like spinal cord compression or cerebral palsy. However, for cases where recording subcortical responses suffices for monitoring, low doses (< 0.5 MAC) of halogenated agents may be acceptable. It is worth noting that these agents have complex pharmacokinetics, requiring 10 to 20 minutes or more to equilibrate concentrations in the brain and lungs. Consequently, changes in evoked potentials may lag considerably behind shifts in end-tidal inhalational agent concentration.

Nitrous oxide

For cases where monitoring of cortical SSEPs is imperative, it is advisable to avoid the use of nitrous oxide. Nitrous oxide is not a reliable amnestic agent and Versed can be substituted instead. When used alone or in conjunction with halogenated inhalational agents or opioid anaesthetics, nitrous oxide leads to reductions in cortical SSEP amplitude and increases in cortical SSEP latencies. At equipotent anaesthetic concentrations compared to other inhalational anaesthetics, nitrous oxide has the most profound impact on cortical SSEPs. Owing to its relatively low solubility, the effects of nitrous oxide can change rapidly with variations in concentration. This makes interpreting the cortical SSEP changes associated with a decrease in nitrous oxide concentration challenging, as they may mask the opposite changes linked to neural

compromise. Therefore, when nitrous oxide is employed, it is essential to avoid significant changes during critical phases of the procedure. Nitrous oxide has also been reported to affect cortical SSEPs synergistically when used alongside other inhalational agents. However, its impact on subcortical and peripheral sensory responses is relatively minor. Hence, if monitoring can be conducted adequately using only subcortical and/or peripheral recordings, nitrous oxide use may be deemed acceptable.[92-93]

Intravenous analgesic agents

In cases where the depressant effects of inhalational agents are incompatible with cortical SSEPs or motor response acquisition, intravenous agents can be combined to create a total intravenous anaesthetic (TIVA). TIVA is the preferred choice for monitoring purposes and typically involves intravenous analgesics (opioids or ketamine) and sedative agents (barbiturates, benzodiazepines, etomidate, propofol, or droperidol). Dexmedetomidine has also been used.[94-95]

Opioid analgesics typically have mild effects on evoked potentials. They lead to minimal changes in spinal or subcortical responses and some amplitude depression with latency increases in cortical responses. These effects seem to be related to drug concentrations, with maximal changes occurring when drug concentrations peak after bolus delivery. Opioid-based anaesthesia is used frequently when cortical responses are employed for monitoring, although it may not provide adequate sedation and amnesia, necessitating concurrent use of an inhalational agent (halogenated or nitrous oxide). However, if sedation can be achieved effectively using a sedative drug like Versed, the use of an inhalational agent may be unnecessary.[94]

Ketamine, known for its unique properties, leads primarily to increased cortical SSEP amplitudes with minimal effects on subcortical and peripheral responses. While it offers excellent analgesia and hypnosis, it can induce post-operative hallucinations in adults and raise intracranial pressure in patients with intracranial abnormalities. Combining ketamine with a benzodiazepine like Versed pre-operatively and intra-operatively can mitigate the risk of post-operative hallucinations.[96]

Intravenous sedative agents, often used in combination with opioids or ketamine, enable a completely intravenous anaesthetic. These agents can be infused slowly to minimise transient changes in monitored responses. Droperidol is one such agent with

minimal effects on cortical SSEPs. Barbiturates are another group used for induction, with thiopental being common. Thiopental induction decreases cortical response amplitudes transiently and increases response latencies, primarily affecting longer-latency cortical response components. However, induction with barbiturates is compatible with SSEP monitoring, as these drugs redistribute and allow monitoring to resume promptly. Phenobarbital, used to induce barbiturate-induced coma, does not affect SSEP acquisition at doses that induce a silent EEG, making SSEPs a suitable monitoring tool during barbiturate-induced coma.[91]

Among benzodiazepines, midazolam, when used at induction doses (0.2 mg/kg) without other agents, mildly depresses cortical SSEPs while minimally affecting subcortical and peripheral sensory-evoked responses. An infusion of midazolam (50-90 micrograms/kg/hr initiated after a 0.1 milligram/kg load) can maintain supplemental hypnosis effectively during opioid analgesia. This combination typically supports cortical SSEP acquisition and helps to reduce the hallucinations associated with ketamine use.[97]

Etomidate, upon injection, increases cortical SSEP amplitudes with no significant effects on subcortical or peripheral components. Sustained amplitude increases with continuous drug infusion have been employed to improve SSEP cortical recordings that were otherwise unsuitable for monitoring.

Propofol, with its rapid metabolism, presents an appealing option for intravenous-based anaesthesia during evoked potential monitoring. Unlike etomidate, propofol does not enhance cortical responses. Instead, it depresses cortical SSEP amplitudes, with rapid recovery following infusion termination. Changes in evoked potential amplitude with propofol are notably smaller than those observed with equipotent doses of halogenated agents. Consequently, propofol is the preferred choice for SSEP recording, particularly for lower-extremity SSEPs, which are more sensitive to the effects of halogenated agents. Propofol's rapid metabolism allows for tightly controlled infusion anaesthesia and quick adjustments to the depth of anaesthesia and its impact on evoked responses.[98]

For monitoring purposes, TIVA is the most suitable choice. However, its widespread adoption may be gradual, as many anaesthesiologists may lack training or comfort with this approach. In cases where only SSEPs, without motor evoked potentials

(MEPs), are being recorded, a reasonable alternative could involve maintaining inhalational agents at levels below 0.5 MAC without nitrous oxide, primarily relying on narcotics. If SSEPs are too compromised for monitoring or if MEPs are being recorded, substituting Versed for inhalational agents is recommended.[97]

Muscle relaxants

Muscle relaxants are generally believed to have no direct effect on SSEPs. However, they can enhance SSEP quality by reducing electromyographic noise or interference from muscle groups near the SSEP recording electrodes. This effect may explain the SSEP improvement noted with low doses of propofol and meperidine. Excessive myogenic artifact, especially from electrodes placed on the back of the neck, may indicate the need for additional muscle relaxants.[99]

Choice of anaesthetic agents

Several factors influence the selection of anaesthetic agents when monitoring is required. These factors encompass how anaesthetic agents interact with a patient's specific pathophysiology, surgical necessities (e.g., conducting a Stagnara wake-up test or keeping the patient awake during a carotid endarterectomy), and the specific monitoring modalities employed.[88]

In general, anaesthetic agents exert an impact on evoked responses consistent with their clinical effects on the central nervous system. Several key observations can be made concerning the effects of anaesthetic agents on SSEPs:

1. Most anaesthetic agents tend to reduce neural conduction and synaptic transmission, leading to decreased SSEP amplitude and increased latency.

2. Anaesthetic effects are most prominent in areas where synaptic transmission is prominent, affecting cortically generated peaks the most and having the least impact on the brainstem, spinal cord, and peripheral responses.

3. Anaesthetic effects generally correlate with dosage, although many agents have a disproportionate impact at lower dosages, typically within the range where significant clinical anaesthetic effects occur.

4. Individual patient responses can vary to the same dose of an anaesthetic drug.

5. Maintaining a steady state of anaesthesia during critical periods when the neurological function is at risk is crucial.[72,88]

Considering these factors, an anaesthetic regimen typically can be chosen to allow effective monitoring.

Somatosensory evoked potentials are less reliable and helpful in patients with pre-existing damage to the spinal cord or the nerve(s) subject to monitoring.[58] In these patients, the current opinion is that their neurologic status before surgery links more closely to post-op outcomes.[1] On occasion, a change in SEP can correlate with a specific temporal event, such as placing a pedicle screw into the spinal cord or a sudden drop in blood pressure. Rectifying the underlying cause in a timely fashion will often restore signal and perhaps prevent long-term or permanent neurological injury.

Intraoperative neuromonitoring, specifically somatosensory evoked potentials, provides a valuable method of identifying impending neurologic injury and avoiding it in vulnerable patients.[100] The entire surgical team should be aware of and involved in the use of SEPs and their management, as this will lead to better patient outcomes.[100] Although it is the role of the anaesthesia provider and surgeon to address physiologic and/or physical changes that could cause SEP changes, the other members of the surgical team, including nurses, neurophysiologists, and technicians, should be aware of and able to assist in doing this, as it will ensure the best outcome for the patient.[12] Nurses should feel comfortable in identifying abnormalities and should report their findings immediately to the clinicians.[100]

1.4.12 Summary

Table 1. Summary of IONM Techniques[2]

Technique	Primary Methods	Purpose	Important results
SEP	Performed by stimulating either the median nerve at the wrist of the patient or the tibial nerve at the patient's ankle and recording potentials received at the scalp over the sensory cortex.	Reflect the integrity of the posterior column of the spinal cord.	A 50% decrease in amplitude or a 10% delay in latency is regarded as a critical change.
Central Sulcus SEP	A strip electrode is placed perpendicularly across the approximate sulcus. The median nerve is then stimulated to generate a near-field response at the sensory cortex.	Mapping to locate the central sulcus.	Identify between which electrodes the SEP phase is reversed, indicating the physiological central sulcus.
Dorsal Column SEP	Stimulation of the spinal cord at fine intervals and recording SEPs on the scalp to observe phase reversal.	Identify the dorsal median raphe of the spinal cord.	Identifying the location on the spinal cord makes the SEP observe a phase reversal.
MEP	Stimulation is conducted by transcranial electrical stimulation via subdermal or surface needle electrodes on the scalp and recording the responses at the spinal cord or relative muscles.	Activating and monitoring motor pathways	Lack of response in the target location, indicating damage to the motor pathway.
EMG	Electrode stickers are applied to the skin (surface electrodes) to measure the speed and strength of signals travelling between two or more points while a stimulus is applied.	Monitor cranial motor nerves, roots, or peripheral nerves during surgery.	If intraoperative EMG signals are activated, it indicates cranial nerve damage.
EEG	Current stimulating and voltage-sensing electrodes are applied to the scalp according to international standards.	Pre- and Post-surgery analyses and diagnosis.	Abnormal or irregular amplitudes or spikes are possible signs of seizures.
BAEP	BAEP stimulator and electrode are placed into the ear. Recording takes place while click stimulation is active.	Monitoring the auditory nerve and brain stem during surgery.	Deviations in amplitude or latency from the baseline tests indicate damage to neural structures.

CHAPTER 2: AIM AND OBJECTIVES

2.1 CHAPTER OBJECTIVE

In this chapter, the aim and objectives of this study will be stated.

2.2 AIM

The study aimed to evaluate the use of continuous SSEP monitoring to provide an ongoing functional assessment of the somatosensory pathway during the resection of intracranial brain tumours.

2.3 OBJECTIVES

The objectives of this research study were to:

1. Compare contralateral and ipsilateral cortical SSEP responses in brain tumour resection surgery.
2. Compare cortical SSEP responses with subcortical responses in brain tumour resection surgery.
3. Compare baseline SSEP responses to specific time points throughout brain tumour resection surgery.

CHAPTER 3: METHODS

3.1 CHAPTER OBJECTIVE

In this chapter, the details and methods applied in the study will be detailed.

3.2 STUDY DESIGN

A retrospective study was implemented on patients who underwent IONM in the form of SSEPs responses in brain tumour reresection surgery during the period between January 2019 and December 2021 at Steve Biko Academic Hospital (SBAH).

3.3 ETHICAL CONSIDERATIONS

The findings of this research will not be divulged on social networks, or to parties not involved in the study. All experiments were conducted at Steve Biko Academic Hospital, where A code of conduct was followed. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee (Ethics reference number: 550/2022). The project proposal was submitted to the National Health Research Database (NHRD) before the commencement of the study, which allowed for access to patient records. All patient records remained confidential and anonymous. All patients referred to in the study were anonymised and numerically labelled. The project conducted was retrospective and made use of existing clinical data obtained from past brain tumour surgeries. The SSEP technique forms part of the IONM protocol when used during brain tumour surgery. No direct participant contact was involved at any stage of the research. It is declared that there is no conflict of interest regarding this study.

3.4 SAMPLING METHOD AND SAMPLE SIZE

Data were collected from patients at the Steve Biko Academic Hospital (SBAH). We endeavoured to include patient data from 50 patients for analysis. To detect a clinically significant difference in SSEP responses in brain tumour surgery a p-value of < 0.05 was used.

After approval from the NHRD, a range of patients was selected who had undergone brain tumour surgery with SSEP monitoring in Steve Biko Academic Hospital between January 2019 and December 2021.

The inclusion criteria for the study comprised:

- Brain tumour resection surgeries in which SSEPs were employed over a period between January 2019 and December 2021.
- Contralateral, ipsilateral, cortical, and subcortical SSEP responses were recorded from patient records.

The exclusion criteria of the study comprised:

- Operated neurological tumour cases where SSEP was not used.
- Tumours that were operated on before January 2019 or after December 2021 where SSEPs were used.

3.5 DATA COLLECTION AND ORGANISATION

This study was conducted as follows: After approval from the ethics committee and NRHD, the patient list was obtained from the neurosurgery department at SBAH to evaluate the data of patients who had undergone IONM in brain tumour surgery procedures. Patient records were retrieved from the SBAH archives to document patient demographics and medical treatment. SSEP data denoting cortical and subcortical responses were extracted from recordings of neurosurgical cases undertaken previously. The patients included those who underwent IONM for contralateral, ipsilateral, cortical, and subcortical responses. Recorded baseline SSEP responses were compared to SSEP responses during and after brain tumour resection to determine whether a change had occurred. Contralateral SSEPs were compared to ipsilateral SSEPs and cortical SSEPs were compared to subcortical SSEPs. In this study, the terms “ipsilateral” and “contralateral” will be used to describe the SSEP waveform or peak about the tumour location in the patient.

