Intraoperative neurophysiological monitoring of the ocular vestibular evoked myogenic potential (oVEMP):

A novel implementation to detect vestibular and oculomotor pathway dysfunction during brainstem surgery.

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Intraoperative neurophysiological monitoring of the ocular vestibular evoked myogenic potential (oVEMP):

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Abstract.

Different intraoperative neurophysiological monitoring techniques can be used to assess the functional integrity of the brainstem during neurosurgical procedures that put the delicate neurovascular structures of the brainstem at risk. Whilst each individual technique has its benefits and limitations, multimodal monitoring can offer a near real-time comprehensive assessment of the neural pathways under investigation. However, not all the pathways that are at risk during tumour resection are able to be assessed with the currently available techniques.

The pathways that convey the vestibulo-ocular reflex, which is responsible for stabilisation of a steady visual image on the retina during movement of the head and body can be disrupted during surgery to remove tumours within the cerebellar-pontine fossa. This disturbance in transmission can lead to disabling gaze deficits and vestibular disturbances.

The ocular vestibular evoked myogenic potential (oVEMP) that can be recorded from the contralateral inferior oblique muscle after air conducted stimulation describes the excitation of this reflex. The oVEMP is mediated via the ascending utricle fibres that connect to the ipsilateral vestibular nuclei and project, via a crossed reflex pathway in the medial longitudinal fascicule in the brainstem, to the contralateral oculomotor nucleus to elicit an excitatory muscle response.

Objective: To determine if oVEMPs could be recorded intraoperatively. To investigate whether changes in amplitude and/or latency correlated with post-operative vestibular pathway dysfunction in those patients undergoing cerebellopontine angle surgery.

Methods: This observational study incorporated 37 patients who were monitored neurophysiologically during brainstem surgery with additional oVEMPs recordings. The sensitivity and specificity of the amplitude decrement of the oVEMP was determined.

Results: Intraoperative oVEMPs were able to be recorded in 31 patients. 21/22 patients who did not show any changes in the oVEMP did not experience any immediate or long term relevant clinical deficit. Eight patients showed immediate post-operative vestibulo-ocular dysfunction with seven of them showing accompanying oVEMP changes. The sensitivity, specificity, and positive and negative predictive values for the oVEMPs to detect vestibular ocular dysfunction in the immediate post-operative period were 75%, 91.3%, 75% and 91.3% respectively, with a test accuracy of 87.1%.

Conclusion: Changes in the oVEMP amplitude <50% (which did not reverse), or loss of the potential intraoperatively, predict post-operative deficits of the vestibulo-ocular pathway.

Significance: The oVEMP is able to be recorded in patients undergoing brainstem surgery to monitor the integrity of the vestibular portion of the eighth cranial nerve, the medial longitudinal fascicule within the brainstem and the oculomotor cranial nerve pathway. Monitoring of this potential intraoperatively may enhance the safety of cerebellar pontine angle surgery.

Declaration.

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Dedication and Acknowledgments.

Without a doubt, any studies that involve patients undergoing surgery of the brain cannot be written without acknowledging first and foremost the bravery of those patients. The fear and anxiety that they, and their families and carers, must go through once receiving a diagnosis and deciding on the next course of treatment should never be taken lightly; especially by those who are then responsible for their clinical outcome.

Any decision to operate on a patient must take into account the patients pre-existing physical and mental well-being and their ability to be able to cope with any subsequent adverse event. But we should also be mindful that these same concerns are constantly on the surgical team's mind as they prepare for, and carry, out the surgery. Therefore, this body of work is also in recognition and acknowledgement of the skill and dedication of all of those who make up the theatre team, including the surgeons themselves, the anaesthetic team and the scrub side, each of whom make complex neurosurgery possible at North Bristol Trust.

I would like to thank Dr Llwyd Orton for his help and advice, as my Academic Supervisor, in reading through this script and offering valued suggestions to help improve its academic worth and content.

Engaging in a thesis, whilst working full time in the Grey Walter Department of Clinical Neurophysiology would not be possible without the valued support of my fellow staff members. They too experience the pressures of working within the NHS to meet their own workload, but their unwavering professionalism is - and always be - an immense source of pride that inspires me on a daily basis, as they go above and beyond to deliver exceptional healthcare to the patients that we see.

Special thanks, however, must go to a few particular colleagues. One of them is my Consultant Neurophysiology colleague Dr Nick Kane, who has guided me through the majority of my professional and clinical career, and who has helped me to develop the necessary skills and expertise that have enabled me to complete this work. Without his encouragement and belief, I would not have undertaken the HSST, so he has a lot to be responsible for. The other colleagues are Hayley Marriott and Nadine Rosenthal, two of the finest friends and work colleagues I have ever had the privilege of being with. They have passion and drive that make the most daunting challenge seem easy and when any of us have faced a difficulty, we have faced it and it overcome together. For that I will always be grateful. They have been involved from the start and have been instrumental in the delivery of intraoperative neurophysiology within the department. With their ability to adapt to the new techniques that have been able to be performed, and by bringing their wealth of knowledge and expertise into the operating theatre environment, they have been able to implement these new procedures to the highest possible standards, on a consistent basis. This has enabled the intraoperative monitoring service to continually develop, so that the patients that we care for can have the best possible outcomes.

Obviously the last and most heartfelt thanks and acknowledgment must go to my wife and two sons. Over the past 5 years I would have finished all the assignments and assessments, and this thesis, sooner if it were not for their interruptions. But they saw the need for me pause and to step away at times. They made me go for a run, to go out with them for a walk and coffee, and to be the husband and father that I always want to be for them. I love them all for this and their understanding of me – and especially for their interruptions.

Preface.

This dissertation is an original and unpublished independent body of work carried out by the author, Peter Walsh. All of the work presented was carried out as part of the Intraoperative Monitoring service that is performed by The Grey Walter Department of Clinical Neurophysiology at Southmead Hospital, Bristol.

Chapter 1.

Introduction.

The posterior fossa is the largest of the three cranial fossae and contains the brainstem, which may be defined as the part of the neuroaxis located between the diencephalon and the spinal cord, into which it continues without definite anatomical demarcation. The brainstem has the most complex array of vascular and neuronal structures in the body, including ten pairs of cranial nerves, the long tracts for motor and sensory integration and the neural centres that regulate complex reflexes which are essential for life (Crucco et al., 2005). These reflexes contain different afferent sensory and efferent motor cranial nerves that are coordinated by cranial nerve nuclei which control balance, oculomotor control and the laryngeal reflexes that involve coughing and swallowing and speech. The brainstem also contains the highly integrated circuitry that controls cardiovascular and respiratory function and mediates consciousness via the reticular activating system.

Surgery in and around the brainstem aims to provide an optimal treatment for those patients with pathological conditions that affect these vital structures and functions within the brainstem (Slotty et al., 2017). Operating within this tightly packed neuronal space involves working close to, and directly on, the critical neurovascular structures and nerves. Due to the lack of redundancy which is specific to this particular part of the nervous system, even a small iatrogenic lesion can lead to debilitating neurological deficits post-operatively (Procaccio et al., 2000).

Despite the recent advancements in intra- and post-operative care, which has significantly reduced the resultant mortality and morbidity related to brainstem surgery, patients still often present with new deficits or a worsening of existing deficits in the early postoperative period (Sala et al., 2015). These deficits can have a severe impact on the patients and their carers quality of life.

Within the service that I manage, there has been a steady increase in the number of cases which have required intraoperative monitoring over the past ten to fifteen years. During that time period there has also been an increase in the complexity of the cases that have presented and subsequently been referred for surgery; resulting in an increase in the number of complex cases that require intraoperative monitoring. Along with this, there has been numerous technological and practical advancement of the neurophysiological techniques that can be brought into the armament of those us providing neurological assessment intraoperatively to benefit the patients. The expectations of the patients, and the surgeons, have also subsequently changed; with each party envisaging a near perfect outcome.

The challenges that are faced by the surgeons when operating on tumours within the cerebellopontine angle are introduced at the start of *Chapter 2*. As well as the operating challenges that the surgeons face, the patients presenting symptoms will differ depending on the various types of tumours and their anatomical localisation (Liu et al., 2020). This is an important distinction, as the extent of surgical resection and the type of intraoperative monitoring that can be utilised at the time of surgery will vary for each individual case (Sala et al., 2015). Therefore, a description of the

typical presenting symptoms that accompany the various lesions is described for some of the more common types of tumours that are seen within my service. These tumour types include vestibular schwannomas, meningiomas, cavernous malformation and lesions in and around the anterior skull base.

Whilst brainstem tumours are a heterogenous group of lesions (Louis et al., 2016), their clinical manifestations give rise to certain specific syndromes. These syndromes can give important localising information to the clinicians about the patient's functional status and vulnerability; that is not always evident with structural anatomical imaging. A knowledge and understanding of the pathophysiology that underlies these syndromes can also be used to help the surgeon avoid inadvertent iatrogenic injury to these delicate neurovascular structures during the course of the surgery (Slotty et al., 2017). This information can also be used pre-operatively to guide the surgeon and the neurophysiological monitoring team as to the most appropriate type of neurophysiological monitoring to be utilised.

Although intraoperative neurophysiological monitoring techniques have been developed that can monitor and map the integrity of various brainstem structures at the time of surgery (Deletis and Fernandez-Conejero, 2016), there is no single test that incorporates all of the aforementioned reflex mechanisms. The application and utility of the routinely used monitoring techniques of somatosensory evoked potentials, brainstem auditory and transcranial motor evoked potentials are described in *Chapter 3*. These techniques are able to assess the ascending tracts of the medial lemniscal pathways and the auditory tracts through the brainstem and the descending corticospinal pyramidal and corticobulbar tracts (Simon, 2011, MacDonald et al., 2013, MacDonald et al., 2019).

However, these techniques only assess a relatively small proportion of the total cross-sectional area of the brainstem (~20%), leaving relatively large areas of the brainstem and specific functional pathways un-monitored (Strauss et al., 1994). The other complimentary monitoring technique of free-running, and the mapping technique of triggered electromyographic recording, which can be used to assess the individual cranial nerves and the surrounding structures, are also discussed in this chapter. However, whereas there is well described warning criterion within the literature for changes in the intraoperative evoked potentials, which have a high degree of correlation with post-operative deficits, the diagnostic test characteristics for free-running electromyographic changes are less impressive (Karakis, 2013). This is especially true for the extraocular muscles which have always been challenging to monitor (Thiramula et al., 2013). The lack of continuous extraocular muscle monitoring has been attributed to several reasons, including the depth of these which muscles which prevents direct visualisation of palpation, the complex anatomy of the orbital contents and the possibility of trauma to the eye and/or the vasculature within this compact and non-compressible site (Lopez, 2011).

One of the pathways that has not been able to be reliably recorded intraoperatively in its entirety is the oculomotor reflex pathway that controls gaze and vestibular function (Sala et al., 2007). The anatomy and physiology of the vestibular structures that detect alterations in the body's orientation

in space are described in *Chapter 4*. The peripheral end organs of the otolithic structures, the utricles and saccules, and their connections to the nuclei within the brainstem that encode the motion of the head relative to the outside world have ascending, and also descending pathways, within the brainstem. The ascending pathways for extraocular motor control incorporate the medial longitudinal fascicule, a centrally located bundle of fibres which can become damaged, along with the peripheral vestibular portion of the eighth cranial nerve and the oculomotor cranial nerve during brainstem surgery. The vascular supply to the brainstem can also become disrupted during the time of surgery and ischaemic changes to the arteries that supply the structures which support the functional integrity of the various vestibular reflexes can cause post-operative neurological deficits. The extraocular reflex is one of three main vestibular reflexes, the others being the vestibulospinal and vestibulocollic, which control the maintenance of balance and the stabilisation of the neck respectively (Fetter 2000). The vestibulospinal reflex pathway can be assessed neurophysiologically by measuring the electromyographic responses of various flexor and extensor muscles in the limbs. Whereas the vestibulocollic reflex can be assessed by the cervical vestibular evoked myogenic potential, which is recorded as an inhibitory potential from the sternocleidomastoid muscle after stimulation of the saccule end organs (Rosengren et al., 2010).

Similar to the cervical evoked myogenic potential, the ocular vestibular evoked myogenic potential (oVEMP) can be assessed after stimulation of the utricle end organs after auditory or vibratory or electrical stimulation (Curthoys, 2010). An overview of the underlying neurophysiological mechanisms of the oVEMP are described at the start of *Chapter 5*. Although this short latency potential has been used predominantly for the diagnosis of peripheral vestibular disorders in the audiological domain, there is mounting evidence that it can be used clinically for central neurological disorders (Taylor et al., 2020). The array of disorders that are able to be diagnosed by oVEMPs include disorders with underlying pathophysiology's that are similar to those that may be accounted intraoperatively. Mechanical stretch and distortion of the vestibular portion of the eight cranial nerve can be seen in patients with vestibular schwannomas which can affect the oVEMP. Other structural lesions that disrupt the transmission along the ascending pathway due to compression, as well as ischaemic changes, have also been shown to be able to be detected with changes in the resultant oVEMP recordings (Rosengren et al., 2019). Various common disorders that involve the inner ear and the vestibular nerve and the central pathways that convey the oVEMP and the diagnostic utility of oVEMPs are described later in this chapter. It is shown that although the changes seen in the oVEMP in these varying neurological conditions are not necessarily aetiology specific, the changes can give important localising information (Taylor et al., 2020), which would be important for the decision making of the surgeons at the time of the patient's operation.

When these changes are incorporated with other neurophysiological recordings at the time of surgery, they may be able to distinguish caudal or rostral peripheral cranial nerve changes (i.e., from the eighth and third cranial nerves respectively) from central medial longitudinal fascicule pathway disruptions. However, the optimal stimulation and recording parameters need to be

carefully considered, so that timely and relevant information can be given to the surgeon about the functional status of the oculomotor reflex. The various parameters that have been used to elicit, record, and interpret the oVEMP in clinical practice are analysed in *Chapter 6*, with careful attention being paid to the safety concerns of presenting high intensity air conducted sound (Portnuff et al., 2017). The judicious optimisation of the different recording montages must be able to distinguish true electrophysiological potentials from erroneous background electrical artefacts - that are common in the hostile recording environment of the operative theatre - and other biological signals from nearby muscle generators (Piker et al., 2011). Therefore, the chosen montage must also be able to provide the most appropriate signal to noise ratio and have the highest response rate. More importantly, the montage and machine settings and stimulator characteristics that are chosen must all have the highest reproducibility for recording the response when the eyes are in the closed position, as this is the eye state when the patient is anaesthetised. The results from oVEMP recordings implementing the optimal parameters in conditions similar to those comparable to those found in the operating theatre are analysed in a group of subjects and are presented in *Chapter 7*.

Although the clinical utility of oVEMP recordings is usually described with the eyes open and positioned with an upward gaze, it is still possible to record the potential with the eyes in a neutral position and even with the eyes closed. The use of an extended upward gaze angle is used to maximise the excitation of the inferior oblique muscle and to bring the muscle closer to the active recording electrode placed beneath the eye (Rosengren et al., 2013). With the reference electrode placed at the inner cantha, more specific recordings from the extraocular muscles are achieved, with higher amplitude responses being seen that are less contaminated by the effects of reference electrode positioning (Sandhu et al., 2013). This montage also has a higher response rate, even when the eyes are closed, and was studied in this chapter in a group of normal subjects to assess the changes that were to be expected when recording with the eyes closed. During surgery the patient is often placed in a lateral position and the gravitational effects placed on the otolithic structures are different for the ear that is in the downward position in comparison to the ear that is uppermost (Asal et al., 2017). These differences would potentially influence the resultant recorded oVEMPs and the responses would also be different for each ear that is stimulated and the recorded responses from the contralateral eye. The statistical significance of these different states, and more importantly the clinical relevance, was investigated further in the same group of individuals, to determine the viability of being able to record the oVEMP in patients intraoperatively.

The final chapter is the culmination of the information that has been gathered in the previous chapters. The results of recording intraoperative oVEMPs, at designated time points, during different surgical approaches in a range of surgical cases is analysed in this observational study. The results of the changes in amplitude of the oVEMPs are correlated with the functional vestibulo-ocular outcomes from 37 patients. The diagnostic test characteristics for the utility of this novel implementation in the immediate and short term and long term follow up period is then assessed. Localisation of the disruption along the oculomotor reflex pathway is expanded upon and tied in with the recording of the brainstem auditory evoked potentials and the neurotonic discharges seen

from the extraocular muscles, so that focal abnormalities and their patterns can be distinguished. Other more recent reflex pathway testing is presented, to show that the innovation and application of these complex tests are able add vital information about the intricate and neural structures that are at risk during cerebellopontine angle surgery (Deletis and Fernandez-Conejero 2016).

Chapter 8 concludes with the introduction and proposal of future applications and developments of intraoperative oVEMPs that may enhance further the clinical implementation of this novel technique into the routine armament of neurophysiological monitoring. As more pathways are able to be assessed and tested at the time of surgery and with improvements in monitoring procedures, it is hoped that the functional outcomes for those patients that we offer care for will also improve.

Chapter 2.

Brainstem tumours and syndromes.

2.1 Introduction

Brainstem tumours are defined as lesions occurring in the midbrain, the pons, or the medulla oblongata (Figure 1) and account for 10-15% of all paediatric nervous system tumours, but only 1-2% of adult brain gliomas (Liu et al., 2020).

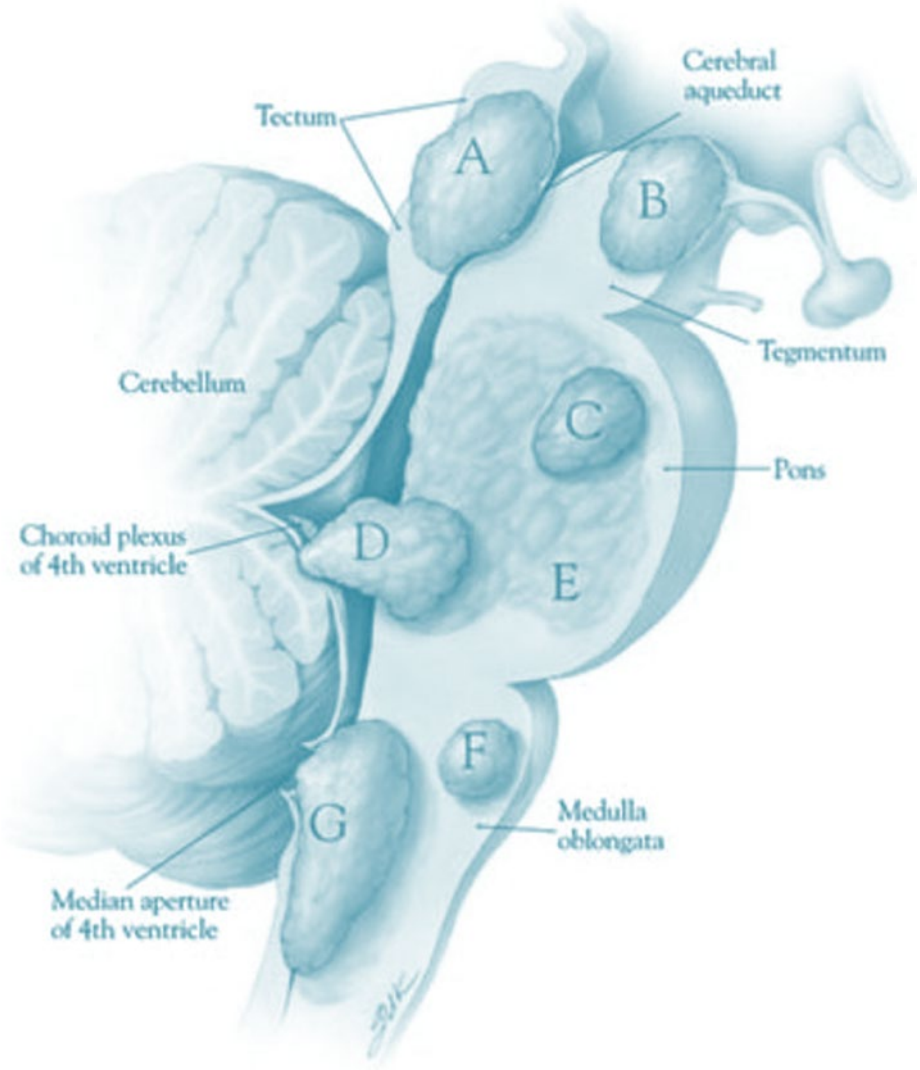


Figure 1: The various locations of brainstem tumours.
Lesion of the midbrain usually occur in the tegmentum and tectal plate (A and B). Focal tumours that are intrinsic are within the brainstem itself and access them involves establishing 'safe entry zones' that do not disrupt the normal tissue surrounding the lesion (C and F). Diffuse tumours have no clear borders and infiltrate the brainstem structures, making them difficult to resect (E). Focal exophytic lesions extend outside of the brainstem tissue at the level of the pons and protrude through the floor of the fourth ventricle (D and G) and enable a safer passage into the brainstem to resect. Although like Type II lesions, the tumour borders are adjacent to viable tissue and resection must not go beyond the margins otherwise normal functioning tissue will be damaged. Lesions at the cervicomedullary junction (G) place the lower cranial nerves and long white tracts at risk (adapted from Frazier et al., 2009).

Tumours within the brainstem are quite concerning in terms of both their anatomical location and their growth patterns although they are usually associated with distinctive clinical presentations and physical findings on examination. Diffuse gliomas within the pontine region have a dismal prognosis as they are highly infiltrative and less amenable to surgery (Slotty et al., 2017) Acute presentation of the patient's symptoms with a neurological examination that reveals the involvement of multiple cranial nerve nuclei is indicative of a diffuse pathology. Whilst symptoms that show an insidious onset with single cranial nerve involvement indicate a focal brainstem tumour.

In comparison to other areas of the central nervous system, surgery for fourth ventricle tumours and brainstem lesions has historically carried a significantly higher risk of morbidity (Cochrane et al., 1994, Aarsen et al., 2004). Although there have been technological advances, this type of surgery causes neurological dysfunction and mortality due to iatrogenic damage to important structures within the brainstem (Sala et al., 2015). This is due to the high concentration of neural structures within a small anatomical space. These include the dense fibre bundles of the ascending and descending long tracts necessary for sensation and movement. There is also the close concentration of the cranial nerve nuclei that control cardiovascular and respiratory function necessary to maintain life and the reticular activating system that mediates consciousness (Figure 2). And the highly integrated reflex circuitry that control swallowing and coughing reflexes and oculomotor control are also within the surrounding tissues.

The lack of redundancy within the brainstem significantly contributes to the high risks associated with this surgery. Even a small injury to parenchymal tissue or vascular structures can result in severe and debilitating functional deficits such as hemiplegia, dysphagia, gaze palsies, coma and possible mortality (Procaccio et al., 2000, Giliberto et al., 2010, Deletis and Fernandez-Conejero, 2016).

These complex neuroanatomic features have made surgery in and around the brainstem high risk procedures for neurosurgeons (Deletis et al., 2000, Slotty et al., 2017), and even until recently, many tumours that were benign were being treated with the same expected outcome of malignant masses (Slotty et al., 2017).

Over the past two decades, the advent of neuroprotective anaesthesia and advances in neurosurgical micro-techniques and post-operative neuro-intensive care has seen the operative mortality decrease and the survival rates for patients following resection of fourth ventricle tumours improve (Sloan, 2010).

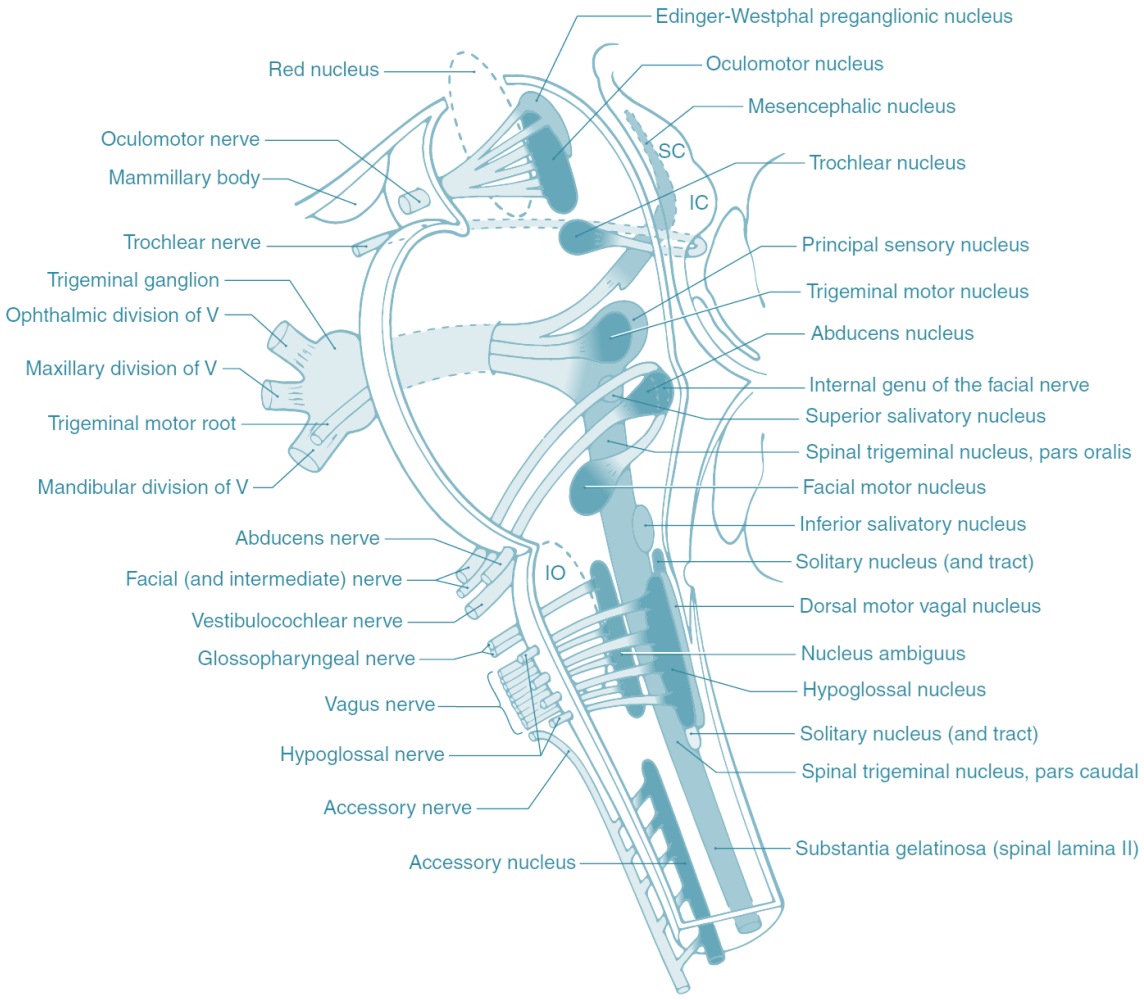


Figure 2: The location of the cranial nerves and their nuclei.
The position of the tightly packed bundles and the course of the intricate connections between the fibres and the individual nuclei within the brainstem are seen (adapted from Haines and Mihailoff 2018).

Whilst preoperative images have become the mainstay of localising lesions before surgery (Figure 3), the similar improvements and advancements in intraoperative neurophysiologic evaluation has been invaluable in the identification and monitoring of critical brainstem structures during surgical manipulation (Sala et al., 2007, Deletis and Fernandez-Conejero, 2016).

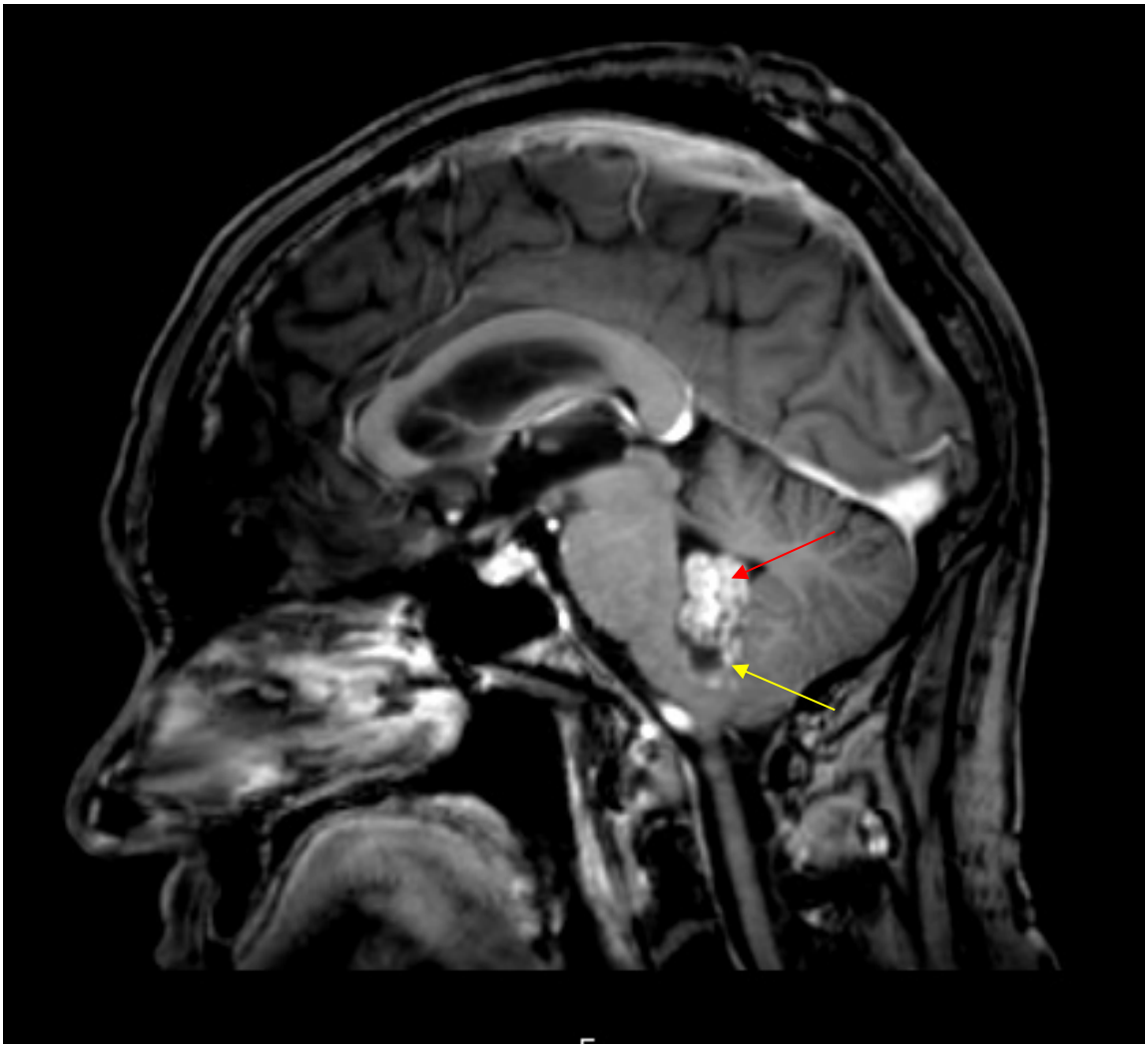


Figure 3: A brainstem subependymoma.
A largely solid mass (subependymoma) – indicated by the red arrow - within the fourth ventricle associated with an inferiorly located cyst – indicated by the yellow arrow.

Instrumental to this change in patient care was the change in surgical strategy that occurred in the late 90s. Rather than an 'anatomical' approach, it was realised that brainstem surgery required a 'functional' approach (Sala et al., 2007). Thus, enabling those patients with tumours, that were previously thought to be inoperable, the opportunity to have tumour resection performed more safely (Abbott, 2010).

However, brainstems tumours need to be categorised into distinct subgroups as advocated by the World Health Organisation, as they do not represent a homogenous nosologic entity (Louis et al., 2016). The surgical resection, and the subsequent intraoperative monitoring that is used to preserve the neural structures, is guided by the type of tumour and the involvement of the surrounding neural and vascular structures (Slotty et al., 2017.) By understanding the sites of origin and the typical growth patterns, along with the presenting syndromes that typically accompany these tumours, functional outcomes can be improved for those patients undergoing brainstem tumour resection.

2.2 Brainstem tumours

2.2.1 Vestibular schwannoma

Tumours that arise from the vestibular portion of the vestibulocochlear nerve were originally called acoustic neuromas, although this is actually a misnomer. These tumours actually arise from the Schwann cells surrounding the vestibular nerve division of the eighth cranial nerve and are now more appropriately called vestibular schwannomas (Eldridge and Parry, 1992). The diagnosis of these tumours is rare and is usually made in adults with a mean age of 46-58 years. However, due to the increased access to earlier neuroimaging the incidence rate of these have gradually increased from 3/million/year 40 years ago to 10-20/million/year in the UK (Evans et al., 2005). Although higher rates are now being citied due to higher rates being diagnosed in more elderly patients; and with more patients undergoing MRI scans, the incidental findings are also increasing (Schmidt et al., 2012). Vestibular schwannomas account for up to 6-10% of primary brain neoplasms and are the most common extra-axial tumour that occur in adults and they comprise over 80-90% of tumours that arise in the cerebellopontine angle region (Figure 4). When found in teenagers these cases of tumours are most often associated with neurofibromatosis type 2 (NF-2) (Myrseth et al., 2007).

Whilst these tumours are usually benign, they represent a largely heterogeneous group of tumours that have a wide variety of clinical manifestations. Their growth patterns can affect the patient outcome, and because of their location within the internal auditory canal and their growth within the cerebellopontine angle, they can result in significant morbidity and even mortality, if left untreated (Whitmore et al., 2011). Although the most common presenting symptoms in patients with vestibular schwannomas are hearing loss and tinnitus, the disorder is primarily a vestibular system one. Vestibular symptoms concerning balance and eye coordination are common problems pre-operatively and are more likely to be exacerbated, or develop as a new neurological deficit, after surgical intervention (Saman et al., 2009).

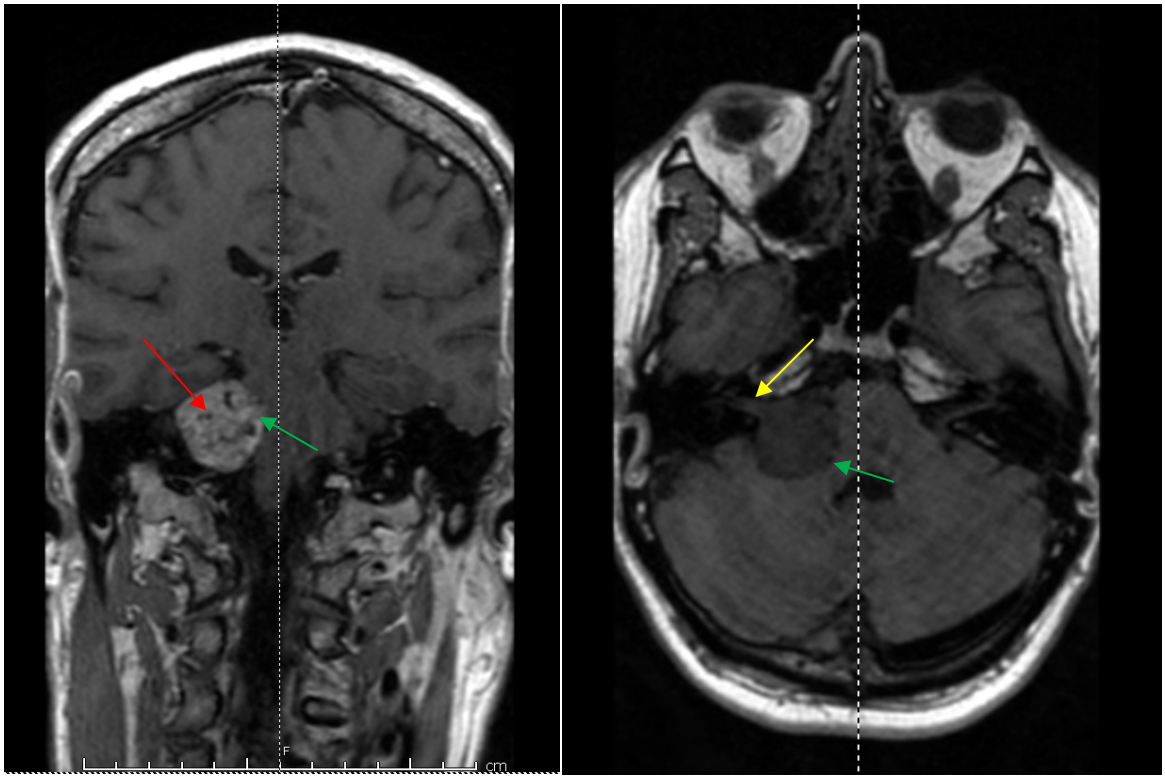


Figure 4: Vestibular schwannoma.
A chronic looking heterogenous smooth lesion (33 x 31 x 27mm) – indicated by the red arrow, with an intracanicular component – indicated by the yellow arrow - indenting the adjacent cerebellar peduncle and pons – indicated by the green arrows. These findings confirm a long standing slowly progressing grade IV vestibular schwannoma.

Vestibular schwannomas typically arise at the transition zone of the central myelin and peripheral myelin sheaths, the Obersteiner-Redlich zone, in the vicinity of the vestibular (scarpia) ganglion, Although the vast majority of vestibular schwannomas arise from the medial portion of the internal auditory canal, some may arise more distal to this region or from the lateral portion of the internal auditory canal (Gianoli and Soileau, 2012). Vestibular schwannomas can arise from either the inferior or superior portion of the vestibular nerve with differing auditory and vestibular functions that can be determined from the site of the tumour's involvement (Rahne et al., 2018).

As the tumour increases in size there is subsequent compression of the surrounding neuronal structures and the evolution of the patient's symptoms can be classified into 4 stages, based on the size of the tumour and its location (Selesnick et al., 1993,). The 'intracanalicular stage' is associated with hearing loss, tinnitus, and vertigo, which is primarily caused by compression of the vestibulocochlear nerve and/or its vascular supply, causing neural dysfunction (Gianoli and Soileau, 2012). When the tumour grows to involve the cistern of the cerebellopontine angle (cisternal stage), auditory symptoms become more pronounced, and the vertigo transitions into disequilibrium; however, if in the early growth stages the tumour invades the cistern, there may not be significant impingement on local structures as the cistern affords the tumour room to grow and the symptoms may not progress. When the brainstem becomes compressed the hearing loss and

the symptoms of disequilibrium worsen (brainstem compressive stage) and the patient may start to experience trigeminal nerve symptoms. As the tumour size increases further, obstruction of the fourth ventricle cause hydrocephalus, with a rapid deterioration in clinical signs; including generalised headache, twitching and weakness of the face, loss of vision and diplopia and dysfunction of the lower cranial nerves (hydrocephalic phase), eventually leading to long tract motor and sensory signs and death due to tonsillar herniation (Selesnick et al., 1993). Interestingly, in direct opposition to what may be expected, vestibular symptoms may occur at the intracanalicular stage, as the vestibular nerve is progressively destroyed, with the patient presenting with peripheral vestibular disorders such as episodic vertigo and as the tumour grows these symptoms diminish. However, as the tumour grows further and compresses the brainstem, disequilibrium and signs of a central vestibular disorder arise.

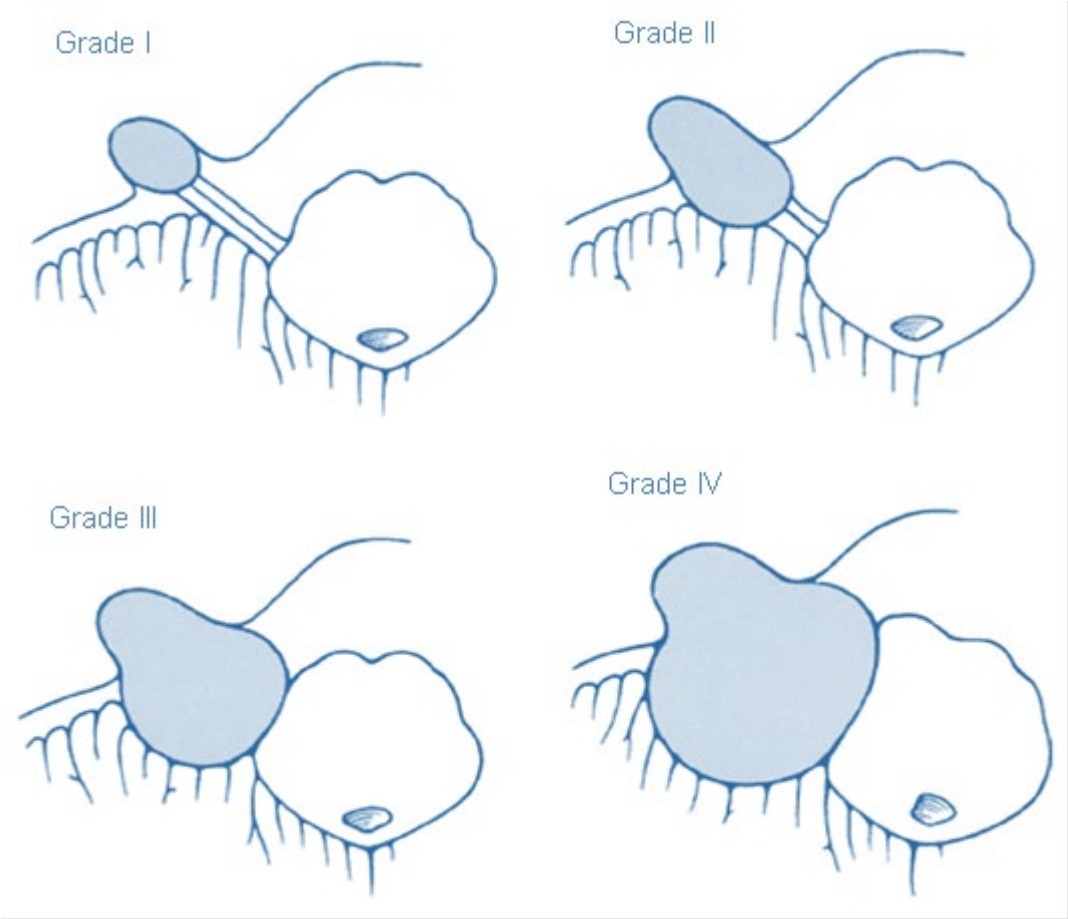


Figure 5: Vestibular schwannoma grading scale.
A small intracanicular tumour = grade I. Protrusion of the tumour into the cerebello-pontine angle = grade II. When the tumour occupies the CPA cistern, without brainstem displacement = grade III. Cranial nerve and brainstem displacement = grade IV. (Adapted from Koos et al., 1998).

Symptoms of vestibular nerve involvement are seen in 40-60% of patients with vestibular schwannoma, with a combination of dizziness, vertigo and unsteadiness being reported (Matthies and Samii 1997, Kentala and Pyykko, 2001). True vestibular vertigo can be distinguished from other types of dizziness by the sensation of movement that occurs because of the mismatch between the visual, vestibular, and somatosensory systems. The vertigo may be constant or may be intermittent, or it may be 'nautical' (like being on a ship) or rotatory, each of which is associated with a significant reduction in the patient's quality of life reporting (Myrseth et al., 2006).

Postoperatively, vestibular function is virtually always altered, as the surgical disruption of the vestibular nerve dramatically changes the patient's vestibular function. In a series of 267 patients who had been operated on, 65% reported signs and symptoms of disequilibrium between 3months and 7 years after surgery, with an impact on their quality of life being reported (Lynn et al., 1999). Similar studies have shown that only 10% of patients reported normal vestibular function, whilst 9% reported a severe handicap from vestibular impairment post-operatively (Wiegand and Fickel, 1989).

The growth rate of vestibular schwannomas is 10.3mm/year, when diagnosed in the first year, slowing to 23%, 5%, 8% and 0% in the second, third, fourth and subsequent year respectively, with an average growth rate of 0.99-1.11mm/year (Stangerup and Caye-Thompson, 2012). This slowly decaying rate of growth causes a gradual decline in vestibular function which enables central compensation to occur during this stage - meaning that patients can adapt to their vestibular-ocular and balance issues. The loss of residual vestibular function post operatively, however, can cause such a profound disturbance in function, that central re-organisation and plasticity cannot compensate for the clinical sequalae.

The cause of these uncompensated vestibulopathies can fall into different categories

1. *Central vestibular abnormalities* that can include vertical nystagmus, gaze nystagmus, impairment of fixation and abnormalities of smooth pursuit and optokinetic changes are typically seen after resection of large vestibular schwannomas that have caused brainstem and/or cerebellar compression.
2. An *incomplete deafferentation*, whereby the vestibular end organ and only one branch of the vestibular nerve has been preserved, can cause fluctuating vestibular functions which are usually seen after middle fossa or retrosigmoid approaches have been used, in those patients with smaller tumour sizes in order to try and preserve hearing, and can manifest as paretic spontaneous nystagmus. When the inferior vestibular portion of the nerve has been preserved, posterior canal benign paroxysmal positional vertigo can be present, whereas atypical benign paroxysmal positional vertigo (from the anterior or horizontal semicircular canal) can be present when the superior vestibular portion of the nerve is preserved.
3. Total deafferentation of the vestibular nerve on the side of surgery can also cause disequilibrium, benign paroxysmal positional vertigo and spontaneous nystagmus that is suggestive of bilateral loss of vestibular function which is caused by a *fluctuating vestibulopathy* arising from the non-surgical ear (Gianoli and Soileau, 2012).

Today, whilst vestibular schwannomas may still be regarded as a chronic disease because they grow slowly, they are only rarely life threatening (Matthies and Samii, 1997). Surgery for vestibular schwannoma resection is technically challenging and there are several neurosurgical approaches that can be used to access the lesion, depending on the tumour size and location (Slotty et al., 2017). The suboccipital/retrosigmoid and translabyrinthine approaches can be used for all tumour sizes, whilst the middle cranial fossa approach is useful for the removal of small vestibular schwannomas arising from the intracanicular region. However, hearing preservation and vestibular function cannot be achieved with the translabyrinthine approach.

2.2.2 Meningioma

Meningiomas typically arise from one of three locations within the cerebellopontine angle,

1. adjacent to the internal auditory canal at the posterior surface of the temporal bone.
2. the meninges of the internal auditory canal itself or
3. from the inferior surface of the tentorium cerebelli

They are the most common non-vestibular schwannoma tumour occurring within the posterior fossa, and account for 3-13% of all intracranial tumours in and around the brainstem (Magill et al., 2018).

These tumours are usually benign, but are locally aggressive lesions, as although they do not invade the cranial nerves themselves - they do stretch and displace them (Figure 6).

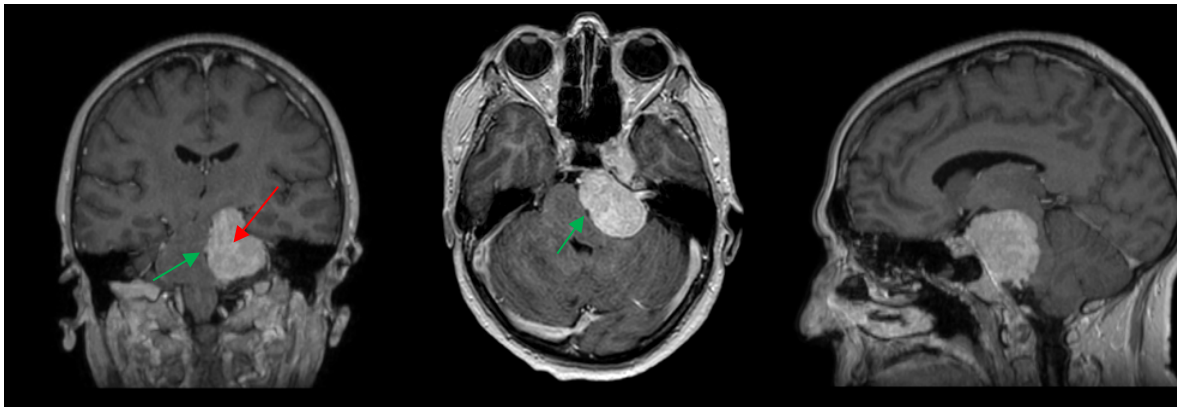


Figure 6: Meningioma.
A solid enhancing mass (meningioma) – indicated by red arrow - extending into Meckels cave and distorting the pons/midbrain – indicated be green arrow.

Macroscopically, they are globular masses, with thin capsules, that originate in the arachnoid villi that are invaginated in the numerous venous sinuses that are located in the region of the sigmoid sinus, jugular foramen, the torcular and the superior and inferior petrous sinuses of the temporal bone. As they grow, they invade the bone along the haversian canals, that can result in an osteoblastic response in approximately 25% of meningiomas (Langman et at., 1990). In comparison to vestibular schwannomas, patients who present with meningiomas are less likely to have audiovestibular symptoms initially because of their extra-neural origin. Typically, patients

present with other cranial nerve deficits earlier, usually hypoesthesia over the trigeminal nerve distribution; and it is only when the tumour increases in size that vestibulocochlear nerve changes and hearing loss occur (Sekhar and Jannetta, 1984).

Those tumours that arise anterior to the porous acousticous have a lower probability of having cochlear neve preservation post-operatively than those that arise from the meatal lip.

Although hearing loss is more common in vestibular schwannomas (95-98%), it is still the most common symptom of large cerebellopontine angle meningiomas (60-75%) (Voss et al., 2000) and so it can be difficult to differentiate between the two based on symptoms and signs alone. And whilst the classic triad of unilateral sensorineural hearing loss, tinnitus and disequilibrium is the common presentation for patients with vestibular schwannoma, these signs together are only 10% specific. Other symptoms, such as trigeminal neuralgia (especially in association with diminished corneal sensation) and hemifacial spasm, are more likely to be associated with meningiomas. And a loss of speech discrimination - which is out of proportion to the pure-tone decay - is more indicative of a vestibular schwannoma, particularly when the pure tone audiometry shows a high frequency hearing loss (Rhoton, 1994).

2.2.3 Cavernous malformations

Cavernomas, or brainstem cavernous malformations are one of a group of four major cerebral vascular malformations, the other three are capillary telangiectasia, developmental venous anomaly, and arterio-venous malformation. Cavernomas are low flow venous vascular malformations with closely packed dilated abnormal blood vessels with endothelial cells that do not exhibit intervening tight junctions (Figure 7).

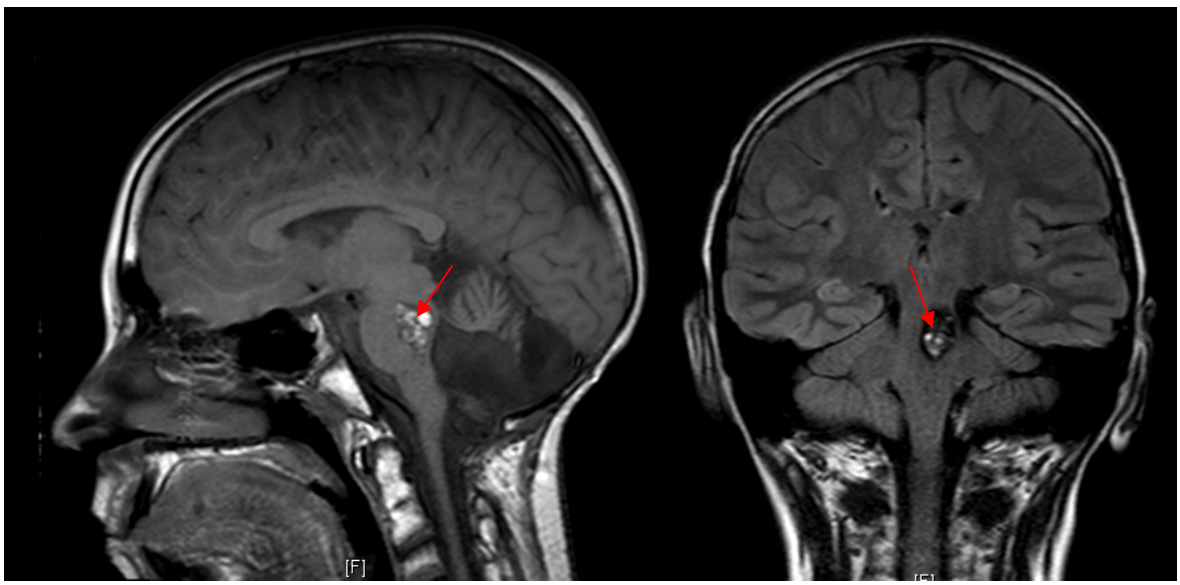


Figure 7: Intrinsic cavernous malformation within the pons – indicated by red arrow.

These vessels lack muscular and elastic layers and are filled with blood at various stages of thrombosis and organisation, because no abnormal vascularity is seen on angiography. Brainstem cavernomas are less common than supratentorial malformations and are commonly associated with an adjacent developmental venous anomaly. Of all the major pathologic categories of vascular malformations with the central nervous system cavernous malformations are the second most common type (after arterio-venous malformations). Cavernous malformations account for 8-15% of the total vascular malformations in the nervous system and have an incidence of 9-35% within the brainstem. The term cavernous malformation is now the preferred term for these anomalies, so that they can be distinguished from the true vascular neoplasms that are suggested by the term angioma. Cavernous malformations have been shown to affect 0.4-0.9% of the population (Gross et al., 2011).

The MRI appearance consists of a reticulated core of high and low signal intensities surrounded by a hypointense rim of hemosiderin. The differential diagnosis includes a very large number of conditions, such as haemorrhagic neoplasms, inflammatory lesions, and mixed lesions, capillary telangectasias, and developmental venous anomalies.

The clinical symptoms of brainstem cavernous malformations are related to the site of bleeding and can be attributed to haemorrhage inside or outside the boundary of lesion, mass effect, or other processes (Zimmerman et al.,1991). The incidence of cavernous malformation haemorrhage within the brainstem is 2.8 per person years, in comparison to 0.3 per person years for non-brainstem haemorrhage, whilst the rate for re-haemorrhage is 32.2 and 6.3 for brainstem malformation and non-brainstem malformations respectively. The risk of bleeding is 0.7% per year per lesion and occurs more frequently in females (Kondziolka et al., 2013).

The most common location for cavernous malformations within the brainstem is the pons, followed by the midbrain and then the medulla. Pontine lesions have a particularly poor prognosis because of the proximity of the oculomotor nuclei resulting in ocular motility deficits, facial lesions, and motor impairment because of the involvement of the circumferential perforated arteries that emerge from the posterior cerebral artery (Washington et al., 2010).

2.2.4 Pituitary tumours

The majority of pituitary tumours are adenomas that are benign and typically arise for the hormone-secreting epithelial cells in the adenohypophysis of the pituitary gland. The classification of these tumours can be defined as functional or non-functional. Functional neoplasms presenting with the characteristic features of excess hormone secretion (Cushings disease, acromegaly, and hyperprolactinemia). Non-functional neoplasms commonly present with symptoms secondary to mass effect and this can present with varying degrees of hypopituitarism. If the tumour grows beyond the confines of the sella turcica, visual field defects become evident due to compression of the visual pathways at the optic chiasm (Melmed, 2011). These tumours are also classified in

accordance with their size and those tumours that are less than 10mm in diameter and are contained with the sella turicica are classically called microadenomas, whilst those more than 10mm or larger and that infiltrate the surrounding extrasellar space are termed macroadenomas (Theodros et al., 2015).

Whilst medical therapy is available for prolactin secreting adenomas, transpehonoidal and endonasal resective surgery remains the treatment for most other pituitary adenomas.

Incidental findings are also seen on autopsy and along with the advances in neuroimaging, and particularly MRI, there have been improvements in the visualisation of the pituitary regions. With this there has also been an increasing number of adenomas that have been incidentally diagnosed when other disorders are being investigated, i.e., sinus disorders (15%), trauma (9%) and stroke (15%). In those patients with these 'incidentalomas' some degree of pituitary dysfunction was present in 15-30%, and visual field deficits were present in 5-15%, rising to 50% when more formal evaluation was carried out (Seltzer et al., 2019).

The high rates of incidental and subclinical discoveries make the determination of incidence and prevalence challenging; as up to 35% of the general population may show these neoplasms at autopsy (Burrow et al., 1981), and 17-23% are found in radiographic studies. However, the prevalence of symptomatic pituitary neoplasms may occur with a population prevalence of 80-90 per 100,000 (Ezzat et al., 2004). The incidence of pituitary tumours rises with age, with 3.5-8.5% being diagnosed before the age of 20, and 30% of patients being diagnosed aged 50-60. Prolactinomas and gonadotrophic (35% each) are the most commonly diagnosed secreting adenomas, followed by corticotrophic and somatotrophic (10-15% each) and thyrotrophic (2%) (Asa and Ezzat, 2009). Overall pituitary tumours represent approximately 10-15% of all neoplasms within the central nervous system and are the cause of ~25% of neurosurgical resections.

Tumours close to the pituitary gland may grow and spread horizontally and invade the cavernous sinus causing dysfunction of the III, IV and VIth cranial nerves along with visual nerve damage (Ho et al., 2015). Craniopharyngiomas make up 3% of all intracranial tumours and 30% of all the new growths in the hypophyseal regions (Muller, 2014). They are benign tumours of ectodermal origin that arise from the squamous cells in the infundibulum between the inferior surface of the brain and the upper surface of the pituitary gland (Figure 8). Ocular signs are frequently the presenting features of these tumours, as well as the other rarer lesions that arise from the sella region, such as suprasellar and parasellar meningiomas; these tumours manifest with dysfunction of the extraocular cranial nerves causing abnormalities of ocular motility and pupillary function. Injury of these structures within the cavernous sinus are associated with complaints of diplopia, ptosis, accommodative difficulties, and ocular motor nerve palsies; with the third nerve being most commonly affected. Such abnormalities may be seen acutely in 21-58% of patients after pituitary apoplexy caused by infarction or haemorrhage (Johnston et al., 2015).

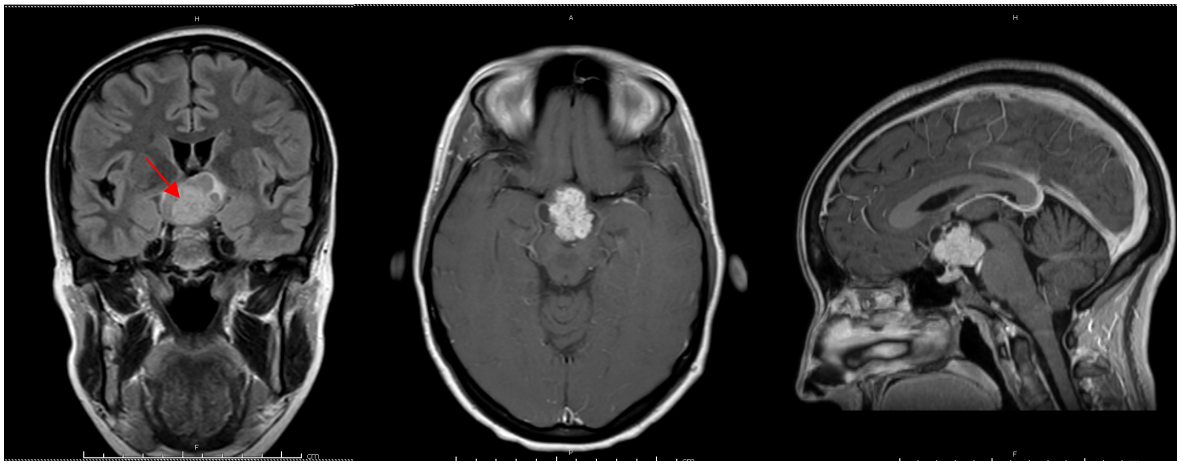


Figure 8: Craniopharyngioma.
Solid/cystic mass (Craniopharyngioma) -indicated by the red arrow - superiorly comprising the anterior margin of the third ventricle and distorting the left foramen of Monro with the optic chiasm splayed over the anterior margin of the mass.

2.3 Brainstem syndromes associated with tumours

2.3.1 Midbrain syndromes

Tumours in the midbrain may result in intranuclear ophthalmoplegia - which is manifested as paralysis of the adducting eye and horizontal nystagmus that is more evident in the abducting eye during horizontal gaze. Parinaud syndrome that is generally secondary to aqueductal compression may also occur. This results in obstructive hydrocephalus and raised intracranial pressure and manifests as a vertical upward gaze palsy with/without a pupillary palsy (Richards et al., 1992). Additional deficits such as ptosis and paralysis of vertical gaze, with preservation of convergence in both eyes, and vertical nystagmus generally indicate a brainstem lesion. As the tumour size increases and invades the tegmentum additional third and/or fourth cranial nerve palsies may also be seen (Richards et al., 1992).

2.3.2 Pontine syndromes

Vascular or tumoral lesions that involve the pons may result in various clinical presentations, depending on the site of involvement. Spastic paralysis due to disruption of the corticospinal tracts; ataxia and facial and abducens nerve paralysis due to damage of the pontocerebellar tracts; and conjugate eye movement deficits due to damage of the medial longitudinal fasciculus and gaze centres of the pons can all be present on clinical examination (Kransnianski et al., 2004). A lesion in the tegmentum of the pons can cause a dorsolateral pontine syndrome that is characterised by ipsilateral gaze palsy and contralateral hemiplegia. The ventral pontine syndrome is characterised by a unilateral abducens nerve palsy and facial nerve palsy with contralateral hemiplegia (Kransnianski et al., 2004).

2.3.3 Medullary syndromes

Medial medullary (Dejerine) and lateral medullary (Wallenberg) syndrome are the most frequently encountered syndromes and are mainly due to a decrease in blood flow to the medulla, resulting in ischaemia and infarction (Gan and Noronha 1995). Medullary tumours and the post-surgical complication caused by removal of these tumours may also cause these common medullary syndromes along with rarer medullary syndromes, such as Babinski-Nageotte syndrome, Cestan-Chenais syndrome and Reinhold syndrome, all of which have variable degrees of overlapping clinical symptoms and signs of both lateral and medial medullary syndromes (Gan and Noronha, 1995).

Due to the involvement of the corticospinal tracts and the medial lemniscal tracts above the decussation of the pyramids, where they are in close proximity to the hypoglossal nerve nucleus, Dejerine syndrome typically presents with a contralateral hemiparesis and loss of proprioception and vibration along with an ipsilateral hypoglossal nerve palsy (Fukuoka et al., 2012).

Infarction within the posterior inferior cerebellar artery territory of the lateral medulla is the main cause of Wallenberg syndrome. Patients suffer from a wide range of symptoms including vertigo, nystagmus, nausea and vomiting due to involvement of the inferior vestibular nucleus; swallowing difficulties and ipsilateral loss of the gag reflex with a hoarse voice due to ninth and tenth cranial nerve involvement; Horner syndrome due to sympathetic nerve fibre involvement; ataxia due to involvement of the inferior cerebellar peduncle and spinocerebellar fibres and the inferior aspect of the cerebellum; loss of pain and temperature sensation ipsilaterally in the face due to descending trigeminal tract involvement and a contralateral loss of pain and temperature sensation in the extremities due to a loss of ipsilateral spinothalamic tract function (Fukuoka et al., 2012).

Traditional end points for tumour resection have been measured by the extent and volume of tumour resection and the incidence of reoccurrence (Myrseth et al., 2007). It has only been more recently - with the widespread adoption of intraoperative neurophysiological monitoring - that the focus has finally moved to the ‘functional’ approach of brainstem tumour resection. With the increased benefit afforded to the patient of the preservation of the neural structures at risk, outcome measures can now incorporate the patient’s symptom relief and the patient’s health-related quality of life.

As more aggressive and radical surgery techniques have become available, the age-old medical adage should always be remembered for the patients benefit that

> *“The treatment of any condition can only be justified if the results of that treatment are better than the natural course of the disease.”*

With this tenant borne in mind, safer resection of brainstem tumours can be undertaken with the use of neurosurgical monitoring and mapping techniques that assess **all** of the neural structures at risk.

Chapter 3.

Modern intraoperative neurophysiological monitoring and mapping techniques during brainstem surgery.

3.1 Introduction

The brainstem is a delicate surgical site as there is the inherent risk of causing devasting injury to the vital neurological functions that it controls (Cochrane et al., 1994, Aarsen et al., 2004). The complex neuroanatomy and the altered structure from space occupying lesions that distort the normal anatomical landmarks renders any surgical intervention precarious (Procaccio et al., 2000, Giliberto et al., 2010). However, the risk of developing new neurological deficits after surgery in and around the brainstem can be minimised by the utilisation of intraoperative neurophysiological monitoring (Deletis and Fernandez-Conejero, 2016, Slotty et al., 2017).

A wide range of routine clinical neurophysiology techniques, including evoked potentials and electromyography (Walsh et al., 2005, Nichols and Manafov, 2012) have been adapted and taken into the operating theatre to be used at the time of surgery to monitor the patient's neurological status. Intraoperative neurophysiological monitoring (IONM) has been widely accepted within other orthopaedic and neurosurgical procedures with the aim of reducing the risk of post-operative neurologic deficits. However, even though there has been a decrease in mortality and an increase in survival rates for patients undergoing surgery in and around the brainstem – due to the advent of neuroprotective anaesthesia and advances in neurosurgical micro-techniques and post-operative neuro-intensive care within the past few decades (Sloan, 2010) – many tumours that are benign are still being treated with the same expected outcome as malignant lesions (Slotty et al., 2017).

The brainstem is a critical part of the nervous system because of the high concentration of ascending, descending, and exiting neural pathways that control vital functions, such as sensation, balance, movement, conjugate gaze, speech, swallowing, arousal and cardiorespiratory function (Karakis, 2013). The lack of redundancy that is specific to this part of the nervous system contributes to the high risks associated with surgery. Even a small iatrogenic lesion to the neighbouring neural tissue or occlusion to the vascular structures can result in debilitating functional deficits such as hemiparesis, hemiplegia, dysphagia, oculomotor dysfunction, coma, and possible death (Procaccio et al., 2000, Giliberto et al., 2010, Deletis and Fernandez-Conejero, 2016).

3.2 Intraoperative neurophysiological monitoring techniques

Modern multi-modality evoked potential recordings taken intraoperatively for brainstem surgery, involving surgical resection of extra-axial and intrinsic lesions, can include many complimentary techniques. Assessment of the long tracts uses somatosensory evoked potential recordings to assess the ascending medial lemniscal pathways (Toleikis, 2005). The ascending auditory pathways can be monitored with auditory evoked potentials (Simon, 2011). The descending corticospinal pathways of the pyramidal long tracts can be assessed with motor evoked potentials

(MacDonald et al., 2013). The corticobulbar pathways of the individual brainstem nuclei can be also be assessed with motor evoked potentials and are used along with cranial nerve monitoring and mapping to investigate the peripheral components of these pathways (Karakis, 2013). For example, in microvascular decompressive surgery of neurovascular conflict of the facial nerve, the ascending auditory pathways and abnormal motor responses after stimulation of the facial nerve can provide prognostic information of the adequacy of the surgery (Fernandez-Conejero et al., 2012).

3.2.1 Somatosensory evoked potentials (SEPs)

Somatosensory evoked potential monitoring allows continuous assessment of the dorsal column pathways of the spinal cord from the periphery to the cerebral cortex (Toleikis, 2005). Typically, the median or ulnar nerves are electrically stimulated at the wrist, causing depolarisation of the mixed nerve and the production of a synchronous action potential volley through the ascending sensory fibres of the dorsal root and the corresponding antidromic motor impulses (Figure 9). The electrical stimulation parameters that are used predominantly activate the large diameter, fast conducting group Ia muscle and group II cutaneous afferent fibres (Halonen et al., 1988, Aminoff and Eisen, 1998) that can be detected from electrodes placed over the lower brachial plexus, at Erb's point, to record the peripheral compound nerve action potential (MacDonald et al., 2019). On passing through the C6-T1 nerve roots after median nerve stimulation, or C8-T1 nerve roots after ulnar nerve stimulation, upon entering the spinal cord at the dorsal root entry zone the action potential travels up through the ipsilateral white matter tracts of the cuneate fascicule in the lateral posterior dorsal column.

These long afferents terminate in the cuneate nuclei situated in the medullary brainstem. From there second-order axons decussate and ascend the contralateral medial lemniscal pathways as the internal arcuate fibres where they synapse in the thalamus in the ventral posterolateral nuclei. Third order axons ascend through the posterior limb of the internal capsule where they fan out through the thalamocortical radiation to terminate in the primary somatosensory gyrus (S1) in the lateral convexity of the parietal lobe (Crucco et al., 2008). Electrodes placed on the scalp over the primary somatosensory cortex can detect the arrival of the electrical volley from the posterior wall of the central fissure (MacDonald et al., 2019).

For surgery within the posterior fossa SEPs are useful for monitoring the medial lemniscus integrity (Sala et al., 2015, Slotty et al., 2017). With tumours that are at the level of the pons and midbrain, SEPs have little localising value but are used to provide nonspecific information about the general functional integrity of the brainstem. As a major impending brainstem failure will be identified by a change in the somatosensory amplitude or latency (Sala et al., 2015). As the upper and lower limb lemniscal fibres are close together within the internal arcuate fibres ascending within the medulla, upper limb somatosensory evoked potentials are usually sufficient to monitor the posterior sensory afferent pathways through the brainstem (MacDonald et al., 2019). Typical recordings are taken from Erbs point to monitor the peripheral conduction to the brachial plexus (N9/EP) and from the scalp using the derivation that increases the signal to noise ratio (i.e., Cc-Fz, Cc-Cz or Cc-Ci);

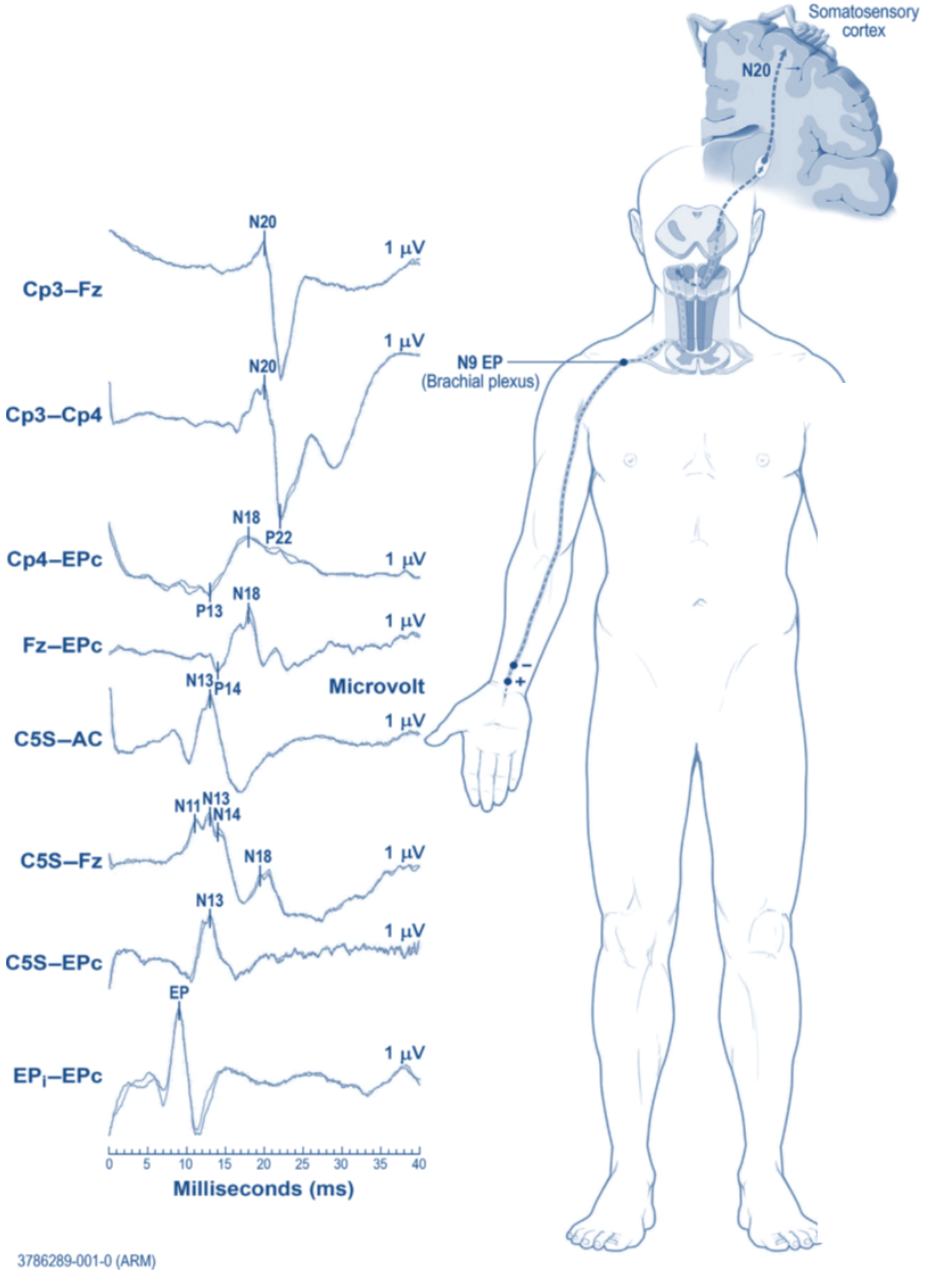


Figure 9: Somatosensory evoked potentials.
The dorsal-medial lemniscal somatosensory pathways after upper limb stimulation can evoke peripheral potentials form the brachial plexus (Erbs points). On entering the spinal cord cervically generated potentials can be recorded from the neural axis (N13). Brainstem potentials (P14 and N18) can be recorded using non-cephalic reference sites. Cortical responses (N20) from the primary somatosensory area can be recorded with different electrode configurations.

cervical and sub-cortical responses tend to have inherently low signal to noise ratio causing low reproducibility and an increase in the time taken to average, therefore, to enhance the efficacy of the monitoring and to hasten surgical feedback these recording derivations are usually omitted without compromising interpretation (MacDonald et al., 2009).

3.2.2 Brainstem auditory evoked potentials (BAEPs)

Monitoring of the auditory brainstem evoked potential (BAEP) is now routine practice during surgical procedures that could potentially compromise the cochlear nerve or the brainstem (Luders, 1988, Legatt, 2002). They are relatively easy to record consistently and are robust to the physiological influences and to the surgical levels of anaesthesia used intraoperatively (Banoub et al., 2003). From the first detailed description of short latency BAEPs, Jewett and Williston (1971) labelled the sequence of stereotyped waveforms with Roman numerals. These waveforms represent a combination of *near-field* and *far-field potentials* that are caused by the activation of deep grey and/or white matter structures that are recorded from surface electrodes *far* from the neural generators after a brief acoustic stimulation (Jewett et al., 1970).

The stimulus usually consists of *clicks* that are generated by passing square wave pulses of 0.1msec duration through transducers that are placed into the external auditory canal (Simon, 2011). The mechanical acoustic stimulation of the cochlear hair cells is converted into electrical impulses that are generated within the cochlea to produce action potentials. Supra-threshold stimulus levels (60-90dBSL) are used during monitoring to elicit supramaximal responses that are recorded from electrodes placed around the mastoid, referenced to an electrode at the vertex. This differential recording montage enables a mixture of near-field potentials from the distal auditory nerve and far-field potentials, that reflect depolarisation of several structures within the auditory pathways up to the upper pons, to be assessed (Legatt, 2018).

Stimuli are delivered monaurally, so that the stimulation of one ear does not obscure the presence of an abnormal or normal response from air conduction stimulation of the other ear. The acoustic stimulation delivered to each ear via earphones can reach the other ear via air and bone conduction, with an attenuation of 40-70dB, thereby generating an evoked response from the contralateral ear. Even though the acoustic stimulus is attenuated further (70-100dB) when using the ear-insert transducers that are typically used intraoperatively, the signal that can potentially reach the contralateral ear can still elicit acoustic cross talk (Atcherson et al., 2012). The-non stimulated ear is therefore presented with white noise at an intensity 30-40dB less than the stimulation presented to the test ear, to ‘mask’ the acoustic cross talk (Legatt, 2018).

When recording BAEPs, the two inputs, from the mastoid and the vertex, are connected to the differential amplifier and cannot be considered as active or referentially, as the voltage distribution after acoustic stimulation extends over most, if not all, of the head; and no cephalic electrode position can therefore be truly inactive for all of the BAEP components (Sherg and von Cramon, 1985).

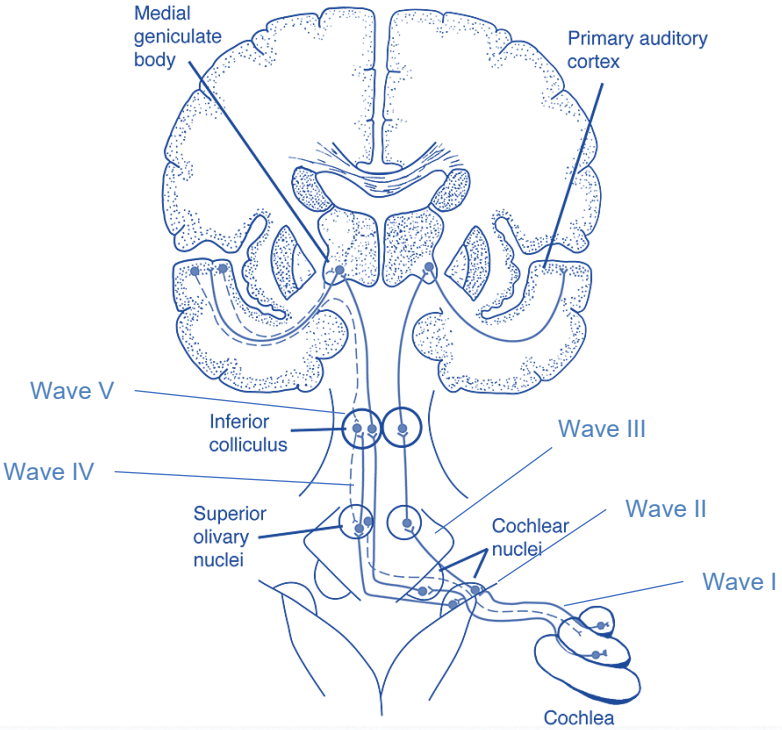
BAEP waveforms typically begins with the stimulus artefact that is synchronous with the stimulus that is produced by the acoustic transducer. The polarity of the square wave stimulus will affect the initial deflection of the diaphragm within the sound transducer; initial outward movement (toward the ear drum) is defined as an acoustic condensation phase stimulus, whereas an initial outward movement of the membrane away from the ear drum is defined as an acoustic rarefaction phase stimulus (Legatt, 2018). Rarefaction click stimuli is generally preferred, as they tend of yield responses with clearer definition of the individual components, because the initial phase of the stimulus will displace the cochlear basilar membrane towards the scala vestibuli, causing maximal depolarisation of the hair cells (Schwartz et al., 1990). Condensation stimuli displaces the basilar membrane away from the scala vestibuli and the resultant activation of the hair cells and auditory nerve is delayed until the subsequent rarefaction phase of the acoustic is generated (Schwartz et al., 1990).

The generator site of wave I is most conclusively localised and arises from the first volley of action potentials in the auditory nerve at the most distal (i.e., closest to the cochlea) portion of the nerve; predominantly reflecting the activity of those eighth nerve fibres that originate from the basilar cochlear turns (i.e., the high frequency end of the cochlea). The origin of wave I in the most distal portion of the auditory nerve is demonstrated by its presence in some patients that fulfil the clinical and electroencephalographic criteria for brain death (Andre-Obadia et al., 2018), and by its occasional persistence after section of the auditory nerve during vestibular schwannoma surgery (Legatt, 2002). It is a surface negative potential that is recordable from a small, circumscribed region of the scalp close to the stimulated ear.

The subsequent BAEP waves are surface positive components and have a widespread distribution over the scalp. Waves II and III are believed to originate in the auditory pathways in the pons, and waves IV and V are thought to originate in the mid and upper pons/lower midbrain respectively (Figure 10), the exact source of activation for each of these waveforms is still controversial (Legatt, 2018).

Wave II is traditionally believed to represent activity of the ipsilateral cochlear nucleus, as it is the earliest component affected by pontomedullary cerebrovascular accidents involving the cochlear nucleus. This has been interpreted as implying a generator within the brainstem, specifically the cochlear nucleus or its outflow (Gersdorff, 1982). However, at the sound intensity levels used for BAEP recordings, two volleys of activity can be elicited within the auditory nerve, that correspond to N1 and N2 of the eighth nerve action potential of the electrocochleogram (ECochG). When the action potential of the N2 component begins in the distal auditory nerve, the activity from the N1 volley has propagated to the proximal auditory nerve or the cochlear nucleus, so that both can contribute to the generation of wave II. This contribution from N2 in the distal auditory nerve has been confirmed by simultaneous BAEP and ECochG recordings and by recordings that have been taken directly from the intracranial eighth nerve (Gersdorff, 1982, Hashimoto et al., 1981). The presence of prominent wave II activity in the trapezoid body in animals (Caird et al., 1985) and the finding that some lesions of the trapezoid body can affect wave II (Wada and Starr, 1983) suggests

A



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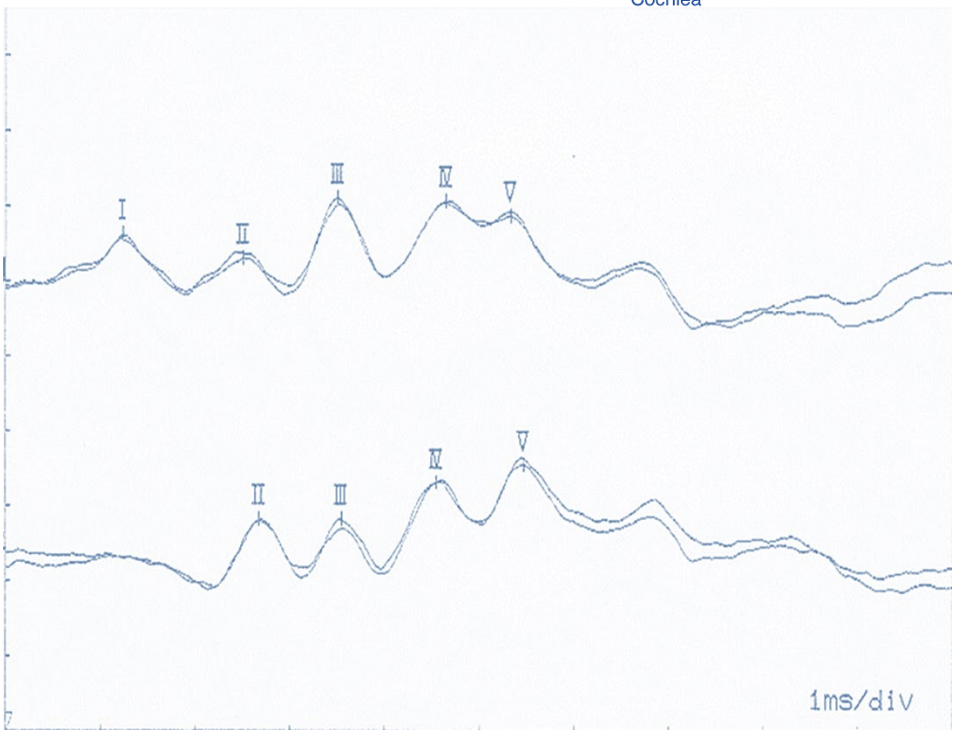


Figure 10: Brainstem auditory evoked potentials.
A) The ascending brainstem auditory pathways with the location of the presumed neural generator sites of the individual BAEP components.
B) Top traces show ipsilateral (Ai-Cz) recording of the brainstem auditory evoked potential, with clear waves I-V.
The bottom traces show the contralateral (Ac-Cz) potentials with clear waves II-V.

that potentially there are multiple sites in auditory pathways of the ipsilateral pons can make a significant contribution to wave II. But more consistently than these rostral brainstem generators, activity from the intracranial portion of the eighth nerve close to the brainstem, with a similar latency to wave II, have been recorded, further suggesting that there is a contribution to the generation of wave II from the proximal auditory nerve (Moller et al., 1981, Moller et al., 1982a). Detailed BAEP recordings utilising different arrays of electrodes produced two distinct components of wave II; with wave IIa being recorded from the proximal portion of the acoustic nerve and IIb representing the presynaptic activity of the acoustic nerve terminating in the cochlear nucleus (Anathanarayan and Durrant, 1991), reconciled the data that wave II has contributions from both the proximal end of the auditory nerve and activity within the cochlear nucleus. However, the distinction between a proximal eighth nerve generator and a generator within the substance of the cochlear nucleus does not have a major impact on the anatomic localisation of the cause of any wave II BAEP abnormality, because the brainstem generator that produces the scalp topography with maximal amplitude over the dorsal part of the head is usually predominant (Scherg and von Cramon, 1985). Wave III, as with all later peaks, also represents a composite of contributions from multiple generators, with human lesion data localising the major generators to the caudal pontine tegmentum in the region of the trapezoid body and the superior olivary body. This is confirmed with lesions in the mesencephalic region of the brainstem usually being associated with the preservation of waves I, II or III (Markand et al., 1989). In contrast to wave II, which is generated in the neural structures ipsilateral to the ear that is stimulated, both ipsi- and contralateral pathways in the pons are likely to contribute to wave III. Intracranial recordings have also shown consistency with a pontine generator (Hashimoto et al., 1981) at the level of the superior olivary complex, likely representing activity in the contralateral trapezoid body or the outflow from the contralateral superior olivary complex ascending in the lateral lemniscus (Moller and Jannetta, 1982a).

According to some authors the tip of wave V probably generates where the lateral lemniscus terminates in the inferior colliculus (Moller and Janetta, 1982b, Moller and Janetta, 1983, Legatt et al., 1988). It is generally accepted that wave V is generated in the high pons or low midbrain at the level of either the lateral lemniscus or the inferior colliculus, subsequently wave IV is generation must be in the mid pons, in the lateral lemniscus. Wave IV/V has the most complex array of generators, with the major sources of wave V considered to be the lateral lemniscus and/or inferior colliculus on both sides. Direct recordings from the dorsal aspect of the brainstem in humans have demonstrated a large potential from the inferior colliculi region coincident to wave V of the scalp recorded BAEP (Hashimoto et al., 1981, Moller and Jannetta, 1982b). Clinicopathologic studies suggest waves IV and V originate in the midbrain because of their consistent attenuation or disappearance with midbrain lesions (Markand et al., 1989). Wave IV is affected by tumours or cerebrovascular accidents of the midpons or rostral pons. Its generators are close to or overlapping with, but not identical to, those of wave V; waves IV and V are usually either both affected of both unaffected by brainstem lesions, but they may be affected differentially by multilevel demyelination, a brainstem infarct (Legatt et al., 1988) or a small brainstem haemorrhage on the lateral lemniscus (Cho et al., 2005). Wave IV may persist in the presence of a lesion of the inferior colliculus that

eliminates wave V (Hirsch et al., 1996). Thus, wave IV appears to reflect activity in ascending auditory fibres within the dorsal and rostral pons, caudal to the inferior colliculus. Although the nucleus of the lateral lemniscus has been implicated as a BAEP generator in animal studies, human data are insufficient to confirm its contribution to wave IV (Curio and Oppel, 1988).

In intracranial recordings, the positive peak corresponding to wave V is largest near the inferior colliculus contralateral to the stimulated ear (Moller and Jannetta, 1982b). Intracranial data also suggests that the mesencephalon contralateral to the stimulated ear is the major generator of wave V. Clinically however, unilateral abnormalities of wave V are associated most often with ipsilateral pathology (Moller and Jannetta, 1983).

3.2.3 Transcranial motor evoked potentials (TcMEPs)

Somatosensory evoked potentials are used to assess the integrity of the ascending pathways through the brainstem during posterior fossa surgery, and even when combined with brainstem auditory evoked potentials they can only monitor about 20% of the cross-sectional area of the brainstem (Strauss et al., 1994), the tegmental somatosensory and auditory pathways also do not cover a large enough area of the brainstem to truly represent its general functional state with a high enough sensitivity (Fahlbusch and Strauss, 1991). Whilst it was thought that the close proximity of the sensory and motor tracts within the spinal cord would mean that major pathophysiology affecting the motor pathways during spinal surgery would also cause disruption and changes that would be able to be detected by monitoring the sensory pathways (MacDonald et al., 2013), this is not the case for microscopic resections that take place during neurosurgery around the brainstem (Sala et al., 2007).

The corticospinal pyramidal tracts are the axons from the pyramidal cells with the cerebral cortex (Figure 11). Thirty percent of the fibres originate from the primary motor cortex, with another 30% originating from the pre-motor and supplementary motor area cortices. The remaining 40% originate from the post-central primary somatosensory and parietal secondary somatosensory and cingulate gyrus (Welniarz et al., 2017). These descending fibres pass through the corona radiata and converge at the internal capsule into a tract that continues downward through the ventral cerebral peduncles and the crus cerebri, basis pontis and the medulla pyramid to arrive at the pons and continue to the spinal cord. The direct fibres are mostly large thickly myelinated axons. The majority of axons terminate on interneurons to reach the lower motor neurones via intermediary synapses, although approximately 2% of axons synapse directly onto lower motor neurones that predominantly innervate distal limb muscles (Welniarz et al., 2017). Usually 75-90% of the corticospinal fibres traverse the midline at the pyramidal decussation at the level of the junction between the medulla and the spinal cord where they descend the lateral - or to a lesser extent - ventral corticospinal pathways. The corticobulbar tract is the descending connection between the cortex and the motor nuclei of the cranial nerves within the brainstem and is critical for the voluntary muscle movements of the cranial nerves. These axons descend alongside the corticospinal tracts before they diverge into the brainstem. Most of these fibres terminate on

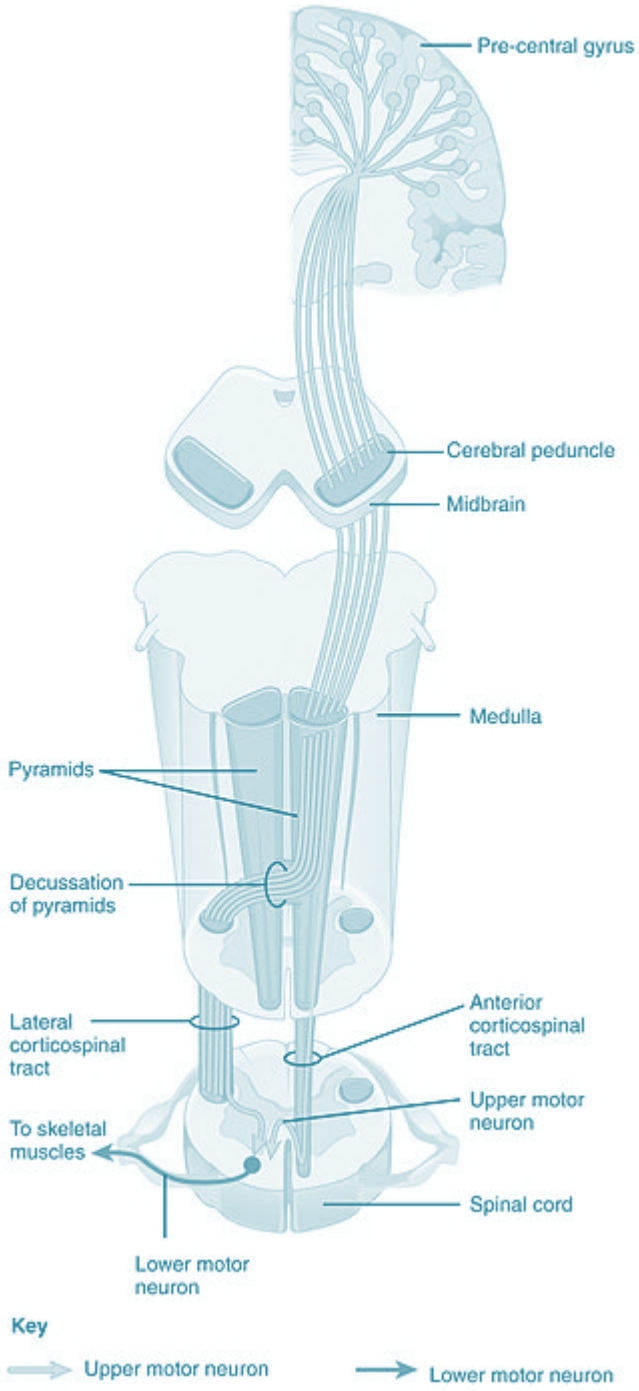


Figure 11: The corticospinal tracts.
The pyramidal cell in the primary motor cortex of the frontal lobe descends via the corona radiata to the cerebral peduncle in the midbrain. In the medulla the fibres decussate and form the lateral and the anterior corticospinal tracts within the cord. The upper motor neurones terminate onto lower motor neurones in the ventral spinal cord grey matter which exit the spinal cord and innervate the muscles.

interneurons, although a few form direct corrections to the lower motor neurones, especially those for the lower face and tongue (MacDonald et al., 2013).

However, because the corticospinal tracts are compressed within an anatomically small portion of the brainstem surface, they are more at-risk during brainstem-related procedures (Sala et al., 2007, Deletis and Fernandez-Conejero, 2016).

High voltage electrical stimulation was initially used to evoke responses from the distal muscle groups in awake subjects (Merton and Morton, 1980); but because of the technical difficulties and co-excitation of pain fibres within the scalp, this methodology was quickly supplanted by the less painful excitation of the cortical fibres using magnetic stimulation (Barker et al., 1987). However, due to the size of the stimulating paddle and the inherent movement associated with the stimulation, meaning that the same area of cortex was not always elicited from trial-to-trial, and the inhibition caused by the halogenated anaesthetic agents at that time, this methodology was not widely utilised intraoperatively (Yamada et al., 1994 Lee et al., 1995).

Following on from the initial findings of direct cortical stimulation using trains of electrical pulses to overcome the effects of anaesthesia on the multi-synaptic pathways through the spinal cord (Taniguchi et al., 1993), and the subsequent modification of the technique to be able to elicit responses trans-cranially (Pechstein et al., 1996), the use of motor evoked potential recording intraoperatively can now be used to specifically assess the descending motor pathways through the brainstem (MacDonald et al., 2013). These corticobulbar tracts are the direct descending connections between the primary motor cortex and the brainstem motor nuclei that are critical for voluntary cranial muscle movements. The corticobulbar axons descend alongside the corticospinal fibres before diverging into the brainstem, where the majority of then terminate on interneurons, with the remaining fibres forming direct connections to their individual motor neurons (Figure 12). These projections to the motor nuclei are mainly bilateral, and so cortical stimulation tends to elicit bilateral responses (MacDonald et al., 2013). Given the anatomical considerations of the corticospinal and corticobulbar tracts within the brainstem, monitoring of these pathways and nuclei have now been incorporated into the multimodal recordings that take place when the lateral and ventrolateral aspects of the brainstem are being accessed (Slotty et al., 2017). The more recent application of corticobulbar motor evoked potential recordings allows near continuous monitoring of the facial pathways (Akagami et al., 2005, Dong et al., 2005) with sub-dermal needle electrodes placed into the orbicularis oculi, orbicularis oris or mentalis; the glossopharyngeal and vagus nerves with hook wire electrodes placed into the stylopharyngeus (Singh and Husain, 2011) and cricothyroid (Holdefer et al., 2013) muscles respectively; and the spinal accessory nerve with recording taken from the upper trapezius (Skinner, 2011) and hypoglossal nerve from the tongue (Skinner, 2011).

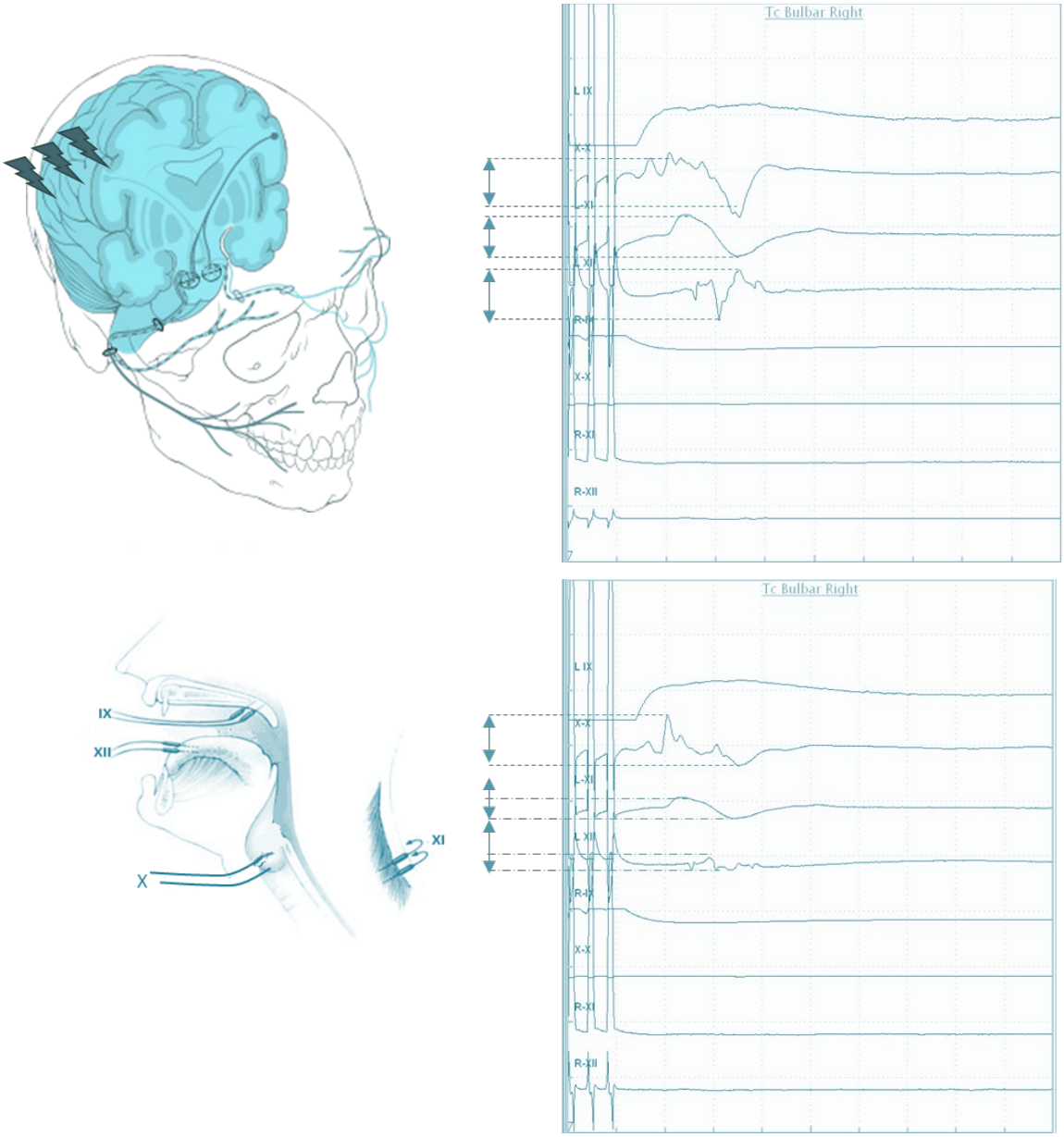


Figure 12: Corticobulbar motor evoked potentials.
Corticobulbar MEPs recorded from the left lower cranial nerves (IX -XIIth, bottom left) after transcranial electrical stimulation of the right hemisphere
Right side. Top traces: baseline responses showing responses from the vagal nerve (Xth), spinal accessory (XIth) and hypoglossal (XIIth) cranial nerves. Bottom traces: Subsequent responses showing preserved responses from the Xth cranial nerve and a reduced response (<50%) from the IXth cranial nerve. and severe reduction (>80%) from the XIIth cranial nerve. The patient awoke with paralysis of the tongue after resection of a left sided brainstem meningioma.

3.2.4 Free-running and triggered electromyographic (EMG) recordings

Techniques have been developed that enable the individual cranial nerves and the surrounding structures to be monitored during brainstem surgery. Electromyographic potentials can be used to record the electrical potentials in the muscle fibres. Unlike other forms of intraoperative monitoring, the expected finding with free-running EMG recordings is for an absence of activity, which is generally assumed to indicate an uninjured nerve or uninterrupted nerve (Daube and Harper, 1989).

The individual cranial nerves reaction to manipulation - and subsequent injury – was described by Kugelberg as “injury activity” (Kugelberg, 1946); and acute ischaemia of the nerve could elicit prolonged “repetitiousness”, with the presumed mechanism being a “breakdown of accommodation” (Kugelberg and Cobb, 1951).

The addition of free-running facial nerve monitoring during vestibular schwannoma resection showed that specific patterns of activity were able to predict facial nerve outcome (Prass and Luders, 1986). Eventually all types of nerve injury were called *neurotonics* (Daube and Harper, 1989). Neurotonic discharges occur when the nerve is depolarised above threshold and can vary in frequency, duration, and pattern (Figure 13). They are generated in response to nerve injury or irritation, and can be elicited following metabolic derangement, mechanical manipulation, thermal changes and ischaemic or traumatic injury to the nerve. After the nerve has been depolarised the nerve action potential travels proximally and crosses the neuromuscular junction to excite the muscle fibres that are innervated by the discharging motor unit/s.

Neurotonic discharges are therefore a distinctive pattern arising from the motor unit which appear as either irregular *bursts* lasting several milliseconds (Figure 13, Bi and Bii) or prolonged *trains* (Figure 13, C and D) lasting several seconds to minutes (Daube and Harper, 1989). Each of the discharges may contain 1 to 10 individual motor unit potentials, firing at a frequency of 50-200Hz.

Those short lasting neurotonic bursts that occur in close temporal relationship to nerve manipulation during surgery are more likely to be caused by nerve irritation are not usually associated with post-operative deficit of the cranial nerve (Figure 13, A, Bi and Bii); whilst the longer lasting trains of neurotonic discharges, that are sustained and continue after the manipulation has ended (Figure 13, C and D), are more likely to represent impending nerve injury or indicate that nerve injury has already occurred and are more predictive of a paresis (Romstock et al., 2000, Singh and Husain, 2011, Skinner, 2011).

The neurotonic discharges provide a sensitive means of informing the surgeon that the nerve is being manipulated and is therefore likely to suffer impending damage if the discharges continue. As multiple nerves can be monitored simultaneously, they can give localising value as to the position of the cranial nerves. This is valuable information, especially when the expected anatomical course of the nerve is altered due to the mass effect of the lesion or when the nerves are obscured by the lesion itself (Sala et al., 2015, Deletis and Fernandez-Conejero, 2016).

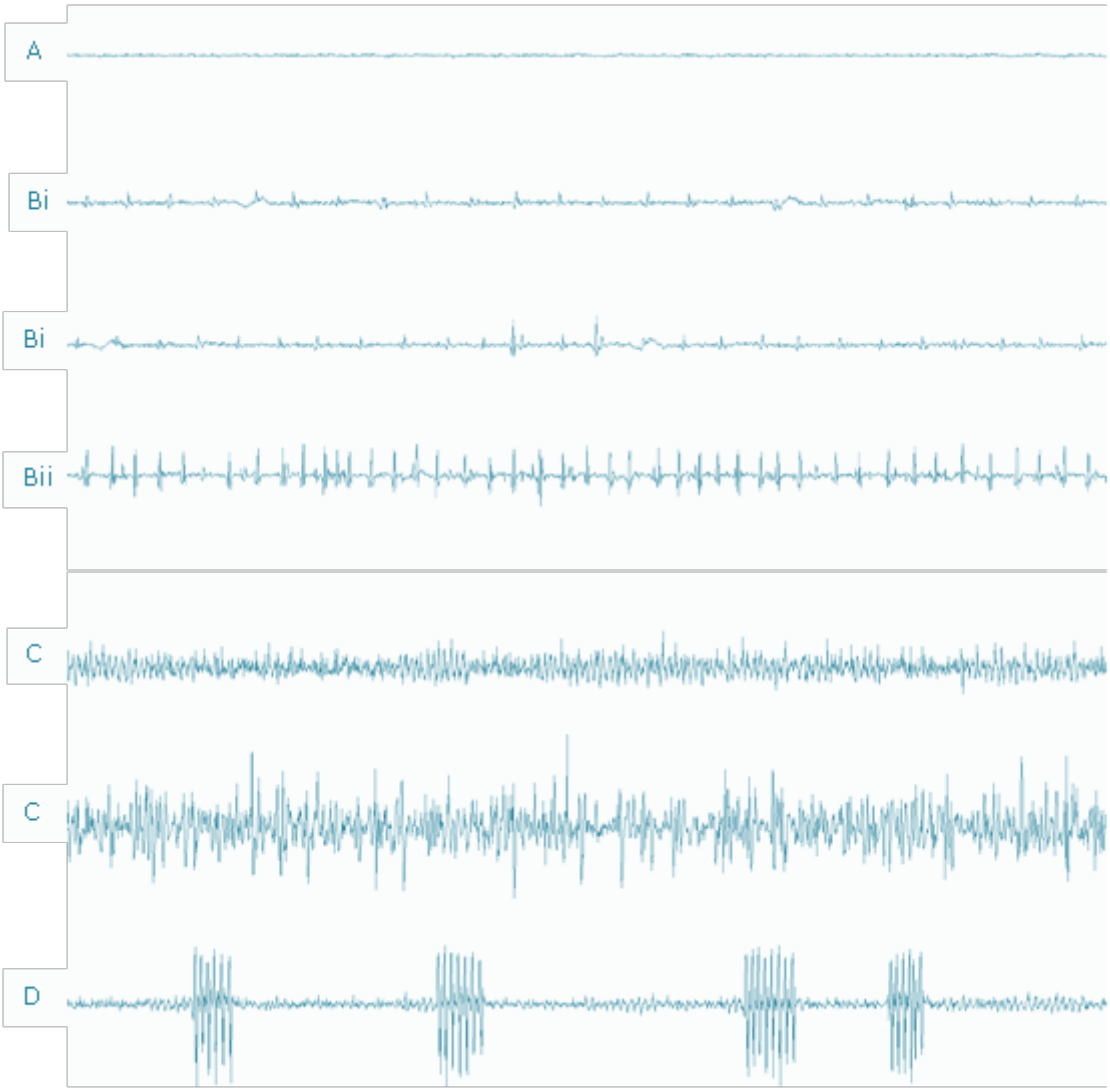


Figure 13: Examples of free-running EMG
A – no spontaneous activity
Bi – example of individual spikes of neurotonic activity
Bii – prolonged bursts of regular neurotonic spike activity
C – prolonged runs of continuous irregular neurotonic EMG activity
D – bursts of regular spike activity (A-trains).