Evaluation and interpretation of SSEP results were conducted with Dr Grobbelaar, Prof Padayachy, and Jessica Farinha. What follows indicates the procedure for SSEP stimulation and recording that was used to gain the data for this study.[55]

3.6 RESEARCH METHODS

3.6.1 SSEP stimulation technique

Somatosensory evoked potentials are elicited by electrical stimulation to major nerve trunks or dermatomes.[55] Upper extremity-mixed or major nerve SSEPs are obtained by stimulating the median nerve or ulnar nerve near the wrist.[55] Lower extremity SSEPs are achieved by stimulating the posterior tibial nerve at the ankle. The anode electrode is placed two to four centimetres distal from the cathode electrode to avoid an anodal block.[55] Subdermal needle electrodes are used for intraoperative SSEP recordings. Needle electrodes are placed close to the underlying nerves.[70]

Constant current stimulation is used for optimal SSEP recording in surgeries, especially for long surgical procedures.[55]

A series of rectangular pulses with certain pulse width and frequency as follows are used as electrical stimuli for SSEP recording:[73]

Pulse width (or pulse duration): 200–300 microsecond.[55]

Frequency: A frequency between 2 and 5 Hz is used. To avoid synchronisation between the responses and the underlying electrical noise, the stimulus rate is not a submultiple of the noise frequency. Sometimes a slight change of stimulus rate, for example from 4.80 to 4.13, improves the quality of the evoked responses.[43-44,55,69]

Intensity: Supramaximal stimulation is used to produce repeatable responses. Some factors, such as pathology of the peripheral nerves, large or oedematous extremities, distance of the electrodes to the underlying nerves, and types of stimulating electrodes limits the effectiveness of stimulation. A stimulus of 50mA or greater is sometimes required.[55,64,66,101]

3.6.2 SSEP recording technique

Subdermal needle electrodes are used in the operating room.[55,69]

Recording sites are as follows:

Cortical recording of upper extremity SSEP: Recording is taken from the post-central gyrus of the somatosensory cortex, contralateral to the stimulated limb. The locations are called CP3 and CP4 which are two centimetres posterior to the C3 and C4

positions of the 10–20 International System of EEG electrode placement. The recording montage is CP3-Fz or CP3-CP4 for right arm stimulation; and CP4-Fz or CP4-CP3 for left arm stimulation.[55,70]

Cortical recording of lower extremity SSEP: CPz is the active electrode site, which is two centimetres posterior to Cz. CPz-CPc (which is CPz-CP4 for left leg stimulation, and CPz-CP3 for right) is used as it produces higher amplitude and more reliable signals.[55,70]

Subcortical: The recording is made at the posterior cervical spine, one or linked earlobes, or mastoid.[55,57,67,70,76,102]

Peripheral nerve: The recording is made at the ipsilateral Erb's point for upper extremity stimulation, and the ipsilateral popliteal fossa for lower extremity stimulation.[55,68]

The SSEP amplitudes tend to be low; as high as only several microvolts or as low as less than a microvolt, especially with pathological subjects. Averaging is required to record the signal against biological and ambient noise. SSEP signal is time-locked to the stimulus and most of the noise occurs randomly, allowing the noise to be averaged out with averaging of repeated responses. With good preparation of the recording sites to reduce impedance, and optimised recording montages, clean signals are recorded in as few as 50 to 200 trials.[55]

Recording parameters are as follows:

Filters: Most of the energy contained in cortical SSEP is present in the frequency bandpass above 30Hz and below 500Hz. Filters are set from (10–30) Hz to (250–1000) Hz. The relative frequency content of the subcortical or peripheral responses is much higher, thus the filters are set to (30–100) Hz to (500–2000) Hz.[55,69-70]

Time base: The time base is set at 50 milliseconds for upper extremity SSEPs, and 100 milliseconds for lower extremity SSEPs. It may need adjustment depending on the age and size of the individual, and if any pathological conditions are present.[55]

Sensitivity: The median amplitude of SSEP is about one microvolt. The recording sensitivity ranges from 0.1 to 5 microvolts/unit. With direct cortical recording during

cranial surgeries, the amplitude can be high, and the sensitivity is set to 20–50 microvolts/unit in such cases.[55]

After adjusting the patient's position for the surgery, the electrodes are loosened and connected to the IONM device. After all the electrodes are connected to the device, an impedance test is performed, and baseline waveforms are recorded. These waveforms provide information about the depth of anaesthesia and whether the IONM device is operating properly.[55]

3.7 DATA ANALYSIS

3.7.1 Data management

The data obtained through IONM techniques were accessed at SBAH and subsequently organised into Excel spreadsheets for analysis, with patient anonymity preserved. This USB was updated weekly by the primary investigator until all data from the patient list was processed. Statistical analysis was carried out utilising R and STATA17. Validation of the data was conducted in consultation with Prof. Padayachy and Dr Grobbelaar upon the culmination of the study. Variances in IONM responses for contralateral, ipsilateral cortical, and subcortical aspects within specific surgery time points were both documented and evaluated.

3.7.2 Statistical analysis

The dataset consisted of information from 52 patients who had undergone tumour resection surgeries, culminating in 303 observations during these procedures. However, three patients were excluded from the analysis owing to incomplete surgical data. As a result, the final dataset comprised 49 patients with a total of 287 observations. This data was condensed into three distinct time points: pre-resection, intra-resection, and post-resection, thus generating 138 data points across the patient cohort.

To address the research objectives, the dataset was stratified into two distinct groups: patients with hemispheric brain tumours (34 patients, 96 data points) and patients with midline tumours (15 patients, 42 data points).

Given the presence of missing data across various waveforms and time points, analyses were performed using varying sample sizes. This approach aimed to maximise the available data for each analysis while ensuring result comparability. In addition to the three patients excluded owing to complete data absence, another patient was excluded owing to inadequate readings from all left waveforms as well as from the right N9 peak, rendering their data unsuitable for analysis.

The initial phase encompassed the utilisation of descriptive statistics for the overall dataset, as well as for hemispheric and midline tumour subgroups, categorised by time. The subsequent analysis involved one-sided paired t-tests to ascertain mean latency discrepancies across waveforms and time points. To maintain result consistency, only patients with complete data for relevant waveforms or time points were used in the analyses, ensuring comparability. Additionally, robustness checks were performed using the maximum available data to counteract any potential analysis bias arising from patients with complete information.

Throughout the analysis, statistical significance was determined using a threshold of $p < 0.05$. All t-tests were one-sided and paired, with the null hypothesis positing ‘no mean latency difference’ while the alternative hypothesis asserted ‘a mean latency difference greater than 0’.

CHAPTER 4: RESULTS

4.1 CHAPTER OBJECTIVE

In this chapter, all statistical analyses will be displayed in table and graph format with necessary explanations provided for each.

4.2 DESCRIPTIVE STATISTICS

Table 2. Descriptive statistics: Aggregate dataset

Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
N9	Right	96	12.29	3.03	10.79	12.41	13.30	6.45	25.30
	Left	96	12.39	3.30	10.75	12.30	13.48	7.00	26.38
N20	Right	129	22.63	3.32	20.83	22.40	24.60	15.50	36.73
	Left	125	22.80	2.91	20.83	22.52	24.63	15.70	33.80
P37	Right	113	42.86	7.01	37.80	42.02	46.80	25.50	60.00
	Left	121	43.16	6.53	38.42	43.65	48.30	26.70	57.95
N45	Right	114	54.42	7.43	48.84	53.76	60.38	39.70	69.07
	Left	121	54.98	7.32	49.65	55.20	60.60	38.08	74.00

Table 2 presents the descriptive statistics of the overall dataset (hemispheric and midline tumours), which includes latency measurements from the N9, N20, P37, and N45 peaks on both the right and left. Table 2 aggregates all readings of SSEP latency, whereas Table 3 splits the data at the different time points.

Table 3. Descriptive statistics: Aggregate dataset by time

Time	Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
Before	N9	Right	37	12.47	3.13	10.83	12.60	13.58	6.60	25.30
		Left	37	12.51	3.28	10.83	12.72	13.93	7.00	26.38
	N20	Right	49	23.14	3.35	21.15	23.15	24.97	17.15	36.73
		Left	48	23.33	2.89	21.34	23.25	25.12	17.80	33.30
	P37	Right	42	43.67	6.72	38.73	43.76	49.30	29.20	56.30
		Left	44	44.26	6.32	39.61	44.25	48.88	29.50	57.95
	N45	Right	42	55.38	6.99	49.65	54.95	61.36	43.30	69.07
		Left	44	55.84	6.49	50.88	56.33	60.91	42.65	69.00
During	N9	Right	31	12.06	3.02	10.47	12.30	13.22	6.45	24.30
		Left	31	12.16	3.42	10.05	11.92	13.51	7.20	26.00
	N20	Right	42	22.37	3.41	20.67	22.22	24.51	16.09	36.50
		Left	41	22.55	3.12	20.93	22.30	24.60	15.70	33.80
	P37	Right	36	43.28	7.11	39.33	42.43	47.39	25.50	56.00
		Left	39	43.05	6.74	38.43	44.00	47.65	26.70	56.00
	N45	Right	37	54.59	7.35	49.00	53.70	60.30	41.70	66.63
		Left	39	55.06	7.15	49.67	54.60	59.97	41.90	66.60
After	N9	Right	28	12.32	2.99	10.88	12.30	13.01	8.43	25.20
		Left	28	12.49	3.30	10.96	12.06	13.33	8.40	25.75
	N20	Right	38	22.26	3.20	20.79	21.92	24.23	15.50	32.60
		Left	36	22.39	2.66	20.54	22.25	23.96	17.60	31.00
	P37	Right	35	41.46	7.22	36.94	41.30	46.45	28.30	60.00
		Left	38	42.00	6.53	38.24	41.97	46.28	28.40	56.60
	N45	Right	35	53.09	8.01	46.62	51.48	59.65	39.70	67.62
		Left	38	53.90	8.38	47.92	53.35	59.30	38.08	74.00

From Table 3 the dynamics of the data can be assessed once divided into different time points.

Table 4. Descriptive statistics: Hemispheric tumours

Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
N9	Ipsi	63	12.29	1.95	11.35	12.62	13.45	7.00	16.00
	Contra	63	12.10	2.01	11.04	12.30	13.45	6.45	16.85
N20	Ipsi	91	22.45	2.66	20.85	22.52	24.53	15.50	27.20
	Contra	89	23.00	2.27	21.17	23.15	24.85	17.79	27.40
P37	Ipsi	89	43.20	6.84	38.42	43.30	48.17	25.50	57.95
	Contra	80	44.73	6.50	38.88	45.55	49.73	33.30	60.00
N45	Ipsi	89	55.14	7.29	48.80	56.00	60.38	40.80	74.00
	Contra	80	56.54	7.81	50.08	57.15	63.34	38.08	69.07

In Table 4 the latency readings are analysed from the patients with hemispheric tumours. The data ranges from 7.00 milliseconds to 74.00 milliseconds on the N9 ipsilateral peak and the N45 Ipsilateral peak respectively.

Table 5. Descriptive statistics: Midline tumours

Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
N9	Right	96	12.29	3.03	10.79	12.41	13.30	6.45	25.30
	Left	96	12.39	3.30	10.75	12.30	13.48	7.00	26.38
N20	Right	129	22.63	3.32	20.83	22.40	24.60	15.50	36.73
	Left	125	22.80	2.91	20.83	22.52	24.63	15.70	33.80
P37	Right	113	42.86	7.01	37.80	42.02	46.80	25.50	60.00
	Left	121	43.16	6.53	38.42	43.65	48.30	26.70	57.95
N45	Right	114	54.42	7.43	48.84	53.76	60.38	39.70	69.07
	Left	121	54.98	7.32	49.65	55.20	60.60	38.08	74.00

In Table 5 it can be seen that the lowest latency was observed in the N9 peak on the right (6.54 milliseconds) and the highest latency on the N45 peak on the left. The highest and lowest means were similarly observed on the same peaks with means of 12.29 milliseconds and 54.98 milliseconds respectively.

Table 6. Descriptive statistics: Hemispheric tumours by the time

Time	Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
Before	N9	Ipsi	24	12.35	2.13	11.44	12.89	14.10	7.00	15.40
		Contra	24	12.31	2.33	11.17	12.77	13.68	6.60	16.85
	N20	Ipsi	34	23.14	2.55	21.50	23.53	24.90	17.15	27.20
		Contra	33	23.50	2.26	21.90	23.50	25.20	19.00	27.40
	P37	Ipsi	33	43.98	6.72	39.10	44.33	48.60	29.20	57.95
		Contra	30	45.14	6.22	40.75	45.55	50.36	34.95	56.30
	N45	Ipsi	33	55.05	6.97	49.30	56.07	60.63	42.65	69.00
		Contra	30	57.11	7.42	51.15	57.40	62.79	43.30	69.07
During	N9	Ipsi	21	12.00	2.12	10.98	12.45	13.45	7.20	15.75
		Contra	21	11.80	2.13	10.83	12.30	13.57	6.45	14.50
	N20	Ipsi	30	21.98	2.88	20.48	22.15	24.35	15.70	27.00
		Contra	30	22.49	2.26	20.92	22.28	24.60	17.79	26.15
	P37	Ipsi	28	43.68	6.96	39.28	44.33	48.02	25.50	56.00
		Contra	26	44.86	6.63	39.70	45.50	49.60	34.64	56.00
	N45	Ipsi	28	55.91	6.88	50.65	56.62	60.36	42.00	66.60
		Contra	26	56.78	7.36	50.70	56.19	64.69	44.66	66.63
After	N9	Ipsi	18	12.54	1.52	11.89	12.88	13.24	9.30	16.00
		Contra	18	12.18	1.35	11.26	12.30	13.15	9.30	14.90
	N20	Ipsi	27	22.09	2.46	20.66	22.30	23.73	15.50	26.80
		Contra	26	22.96	2.25	21.14	23.70	24.49	18.00	26.60
	P37	Ipsi	28	41.79	6.89	36.63	41.03	45.70	28.30	56.60
		Contra	24	44.08	6.91	38.75	44.97	47.40	33.30	60.00
	N45	Ipsi	28	54.49	8.19	46.56	54.30	60.01	40.80	74.00
		Contra	24	55.55	8.92	48.52	57.95	62.00	38.08	67.95

Table 6 contains descriptive statistics for SSEP latency readings for patients with tumours that were either on the right or the left. Table 6 illustrates that, before the surgery, the mean latency was lowest on the N9 contralateral peak with a reading of 12.31 milliseconds and the highest was 57.11 milliseconds on the N45 contralateral peak. During the surgery, the mean of the latency ranges from 11.8 milliseconds (N9 contralateral) to 56.78 milliseconds (N45 contralateral). After the surgery, the mean latency ranges from 12.18 milliseconds to 55.55 milliseconds.