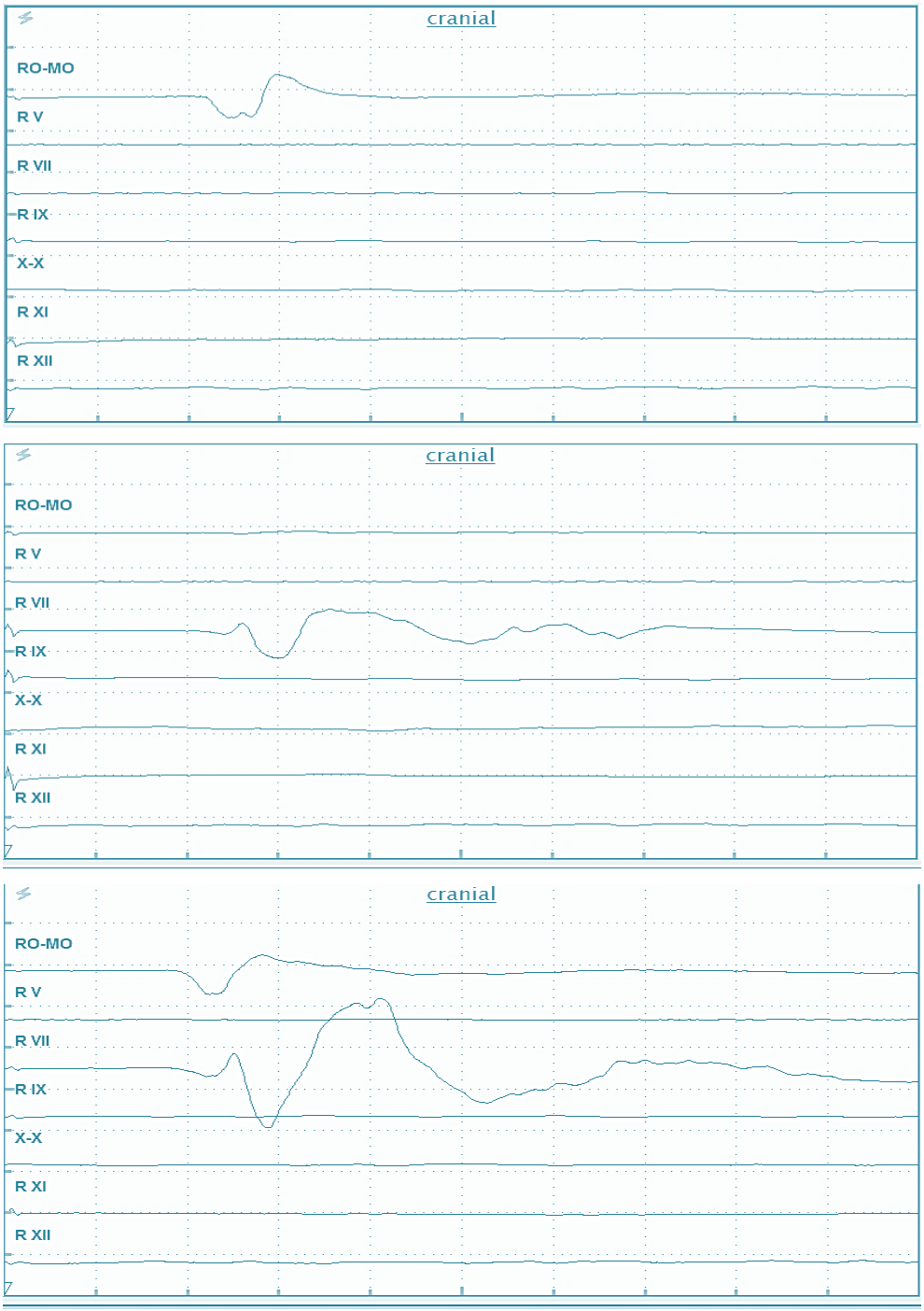


Figure 14: Triggered EMG
Multi-channel cranial nerve monitoring from the right side.
Top traces: responses to stimulation of the exposed VIth cranial nerve.
Middle traces: response to stimulation of the exposed VIIth cranial nerve.
Bottom traces: response from the VIth and VIIth cranial nerve after stimulation within the pons at the level of the individual brainstem nuclei.

In these situations, triggered EMG can be used to identify and localise the nerve by using intra-field electrical stimulation to elicit compound motor action potentials from the muscles innervated by the cranial nerves being stimulated (Karakis, 2013).

Electrical stimulation during brainstem surgery is based on similar principles for identifying and monitoring peripheral nerves and motor evoked potentials (Figure 14). The surgeon can use a hand-held probe to stimulate the presumed neural structure under investigation, to determine if a response is able to be produced, and from the resultant presence or absence of a response can ascertain if neural tissue is contained within the structure (Deletis et al., 2000). The electrical stimulus is typical a short duration (0.05-0.2 msec) square wave pulse that can be delivered via a bipolar or monopolar probe with excitation of the nerve occurring beneath the electrified tips of the electrode. Recently, more discrete and localised delivery of the current has been described when using a concentric probe placed on the tissue under investigation (Morota et al., 2010). Excitation of the cranial nuclei through the floor of the fourth ventricle can be achieved using stimulus intensities of 0.01-2mA and based on the evidence that the time constant for stimulation of centrally myelinated axons is 50-100μsec (compared to 1-10msec for other neurones and their dendrites) (Shannon et al., 1997), it was determined that the peripheral motor neurones are the site of electrical stimulation (Strauss et al., 1999).

3.3 Warning criteria

The use of multi-modal intraoperative EPs has long been recommended for those patients undergoing brainstem surgery (Albright and Sclabassi, 1985) and the use of one modality does not obviate the need to monitor another, as the individual pathways through the brainstem may be compromised during surgery without the concurrent compromise of other tracts or nuclei in close proximity (Sala et al., 2007, Deletis and Fernandez-Conejero, 2016). The concurrent monitoring of TcMEP, SEP (Kodama et al., 2014) and BAEP (Simon, 2011) can therefore detect compromise of the sensory or motor or auditory tracts and can also provide a measure of redundancy, so that potentially at least one of the methods is able to be utilised at the time of surgery to monitor the integrity of the brainstem nervous system, especially when pre-existing neurologic deficit, unavoidable anaesthetic choice or technical problems make it difficult to record from all of the pathways.

The changes in intraoperative evoked potentials are usually progressive or stepwise, and when promptly recognised, a modification of the surgical strategy can be performed to reverse the injury in order to mitigate the potential neurological deficit. A 50% decrease in the cortical somatosensory evoked potential with or without an increase in latency, has traditionally been used as the warning criteria that has been used to establish the efficacy of somatosensory evoked potential monitoring (Nuwer et al., 2012), but such stringent interpretation, does not take into account baseline drift or reproducibility (MacDonald et al., 2019). An *adaptive warning criterion* of a visually obvious reduction in pre-change values - that clearly exceed the variability and reproducibility of the baseline potentials - reduces the likelihood of false results; especially when they are abrupt and

focal and are correlated with a high-risk surgical manoeuvre (MacDonald et al., 2019). Therefore, a 30% decrease in the cortical waveform can be used when the waveform variability is high (or nearly exact) and the amplitude variation is <20%, or a 40% decrease in the cortical waveform can be used as the early warning signs of impending damage when the inter-trial reproducibility is medium and the amplitude variation is 20-30% (MacDonald et al., 2019).

The standard criteria to interpret brainstem auditory evoked potentials are based on the examination and latency of waves I, III and V. Changes in amplitude are more common than changes in latency and usually occur earlier. A decrease in the amplitude of wave V more that 50% is considered a warning sign; along with an increase in its latency of >1msec or a delay of more than 10% of the baseline peak V latency (Legatt, 2002).

Conversely when the intraoperative monitoring recordings remain unchanged, the surgeon may be reassured that there is no impending injury to the neural pathways under investigation and a more radical resection may be encouraged.

3.4 Anaesthesia

Different anaesthetic regimes can be used during intraoperative monitoring and mapping (Table 1), including the use of halogenated gases, nitrous oxide, barbiturates, and other intravenous narcotics (Sloan, 2010). However, when any recordings are taken from the muscles (MEPs, free-running EMG or triggered-EMG) then muscle relaxants must be avoided; although short acting neuro-blocking agents may be used to aid induction of the tracheal tube (Sloan, 2013); Whilst inhalational and intravenous agents do not have an effect on EMG recordings, they do have a dose-dependent effect on the amplitude and latency of the other sensory and motor evoked potentials (Banoub et al., 2003, Wang et al., 2009).

Table 1: Anaesthetic effects on evoked potentials.

Drug name	**Drug class**	Effect on SSEP		Effect on TcMEP		Effect on BAEP	
		lat	amp	lat	amp	lat	amp
Isoflurane	Inhalation	↑ 10-15%	↓ 50-70%	↑ 10-15%	↓↓↓	↑ <10%	NE
Sevoflurane	Inhalation	↑ 5-10%	↓ 40-50%	↑ 10-15%	↓↓	↑ <10%	NE
Desflurane	Inhalation	↑ 3-8%	↓ 40-60%	↑ 10-15%	↓↓	↑ <10%	NE
N_2O	Inhalation	NE	↓ 50-55%	↑ 10-15%	↓↓	NE	
Propofol	GABA-agonist	↑ 10-15%	<50%	↑ <5%	↓	NE	
Etomidate	GABA-agonist	↑ <10%	↑ 40-150%	↑ 5-10%	~	NE	
Midazolam	Benzo-diazepine	↑ <10%	↓ 25-40%	↑ <5%	↓ <15%	NE	
Ketamine	NMDA antagonist	NE	↑ 5-30%	↑ <5%	~ or ↑	NE	
Dexmedetomidine	α-2 agonist	↑ <10%	↓ 10-30%	↑ 5-10%	↓ 10-20%	NE	
Remifentanil	Opiod synthetic	NE	↓ 15-40%	NE	↓ 10-20%		
↑ = increase, ↓ = decrease, ~ = minimal effect, NE = no effect							

Brainstem auditory evoked potentials are only minimally affected by the volatile anaesthetic agents, with only a small increase in component latency, without a change on wave I-V amplitude; reflecting the depressant effect of these gases on brainstem neuronal activity (Manninen et al., 1985, Heneghan et al., 1987). Continuous infusion of propofol increases the absolute latencies of waves I, III and V by less than 5%, with no changes in amplitude (Chassard et al., 1989); whilst opioids do not alter the amplitude or latency of the responses (Samra et al., 1984).

As general anaesthesia has an inhibitory effect on neurotransmission, the effect is greatest on synaptic transmission than in the conduction along the axon (Richard, 1983); therefore, the responses recorded from polyphasic pathways are affected to a much greater extent than subcortical recordings (i.e., brainstem auditory responses). Each of the volatile anaesthetic agents produce a dose-dependent increase in the latency of the somatosensory potential, an increase in the central conduction time and a decrease in the cortical amplitude (Peterson et al., 1986, Pathak et al., 1989). The reproducibility of the somatosensory evoked potential cortical waveform is directly related to the amplitude of the response and is inversely related to the amplitude variability (Lubicky et al., 1989). Smaller amplitude responses are subject to more baseline variation, extraneous electrical noise and a reduced signal to noise ratio (Nuwer et al., 1984, Kalkman et al., 1991). The preservation of the cortical amplitude and the maximisation of its response is an important consideration when choosing the anaesthetic regime, especially when the baseline amplitude is already low and the variability is expected to be high, such as can occur in very young (<5 yrs of age) or elderly patients (>60 yrs of age), and those with pre-existing neurological deficits caused by tumours etc (Nuwer, 1984, Sala, 2015).

Although satisfactory recordings of the early cortical N20 potential are possible with minimal alveolar concentrations (mac) of 0.5-1.0 using halothane or isoflurane, responses are only reliably recordable in ~90% of patients and there is a decrease in amplitude of 50-70% (Banoub et al., 2003). The newer volatile gases sevoflurane and desflurane show a less marked effect at equipotent concentration, but still produce a reduction in amplitude of ~40% of baseline (Schindler et al., 1998). The addition of nitrous oxide compounds the depressant effect of volatile anaesthetics and decreases in amplitude of the cortical potential with a >75% attenuation being seen when 60% nitrous oxide is added to 1.0mac of the halogenated gases (Pathak et al., 1989). Morphological changes of the cortical N20 potential after upper limb stimulation may also been seen at high mac levels, with a contraction of early cortical potentials into a more simplified monophasic wave, giving rise to the possibility of false positive information if the level of anaesthesia is not maintained at a constant level (Scheepstra et al., 1989). Therefore, these inhalational regimes are now regarded as *suboptimal* when recording somatosensory evoked potentials intraoperatively (Bernard et al., 1996, Porkkala et al., 1997, Sloan 2010).

There is less of an effect on cortical responses from intravenous anaesthetics, which is important because when using propofol at anaesthetic concentrations during prolonged neurosurgical cases, it allows rapid emergence for timely postoperative assessment of the patient's neurological status (Sloan, 2010). When used as a sedative hypnotic, along with opioids, as part of a total intravenous administration, there is an increase in cortical latency of ~8% and an increase in central conduction time of ~10-15%, along with a decrease in cortical amplitude of 50%; however, the resultant responses are compatible with reliable monitoring in all patients (Scheepstra et al., 1989, Banoub et al., 2003). It is now recommended that total intravenous administration is used when recording somatosensory evoked potentials intraoperatively (MacDonald, 2019), particularly as post-induction, the titration levels are kept constant, and further bolus administration is rarely required, ensuring a stable plane of anaesthesia during the time of monitoring (Sloan, 2010).

From the inception of their use intraoperatively, the tendency for halogenated gases to depress motor neurone activity, prompted studies to investigate intravenous anesthesia during transcranial motor evoked potential monitoring (Wang et al., 2009). Motor evoked recordings are known to be markedly affected by many of the halogenated anaesthetic regimes, due to the inhibitory effect of inhalational agents at the cortical axon synapse and at the level of the anterior horn cells in the spinal cord and the brainstem motor nuclei (Wang et al., 2009). All the volatile halogenated anaesthetics, as well as nitrous oxide, have been shown to produce a dose-dependent reduction in the amplitude and response rate of the resultant evoked potential signal. As the signal amplitudes are already quite small, these decreases in amplitude can limit the ability to detect significant changes intraoperatively. At a concentration level of 0.5mac effective monitoring can be achieved in 90% of neurologically normal patients receiving isoflurane, but only 55% of patients receiving sevoflurane produce responses at this level, as the concentration levels increase to 0.75-1.0mac the variability of the successive responses increases and the reliability of eliciting the responses decreases, with only 8-43% of patients on isoflurane showing responses and 0-10% of patients on sevoflurane eliciting recordable responses (Lotto et al., 2004).

Whilst propofol does also demonstrate a dose-dependent reduction in motor evoked signal amplitude, without an effect on latency (Jellinek, 1991), it has been shown repeatedly to produce a more stable and environment for monitoring, in comparison to volatile anaesthetics for all monitoring techniques (Pechstein et al., 1998, Pelosi et al., 2001, Nathan et al., 2003). Opioids have been shown to have a minimal effect on the latency and amplitude of sensory and motor evoked potentials and are an invaluable part of the total intravenous regime (Sloan, 2010). The choice of anaesthetic agents to be used intraoperatively must take into consideration the issues of the patient (e.g., medical issues), the intraoperative modalities being employed, any specific requirements of the surgery being undertaken and the pre-existing neural dysfunction that may make neurophysiological monitoring more difficult. The use of Propofol and Remifentanil as a total intravenous administration has overcome many of these issues and is now part of the routine surgical, anaesthetic, and neurophysiological protocol (Banoub et al., 2003, Sloan, 2010).

3.5 Conclusion

Despite the development and implementation of these sophisticated multi-modality intraoperative monitoring and mapping techniques (Figure 15) that can be recorded and analysed to assess the functional integrity of the brainstem pathways and nuclei, posterior fossa surgery still has high morbidity associated with it (Sala et al., 2007, Sala et al., 2015, Slotty et al., 2017). The rational integration and combined use of these different neurophysiological techniques allows the most reliable and timely evaluation for the functional integrity of some of the numerous brainstem structures and pathways to provide the best idea of “what is going” on in the brainstem.

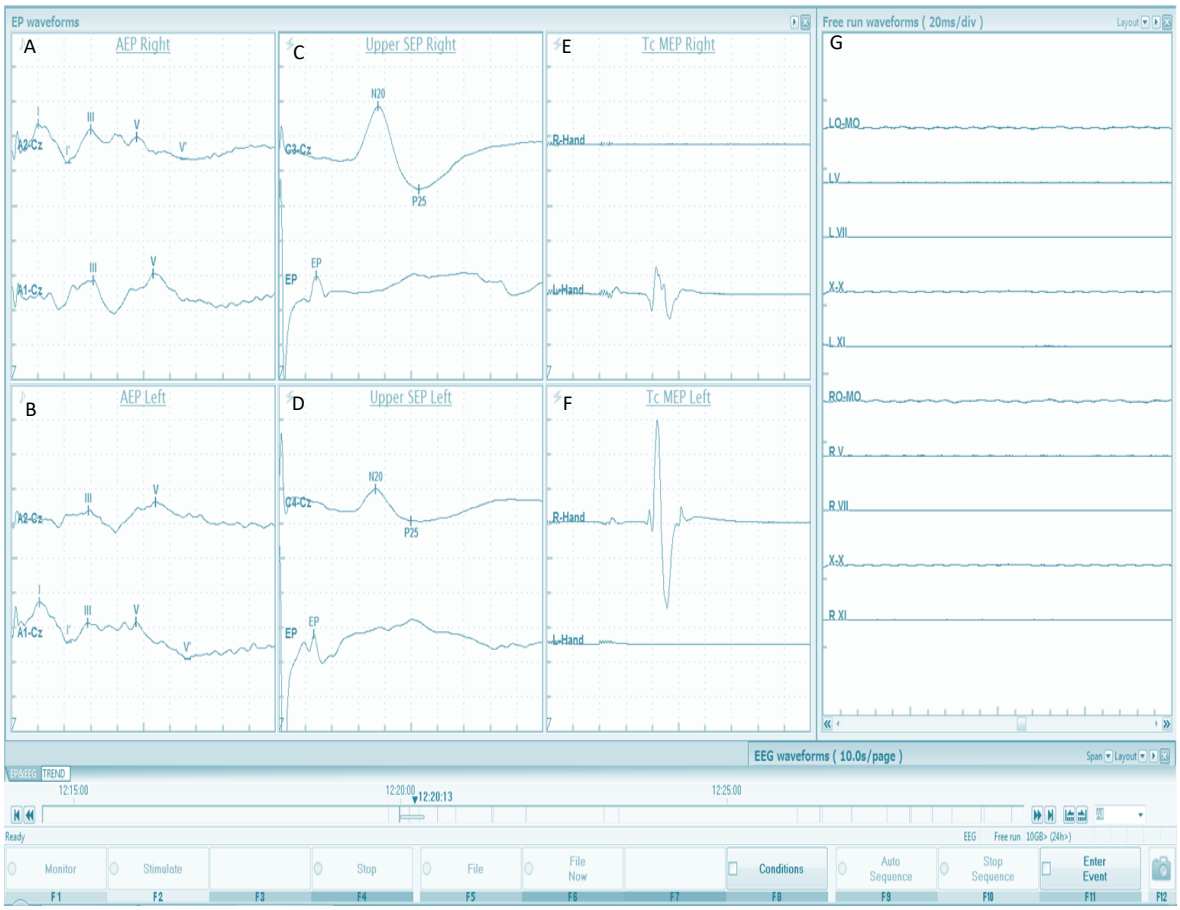


Figure 15: Multi-modal intraoperative monitoring.
‘Screen snap shot’ Showing (A) right BAEP (B) and Left BAEP and upper limb SEPs from the (C) the right median nerve recorded from erbs point and the contralateral scalp and (D) the responses from the left median nerve. The TcMEP responses from the left hand after right sided cranial electrical stimulation (E) and the responses from the right hand after stimulation of the left scalp (F). Free-running EMG responses from the cranial nerves (G).

However, the brainstem contains numerous neurons and intricate circuits within the neural structures that control oculomotor and vestibular function, and any disruption along these pathways, from the cervicomedullary to mesodiencephalic junction, can cause specific disorders of eye movement when they are damaged (Lee et al., 2018). Monitoring and mapping of these ascending vestibulo-ocular pathways is currently not available and because of this internuclear ophthalmoplegia, and other disturbances of oculomotor control and coordination are most likely to remain a nonpreventable surgical complication (Deletis et al., 2000, Sala et al., 2007); with postoperative oculomotor deficits likely to occur frequently (Indaram et al., 2017, Peeler, 2017).

In order to be able to bring neurophysiological monitoring of these pathways into the operating theatre, there needs to be a detailed understanding of the neural structures that are involved in the generation and control of oculomotor and vestibular pathways. The ability to record intraoperatively the potentials that are generated within these pathways, would potentially enable the detection of deficits to be identified at an early and reversible stage and subsequently averted.

Chapter 4.

Vestibular nerve anatomy and physiology.

4.1 Overview of the vestibular system

One universal task for living creatures is keeping track of their orientation relative to the outside world. Mobile creatures also have the added task of adjusting their orientation in response to self-generated or externally imposed movements. There are three main systems that are required to be working collaboratively for safe ambulation to occur and to avoid falls, which represents a major health risk.

- The proprioceptive nerves that detect joint position and pressure within the somatosensory system detect those parts of the body that are in contact with the environment, such as the feet contacting the floor.

-The visual cues that are received are important in orientating a person's position in space and are used when assessing movement of both the individual and the environment.

- The vestibular system is critical for the detection of movement and maintaining balance.

Balance is particularly important for bipedal species, such as humans. The activities that are commonly engaged in during everyday lives are all characterised by complex multidimensional motion patterns that dynamically and simultaneously stimulate the vestibular apparatus (Cullen, 2016). The vestibular system encodes the motion of the head relative to the outside world.

The vestibular system is made up of three component parts: a peripheral sensory apparatus, central processing systems and a mechanism that controls motor output. The peripheral apparatus consists of various sensors that are able to detect motion and send information to the central nervous system (the vestibular nucleus complex and cerebellum) about the heads angular velocity and linear acceleration. The central nervous system then processes these signals, and in combination with other sensory information, estimates the orientation of the head and body. The output of the central vestibular system projects to the extraocular muscles and the spinal cord to serve various important reflexes. The vestibulospinal reflex generates compensatory movements of the body in order to maintain head stability and postural control, and thereby prevent falls. The vestibulocollic reflex stabilises the head by controlling the muscles in the neck and the vestibulo-ocular reflex generates eye movements that enables clear vision when the head is in motion (Figure 16).

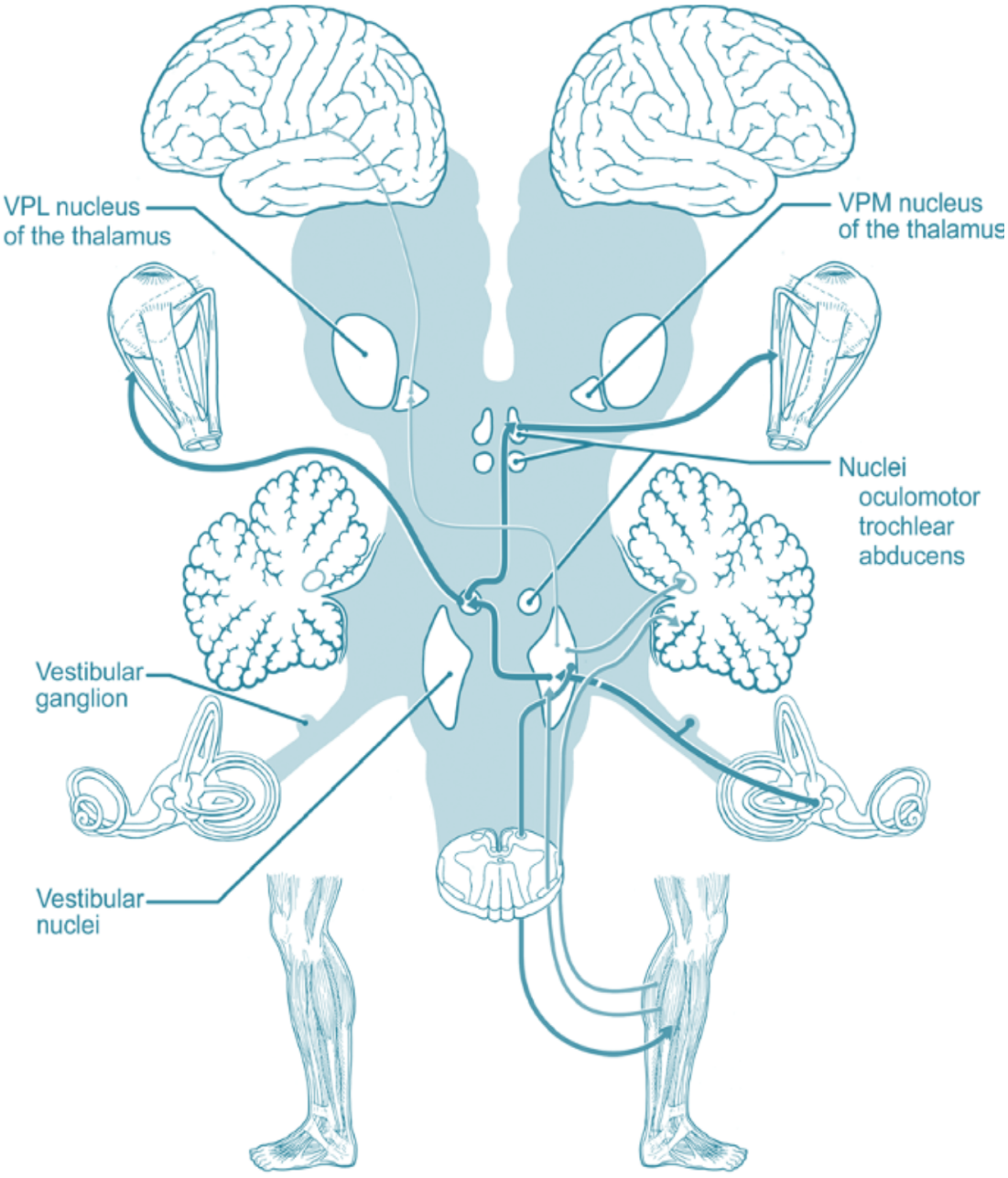


Figure 16: Overview of the vestibular system.
Ipsilateral muscle tone, cerebellar responses and ocular motility are influenced by the peripheral and central processing centres that control motor output (adapted from Fife, 2010).

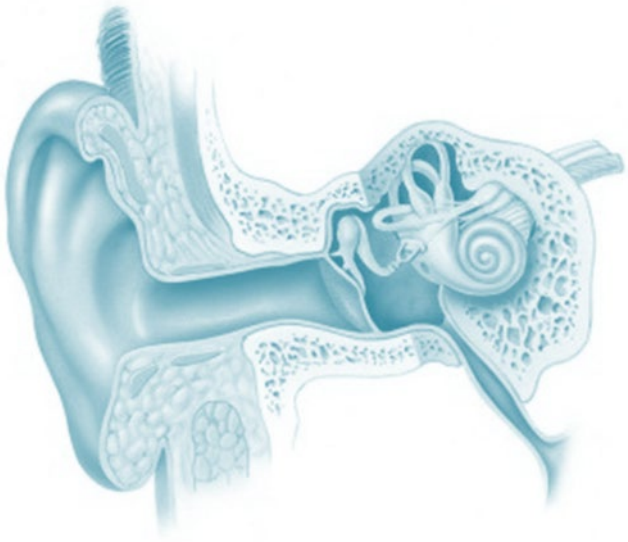
4.2 Peripheral vestibular labyrinth

Small structures located in the inner ear make up the vestibular apparatus that detect the gravitational forces on the body and the motion of the head (Figure 17A). The otolith organs and the semi-circular canals are the vestibular end-organs, and their function is to monitor the linear acceleration and rotational movement of the head and the orientation of the head to gravity respectively. The peripheral vestibular labyrinth in the inner ear contains the specialised sensory receptors and is formed from, and is located within, the petrous portion of the temporal bone. The labyrinth is composed of two distinct components, the bony and membranous labyrinths.

The bony labyrinth is the surrounding shell which protects the vestibular sensory structures and inside of this is the membranous labyrinth, which consists of connecting tubes and prominences which are the specialised regions of the vestibular receptors. The bony labyrinth is lined with periosteum and consists of the three semicircular canals, the cochlea and the vestibule (Figure 17B) and is filled with perilymphatic fluid. The vestibule is the central chamber of the bony labyrinth and is ~4mm in size, situated medially to the middle ear with the cochlea anteriorly and the semicircular canals posteriorly. The elliptical recess, spherical recess and the cochlear recess are embedded in the medial wall of the vestibule and house the utricle, saccule and the basal end of the cochlear duct respectively. Each of these depressions has small perforations called a macula cribosa, which transmit the nerves to each of the structures.

The membranous labyrinth is an epithelium-formed series of spaces that is suspended within the bony labyrinth via small connective tissue fibres and surrounded by perilymph but is filled with a different fluid called endolymph. The major constituents of the membranous labyrinth are the utricle, saccule and the semicircular canals.

A



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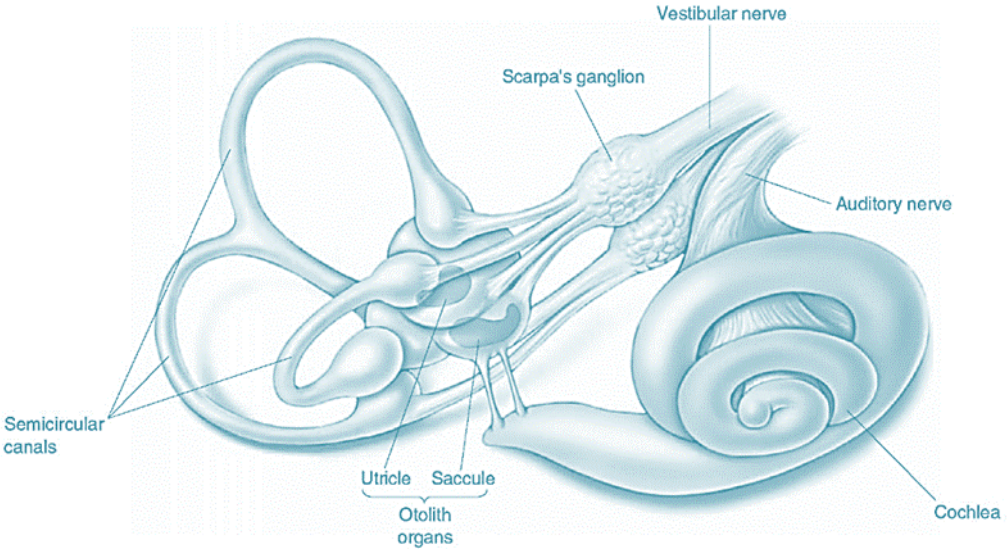


Figure 17: The peripheral vestibular labyrinth
The position of the labyrinth apparatus within the petrous temporal bone (A) and the outline of the bony labyrinth (B). (adapted from Fife, 2010).

4.3 Labyrinthine fluid

In the intact vestibular system, the water-tight membrane-lined sac that is the membranous labyrinth is suspended in the perilymph within the bony labyrinth, and as such the fluid within the bony labyrinth does not come into contact with the perilymph. In a simple form, the membranous labyrinth can be conceptualised as a complex, fluid filled balloon that is inflated in a container that is filled by a different fluid (Khan and Chang, 2013).

The difference in these ionic concentrations is important, as both are involved in the normal functioning of the vestibular system. Ionic cells within the stria vascularis actively secrete endolymph and are electrogenic, and the difference in ionic composition of the endolymph from the perilymph, where there is a higher concentration of potassium and a lower concentration of sodium, produces a voltage difference of +80mV between the endolymph and perilymph (Smith et al., 1965).

4.4 Vestibular receptor cells

Like those of the cochlea, the vestibular receptor cells are referred to as hair cells, with the hair cells being modified microvilli called stereocilia. These cells that change the mechanical energy of fluid motion into electrical signals that are conveyed as vestibular nerve action potentials. The basic structure of the hair cell includes a cell body and cilia at the apical end and the nerve endings at the basolateral end (Figure 18). Each hair cell has a single large eccentrically placed kinocilium -which is non-motile - arising from the apical region of the cell and approximately 70-100 hexagonally arranged stereocilia. The stereocilia contain a core of actin filaments that are organised in rows, with the tallest being closed to the kinocilium, decreasing in size to the shortest stereocilia that are furthest for the kinocilium (Flock and Orman, 1969).

Within the vestibular labyrinth there are two morphologically distinct types of hair cell that provide different information to the vestibular system (Figure 18). Based on the regularity of firing, the vestibular afferent nerves can be classified further into *regular* and *irregular* firing fibres; that is determined by the inter-spike intervals of their action potentials (McPherson, 2018).

Type I hair cells are shaped like flasks, with each of the cells surrounded by a large calyceal afferent nerve terminal ending, and these cell types are associated with *irregular* afferents that are thick/medium sized. These fibres that have phasic-tonic response dynamics with a high variability of resting discharge and have a high sensitivity to head rotation and linear forces. Type II hair cells, which make up the majority of the hair cells, are cylindrical and have a more simplified bouton nerve ending that synapse onto *regular* afferents. These regular firing fibres are medium/thin sized axons and have tonic response dynamics and a low sensitivity to head rotation or linear forces. As the irregular nerve fibres are larger, they therefore have a higher conduction velocity and are more efficient at transmitting excitatory information, making them more sensitive to transient motion (Goldberg, 2000).

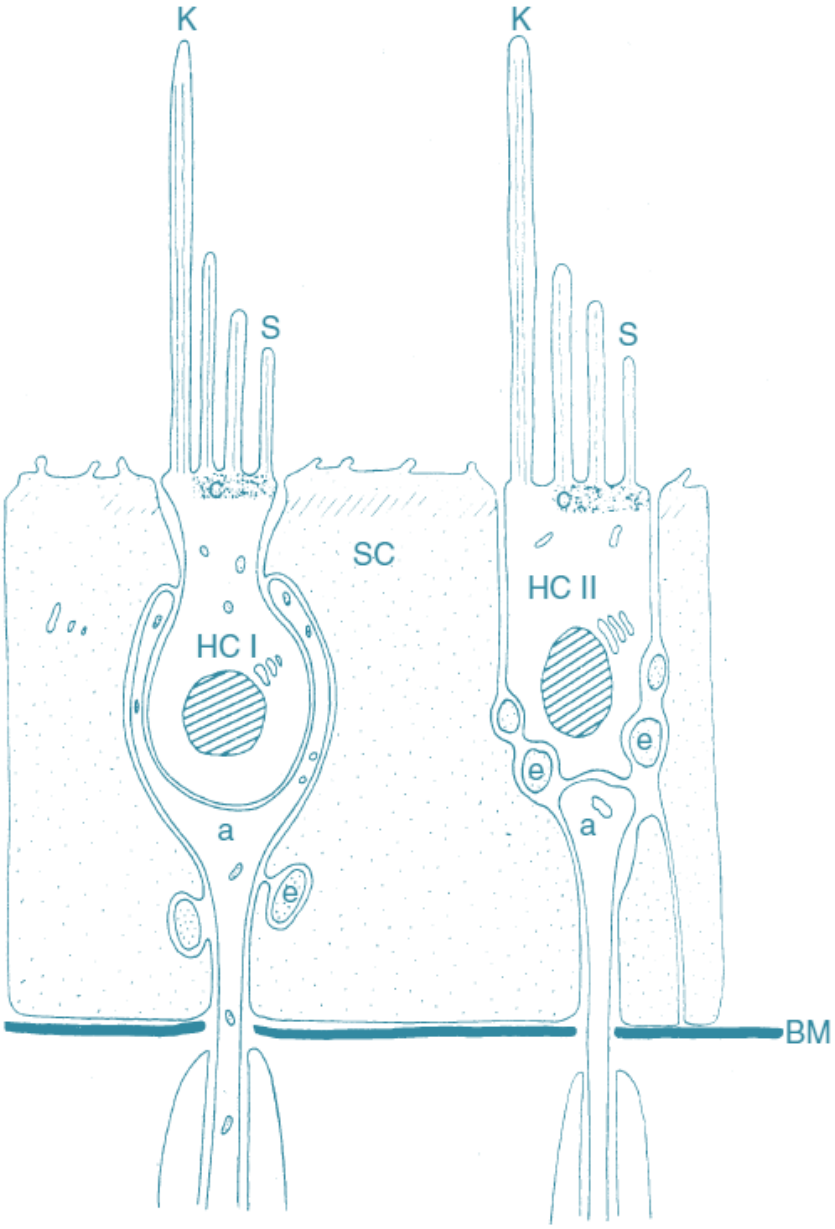


Figure 18: Hair cells of the labyrinth.
The different morphology of type I and type II receptor cells is illustrated. K = *kinocilia,* S = *stereocilia,* a = *afferent nerve*, e = *efferent nerve*, SC= *supporting cell* BM = *basal membrane.* (adapted from Baloh and Honrubia, 1990).

Each stereocillia arises from the cuticular plate, a region of dense actin that is located on the apical end of the hair cell. The cuticular plate acts like an elastic spring and returns the stereocillia to an upright position after it has been displaced. The asymmetrical organisation of the apex of hair cells leads to a polarisation of each hair cell, and the resultant process of transducing the mechanical forces exerted on the hair cells into electrical signals, is dependent on the unique features that are at the tips of the hair cells.

The hair cells are bathed in endolymph that has a high concentration of potassium, which makes it highly electrically positive - relative to the inside of the hair cell (potential difference ~ 135mV). This large electrochemical driving force causes the rapid entry of potassium from the endolymph into the hairs whenever the channels are opened. These mechanically sensitive potassium cells that are located on the tips of the hair cells are attached to protein filaments, called tip links that are connected to the side of the taller adjacent stereocilium (Assad et al., 1991). These tip links enable the stereocilia to act in concert and produce action potential discharge rates that are proportional to the degree of deflection of the stereocilia.

Head motion that results in tilting of the stereocilia toward the kinocilium causes the tip links to mechanically open the transduction channels, leading to an influx of potassium. The resultant depolarisation of the hair cells opens voltage-gated calcium channels at the base of the hair cell which stimulates neurotransmitter (glutamate) release into the synapses, causing an increase in the afferent vestibular nerve firing rate. When the stereocilia are bent away from the kinocilium, the decrease in the tip link tension causes mechanical closure of the channel, which results in hyperpolarisation of the hair cell and closure of the calcium channels and a decrease in the neurotransmitter release and a subsequent reduction in the vestibular nerve firing rate. Therefore, each individual hair cell can detect deflection of the hairs, towards or away from the kinocilium, thereby increasing or decreasing the frequency of the action potential generation (Figure 19).

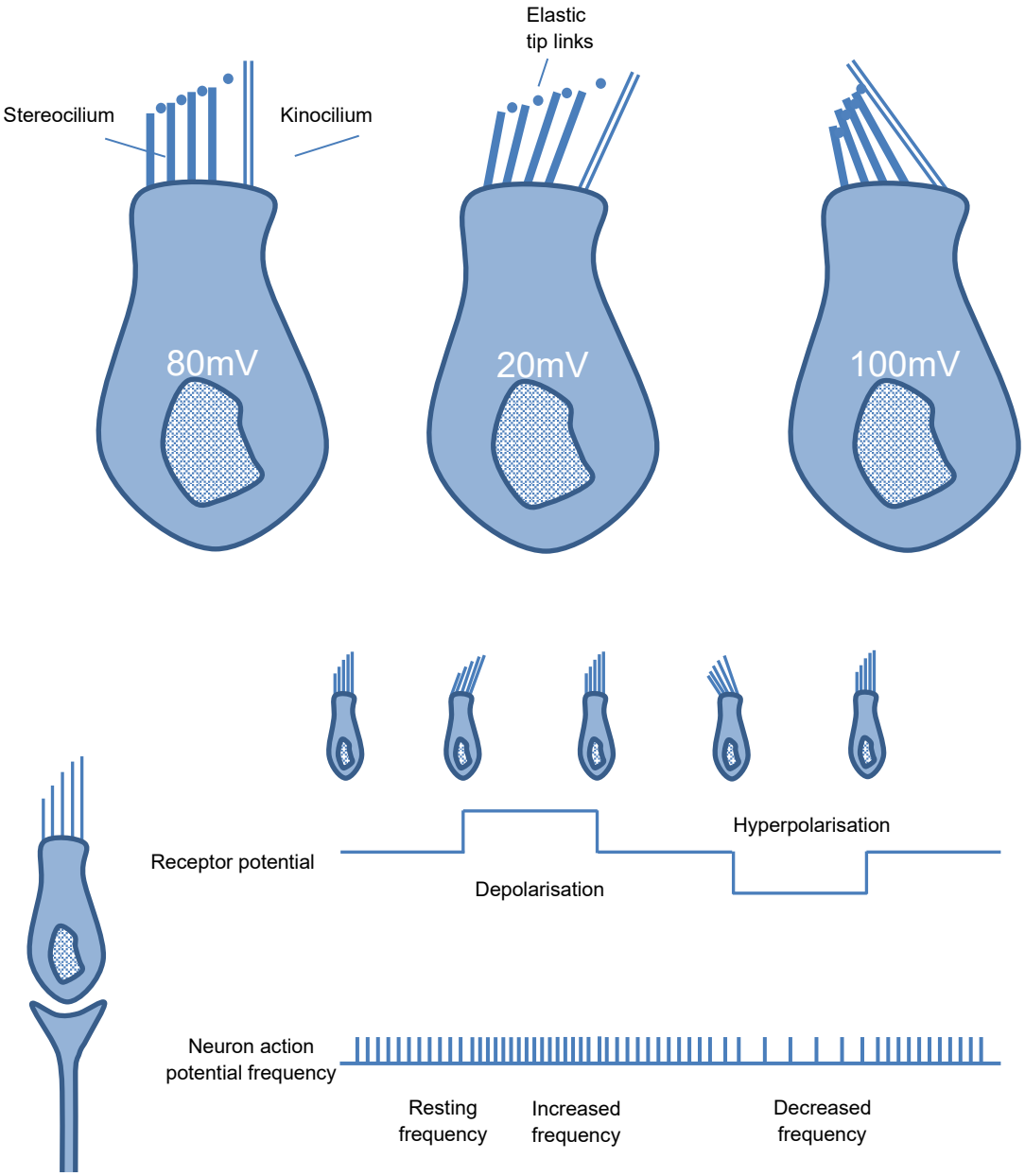


Figure 19: The effect of hair cell deflection.
Deflection of the hair cells towards the kinocilium places tension on the tip link, which opens the potassium channels and increases the neurotransmitter release with the resultant increase in the firing rate of the action potential from its baseline resting state.

4.5 Vestibular sensory epithelium

Within the vestibular apparatus there are two types of sensory epithelium, the crista ampullaris and the macula (Tascioglu, 2005). The specialised sensory epithelium within the semicircular canals is the crista ampullaris and detects angular acceleration, whilst it is the macula, within the otolithic organs, that senses the orientation of the head in space in response to linear acceleration.

4.5.1 Semicircular canals

There are three semicircular canals on each side of the head: the anterior (superior), the lateral (horizontal) and posterior (inferior). These bony canals are approximately 1mm in diameter and cover and arc of 240^{o}. Each canal has a different spatial orientation that are aligned to form a 3D coordinate system that senses angular acceleration (Figure 20). The anterior and posterior canals are in vertical positions which are almost orthogonal to each other, whilst the lateral canal makes a 25-30^{o} angle to the horizontal plane. The slightly tilted plane of the horizontal semicircular canal, in the anterodorsal plane relative to the nasooccipital plane in humans, is because when a person walks or runs the head is normally pitched downward, this so that the line of sight is directed several metres in front of the feet.

The nearly orthogonal orientation of these angular accelerometers means that any turning movement of the head will be detected by some combination of stimulation of these canals. There are 3 important spatial arrangements that characterise the alignment of the semicircular canals

1. Each canal plane in each labyrinth is positioned perpendicularly to the other canal planes.
2. Paired planes of the semicircular between the labyrinths conform very closely to each other with the *six individual* semicircular canals becoming *three co-planar* pairs i.e. right and left lateral, right posterior and left anterior, and right anterior and left posterior.
3. The planes of the semicircular canals are closely related to the planes of the extraocular muscles which allows relatively simple connection between the sensory neurons (related to the individual semicircular canal) and the motor output neurones (related to the individual ocular muscles).

On one end of each canal there is a dilation, which measure approximately 2mm in diameter, called the ampulla, the ampulla of each canal opens into the vestibule. Within each ampulla are the individual hair cells and their supporting cells, these are embedded in a saddle-shaped neuroepithelial ridge called the crista.

The crista extends across the ampulla at a right angle and is attached at its base and its roof to the walls of the ampulla, creating a fluid tight seal that prevents endolymph from freely passing; together these two structures form the crista ampullaris (McLaren and Hillman, 1979). The crista ampullaris is coated by the cupula, which is a gelatinous mucopolysaccharide substance that has the same specific gravity density as endolymph. It is this gelatinous mass through which the hair cells are embedded. Type I hair cells are concentrated on the crest of the crista, whilst type II hair cells are more numerous in the peripheral sloping areas. The cupula is therefore an important component of the vestibular apparatus, as it is displacement of this structure that is responsible for the deflection of the underlying stereocilia, and which leads to neural stimulation.

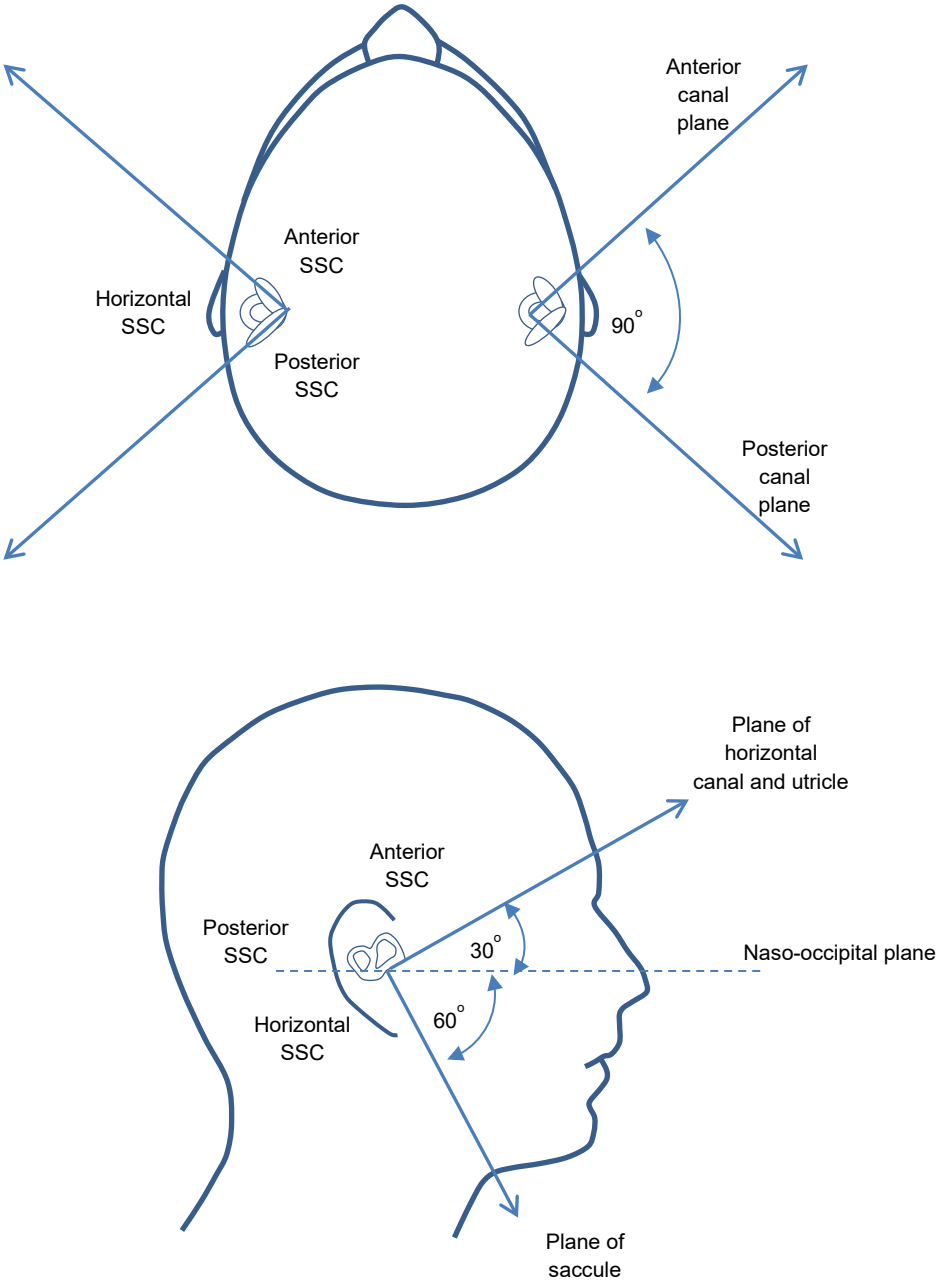


Figure 20: Spatial orientation of the semicircular canals.
The horizontal canals are in the same plane at right angles to each other and act as a functional pair. The horizontal semicircular canal and the utricle are at an angle relative to the naso-occipital plane. The anterior canal and the opposite posterior canal are in parallel pairs and act as a functional pair.

Rotational acceleration causes endolymph motion that displaces the cupula and therefore bends the hair cells in the opposite direction of the rotation. This results in the opening of the ion channels and the depolarisation of the hair cell which increases the firing of its afferent fibres. When the rotational velocity of the head becomes constant the cupula returns to an upright position and the membrane potential of the cell normalises. Rotational deceleration of the head results in cupula displacement in the same direction as the head movement and closes the ion channels of the hair cell which causes it to become hyperpolarised and results in a reduction in afferent nerve firing (Figure 21).

Due to its elasticity the cupula sways or bulges to and fro with movement of endolymph. As well as the population of hair cells being distributed differently within the crista, the actual kinocilium of each hair cell is also orientated differently across each of the canals, and this influences the excitation and inhibition of the hair cells and their vestibular nerve fibres. In the crista ampullaris of the lateral canal the kinocilium is located closest to the utricle; therefore, turning of the head to the right for example causes excitation of the right lateral canal crista and inhibition of its counterpart on the left. The anterior and posterior canals are different again since the kinocilia are on the canal side; therefore, ampullopetal endolymph flow (toward the ampulla) in the long arm of the semicircular canal is excitatory in lateral canals but inhibitory in the anterior and posterior canals.

The semicircular canals provide sensory input about the heads velocity and enables the vestibulo-ocular reflex to generate eye movements that match the velocity of the heads movement; with the result that the eyes remain still in space to enable a clear image on the retina whilst the head is in motion. The firing of the vestibular nerve is proportional to the common range of frequencies (0.5-7Hz) that the head commonly moves. The semicircular canals and their output can therefore be considered as ‘rate sensors’.

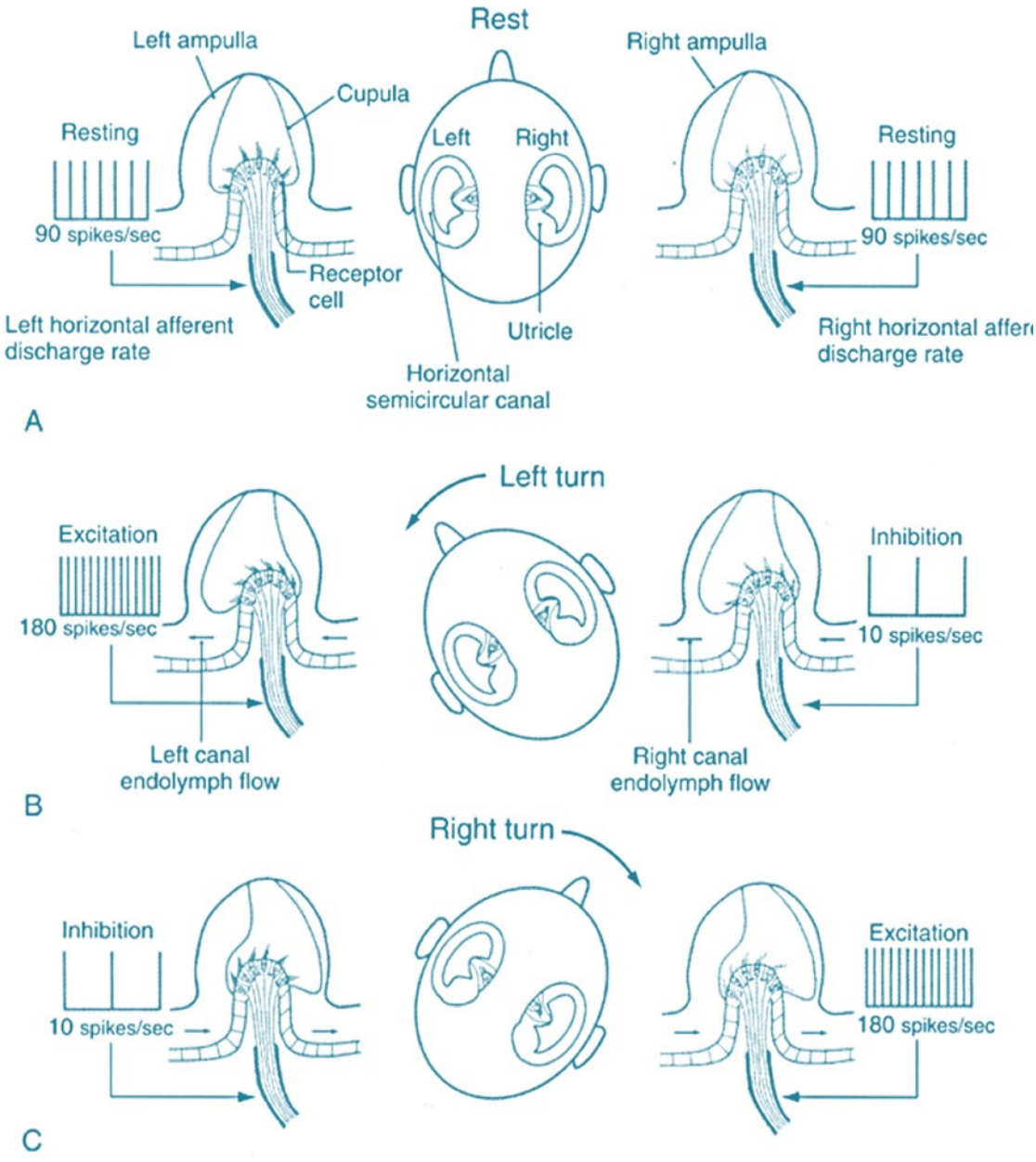


Figure 21: Responses from the horizontal semicircular canal.

A) The firing rates of the right and left afferents are equivalent when there is no detection of head rotation

B) When the head is turned to the left the endolymph pressure in the left horizontal canal deflects the stereocilia towards the kinocilia causing excitation of the afferent fibres, whilst on the right side the stereocilia are deflected away from the kinocilia causing inhibition.

C) Turning the head to the right causes excitation of the right afferent fibre and inhibition of the left afferent nerve (adapted from Dickman, 2018)

4.5.2 Otolithic organs: The saccule and utricle

The sensory epithelia of the otolith organs are flattened structures that measure less the 1mm in diameter, called maculae that are analogous to the cirista of the semicircular canals. There are two otolithic organs, the utricle and the saccule (Figure 22), each of which is a dilation of the membranous labyrinth and located with the vestibule (Lindeman, 1973).

The macula contains the stereocilia hair cells which project into a gelatinous matrix that contains thousands of calcium carbonate crystals (otoconia) (Walther et al., 2014). The otoconia are produced by the supporting cells of the sensory epithelium and although they are small (5-7 um in diameter) they have a specific gravity of ~2.7g/ml, which is denser in comparison to the endolymph (~1g/ml). The difference in the specific density of the macula provides an inertial mass that allows the sensory hair cells to be stimulated by linear acceleration. As the otoliths are in endolymph, and the specific gravity of the otolithic membrane is the same as that of endolymph, without the addition of otoconia to the otolithic membrane, the otolithic organs would not be able to detect the acceleration. So, when a linear acceleration occurs, the otolithic membrane, with its attached otoconia, lags behind that of the hair cells, which then transmit a shearing force to the underlying hair cells embedded within the otolithic membrane.

Therefore, because of this difference, the macula can also be considered a bio-accelerometer, as it can react to linear acceleration due to three key components: a heavy mass load (the calcium carbonate), a sensor (the hair cell) and an elastic connection between the two (the matrix of the otolithic membrane) (Ross et al., 1987).

The otoconical membrane contains otoconia and a gelatinous layer that is composed of otogelin and is made up of two distinct layers; the outer layer of otoconia that is enmeshed in an organic layer and an underlying gelatinous membrane that contains glycosaminoglcans and glycoprotein. Within the gelatinous layer itself there are two parts, a dense outer layer that contains highly cross-linked fibrils which support the otoconia and a layer that is organised as a loose meshwork of columns with elastic properties. It is these layers that distribute the inertial forces of the otoconia equally to the underlying sensory epithelia and the top-heavy mass of calcium carbonate crystals, on top of the elastic intermediary structures, means that the macula receptors are very sensitivity in transmitting the detected linear accelerations to the stereocilia bundles in the sensory epithelium (Ross et al., 1987).

The otoliths register the forces that are related to linear acceleration and respond to both linear head motion and static tilt, with respect to the gravitational axis. Similar to the semicircular canals the macula are arranged so that they are able to respond to motion in all three dimensions, but unlike the semicircular canals, which have one sensory organ for each possible axis of angular motion, the otoliths only have two sensory organs for each of the three axes of motion. The saccular macula is hook shaped and lies predominantly in a vertical position on the medial wall of the vestibule in a spherical recess inferior to the utricular macula which is oval shaped and lies almost orthogonal to the saccular macula in a horizontal position.

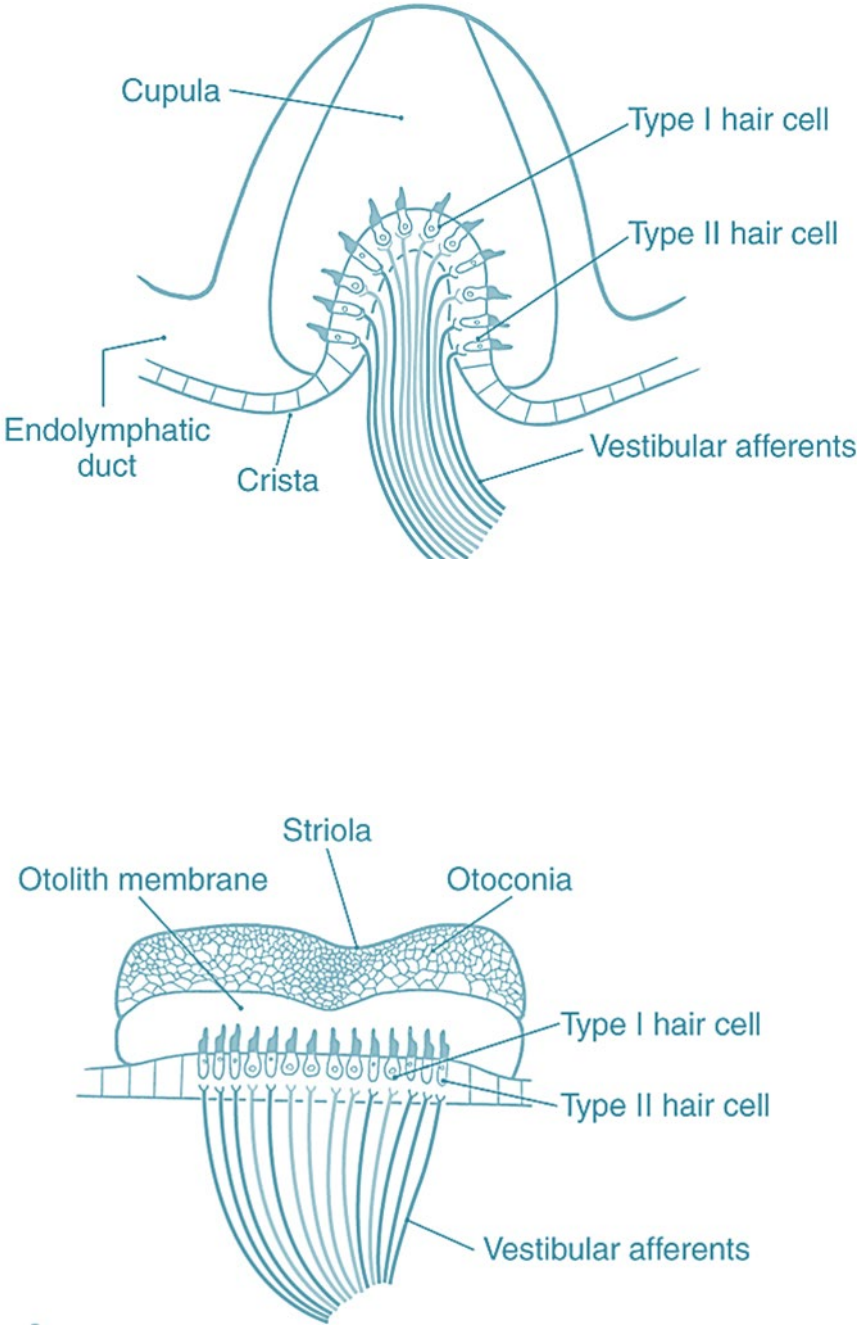


Figure 22: The otolith organs.
Hair cells in the cristae (top) and maula (bottom) are displaced when the endolymph is displaced by movement of the head (adapted from Dickman, 2018).

Within the macula there is a curvilinear dividing line, called the striola, this area is a line of thinning in the utricle and in the saccule this line is an area of thickening. This line separates the hair cell bundles that are in one orientation from those in another. The calyx units of the type I hair cells are seen close to the central zone of the striola with unbranched axons giving rise to a single calyx ending. Bouton units are seen in the peripheral and extrastriolar zones of the macula with axons providing bouton endings to several type II hair cells. In the utricle the kinocilia and stereocilia are orientated towards the striola whereas they are orientated away from the striola in the saccule.

Because of the differing distribution of hair cells in different directions there are various patterns of hair cell stimulation that may occur, depending on the degree to which the head is tilted. Every linear translation will stimulate one group of hair cells causing excitation, whilst inhibiting another group and at the same time having no net effect on another group of hair cell receptors. This enables representation of linear movement from each macula, and an integrated representation which includes information from the contralateral otolith organs too. Due to the position of the macula in the saccule, this is the vestibular sense organ which responds to vertical linear acceleration in the plane that it is aligned (which is the occipito-caudal axis and the anterior-posterior axis) - and is most associated with the detection of gravity - whist the utricle can sense acceleration laterally across the interaural axis as well as anterior-posteriorly and is more suited to the detection of horizontal linear acceleration. The end result is that because of their shape and spatial position, the macula is able to respond to linear motion in *all* directions and is able to relay accurate information about the head position to the central nervous system.

4.6 Vestibular ganglion and nerve

The vestibular primary afferents from the vestibular end organs consist largely of the central processes of bipolar afferent neurons, with their cell bodies within the superior and inferior ganglia, which is known collectively as the vestibular (Scarpa's) ganglion, with their peripheral processes forming the post-synaptic connection to the hair cells. The vestibular nerve central processes are in the in the internal auditory meatus which is within the petrous portion of the temporal bone. The vestibular nerve is subdivided into the superior and inferior vestibular nerve. The superior vestibular nerve innervates the cristae of the anterior and lateral semi-circular canals, the macula of the utricle and the anterosuperior part of the saccular macular, whereas the main part of the saccular macula and the cristae of the posterior semi-circular canal is innervated by the inferior vestibular nerve (Naito et al., 1995).

Axons from the inferior and superior divisions of the vestibular ganglion merge, to form the vestibular nerve, and combine with the more anteriorly located cochlear nerve to form the vestibulocochlear nerve. This nerve passes, along with the facial nerve, nervus intermedius (a branch of the facial nerve that carries sensation) and labyrinth artery, through the petrous temporal bone, via the internal auditory canal (that averages 8mm in length and 3.7mm in diameter), to the posterior fossa. The nerve fibres pass the cerebellopontine angle to enter the brainstem at the

pontomedullary junction, where at this point the vestibular nerve diverges from the cochlear nerve (Figure 23).

The vestibular nerve contains between 15,000-25,000 fibres, although there can be wide variability between individuals, particularly as this population of fibres decreases with age (Lopez et al., 1997).The nerve enters the brainstem at the cerebellopontine angle where it proceeds posteromedially through the upper medulla to synapse in the medial, lateral, inferior and superior vestibular nuclei that are grouped together along the floor of the fourth ventricle from the mid pons, at the level of the abducens nuclei, to the mid medulla, at the level of the inferior olive. At the point that the vestibular nerve enters the medulla, the fibres from the semicircular canals are located rostrally and the fibres from the macula and saccule are located in the caudal part of the nerve. The afferent fibres of the superior branch of the vestibular nerve synapse in the superior, medial and lateral vestibular nuclei. The fibres from the inferior vestibular nerve synapse in the medial, lateral and inferior vestibular nuclei (Naito et al., 1995).

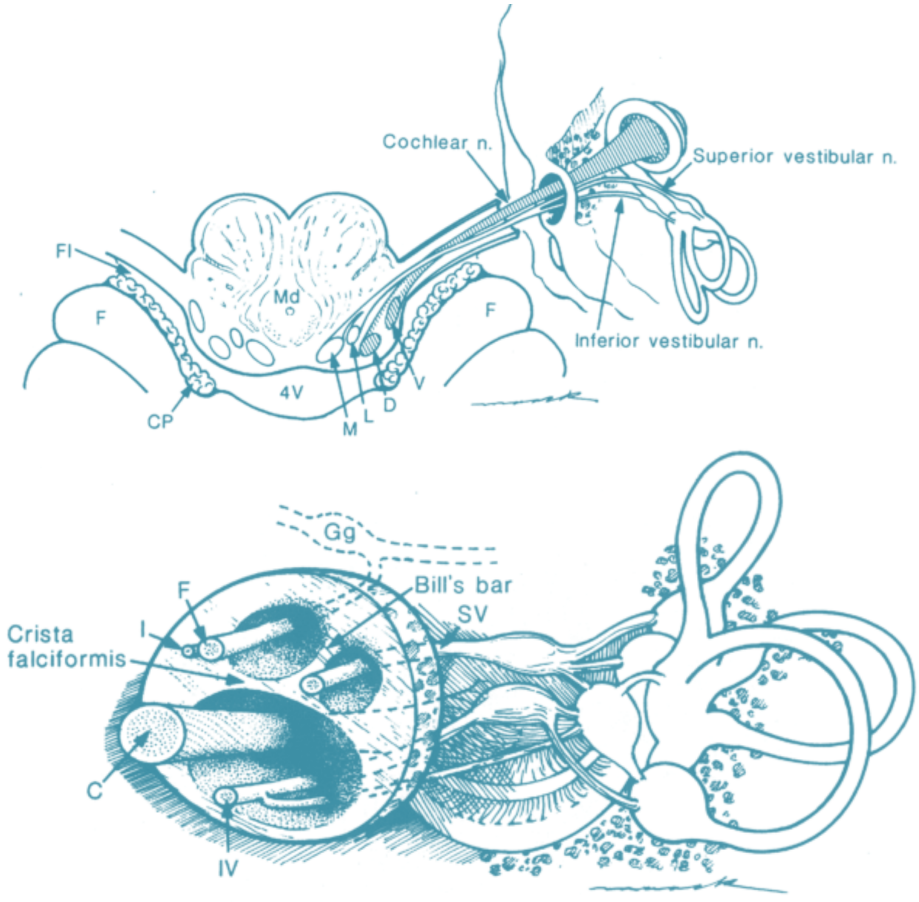


Figure 23: Formation of the vestibular and cochlea nerve.
Axons from the superior vestibular (SV) and inferior vestibular (IV) nerve converge with the cochlea branch (C) of the eighth nerve and pass together, along with the facial nerve (F) and nervous intermedius (I) into the brainstem. From here they separate to with the vestibular terminating in the medial (M), lateral (L), dorsal (D) and ventral (V) nuclei in the medulla (Md). (Adapted from Binder et al., 2010).

4.7 Vestibular afferent inputs and nuclear complex

The vestibular nuclear complex is the primary processor of vestibular input and extends from the rostral medulla to the caudal pons in two major columns, the medial vestibular nucleus is the largest of the four nuclei and makes up the medial column; the superior, lateral and inferior vestibular nuclei make up the lateral column (Figure 24). Each vestibular nucleus differs in its cytoarchitecture and its connection between the afferent and efferent fibres.

The processing of the information, obtained from positional and movement related inputs, takes place in the nuclei and controls the postural and visual reflexes that are mediated by the efferent targets such as the oculomotor nuclei, the spinal cord and the contralateral vestibular nuclei.

The medial vestibular (Schwalbe) nucleus is located caudal to the superior vestibular nucleus, although its morphologic appearance is not always distinct. This nucleus receives the small diameter afferents from the crista ampullaris of the lateral semicircular ducts, with the ascending fibres travelling via the medial longitudinal fasciculus to the motor nucleus of the extraocular muscles, where they mediate the vestibulo-ocular reflex. Projections that descend bilaterally via the vestibulospinal tract to the spinal cord from this nucleus also control the vestibular spinal reflex to modulate coordination of head and neck motion.

The superior vestibular (Bechterew) nucleus is located in the rostral floor of the fourth ventricle where it is bordered by the middle cerebral peduncle (brachium pontis) superiorly and the restiform body laterally. Much of the input to this nucleus is received from afferent inputs from the crista ampullaris of the superior and posterior semicircular ducts and, similar to the medial vestibular nucleus, sends efferent fibres via the ipsilateral and contralateral ascending portion of the medial longitudinal fasciculus on each side, to the extraocular muscles to modulate the vestibulo-ocular reflex.

The lateral vestibular (Deiter) nucleus has the largest cell bodies of the vestibular nuclei and also receives afferent input from the crista ampulla, as well as the macula and the vestibulo-cerebellum. The efferent projections from this nucleus join the lateral vestibular tract on the ipsilateral spinal cord. This tract coordinates the reflex tone in the muscles of the trunk and proximal extensors via the vestibular spinal reflex to maintain balance and posture.

Afferent information from the macula of the utricle and saccule are received in the inferior (descending) vestibular nucleus, where they project to the other three vestibular nuclei, as well as the cerebellum and spinal cord. The inferior vestibular nucleus is caudal to the lateral nucleus and blends morphologically with the adjacent medial vestibular nucleus (Curthoys and Halmagyi, 1999).

Axons from the vestibular nuclei then spread widely throughout the brainstem to form secondary pathways of the vestibular pathway and the vestibular nuclei between the two sides of the brainstem are connected by a complex system of commissures (Barmack, 2003). The commissures, which are mutually inhibitory, allow information to be shared between the two sides

of the brainstem, although the connections between the superior and medial nuclei appear to be most prominent. Many of the commissural fibres are formed from reciprocal connections from the analogous contralateral nucleus, and so these pathways enable the information from pairs of corresponding semicircular canals and otolithic organs to be compared. The majority of the vestibule-vestibular cells contain inhibitory neurotransmitters, such as gamma aminobutyric acid (GABA) and glycine, although excitatory amino acids may also be involved.

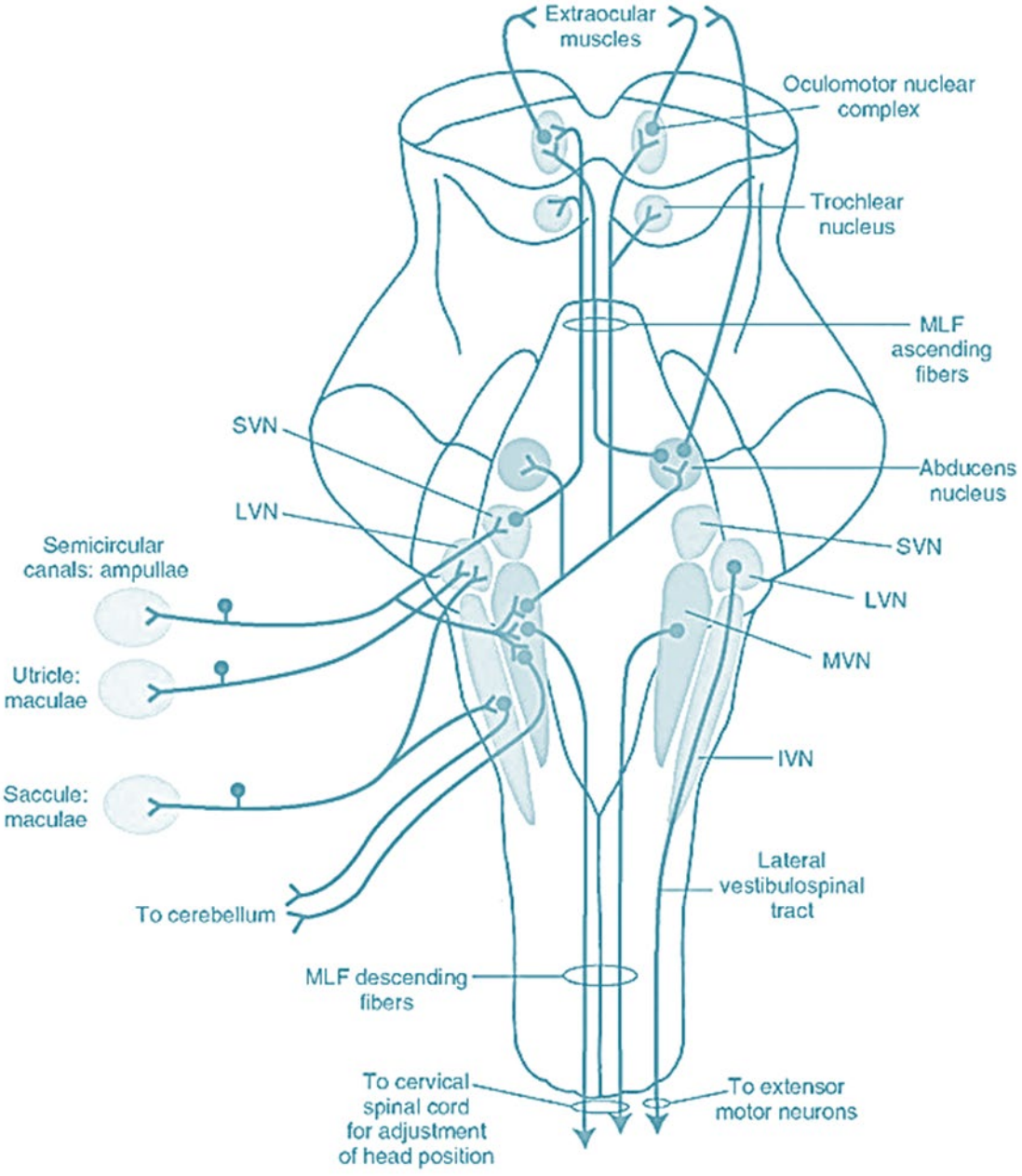


Figure 24: The vestibular nuclei.
SVN = superior vestibular nucleus; LVN = lateral vestibular nucleus; MVN = medial vestibular nucleus; IVN = inferior vestibular nucleus.

4.8 Efferent vestibular system

When considering the physiology of hair cells and their transduction of physical movement to neuronal impulses, it is important to also consider the efferent connections from the vestibular nuclei that control the vestibular sensory nerve fibres and hair cells. Approximately 2% of the vestibular nerve axons are efferent, and these small neurones of the vestibular efferent system arises from a cluster of cell bodies on the posterolateral border of the abducens nucleus, medial to the superior vestibular nucleus, referred to as Group E (Goldberg and Fernandez, 1980).

These fibres project with cochlear efferent fibres within the vestibulocochlear nerve (olivo-cochlear bundle) both ipsilaterally and contralaterally to the vestibular nerve roots of both labyrinths. It is here that these efferent fibres synapse with the calciform endings of the type I and II hair cells in the five vestibular end organs and release acetylcholine and other neurotransmitters, such as adenosine triphosphate (ATP), peptides, opioids and GABA. This results in responses that regulate the sensitivity of the hair cells, which therefore modulates the dynamic range of these afferent fibres to acceleration.

4.9 Medial longitudinal fasciculus

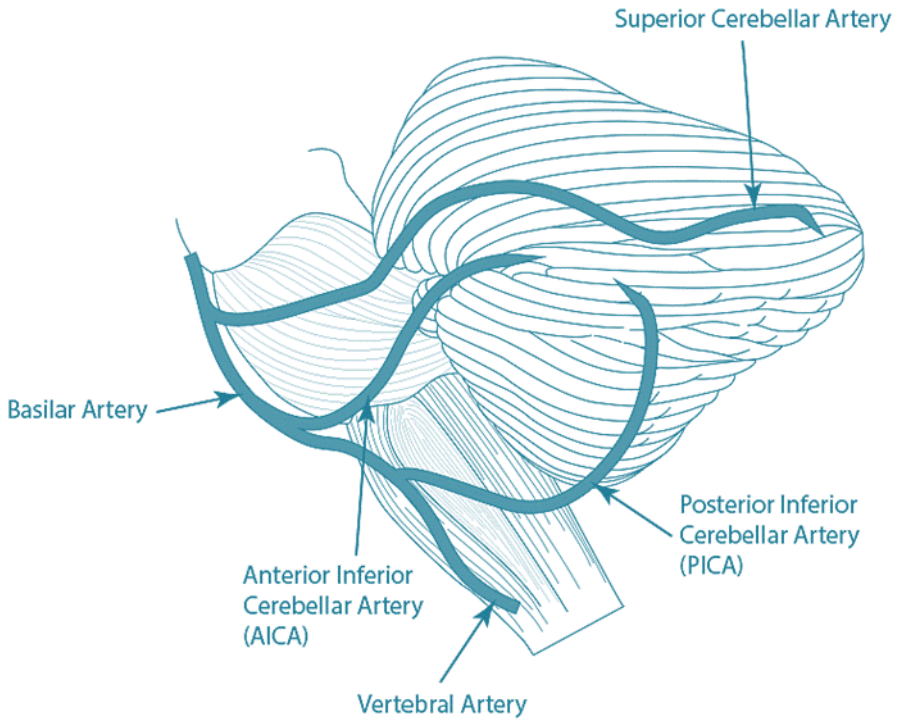
The medial longitudinal fasciculus (MLF) consists of a pair of white matter tracts within the brainstem which lie close to the midline (Figure 24). The MLF lies ventral to the cerebral aqueduct in the midbrain and ventral to the fourth ventricle in the pons and medulla. The ascending and descending fibres, along with excitatory and inhibitory decussating interneurones within the MLF connect several brainstem nuclei together to coordinate the activity of agonist and antagonist muscles during vertical, horizontal, and torsional eye movements (Virgo and Plant, 2017).

4.10 Vascular supply

It is the labyrinthine (internal auditory) artery, which is usually a branch of the anterior inferior cerebellar artery, but can also arise from other vessels, such as the basilar artery (24%) – or the superior cerebellar artery (16%) - that supplies the vestibular end organs (Mazzoni, 1990). After entering the inner ear via the internal auditory meatus, the labyrinthine artery divides into the anterior vestibular artery and the common cochlear artery (Figure 25). The anterior vestibular artery supplies the utricle and a small proportion of the saccule as well and the anterior and lateral semicircular canals. The common cochlear artery branches into the cochlear artery and the vestibulo-cochlear artery, which divides further into the cochlear ramus and the posterior vestibular artery. The posterior vestibular artery runs along the medial aspect of the vestibule that supplies the posterior semicircular canal ampulla and the larger proportion of the saccule (Mazzoni, 1990).

The labyrinth has no collateral anastomotic network, which makes it highly susceptible to ischaemia, and only 15 seconds of reduced blood flow is sufficient to abolish excitability of the vestibulocochlear nerve (Perlman et al., 1959).

A



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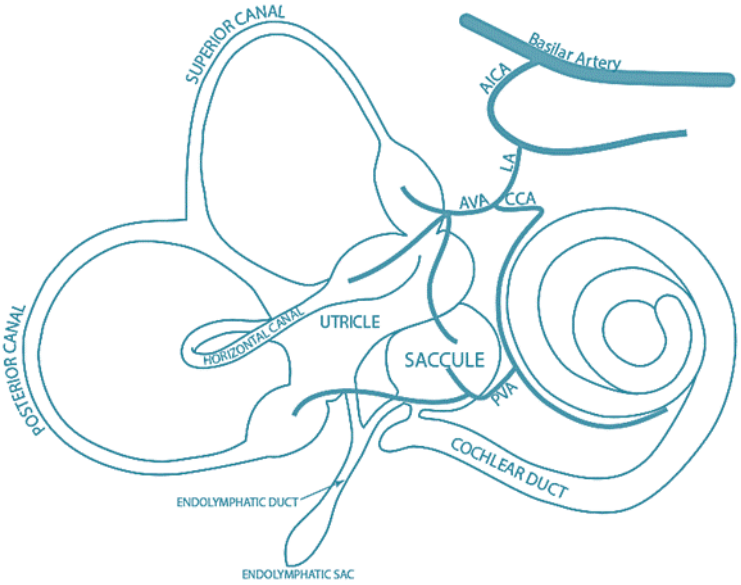

Figure 25: Arterial vascular supply of the brainstem (panel A) and vestibular system (panel B).

The posterior cochlear vein collects the blood from the superior and lateral semicircular canal ampulla and from the utricle, whilst the anterior vestibular cochlear vein drains the blood from the saccule and the posterior semicircular canal ampulla. The blood from the semicircular canals also drains via the vestibular aqueduct vein to drain into the lateral venous sinus. The posterior and anterior cochlear veins join to form the vestibulo-cochlear vein, which converges with the common modiolar vein to converge with the cochlear aqueduct vein to ultimately drain into the inferior petrosal sinus.

4.11 Vestibular reflexes

4.11.1 Vestibulospinal reflexes

There is likely a family of vestibulospinal reflexes that are activated, depending on the nature of the motion and the strategy chosen by the vestibular system, to maintain the balance and posture post-perturbation (Fetter, 2000). Linear and angular head acceleration causes various patterns of activation in the neck and body muscles to maintain stabilisation of the head and control of an erect upright body stance relative to gravity. The different reflexes can be defined according to their timing (static and dynamic and tonic) and by their sensory input (canal vs otolith).

Acceleration of the head causes reflex responses in the upper and lower limbs with extension of the limbs in the in the direction of the acceleration and contraction of the limbs contralateral to the direction of movement (Fetter, 2000). This vestibulospinal reflex prevents falling and maintains the body's posture via three major pathways: the lateral vestibulospinal tract; the reticulospinal tract; and the medial vestibulospinal tract.

The vestibulospinal reflex involves many complex connections that have integrated input from the macula, crista ampullaris, visual system and the axial and limb muscles. The medial vestibulospinal tract originates in the medial, inferior, and lateral nuclei and descends in the medial longitudinal fasciculus bilaterally to innervate postural muscles as far as the mid-thoracic region.

The lateral vestibulospinal is however the main pathway (Figure 26), with its tracts originating in the lateral vestibular nucleus; efferent vestibular signals, in response to the input from the macula of otolithic organs, are conveyed to the lateral vestibular tract. From here they project in the ipsilateral ventral funiculus of the spinal cord to neurons at all spinal levels. This reflex generates increased muscle tone in the ipsilateral trunk and proximal limb extensor muscles via monosynaptic activation - and decreased muscle tone in the ipsilateral flexor muscles and contralateral proximal extensors via disynaptic inhibition - when linear and angular head acceleration is detected (Fetter, 2000).

Detection of angular rotation by the semicircular ducts is transmitted to the medial vestibular nucleus and on to the medial vestibulospinal tract where bilateral descending fibres terminate on the motor neurones of the cervical spinal cord to activate cervical mediated axial muscles that coordinate head and neck motion.

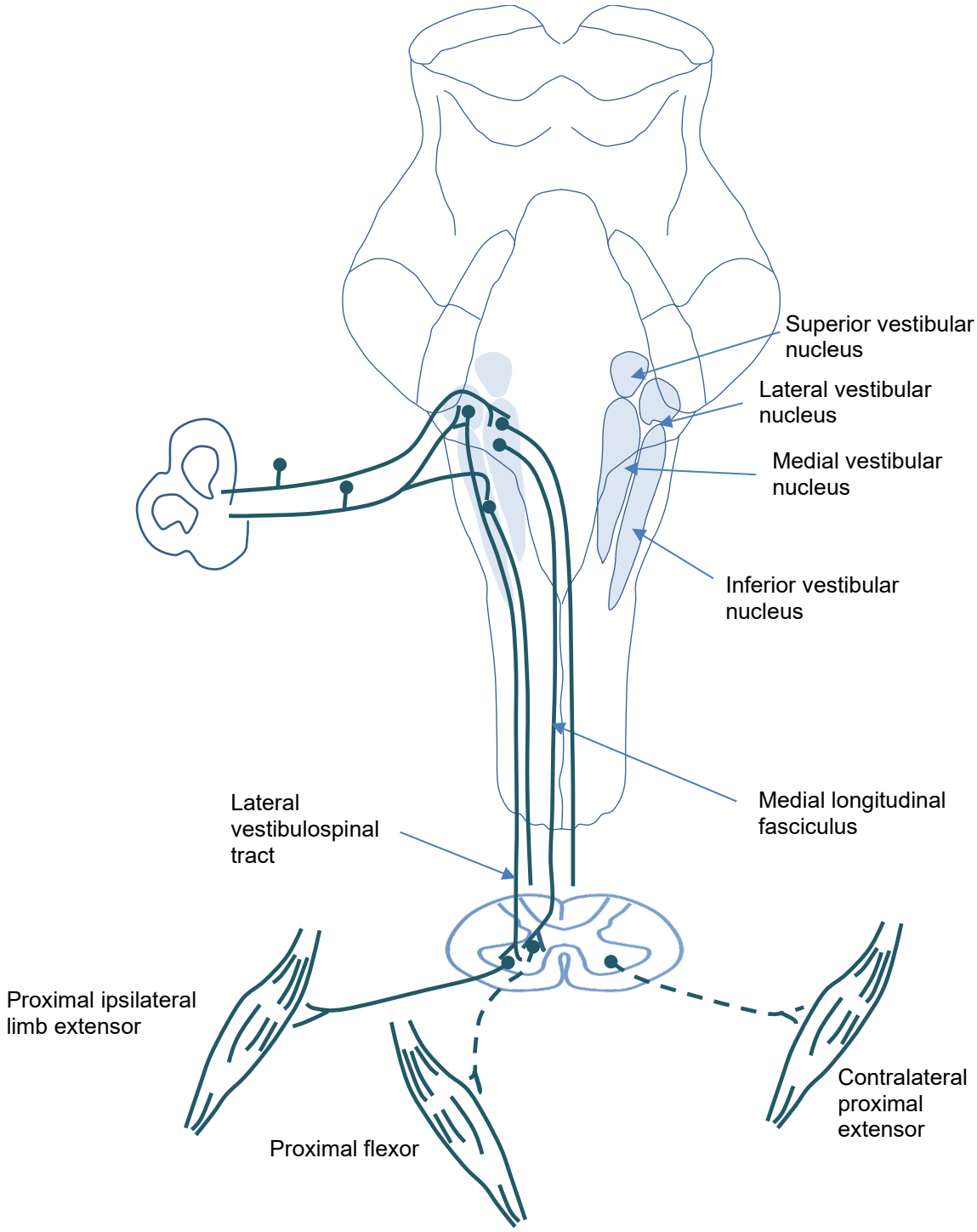

Figure 26: The vestibulospinal reflex.
Angular acceleration of the head is detected in the macula. Inter-nuclei connections convey the signal, via the medial longitudinal fasciculus bilaterally, to the spinal cord. Innervation of the ipsilateral extensors and flexors and contralateral extensors via the lateral vestibulospinal pathway prevent falling.

4.11.2 Vestibulocollic reflex

Stabilisation of the neck in space is mediated by the vestibulocollic reflex, which has direct and indirect connections between the medial and lateral vestibulospinal tracts and the motoneurons of the extensor, flexor and rotator muscles of the neck (Colebatch and Rothwell, 2004). This reflex can be recorded electrophysiologically as a transient, short-latency inhibition in the tonically activated sternocleidomastoid muscle after vestibular stimulation and can be used clinically to assess the function and integrity of the disynaptic vestibular pathway that mediates this reflex (Papathanasiou et al., 2014). Specifically, this pathway involves activation of the saccule, the inferior portion of the vestibular nerve (Figure 27), the lateral and descending vestibular nuclei within the brainstem that connect to the medial vestibulo spinal tract to output via the motonucleus of cranial nerve XI through the spinal accessory nerve to the ipsilateral sternocleidomastoid muscle (Papathanasiou et al., 2014).

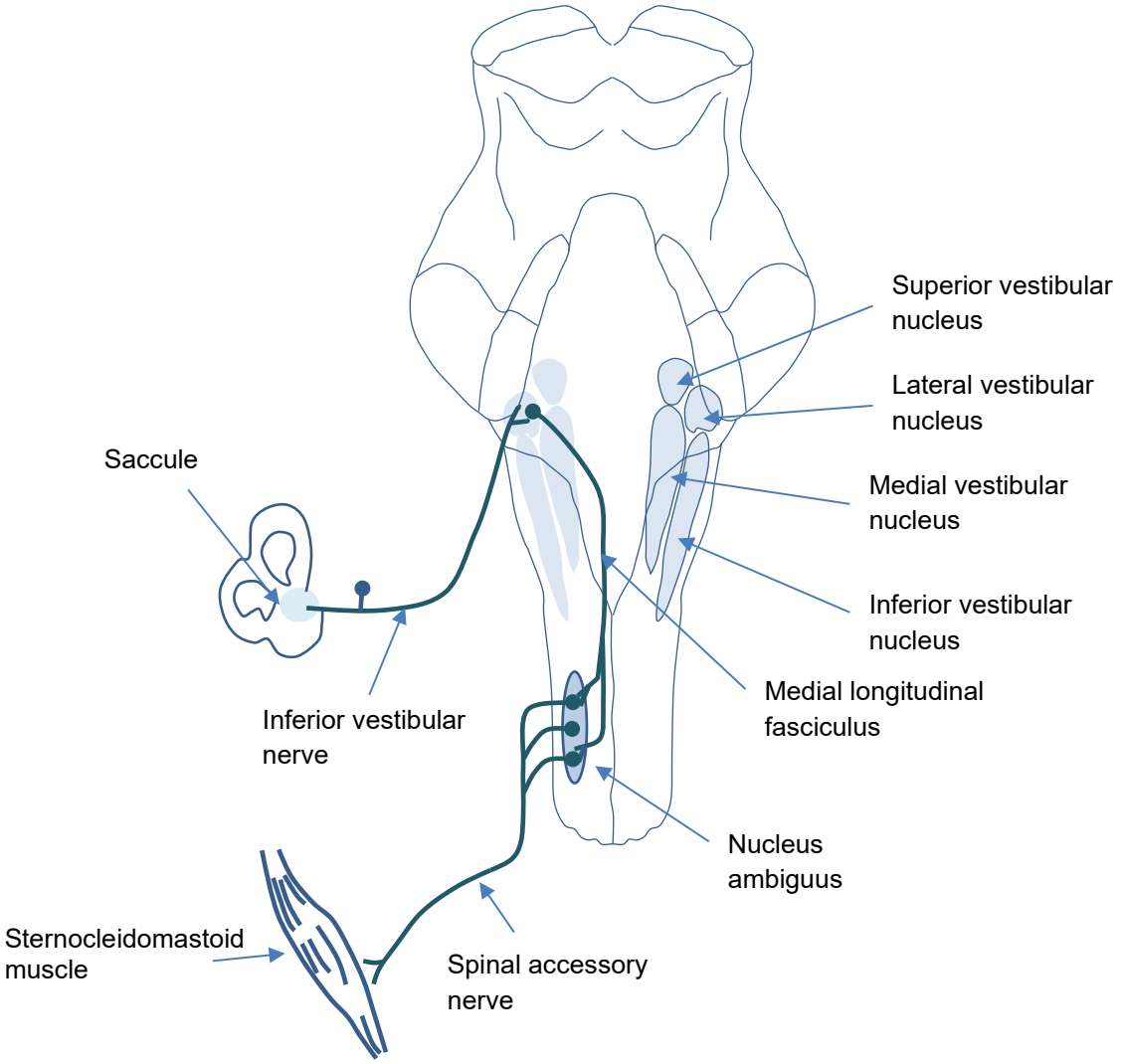

Figure 27: The vestibulocollic reflex.
Saccular activation is transmitted along the inferior vestibular nerve to the medial vestibulo spinal tract, via the lateral vestibular nucleus. From here the nerve action potential is conveyed via the nucleus ambiguus to innervate the ipsilateral sternocleidomastoid muscle. This pathway stabilises the neck and head.

4.11.3 Vestibulo-ocular reflex

Movement of the eyes contrary to head movement is controlled via the vestibulo-ocular reflex to ensure a stable line of sight in space and retinal images during head rotation (Cullen, 2016). It involves a three-neuron reflex arc from the peripheral end organ via the superior vestibular nerve (Figure 28), to the vestibular nuclei and then to the extraocular muscles, via the medial longitudinal fasciculus, to produce conjugate eye movement in the direction that is opposite to head turning following extraocular muscle excitation (Weber et al., 2012).

All of the vestibular nuclei make some contribution to the vestibulo-ocular reflex, although it is the superior vestibular nucleus that makes the most substantial contribution. The axons from the superior vestibular nucleus travel ipsilaterally in the medial longitudinal fasciculus and the axons from the other nuclei project bilaterally.

The semicircular canals make preferential connections to the motoneurones that in the cranial nerve nuclei that control particular eye muscles. The horizontal canals drive the motoneurones of the abducens nucleus that innervates the contralateral lateral rectus muscle and the oculomotor nucleus that innervates the ipsilateral medial rectus muscle, whilst also producing the appropriate amount of inhibition to the antagonist muscles. The vertical horizontal canals drive the motoneurones of the oculomotor nucleus that innervate the superior and inferior recti and obliques muscles.

When the head is turned to the right, the endolymph flow in the ampulla of the semicircular ducts will cause deflection of the cupula to the left, causing a depolarisation of the hair cells on the right and a simultaneous hyperpolarisation of the hair cells on the left. The resultant increase in the firing frequency along the afferent fibres of the right vestibular nerve conveys the signals to the ipsilateral superior and medial vestibular nuclei. Excitatory impulses are then transmitted, via the medial longitudinal fasciculus, to the right oculomotor nuclei and via the ascending tract of the lateral vestibular nucleus to the left abducens nuclei. This then causes ipsilateral medial rectus and contralateral lateral rectus contraction the produces eye movement to the left (opposite to the side that the head turned).

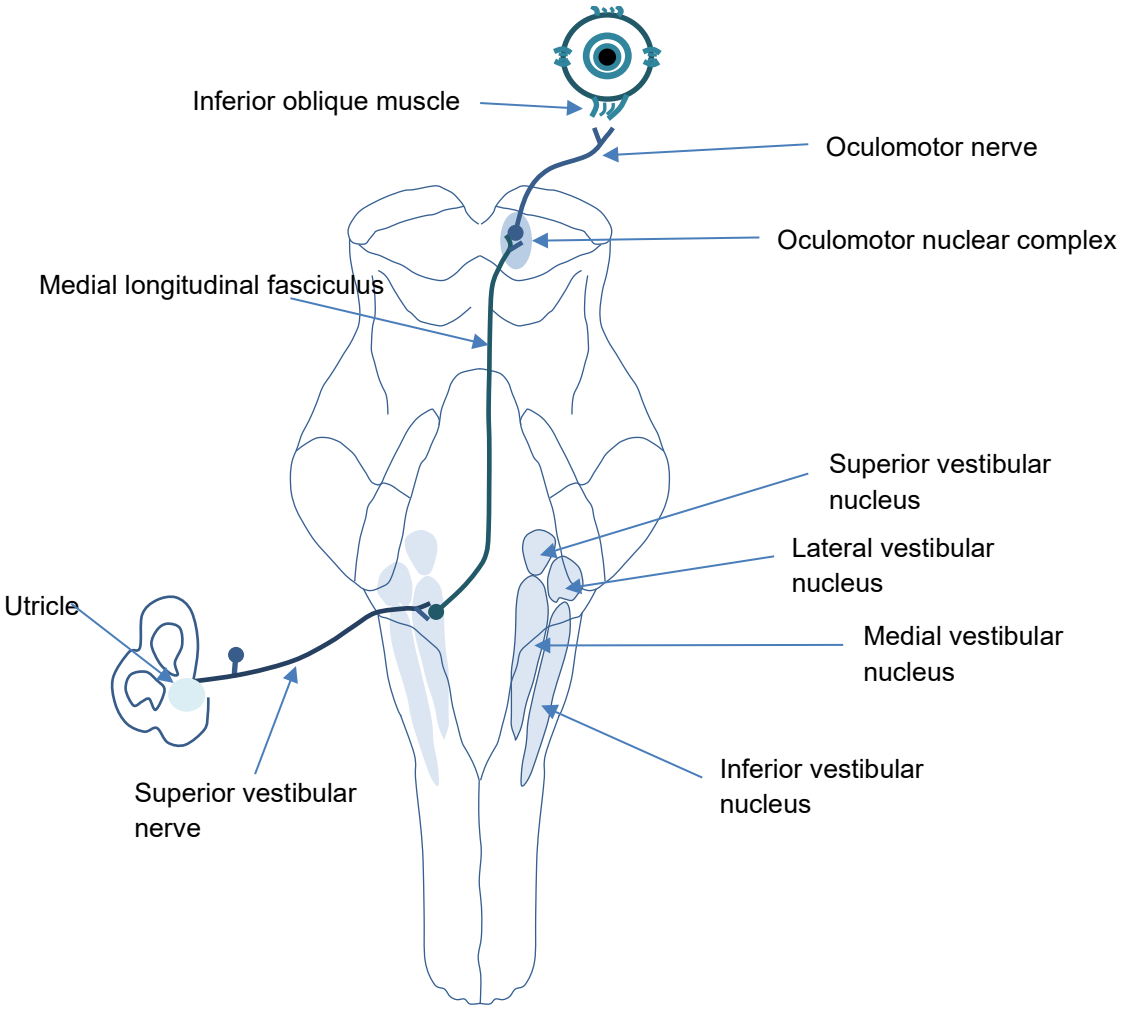

Figure 28: The vestibulo-ocular reflex.
Activation of the utricle is transmitted via the superior vestibular nerve to the medial vestibular nucleus. The nerve pulse ascends and crosses the mid-line via the medial longitudinal fasciculus to activate the oculomotor nucleus. This produces conjugate eye movement in the direction that is opposite to head turning that stabilises visual input.

In clinical practice, the ocular vestibular evoked myogenic potential that is recorded from the inferior oblique muscle, contralateral to the side of stimulation, describes the excitation of the translational vestibulo-ocular reflex (Bogle, 2018). The ocular vestibular evoked myogenic potential can be used to aid diagnosis, test the extent of a lesion and monitor disease progression or recovery in a wide variety of peripheral and central diseases of varying aetiology (Weber and Rosengren, 2015, Taylor et al., 2020).

Chapter 5.

Ocular vestibular evoked myogenic potentials (oVEMPs) and their clinical application.

5.1 Introduction

The vestibular system contributes to the optimisation of visual acuity during head movements, the enhancement of balance control and the detection of self-motion and orientation relative to gravity.

Although a brief head movement would be one of the obvious choices of stimulation to evoke the vestibular reflex, these are not practical and are not used in routine clinical practice (Welgampola, 2008). However, in recent years it has been shown that in addition to head acceleration, other stimulation protocols can be used to excite the vestibular afferents (Rosengren et al., 2005, Todd et al., 2007), and the introduction of vestibular evoked myogenic potentials (VEMPs) into clinical practice has now been realised as a safe and simple means of assessing otolithic function (Fife et al., 2017). With stimulation delivered above vestibular threshold a vestibulo-ocular reflex can be elicited, even in the absence of head movement (Isawaki, 2007).

5.2 Overview of ocular vestibular evoked myogenic potentials (oVEMPs)

The ocular vestibular evoked myogenic potential (oVEMP) consists of a series of waves that originate from the extraocular muscles in response to stimulation of the vestibular apparatus (Figure 29) (Dlugaiczyk, 2017). These recorded potentials arise from a form of *sensory crosstalk*; in that the sensory receptor is activated by energies that arise from a stimulus other than that to which it is most sensitive (Curthoys, 2010). The stimulation of the vestibular organs can be via air conducted sound (ACS), bone vibration (BV) or galvanic current stimulation (GVS) (Curthoys, 2010), and the subsequent recordings reflect the synchronous change in muscle activity to these abrupt stimuli (Fife et al., 2017).

With unilateral stimulation, a clear response can be recorded with a surface electrode placed beneath the contralateral eye, which suggests excitation of the predominantly contralateral projection of the translational vestibulo-ocular reflex (Dlugaiczyk, 2017).

Evidence from human and animal models show that the reflex circuitry that is involved in the generation of the oVEMP is a crossed three-neuron reflex (Figure 29). The utricle is the primary end organ responsible for the generation of the oVEMP (Curthoys and Manzari, 2011), and from this peripheral end organ the action potential travels through the superior branch of the vestibular nerve (cnVIII) to terminate in Scarpa's ganglion within the vestibular nucleus. From here the secondary vestibular neurons cross the midline and ascend through the medial longitudinal fasciculus (MLF) to the contralateral motor nucleus of the oculomotor nucleus (cnIII). The final pathway is to the contralateral inferior oblique muscle with the resulting recording being excitation of the inferior oblique muscle (Rosengren et al., 2010).