Table 7. Descriptive statistics: Midline tumours by the time

Time	Peak	Side	n	Mean	SD	Q1	Median	Q3	Min	Max
Before	N9	Right	13	12.64	4.39	10.30	12.60	12.97	7.80	25.30
		Left	13	12.92	4.79	10.30	12.40	13.30	8.00	26.38
	N20	Right	15	22.91	4.89	19.48	22.50	25.01	17.30	36.73
		Left	15	23.20	3.93	20.75	23.07	24.38	17.80	33.30
	P37	Right	11	42.07	5.84	38.03	41.57	46.50	33.87	50.30
		Left	12	42.79	7.23	36.28	44.12	48.88	29.50	51.53
	N45	Right	11	53.96	4.75	50.15	54.40	57.38	48.17	62.30
		Left	12	54.96	5.50	49.94	55.77	59.15	46.40	62.00
During	N9	Right	10	12.49	4.53	9.74	12.10	12.60	8.17	24.30
		Left	10	12.62	5.30	9.30	11.30	13.09	8.17	26.00
	N20	Right	11	22.95	5.20	20.35	21.80	24.68	16.77	36.50
		Left	12	23.11	4.18	21.00	22.35	24.59	17.77	33.80
	P37	Right	9	40.26	5.84	33.77	41.23	46.30	32.20	46.98
		Left	12	40.45	7.21	35.23	42.85	45.54	26.70	48.60
	N45	Right	10	50.14	5.11	48.05	50.23	53.25	41.70	57.60
		Left	12	52.03	7.24	47.15	51.57	55.60	41.90	65.65
After	N9	Right	10	12.39	4.85	9.38	11.70	12.52	8.43	25.20
		Left	10	12.60	5.30	9.15	11.30	12.98	8.40	25.75
	N20	Right	11	21.58	4.40	18.65	21.60	22.27	17.00	32.60
		Left	10	22.11	3.79	20.05	21.92	22.28	17.60	31.00
	P37	Right	10	38.65	5.16	35.47	39.86	41.83	30.00	45.95
		Left	11	39.35	6.69	34.07	41.85	43.85	28.40	50.00
	N45	Right	10	48.79	4.54	46.41	50.30	51.32	39.70	55.30
		Left	11	50.86	7.30	44.99	52.10	56.10	40.30	60.60

Table 7 contains descriptive statistics for SSEP latency readings for patients with tumours that were midline. Table 7 illustrates that, before the surgery, the mean latency was lowest on the N9 right peak with a reading of 12.64 milliseconds and the highest was 54.96 milliseconds on the N45 left peak. During the surgery, the mean latency ranges from 12.49 milliseconds (N9 right) to 52.03 milliseconds (N45 left). After the surgery, the mean latency ranges from 12.39 milliseconds (N9 right) to 50.86 milliseconds (N45 left).

It is important to acknowledge that the descriptive statistics give a brief overview of the central tendency of the data but they do not give sufficient information to make any meaningful conclusions about the research questions of this study. Furthermore, the descriptive statistics are calculated using varying sample sizes (to use as much data as possible and to take advantage of statistical power) so comparability is limited using only the information from the descriptive statistics.

4.3 CONTRALATERAL AND IPSILATERAL CORTICAL SSEP RESPONSES

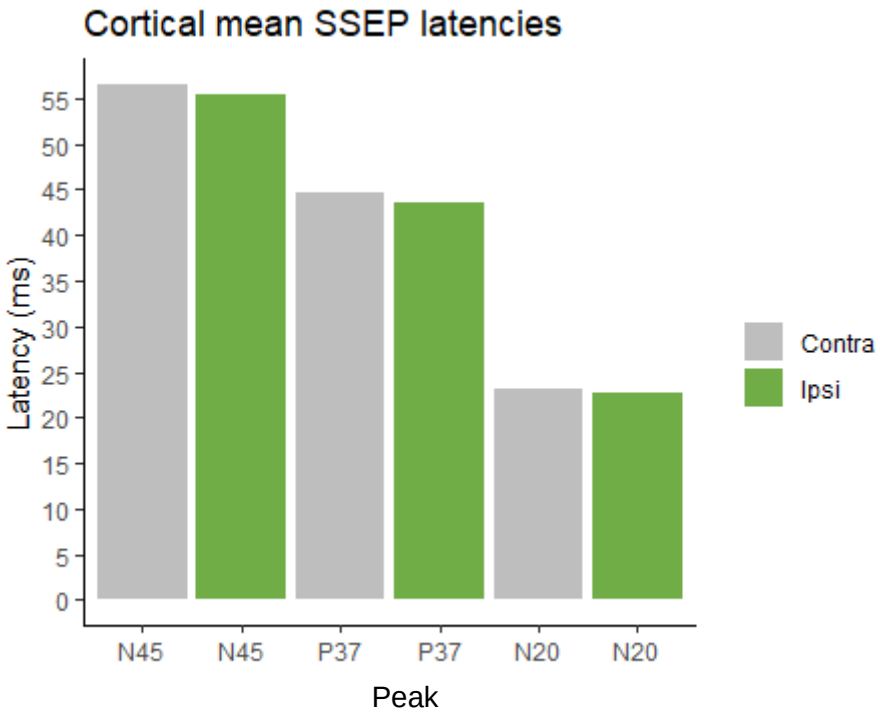

Figure 9. Cortical mean SSEP latencies
The bar graph represents the average contralateral and ipsilateral SSEP latencies across the different cortical waveforms (N45, P37, and N20). Latency represented in milliseconds (ms).

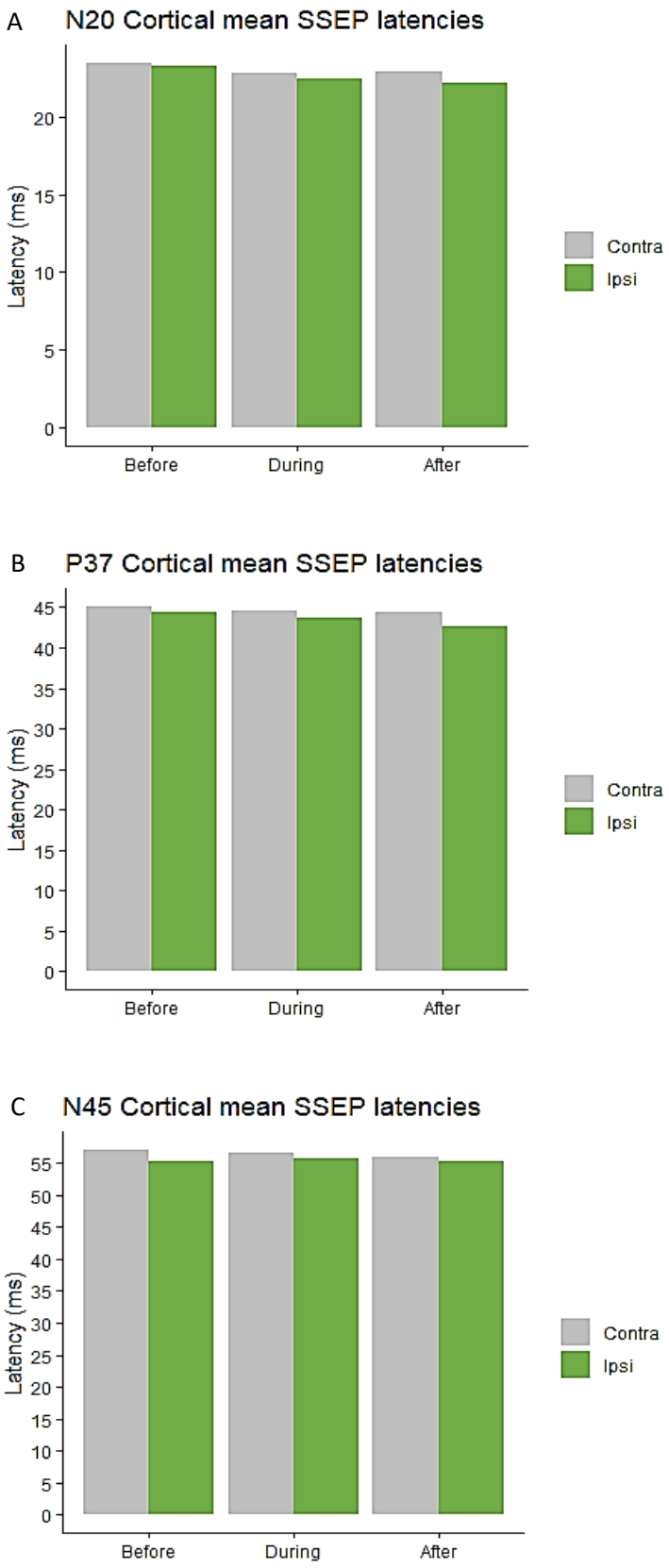

Figure 10. Cortical mean SSEP latencies by time
The bar graphs represent the average contralateral and ipsilateral SSEP latencies across the different time intervals. (A) N20 peak, (B) P37 peak, (C) N45 peak.

Table 8. T-test results for contralateral and ipsilateral cortical SSEP responses

Time	Peak	Contralateral		Ipsilateral		% diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	Mean					
Overall	N20	23.07	2.19	22.66	2.26	1.82	3.00	76	0.00	Yes
	P37	44.69	6.54	43.65	6.41	2.37	2.49	76	0.01	Yes
	N45	56.59	7.82	55.43	7.15	2.09	2.65	76	0.00	Yes
Before	N20	23.45	2.28	23.26	2.34	0.81	0.93	29	0.18	No
	P37	45.14	6.22	44.42	6.41	1.62	1.41	29	0.08	No
	N45	57.11	7.42	55.31	7.02	3.26	2.20	29	0.02	Yes
During	N20	22.75	2.06	22.37	2.39	1.70	1.60	23	0.06	No
	P37	44.48	6.77	43.72	6.08	1.74	0.81	23	0.21	No
	N45	56.66	7.35	55.73	6.42	1.66	2.03	23	0.03	Yes
After	N20	22.91	2.22	22.17	1.93	3.33	2.62	22	0.01	Yes
	P37	44.31	6.97	42.57	6.84	4.08	2.35	22	0.01	Yes
	N45	55.84	9.01	55.27	8.28	1.03	0.64	22	0.27	No

For this objective, only the patients who have hemispheric brain tumours were used to analyse the differences between the contralateral and ipsilateral latencies. This objective analyses the cortical latencies, which are: upper limbs cortical (N20), lower limbs cortical (P37), and lower limbs cortical (N45) as can be seen in table 8.

Testing to see whether the results seen in the bar charts are statistically significant, one sided paired t-tests were performed with a null hypothesis that the true mean difference between cortical contralateral SSEP latencies and ipsilateral are equal to 0. This null hypothesis was rejected at a 0.05 level of significance for the data of patients with hemispheric tumours before splitting them into different time points.

Once the data was split into different time points, some of the differences between the contralateral and ipsilateral waveforms became insignificant. For the N20 and P37 peaks, the mean differences are insignificant both before and during the surgeries; however, the contralateral latencies are still higher than the ipsilateral. On the N45 peaks, the differences are significant before and during the surgeries but not after.

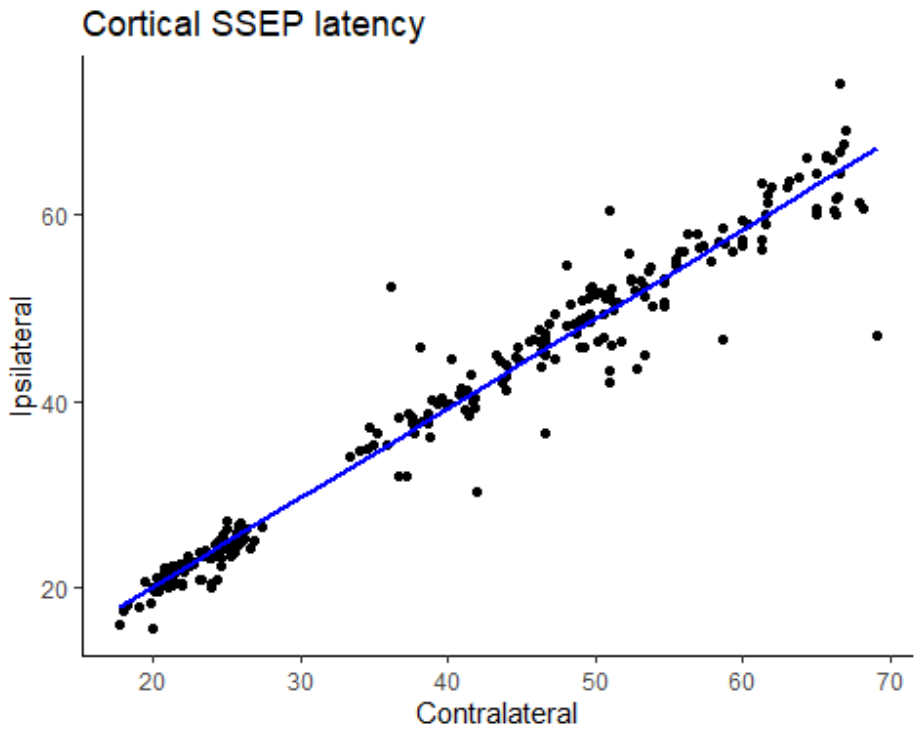

Figure 11. Correlation of cortical SSEP latencies:
The scatter plot shows a strong positive correlation between contralateral and ipsilateral SSEP latencies (measured in ms).