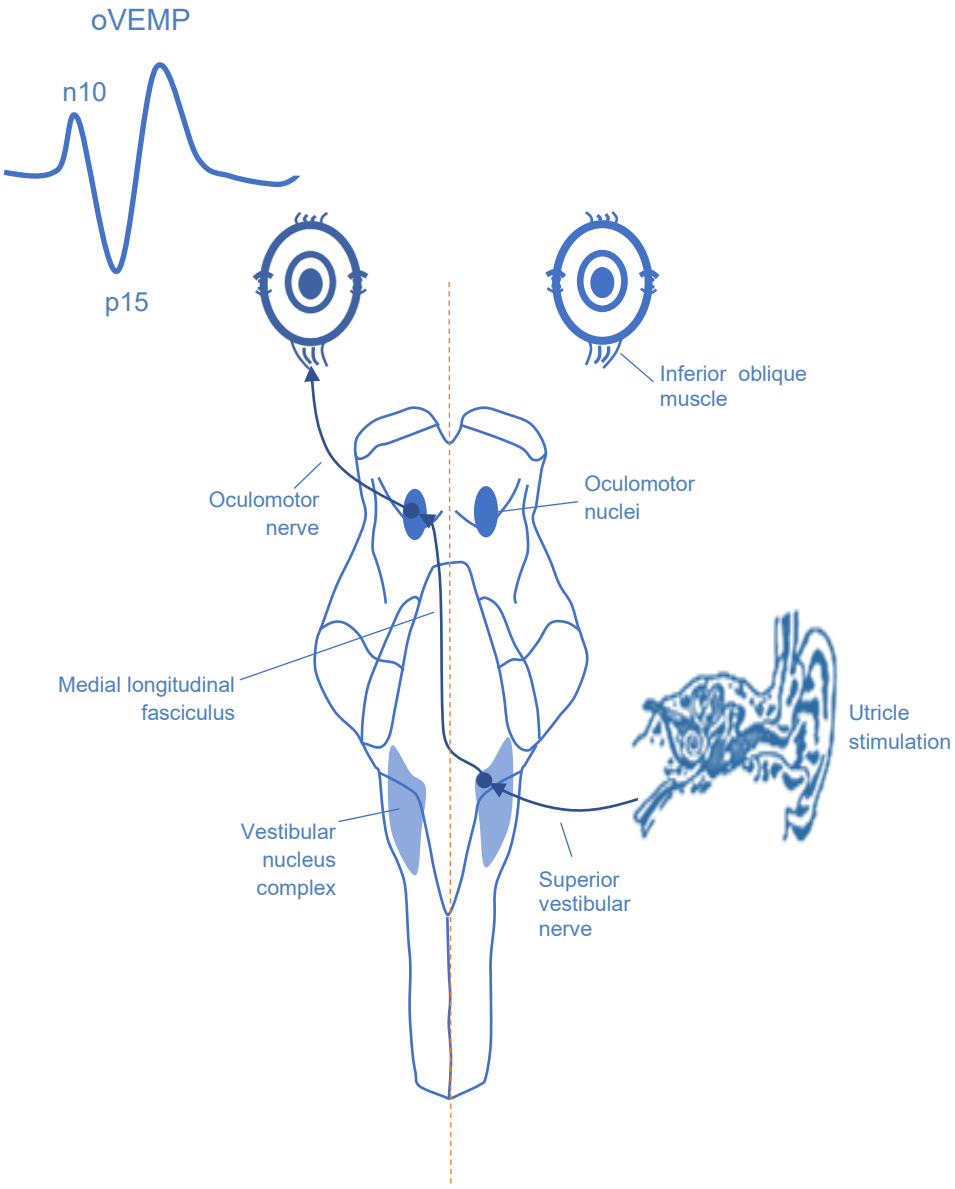

Figure 29: The neural pathway of the ocular vestibular evoked myogenic potential. After stimulation of the utricle, the action potential travels to the vestibular nucleus complex via the superior vestibular nerve. From here the potential ascends and crosses the mid-line via the medial longitudinal fasciculus to terminate in the contralateral oculomotor (cnIII) nerve nuclei. Excitation along the oculomotor nerve causes contraction of the inferior oblique muscle which produces the oVEMP from electrodes beneath the eye.

The electrical response (Figure 29) starts at approximately 5-7msec with the first consistent peak for the most commonly used stimuli of the vestibular apparatus appearing with a negative polarity at around 10msec in latency (and is therefore termed n10 or n1). This is followed by a positive potential with a latency of around 15msec, the p15 or p1, with further inconsistent negative and positive peaks appearing at 5msec intervals (Piker et al., 2011, Bogle, 2018).

5.3 oVEMPs in clinical practice

Lesions along the oVEMP pathway can affect the crossed otolith-ocular pathways of the oVEMP and be used to provide valuable localising and diagnostic information about the distribution and severity of various diseases (Taylor et al., 2020, Oh et al., 2013, Rosengren and Colebatch, 2011). Many studies have concentrated on audiological and peripheral vestibular disorders that can be detected with the use of this test in clinical practice (Table 2). As well as those disorders that are confined to the inner ear and vestibular nerve, other diseases of the central vestibular pathways and effector can also be detected (Weber and Rosengren 2015, Murofushi, 2016).

Table 2: oVEMPs in peripheral and central pathologies.

Condition	Usefulness
Inner ear	
Meniere's Disease	Can be used in the differential diagnosis
SSCD	To confirm presence of thin/incomplete bony canal
BPPV	Potentially useful for determining refractory cases
Vestibular nerve	
Vestibular neuritis	Prolonged latencies are a good prognostic sign
Vestibular schwannoma	Evaluation as part of a neurophysiological battery as part of pre-operative screening
Central vestibular pathways	
Vestibular migraine	Difficult to distinguish between Meniere's disease and normal controls
Stroke	Low amplitude/absent responses correlate with vascular territory and clinical signs
Intraocular ophthalmoplegia	Absence of responses does not give localising information
Multiple Sclerosis	Complement other neurophysiological para-clinical evoked potentials and aids in localisation of 'silent' demyelinating plaques

5.3.1 Inner ear

5.3.1.1 Meniere's disease

The diagnosis of Meniere's Disease is currently based on clinical criteria that includes recurrent attacks of spontaneous vertigo, hearing loss, aural fullness and tinnitus that can fluctuate over time with recurrent attacks being interspersed between periods of quiescence (Lopez-Escamez et al., 2015).

Patients with Meniere's disease show higher rates of absent or attenuated oVEMPs, with the detection of abnormalities being seen to increase with advancing disease (Taylor et al., 2020). Lower response rates and reduced amplitudes and the need to use higher thresholds of stimulation to elicit responses have also been seen, although to a lesser extent in the clinically unaffected ear (Winters et al., 2011). Meniere's disease is associated with the development of endolymphatic hydrops in the vestibule and cochlea, and then most often in the saccule and the utricle and the semicircular canals (Okuno and Sando, 1987).

The oVEMP may also be augmented in patient with Meniere's Disease, as it was found that in patients with either an augmented or reduced oVEMP (asymmetry ratio >40 and less than 100%), augmented responses were seen more frequently in those patients with earlier stages of Meniere's disease (Wen et al., 2012). These patients with augmented oVEMPs also showed earlier latencies which was interpreted as being indicative of a larger population of utricular afferents being intact in the early disease stages (Wen et al., 2012).

5.3.1.2 Semicircular Canal Dehiscence Syndrome

Various vestibular and/or auditory symptoms can be manifest when there is dehiscence of the bone overlying the superior semicircular canal (Minor et al., 1998, Mikulec et al., 2004); this can lead to sound and/or pressure induced symptoms that are due to the opening of the 'third window' in the labyrinth, which creates a path of lower impedance. The symptoms can be induced by loud sounds at certain frequencies and are usually manifested as distinctive features such as autophony (a louder than normal perception of the patients own voice), hearing loss, pulsatile tinnitus, vertigo and oscillopsia. As has been described previously, in a structurally normal ear the sound energy that is conveyed through the ossicular chain reaches the inner ear via the oval window and passes through the incompressible perilymph of the scala vestibule and the scala tympani to produce an outward motion of the round window. The presence of an additional opening allows *shunting* of the sound pressure away from the cochlea resulting in reduced hearing. This additional opening also has the effect of enhancing the transmission of sound through the vestibular organs that results in greater displacement of the endolymph fluid and an incremental increase in stimulation in the vestibular hair cells. Whilst it is the superior semi-circular canal that is involved pathoanatomically, the associated eye movement abnormalities have been attributed to stimulation of the otoliths (Watson et al., 2000). The cause of the dehiscence is usually unknown and routine neurological and otologic examinations are usually unremarkable although a genetic contribution has recently been proposed (Heidenriech et al., 2017).

The alteration of the mechanical properties of the labyrinth produces oVEMPs that have higher amplitudes, and which can be elicited at lower thresholds that range from 80 to 100dB nHL (Janky et al., 2013). Using absolute cut off criteria, an initial negative (n10) potential amplitude more than 9.9μV and a peak-to-peak amplitude greater than 17.1μV exhibits there was a near 100% sensitivity and specificity between normal controls and dehiscence patients (Zuniga et al., 2012a). Similarly, Janky et al showed that there was a 10-fold increase in the amplitude of the n10 potential, and when compared to age matched normative control data, there was no overlap between the two groups giving a sensitivity and specificity of 100% (Janky et al., 2013).

Superior canal dehiscence also produces a characteristic change in frequency and tuning. The optimal response of the oVEMP to air-conducted sound is between 400 to 1000Hz, whereas patients with dehiscence have wider amplitude and threshold tuning curves that are shifter upwards (Taylor et al., 2012a). By using a stimulus that only elicits responses in patients with superior canal dehiscence, a 1 trial indicator using 4000Hz - rather than repetition of multiple tests using various

frequencies and thresholds – the presence of the oVEMP was perfectly able to distinguish healthy controls from patient with CT-verified dehiscence (Manzari et al., 2013).

Whilst high resolution CT imaging is essential for the final diagnosis of semicircular canal dehiscence, 3-9% of patients who have undergone CT imaging for other unrelated reasons have shown incidental anatomic dehiscence (Ward et al., 2013) and 4% of cases that were identified on retrospective canal plane reconstruction with dehiscence, which is higher than the estimated 0-5-0.6% incidence from cadaver studies, indicates that screening with CT alone may lead to false positive diagnoses (Crovetto et al., 2010). Conversely, patients may have a thinned but still compliant bony covering but may still be symptomatic, a term called *near dehiscence* (Ward et al., 2013). Whilst these patients all had elevated oVEMP amplitudes, the values were lower than those found in patients with semicircular canal dehiscence (median 20.7μV (IQR 6.7-22.1μV) versus median 45.6μV (IQR 32-67.8μV)), but they were still significantly higher than the laboratory control (median 3.7μV (IQR 2.8-6.9μV) (Ward et al., 2013).

It is now considered best practice to interpret the results of the CT, the patient's symptoms and audiovestibular tests, prior to surgical intervention (Ward et al., 2017). oVEMP testing provides an excellent screening test for the confirmation of frank dehiscence and/or a thin plate of bone that can give rise to similar symptoms, without the exposure to the strong ionising radiation of CT imaging to assess longitudinally; and normalisation of the oVEMP waveforms and stimulation threshold after plugging of the window has been used to assess surgical outcomes (Ward et al., 2017).

5.3.1.3 Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo is a common cause of vertigo and is characterised by brief episodes of rotational vertigo that is usually triggered by a change in the position of the head with respect to gravity. It is thought to be caused by detached otoconia debris that have become dislodged from the utricle and enter (most often) the posterior semicircular canal upon head movement. Studies have shown increased rates of absent oVEMPs in comparison to age matched controls, and reduced amplitude oVEMPs from the affected ear, with up to 84.5% of diagnosed cases showing absolute inter-side amplitude differences rather than latency changes (Singh and Barman 2014). It was also reported that two thirds of BPPV patients showed abnormal oVEMPs, with 75% of them showing bilaterally abnormal responses (Nakahara et al., 2013). These reported rates of abnormalities are also more frequent in patients with recurrent symptoms (Lee et al., 2013) and a decreased interaural amplitude ratio from the affected side can predict that a single Epley canalith repositioning manoeuvre would not be enough to resolve the problem (Chang et al., 2017). It has been assumed that the reduced responses of the oVEMP on the affected side in acute cases may be the result of partial degeneration of the utricular hair cells (Singh and Barman, 2014)

5.3.2 Vestibular Nerve

5.3.2.1 Vestibular Neuritis

Loss of peripheral vestibular function causing acute onset of prolonged rotational vertigo and postural imbalance (>24hrs to several days), that is accompanied by spontaneous nystagmus, nausea and vomiting which is not accompanied with any other audiological or neurological symptoms or signs is characteristic of vestibular neuritis (Jeong et al., 2013). Although both the inferior and superior nerves are affected, the superior portion is most involved. Inflammation of the ganglion, possibly due to a virus, and the apparent selectivity of the superior nerve portions is attributed to the increased confinement of the superior nerve afferents that pass through a longer and narrower bony canal, which makes them more vulnerable to inflammatory processes (Goebel et al., 2001).

In this innocuous and self-limiting condition, the oVEMP abnormalities that are typically seen are either higher rates of absent responses or asymmetrical amplitudes, which are lateralised to the side of involvement or prolonged latencies; and during the acute stage these oVEMP these abnormalities range from 60-80% (Walther and Blodow, 2013, Magliulo et al., 2014). Serial monitoring has shown that there is an increased rate of oVEMP detection and return of amplitude values towards normal limits for up to 12 months as symptoms abate. It was found that in those patients the showed more severe pathological oVEMP changes i.e., an accompanying prolonged latency suggestive of utricular involvement, they had a less favourable outcome; with those patients continuing to show showing persistent vestibular symptoms 3 months later (Magliulo et al., 2014). From a clinical perspective, the analysis of selective parameters i.e., latency and amplitude can be utilised to differentiate those patients likely to improve. oVEMP amplitude recovery can potentially predict a favourable outcome as it was found that in the 60% of patients who did have an improvement in their oVEMP amplitude there were more apparent signs of functional recovery, whilst those without oVEMP amplitude restoration and prolonged latencies had worse outcomes, suggesting permanent utricular damage (Adamec et al., 2014).

5.3.2.2 Vestibular Schwannoma

Vestibular schwannomas (previously known as acoustic neuromas) are benign tumours that usually originate from the distal neurilemmal portion of the vestibular nerve close to the neurilemmal junction. They are sporadic and are typically slow growing and they are usually unilateral. They the most common tumour that occurs in the internal auditory canal and they cause gradual changes in cochlear and vestibular function (Sammi and Matthies, 1997). It is therefore expected that oVEMP recordings will be affected, not only because of the origin of the tumour but also because of compression of the neighbouring tissue, if either the superior or the inferior division of the nerve is selectively involved.

Whilst VEMPs should not be used as a diagnostic replacement for MRI (Lachowska et al., 2003), they are a useful part of an auxiliary test battery along with other vestibular testing, as vestibular schwannomas can selectively impair the saccular and the auditory and horizontal semicircular afferents. When evaluating the clinical utility of VEMPs in patients who had not had surgery for their vestibular schwannoma, it was found that 65% of the patients had oVEMP abnormalities, and in some patients (16%) they were the only abnormality discovered (Chiaravano et al., 2014). oVEMPs are often attenuated, with an asymmetrical amplitude ratio, or absent in those patients with cerebellopontine angle tumours affecting the vestibular nerve (Su et al., 2013). With pre-operative studies prior to stereotactic surgery, 70% of patients with MRI confirmed vestibular schwannomas showed abnormalities following oVEMP testing; with 55% showing absent responses, 5% showing reduced amplitudes and 10% showing responses with delayed latencies, and in this study the majority of patients showed a slight increased prevalence of superior vestibular nerve dysfunction, giving physiological identifying information that was not otherwise obtainable (Lin et al., 2013).

When looking at other skull-based lesions, when used in conjunction with caloric testing, a correlation between the caloric test and the oVEMPs showed that a *schwannoma nature* was indicated, whereas when there was dissociation between the results of these two tests then a *meningioma character* was indicated; these results were resultant on the oVEMP being more sensitive to the distension/compression effects of the vestibular nerve (Su et al., 2013). For other space occupying lesions in the cerebellar region (i.e., primary lymphoma), it was found that in those lesions that extended to involve the brainstem the oVEMP was able to distinguish these two localising groups, as the oVEMPs were abnormal in 88% of the patients, in comparison to no abnormalities being detected in those patients with lesions localised to the cerebellum (Su et al., 2011).

The information that is gathered by BAEP and VEMPs together may also be used by the surgeon to provide information on the involvement of the vestibular and cochlear nerves within the internal auditory canal, especially as the origin of the tumour may be a factor in hearing outcome (Lin et al., 2014). Although the majority of schwannomas originate from the vestibular division, secondary changes in the labyrinth maybe noted, with a 60% reduction in hair cell density of both otolithic maculae and a higher proportion of endolymphatic hydrops and precipitate in the labyrinthine fluid; indicating that labyrinthine, as well as retrolabyrinthine pathology may account for vestibular dysfunction in those patients with vestibular schwannomas (Hizli et al., 2016). This additional inner ear pathology may explain the dominant pattern of absent and/or reduced amplitude oVEMP responses - rather than an increase in latency - that is typically seen. These findings could modify the surgical approach through the skull base and determine whether hearing preservation should be the main objective. Similarly, using a regression model, the size of the vestibular schwannoma could be predicted as being less than 2cm if the VEMP responses were present, and again could be used to indicate the preferred surgical procedure, resection, or stereotactic radiosurgery, based on these findings (Lin et al., 2014).

Pre-surgically oVEMPs may be used as an adjunct tool to counsel the patients and to instigate rehabilitation planning, as a good pre-operative vestibular function may be expected to result in post-operative vertigo, because of sudden deafferentation (Tufarelli et al., 2007). Pre-surgical ablation of inner ear function, with an intratympanic injection of gentamicin to induce compensation prior to surgery improves post-surgical recovery, as there are less acute symptoms from surgery and the initiation of a rehabilitation programme can be started whilst the patient is comparatively well (Tjernstrom et al., 2016).

5.3.3 Central vestibular pathways

More recently oVEMPs have been used to evaluate the central pathways to detect pontine and medullary lesions caused by varying aetiology in a wide range of pathologies. A recent PubMed literature review identified articles that used the oVEMP to identify brainstem disorders (Table 3).

5.3.3.1 Vestibular Migraine

There is considerable overlap between the clinical presentation of symptoms and signs between Meniere's disease and the emerging diagnosis of vestibular migraine (Shepard, 2006). Patients with vestibular migraine present with vertigo and/or disequilibrium along with other typical symptoms that may be compatible with migraine, including headache and aura as well as photophobia and/or phonophobia, but they may also present with tinnitus and aural fullness (Shepard, 2006). However, oVEMPs have been used to help diagnose and classify these groups (Zuniga et al., 2012, Taylor et al., 2012); Zuniga et al found that a group of vestibular migraine patients were indistinguishable from normal controls, and although the patients with Meniere's disease showed lower amplitude potentials, the segregation of the two diseases occurred at the group level, but not the individual level. However, using a battery of vestibular tests and utilising an elevated amplitude ratio of the oVEMP as the distinguishing parameter, Taylor and colleagues (2012) were able to differentiate Meniere's disease from vestibular migraine with a sensitivity of 90% and specificity of 70%. Further studies have also shown that although there was not a significant difference between the prevalence of abnormalities between patients with vestibular migraine and controls, there was a significant difference when analysing the amplitude ratios between the two groups (Inoue et al., 2016).

Although vestibular migraine is one of the most common causes of episodic vertigo that is mediated by the central pathways of the VEMP, it has been shown that migraine is associated with changes in both the central and the peripheral central nervous system. It has been shown that patients with vestibular migraine can have two types of abnormality; one is an increase in latency which suggests a lesion in the retro-labyrinth or central portion of the nervous system, whilst the other is a shift in frequency, suggesting endolymphatic hydrops in the otolith organ (Murofushi et al., 2009). It therefore may be that there are several potential sites of lesions and that the overlap between Meniere's disease and vestibular migraine may also be due to the increased sensitivity of

Table 3: oVEMP findings in various brainstem disorders				
Author	**Year**	**Population/ sample**	**Study context**	**Findings**
Gabelic et al.,	2013	30pts with MS 15 healthy controls	Evaluation of VEMP in pts with relapsing-remitting MS.	19/30 pts showed oVEMP abnormalities. 9 (30%) pts showed prolonged latencies and 12 (40%) had conduction block. The n10 showed significant prolongation in the MS group in comparison to controls
Gabelic et al.,	2015	100pts with MS (50pts with brainstem involvement and 50 pts without) 50 healthy controls	To explore the role of oVEMP (and cVEMP) and the development of 'VEMP score' as a possible marker of brainstem involvement in MS pts.	MS pts with clinically evident brainstem involvement have a significantly higher percentage of conduction block in oVEMP compared with MS pts without brainstem involvement
Crnosija et al.,	2017	52 pts with clinically isolated syndrome	Correlation of VEMP score with Paced Auditory Serial Addition Score (PASAT), 9-hole peg test (9HPT) and timed 25-foot walk (T25FW)	oVEMP abnormalities were correlated with brainstem functional scores. 16 (30%) pts had normal responses, 25 (48%) had reduced amplitudes and 11 (21%) had absent potentials.
Gazioglu and Boz	2012	62 MS pts and 35 age/sex matched healthy volunteers	oVEMPs were not correlated to clinical or MRI findings but were significantly correlated to EDSS	oVEMP abnormalities were seen in 45% of pts. Mean interaural latency (n10 and p15) were significantly prolonged in MS pts.
Ivankovic	2013	32 pts diagnosed with MS	To determine the role of MRI, BAEP and VEMP in the evaluation of brainstem involvement of MS	oVEMP showed brainstem involvement in 12 (38%) of patients and was significantly significant in those with brainstem involvement
Su, Chen and Young	2013	11 pts with meningioma and 11 pts with schwannoma in the CPA underwent a battery of audiovestibular tests	Utility of vestibular battery testing to differentiate between meningioma and schwannoma in the cerebellopontine angle	Correlation between oVEMP and caloric tests indicates a schwannoma while dissociation depicts a meningioma. All patients in the meningioma group showed abnormal responses (57% absent and 43% reduced amplitude). 91% of the schwannoma group showed abnormal responses (9% reduced, 9% prolonged, 72% absent).

Table 3 cont				
Oh, et al.,	2013	52 pts with acute brainstem lesions	Defining oVEMP abnormalities in patients with acute brainstem lesions to determine the brainstem structures that are involved in the generation of oVEMPs.	80% of the 5 pts with midbrain lesions showed abnormal oVEMP (3 absent and 1 delayed). 57% of the 28 pts with a pontine lesion showed abnormal oVEMPs. All five pts with an upper medullary lesion showed abnormal oVEMP, whereas only 4 out of 14 pts with lateral medullary lesions showed abnormalities. 54% of pts with acute brainstem lesion show abnormal oVEMP with most associated with lesions of the dorsomedial tegmentum from the upper medulla oblongata to the midbrain.
Oh, Kim and Kim	2016	29 pts with brainstem infarcts		47% of pats with medullary strokes showed abnormal oVEMP
Su and Young	2011	12 pts in total, 8 pts with an extended cerebellar lesion involving the brainstem and 4 with a localised cerebellar lesion (excluding the brainstem)	To determine if VEMP testing can differentiate brainstem and cerebellar lesions	Abnormal oVEMPs may indicate brainstem involvement in patients with cerebellar disorder. Seven (88%) of the pts with extended cerebellar lesions showed abnormal oVEMP (absent in six and delayed in 1). All the pts with localised lesions had normal oVEMP.
Venhovens et al.,	2016	Examples from the literature	Localisation of oVEMP	VEMPs can give insight into the pathophysiological hallmark of central disorders
Kim et al.,	2014	12 pts with ION confirmed by MRI to be due to brainstem infarctions	To determine if the medial longitudinal fascicule (MLF) contain the otolith-ocular reflex fibres from the contralateral ear	8 (67%) of pts showed abnormal oVEMP. 1 showed bilateral absence, 4 showed unilateral absence on the lesion side and 3 showed a decreased amplitude. The oVEMP amplitude was statistically smaller on the lesion side and in comparison, to controls.
Kinoshita et al.,	2013	45 pts with untreated unilateral vestibular schwannoma	To clarify the origin and pathways of the oVEMP to air-conducted sound	28/45 (63%) of pts showed either an absent (25/28) or decreased (3/28) oVEMP response on the affected side.

migraineurs to activation of sensory systems (i.e., vertigo and dizziness due to other causes may cause migraines).

5.3.3.2 Stroke

Ischaemic changes occurring in the vascular territory of the vertebrobasilar artery system show oVEMP changes in 50-80% of cases, with most of the abnormalities consisting of absent responses or a diminished amplitude (Kim et al., 2009, Su and Young 2011, Weng and Young 2014).

Lesions in the brainstem may also affect the crossed otolith-ocular pathways of the oVEMP. Studies in patients with acute brainstem lesions have shown that more than half (54%) of those patients showed abnormal oVEMPs with confirmation from MRI-based voxel-wise lesion behaviour mapping showing lesions confined to the medial longitudinal fasciculus and crossed ventral tegmental tract of the dorsomedial brainstem and the oculomotor nuclei and its nerves (Oh et al., 2013). Within this study 4 out of the 5 patients who had ischaemic stroke that caused midbrain lesions had abnormal oVEMPs; 3 patients had absent potentials unilaterally and each of these had oculomotor nerve palsy and unilateral internuclear ophthalmoplegia, the remaining patient showed a delayed n10 potential. Of those patients with pontine lesions sixteen showed abnormalities of the oVEMP (57%); those patients with internuclear ophthalmoplegia showed absent responses unilaterally, the patient with *neuromyelitis optica* had absent responses bilaterally and of the two patients with one-and-a-half syndrome, one showed an absent response and the other showed prolonged latencies. Patients with infarction of the anterior inferior cerebellar artery showed a unilateral absence of responses, but this was due to concurrent profound hearing loss. Of the five patients with upper medullary lesions all showed an absence of potentials, either contralaterally or ipsilaterally to the side of the lesion, and those patients with lateral medullary lesions were less likely to show abnormal results than those with medial medullary lesions (41% v 100% respectively). Most of the patients with abnormalities showed an absent response (24/28, 86%) rather than a delayed response (4/28, 14%) and this finding would be consistent with the ischaemic pathology detected in most of the patients. All the patients within the study presenting with internuclear ophthalmoplegia showed absent responses (7/7, 100%). Similar findings were described by Weng and Young, with all of the patients with anterior inferior cerebellar artery ischaemia having severely abnormal hearing, which contributed to 50% of these having absent or reduced oVEMP responses; of those patients with infarction affecting the posterior inferior cerebellar artery slightly more, 57% of patients, showed abnormalities, even though the hearing loss was only slightly impaired (Weng and Young, 2014).

5.3.3.3 Internuclear Ophthalmoplegia

Rosengren and Colebatch (2011) found that in a series of 12 patients who presented with internuclear ophthalmoplegia, eleven of whom had multiple sclerosis, the rate of oVEMP abnormalities was significantly different to those found in normal subjects using the same recording and stimulus parameters (69% versus 7%). For those patients with bilateral internuclear ophthalmoplegia the responses were absent in nine cases, delayed in two cases and normal in three; for those with unilateral internuclear ophthalmoplegia the 50% showed abnormalities, with two showing abnormal responses ipsilaterally and three showing abnormalities contralaterally.

A similar sized study of eleven patients with isolated unilateral intranuclear ophthalmoplegia due to brainstem infarction showed that eight (67%) of them had abnormal oVEMPs (Kim et al., 2014). Five of these had absent waveforms either unilaterally (4/5) or bilaterally, and three patients showed a reduction in amplitude that was smaller on the side of the lesion in comparison to normal controls (6.0 ± 5.6 μV v 11.7 ± 5.5μV) and higher amplitude asymmetry ratios (43.6 ± 41.2 v 9.1 ± 6.2).

5.3.3.4 Multiple sclerosis

oVEMPs may be helpful in assessing the involvement of the brainstem in patients with multiple sclerosis, a chronic idiopathic demyelinating disease that is the leading cause of disability in young adults. Demyelination can occur throughout the brain, and whilst it is not uncommon for symptoms relating to the vestibular system to be frequently reported, it is common for there to be an absence of structural abnormalities seen on the MRI scan (Nerrant and Tilikete, 2017). Whilst there is a relatively good correlation between brainstem impairment and for T2 MRI scans, the association between the clinical findings and the radiological extent of the involvement is poor; this is the *clinic-radiological paradox* (Barkhof, 2002). The low specificity of MRI scans in the differentiation between the heterogeneous pathophysiological mechanisms of tissue damage of neuroinflammatory and neurodegeneration is the main reason for this paradoxical finding (Barkhof, 2002). Throughout the course of the disease around 65% of patients will develop one or more signs of brainstem dysfunction (Habek, 2013), but only approximately 60% of these patients will show relevant structural and anatomically localised changes on their MRI (Tintore et al., 2010).

Evoked potentials are reliable procedures to predict disability in patients with multiple sclerosis and when using an index of global evoked potential abnormality from the results of visual, somatosensory and brainstem auditory recording, there is significant correlation with the patients disability score at the time of recording (Invernizzi et al., 2011); although the brainstem auditory evoked potential is insufficient on its own to detect subclinical lesions within the brainstem (Comi et al., 1993). Whilst the role of VEMPs in the diagnosis of multiple sclerosis is not part of the international diagnostic criteria (Thompson et al., 2017); they do potentially have a role in assessing patients with multiple sclerosis.

Initial studies that only utilised the cervical oVEMP were limited; as they were unable to distinguish between a lesion of the brainstem from one in the upper cervical cord, and obviously gave no information of the ascending brainstem pathways involvement (Murofushi et al., 2001). The application of VEMP testing in patients with MS improved with the introduction of oVEMPs, as these show higher rates of abnormality (Gazioglu and Boz, 2012) and are more often absent than delayed (Gabelic et al., 2013). This finding implies that there is conduction block caused by severe demyelination and as the medial longitudinal fasciculus is a common site of involvement for MS lesions, this finding is not unexpected (Nerrent and Tilikete, 2017).

In patients with relapsing-remitting multiple sclerosis, there was a statistically significant difference between the oVEMP abnormalities and brainstem clinical findings, even though there was no statistical difference between the MRI findings and oVEMPs (Ivankovic et al., 2013). This same patient group showed that 40% of patients had conduction block and 30% had prolonged latencies that were significantly prolonged in comparison to normal controls (10.3 v 9.5 msec) (Gabelic et al., 2013).

The discrepancy between EP scores and the expanded disability severity score, that is widely use measure disability and disease progression, is because brainstem function is underrepresented in the overall score (Polman and Rudick, 2010). To analyse this further, Crnosija and colleagues (2015) looked at the individual VEMPs in 52 patients with clinically isolated syndrome and found that there was a positive correlation between the oVEMP abnormalities and the nine-hole peg test ($r_s = 0.581$) and the brainstem functional score of the extended disability severity score ($r_s = 0.308$). By converting the oVEMP abnormalities into an ordinal score, where 0 = normal, 1 is an increased latency and normal amplitude/morphology, 2 is a decreased amplitude and 3 is an absence of a response, it was found that there was a statistically significant influence, based on multivariate linear regression between the extended disability severity score and oVEMP grade (Gabelic et al., 2015). Further analysis by the same group of authors (Crnosija et al., 2017), consisting of 121 patients with clinically isolated syndrome, showed that patients with brainstem involvement on the neurological examination had a higher oVEMP score in comparison to those that had not shown signs of brainstem involvement. In the validation of the oVEMP scoring system, there was a significant correlation between increased latencies and an absence of responses when pontine/medulla oblongata lesions were seen on the MRI ($p = 0.023$) (Crnosija et al., 2017). These findings are in keeping with the changes caused by demyelination that produce slowing of conduction along the nervous system pathways, partial or complete conduction block and secondary degeneration of the axons (McDonald and Sears, 1970).

In those MS patients with clinically evident brainstem involvement, studies have shown that the oVEMP has a significantly higher percentage of abnormality, with not only changes in latency, but also amplitude ratio asymmetries and conduction block.

5.4 Conclusion

Even though VEMP abnormalities may be common in a range of central neurological disorders, they are not disease specific and do not necessarily give any information about the underlying aetiology (Venhovens et al., 2016), they can however give important localising information about the status of the peripheral and central systems (Katner and Gurkov 2012, Oh et al., 2016, Venhovens et al., 2016).

Given that the abnormalities seen are relatively sensitive and specific to the sites of involvement, when used in conjunction with other neurophysiological recordings, they may enable detection of vestibulopathy and extraocular nerve damage along the peripheral pathways and central medial longitudinal fascicular pathways intraoperatively.

Chapter 6.

Novel evidence that oVEMPs can be recorded intraoperatively.

6.1 Introduction

With the evidence that oVEMPs can detect pathophysiological changes of different aetiology, the questions to be answered are.

1. can oVEMPs be recorded intraoperatively?

2. If yes to 1, what are the optimal stimulating and recording conditions?

3. Can intraoperative oVEMPs detect changes along the vestibular ocular reflex pathway?

4. Are detected changes in intraoperative oVEMPs of clinical utility in averting post-operative neurological deficit?

It is known that the cervical vestibular evoked potential can be recorded from the sternocleidomastoid muscle after acoustic, vibratory or galvanic stimulation (Curthoys, 2010) and reflects the input from the saccule and relates to the integrity of the inferior vestibular nerve, the vestibular nuclei and its interconnections and the excitability of the motoneurones controlling the sternocleidomastoid muscle (Rosengren et al., 2010). In a series of seven patients who were undergoing cerebellopontine otoneurosurgery (i.e., microvascular decompression and tumour resection) electrical stimulation of the exposed inferior vestibular nerve was attempted to record the cervical vestibular evoked potential intraoperatively (Basta et al., 2005). Using a concentric bipolar stimulating electrode and stimulating at 0.4 to 1.0mA, whilst the patient was anaesthetised with a Propofol and Fentanyl total intravenous regime, all patients were able to elicit an ipsilateral response from the sternocleidomastoid muscle that was linearly correlated with the stimulus strength. Also, stimulation of the superior vestibular nerve did not elicit any responses either ipsilaterally or contralaterally (Basta et al., 2005). The recordings obtained at the time of surgery also correlated with the morphology of those potentials recorded pre-operatively, although the mean latencies of the P13 and N23 (9.1 ± 2.2msec and 13.2 ± 2.3msec respectively) were significantly shorter, as the receptor excitation and synaptic transmission time were not part of the reflex pathway (Basta et al., 2005). The same group reported on a further 5 patients operated on for vestibular schwannoma resection and 4 patients undergoing microvascular decompression surgery of the eighth cranial nerve, and showed similar results (Ernst et al., 2006). All the surgical patients were able to elicit ipsilateral responses from the sternocleidomastoid muscle after direct electrical stimulation of the inferior vestibular nerve, even in those six patients (67%) who were unable to show elicitable responses to acoustic stimulation prior to surgery, For those patients in which the inferior vestibular nerve was preserved during surgery, the cervical vestibular evoked response could be elicited throughout the surgical procedure following electrical stimulation and subsequently at follow-up postoperatively to acoustic stimulation (Ernst et al., 2006).

This indicates that the reflex pathway sub-serving the vestibulocollic reflex can be assessed after direct stimulation of the exposed portion of the vestibular nerve intraoperatively. The use of a total intravenous anaesthetic regime was amenable to the conduction through the cranial nerves and the interconnections within the lower brainstem pathways. The use of this same anaesthetic regime for this current proposed study would indicate that the ascending interconnections, through the brainstem via the medial longitudinal fasciculus, would also be amenable for the ocular vestibular pathway to be assessed via stimulation of the end organ receptors.

However, to be able to reliably record and interpret the oVEMPs intraoperatively, the selection and adaptation of the stimulus and the recording parameters must be considered, so that accurate warnings can be given to the surgeon.

It is known that the recording and stimulation protocols used to collect the data vary within the literature with varying types of stimulation, namely air conducted sound and bone conducted vibration being used. Differing recording settings (i.e., patient sitting or supine) and different machine settings used for the acquisition of oVEMPs, and placement of the recording electrodes have also been used (Table 4). Each of these alterations can affect the resultant waveforms latency, amplitude and response rate; but each of them needs to be optimised intraoperatively, so that consistent results can be obtained.

Table 4: The variability of published stimulating and recording parameters for oVEMPs

Author	Year	Stimulation mode	LFF (Hz)	HFF (Hz)	Number of sweeps	Rate (Hz)
Iwasaki et al.,	2008	BCV	20	500	50	3
Smulders et al.,	2009	BCV	3	10,000	30	3
Cheng et al.,	2009	ACS, BVC, GVS	1	1,000	100	5
Rosengren et al.,	2009	GVS	5	1,000	200-300	5
Gozke et al.,	2010	ACS	200	1,000	150	10
Murnane et al.,	2011	ACS	1	1,000	500	5
Piker et al.,	2011	ACS	1	1,000	100	5.1
Murofushi et al.,	2011	ACS	20	2,000	100	5
Singh et al.,	2014	ACS	10	1,000	200	5.1
Rosengren et al.,	2013	BCV	5	2,000	200	7.5
Bogle et al.,	2015	ACS	10	1,500	100	1.6-26.6
Kim et al.,	2015		30	3,000	100	5
Bogle et al.,	2018	BCV, ACS	10	1500	100-150	≤5
Rosengren et al.,	2019	ACS	2	5000	50-200	5
Dlugaiczyk	2020	ACS	10	1000	50-200	5

ACS = air conducted sound; BCV = bone conducted vibration: GVS = galvanic vestibular stimulation

Therefore, there is the need to ensure that the collection of data enables accurate interpretation of the waveforms so that alterations that exceed any warning criteria are valid and related to the presumed pathophysiological impairment. The development of intraoperative monitoring ocular vestibular evoked myogenic potentials requires the development of an effective protocol that utilises the optimisation of the recording and stimulus parameters. The clinical protocols that are already in use need to be evaluated, and the various parameters need to be optimised to ensure the monitoring is reliable, reproducible, and safe (Rosengren et al., 2019, Taylor et al., 2020).

6.2 What is the optimum recording montage?

As the inferior oblique muscle is the most superficial of the extraocular muscles, electrodes placed beneath the eye are used to record the excitatory response after upward gaze, which brings the muscle closer to the surface (Rosengren et al., 2013). The 'conventional' recording montage is for the *active* electrode to be placed directly below the eye when in the neutral position, and for the *reference* electrode to be positioned 2-3cm inferiorly (Figure 30). This *bipolar* arrangement can reduce the impact of other distant sources (facial muscles, electrical noise etc) and can provide a more selective recording of the inferior oblique muscle activity, in comparison to a wide spaced *referential* montage (Figure 30) with the reference electrode placed on the chin (Todd et al., 2007).

However, with the *bipolar* configuration, the reference site may not be totally indifferent and may result in lower amplitudes and response rates due to phase cancellation of the signal (Piker et al., 2011).

Alternative reference sites have been utilised that avoid 'contamination' from other ocular muscle groups. With the active electrode placed slightly more lateral to the traditional mid-line placement, over the main bulk of the inferior oblique (Figure 30), there is an increase in the response amplitude which is enhanced further with the reference electrode placed at the medial canthus (Sandhu et al., 2013, Govender et al., 2016); the test-retest reliability is also increased with this "belly-tendon" recording configuration (Leyssens et al., 2017).

In order to compensate for the expected reduction in response amplitude caused by the oVEMPs being recorded in the eyes closed state, the judicious choice of the "belly-tendon" montage should overcome this potential co-founding issue, whilst maintaining the signal-to-noise ratio and also cancel out much of the stimulus artefact and environmental electrical noise due to the common mode rejection.

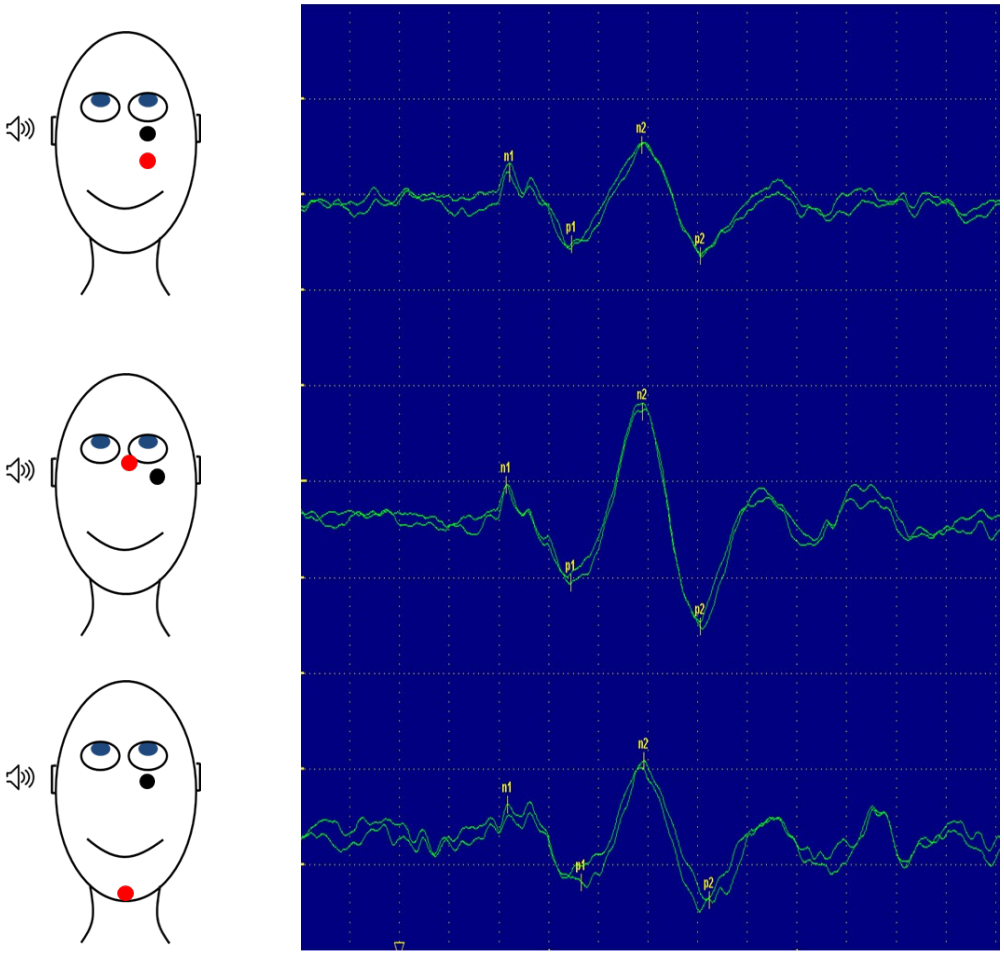

Figure 30: oVEMPs recorded with different recording montages.
The amplitude and morphology of the oVEMP is influenced by the recording montage used (Top traces: 'Conventional' recording montage. Middle traces: 'belly-tendon' montage. Bottom traces: 'bipolar' montage.

6.3 What should the stimulus rate be?

The effect of stimulus frequency has been shown to affect the oVEMP (Singh et al., 2014a, Bogle et al., 2015); with a prolongation in peak latencies from 11.01 (± 0.6) msec and 11.22 (± 0.94) for the n10 component at 3.1 and 5.1Hz respectively, to 12.47 (± 1.23) msec and 13.18 (± 1.36) msec at 25.1 and 30.1Hz.

With an increase in repetition rate there was also a decrease in the amplitude from 10.26 (± 7.4) μV and 9.40 (± 5.32) μV at the lower rates, to 4.64 (± 2.88) μV and 4.38 (± 2.95) μV at the higher rates, there was also a corresponding decrease in the response rate from 100% at 3.1 and 5.1Hz, to 32.7% at 25.1Hz and 17.3% at 30.1Hz respectively (Bogle et al., 2015).

Therefore, to maintain the response rate and reduce false negatives (not recording a response because of inadequate stimulus rate rather than a pathological reason), the stimulus frequency should ideally be delivered at ≤5Hz (Table 4).

3.4 How many samples need to be averaged?

To optimise the test time further, the number of stimuli used should be as small as possible, whilst still maintaining the optimal signal to noise ratio, to maintain waveform morphology (Mallison et al., 2018). The signal to noise ratio is proportional to the square root of the number of trials (*n*) and is determined by the optimal size of the recordable signal and the amount of 'noise' (any signal detected that is not from the desired response being recorded) entering the recording circuitry (Merlo and Campanini, 2010).

Increasing the number of stimuli into the averaged total does not significantly alter the latencies of the n10 and p15 components, although the amplitude of the response decreased from 11.9 ± 7.7μV when using 30 stimuli to 9.51 ± 6.7μV (p = 0.03) when doubling the number of sweeps averaged (Mallinson et al., 2018). The effect could reflect attenuation of the reflex either by a central or peripheral mechanism and it is important to ensure that any 'test effect' that could influence the result is eliminated so that any potential inter-trial anomalies are removed.

When using high acquisition numbers of 1,500 sweeps it was found that the number of absent responses was considerably higher unilaterally (35% versus 13%) in patients with migraine compared to normal controls (Gozke et al., 2010); and the number of absent responses bilaterally was considerably higher (19%) in the patient group compared to other similar studies using lower acquisition numbers (e.g. only 2.6% showed bilateral absence in the study by Kim et al., 2015 and 1.8% in the study by Makowiec et al., 2018).

Therefore, to ensure timely feedback of the information, and to ensure a maximal response rate, the number of responses averaged should be as low as possible; but be of a sufficient number to produce a satisfactory and consistent response, with 50-100 being a seemingly acceptable number (Table 4).

6.5 Which filter settings (HFF/LFF) are most appropriate?

The band pass filters used when recording the oVEMP should encompass the dominant frequencies that are contained within the signal of interest. Any unnecessary or irrelevant high and low frequency activity above and below the signal of interest arising from internal patient generated signals such as electroencephalographic or electromyographic signals or from external electrical sources, such as 50Hz mains interference, should be eliminated or reduced from the analysis using low and low high filters, so that they do not fall within the frequency spectrum of the desired response. However, excessive filtering may distort the latency and amplitude of the oVEMP, leading to false negative results (Jones et al., 2002).

Different high-pass (500-2000Hz) and low-pass filters (0.1-20Hz) have been used within the literature (Table 4). Analysis of the response energy of the oVEMP across frequency domains can provide a basis for selecting the optimal filter settings so that the entire signal of interest can pass through the electrical circuits without distortion. When recording with wide open filter settings, and using power spectrum analysis, it has been shown that the major energy of the response is seen

up to 500Hz, with the peak of the energy being seen at around 100Hz (Singh et al., 2019) and there is almost no energy above 1000Hz (Wang et al., 2013, Singh et al., 2019).

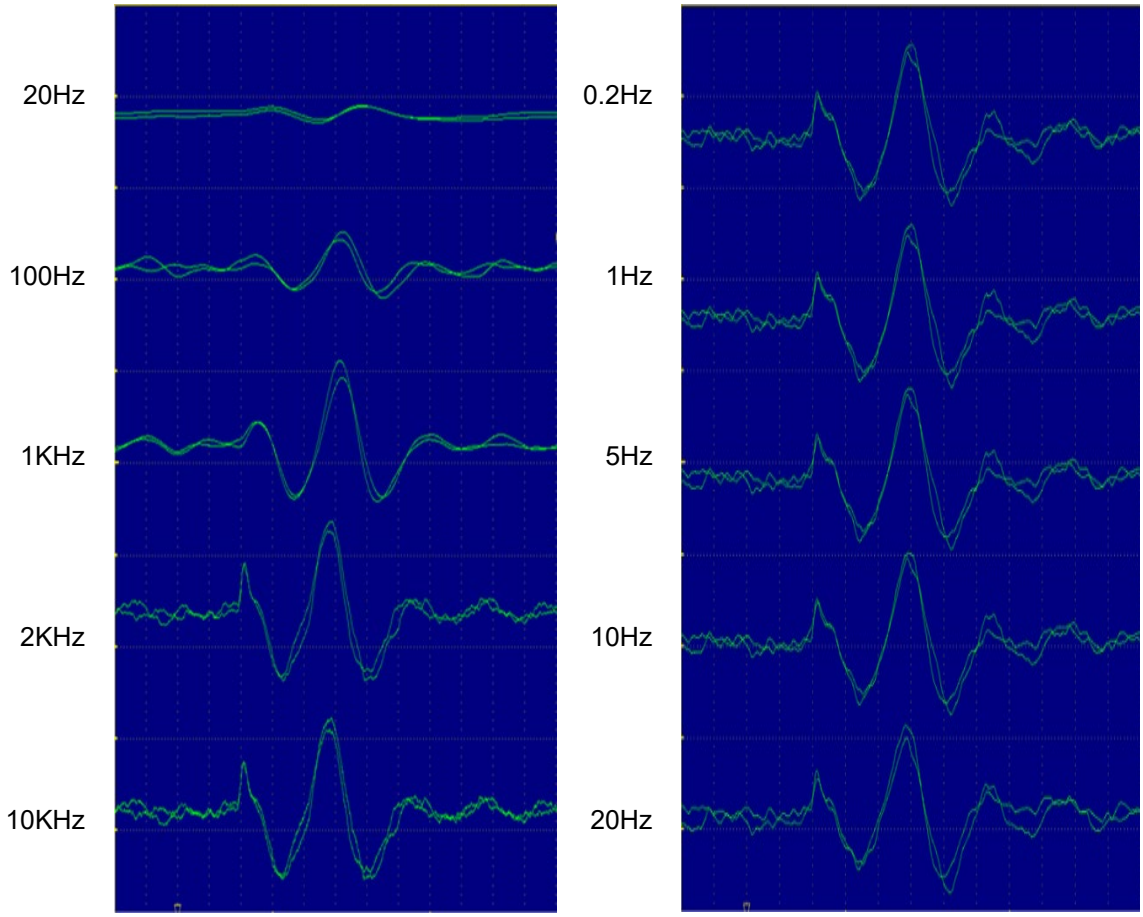

Figure 31: The effects of differing filter settings on the oVEMP.
Right panel: Increasing the low pass filters (and keeping the high frequency filter constant at 10KHz) has little effect on the resultant oVEMP.
Left panel: Increasing the high pass filter (whilst keeping the low frequency filter constant at 1Hz) allows better recognition of the waveforms.

Excessive high pass filtering can reduce the response rate of the oVEMP from 100% when the low frequency filter is set at either 1Hz or 10Hz, down to 83% with the filter settings at 100Hz (Wang et al., 2013). However, when the high pass filter is set <10Hz the resultant waveforms may be contaminated by erroneous low frequency noise caused by baseline drift, electrode artefact and movement artefacts (Jones et al., 2002). The use of excessive high pass filtering can also significantly reduce the amplitude of the n10-p15 amplitude from 25.2 ± 11.3μV and 22.2 ± 9.4μV using 1Hz and 10Hz high pass filters respectively, down to 13.3 ± 5.6μV using a 100Hz high pass filter (p <0.05) (Taylor et al., 2014). There was also a significant progressive reduction in the n10-p15 amplitude with an increase in the high pass filter 9.95 ±7.36μV at 0.1Hz, down to 8.23 ±5.55 μV at 30Hz (Singh et al., 2019).

The effect of low pass filtering is less apparent on the resultant oVEMP latency and amplitude values, reducing the low pass filter to 500Hz probably does not alter the energy content of the resultant waveforms (Figure 31), as the majority of power spectrum lies between 100 and 500Hz (Taylor et al., 2014). Also, the skin and the subcutaneous tissue that separates the recording electrode from the active muscle act as low pass filters that reduce the recordable frequency components from the resultant electromyographic signal above ~500Hz (Merletti et al., 2010). The latencies of the n10 and p15 waveforms were seen to be significantly influenced by the increase in high pass and low pass filters (Sing et al., 2019); using a low pass filter of 0.1Hz the n10 latency was seen to decrease from 10.59 ± 0.5msec to 10.26 ± 0.63msec when the high pass filter was increased from 500 to 3000Hz, whilst under the same conditions the n15 latency was seen to increase from 15.65 ± 0.92msec to 15.82 ± 0.86msec. The reduction in the latencies with an increase in the high pass and low pass filters can be attributed to the *smoothing* of the high frequency components of the oVEMP with the increase in the low pass filter and the negative delay that is caused by the increase in the high pass filter, which is seen in other auditory evoked responses arising from the brainstem (Legatt, 2018).

The filter band width must also eliminate the stimulus artefacts that are inherent with the various stimulus (Jones et al., 2002, Rosengren et al., 2009). Whilst the common mode rejection ratio of modern differential amplifiers within the electrodiagnostic equipment can reduce the influence from some of these artefacts, meticulous skin preparation and electrode application to reduce the mean electrode impedance levels and interelectrode impedance differences is also able to reduce further these low frequency signals (Taylor et al., 2014).

However, the judicious use of filtering on the physiological potential must also consider the erroneous electrical interference within the theatre environment caused by ancillary equipment (diathermy, microscopes, aspirators etc), that each have their own high frequency electrical signature. Therefore, the optimum filter setting should be capable of producing responses in all healthy individuals and should be able to record the highest possible signal; whilst removing as much of the erroneous background noise (both external and internal), to maximise the signal to noise ratio. The signal to noise ratio is the difference between the signal level, which over successive recording should remain relatively stable, and the amount of extraneous noise recorded from the surrounds. As the previous studies above have shown, using a high pass filter above 1000Hz will not affect the response amplitude, but would increase the likelihood of allowing high frequency noise to be injected within the signal. In any recording environment the amount of physiological *internal* noise will vary from one patient to another whilst in the intended theatre setting the *external* noise caused by ancillary equipment would be expected to vary from one epoch to another. In the laboratory-controlled studies it was shown that low pass filter settings of 0.1Hz or 1Hz produced the highest signal to noise ratios, 30.25 ±13.17 and 28.43 ±12.18 respectively (Table 4), when used with a high pass filter of 1000Hz (Singh et al., 2019).