Table 9. Correlation analysis for contralateral and ipsilateral cortical SSEP responses

Time	Peak	Correlation	P_Value	Significant
Overall	N20	0.85	0	Yes
	P37	0.84	0	Yes
	N45	0.87	0	Yes
Before	N20	0.89	0	Yes
	P37	0.90	0	Yes
	N45	0.81	0	Yes
During	N20	0.87	0	Yes
	P37	0.75	0	Yes
	N45	0.96	0	Yes
After	N20	0.80	0	Yes
	P37	0.87	0	Yes
	N45	0.88	0	Yes

The analysis of correlations represented in Table 9 investigates the relationship between the ipsilateral and contralateral peaks. There are strong linear relationships between the contralateral and ipsilateral latencies on the cortical peaks at all points in time.

4.4 CORTICAL AND SUBCORTICAL SSEP RESPONSES

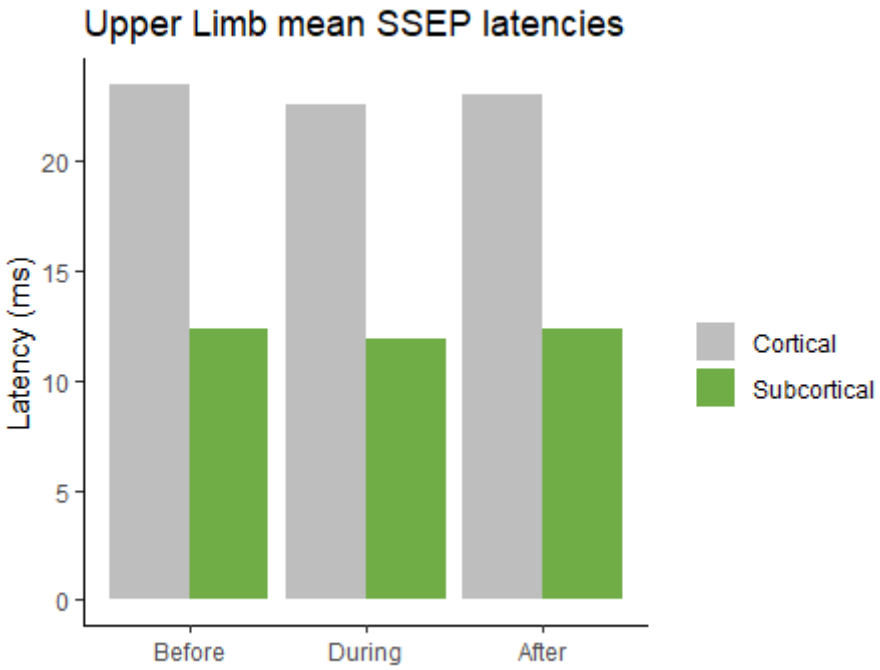

Figure 12. Upper limb mean SSEP latencies by time
The bar graph represents the average cortical and subcortical upper limb SSEP latencies across the different time intervals.

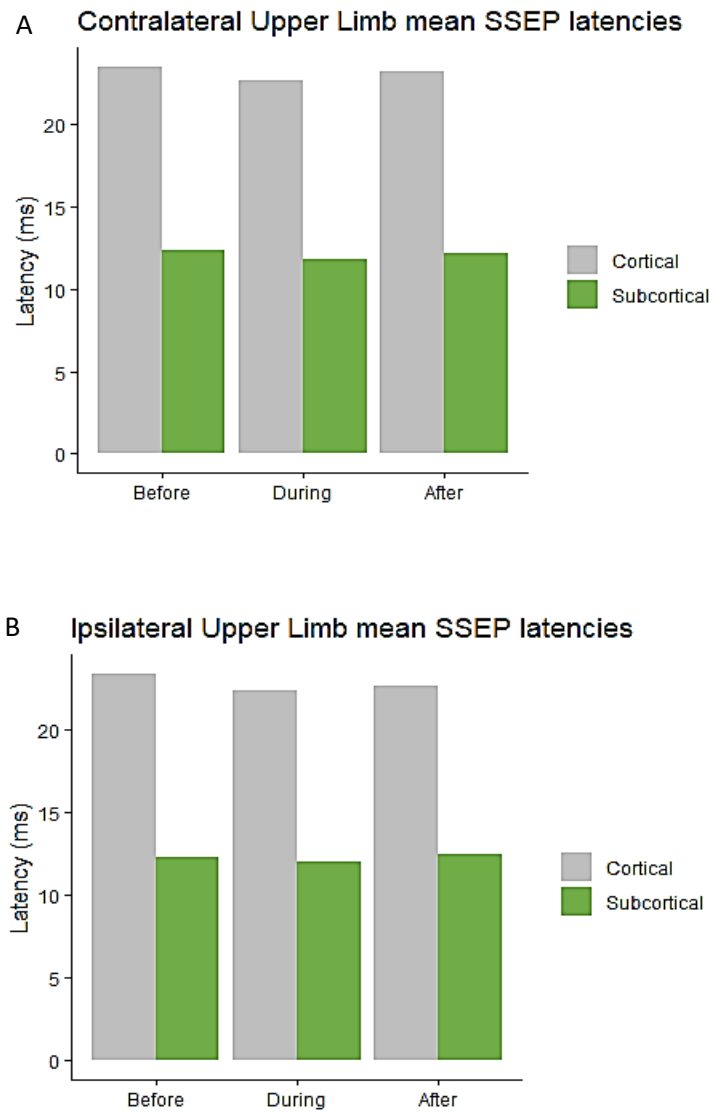

Figure 13. Contralateral and Ipsilateral mean Upper limb SSEP latencies by time
The bar graphs represent the average cortical and subcortical upper limb SSEP latencies across the different time intervals. (A) Contralateral SSEP latencies, (B) Ipsilateral SSEP latencies.

Table 10. T-test results for cortical and subcortical SSEP responses on hemispheric brain tumour patients

Time	Peak	Cortical		Sub-cortical		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
Overall	Ipsi	22.87	2.29	12.29	1.95	86.09	64.31	62	0	Yes
	Contra	23.16	2.23	12.10	2.01	91.38	54.49	62	0	Yes
Before	Ipsi	23.43	2.32	12.35	2.13	89.69	43.68	23	0	Yes
	Contra	23.52	2.20	12.31	2.33	91.05	33.05	23	0	Yes
During	Ipsi	22.38	2.49	12.00	2.12	86.50	34.68	20	0	Yes
	Contra	22.67	2.31	11.80	2.13	92.20	33.50	20	0	Yes
After	Ipsi	22.68	1.95	12.54	1.52	80.89	37.64	17	0	Yes
	Contra	23.25	2.20	12.18	1.35	90.91	26.89	17	0	Yes

Table 11. T-test results for cortical and subcortical SSEP responses on midline brain tumour patients

Time	Peak	Cortical		Sub-cortical		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
Overall	Right	21.07	2.79	12.57	4.54	67.69	10.74	30	0	Yes
	Left	22.00	2.73	12.70	5.02	73.26	11.52	30	0	Yes
Before	Right	21.69	3.16	12.64	4.39	71.57	7.53	12	0	Yes
	Left	22.43	2.97	12.92	4.79	73.63	8.17	12	0	Yes
During	Right	21.24	2.68	12.81	4.69	65.77	5.46	8	0	Yes
	Left	22.25	2.88	12.95	5.51	71.76	5.61	8	0	Yes
After	Right	20.02	2.27	12.21	5.11	63.89	4.95	8	0	Yes
	Left	21.12	2.29	12.12	5.39	74.31	5.47	8	0	Yes

To compare the cortical and subcortical SSEP latencies, analysis is done on readings from the upper limbs (N9 and N20) owing to the unavailability of subcortical readings from the lower limbs. In the initial visual analysis of the bar charts, it looked as though the mean difference between cortical and subcortical SSEP response times was greater than 0.

To confirm the results from the charts, using t-tests, it was found that at all time points, on the ipsilateral, contralateral, and using a combination of the contralateral and ipsilateral, the mean difference between the cortical and sub-cortical readings is statistically greater than 0 at a 1% level of significance.

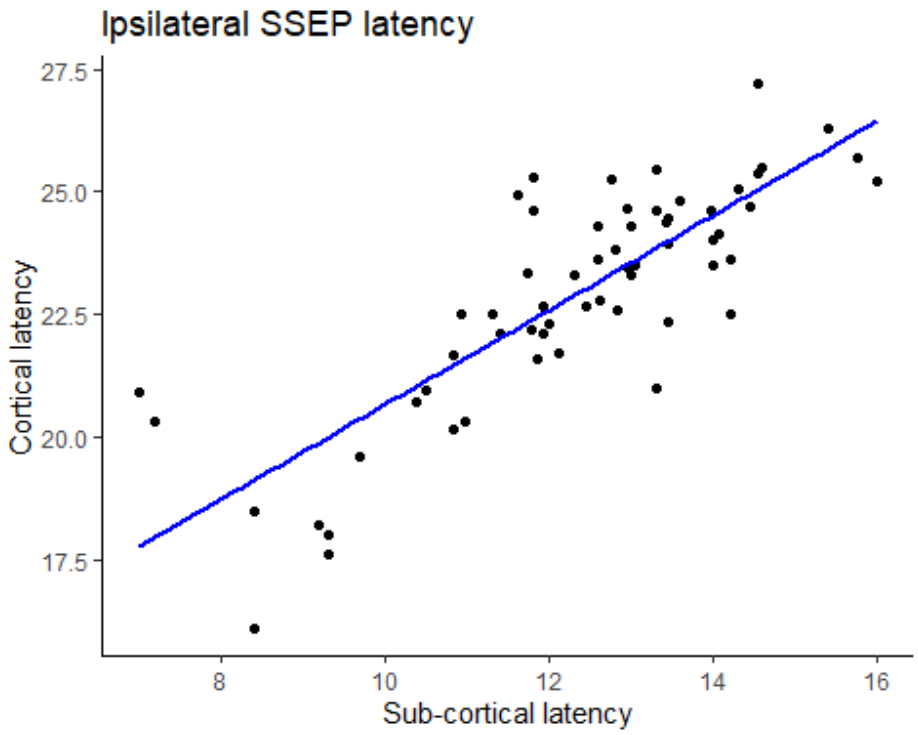

Figure 14. Correlation of ipsilateral SSEP latencies in hemispheric brain tumours
The scatter plot shows a strong positive correlation between subcortical and cortical ipsilateral SSEP latencies.

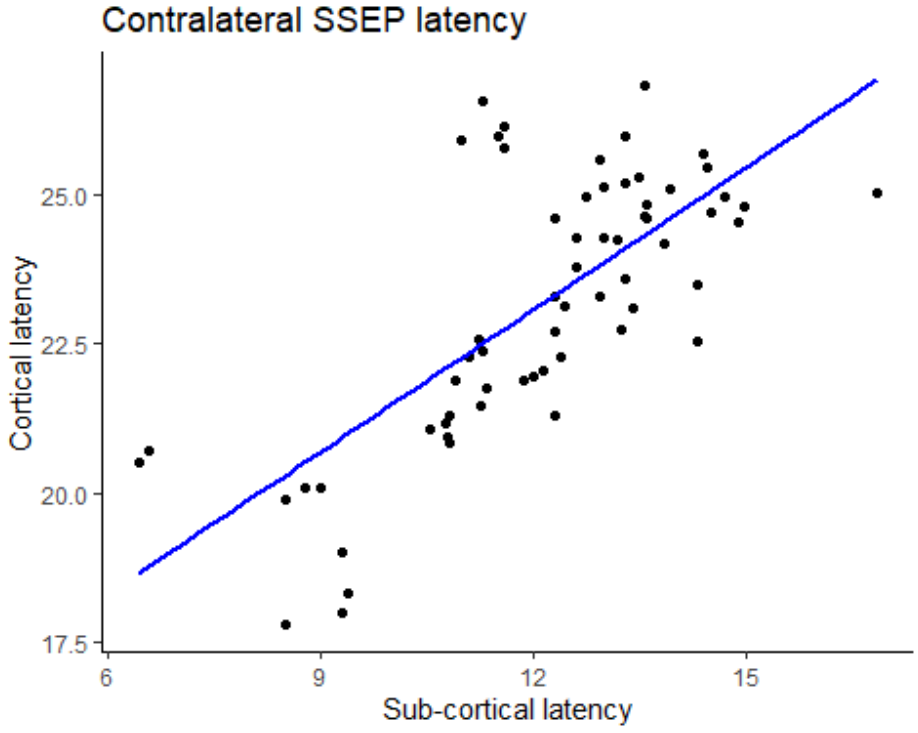

Figure 15. Correlation of contralateral SSEP latencies in hemispheric brain tumours
The scatter plot shows a strong positive correlation between subcortical and cortical contralateral SSEP latencies.