6.6 Intraoperatively, what is the best stimulus (ACS v BC v GVS)?

Adequate stimulation of the vestibular apparatus can be achieved by a variety of stimuli (Curthoys, 2010). Bone conducting stimuli requires a heavy and cumbersome 'minishaker' to be positioned and maintained in place throughout the period of testing (Rosengren et al., 2005); and this would not be practically amenable to the confines of the surgical environment and the positioning of the patient in Mayfield head holder. Acoustic stimulation requires tone bursts to be delivered, via foam ear inserts, at relatively high stimulus intensity levels (Piker, 2011, Bogle, 2018). Whilst these levels may be safe in the initial screening and assessment of oVEMPs for patients in the out-patient setting, continual and prolonged exposure for the length of the surgical procedure, may potentially cause noise induced hearing loss (Portnuff et al., 2017), especially in children, where the paediatric population is known to be more at risk (Thomas et al., 2017, Rodriguez et al., 2018).

A short duration pulsed current delivered via electrodes attached to the mastoid can activate the end organs of the vestibular apparatus, at the terminal part of the primary vestibular afferent (Rosengren et al., 2009). Cathodal stimulation increases, whilst anodal currents decrease the spontaneous firing rates of the vestibular sensory organs (Cheng et al., 2009). However, such a current, in close proximity to the recording site, causes a large stimulus artefact to encroach and contaminate the earlier components of the oVEMP signal, requiring specific off-line subtraction techniques to recover the response of interest (Watson and Colebatch, 1998). This artefact is particularly evident when the recording electrodes are spaced further apart ('conventional' and 'bipolar' montage recordings) but is reduced when the 'belly-tendon' montage is utilised (Sung et al., 2014).

The amplitude of the n10-p15 to galvanic stimulation is also higher (13.7 ± 5.4μV) in comparison to air-conducted sound (4.4 ± 1.5μV) (Cheng et al., 2009) and has a 100% response rate at an intensity of 5mA and duration of 2msec, in comparison to the lower response rates produced by air-conducted sound (Sung et al., 2014).

6.7 Is ACS safe to use intraoperatively?

The safety of any diagnostic tests must be an important consideration when they are used to be used on large numbers of patients or in healthy volunteers; although some diagnostic investigations, e.g., conventional radiology with ionising radiation, do carry some risk to the patient. Prolonged exposure to any noise at high intensity can damage the sensory hair cells of the inner ear leading to the development of a permanent shift in hearing threshold. Noise exposure can also lead to tinnitus and other alterations on central auditory function that may significantly alter the patient's quality of life and can be a major limitation in hearing-critical jobs. Noise induced hearing loss therefore not only has a personal effect on the subject's health but can also be a major social problem (Silwinska-Kowalska and Davis, 2012).

It is generally thought that hearing damage is related to total sound energy or to the peak intensity of sound pressure (blast injury) (Atherley and Martin, 1971). However, when the sound exposure

from VEMPs is evaluated, the instantaneous noise level and the actual exposure measured over time need to be considered. An individual could be exposed to an increased risk of hearing loss if the output level of the stimulating device exceeds the recommended exposure level for a specific damage-risk criterion. The legislation regarding industrial nose exposure typically specifies both the maximal sound pressure level (SPL) and the total sound energy that is exposed over a given time period (i.e., 8 hours). However, as there is no established damage-risk criteria for patient noise exposure in the healthcare setting (Portnuff et al., 2017); it is typical to use the industrial recommended values in the clinical context. In the UK, the guidelines for occupational exposure specify the upper limit of 200 Pa (equivalent to 140dB peak SPL) and an exposure limit of 85dB (averaged over the course of a day or a week) (HSE 2005).

When hearing loss due to noise exposure is described in relation to a 'damage-risk criteria', the individual's exposure can be represented as a noise dose, with a 100% noise dose being equivalent to an 8 hour exposure to the recommended exposure level (HSE, 2005). Noise dose is however a cumulative measure and the exposure from individual activities in any given day should be added together to give a total noise dose. Continual exposure to a daily dose greater than 100% over a prolonged period (i.e. a workers career) will increase the risk of developing noise induced hearing loss. The damage risk criteria from the European Union and the National Institute for Occupational Safety and Health set an upper limit of normal of 140dB (C-weighting) for those impulsive sounds that last less than 1second (HSE, 2005). The stimulus intensities used for oVEMP recordings are relatively high and it is essential to use correctly calibrated stimuli (Rosengren et al., 2009a). The auditory stimulus typically used for elicitation of the oVEMP is the tone burst, and whilst this is an impulse noise, it is not typical of naturally occurring impulse noise. The tone burst is better regarded as being an interrupted sinusoidal waveform (Rosengren et al., 2009a).

There have been few reported side effects when testing patients with oVEMPs (Krause et al., 2013, Mattingly et al., 2015, Stromberg et al., 2016). There have been subjective complaints of 'muffled hearing' and some reduction in high frequency otoacoustic emissions 5 minutes after recording VEMPs, without any significant change in pure-tone audiometry (Krause et al., 2013). Similarly, pre and post exposure audiometry did not show and significant reduction in measurable hearing thresholds, although a reduction in the amplitude of distortion produce otoacoustic emissions (2.1dB), over a range of frequencies was noted following stimulation that was equivalent to half the maximal occupational noise for an 8hour work day (Stromberg et al., 2016) Whilst these changes were resolved by the following day, the risk of adverse hearing symptoms is something that would need to be considered for all subjects (Colebatch and Rosengren, 2014). Mattingly et al (2015) reported a single case study of sudden and permanent bilateral sensorineural hearing loss after VEMP testing with the intensities of the stimulation varying between 128-135dB pSPL. Whilst the information regarding side effects is limited, these reports raise some concerns for VEMP testing, indicating that care must be taken to safely measure VEMP responses to avoid cochlear organ damage (Portnuff et al., 2017).

Vestibular evoked myogenic potentials, using either click or tone bursts, typically specify the stimulus intensities in dB SPL, or reference them to normal hearing level (nHL); neither of which reflect the total sound energy, as the stimulus duration is not taken into account (Rosengren et al., 2009a). The sine waves used for tone burst stimulation can also vary within the literature for frequency, rise/fall and plateau cycles (Park et al., 2010, Cheng et al., 2012, Kantner et al., 2014, Lim et al., 2013).

The effects of the different acoustic waveforms and their corresponding energies have been investigated, and it has been shown that the sound energy delivered is an important determinant of the VEMP amplitude (Rosengren et al., 2009a). Whilst sound energy is the main determinant of the effectiveness of the stimulus intensity that reaches the inner ear, the rise/fall time and frequency content are also relevant; this is because the middle ear has a significant filtering effect on air conducted sound. It has been shown that the oVEMP is larger when evoked by sine waves, especially when using 500Hz stimulus, which can be explained by the tuning effects in the vestibular system (Rosengren et al., 2009a).

It is therefore important to limit both the maximum intensity and also the total sound exposure whilst the patient is being monitored. A maximum sound energy exposure of L_{Aeq8hr} of 85dBA is based on daily exposure to a maximum intensity of 140dB SPL over a 40year period. However, whilst the published damage-risk criteria limits for impulsive noise were developed to prevent hearing loss in the majority of workers, they will still leave the 25th percentile potentially susceptible to hearing loss (i.e., 75% of ears would not be at risk of hearing damage at 140dBpSPL). The 5th percentile could be susceptible to hearing loss or damage at an intensity as low as 132dBpSPL. Therefore, it must be borne in mind that the regulatory standards do not protect *al*l individuals because a small percentage of ears may sustain cochlear damage at lower than stated levels.

The clinical protocols for safe VEMP testing need to evaluate the various stimulus parameters that can be altered as variations in any of these parameters will affect the overall exposure (Rosengren et al., 2009a). If the intensity of the stimulus or the number of sweeps is altered, then this will alter the output level and the total exposure time respectively. However, a small reduction in the maximum intensity will significantly reduce the patient's exposure; reducing the output by 3dB will reduce the patients' overall dose by 50% without significantly altering the diagnostic utility of the test. Altering the stimulus duration will undoubtedly affect the amplitude and latency of the responses but reducing the stimulus duration may not have a clinically significant effect on the responses response rate (Colebatch and Rosengren, 2019).

6.8 How should the waveforms be interpreted?

Analysis of the oVEMP considers the interpretation of the absolute latency time of the n10 and p15 potentials, along with the inter peak latencies and inter-side difference, each of which would indicate a *conduction delay*, which would indicate stretch or compression of the neural fibres along the pathway (Figure 32, Top traces). The amplitude of the n10-p15 potential is used to detect *conduction block* resulting from an interruption in conduction integrity and synchronicity of the

ascending action potential volley (Figure 32, Bottom traces). By employing a ratio formula, the side-to-side differences in amplitude can be expressed as an *asymmetry ratio* and can be used as a metric to evaluate the difference in response size between the two sides.

$$\text{Amplitude asymmetry} = 100 \times \frac{\text{right eye amplitude} - \text{left eye amplitude}}{\text{right eye amplitude} + \text{left eye amplitude}}$$

The usual amplitude ratios are less than 34% (Piker et al., 2011).

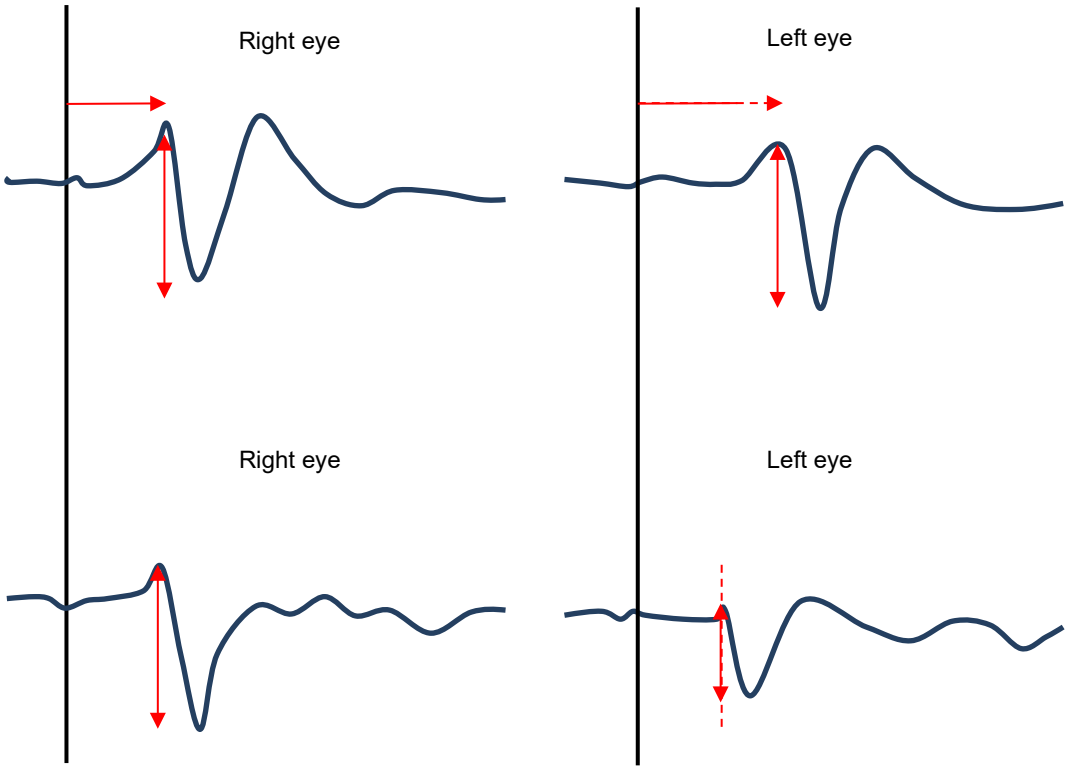

Figure 32: Interpretation of the oVEMP
Top traces show a prolonged latency from the left eye in comparison to the right eye, but both are of similar amplitude and normal asymmetry ratio.
Bottom traces show a normal response from the right eye and a lower amplitude response from the left eye producing an abnormally high amplitude asymmetry ratio.

6.9 Validating the warning criteria

The warning criteria that is to be implemented must be sensitive and specific whilst minimising *false positive* (the warning criteria is exceeded but no damage to neural structures is occurring) and *false negative* (the warning criteria is not exceeded but the patient awakens with a neurological deficit from the presumed pathways being monitored) rates.

By understanding the anatomical pathways and the neural generators of the oVEMP, intraoperative changes can be correlated to the site of injury and the presumed pathophysiology. In conjunction with the other recording modalities that are closely associated with the generation of oVEMPs, more reliant localising and pathophysiological detail can be given to the surgeon (Table 5).

An ipsilateral increase in the wave I to III interpeak latency of the brainstem auditory evoked potential (BAEP) would localise the contralateral change of the oVEMP n10 latency to the vestibulo-cochlear nerve (Legatt, 2018). Tonic activity seen on the free-running EMG activity of the oculomotor nerve (Lopez, 2011) would be consistent with iatrogenic compressive and traction forces being put on the third cranial nerve (cnIII) and would be associated with a decrease in the oVEMP on that side and an alteration in the asymmetry ratio.

Table 5: Localisation of neural dysfunction based on intraoperative neurophysiological changes

Affected site	**IOM changes**				
	oVEMP		BAEP		cn III
	ipsilateral	contralateral	ipsilateral	contralateral	
cnVIII	-	↑ latency	↑ I-III latency	-	-
MLF	-	↑ latency, ↓ amplitude	-	-	-
cnIII	-	↓ amplitude	-	-	↑ EMG activity ipsilaterally

- = unchanged; ↑ = increase; ↓ = decrease.

6.10 Can the oVEMP be recorded in patients with their eyes closed?

Several studies have shown that there is a strong modulatory of gaze direction on the oVEMP amplitude, with larger responses being seen with an upward gaze, consistent with activation of the inferior oblique muscles which act to extort and elevate the eyes (Govender et al., 2009, Welgampola et al., 2009). When using five different gaze elevations (+max, +30°, +20°, +10° and neutral) Govender et al., found that each gaze angle showed the same biphasic waveform, with the n10-p15 amplitude increasing as gaze elevation increased (Govender et al., 2016). A previous study, by the same group, showed that all subjects had an identifiable contralateral oVEMP response with neutral gaze, with 90% also showing an identifiable ipsilateral response (Govender et al., 2009).

However, with maximal upward gaze there was a 160% increase in the oVEMP amplitude contralaterally, compared to a 12.5% increase ipsilaterally (Govender et al., 2009). The group difference in amplitude between neutral gaze versus maximal upward gaze was 1.0μV versus 2.6μV, although there was no large change in peak latencies during upward gaze in comparison to neutral gaze (Govender et al., 2009), indicating that oVEMPs are feasibly recordable without upward gaze.

To investigate the feasibility of recording the oVEMP under different conditions further, Huang and colleagues (2012) tested 23 healthy adults, comparing 30° upward gaze with the oVEMPs recorded with the eyes closed (Huang et al., 2012). The waveform characteristics were found to be different between the two conditions, with a significant difference in latency between the n10 and p15 with the eyes looking upwards (8.7 ± 0.5msec and 13.3 ± 1.0msec) and with the eyes closed (9.9 ± 1.5msec and 15.5 ± 1.5msec respectively). There was also a significant decrease in amplitude between the two states (25.8 ± 9.8μV versus 19.3 ± 8.5μV) with the morphology also being 'blunted' in the eyes closed condition (Figure 33).

Whilst it is evident that an upward gaze of >+20° may be *optimal* to elicit oVEMP responses of maximal amplitude and shorter latency, the responses are still able to be recorded with the eyes closed and in their natural neutral position, which would be the conditions intra-operatively.

To test this statement further, a group of normal volunteers were investigated to compare the oVEMP responses recorded with the eyes open and then with the eyes closed. To replicate further the conditions that would be encountered intraoperatively, the oVEMPs were also recorded after independent stimulation of each ear whilst the subjects were in the left and right recumbent position, to see if the effects of the heads position would affect the latencies and amplitudes of the waveforms.

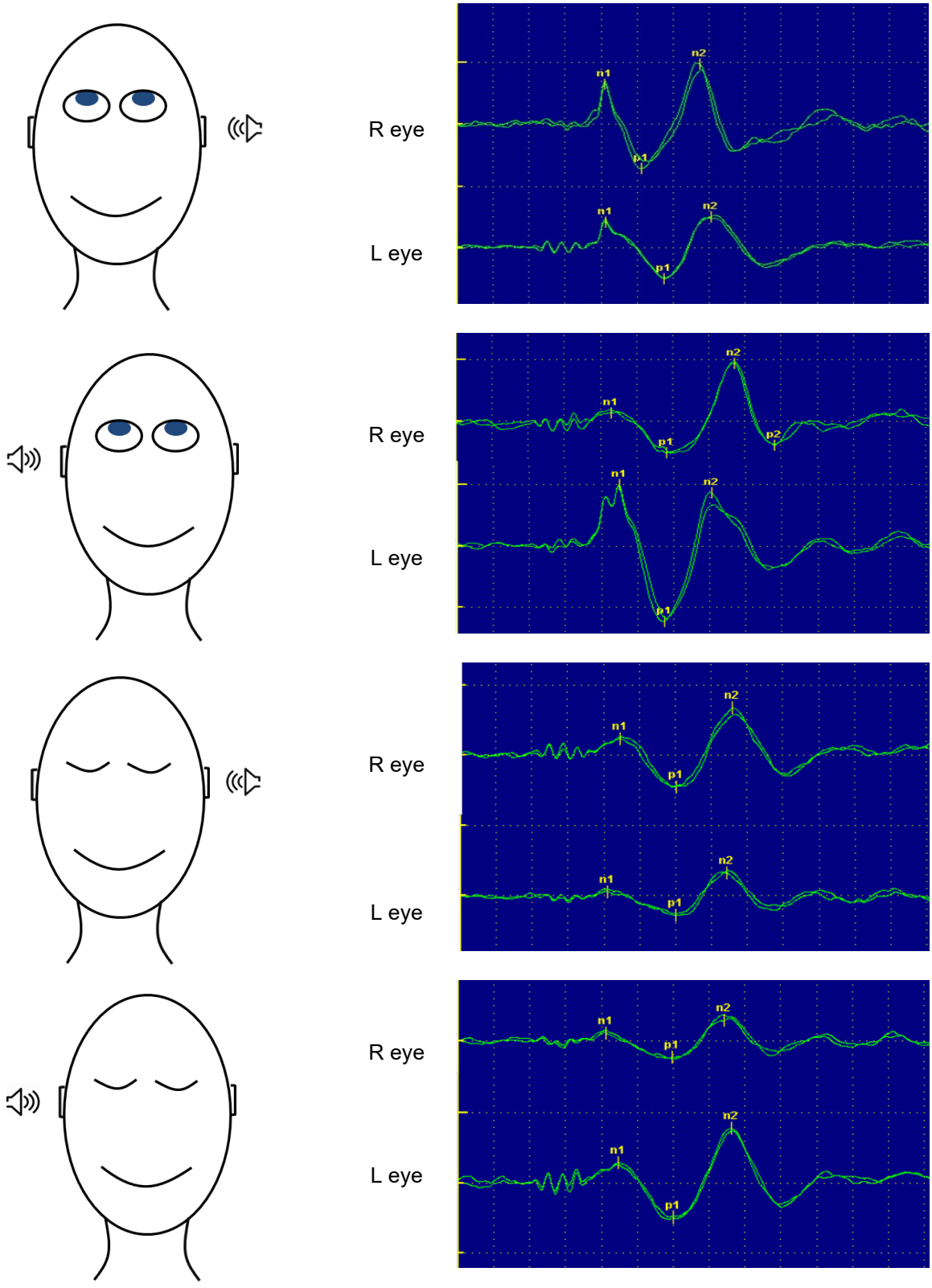

Figure 33: The oVEMP in different eye states.
oVEMPs recorded after acoustic stimulation in different eye conditions. The bottom traces show the lower amplitude and more 'blunted' morphological responses when the eyes are closed.

Chapter 7.

Recording the ocular vestibular evoked myogenic potential (oVEMP) in different eye states and body positions.

7.1 Introduction

The ocular vestibular evoked myogenic potential (oVEMP) represents the synchronous excitation of the extraocular muscles that are mediated by the vestibular end organ (Curthoys, 2010). The response can be elicited by vestibular stimulation following vibration (bone conducted vibration), sound (air conducted sound) or electrical (galvanic) stimulation (Curthoys, 2010). When evoked by air conducting sound, the oVEMP is predominately a crossed vestibulo-ocular potential. This can be recorded with an initial short latency (~10msec) from electrodes places beneath the eye and corresponds to the net excitation of the underlying inferior oblique muscle (Iwasaki et al., 2007). Several studies have shown that there is a strong modulatory effect with gaze direction on the amplitude and latencies of the oVEMP, with an increase in amplitude and a reduction in latency with upward gaze; regardless of which stimulus type is delivered (Iwasaki et al., 2008, Todd et al., 2008, Rosengren et al., 2013). These effects can either be explained by the movement of the inferior oblique muscle belly in relation to the recording electrode or to changes in the tonic activation of the inferior oblique at varying vertical gaze angles (Rosengren et al., 2005, Govender et al., 2009).

Due to their unique anatomical pathway, the ability to record reliable oVEMPs at the time of cerebellopontine angle neurosurgical procedures could be of benefit to the patient, to preserve vestibulo-ocular function. The propagation of the oVEMP encompasses the superior vestibular portion of the eighth cranial nerve, the medial longitudinal fasciculus of the brainstem up to the oculomotor nuclei and conduction along the oculomotor nerve to the inferior oblique muscle. Depending on the type of surgery and the site of surgery, one or several of these sections of the oVEMP pathway can become damaged due to mechanical or iatrogenic or ischaemic injury (Sala et al., 2015). Other neurophysiological modalities can monitor and map the functional integrity of nearby structures (Deletis and Fernandez-Conejero, 2016). However, there is currently no methodology that simultaneously assess the vestibulo-ocular pathway, in its entirety.

To be able to record the oVEMPs intraoperatively it is necessary to investigate whether the potentials can be reliably recorded when the patient has their eyes closed, as this is their condition in the anaesthetised state. It is also important to determine if the position of the head also influences the recorded potentials; as it has recently been shown that this can alter the amplitudes of the responses (Iwasaki et al., 2012, Wang et al., 2013a, Asal et al., 2017). The otolith maculae have different anatomical orientation, and so in those patients undergoing skull-based surgery in the lateral decumbent position, the gravitational forces on the otoconial membranes of the utricle could give rise to differential gravity specific resting potentials. These differences could affect the recordings being taken (Asal et al., 2017).

Therefore, the inter-side comparison between the recordings taken from the contralateral eye after air conducted auditory stimulation need to be considered with the head position in different planes, particularly if changes in inter-aural amplitude ratios are to be considered as an intraoperative warning criterion.

7.2 Materials and Methods

7.2.1 Subjects

A total of 17 healthy volunteers were included in the study (11 females and 6 males, ranging in age from 22 to 62 years of age with a mean of 39±10.6yrs). The subjects were identified from the staff in the Grey Walter Department of Clinical Neurophysiology, with no age or sex limit and with no previous complaints of dizziness, imbalance or ontological or neurological disease. The study was approved by the Trusts' review board and each subject signed the informed consent prior to participation after a full explanation of the experimental procedure.

7.2.2 Optimised stimulus and recording parameters

A 500Hz tone burst, with a rise/plateau/fall time of 1-2-1msec, was delivered monaurally via external circum-aural audiometry earphones (TDH 39) at a rate of 5.1Hz and at an intensity of 115dB nHL. A multichannel evoked potential recording system (Nihon Kohden, Neuromaster) was used to record the responses from each eye simultaneously. The responses were amplified x100,000 and were signal averaged 100 times over a 100msec time-base (10msec pre-stimulus and 90msec post-stimulus) using a low frequency filter of 10Hz and high frequency filter of 100Hz.

Disposable self-adhesive surface electrodes (Ambu, Neuroline 700) were applied after the skin had been gently abraded to minimize skin impedance. The absolute impedance of each electrode was <5kΩ with an inter-electrode impedance <2KΩ. A belly-tendon recording montage was used with the active electrode placed on the orbital rim, mid-way between the centre of the eye and the lateral canthus and with the reference electrode placed at the inner canthus, and the ground placed on the forehead (Fpz). Negative extraocular potentials recorded on the active electrode were displayed as an upward deflection.

7.2.3 Experimental design

The oVEMPs were recorded from the contralateral and ipsilateral eye to the side of stimulation after monaural stimulation using air conducted sound and the recording was replicated to confirm the presence of the response in each of the conditions studied. For the analysis of the results, only the crossed reflex will be considered.

Condition 1

The right and left ears were stimulated independently with the subject sat upright in a comfortable position on an examination couch with their neck supported by a head roll, to relieve tension in the neck and jaw. The oVEMPs were recorded with the eyes in 2 different test states and positions. The oVEMPs were recorded with their eyes open and elevated, and with their eyes closed and in a

neutral position. When the eyes were open the subject was instructed to fixate on an object 2-3 metres in front of them with their eyes elevated to a comfortable angle of 30-35^{o} above the horizontal line. The same body position was then used with the subject instructed to keep their eyes closed and to let their eyeballs rest in a neutral and comfortable position.

Condition 2

The oVEMP was recorded after independent monoaural stimulation of either the left ear or the right ear whilst the subject was lying comfortably on either side, in a recumbent lateral decubitus position (right ear down or left ear down). This produced four possible recording positions. With the subject lying either in the right lateral position (right ear down) and either the right ear (RearRD) or left ear (LearRD) stimulated monaurally; and in the left lateral position (left ear down) with either the right (RearLD) or left ear (LearLD) stimulated monaurally. Attention was taken to avoid any change in the electrodes or in the earphone position when the patient re-adjusted their position. The different test conditions were recorded in a randomised order.

7.2.4 Data analysis

Changes in the measures of interest between the various conditions of the eye (Condition 1, eyes open v eyes closed) and the position of the head, relative to ear being stimulated (Condition 2, right ear down v left ear down after right ear or left ear stimulation, labelled RearRD, LearRD, RearLD, LearLD respectively) were analysed. The latencies of the first negative peak, n10 (n1), and the subsequent positive peak, p15 (p1) in milliseconds after the onset of the stimulus from the contralateral eye were used for analysis. The interpeak latencies between these two points from the contralateral eye were also calculated. Analysis of the peak-peak amplitude in microvolts was taken from the maximal n10 (n1) peak to the subsequent minimal p15 (p1) trough from the contralateral eye. The analysis between conditions with the descriptive statistics expressed as the mean ± standard deviations were tabulated and statistically analysed (Tables 6-9). The amplitude asymmetry ratio (AAR) was calculated by taking the n1-p1 amplitudes from the right and left eyes using the equation

$$\text{Amplitude asymmetry} = 100 \times \frac{\text{right eye amplitude} - \text{left eye amplitude}}{(\text{right eye amplitude} + \text{left eye amplitude})}$$

7.2.5 Statistical analysis

The mean and standard deviations of the latencies, inter-peak latencies, amplitudes, and amplitude asymmetry ratios were calculated. For comparison of these characteristic parameters between each condition, the Mann-Whitney test was used to compare the results and the analysis was performed with the threshold for statistical significance being determined at the $p<0.05$ level.

7.3 Results

Condition 1 (Eyes open v eyes closed)

All of the subjects produced a clear and reproducible oVEMP response from the contralateral eye after monaural stimulation (100% response rate) with the eyes open and with the eyes closed.

Figure 34 shows the raw traces from the simultaneous right and left eye recordings, and the superimposed 'grand average', of all the responses to in the eyes closed and eyes open states to right and left ear stimulation. The oVEMP responses are larger from the contralateral eye and are larger when the eyes are open.

The right and left eye mean n1 latencies ± standard deviation with the eyes open were 10.08±0.58msec (range 9.3-11.8msec) and 10.23±0.68msec (range 9.4-12.1) respectively (Table 6); the corresponding p1 latencies were 15.37±1.04 (range 13.7-17.8) and 15.55±1.23msec (range 14.0-18.7msec). The n1-p1 inter-peak values were 5.29±0.93msec (range 4.4-6.3msec) and 5.32±0.83msec (range 1.9-9.3msec) for the right and left eyes. The amplitude of the n1-p1 was 14.94±10.41μV (range 2.8-33.4μV) and 10.49±8.43μV (range 0.6-27.0μV) from the right and left eye respectively. With the eyes open, the amplitude asymmetry ratio showed a range of -34.9 to 81.5% with a mean value of 19.1% (±33.0%).

With the eyes closed the mean n1 latencies (± standard deviation) of the right and left eyes were 11.72±1.24msec (range 9.8-14.0msec) and 12.23±2.30msec (range 9.8-20.4msec) respectively (Table 6), with the p1 values being 18.09±1.28msec (range 15.1-20.9msec) and 18.06±2.65msec (range 12.0-27.4msec). The inter-peak latencies of the right and left n1-p1 were 6.37±1.61msec (range 5.3-6.9) and 5.83±1.84msec (range 2.2-7.0msec). The amplitude of the n1-p1 was 5.40±3.37μV (range 1.4-11.0μV) and 4.61±3.07μV (range 0.6-13.5μV) from the right and left eye respectively. The amplitude asymmetry ratio showed a range of -44.75 to 44.3% with a mean of 6.01% (±32.6%).

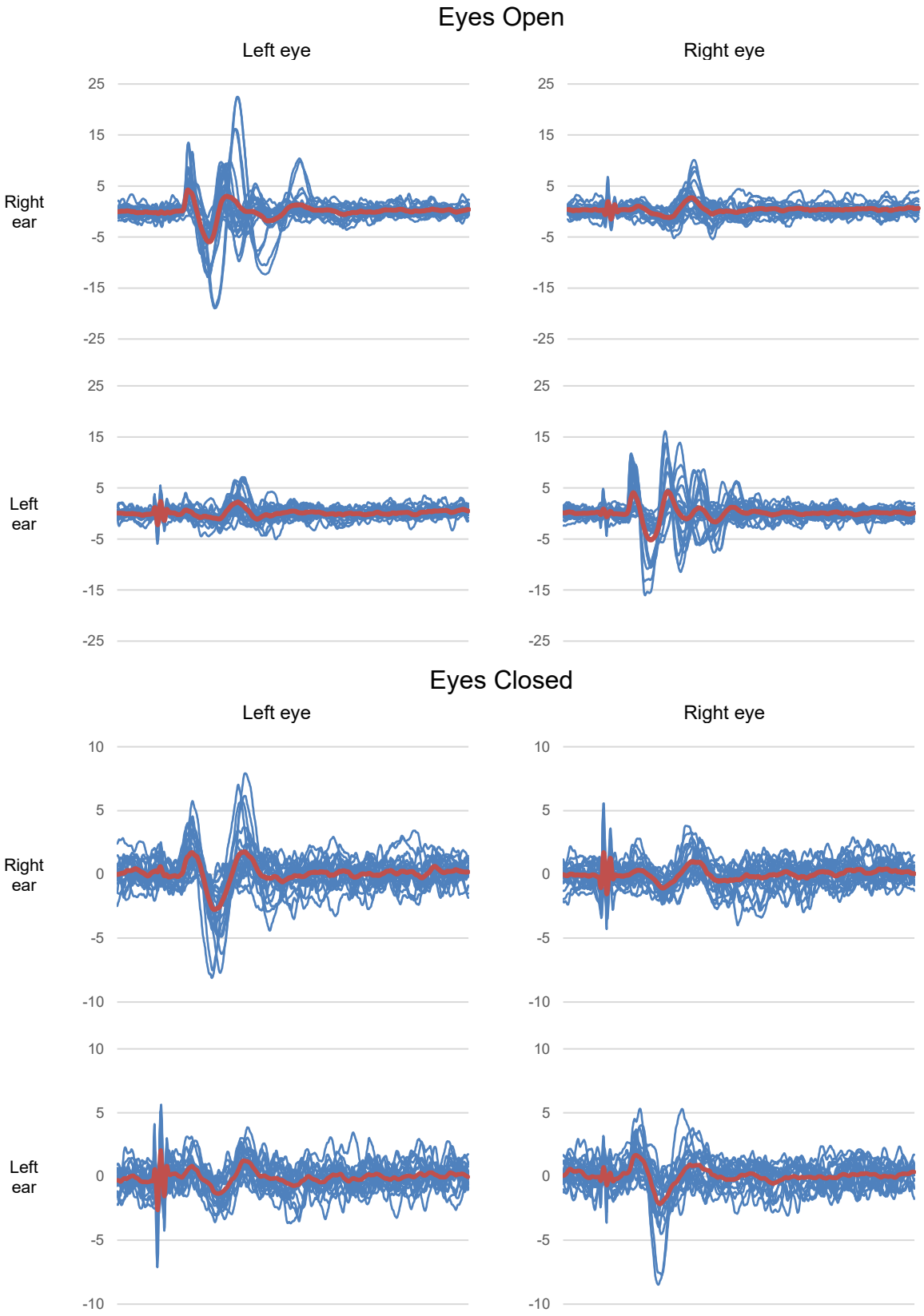

Figure 34: Different effect of eyes open and eyes closed on the oVMEP.
Individual raw data (blue lines) and 'grand average' of responses (brown line) from the left eye and right eye after monoaural right and left ear stimulation in the eyes open and eyes closed states. Time base 100msec (with a 10msec pre-stimulus delay).

Table 6: Data for the amplitude and latencies from Condition 1			
Eyes Open			
		Right eye	Left eye
n1 latency (msec)	mean	10.08	10.23
	range	9.3-11.8	9.4-12.1
	s.d.	0.58	0.68
p1 latency (msec)	mean	15.37	15.55
	range	13.7-17.8	14.0-18.7
	s.d.	1.04	1.23
n1-p1 interpeak latency (msec)	mean	5.29	5.32
	range	4.4-6.3	1.9-9.3
	s.d.	0.93	0.83
n1-p1 amplitude (μV)	mean	14.94	10.49
	range	2.8-33.4	0.6-27.0
	s.d.	10.41	8.43
AAR (%)	mean	19.1	
	range	-34.9 – 81.5	
	s.d.	33.0	
Eyes Closed			
		Right eye	Left eye
n1 latency (msec)	mean	11.72	12.23
	range	9.8-14.0	9.8-20.4
	s.d.	1.27	2.36
p1 latency (msec)	mean	18.09	18.06
	range	15.1-20.9	12.0-27.4
	s.d.	1.31	2.72
n1-p1 interpeak latency (msec)	mean	6.37	5.83
	range	5.3-6.9	2.2-7.0
	s.d.	1.65	1.88
n1-p1 amplitude (μV)	mean	5.40	4.61
	range	1.4-11.0	0.6-13.5
	s.d.	3.45	3.15
AAR (%)	mean	6.01	
	range	-47.75 – 44.3	
	s.d.	32.6	

The boxplots of the latencies of the contralateral n1 and p1 oVEMP responses to the eyes opened and eye closed states are shown in Figure 35 and the boxplots of the inter-peak latencies of n1-p1 in these conditions are shown in Figure 36.

The boxplots of the n1-p1 amplitudes are seen in Figure 37. The amplitude asymmetry ratios showing the comparison between the eyes open and the eyes closed states are shown as boxplots in Figure 38. Given the wide range of values for these ratios, these were not analysed further.

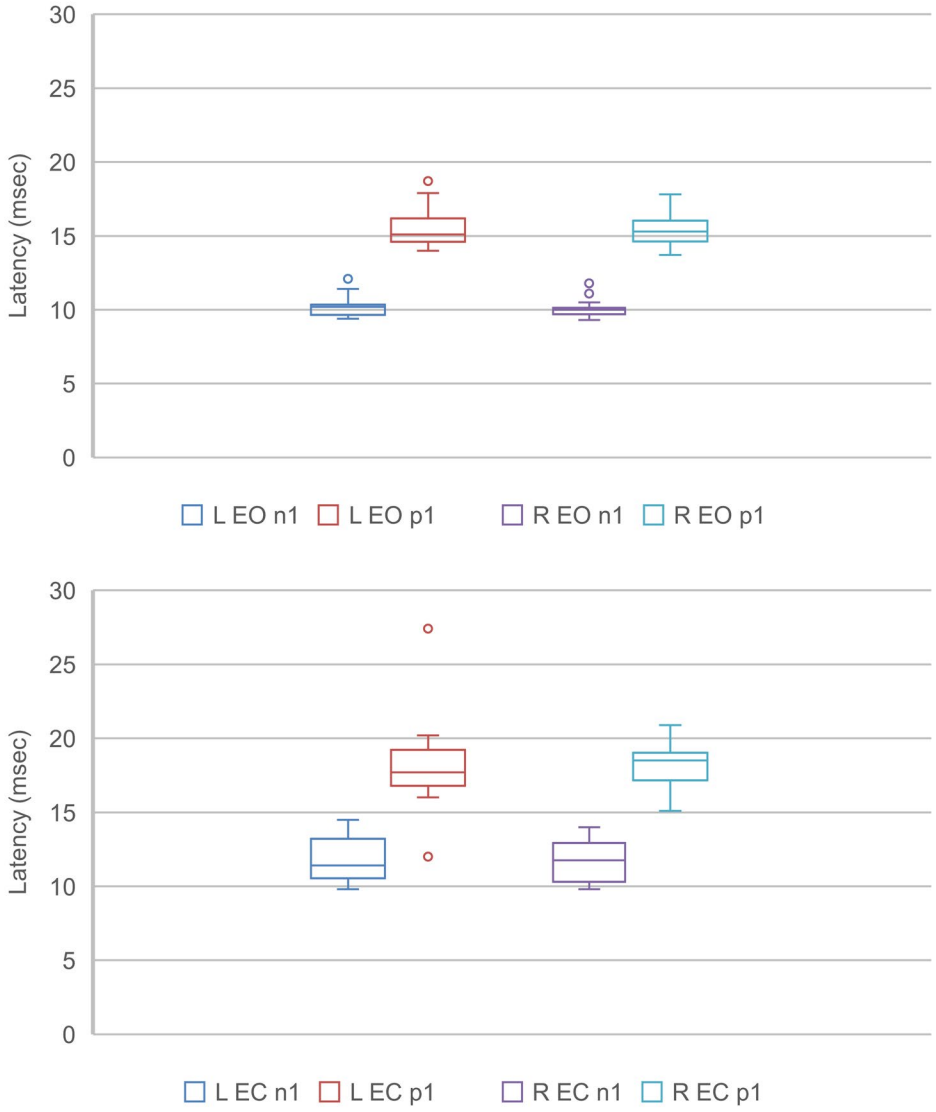

Figure 35: The boxplots of the n1 and p1 latencies in the eyes open and eyes closed state
Top. Boxplots shows the latencies when the eyes were open
Bottom. Boxplots shows the latencies when the eyes were closed.
The latencies of the responses are longer when the eyes are closed.

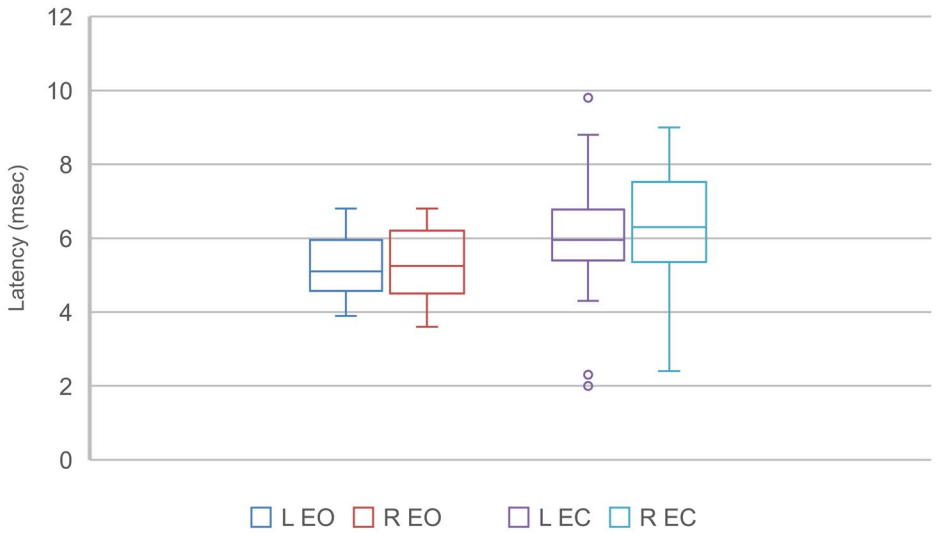

Figure 36: The boxplots of the inter-peak latencies when the eyes are open and closed. Larger n1-p1 inter-peak latencies are seen when the eyes are closed than when the eyes are open.

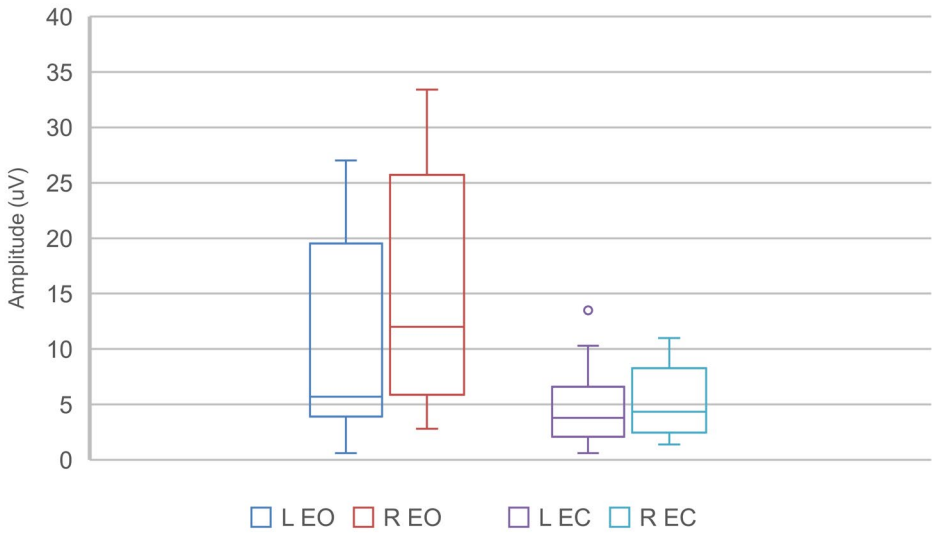

Figure 37: The boxplots of the oVEMP amplitudes when the eyes are open and closed. The displayed boxplots show larger n1-p1 amplitudes when the eyes are open and elevated.

In the eyes open state there was no significant statistical difference between the right and left n1 latencies ($p = 0.253$), the p1 latencies ($p = 0.689$) or the inter-peak (n1-p1) latencies ($p = 0.915$). There was also no statistically significant difference between the n1-p1 amplitudes ($p = 0.110$). When the eyes were closed there was no significant difference between the right and left n1 latencies ($p = 0.681$), the p1 latencies ($p = 0.580$), the inter-peak (n1-p1) latencies ($p = 0.301$) or the n1-p1 amplitudes ($p = 0.518$) (Table 7).

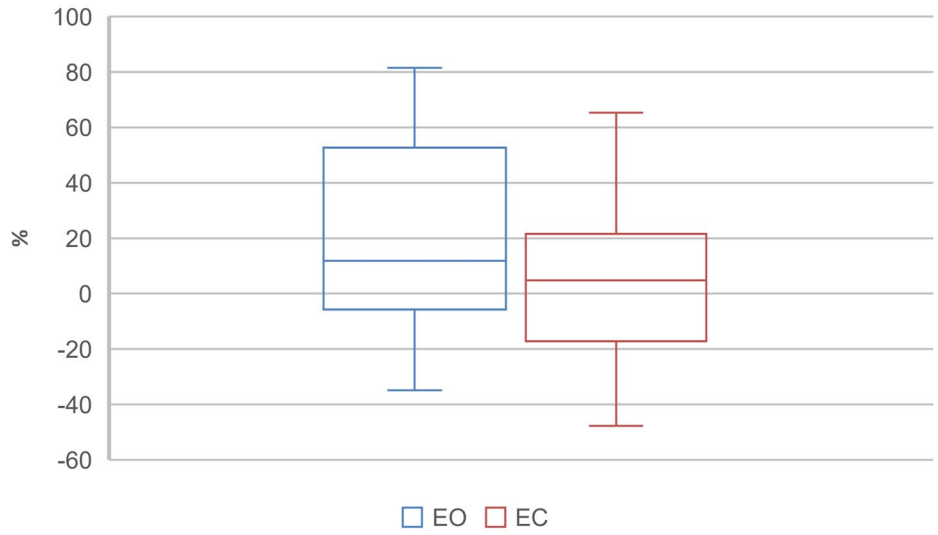

Figure 38: Boxplots of the amplitude asymmetry ratios when the eyes are open and closed. Note the wide variation in value in both states.

There were highly significant statistical differences between the n1 and p1 latencies and the n1-p1 amplitudes when comparing the eyes open and eyes closed state between the left and right eyes (Table 7). Although when comparing the n1-p1 interpeak latencies, there was no statistical difference from the left eye ($p = 0.067$) between the two states, there was a statistical difference from the right eye ($p = 0.013$).

Table 7: Statistical results of Condition 1	
Eyes Open	
	Significance
R v L n1 latency	0.253
R v L p1 latency	0.689
Interpeak R v L n1-p1 latency	0.915
R v L n1-p1 amplitude	0.110
Eyes Closed	
	Significance
R v L n1 latency	0.681
R v L p1 latency	0.580
Interpeak R v L n1-p1 latency	0.301
R v L n1-p1 amplitude	0.518
Right eye	
	Significance
EO v EC n1 latency	0.000007009*
EO v EC p1 latency	0.00000005*
Interpeak EO v EC n1-p1 latency	0.013*
EO v EC n1-p1 amplitude	0.0004*
Left eye	
	Significance
EO v EC n1 latency	0.00005*
EO v EC p1 latency	0.00001906*
Interpeak EO v EC n1-p1 latency	0.0668
EO v EC n1-p1 amplitude	0.01664*
*p<0.05 significance	

Condition 2 (Right ear down and left ear down

Reliable responses were seen from each of the subjects from the right and left eye after stimulation of the left and right ears respectively in both of the different body positions (i.e., lying on the right side = left ear down and lying on the left side = right ear down). The averaged waveforms from all the subjects across the various conditions are seen in Figure 39.

The resultant values of the n1 and p1 latencies and the n1-p1 inter-peak latencies and amplitude and are tabulated, along with the amplitude asymmetry ratios (Table 8).

Table 8: Data for the amplitude and latencies from Condition 2

Right ear Down			
		Right ear	Left ear
n1 latency (msec)	mean	10.32	12.15
	range	8.9-12.4	10.2-18.1
	s.d	0.86	1.97
p1 latency (msec)	mean	16.6	18.46
	range	14.5-19.7	12.5-30.5
	s.d	1.29	3.99
n1-p1 interpeak latency (msec)	mean	6.29	7.05
	range	4.4-8.0	3.3-13.9
	s.d.	1.31	2.30
n1-p1 amplitude (μV)	mean	9.24	4.08
	range	1.6-20.1	1.4-11.0
	s.d.	5.76	2.30
AAR (%)	mean	33.50	
	range	-15.79 – 82.66	
	s.d.	26.75	
Left ear Down			
		Right ear	Left ear
n1 latency (msec)	mean	11.19	10.11
	range	9.7-12.5	8.8-11.0
	s.d.	0.79	0.55
p1 latency (msec)	mean	17.83	16.19
	range	15.9-20.4	13.1-19.8
	s.d.	1.49	1.63
n1-p1 interpeak latency (msec)	mean	6.64	6.09
	range	4.1-8.9	3.7-9.8
	s.d.	1.30	1.69
n1-p1 amplitude (μV)	mean	4.93	8.62
	range	1.4-9.4	2.3-21.8
	s.d.	2.48	6.30
AAR (%)	mean	-20.50	
	range	-79.41 – 28.44	
	s.d.	28.91	

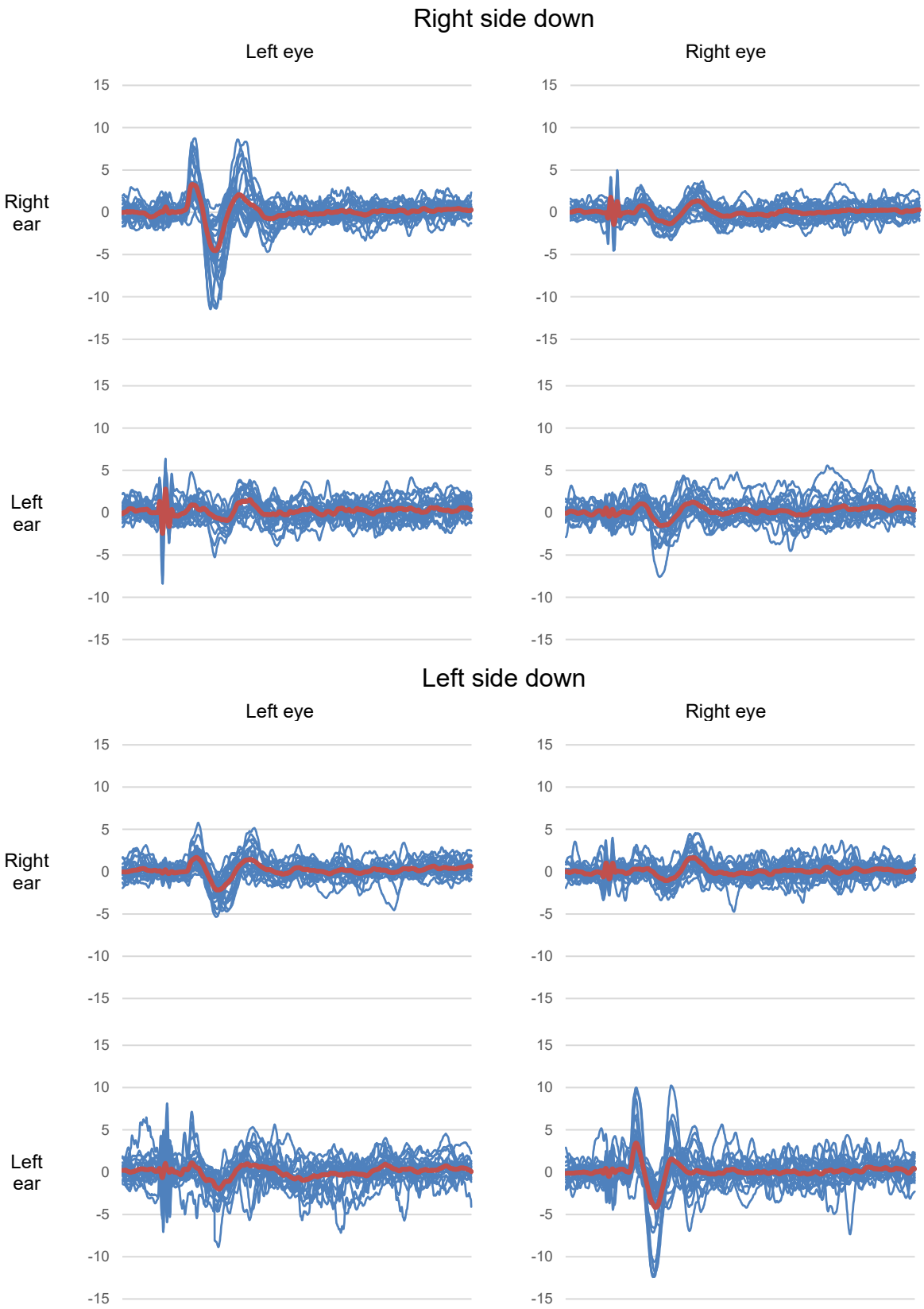

Figure 39: oVEMPs after right ear down and left ear down.
Individual raw traces (blue lines) and 'grand average' (brown lines) of the oVEMP responses from the right and left eyes after monaural stimulation of the right and left ears in the left and right lateral decubitus positions (condition 2).
Time base = 100msec (10 msec pre-stimulus delay).

The responses from the left eye following right ear stimulation showed a shorter n1 latency (mean 10.32±0.86msec) and p1 latency (mean 16.6±1.29msec) than those same responses from the right eye after stimulation of the left ear when that ear was in the down position; where the n1 was seen with a latency of 11.19±0.79msec and the p1 latency was seen at 17.83±1.49msec. After stimulation of the left ear the recordings from the right eye showed longer n1 latencies when the right ear was down (12.15±1.97msec) then those from the left eye following stimulation of the right ear (10.11±0.55msec). The p1 latencies were also longer following left ear stimulation in this position (18.46±3.99 versus 16.19±1.63msec) (Figure 40).