Table 12. Correlation analysis for cortical and subcortical SSEP responses on hemispheric brain tumour patients

Time	Peak	Correlation	P_Value	Significant
Overall	Ipsi	0.82	0.00	Yes
	Contra	0.72	0.00	Yes
Before	Ipsi	0.85	0.00	Yes
	Contra	0.73	0.00	Yes
During	Ipsi	0.83	0.00	Yes
	Contra	0.78	0.00	Yes
After	Ipsi	0.81	0.00	Yes
	Contra	0.61	0.01	Yes

Table 12 shows the analysis of the relationship between the cortical and subcortical peaks for hemispheric brain tumours. There are strong linear relationships between the subcortical and cortical latencies at all points in time.

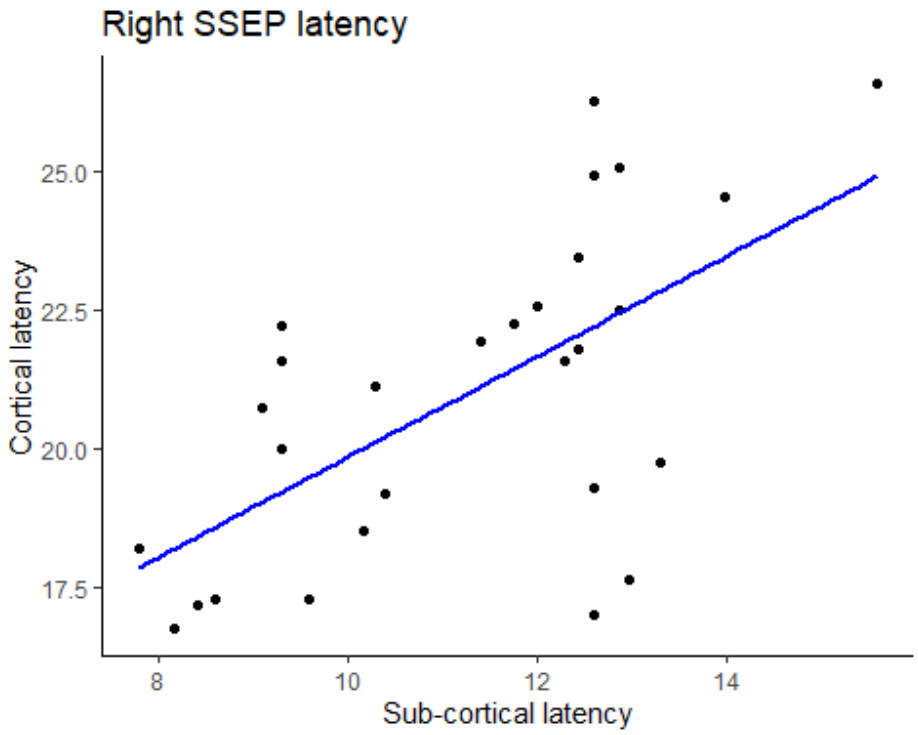

Figure 16. Correlation of right SSEP latencies in midline brain tumours
The scatter plot shows the positive correlation between subcortical and cortical right SSEP latencies.

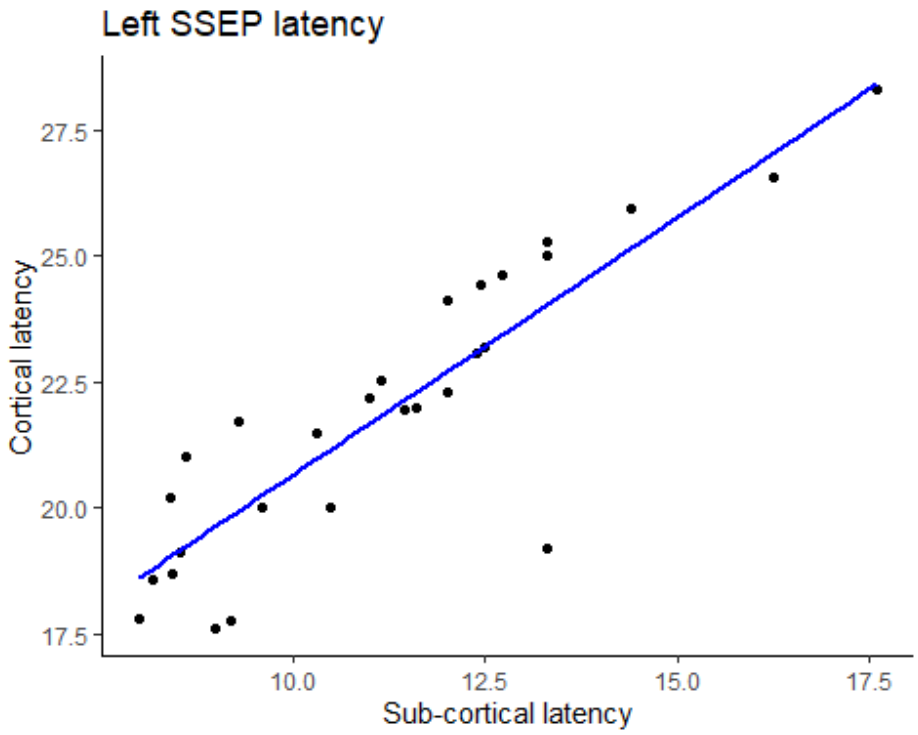

Figure 17. Correlation of left SSEP latencies in midline brain tumours
The scatter plot shows a strong positive correlation between subcortical and cortical left SSEP latencies.

Table 13. Correlation analysis for cortical and subcortical SSEP responses on midline brain tumour patients

Time	Peak	Correlation	P_Value	Significant
Overall	Right	0.62	0.00	Yes
	Left	0.88	0.00	Yes
Before	Right	0.62	0.03	Yes
	Left	0.83	0.00	Yes
During	Right	0.73	0.04	Yes
	Left	0.92	0.00	Yes
After	Right	0.36	0.38	No
	Left	0.91	0.00	Yes

For the midline tumours, the subcortical and cortical latencies are strongly positively correlated, except for the right peaks after resection which are not strongly correlated but remain positively correlated. This analysis was done after the exclusion of one patient where the subcortical readings were outliers which skewed the data.

4.5 BASELINE SSEP RESPONSES OVER TIME

This objective investigates the differences between the SSEP latencies at the baseline point in time (before resection) from the latencies recorded during and after resection. To allow for comparability, the initial analysis was done using only the patients with complete data for all waveforms at all points in time. To verify these results, the results were further investigated using as much data as possible to take advantage of the statistical power of a larger sample.

4.5.1 Hemispheric brain tumours

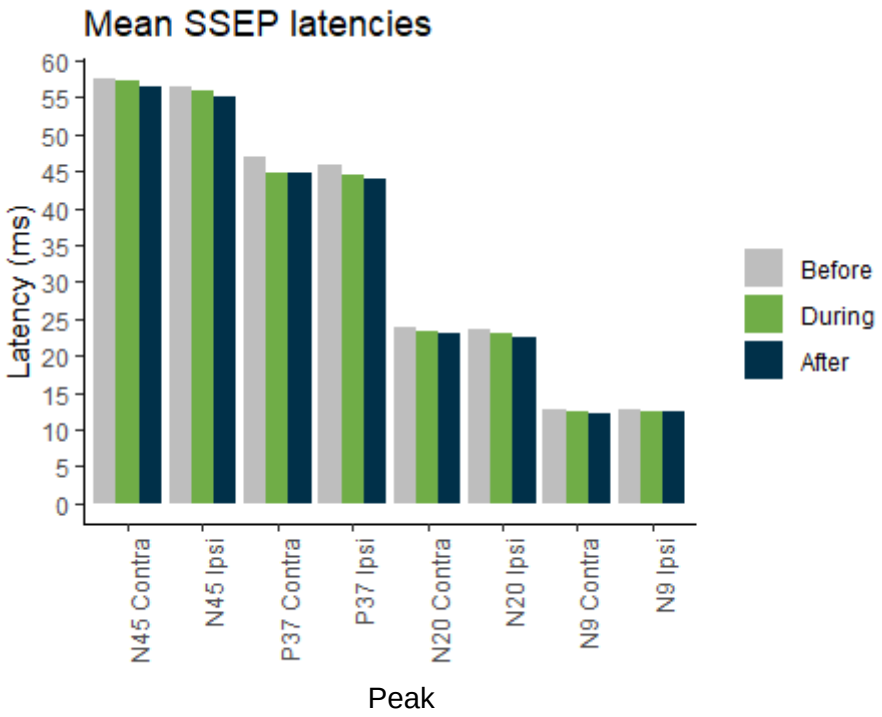

Figure 18. Mean SSEP latencies for hemispheric brain tumours
The bar graph represents the average time interval SSEP latencies for contralateral and ipsilateral hemispheric brain tumours across the different peaks (N45, P37, N20, N9).

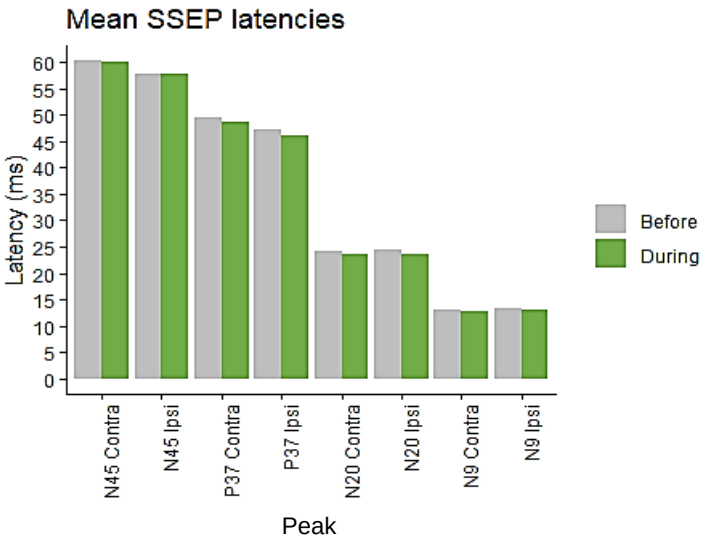

Figure 19. Mean hemispheric SSEP latencies before and during resection
The bar graph represents the average baseline and during resection SSEP latencies for contralateral and ipsilateral hemispheric brain tumours across the different peaks (N45, P37, N20, N9).

Table 14. T-test results for hemispheric brain tumours before and during resection using complete data only

Peak	Side	Before		During		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Ipsi	12.80	1.63	12.49	1.62	2.43	3.30	15	0.00	Yes
N9	Contra	12.71	1.58	12.34	1.45	3.02	4.28	15	0.00	Yes
N20	Ipsi	23.65	1.97	22.99	2.07	2.86	3.56	15	0.00	Yes
N20	Contra	23.73	2.11	23.24	2.10	2.12	3.21	15	0.00	Yes
P37	Ipsi	45.83	4.89	44.64	5.49	2.66	3.97	15	0.00	Yes
P37	Contra	46.93	5.75	44.85	6.78	4.64	2.23	15	0.02	Yes
N45	Ipsi	56.42	6.16	56.04	6.88	0.68	0.67	15	0.26	No
N45	Contra	57.50	7.34	57.24	7.82	0.47	0.54	15	0.30	No

Table 15. T-test results for hemispheric brain tumours before and during resection using as much data as possible for each peak

Peak	Side	Before		During		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Ipsi	12.24	2.21	12.00	2.12	1.99	3.11	20	0.00	Yes
N9	Contra	12.11	2.25	11.80	2.13	2.67	4.44	20	0.00	Yes
N20	Ipsi	23.18	2.32	22.19	2.70	4.47	2.62	28	0.01	Yes
N20	Contra	23.38	2.30	22.59	2.23	3.48	2.99	28	0.00	Yes
P37	Ipsi	45.46	5.99	44.32	6.20	2.58	4.68	25	0.00	Yes
P37	Contra	46.02	6.03	44.86	6.63	2.59	1.81	25	0.04	Yes
N45	Ipsi	56.80	6.28	56.31	6.54	0.86	1.27	25	0.11	No
N45	Contra	57.63	6.92	56.78	7.36	1.50	1.63	25	0.06	No

Using t-tests it was found that, at a 5% level of significance, the null hypothesis was rejected that the mean difference between the baseline SSEP latencies and during resection SSEP latencies is equal to 0 for all peaks, except for the N45 peaks. These results hold true both where as much data as possible were used and where just the complete data were used.

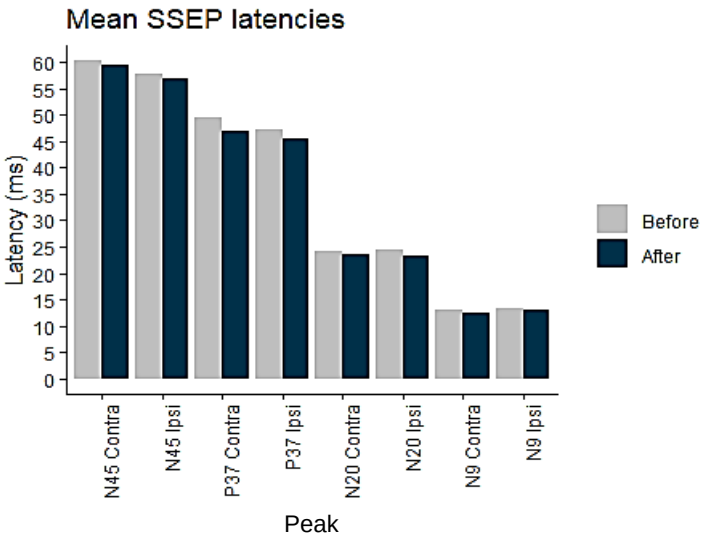

Figure 20. Mean hemispheric SSEP latencies before and after resection
The bar graph represents the average baseline and after-resection SSEP latencies for contralateral and ipsilateral hemispheric brain tumours across the different peaks (N45, P37, N20, N9).

Table 16. T-test results for hemispheric brain tumours before and after resection using complete data only

Peak	Side	Before		After		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Ipsi	12.80	1.63	12.49	1.61	2.44	2.10	15	0.03	Yes
N9	Contra	12.71	1.58	12.17	1.41	4.43	4.66	15	0.00	Yes
N20	Ipsi	23.65	1.97	22.41	1.91	5.52	6.78	15	0.00	Yes
N20	Contra	23.73	2.11	23.01	2.20	3.15	3.54	15	0.00	Yes
P37	Ipsi	45.83	4.89	43.88	5.62	4.46	4.80	15	0.00	Yes
P37	Contra	46.93	5.75	44.83	6.05	4.68	4.88	15	0.00	Yes
N45	Ipsi	56.42	6.16	55.06	6.78	2.47	2.38	15	0.02	Yes
N45	Contra	57.50	7.34	56.37	7.81	2.01	1.72	15	0.05	No

Table 17. T-test results for hemispheric brain tumours before and after resection using as much data as possible for each peak

Peak	Side	Before		After		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Ipsi	12.74	1.56	12.54	1.52	1.64	1.35	17	0.10	No
N9	Contra	12.61	1.53	12.18	1.35	3.51	3.35	17	0.00	Yes
N20	Ipsi	23.41	2.06	22.35	2.11	4.76	6.08	25	0.00	Yes
N20	Contra	23.60	2.10	22.96	2.25	2.81	3.46	25	0.00	Yes
P37	Ipsi	45.04	5.85	42.31	6.81	6.47	3.39	23	0.00	Yes
P37	Contra	46.00	6.23	44.08	6.91	4.35	3.56	23	0.00	Yes
N45	Ipsi	55.90	7.21	54.87	8.33	1.88	1.87	23	0.04	Yes
N45	Contra	57.11	7.61	55.55	8.92	2.80	2.15	23	0.02	Yes

When comparing the baseline period to the period after resection, it was found that all mean differences between the two periods were statistically significant at a 5% level of significance, except for the N45 contralateral peak when complete data were analysed and the N9 ipsilateral when the analysis was based using as much data as possible. These two are, however, significant at a 10% level of significance. This means that the null hypothesis can be rejected that the mean difference between the baseline and period after resection is equal to 0.

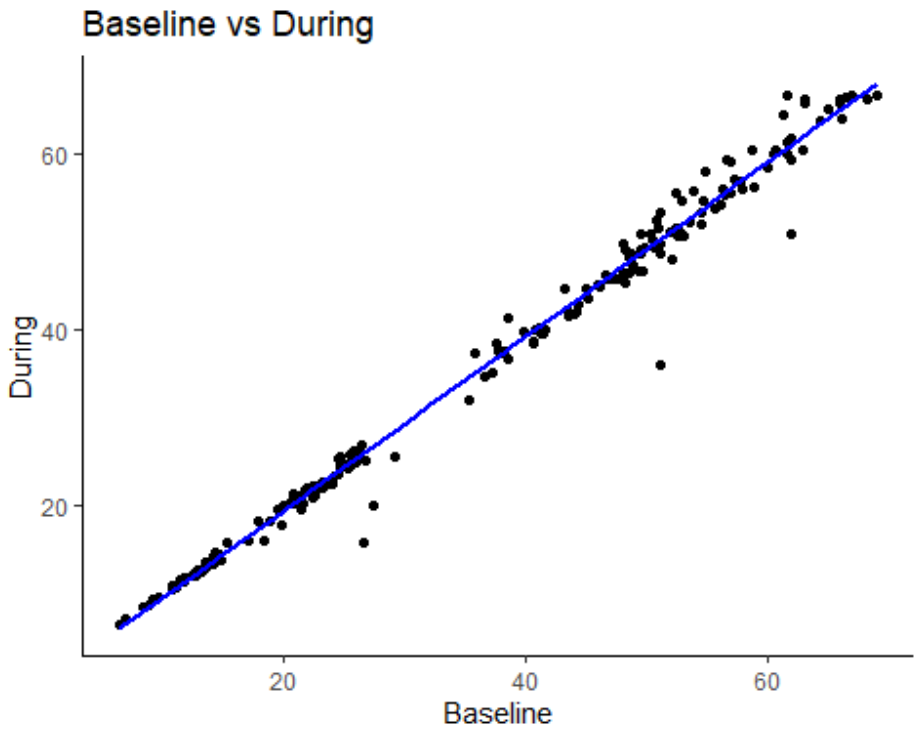

Figure 21. Correlation of SSEP latencies before and during resection of hemispheric brain tumours
The scatterplot shows a strong positive correlation between the baseline and during resection SSEP latencies for hemispheric brain tumours.

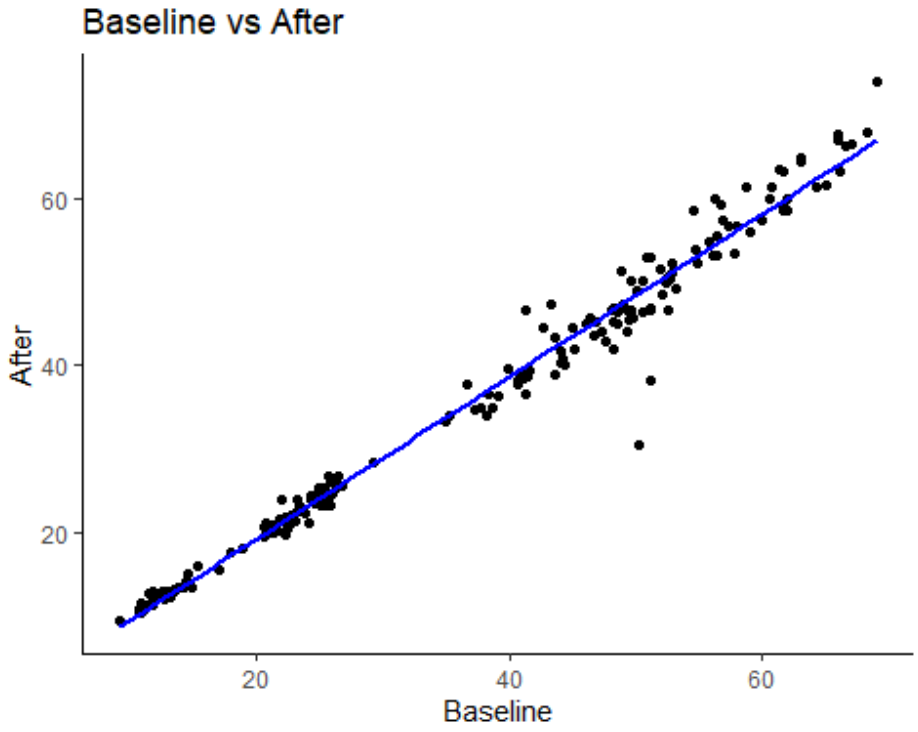

Figure 22. Correlation of SSEP latencies before and after resection of hemispheric brain tumours
The scatterplot shows a strong positive correlation between the baseline and after-resection SSEP latencies for hemispheric brain tumours.

4.5.2 Midline brain tumours

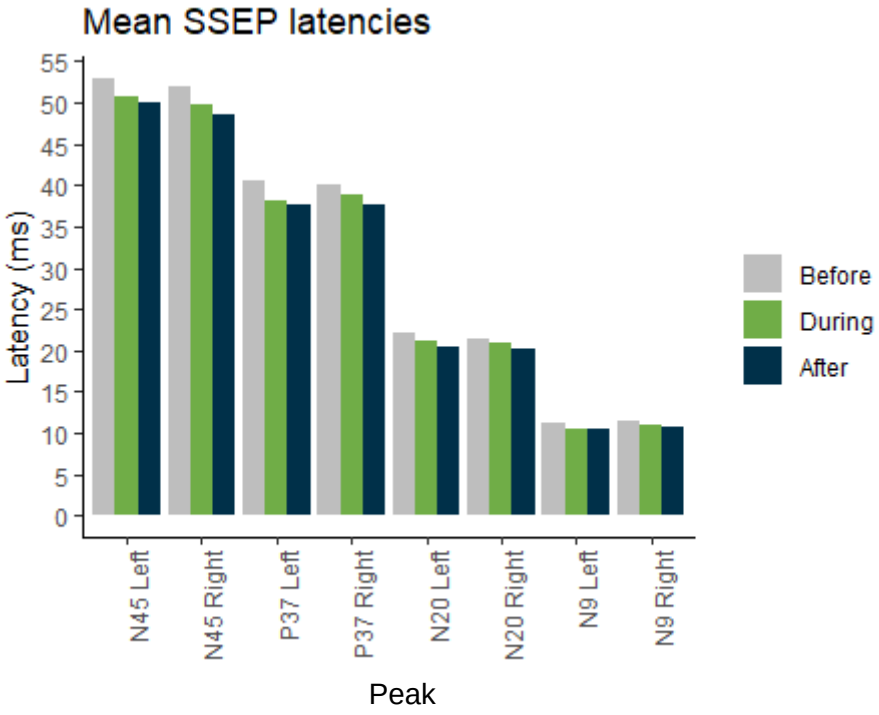

Figure 23. Mean SSEP latencies for midline brain tumours
The bar graph represents the average time interval SSEP latencies for left and right midline brain tumours across the different peaks (N45, P37, N20, N9).

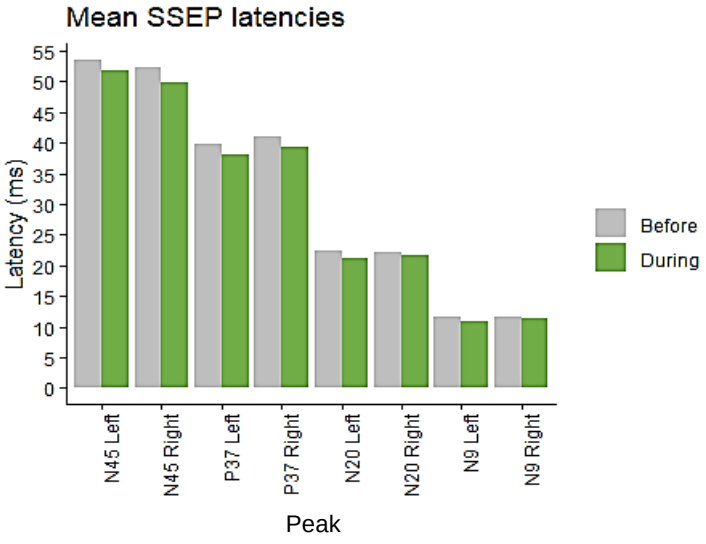

Figure 24. Mean midline SSEP latencies before and during resection
The bar graph represents the average baseline and during resection SSEP latencies for left and right midline brain tumours across the different peaks (N45, P37, N20, N9).

Table 18. T-test results for midline brain tumours before and during resection using complete data only

Peak	Side	Before		During		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Right	11.44	1.89	11.03	1.87	3.70	5.17	4	0.00	Yes
N9	Left	11.23	1.73	10.48	1.75	7.14	3.93	4	0.01	Yes
N20	Right	21.51	3.19	20.86	3.23	3.11	3.70	4	0.01	Yes
N20	Left	22.18	2.49	21.06	2.81	5.36	3.08	4	0.02	Yes
P37	Right	40.12	5.51	38.85	5.82	3.26	2.62	4	0.03	Yes
P37	Left	40.54	5.23	38.10	5.94	6.39	3.92	4	0.01	Yes
N45	Right	51.90	3.40	49.79	4.66	4.24	2.58	4	0.03	Yes
N45	Left	52.96	5.90	50.79	6.50	4.27	2.21	4	0.05	Yes

Table 19. T-test results for midline brain tumours before and during resection using as much data as possible for each peak

Peak	Side	Before		During		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Right	13.06	4.78	12.49	4.53	4.59	3.92	9	0.00	Yes
N9	Left	13.41	5.26	12.62	5.30	6.31	6.57	9	0.00	Yes
N20	Right	23.48	5.33	22.95	5.20	2.29	1.90	10	0.04	Yes
N20	Left	24.21	3.96	23.30	4.33	3.88	3.95	10	0.00	Yes
P37	Right	41.37	5.95	40.26	5.84	2.75	2.60	8	0.02	Yes
P37	Left	42.36	7.55	39.70	7.73	6.72	5.10	8	0.00	Yes
N45	Right	53.58	4.03	51.08	4.42	4.90	4.80	8	0.00	Yes
N45	Left	54.77	5.43	52.14	7.27	5.05	1.66	8	0.07	No

For the patients with midline tumours, the mean differences between the baseline and during resection are all statistically significant at a 5% level of significance, except for the N45 left peak which is significant at a 10% level of significance.