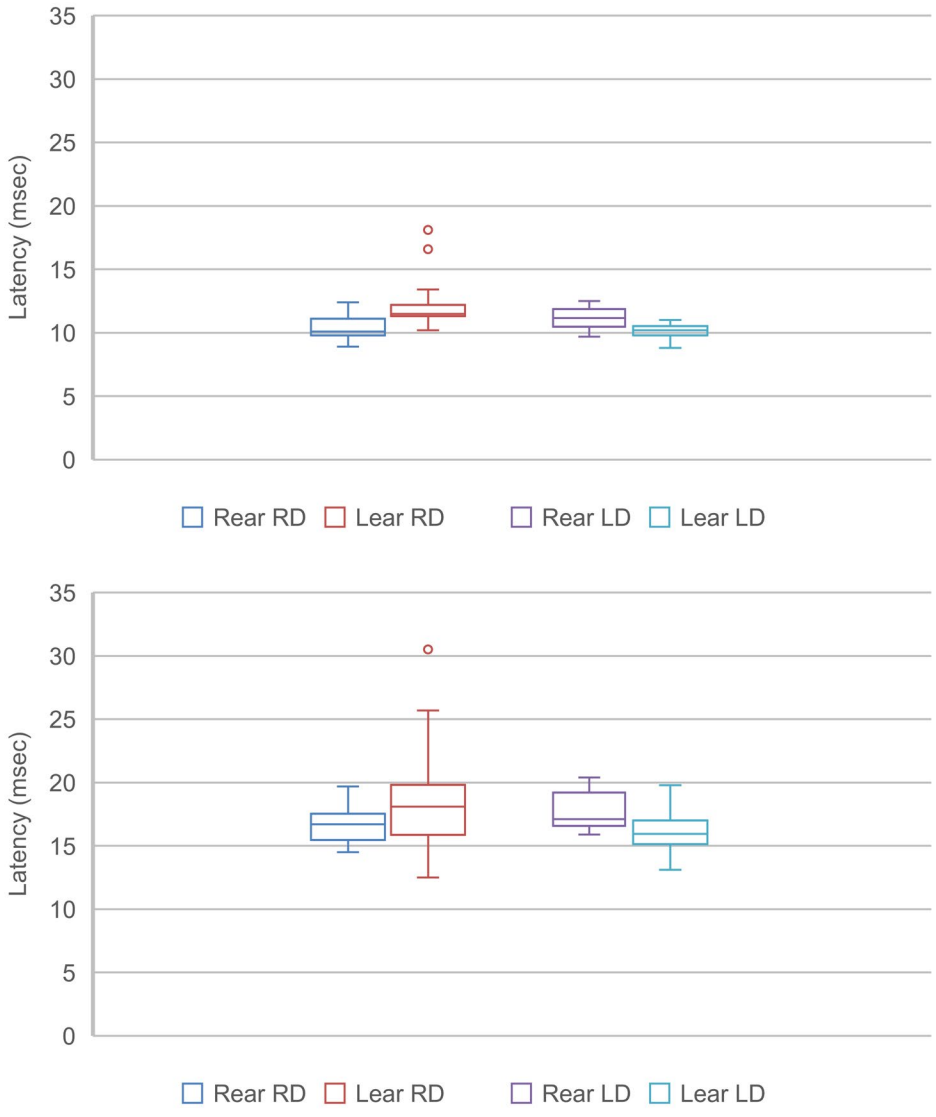

Figure 40: The boxplots of the n1 and p1 latencies after right and left ear stimulation with the subjects right side and left side down.
Top. Boxplots of n1 latencies in the different positions
Bottom. Boxplots of the p1 latencies in the different positions.

The n1-p1 inter-peak latencies from the left eye following stimulation of the right ear was slightly shorter (6.29±1.31 versus 6.64±1.30msec) when the right ear was down in comparison to when the left ear was down. When the left ear was down the n1-p1 inter-peak latency was shorter from the left eye following right ear stimulation than that of the right eye following left ear stimulation (6.09±1.69 versus 7.05±2.30msec) (Figure 41).

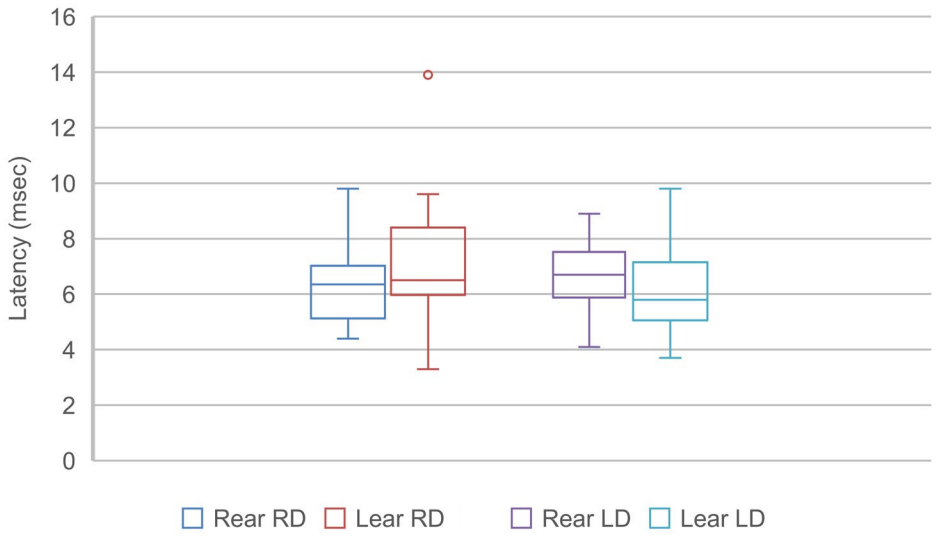

Figure 41: Boxplots of the interpeak n1-p1 latencies following stimulation of the right and left ears in different body positions.

When the right ear was down, the amplitude of the responses from the left eye after right ear stimulation were larger (9.24±5.76μV) that those from when the left ear was down (4.93±2.48μV). However, when the left ear was down the amplitude of the responses from the right eye after left ear stimulation were larger (8.62±6.30μV) than when the right ear was down (4.08±2.30μV) (Figure 42).

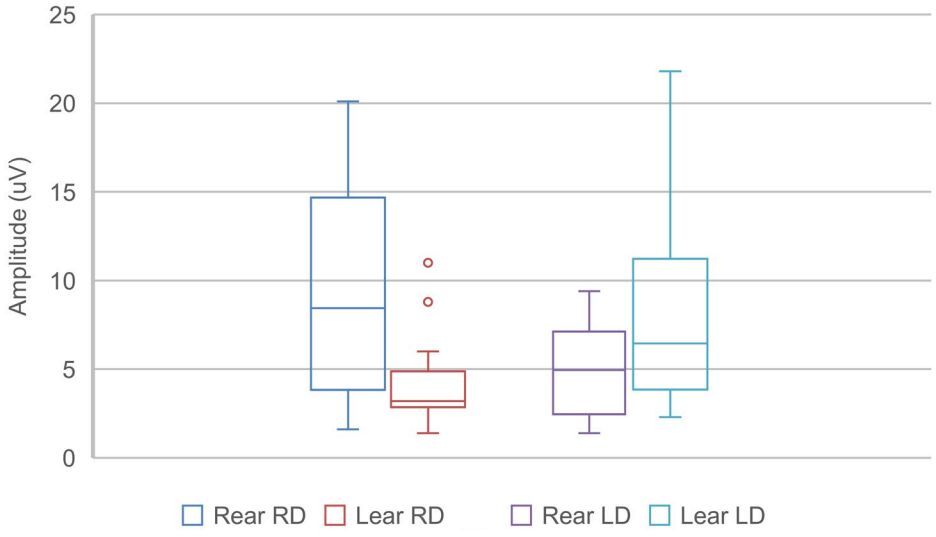

Figure 42: Boxplots of the n1-p1 amplitudes in different body positions.
The oVEMP has a larger amplitude when the ear that is stimulated is in the *down* position.

The amplitude asymmetry ratios between the eyes open and the eyes closed state (condition 1) showed wide inter test variability. The mean values for the eyes open and eyes closed were 19.1±33.0 and 6.9±32.6% respectively; with a wide range of values being seen also, -34.9 to 81.5% when the eyes were open and -47.75 to 44.3% when the eyes were closed (Table 6). Similar variation was seen between the ratios when the subjects were lying on their left and right sides (condition 2). When the right ear was down the mean ratio was 33.5±26.75% (range -15.79 to 82.66%) and when the left ear was down the mean ratio was -20.5%±28.91% (range -79.41 to 28.44%) (Table 7). Given the wide variation of these values (Figure 43) these ratios were not considered further for analysis.

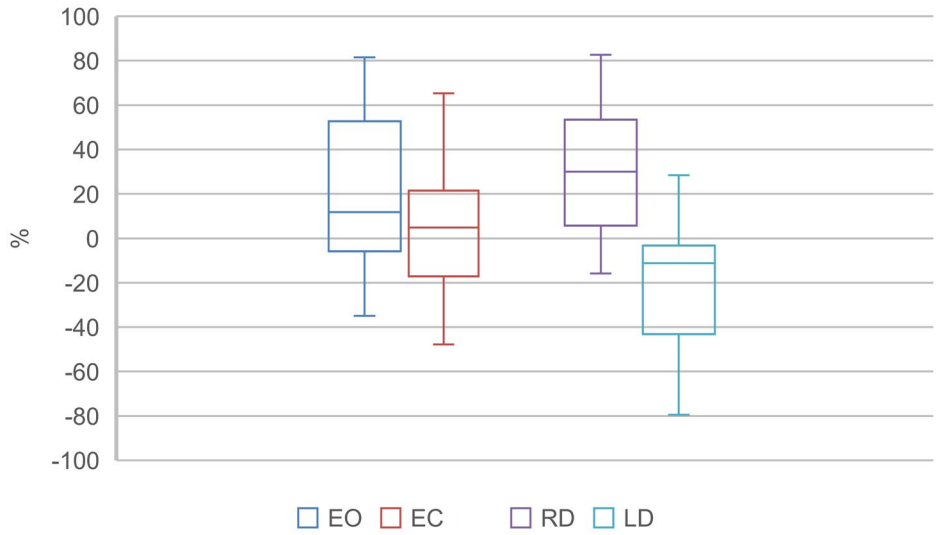

Figure 43: The amplitude asymmetry ratios.
Boxplots of the amplitude ratios from the eye open and eyes closed state (Condition 1) and when the right (RD) and left (LD) ears were down (Condition 2).

Table 9: Statistical results of Condition 2	
Right ear Down	
	Significance
R v L n1 latency	0.05566
R v L p1 latency	0.03073*
Inter-peak R v L n1-p1 latency	0.2174
R v L n1-p1 amplitude	0.002266*
Left ear Down	
	Significance
R v L n1 latency	0.00005572*
R v L p1 latency	0.0006568*
Inter-peak R v L n1-p1 latency	0.1269
R v L n1-p1 amplitude	0.05566
*p<0.05 significance	

The n1 latency between the right and left sides when right ear was down did not show a significant difference, although there was a significant difference between the two sides when the left ear was down (*p = 0.0553 versus p <0.05*) (Table 9). In both the right ear down and left ear down positions there was a significant statistical difference between the right and left p1 latency and there was a difference in n1-p1 amplitudes with the right ear down. However, there was no statistical difference between the two eyes in the two different states for the inter-peak n1-p1 latencies (Table 9).

The ocular vestibular evoked myogenic potentials recorded when the eyes are closed are of longer latency with a reduced amplitude, in comparison to those recorded when the eyes are open and maintained in an upward gaze. The morphology of the waveforms in the eyes closed are also altered with a more 'blunted' appearance caused by the reduced slope the n1-p1 component. When the subject is lying in the recumbent decubitus position, the responses show greater inter-side variability than those seen when the patient is sat upright. The contralateral eye responses that are recorded after stimulation of the ear that is in the downward position show shorter latencies and higher amplitude following stimulation of that ear, than from the ear that is upper most.

7.4 Discussion

The basic morphology of the oVEMP under most recording conditions can be attributed to a combination of the tonic muscle activity of the inferior oblique muscle and the proximity of the recording electrode to this muscle (Piker et al., 2011).

As the inferior oblique muscle is mainly activated with extorsion and elevation of the eyeball, it is highly activated during upward gaze; and this upward gaze brings the belly of the inferior oblique closer to the surface of the skin and therefore closer to the recording electrodes (Iwasaki et al., 2008). The inferior oblique muscle moves anteriorly as the eye is elevated, moving 4.3±0.3mm with a change of gaze from 24^{o} depression to 24^{o} elevation upwards (Demer et al., 2003). Therefore, the size of the recorded electrical response is expected to increase as the distances between the source and the electrode is decreased. This is because the activity recorded from the surface electrode is the algebraic sum of the trains of action potentials that are generated by the activated motor units (Keenan et al., 2005). However, in one study, whilst placing the electrodes on the skin further away from the eye did result in lower oVEMP amplitudes of ~20-25%, this effect was not as marked as the 74% decrement in the response between an upward gaze (24^{o}) and the neutral gaze (Rosengren et al., 2013). Similarly, when using several different electrode placements around the orbit of the eye, Govender et al (2016) found that whilst there was a linear relationship between the gaze angle and the amplitude of the oVEMP - with all the varying electrode configurations that were used - there was little difference between the values recorded. In other studies, there was an almost fivefold increase in the n1-p1 amplitude (average 1.3 to 6.2μV) when comparing the neutral to 30^{o} upward gaze (Murnane et al., 2011) and a two to threefold increase in amplitude from 0 to 20^{o} (Govender et al., 2009, Welgampola et al., 2009).

Govender et al (2016) had also noticed that with electrodes placed in a similar position to the one used in this experimental design, that when the eyes were in a neutral position, they were still able to produce a response rate of 83%. Therefore, whilst an upward gaze undoubtedly produces higher amplitude responses, a neutral gaze does still enable an oVEMP to be recorded, even when the eyes are closed. Whilst the proximity of the inferior oblique to the recording electrode does obviously contribute to some of the observed amplitude reduction seen in most studies, it is actually the amount of tonic activation of the inferior oblique that is the major contributing factor.

However, even when the eyes are closed there is a tendency for the eyes to still undergo tonic upward movement of approximately 10-15^{o} (Takagi et al., 1992); this is due to the so-called 'Bells phenomena'. In a similar study to this current investigation, Huang et al (2012) compared the characteristic parameters of the oVEMP to evaluate the feasibility of recording this potential with the eyes closed after bone conducting vibration applied to the forehead. In their case series, they found that clear oVEMPs could be recorded in both the eyes open and elevated condition and the eyes closed and neutral condition in all 20 normal subjects. They found that the mean latencies of the n1 and p1 were significantly prolonged (p <0.001) with the eyes closed and that the mean n1-p1 interval and amplitude were also significantly longer and smaller than those recorded with the eyes looking up. These findings are similar to the results between the eyes states in this study after air-conducted sound (Table 6). Considering that when the eyes are closed the natural upward deflection of the eyeball is roughly half the angle of the stated maximal upward angle in the studies described, the corresponding amount of muscular contraction in the inferior oblique would obviously be reduced and could therefore result in the observed reduced amplitudes (Huang et al., 2012). The finding that there is a 100% response rate when the eyes are closed, would therefore potentially indicate that the oVEMPs would still be recordable when the patient is under general anaesthesia. Indeed, it has been noted that there is still an upward deviation of the eye (the Bells phenomena) in patients under general anesthesia (Paez et al., 1984), which persists at sufficient deeper levels of anaesthesia (Rossiter et al., 2006). These subsequent findings and observations would also contribute to the generation and identification of these potentials intraoperatively.

Whilst the tonic activation of the inferior oblique muscles and the recording electrodes proximity to that muscle contribute to the resultant waveform, the neural input to the reflex in different head positions also needs to be considered (Iwasaki et al., 2012, Asal et al., 2017).

Recently published studies have investigated the effects that postural change can have on the oVEMP (Iwasaki et al., 2012, Wang et al., 2013a, Taylor et al., 2013). The sitting position can show a shorter latency of the n1 potential in comparison to the supine position (10.76±0.73 v 10.94±0.77msec). This may be attributed to the fact that in the supine position the gravitational forces are aligned with the polarization vectors of the saccular, whereas in the sitting position the gravitational forces exert maximal forces on the utricular hair cells (Asal et al., 2017).

In comparison to the supine position, there can be a distinct reduction in the amplitude of the oVEMP in the lateral position, especially when the stimulated ear is down (Gurkov and Katner, 2013). It has also been shown in subjects undergoing tilting of the head and body in the roll plane, that there is a significant effect on the oVEMP amplitude. The amplitude decreases which are seen with the increasing angular departure of the body from the upright position are most significant when the head and body are below the horizontal plane (Taylor et al., 2013). Consequently, this effect of head orientation also has a significant effect on the amplitude ratio (Taylor et al., 2013). The effect on the amplitude ratio with increasing orientation was attributed to a reduction in the amplitude of the oVEMP from the ear that was downward, which could be the result of the sensitivity bias of the utricle for sheer forces that are laterally directed (Dai et al., 1989). However, a more plausible explanation proposed for the effects on the amplitude ratio by Taylor et al, (2013) could be that the changes in position of the head impose mechanical constraints that increase the intra-cochlear pressure. The secondary effects of this would lead to an increase in intracranial pressure that impedes the sound transmission through the middle ear, as the lower ear would experience more pronounced pressure on the cochlear window and the stapes on that side would be moving against the effects of gravity (Voss et al., 2010). The weight of the otoconial membrane when the head is tilted ±90^{o} would also bring the utricular macula into the plane of the gravitational axis, so that the mechanical load on the utricular hair cells is maximal, causing the capacity for further hair cell displacement to be limited (Shojaku et al., 2008).

Although another study did not observe any significance in the amplitude asymmetry ratio using air conducted stimuli with the head tilted in the roll plane, there was a significant increase in the amplitude ratio using bone conducted vibration (Iwasaki et al., 2012). The reason for this discrepancy may be given that different stimulating conditions reflect the activity of different populations of vestibular afferents in the utricle (Iwasaki et al., 2012). Based on their spontaneous firing rates, vestibular afferents can be classified into regular and irregular types (Goldberg, 2000). Large axons that originate from the central region of the cristae and the striola region of the maculae show a large and irregular variation in their spontaneous firing rates, whereas smaller axons have a smaller variability their spontaneous firing rate and these regular neurons arise from the extra-striola and peripheral regions. The irregular neurons show a greater sensitivity and phasic response dynamic to angular and linear forces that act on the head, whereas the regular neurons show a lower sensitivity and tonic response dynamics (Goldberg, 2000). When the body is tilted on a tilt table, the inclination of the head also changes the otoliths with respect to the gravitational force vector, particularly the utricle, which is the main origin of the oVEMP. Lateral head tilts that alter the gravity forces upon the utricle – without a change in the relative evaluation of the head in respect to the body – can therefore modulate the oVEMP amplitude.

7.4.1 Strengths and limitations

Whilst the sample size of this is relatively small, it indicates that reliable and reproducible potentials are able to be recorded in different eye states - although the symmetry of the responses seems to be altered with the patient's body position. Further studies would need to be performed on patients, ideally pre-operatively, to see whether these findings are translated into the patient population with pre-existing vestibular disturbances.

It was not possible to study the longer lasting effects of the subject's body position and whether these differences in the waveform amplitude and latency were transient. The values of these responses could potentially alter over several minutes/hours as the otolithic structures re-adjust to their altered gravitational pull. If this were to occur over a more prolonged period (i.e., hours), then it could result in 'false-positive' results being fed back to the surgeon during the operation. In that case more detailed analysis of the values being obtained, and consideration to the stage of surgery and the manoeuvres being undertaken at that time, would need to be factored in before any information could be fed back to the surgical team.

As there is a high variability in the amplitude of the oVEMP (Figure 37), using an amplitude asymmetry ratio was considered as a potential single metric to analyse the inter-side differences in amplitude intraoperatively. The amplitude asymmetry is considered an indicator of pathology, with an amplitude ratio of <34% considered as normal (Bogle, 2018). However, data from this study was too inconsistent for this criterion to be used. Although not part of this study, it was noted that an oVEMP potential could be detected ipsilaterally in approximately 70% of the ears tested. There are several projections that travel from the utricle to the ipsilateral eye muscles (Uchino and Kushiro, 2011), with secondary efferent utricular-ocular pathways that terminate in the ipsilateral superior rectus muscle and the inferior rectus ipsilaterally (Weber et al., 2012).

Therefore, future warning criteria could take advantage of the contralateral to ipsilateral amplitudes when determining the cut-off values for the amplitude ratios using a novel modified equation of

$$\text{Amplitude asymmetry} = 100 \times \frac{(\text{contralateral amplitude} - \text{ipsilateral amplitude})}{(\text{contralateral amplitude} + \text{ipsilateral amplitude})}$$

An increase in the ratio would indicate an ipsilateral pathway abnormality whilst a decrease in amplitude asymmetry ratio would indicate a contralateral pathway abnormality. This alteration could be an earlier indicator of impending neurological deficit, as the usual 50% decrease in absolute amplitude that is typically used for other neurophysiological amplitudes would not have been exceeded.

7.5 Conclusion

It was possible to record the oVEMP in all the subjects when their eyes were closed. In comparison to the conventional eyes open and eyes elevated condition that is used in routine clinical practice, the potentials that are recorded when the eyes are closed are of lower amplitude, with increased latencies of the n1 and p1 peak potentials and they also show increased interpeak latencies.

Whilst some of these descriptive parameters may be statistically significant, they are not necessarily clinically relevant in the context of intraoperative monitoring. At the time of the recording intraoperatively, the patient acts as their own normative control, and any changes in amplitude or latency are assessed at the various stages of the surgery and are compared to the baseline recordings that are taken prior to the initiation of the surgical resection. Therefore, the conventional upper and lower limits of normal, based on standard deviations or upper and lower quartiles used in the clinical diagnostic setting (Walther et al., 2011), are not required for interpretation in this context.

The marked differences that were seen in the recordings when the patient is in a recumbent decubitus position from stimulation of one ear to the other would mean that the amplitude ratios would not be an indicative value to use as a warning criterion. However, the inter-peak amplitudes of the responses were of high enough voltage to be monitorable from either ear in either position.

The 100% response rate from all normal subjects under investigation in the eyes closed state would mean that oVEMP recordings using air conducted stimulation are potentially amenable to be recorded intraoperatively.

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Chapter 8.

Neurophysiological monitoring of the ocular vestibular evoked myogenic potentials (oVEMPs) intraoperatively for brainstem surgery.

8.1 Introduction

In adults, 15-20% of brain tumours occur within the posterior fossa and are typically metastatic tumours, lymphomas or haemangioblastomas. The prevalence of brainstem tumours in the paediatric age group is higher at ~55-70%, with medulloblastomas, ependymomas and pilocytic astrocytomas being seen most often. The patient's clinical presentations will vary depending on the tumour site; with the symptoms being due to either focal compression of the cerebellum and/or brainstem or from raised intracranial pressure. Whilst nerve dysfunction is an *indirect* consequence of posterior fossa tumour growth, *direct* compression or infiltration of the pons, midbrain and cerebellum can also cause oculomotor issues (Peeler, 2017). Oculomotor dysfunction including cranial nerve neuropathies and nystagmus is cited as the most common presenting symptom, after headache and vomiting, in patients diagnosed with brainstem tumours, especially in the paediatric population (Harbert et al., 2012, Peeler, 2017).

Gaze deficits and vestibular disturbances can result from injury or dysfunction anywhere along the oculomotor system pathway (Rosenberg and Colebatch 2011, Oh et al., 2016). A failure to move the eyes due to paralysis of the muscles that control the eye (ophthalmoplegia), or to hold them still (nystagmus), or to maintain proper eye alignment (strabismus) can cause a variety of disabling visual symptoms (Horn and Leigh, 2011). The paresis of the extra ocular muscles can cause suppression of vision and loss of visual acuity from the eye (amblyopia), the illusion that the world is moving (oscillopsia) and double vision (diplopia). Diplopia can cause a loss of stereoscopic vision – which often requires monocular occlusion – and carries the risk of a reduction in the peripheral visual field that can lead to secondary amblyopia and even functional blindness (Sekhar et al., 1986, Schlake et al., 2001). These disorders can have a serious impact on the patient's quality of life and their ability to function in a world that relies on the rapid interpretation of visual information to survive (Strupp et al., 2014).

The survival and outcome of patients with posterior fossa tumours has improved over the last 20 years. The increased fidelity and availability of radiological imaging has facilitated the earlier detection and staging of surgical resection, as well as the operative planning and post-surgical surveillance and follow-up in these patients. The implementation of microsurgical techniques and modern neuro-anaesthesia and post-operative care has also enabled more patients to be afforded the benefit of neurosurgical resections. In recent years the use of adjuvant radiosurgery has altered the surgical strategy for tumour resection in and around the brainstem. However, the surgical treatment of these tumours still represents a considerable challenge for neurosurgeons (Sala et al., 2015, Slotty et al., 2017). The priority now is to preserve the patient's neurological function, rather than achieving a total resection of the lesion within the posterior fossa.

This shift in paradigm, from an ‘anatomical’ approach to a more patient centred ‘functional’ approach, has required sophisticated neurophysiological recording techniques to be available and implemented at the time of surgery. Intraoperative neurophysiological monitoring can predict impending deficits of the pathways that are being assessed, which can lead to the appropriate timing of when to stop the surgical resection (Seidel et al., 2020).

For neurological deficits to be avoided, the neurophysiological signals that are being recorded need to be acquired in near real-time, so that any signal changes that are beyond the warning criteria are able to be communicated to the surgeon in a timely manner.

The current monitoring techniques utilised can monitor the ascending and descending long tracts through the brainstem. To do this somatosensory evoked potentials and corticospinal motor evoked potentials after transcranial electrical stimulation are used (MacDonald et al., 2013, MacDonald et al., 2019). The descending corticobulbar tracts to the trigeminal and facial nerves, and to the lower cranial nerves, can also be reliably assessed to monitor the function through the medullary part of the brainstem (Deletis and Fernandez-Conejero, 2016). The addition of brainstem auditory evoked potentials can inform that surgeon about the integrity of the peripheral auditory portion of the cochlea-vestibular nerve and the ascending lateral lemniscal pathways in the brainstem up to the level of the inferior colliculus in the midbrain (Simon, 2011). To assess the continuity and functional integrity of the individual cranial nerves, and their nuclei, direct electrical stimulation can be used to record the responses from the muscles that the individual cranial nerves supply (Karakis, 2013). This also gives valuable localisation information too, especially when the normal anatomical landmarks are distorted by the mass effect of the lesion (Procaccio et al., 2000). Although neurophysiological recordings can be used intraoperatively to assess several ascending and descending neural pathways within the brainstem, it has been recognised that intraoperative neurophysiology of the upper brainstem is still an unfulfilled area (Sala, 2017).

From a neurophysiological perspective, postoperative deficits in eye movement coordination remains an unsolved problem. Internuclear ophthalmoplegia is also far from being solved since techniques to monitor and map the internuclear fascicles have not yet been developed. The continual intraoperative assessment of the circuitry and neural pathways that control the oculomotor nerves need a reliable surrogate biomarker that can be used at the time of surgery to avert oculo-vestibular dysfunction (Sala, 2017).

However, there is currently **no** established technique that can specifically evaluate and continuously monitor the **entire** peripheral and internuclear connective pathways that serve vestibular and oculomotor reflex control intraoperatively (Karakis, 2013).

The ability to assess the functional integrity of the entire pathway that maintains extraocular control, at the time of surgery, is necessary because long-term dysfunction can affect many of the patients undergoing resective brainstem surgery. In the paediatric population it has been shown that 25-29% of survivors suffer from persistent strabismus, whilst 13-18% continue to have nystagmus post-operatively (Indaram et al., 2017, Peeler, 2017). For those patients undergoing vascular decompressive surgery for hemifacial spasm, vestibular nerve damage can cause nystagmus and gait imbalance in 5.4% of patients (Sindou and Mercier, 2018).

Although percutaneous techniques have been developed for the placement of needle or hook-wire electrodes to record the electrical activity of the extraocular muscles (Lopez, 2011), because of the technical difficulties associated with these techniques, they are not routinely performed. The extraocular unit is small and thin, being 10-40 times smaller than the limb skeletal muscle unit and they are deep within the orbital cavity, which makes them difficult to access. There is also the risk of accidental perforation of the globe if the needle moves after insertion, which can cause intraorbital bleeding (Lopez, 2011).

Electromyographic monitoring of the extraocular cranial nerves has been used during conventional skull-based surgery to detect impending cranial nerve injury and reduce the resultant incidence of neurological deficits postoperatively (Sekiya et al., 1993, Schlake et al., 2001). The resultant free-running EMG potentials that are recorded with this modality allows continuous recording of the electrical activity from the muscles innervated by the specific cranial nerves (Romstock et al., 2000). The different neurotonic discharges (i.e., spikes, bursts, and trains) that occur during surgery are secondary to the unintended activation of those cranial nerves that supply the extraocular muscles (Lopez, 2011). However, as damage may already have occurred to the nerve when these discharges are detected, they may have limited value in predicting post-operative function of the oculomotor nerves (Schlake et al., 2001).

The immediate and long-term functional outcomes of cranial nerve function, including the extra ocular muscles, were investigated by Byun and colleagues in a series of patients undergoing surgery for brainstem cavernous malformations (Byun et al., 2018). In a subset of the 47 patients investigated, some were afforded the benefit of intraoperative neurophysiological monitoring, whilst the remaining patients did not have monitoring performed.

It was seen that the total recovery rates of the cranial nerves involved in eye movements were higher than in those patients that had monitoring performed (cnIII: 55.6% v50%, cnIV: 50% v 50% and cnVI: 52.4%v 42.1%) (Table 10). This calls into question the benefit of using this modality at the time of surgery.

Table 10: Postoperative recovery rates for un-monitored and monitored extraocular motor cranial nerves (adapted from Byun et al., 2018).							
		Patients with pre-operative deficits	Number of recovered patients postoperatively				
			1 month	3 months	6 months	12 months	Total recovery rate
cn III	Surgery without IONM	3 (25%)	1 (33.3%)	1 (33%)	1 (33%)	2 (66.7%)	55.6 %
	Surgery with IONM	6 (17.1%)	1 (16.7%)	3 (50%)	3 (50%)	3 (50%)	
cn IV	Surgery without IONM	0	0	0	0	0	50%
	Surgery with IONM	2 (5.7%)	0	1 (50%)	1 (50%)	1 (50%)	
cn VI	Surgery without IONM	3 (25%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	3 (100%)	52.4%
	Surgery with IONM	19 (54.3%)	1 (5.3%)	6 (31.6%)	6 (31.6%)	8 (42.1%)	

The diagnostic test characteristics of extraocular nerve monitoring were seen to be variable in a series of 22 patients undergoing brainstem surgery (Table 11). Li et al showed that the spontaneous EMG activity had limited value in predicting post -operative function a week after surgery and at post-operative follow-up (Li et al., 2017). Whilst the sensitivity and negative predictive values (NPV) remained high in the immediate post-operative period and at subsequent follow-up (Table 11), the specificity and positive predictive values (PPV) were poor initially and then declined to lower values at follow-up.

Table 11: Prediction of EMG changes to post-operative extraocular dysfunction (adapted from Li et al., 2017).					
		Sensitivity	Specificity	PPV	NPV
cn III	One week after surgery	87.5	36.4	50	80
	Follow-up	100	35.7	35.7	100
cn VI	One week after surgery	25.0	72.2	16.7	81.3
	Follow-up	0	71.4	0	93.8

Even in minimally invasive techniques that can be used to resect skull-based tumours that involve the cavernous sinus and petroclival region, there is still a potential risk to neurovascular structures (i.e., the internal carotid and anterior cerebral arteries) and cranial nerves. Expanded endonasal surgery (EES) is a surgical technique that involves neurosurgical and otolaryngology teams working together at various stages of the surgery to enable access the ventral skull base. Using an endoscope, and complex neuro-navigational equipment, access can be gained from the crista galli to the odontoid in the sagittal plane and the middle fossa in the lateral plane. The various

approaches can be classified into transcribiform, transdorsum sellar and transclival. (Cavallo et al., 2019). This surgical approach can also give rise to post-operative deficits of the extraocular muscles and vestibular control (Singh et al., 2016).

In their study of 200 patients undergoing EES, where a total of 696 extraocular nerves were monitored, Thirumala and colleagues found that the percentage incidence of deficits in the cranial nerves supplying the extraocular muscles was 2.27% when there was significant EMG activity seen (Table 12). This did not differ significantly to the percentage incidence of those cranial nerves without significant free-running EMG changes, which was 2.3%. They concluded that there was no correlation between the incidence of free-running EMG activity and the detection of postoperative deficits and warned that the absence of free-running EMG activity may provide a false sense of security to the surgeon. This may result in a more aggressive resection, which could result in an increased risk of nerve injury (Thirumala et al., 2013).

Table 12: Incidence of free-running EMG activity and post-operative extraocular nerve outcome (adapted from Thirumala et al., 2013).

	Cranial nerve		
	cn III	cn IV	cn VI
Total number of patients monitored	153	135	187
Total number of nerves monitored	219	192	285
Total number of cranial nerves with significant activity	46 (21%)	21 (11%)	21 (7%)
Post-operative deficits with significant activity	0	0	2 (9.5%)
Total number of cranial nerves with no significant activity	173 (79%)	171 (89%)	264 (93%)
Post-operative deficit with no significant activity	3 (1.73%)	2 (1.16%)	9 (3.4%)

The various physiological substrates of the vestibulo-ocular motor system can be divided according to their anatomic location into infranuclear, nuclear, internuclear and supranuclear components (Karatas, 2009) (Figure 16). The supranuclear components refer to those cortical structures and pathways that are proximal to the ocular motor nuclei and that descend onto the brainstem (Horn and Leigh, 2011). The internuclear component refers to the connections between the individual ocular motor nuclei (oculomotor, trochlear and abducens nucleus) and the ascending, descending and decussating fibres within the brainstem (Karatas, 2009). These white matter fibre tracts act as a conduit for many brainstem pathways, they extend as a pair of tracts through the brainstem, the medial longitudinal fasciculus (MLF). The MLF passes through the brainstem near the midline and ventral to the fourth ventricle in the medulla and the pons and up to the cerebral aqueduct in the midbrain (Virgo and Plant, 2017). The MLF is the final common pathway for the ocular motor control circuitries that are involved in the coordination of vertical, horizontal and torsional eye movements. It is these ascending and descending fibres that link together the brainstem nuclei at the infranuclear level which enable coordinated eye movements to bring visual stimuli to the fovea so that foveal fixation can be maintained during head movement. Therefore, the preservation of these upper brainstem pathways is vital for the control and maintenance of oculomotor function.

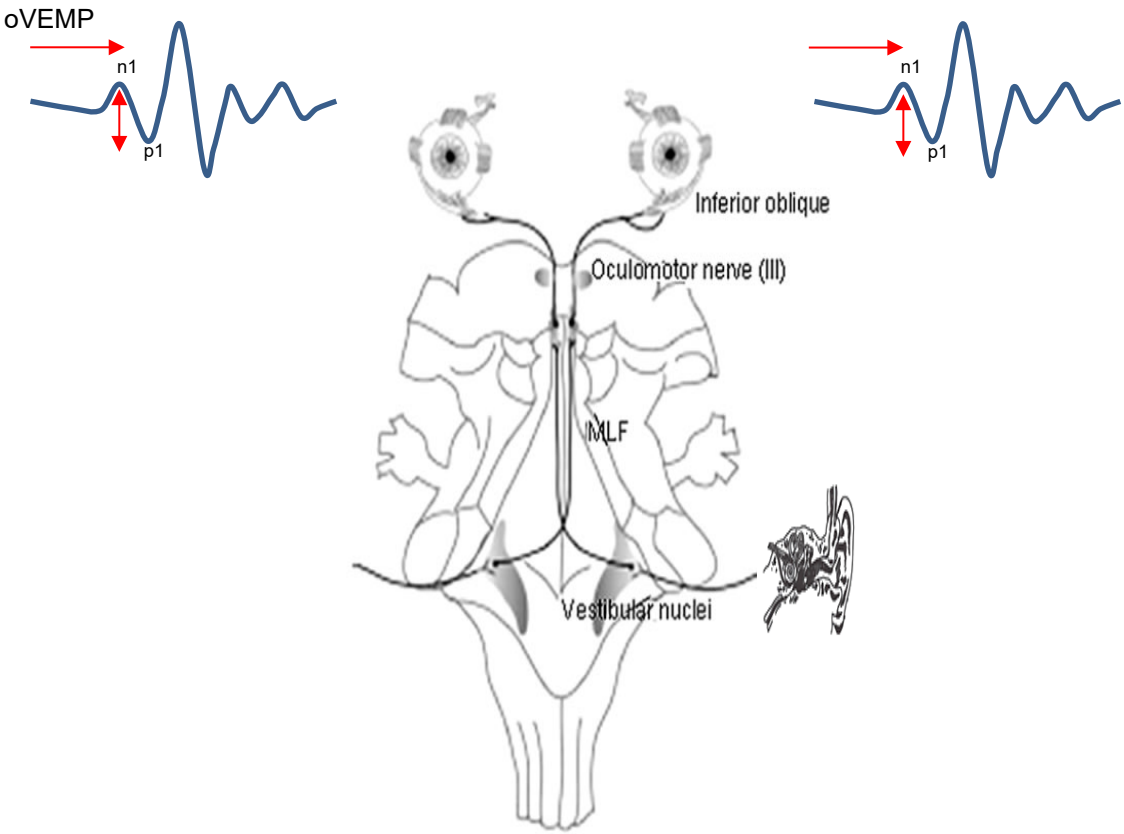


Figure 44: Intact vestibular, central and oculomotor pathways.
oVEMPs are of normal amplitude and latency and morphology.

Short latency otolithic reflexes can be recorded from the extra ocular muscles after air conducted stimulation (Dlugaiczyk, 2020). These ocular vestibular evoked myogenic potentials (oVEMPs), which can be recorded from the contralateral inferior oblique muscle, describe the excitation of the translational vestibulo-ocular reflex (Rosengren et al., 2010). Ascending utricle fibres connect to the ipsilateral vestibular nuclei and project via crossed the reflex pathway in the MLF to the contralateral oculomotor nuclei to elicit an excitatory muscle potential (Bogle, 2018) (Figure 44). Current clinical evidence shows that the oVEMP can provide important localising information about lesions that occur along these brainstem pathways (Rosengren et al., 2019, Taylor et al., 2020).

With so many patients experiencing significant vestibulo-ocular impairment after brainstem surgery, this observational study was designed to determine if the intraoperative changes in the oVEMP were able to be correlated to the patients post-operative vestibulo-ocular function. The patients included in the study were undergoing surgery via various routes (sub-occipital, retrosigmoid, endonasal etc.) for a range of common conditions (microvascular decompression, resection and debulking of space occupying lesions).

8.2 Patients and methods

8.2.1 Patients

A total of 37 patients were included in the study (Table 13). There were 19 females and 18 males with a mean age of 50.4yrs (range 22-77yrs) that were enrolled after giving informed written consent to participate, in accordance with local ethical committee regulations. The patients were those who were undergoing brainstem surgery in which brainstem auditory evoked potentials and facial nerve monitoring had been requested by the referring neurosurgeon, as the lesions and underlying pathology involved these cranial nerves.

The patients were positioned depending on the surgical approach and were prone for the mid-line sub-occipital approach (10 patients) and supine for the 5 endoscopic endonasal cases. Variations of the lateral suboccipital or retro-sigmoid approach were used for the remaining patients (22 patients), where they were placed in the lateral decubitus (park bench) position.

Eight patients (22%) were undergoing microvascular decompressive surgery for hemifacial spams, two or which were secondary explorations for surgery done elsewhere, where the spasms had persisted post-operatively. Eight patients (22%) were undergoing resection of cranial nerve schwannomas (6 vestibular and 2 trigeminal). The five patients (13%) undergoing endoscopic endonasal surgery harboured tumours in the base of the skull (2 craniopharyngiomas, 2 pituitary tumour/adenoma and a clival chordoma). There were four (11%) vascular abnormalities (3 cavernous malformation and one arteriovenous malformation). The remaining 12 patients (32%) showed a mixture of tumour types involving the cerebellopontine angle (4 meningioma, 4 epidermoid, 3 subependymoma and 1 cystic lesion).

8.2.2 Anaesthesia

The anaesthesia was induced with either a bolus of Propofol or by the use of inhalation gases. Once the patient was inducted, the anaesthesia was then maintained with a total intravenous anaesthesia using Propofol (6-10mg/kg/hr) and Remifentanil (0.2-0.4µg/kg/min), and all other halogenated anaesthesia was discontinued. A short acting neuromuscular blockade (typically Alcuronium or Rocuronium) was used for intubation only and no further administration of this drug was given. The presence of any residual neuromuscular blockade was assessed, prior to any motor function monitoring, by stimulating the median nerve at the wrist and recording the compound motor action potential from the abductor pollicis brevis after a ‘train of four’, to ensure that 4 supra-maximal compound motor responses were present (Sloan, 2013).

Table 13: Patient demographics, diagnosis and presenting signs.					
Pt no	Sex	Age	Diagnosis	Side	Presenting signs
1	m	47	Cavernoma	M	Sensory and motor dysfunction UL>LL
2	f	24	Vestibular schwannoma	R	Hearing loss, vertigo
3	m	22	Epidermoid	R	Ataxia, R facial paresis, nystagmus
4	f	55	HFS*	L	Left sided hemi-facial spasms
5	m	77	HFS	L	Left sided hemi-facial spasms
6	f	72	Cavernoma	R	V2 numbness and facial weakness
7	m	62	Cystic mass	L	Raised ICP, headache
8	m	56	Subependymoma	M	Weakness and gait ataxia
9	f	63	Trigeminal schwannoma	R	Facial pain
10	f	60	Vestibular schwannoma	L	Left sided deafness
11	m	47	HFS	R	Right sided hemi-facial spasms
12	m	61	HFS*	L	hemi-facial spasms
13	f	71	Petrous clival meningioma	L	Diplopia, headache
14	m	28	Subependymoma	M	LL sensory loss
15	m	47	Subependymoma	M	Sz, pyramidal tract signs
16	f	33	Cavernoma	M	L hemiparesis, ataxia
17	f	45	HFS	L	Left sided hemi-facial spasms
18	f	51	HFS	R	Right sided hemi-facial spasms
19	f	49	Vestibular schwannoma	R	Right sided hearing loss
20	m	74	Arteriovenous malformation	M	Headache motor/sensory dysfunction
21	f	38	Epidermoid	M	R facial weakness, diplopia
22	m	49	Craniopharyngioma	E	Nausea, vertigo
23	m	49	HFS	L	Left sided hemi-facial spasms
24	f	48	HFS	L	Left sided hemi-facial spasms
25	m	54	Petrous meningioma	R	Headache, visual blurring
26	f	33	Pituitary tumour	E	Bitemporal hemianopia
27	m	39	Meningioma	M	Headache nausea
28	f	54	Vestibular schwannoma	R	Deafness, vertigo
29	f	36	Epidermoid	L	L sided tinnitus and facial numbness
30	f	41	Craniopharyngioma	E	Headache, nausea
31	m	50	Vestibular schwannoma	R	Increased hearing threshold
32	m	63	Pituitary adenoma	E	Hypothyroidism
33	f	72	Trigeminal schwannoma	L	Pain V1/2
34	f	49	Epidermoid	M	Gait unsteadiness
35	f	40	Clival chordoma	E	Diplopia, headaches
36	m	63	Meningioma	M	Headache
37	m	44	Vestibular schwannoma	R	Hearing and balance disturbances
m = male; f = female; R = right; L = left; M = midline; E = endonasal; * = redo.					

8.2.3 Intraoperative monitoring techniques

8.2.3.1 General monitoring techniques

Depending on the site of the surgery and the underlying pathophysiology and the neurosurgeons request, a variety of multi-modal neurophysiological monitoring techniques were performed. For all patients involved in the study, brainstem auditory evoked potentials and facial nerve monitoring was performed. The brainstem auditory evoked potentials were recorded from needle electrodes placed at the mastoid with the reference electrode at the vertex (Simon, 2011). Foam ear inserts were placed into the external auditory meatus and 0.1msec click stimuli with either a rarefaction or an alternating phase were delivered monaurally at an intensity of 115dB nHL. The opposite ear was masked with white noise at 75dB. The stimulus rate was set at 30Hz and 1000-2000 repetitions were averaged. The potentials were amplified, with the negative potential displayed as an upward deflection, with a display gain of 0.2-0.5μV/div and the filtering bandwidth was set at 100-3000Hz across a time base of 15msec. The latencies of waves I, III and V from the stimulated ear and their inter-peak latencies, I-III, III-V and I-V, were used for interpretation, along with the amplitudes of wave I and V that was taken from the peak of that potential to the succeeding trough. Any changes in the absolute latencies of wave V of more than 1.0msec, or an increase in inter-peak latencies or a decrease in amplitude of wave V >50% were considered as a warning criterion (Simon, 2011). Facial nerve monitoring was performed using sub-dermal needle electrodes placed into the lower orbicularis oculi muscle at the orbital rim and referenced to the upper eyelid and in the upper and lower lip, close to the oral commissure for the orbicularis oris muscle (Minahan and Mandir, 2011). The free-running EMG recordings were amplified, with the filtering bandwidth set at 30-3000Hz across a time base of 200msec/div with a display gain of 100-500μV/div. Prolonged neurotonic discharges and A-waves, that were seen in association with a surgical event, were identified as a significant warning criterion (Romstock et al., 2000).

The extraocular muscles were recorded with electrodes placed at each lateral cantha, referenced to the glabella to record the activity from the oculomotor and abducens nerves (Fukaya et al., 1999). The recording parameters and warning criteria were similar to those used for the facial nerve monitoring. Additional cranial nerve monitoring was utilised to monitor the trigeminal (masseter or temporalis), glossopharyngeal (soft palette), vagus (cricothyroid), spinal accessory (upper trapezius) and hyoglossus (tongue) nerves depending on the site and access to the brainstem.

For monitoring of the upper limb somatosensory evoked potential, either the median nerve or ulnar nerve was stimulated at the wrist, using a 0.2-0.5msec duration electrical square wave pulse at a stimulus a rate of 5Hz.The recordings were taken with electrodes placed over the brachial plexus to record the peripheral erbs point and over the contralateral primary somatosensory cortex with the electrode referenced to the mid-frontal area (Ci-Fz). The waveforms were analysed over a 20msec time base and were filtered with a low frequency filter of 30Hz and a high frequency filter of 500Hz displayed with a gain of 0.5-2μV/div. An increase in the recorded N20 potential latency of more

than 10% of the absolute latency recorded at baseline, or a decrease in the N20-P25 amplitude >50%, was considered a warning criterion (MacDonald et al., 2019). Transcranial electrical stimulation through corkscrew electrodes placed in the scalp over the primary motor cortex at C1 and C2 were used to elicit the motor responses. A train of 3-5 pulses of 0.5msec duration with an interstimulus interval of 1-2msec were used with the C1 as the anode and C2 for the cathode for left cortical stimulation and C2 as the anode and C1 as the cathode for right cortical stimulation. The muscle potentials were recorded from needle electrodes placed into the small hand muscles over a 50msec time base with low and high frequencies of 30Hz and 3000Hz respectively. The responses were displayed with a gain of 0.2-2mV/div and a >50% decrease in the peak-to-peak amplitude was considered as a warning criterion (MacDonald et al., 2013).

SEPs and MEPs were not used in those patients undergoing microvascular decompressive surgery.

8.2.3.2 Intraoperative oVEMPs

A multichannel intraoperative neurophysiological monitoring system (Nihon Kohden Neuromaster) was used to for each surgical case to acquire the data. The oVEMPs were recorded with disposable self-adhesive surface electrodes (Ambu Neuroline 700) that were applied after the skin had been gently abraded. The absolute impedance of each electrode was <5KΩ with an inter-electrode impedance <2KΩ. The responses were amplified x100,000 and were signal averaged 100 times over a 100msec time-base (10msec pre-stimulus and 90msec post-stimulus) using a low frequency filter of 10Hz and high frequency filter of 100Hz. A belly-tendon recording montage was used with the active electrode placed on the orbital rim, mid-way between the centre of the eye and the lateral canthus and with the reference electrode placed at the inner canthus (Sandhu et al., 2013). The ground electrode was placed on the upper arm. A 500Hz tone burst, with a rise/plateau/fall time of 1-2-1msec was amplified and delivered via foam ear inserts at a rate of 5.1Hz at an output intensity of 115dB nHL. The oVEMPs were recorded from the contralateral eye after monaural stimulation and a negative extraocular potential recorded on the active electrode was displayed as an upward deflection.

8.2.4 oVEMP interpretation

The absolute latencies of the major negative and subsequent positive peaks corresponding to the n1 and p1 components of oVEMP were taken from the onset of the stimulus. The inter-peak amplitudes of the n1-p1 components were calculated and documented, along with the latencies, at the specified time points in surgery. The percentage decrease in amplitude taken from the baseline when the patient had been positioned was calculated.

8.2.5 Outcome

The neurological examination for the patients was taken at the pre-operative consultation and assessment and comprised a full neurological examination, including physical cranial nerve function testing with the results documented into the patient's electronic records.

The patient's general neurological function was assessed in the recovery suite post-operatively, with more detailed examinations and tests being performed when required. The patients were then assessed on the ward prior to discharge from the hospital and then again at their follow-up review several weeks later. The neurological status of the patient, including the cranial nerve function was documented in the patient notes. Particular attention was taken to any evidence of vestibular dysfunction or paresis of the oculomotor system and diplopia (with or without evidence of eyeball movement dysfunction). A transient deficit was one that had documented evidence of complete improvement to the baseline value; whilst a permanent deficit was defined as an impairment that had not improved to the baseline value at the subsequent review several weeks later.

8.2.6 Data analysis

Baseline values for the latencies of the n1 and p1 components and the n1-p1 inter-peak amplitude were taken once the patient has been positioned on the operating table and prior to any surgical intervention. Subsequent recordings were taken at various specified time points throughout the course of the surgery (when the surgical site was exposed, when the dura was opened, whilst the surgical manoeuvres were taking places, and when the dura and surgical site were closed). The alterations in the latencies and amplitude of the oVEMP were correlated with the patient's clinical outcome to calculate the diagnostic test characteristics.

The local ethics committee for the Trust approved and supported this observational study.

8.3 Results

oVEMP recordings were attempted in all 37 patients. None of the patients referred with vestibular schwannomas had recordable oVEMPs and therefore these patients were excluded from subsequent analysis. The latencies of the n1 potentials were stable throughout the procedures and did not seem to vary more than 10% of the original baseline value and so these were not analysed further. The latency and detection of the p1 component was more variable, particularly when there was a marked decrease in the amplitude of the oVEMP, which made documentation uncertain, and for this reason further analysis of this component was not attempted.

Twenty-two patients (70.9%) did not show any significant alterations in the recorded oVEMP parameters and 21 of these did not suffer any immediate or long-term relevant clinical dysfunction.

Eight patients (25.8%) had immediate post-operative vestibular ocular dysfunction with seven of these being were accompanied by changes in the oVEMP parameters (Table 14). Two patients (6.5%) experienced a decrease in their oVEMPs amplitudes of 50% or more during surgery (patients 20 and 24), but neither of these exhibited any relevant clinical changes post-operatively.

Table 14: Patient outcomes and oVEMP change at the end of surgery.						
		Post-operative changes	Clinical outcome	oVEMP % close	Discharge	Follow-up
1	Cavernoma	Pontine bleed	Permanent	90	FN	FN
6	Cavernoma	MLF dysfunction	Permanent	Loss	TP	TP
12	HFS*	Loss of VIII nerve/deaf	Permanent	Loss	TP	TP
16	Cavernoma	MLF dysfunction	Transient	~50	TP	FP
20	AVM	normal	Unchanged	50	FP	FP
24	HFS	normal	Unchanged	50	FP	FP
27	Meningioma	Muffled hearing/balance	Permanent	50-60	TP	TP
29	Epidermoid	IIIrd nerve dysfunction	Permanent	Loss ?20%	TP	TP
33	Trigeminal schwannoma	Hearing loss	Transient	60	FN	TN
36	Meningioma	IIIrd nerve dysfunction	Transient	50	TP	FP

Three of the six patients, that showed intraoperative changes of the oVEMPs during the time of surgery and were found to have functional deficits in the immediate post-operative period, showed a resolution in their symptom by the time of follow-up (patients 16, 33 and 36).

Three of the eight patients (37.5%) that showed oVEMP changes demonstrated a loss (patient 6 and 12) - or near complete loss (patient 29) - of the oVEMP; and these all showed a permanent neurological dysfunction.

Further description of individual patient outcomes is presented below.