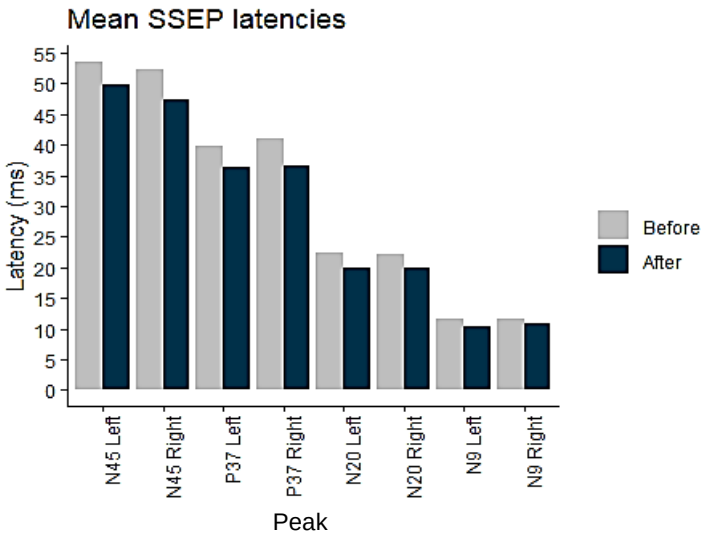

Figure 25. Mean midline SSEP latencies before and after resection
The bar graph represents the average baseline and after-resection SSEP latencies for left and right midline brain tumours across the different peaks (N45, P37, N20, N9).

Table 20. T-test results for midline brain tumours before and after resection using complete data only

Peak	Side	Before		After		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Right	11.44	1.89	10.75	1.67	6.42	4.63	4	0.00	Yes
N9	Left	11.23	1.73	10.40	1.60	7.94	3.68	4	0.01	Yes
N20	Right	21.51	3.19	20.12	2.66	6.87	3.41	4	0.01	Yes
N20	Left	22.18	2.49	20.56	2.24	7.93	4.25	4	0.01	Yes
P37	Right	40.12	5.51	37.64	4.69	6.59	2.86	4	0.02	Yes
P37	Left	40.54	5.23	37.72	4.99	7.47	4.65	4	0.00	Yes
N45	Right	51.90	3.40	48.63	2.87	6.73	2.95	4	0.02	Yes
N45	Left	52.96	5.90	50.02	6.90	5.89	2.81	4	0.02	Yes

Table 21. T-test results for midline brain tumours before and after resection using as much data as possible for each peak

Peak	Side	Before		After		% Diff	T Stat	DF	P Value	Significant
		Mean	SD	Mean	SD					
N9	Right	13.06	4.78	12.39	4.85	5.46	4.37	9	0	Yes
N9	Left	13.41	5.26	12.60	5.30	6.43	7.09	9	0	Yes
N20	Right	22.78	5.51	21.28	4.52	7.09	4.18	9	0	Yes
N20	Left	23.64	3.98	22.11	3.79	6.90	6.81	9	0	Yes
P37	Right	40.26	5.26	37.56	5.00	7.18	4.47	7	0	Yes
P37	Left	41.24	7.24	38.25	6.28	7.83	5.79	7	0	Yes
N45	Right	52.99	3.87	49.49	3.52	7.08	5.20	7	0	Yes
N45	Left	54.33	5.63	49.90	6.27	8.88	4.43	7	0	Yes

For patients with midline tumours, the mean differences between the baseline and after resection are all statistically significant at a 5% level of significance.

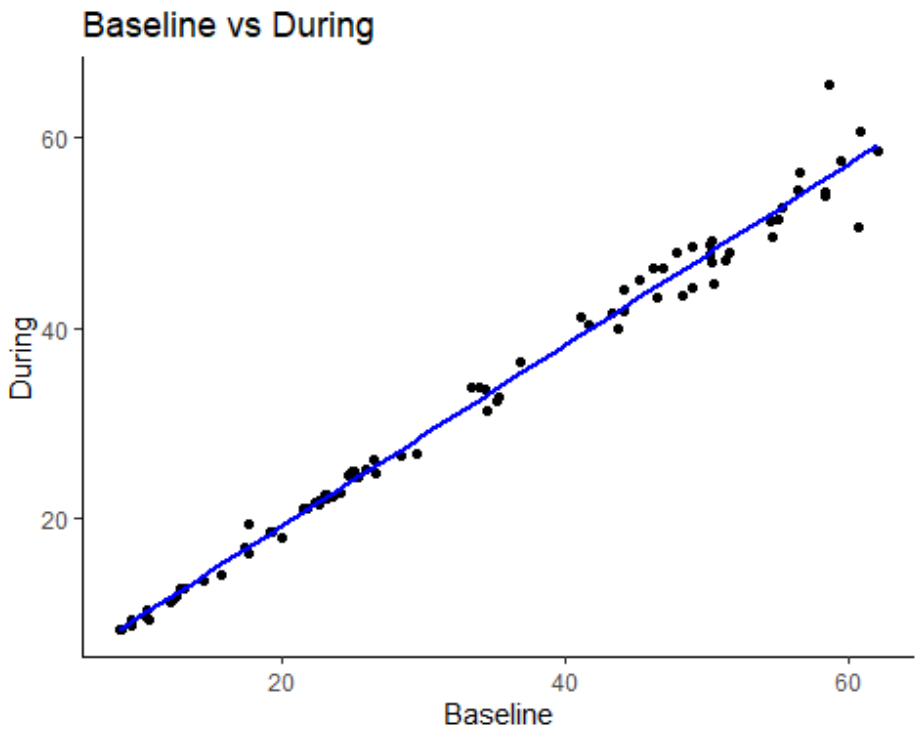

Figure 26. Correlation of SSEP latencies before and during resection of midline brain tumours
The scatterplot shows a strong positive correlation between the baseline and during resection SSEP latencies for midline brain tumours.

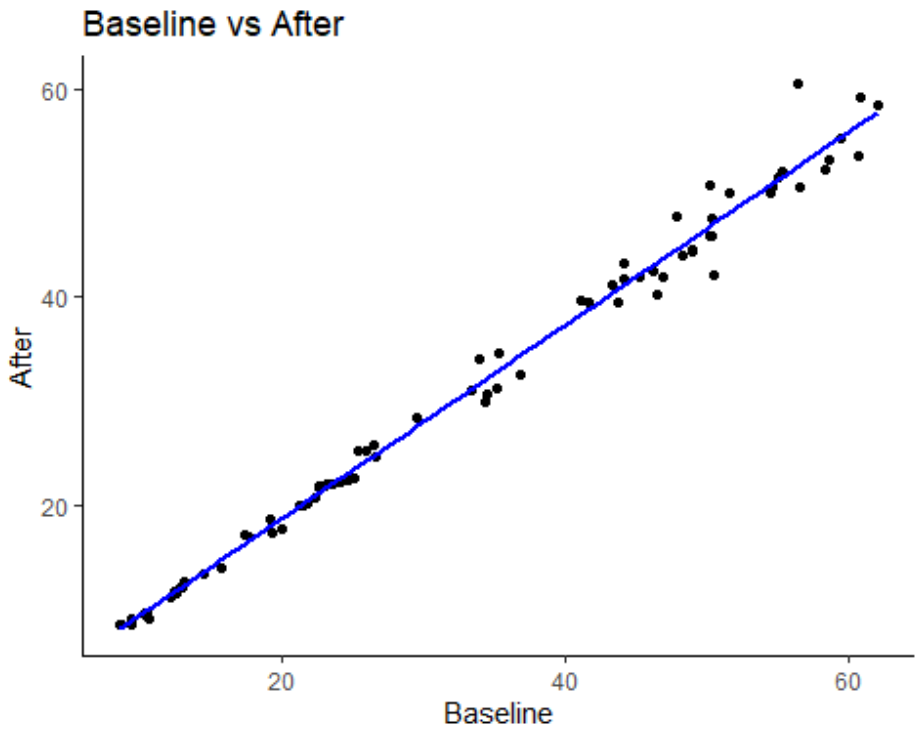

Figure 27. Correlation of SSEP latencies before and after resection of midline brain tumours
Scatterplot showing the strong positive correlation between the baseline and after-resection SSEP latencies for midline brain tumours.

Figures 21, 22, 26, and 27 show the analysis of the relationship between the different periods of the surgery. For both midline and hemispheric tumours, there are strong positively correlated relationships between the latencies at the baseline period and during the resection as well as between the baseline period and after the resection. The correlation coefficients were all greater than 0.98.

CHAPTER 5: DISCUSSION

5.1 CHAPTER OBJECTIVE

In this chapter, all the results will be discussed.

5.2 DESCRIPTIVE STATISTICS

According to Table 2, there are slight differences between the right and left on each peak, but consistently on all peaks, on average, the right peaks had lower readings compared to the left. The observation of consistently lower Somatosensory Evoked Potential (SSEP) readings on the right hemisphere compared to the left hemisphere across multiple peaks can be attributed to various factors, including both physiological and technical aspects such as:

1. Hemispheric Dominance: This phenomenon may be linked to the dominance of one hemisphere over the other. In most right-handed individuals, the left hemisphere is dominant for language and fine motor skills, which can lead to variations in how the brain responds to sensory stimuli and, consequently, differences in SSEP readings.[103-104]

2. Individual Variability: SSEP responses can vary significantly from person to person due to differences in brain anatomy, neural pathways, and sensory processing. Some individuals may inherently exhibit lower SSEP readings on one side of their brain due to these inherent dissimilarities.[104]

3. Technical Variability: Recording SSEPs is a delicate process, and minor differences in electrode placement, impedance (electrode-skin contact quality), or other technical aspects can influence the recorded SSEP amplitudes and latencies. Inconsistencies in electrode positioning or contact quality on one side of the head can result in lower readings.[55]

4. Pathological Factors: Certain medical conditions, such as brain lesions or tumours, can impact SSEP responses. If there are subtle disparities in the structure or function of one hemisphere due to factors like previous injuries or diseases, it could lead to lower SSEP readings.[55]

5. Measurement Variability: SSEP measurements can be affected by factors like the patient's positioning, precise electrode placement, and the depth of anaesthesia.[90]

Variability in any of these aspects during data collection can influence the SSEP readings.

As seen in Table 3, the latencies tended to be higher before surgery than they were during surgery across all peaks. Apart from the N9 peaks, the latency decreased further when the readings taken during the surgery were compared with those taken after the surgery. This tendency is further discussed in Section 5.5.1. Although the mean latency does not decrease when comparing the measurements during surgery to those after surgery, it does not increase past the before-surgery levels for both the left and right N9 peaks.

From Table 4 it can be seen that the hemispheric contralateral readings tended to be higher than the ipsilateral readings apart from the N9 peaks. This could be due to the subcortical nature of the N9 peak. As seen in Table 5, the data of the patients who had midline tumours follow the same trends as the full data and that of the sample of patients with hemispheric tumours.

In Table 6, for peaks N9 and N20, the latencies tended to decrease from before resection to during resection. The latencies then increased again after resection while still being less than the before-resection latencies. For peaks P37 and N45, the latencies decreased from before resection to during resection and then continued to decrease after resection.

As seen in Table 7, the mean latencies on all peaks decreased as the time progressed over the brain tumour resection surgery. The only exception is that on the N20 right peak, although this can be attributed to the differences in the samples as 15 patients were used to calculate the mean before surgery and only 12 patients were used to calculate the mean for during the surgery owing to missing readings in the surgeries.

5.3 CONTRALATERAL AND IPSILATERAL CORTICAL SSEP RESPONSES

Upon visual and statistical analysis of the mean cortical SSEP latencies, contralateral latencies were, on average, higher for all the cortical readings than ipsilateral readings. In some cases, involving brain tumour patients, there can be higher SSEP readings on the side opposite to the tumour, known as contralateral readings, when compared to the readings on the same side as the tumour, known as ipsilateral readings. Several factors may contribute to this phenomenon:[55,103]

1. Tumour Pressure: Brain tumours can exert pressure on nearby brain tissue, leading to localized compression. This compression can influence the neural pathways responsible for SSEPs. In certain situations, this pressure might increase the activity or sensitivity of neurons on the contralateral side, resulting in higher SSEP readings.[103,105]

2. Neural Plasticity: The brain can adapt and reorganize itself in response to injury or pathology. When a brain tumour is present, neural circuits may undergo adaptive changes. This could lead to heightened activity or responsiveness on the contralateral side as the brain attempts to compensate for the tumour's impact on neural function.[106]

3. Referred Responses: SSEPs reflect the transmission of sensory signals along neural pathways. Brain tumours can disrupt normal neural signalling, occasionally leading to "referred" responses. This means that sensory signals originating on one side of the body might be detected more prominently on the contralateral side due to abnormal neural activity induced by the tumour.[55]

4. Individual Variability: From the explanation given in section 5.2, SSEP responses can vary from one person to another. Some patients may naturally exhibit higher SSEP readings on the contralateral side, even without a brain tumour.[104]

5. Tumour Characteristics: Specific characteristics of the brain tumour, including its size, location, and impact on nearby neural structures, can affect SSEP readings. Larger tumours or those situated in critical brain regions may have a more pronounced effect on SSEPs.[55,103]

6. Treatment Effects: SSEP readings may change in response to treatments like surgery or radiation therapy. The timing and nature of the treatment can impact SSEP patterns, and contralateral readings may respond differently than ipsilateral readings.[55]

The linear relationship between contralateral and ipsilateral peaks indicates that the presence of the tumour could cause increases in latency proportionally on the contralateral and ipsilateral sides. Furthermore, the resection of the tumour may cause a reduction of latency proportionally on the contralateral and ipsilateral sides.

5.4 CORTICAL AND SUBCORTICAL SSEP RESPONSES

There is enough evidence to conclude that, on average, the cortical latencies are higher than the subcortical latencies. The results hold when the analysis is performed on the patients with midline and those with hemispheric tumours, as illustrated by Tables 9 and 10. The reason cortical latencies in Somatosensory Evoked Potentials (SSEPs) may be higher than subcortical latencies can be explained by the intricate processing that occurs as sensory signals travel through the central nervous system (CNS). Several factors contribute to this phenomenon:[103]

1. Sequential Processing: Sensory information follows a step-by-step processing pathway in the CNS. It starts at sensory receptors, travels through peripheral nerves, and the spinal cord, and finally reaches the brain's cortex for more advanced processing. Each step along this pathway adds a bit of time to the latency of cortical responses compared to subcortical responses.[105]

2. Synaptic Delays: At each processing stage, there are synapses, or junctions between nerve cells, where signals are transferred from one neuron to another. These synaptic transmissions introduce slight delays in signal conduction, which accumulate as information progresses through these relay points, leading to longer latencies for cortical responses.[45]

3. Cortical Complexity: The cortex is a complex structure with multiple layers and intricate networks of nerve cells. Information processing in this intricate environment involves both parallel and sequential pathways, naturally requiring more time compared to simpler pathways in subcortical regions.[105]

4. Signal Travel Distance: Signals must travel a longer distance to reach the cortex compared to subcortical regions. This additional travel distance contributes to increased latencies.[107]

5. Differences in Neuronal Density: Cortical regions have a higher density of nerve cells and more complex connectivity patterns. This higher neural density can slow down signal conduction compared to regions with simpler neural arrangements.[106]

6. Neuromodulation: Cortical areas are subject to neuro-modulatory influences, which can dynamically alter the speed of neural processing. Factors like attention, arousal, and cognitive load can influence cortical latencies.[106]

In summary, the longer latencies observed in cortical SSEP responses, compared to subcortical SSEP responses, result from the hierarchical and complex nature of sensory processing within the CNS. This involves multiple synapses, integration of sensory information, and cognitive interpretation as signals move from peripheral receptors to the cortex.[103]

The linear relationship between cortical and subcortical latencies indicates that, as the resection surgery progresses, the readings offered by the cortical waveforms change proportionately to those on the subcortical waveforms in both midline and hemispheric brain tumours.[55]

5.5 BASELINE SSEP RESPONSES OVER TIME

5.5.1 Hemispheric brain tumours

Visually investigating the mean latencies in hemispheric brain tumour patients, from Figure 13, it was found that the latencies before tend to be greater than those during and after resection.

Upon statistical analysis, it could be seen that latencies decrease from before to during resection on all peaks, except peak N45. Although a decrease is seen in the N45 peak data, this decrease was not statistically significant.

Across all peaks, the latencies decreased from before resection to after resection. This leads to the conclusion that latency does indeed decrease throughout surgery. Latency is expected to decrease throughout surgery to show an improvement in sensory pathways after the removal of the brain tumour.

5.5.2 Midline brain tumours

From the data in Tables 15–18, latencies decrease from before resection to both during and after resection. This is like the results seen from hemispheric brain tumours. From this, it can be concluded that the change in the latency over time can be attributed to the progression of the surgery and the following factors:[103]

1. Tumour Compression Relief: Brain tumours can compress and impede the normal functioning of neural pathways involved in sensory processing. This compression can slow down the conduction of sensory signals along these pathways, leading to prolonged SSEP latencies before surgery. As the tumour is gradually removed during

surgery, the pressure on these pathways is relieved, allowing signals to travel more freely and at a faster pace, resulting in reduced latencies.[108-109]

2. Improved Neural Conductivity: Brain tumours can disrupt the normal electrical conductivity of neurons by interfering with their membrane properties. During surgery, as the tumour is excised, the affected neurons can regain their normal membrane function. This restoration of neural conductivity contributes to the observed reduction in SSEP latencies.[106]

3. Inflammatory Response: Brain surgery, including tumour resection, often triggers an inflammatory response in the brain tissues. While inflammation can have detrimental effects, it can also stimulate neural activity and promote faster signal transmission. This transient enhancement in neural function can lead to decreased SSEP latencies during and after surgery.[110-111]

4. Neuroplasticity: During surgery, as the tumour is removed, the surrounding brain tissue may undergo adaptive changes to compensate for the loss of function caused by the tumour. These adaptive changes can include improved neural conduction, resulting in shorter SSEP latencies.[106]

5. Removal of Tumour-Induced Anomalies: Brain tumours can disrupt normal neural pathways and create anomalies in signal transmission. The surgical removal of the tumour eliminates these anomalies, allowing SSEPs to return to a more normal and faster pattern of conduction.[112]

6. Surgical Techniques: Neurosurgeons employ various surgical techniques to minimize tissue damage and preserve neural function during brain tumour resection. These techniques aim to minimize disruption to neural pathways, which can contribute to quicker signal conduction and reduced SSEP latencies.[55]

In summary, the decrease in SSEP latencies during brain tumour resection surgery, both for midline and hemispheric brain tumours, is a result of the removal of the tumour and the subsequent restoration of normal neural function. It reflects the improvement in neural conductivity, relief of compression, and adaptive changes that occur as the surgery progresses. These observations underscore the importance of SSEP monitoring as a valuable tool for assessing the functional integrity of sensory pathways during neurosurgical procedures.[55,103]

The linear relationship between the different periods of surgery indicates that patients with high latencies at the baseline period will have high latencies during and after resection relative to other patients. This applies to both midline and hemispheric brain tumour patients.

CHAPTER 6: CONCLUSION

6.1 CHAPTER OBJECTIVE

This chapter states the limitations of the research and mentions further research that is needed. Finally, the conclusions of the study will be drawn.

6.2 LIMITATIONS

Not all data were available across objectives. Measures were used to reduce the effect of this on the results. Minimal data were available for subcortical waveforms, impacting that area of research.

6.3 FURTHER RESEARCH

Future research in the field of somatosensory evoked potentials (SSEPs) could focus on several key areas to advance understanding and improve clinical applications. Here are some potential directions for future SSEP research:

1. Standardisation and guidelines: Developing standardised protocols and guidelines for SSEP monitoring across different clinical scenarios and patient populations. This would help to ensure consistency in data collection and interpretation, making results more reliable and comparable.

2. Intraoperative monitoring: Investigating the role of SSEP monitoring in guiding surgical decision-making in real-time. Research could explore how changes in SSEP waveforms correlate with intraoperative events and how this information can be used to modify surgical approaches to minimise neural injury. In this investigation, retrospective data were used and there was no access to the real-time actions of the surgeon; therefore, the intraoperative events could not be correlated accurately to the SSEP waveforms.

3. Clinical applications: Expanding the clinical applications of SSEP monitoring to different surgical specialties and medical conditions. This could include exploring SSEPs in neurosurgery, orthopaedic surgery, vascular surgery, and critical care settings.

4. Predictive value: Assessing the predictive value of SSEPs for postoperative neurological outcomes. Research could focus on identifying specific SSEP patterns

that are indicative of a higher risk of neurological deficits or complications after surgery.

5. Technological advancements: Investigating new technologies and techniques for SSEP recording and analysis. This includes the development of more portable and user-friendly SSEP monitoring systems and advances in signal processing and data analysis.

6. Neuroplasticity: Studying the effects of SSEP monitoring on neuroplasticity and functional recovery. Research could explore how the brain adapts to injuries and interventions based on SSEP-guided surgical approaches.

7. Combining modalities: Exploring the integration of SSEP monitoring with other neurophysiological and imaging modalities, such as intraoperative MRI or functional MRI (fMRI), to provide a more comprehensive assessment of neural function during surgery.

8. Paediatric SSEPs: Tailoring SSEP techniques and guidelines specifically for paediatric patients, considering the unique characteristics of the developing nervous system.

9. Machine learning and artificial intelligence: Applying machine learning and AI algorithms to SSEP data to improve predictive modelling, early detection of neural injury, and personalised patient care.

10. Long-term follow-up: Conducting long-term follow-up studies to assess the durability of surgical outcomes and the impact of SSEP-guided interventions on patients' quality of life.

11. Ethical considerations: Investigating the ethical implications of SSEP monitoring, especially in cases where surgical decisions are influenced by monitoring results. This includes discussions on patient autonomy, informed consent, and the potential for false positives/negatives.

12. To precisely determine the cause of consistently lower SSEP readings on one side, a comprehensive clinical evaluation is essential. This evaluation should encompass a review of the patient's medical history, neuroimaging studies, and possibly additional neurophysiological assessments. Interpreting SSEP data requires

careful consideration of both the patient's clinical context and the technical factors involved in data acquisition to arrive at meaningful conclusions regarding brain function and sensory pathways.

Collaboration between clinicians, neurophysiologists, engineers, and data scientists will be essential in driving forward SSEP research and its clinical applications. Additionally, as technology continues to advance, SSEP research should remain adaptable to incorporate emerging innovations and methodologies.

6.4 CONCLUSION

Based on the data and analysis presented in this study, several key conclusions can be drawn:

1. Right vs left peaks: The data from Table 2 indicate that there are slight differences between the peak readings obtained from the right and left hemispheres of the brain, with consistently lower readings on average for the right hemisphere peaks across all waveforms.

2. Latency changes: Table 3 shows that latency tends to be higher before surgery compared to during surgery, with a further decrease in latency observed after surgery. This pattern is observed for most peaks, except for the N9 peaks, where latency does not increase past the pre-surgery levels after surgery.

3. Midline vs. hemispheric tumours: The data in Tables 4 and 5 suggest that hemispheric contralateral readings tend to be higher than ipsilateral readings, except for the N9 peaks. This could be due to the subcortical nature of the N9 peak. These trends hold for both midline and hemispheric tumour patients.

4. Intraoperative changes: In Table 6, for peaks N9 and N20, latencies tend to decrease from before resection to during resection, then increase after resection, although remaining lower than the pre-resection levels. For peaks P37 and N45, latencies decrease from before resection to during resection and continue to decrease after resection.

5. Overall latency trends: Table 7 demonstrates that mean latencies on all peaks decrease over the course of brain tumour resection surgery, except for the N20 right peak, which can be attributed to differences in sample sizes.

6. Contralateral vs ipsilateral cortical SSEP responses: Contralateral latencies are consistently higher than ipsilateral latencies for cortical SSEP responses, indicating that the presence of the tumour may cause proportional increases in latency on both sides. Tumour resection appears to lead to a proportional reduction in latency on both sides.

7. Cortical vs subcortical SSEP responses: On average, cortical latencies are higher than subcortical latencies, a trend that holds for both midline and hemispheric tumour patients. Linear relationships between cortical and subcortical latencies suggest that changes in readings occur proportionately during tumour resection.

8. Baseline SSEP responses over time: In hemispheric brain tumour patients, latency tends to decrease from before resection to during and after resection. This decrease is statistically significant for most peaks, indicating an improvement in sensory pathways after tumour removal. Similar trends are observed for midline brain tumour patients.

9. Linear relationships: The linear relationships observed between different periods of surgery suggest that patients with high latencies at the baseline period are likely to have high latencies during and after resection compared to other patients, irrespective of tumour location.

In summary, this study provides valuable insights into the changes in SSEP responses during brain tumour resection surgery. The data suggests that latency tends to decrease over the course of surgery, reflecting improvements in sensory pathways following tumour removal. Additionally, the study highlights the influence of tumour location on SSEP responses and the importance of analysing both midline and hemispheric tumour patients. These findings contribute to our understanding of SSEP monitoring in the context of brain tumour surgery. Further research is still needed to validate these conclusions and to explore their clinical implications. This can be done by analysing a more complete set of data samples over a larger population size.

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APPENDICES

Appendix A (Ethics)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001762 OMB No. 0990-0278 Approved for use through August 31, 2023

Faculty of Health Sciences **Research Ethics Committee**

13 October 2022

Approval Certificate
New Application

Dear Mr MY Rasool

Ethics Reference No.: 550/2022
Title: An investigation of somatosensory evoked potential responses during brain tumour surgery

The **New Application** as supported by documents received between 2022-09-19 and 2022-10-12 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2022-10-12 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2023-10-13.
- Please remember to use your protocol number (550/2022) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
***Deputy Chairperson** of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

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Lefapha la Litsebene tsa Maphelo

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH GCP guidelines and has US Federal wide Assurance.
- FWA 00002567. Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001762 OMB No. 0990-0278 Approved for use through August 31, 2023

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Faculty of Health Sciences **Research Ethics Committee**

19 January 2023

Approval Certificate
Amendment

Dear Mr MY Rasool,

Ethics Reference No.: 550/2022 – Line 1
Title: An investigation of somatosensory evoked potential responses during brain tumour surgery

The **Amendment** as supported by documents received between 2023-01-05 and 2023-01-18 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2023-01-18 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Please remember to use your protocol number (550/2022) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
***Deputy Chairperson** of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 46 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2016 (Department of Health).

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Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through June 30, 2025 and Expires 07/28/2026.

Faculty of Health Sciences **Research Ethics Committee**

14 March 2024

Acknowledgement Certificate
Research Completed or Terminated

Dear Mr MY Rasool,

Ethics Reference No.: 550/2022 – Line 3
Title: An investigation of somatosensory evoked potential responses during brain tumour surgery

The **Research Completed Report** as supported by documents received between 2024-02-14 and 2024-03-13 for your research, was acknowledged by the Faculty of Health Sciences Research Ethics Committee on 2024-03-13 as resolved by its quorate meeting.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
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***Deputy Chairperson** of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

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Editing Certificate

Appendix B

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To Whom It May Concern

University of Pretoria

Editing of a Dissertation

I, Marietjie Alfreda Woods, hereby certify that I have completed the editing and correction of the dissertation: **An investigation of somatosensory evoked potential responses during brain tumour surgery** by **Muhammed Yusuf Rasool.** I believe that the dissertation meets with the grammatical and linguistic requirements for a document of this nature.

Name of Editor: Marietjie Alfreda Woods

Qualifications: BA (Hons) (Wits); Copy-editing and Proofreading (UCT); Editing Principles and Practice (UP); Accredited Text Editor (English) (PEG)

MA (Ricky) Woods

27 August 2023

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Promoting excellence in editing

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