8.3.1 Case presentations

Patient 1

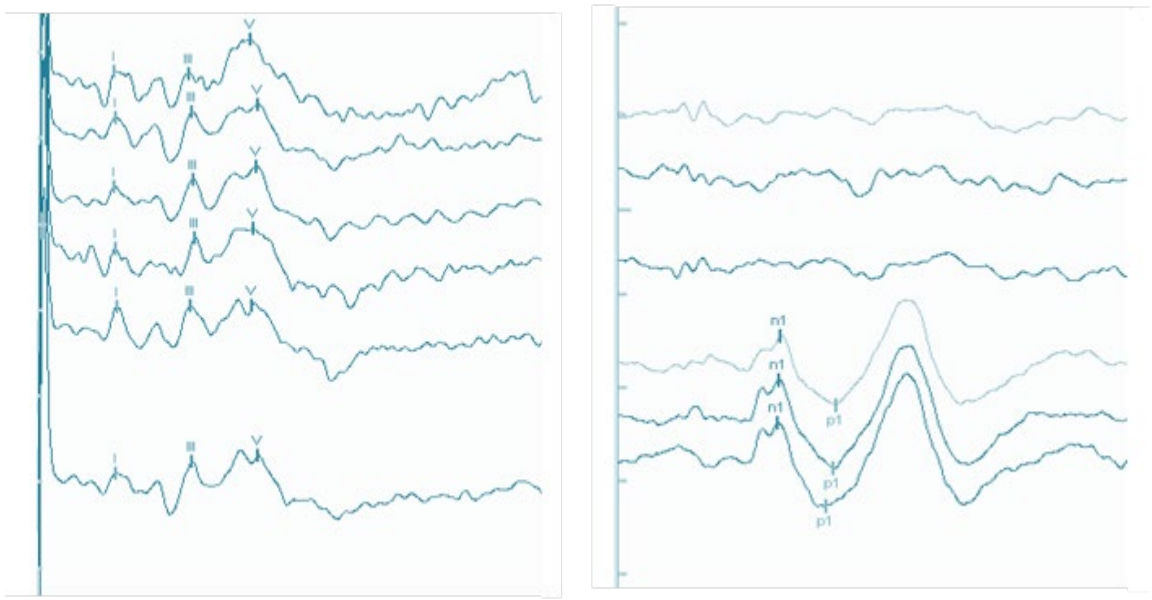
The patient had removal of an intrinsic intra-axial cavernous malformation via a mid-line craniotomy. The oVEMPs and the BAEPs remained stable and recordable throughout the surgical procedure. There were no spontaneous EMG changes seen during the time that the malformation was being excised. In the immediate post-operative period, the patient showed bilateral facial nerve palsies and right sided hemiplegia. The post-operative MRI showed a haemorrhage within the evacuated surgical site, which was not evident when the lesion had been removed. The symptoms were still present at follow-up with spasticity and ataxia being evident on walking. Although this is classed as a false negative, it would not be expected that intraoperative neurophysiological changes are able to predict vascular events that occur in the post-operative period.

Patient 6

This patient presented with subacute right sided facial numbness, predominantly in the V2 trigeminal division along with an upper motor neuron facial weakness affecting the orbicularis oris. The MRI showed an intrinsic pontomedullary lesion. A right retrosigmoid surgical approach was used to access the brainstem. During the procedure the BAEP remained unchanged from baseline.

A. BAEP from Right ear

B. oVEMP from the left eye



C. BAEP from Left ear

D. oVEMP from the right eye

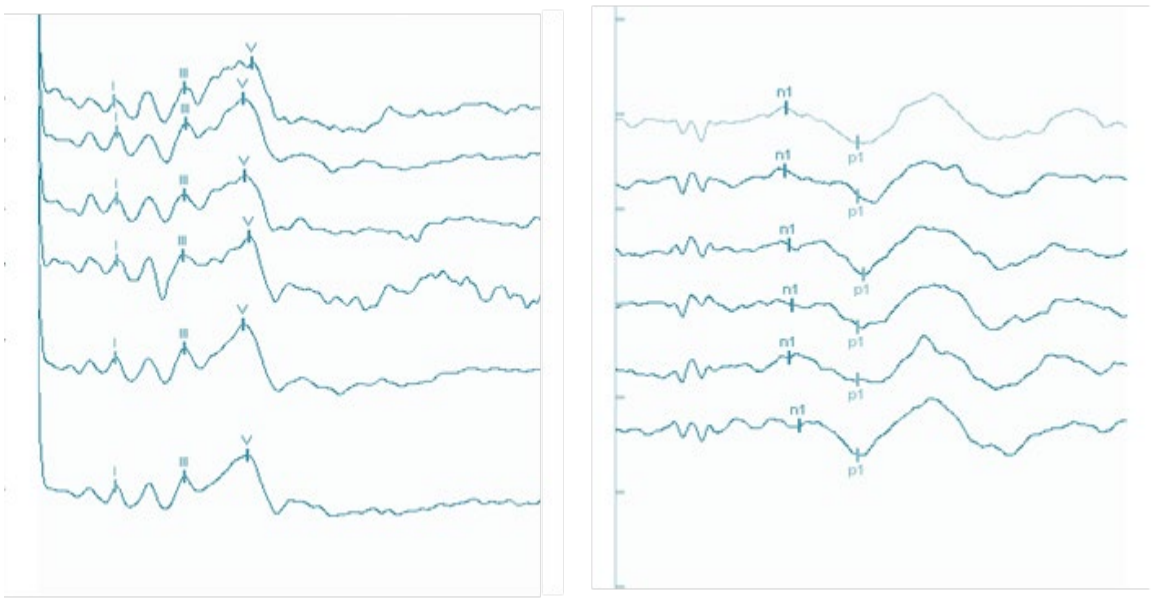


Figure 45: Intraoperative recordings from patient 6.
There is a loss of the oVEMP from the left eye (B). The oVEMPs from the right eye (D) remains recordable. The right and left BAEPs (A and C) remain unchanged. *

** In this, and the subsequent figures 46-49, the bottom trace in each panel was taken when the patient was positioned onto the operating table, working* upwards *through the time that the skin and the dura was opened and the site was exposed, until the final (top) trace when the site was closed.*

There were no excessive neurotonic discharges seen from the extraocular muscle groups (although occasional neurotonic bursts were seen from the masseter and orbicular oculi and oris when the site was being exposed). The cavernous malformation was excised *en bloc*. At closure the oVEMP from the right side was preserved, the oVEMP from the left side following right ear stimulation was lost (Figure 45). The patient awoke with adduction of the right eye, indicative of medial longitudinal fascicule pathway damage. On subsequent post-operative review the facial pain and palsy were improved although the right eye adduction was still evident.

Patient 12

This man had experienced left sided spasms involving the orbicularis oculi, nasalis and orbicularis oris muscles for more than 10 years. Previous surgery elsewhere had not resolved this issue. At the time of surgery extensive retraction of the cerebellum was required to access and remove the previously placed Teflon that was adhered to the facial nerve and vestibulo-cochlear bundle.

As the new Teflon was being placed there was an abrupt loss of all of BAEP components on the left side, along with the loss of the oVEMP potentials following left sided stimulation (Figure 46). The surgeon was immediately informed of the loss of the BAEP potentials on this side and they said that this was due to partial avulsion of the thinned eighth nerve at the root entry zone. The patient awoke with complete and permanent hearing loss on the left side. At closure the oVEMPs that had initially been present from the right eye after left ear simulation were absent. The contralateral oVEMPs were present and remained unchanged.

Patient 16

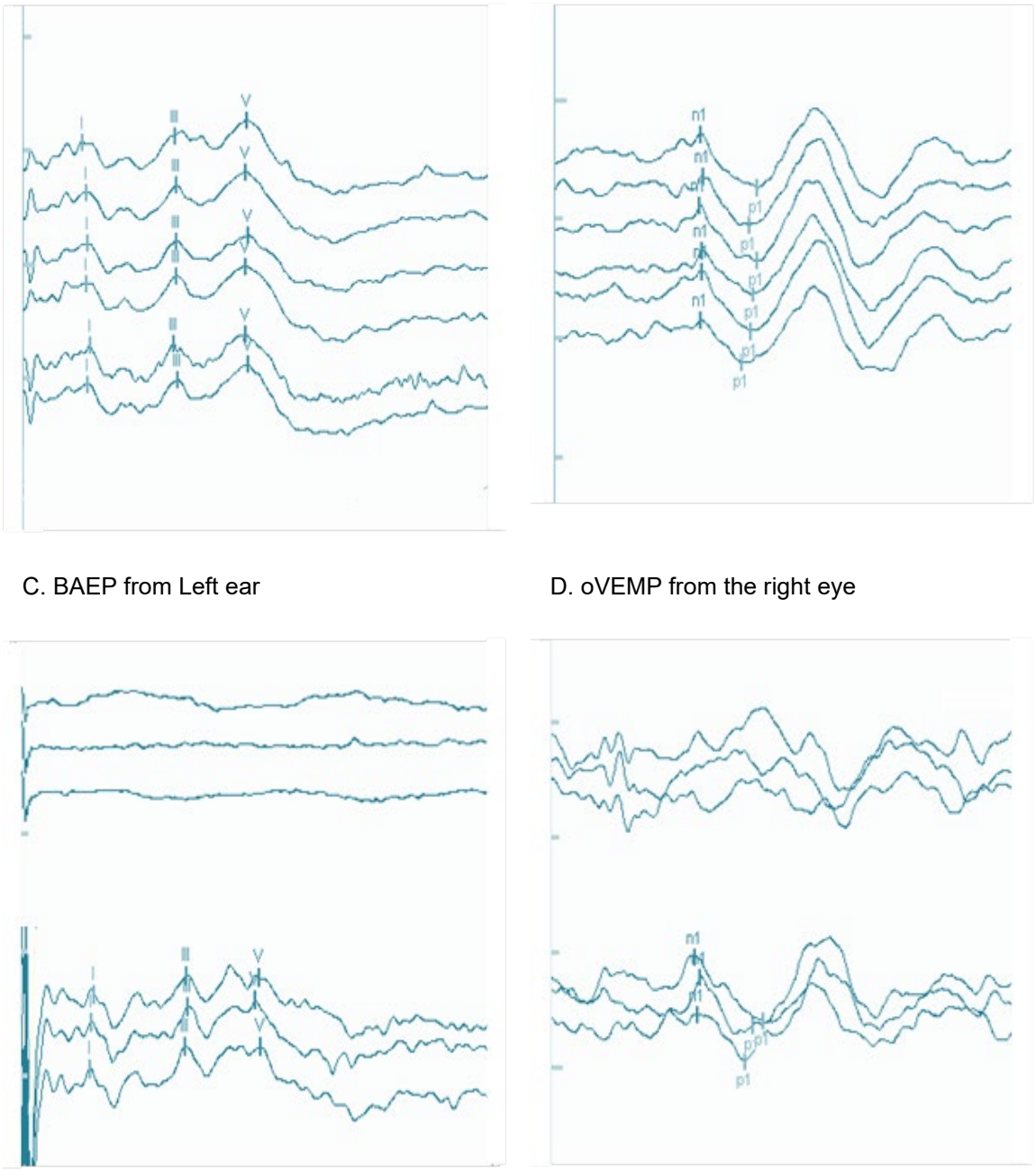
Following a bleed which caused left sided hemiparesis (which had resolved over several weeks) this patient underwent surveillance for her intra-axial cavernous malformation. Two years later a further haemorrhage caused left sided sensory deficits in the upper limbs with ataxia noted on examination. There was also some mild weakness of the left upper arm with loss of dexterity and fine finger control. The patient underwent a sub-occipital craniotomy 2 weeks after this recurrence, when her symptoms had abated. The intraoperative monitoring was uneventful with no changes in the SEPs, MEPs or BAEPs. There were no neurotonic discharges seen from the cranial nerves that were monitored. The oVEMPs were seen to be attenuated bilaterally when the dura was closed, and these remained decreased in amplitude by ~50% when the site was closed. The patient's recovery was unremarkable except for nausea in the immediate post-operative period. There was a fixed downward gaze seen for 48 hrs, along with possible nystagmus, which resolved by the time the patient was discharged.

Patient 24

This lady had presented with a 3-year history of left sided hemifacial spasm that was due to an anterior inferior cerebellar artery impinging upon the facial nerve at the root entry zone. The BAEP and oVEMP potentials were recordable and stable whilst the nerve was being exposed and the

A. BAEP from Right ear

B. oVEMP from the left eye



C. BAEP from Left ear

D. oVEMP from the right eye

Figure 46: Intraoperative recordings from patient 12.
The BAEPs from the right ear (A) and the oVEMP from the left eye (B) remain unchanged. There is a loss of all the BAEP waveforms from the left ear (C top traces) and a loss of the oVEMP from the right eye (D top traces).

offending vessel was being removed. As the angle of retraction of the cerebellum was altered and then increased in order to place the Teflon, there was an increase in the I-V latency of 0.9msec, with a decrease in wave V amplitude of 60%. The surgeon was informed of this finding, and once the retractor was released - and the site was irrigated with warm CSF - the BAEP wave I-V interpeak latency was seen to be 0.5msec with the wave V amplitude being seen at 80% of its baseline value. The oVEMP following left ear stimulation did not show any alteration in latency of the n1 or p1 but showed a decrease in amplitude of 50% that persisted for the remainder of the surgery. The patient awoke with no new changes to their hearing or any vestibular disturbance and there was a complete resolution of their spasms.

Patient 27

A sub-occipital mid-line approach was used in order to resect this large meningioma that was causing severe headaches and nausea. During the procedure the BAEPs remained stable and recordable from both sides and due to the 'narrow' surgical approach the individual cranial nerves were not exposed and no neurotonic discharges were observed. When the oVEMPs were recorded at the time that the dura was closed there was a bilateral decrease in amplitude noted of 50-60%, with no obvious change in n1 or p1 latency (Figure 47).

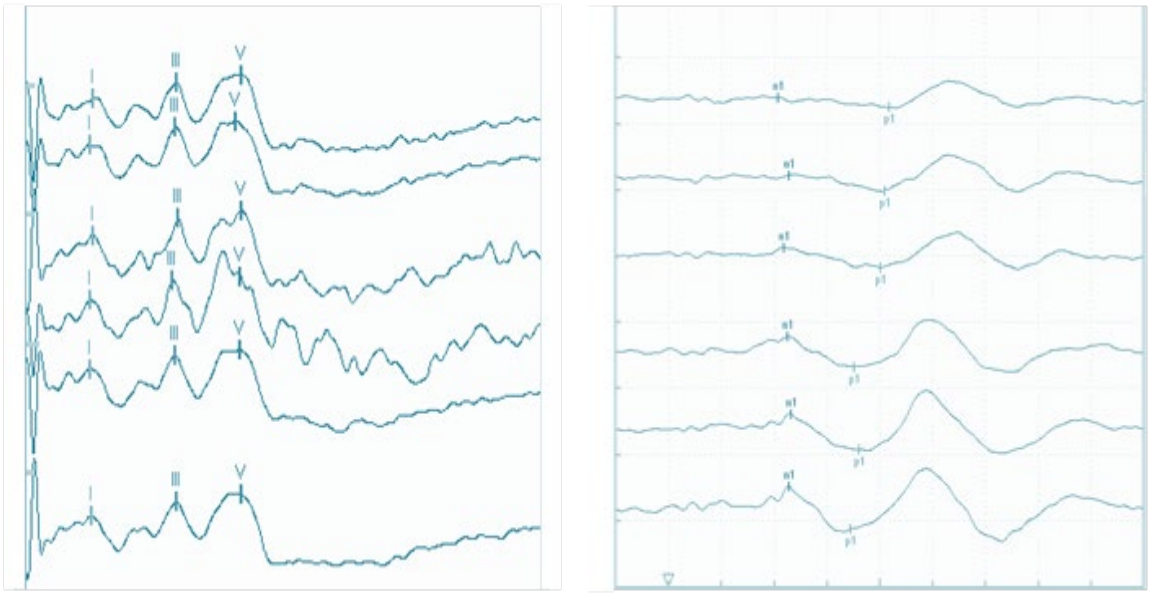
The patient did not complain of any vestibular disturbance in the immediate post-operative period, but at discharge he said that his 'hearing was muffled' and he had a strong sense of unsteadiness and nausea. At follow-up the patient again mentioned that 'his hearing was not as good as it was', although there was no subjective hearing loss and pure tone and speech discrimination testing was normal. Rombergs sign was positive, but the patient said that he was learning to live with the continual feeling of unsteadiness, which on reflection may have been resolving.

Patient 29

This patient had developed tinnitus and had also noticed episodic facial numbness. On examination there was a loss of sensation on the left side of the face with a mild loss of hearing on the left. The MRI showed an epidermoid cyst surrounding the upper and anterolateral brainstem. A left sided retro-sigmoid approach was performed and as the capsule, that was adhered to the brainstem, was being manipulated there were prolonged runs of neurotonic discharges (trains) seen from the extraocular muscle groups. The surgeon irrigated the site with warm CSF, but these discharges continued unabated whilst the capsule continued to be removed. When the capsule had been resected and the dura was closed there were no neurotonic EMG discharges seen. The oVEMP amplitude on the left side was seen to be lost during surgery, when the site was being closed there was possibly a residual oVEMP seen that was ~20% of the baseline value (Figure 48). The patient awoke with a dilated pupil (resolving within 72 hours) and at discharge and subsequent follow-up the patient was experiencing mild ptosis and third nerve palsy causing diplopia. The protracted EMG discharges were indicative of third nerve/nuclei damage.

A. BAEP from Right ear

B. oVEMP from the left eye



C. BAEP from Left ear

D. oVEMP from the right eye

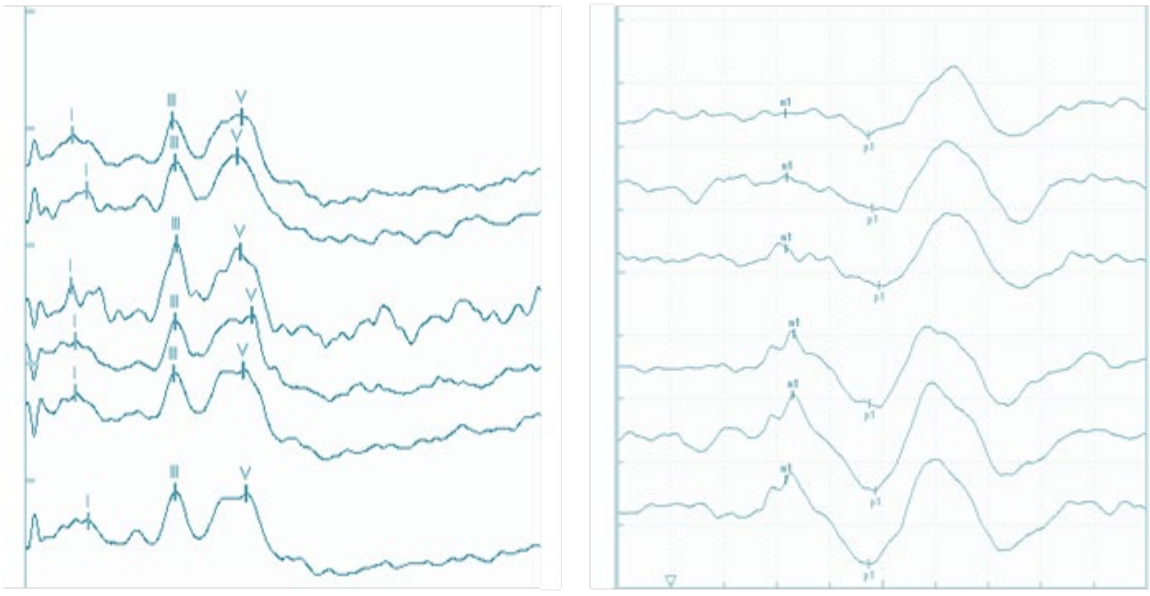
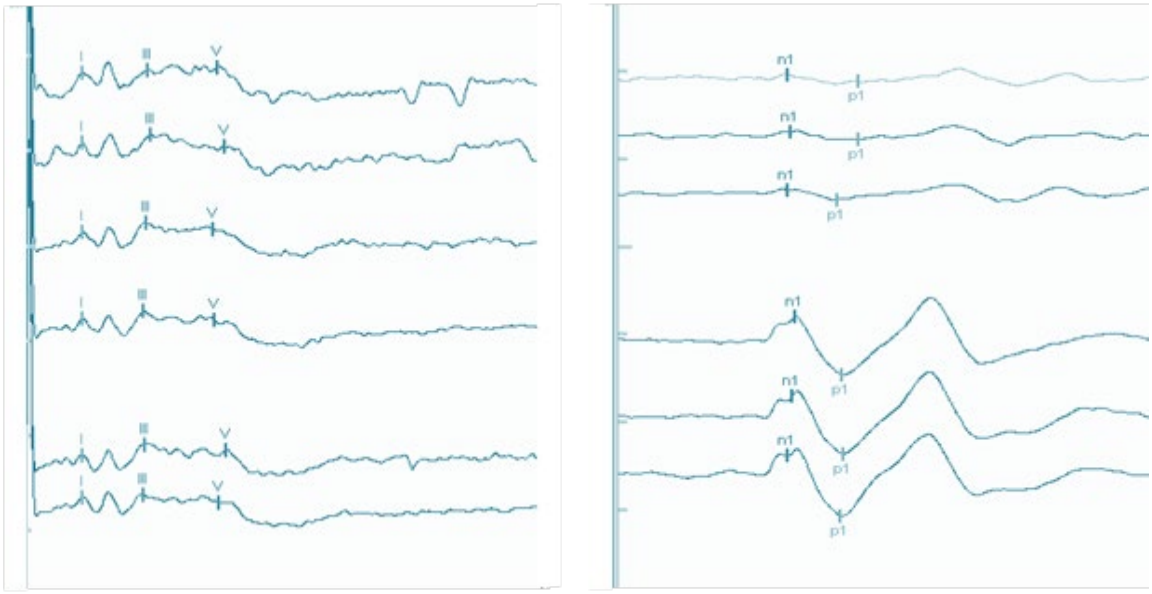


Figure 47: Intraoperative recordings from patient 27.
The right and left BAEPs (A and C respectively) remain unchanged. The oVEMPs from the left eye and right eye (B and C respectively) show a reduction in amplitude of 50-60% which is maintained until the end of surgery.

A. BAEP from Right ear

B. oVEMP from the left eye



C. BAEP from Left ear

D. oVEMP from the right eye

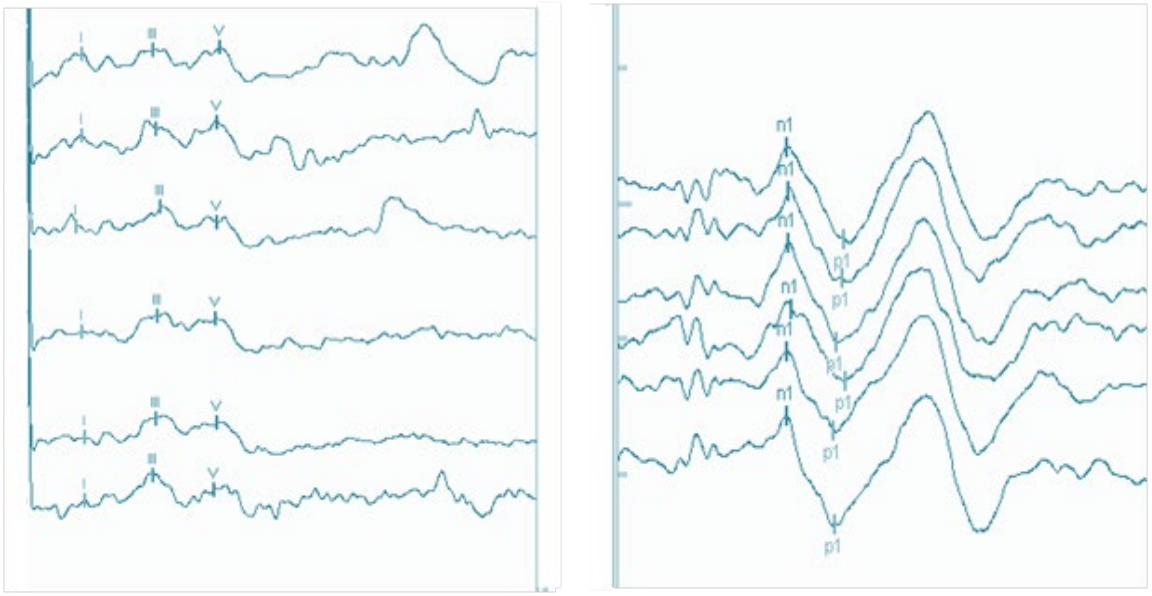


Figure 48: Intraoperative recordings from patient 29
The right (A) and left (B) BAEPs remain stable and recordable, as does the oVEMP from the right eye (C). The oVEMP from the left eye shows a decrease in amplitude of the n1-p1 ~80%.

Patient 33

This patient has been experiencing sharp lancing pain in the left V1 and 2 trigeminal nerve distribution for 4 years that had gradually increased in frequency and intensity. An MRI showed a trigeminal schwannoma of the left side. As the cerebellum was retracted to expose the nerve, there was an increase in the BAEP inter-peak latencies I-III, and I-V of 0.8msec seen on the left side (the wave V amplitude remained stable). This latency increase remained even when the retractor had been removed once the schwannoma had been removed and the site had been closed. The patient awoke with a left sided hearing loss (increased threshold) and vertigo/unsteadiness. These symptoms resolved within 72 hours once she was back on the ward and ambulating. The oVEMPs after left sided stimulation did not show any corresponding alteration in latency or amplitude.

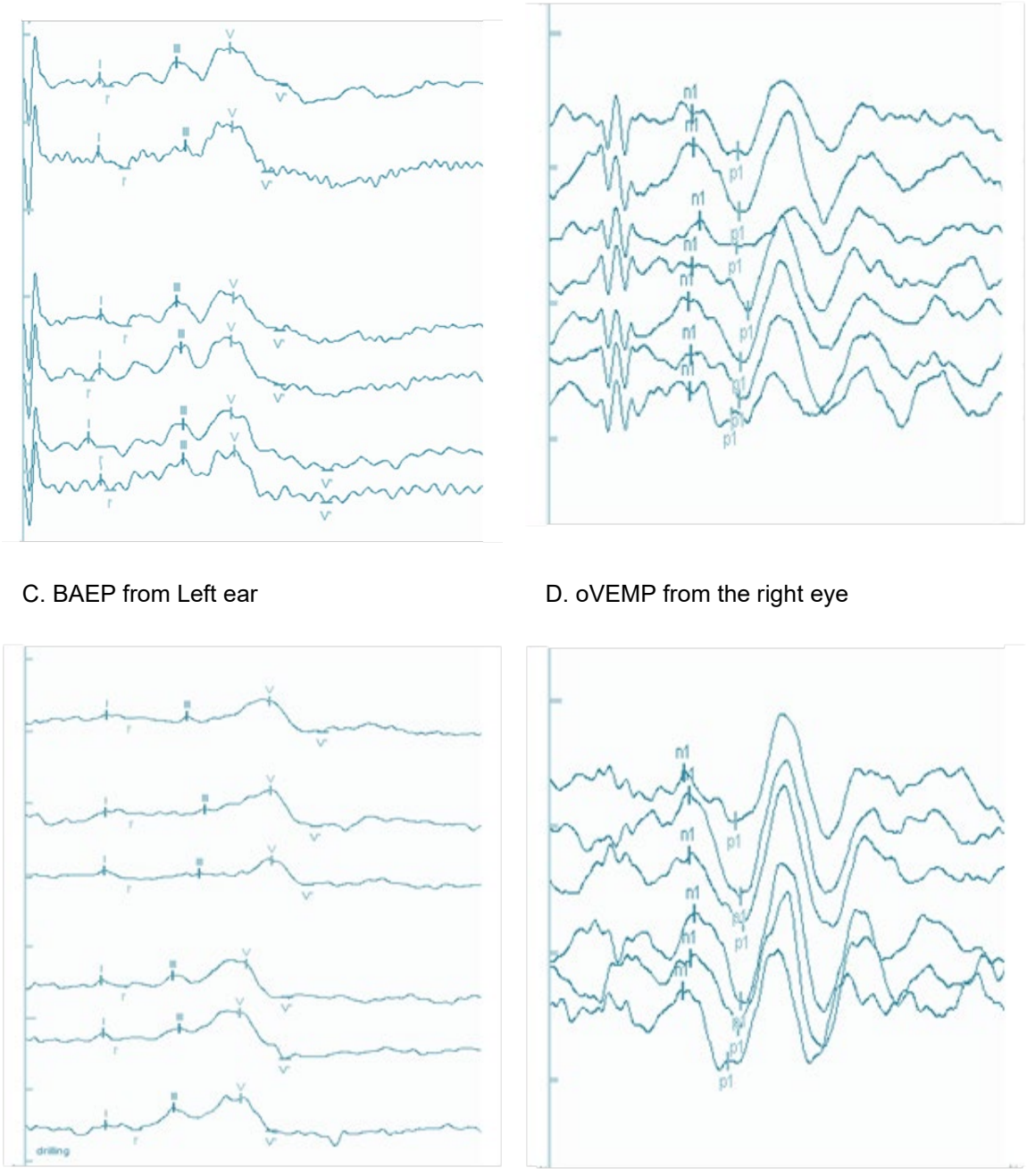
Patient 36

During the surgical resection of this brainstem meningioma that was performed via a sub-occipital midline approach there were persistent and at times prolonged (>20seconds) runs of neurotonic bursts and trains (B and C) seen from the extraocular muscles. The surgeon was informed of these changes at the time that they occurred, and the site was irrigated with warm CSF, and where possible the resection was halted until the EMG activity diminished. There were no neurotonic discharges seen on the other cranial nerves that were monitored (V, VII, IX, X) and the BAEPs and the upper limb SEPs and MEPs remained stable. On the ward afterwards examination showed a right sided ptosis and an unreactive pupil and oculomotor paresis, with a downward gaze. At discharge on day 9 the pupils were equal and reactive and there was some recovery of oculomotor movement, although the ptosis remained. At follow-up there was no evidence of a third nerve dysfunction. It was noted that there had been a drop in the oVEMP n1-p1 amplitude of 60% from the right eye, with no alteration in latency, when the dura was closed. The oVEMP recorded from the left eye remained stable and recordable.

Two patients had reduced oVEMP potentials that did not correlate with any post-operative deficits. Patient 20 was undergoing resection a lower pontine arterio-vascular malformation via a mid-line approach. The oVEMPs were recordable from both sides from the start of the surgery, but when the dura and site were closed it was noted that there was a decrease in amplitude on both sides of ~50%. The other case (patient 24) was undergoing microvascular decompression for left sided hemi-facial spasms. During the procedure there were no adverse changes seen in the left BAEPs. The oVEMPs recorded from the right side after left ear stimulation were seen to be reduced by 50%, whilst the oVEMPs from the other side had remained unchanged.

A. BAEP from Right ear

B. oVEMP from the left eye



C. BAEP from Left ear

D. oVEMP from the right eye

Figure 49: Intraoperative recordings from patient 33.
The right BAEPs (A) and the oVEMPs from the left eye (B) remain unchanged. There is an increase in the wave I-III and I-V interpeak latencies from the left ear BAEP (C), although the oVEMPs from the right eye remain unchanged (D).

8.3.2 Sensitivity, specificity, and predictive outcome values for oVEMPs

The sensitivity, specificity, and positive and negative predictive values for the oVEMPs to detect vestibular ocular dysfunction in the immediate post-operative period were 75%, 91.3%, 75% and 91.3% respectively, with a test accuracy of 87.1% (Table 15).

Table 15: Diagnostic test characteristics for the oVEMP to detect vestibular ocular deficits in the immediate and subsequent post-operative periods.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Discharge	75	91.3	75	91.3	87.1
Follow-up	80	84.6	50	95.6	83.9

For the follow-up period the respective values for sensitivity and specificity were 80% and 84.6% with positive and negative predictive values of 50% and 95.6%, with an overall test accuracy of 83.9% (Table 15).

8.4 Discussion

It was not surprising that none of the six patients referred with vestibular schwannoma had recordable oVEMPs at the time as surgery. All of the tumours were classified as being ‘large’ (>2.5cm) and all of the patients experienced either severe or total hearing loss with mass effect involving the brainstem, which are each known to be co-factors for absent oVEMP responses (Lin et al., 2013, Su et al., 2013). However, these patients did benefit from having the other forms of intraoperative monitoring performed.

As the majority of patients (70.9%) did not show any significant changes in the oVEMPs at the time of surgery and did not experience any relevant ocular-vestibular dysfunction, it can be assumed that the neural pathways that conducted these potentials remained intact (Figure 50).

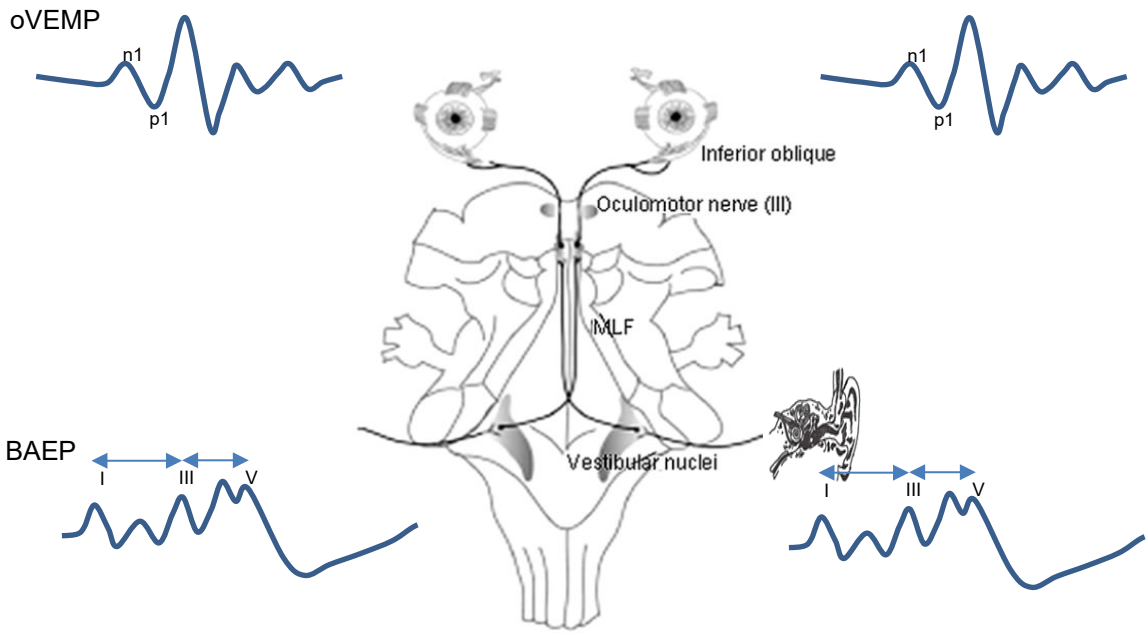


Figure 50: Normal caudal oVEMP pathways.
Intact auditory pathways show BAEPs of normal amplitude and latency and morphology with normal oVEMPs, indicating no disruption along the vestibulo-ocular pathway.

8.4.1 Localising patterns of abnormality

Seven of the eight patents (87.5%) of the patients that showed post-operative deficits showed evidence of dysfunction along the ocular-vestibular pathways. The different segments of the pathway that were affected were able to be localised more accurately with the accompanying changes in the BAEPs and the extraocular free-running EMG.

For those patients that had mild dysfunction of the VIIIth nerve caused by compression or traction, it would be assumed that there would be a corresponding increase in the latency of the oVEMP with a decrease in the oVEMP recorded from the contralateral eye (Figure 51A). This pattern of dysfunction was seen in patient 24. Although the BAEPs were seen to show an increase in I-V and a decrease in amplitude, indicative of a conduction block, the oVEMP potentials only showed a decrease in amplitude.

Retraction of the cerebellum causes neurophysiological dysfunction of the eighth nerve (Simon, 2011). The retraction of the cerebellum moves the brainstem away from the internal auditory meatus and stretches the nerve. Different mechanisms may cause the resultant dysfunction; including compression and stretch of the vessels that supply the vestibulocochlear nerve that result in subsequent nerve ischaemia, and direct mechanical mechanism from the stretch or compression of the nerve (Legatt, 2002). Unlike some cerebellopontine tumours, that have been gradually pushing the brainstem away over the course of many months and allowing the eighth nerve to adapt to the gradual stretch forces, microvascular decompressive surgery can cause an

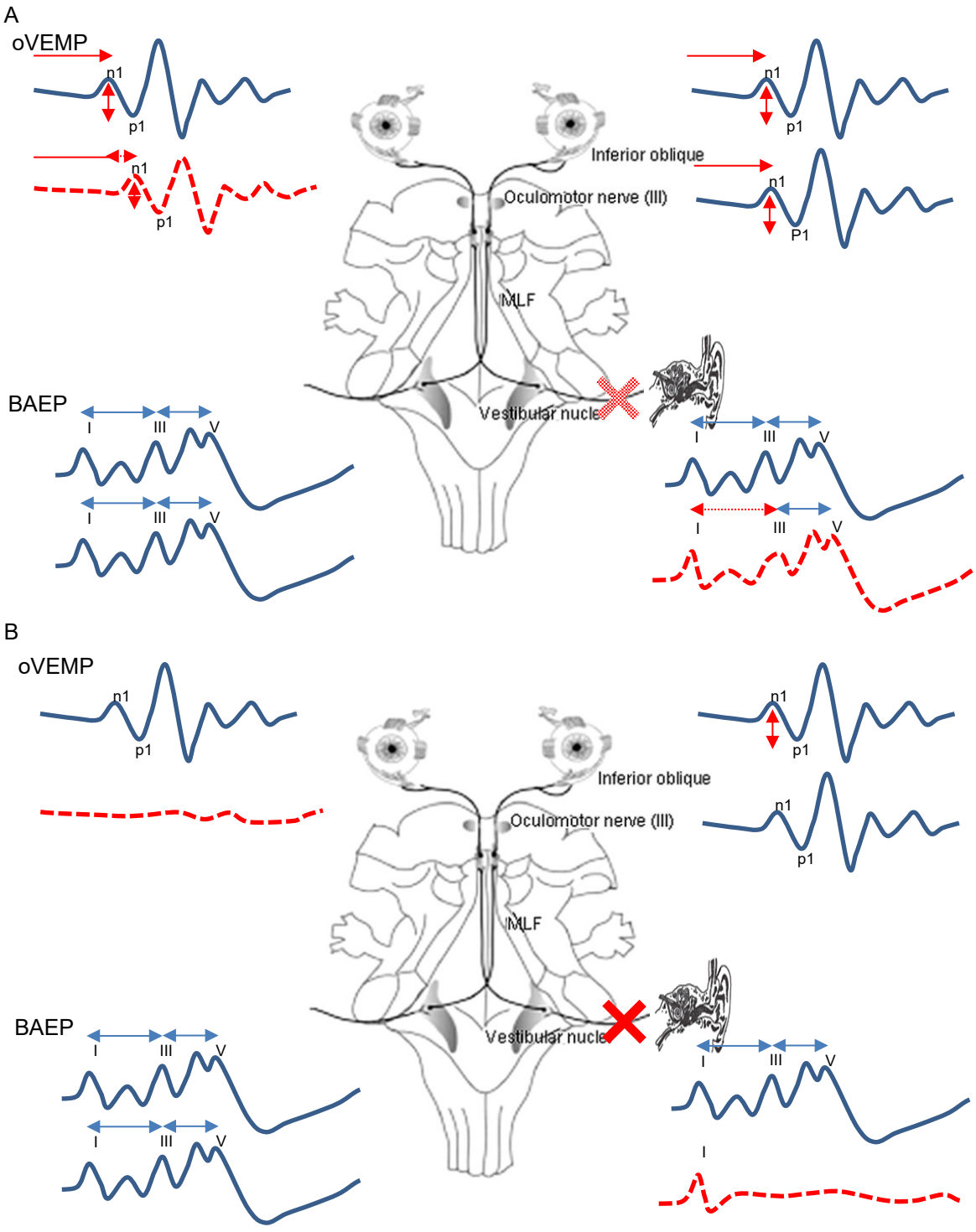


Figure 51: Caudal disruption of the oVEMP pathway.
A. Mild dysfunction. Traction or compression of the VIIth nerve will cause an increased I-III interpeak latency from the ipsilateral BAEP, whilst the contralateral BAEP would remain normal. The oVEMP recorded from the contralateral eye to the side of stimulation would show an altered morphology with a change in latency/amplitude due to the caudal slowing along the superior vestibular portion of the VIIIth nerve.
B. Severe dysfunction. A total loss of the VIIIth nerve function proximal to the cochlea would cause a loss of all the BAEP waves beyond wave I on the side of stimulation. The oVEMP recorded from the contralateral eye to the side of stimulation would be absent due to the severe disruption of the superior vestibular nerve conduction. The BAEP from the contralateral ear and the corresponding ipsilateral oVEMP would remain present.

abrupt change to the eighth nerves functional status. The selective vascular supply between the common cochlear artery and the anterior vestibular artery to vascularise the different respective branches of the eighth nerve may be the reason why there was a preserved latency of the oVEMP.

Similarly, it is known that local oedema can gradually occur and develop in the immediate post-operative phase after brainstem surgery. This can be seen to occur at the sites where cranial nerves pass through a bony canal (Sekiya et al., 1990). The different courses of the cochlear and superior vestibular branches of the eighth nerve (Figure 23), and their different orientations in relation to the angle of retraction, may also potentially explain the seemingly discordant findings in patient 33 (Figure 49), who had preferential involvement of the cochlea division of the eighth nerve. The quickly resolving oedema may have accounted for the transient neurological deficits.

More severe disruption of the peripheral component of the vestibulocochlear nerve would be expected to show a more pronounced change in the resultant oVEMP. This pathophysiological change was seen in patient 12 (Figure 46), where avulsion of the eighth cranial nerve at the level of the brainstem caused a complete loss of the BAEP on the affected side and a complete loss of the oVEMP after left ear stimulation (Figure 51B). Cranial nerves are only fixed at their point of exit from the brainstem and at their entry point in the dural layer of the skull and much of the length of the cranial nerve is unattached within the cerebrospinal fluid (Lang, 1981). The transitional zone between the cranial nerve and the brainstem is typically wedge shaped where there is a differentiation between the central oligodendrocytic myelinated fibres to the peripheral Schwann cell myelinated fibres. It is this junction that is considered to be the most vulnerable point of the nerve (Lang, 1982). As the individual cranial nerves are not embedded in surrounding tissue and do not usually undergo movement they are therefore not adapted to external mechanical forces. Manipulation of the already thinned and unstable vulnerable nerve at the root entry zone in this patient caused avulsion and a loss of continuity of the nerve pathways. In cases such as these, wave I of the BAEP may be preserved if the arterial supply to the cochlea is still preserved (Legatt, 2002).

Surgery that involves the resection of rostrally placed lesions, such as extended endoscopic surgery, places the third nerve at risk. An unchanged oVEMP with no, or only minimal free-running EMG changes from the extra ocular muscle, would indicate that the oculomotor nuclei and third nerve were not being extensively manipulated (Figure 52). During EES, the extraocular nerves are usually situated posteriorly to the access of the tumour. Therefore, it is only in the latter stages of the surgical resection that the surgeons can localise the course of the nerve with direct electrical stimulation. However, if the nerve has already partially damaged the resultant compound muscle action potential may not be elicited due to a conduction block. This could result in a false negative and further inadvertent damage to that nerve may occur, which may cause permanent damage. Electrical stimulation of the nerve is also only usually performed intermittently, and so the continual presence of the oVEMP can give the surgeon reassurance that the rostral portion of the oVEMP is still in continuity.

If the third nerve or the oculomotor nuclei does become stretched or compressed, then neurotonic discharges may be seen. These individual bursts and trains of electrical activity give information that the nerve is being damaged, and it would be expected that there would be a concomitant alteration in the oVEMP from that side. The preservation of the contralateral BAEPs would give further supporting evidence that the compression was not from the distal segment of the oVEMPs pathway. Similarly, the presence of the ipsilateral BAEPs would give confirmation that there is preserved conduction to the level of the inferior colliculus in the midbrain (Figure 53A).

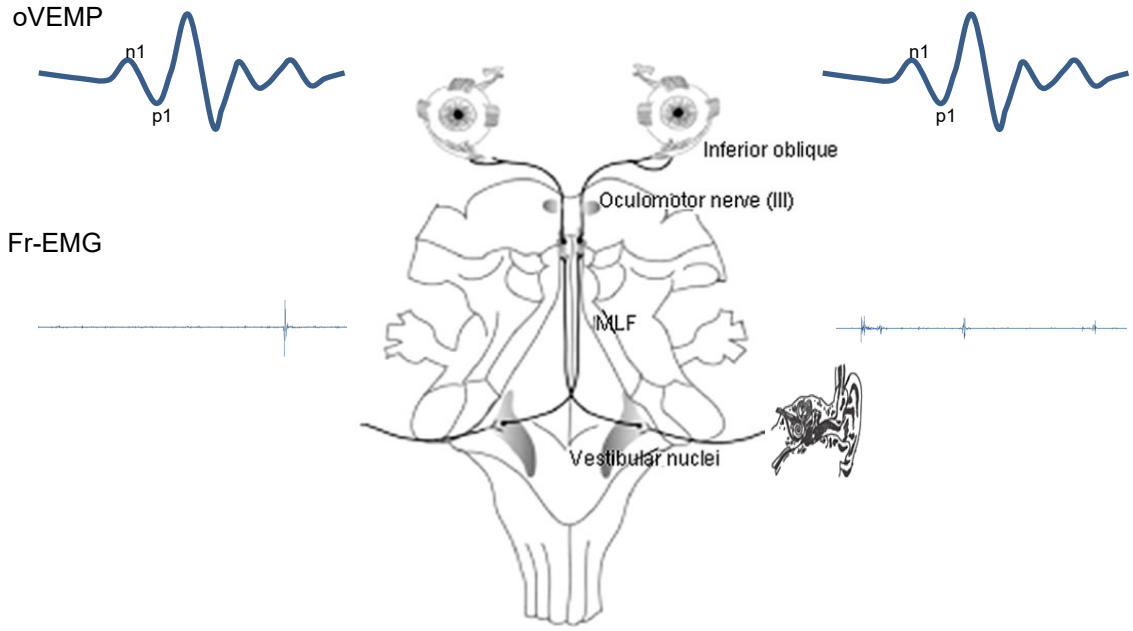


Figure 52: Normal rostral conduction along the oVEMP pathway.
Intact IIIrd nerve integrity would not show any alteration in the free-running EMG activity recorded from the extraocular nerves and the oVEMPs would remain unchanged.

Cranial nerves are more prone to damage after surgical manipulation than peripheral nerves because of their differing structure (Menovsky and van Overbeeke, 1999). Cranial nerves do not possess an epineurium and do not have a firm perineurium, instead they are covered by a single layer of sheath cells and do not have the usual continuous basal lamina. Unlike the connective tissue in peripheral nerves there is less collagen content in cranial nerves that is finer, with no interfascicular connective tissue of note to separate the individual nerve fibres into fascicules. This lack of structural support reduces the cushioning effect and makes cranial nerves more susceptible to external mechanical forces.

In the instance of patient 36 there was considerable manipulation of the meningioma to resect it from the brainstem which was evident by the excessive and significant neurotonic discharges. As the third nerve emerges from the anterior surface of the mesencephalon it passes forward and

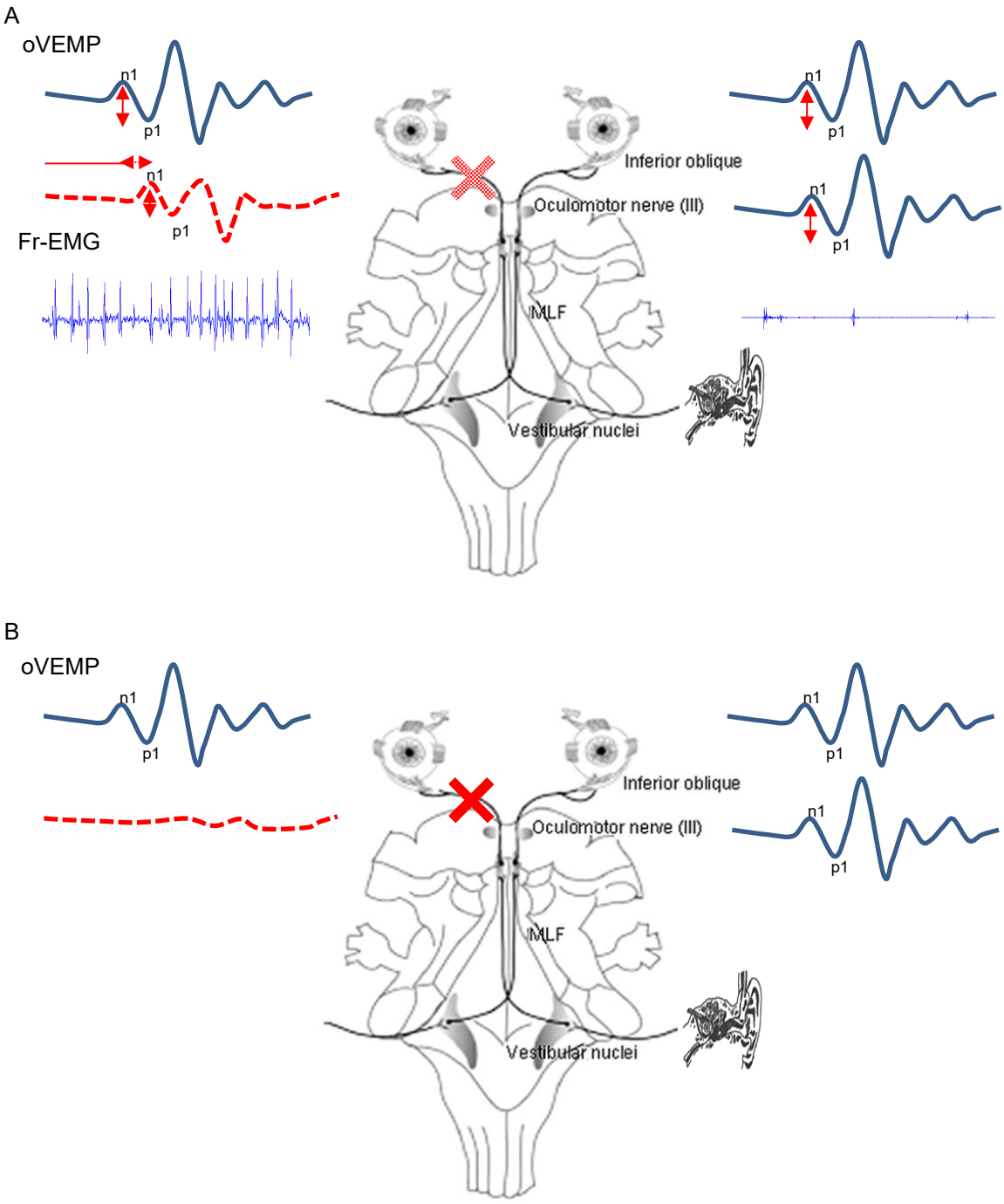


Figure 53: Disruption of the rostral oVEMP pathway
A. Mild disruption. Compression or stretch on the IIIrd nerve would cause neurotonic discharges to be recorded from the oculomotor muscle onside of compression. The resultant oVEMP recorded from that side would show an altered morphology with a change in latency/amplitude. The BAEP (not shown) would remain normal.
B. Severe disruption. A total loss of integrity and conduction through the IIIrd nerve would result in an absent oVEMP on that side. Whilst the contralateral side would still show a preserved oVEMP.

horizontally on the lateral wall of the cavernous sinus (Hariharan et al., 2018). As anterior skull-based tumours grow and extend laterally they apply pressure that compresses the third nerve between the interclinoid ligament and the tumour. If the manipulation of the tumour at the time of surgery causes an increase in the compression of the third nerve this can result in a third nerve palsy. Although there was no obvious macroscopic injury to the third nerve, compression of the nerve from the tumour and/or the surgical instruments close to it as it was being manipulated could have caused indirect trauma resulting in the transient deficit.

With more pronounced or sustained damage to the IIIrd nerve, that results in a total loss of conduction, it would be expected that there would be a complete loss of the oVEMP on that side (Figure 53B). As the cranial nerves lack adequate connective tissue they cannot compensate as well as peripheral nerves with direct trauma. This paucity of firm epineurium also makes cranial nerves more susceptible to ischaemic changes. The lack of surrounding tissue that is in close contact with the individual cranial nerves means that they have to rely on direct vascularisation from the surrounding vessels and the vessels within the pia matter (Krisht et al., 1994). Mechanical forces can disrupt the micro-circulation of the small vessels that primarily supply the central portion of the nerve and can lead to scattered ischaemic changes intra-neurally. When extrinsic tumours are abutted to the surface of the brainstem and are adhered to significant portions along the length of a cranial nerve, the vascularisation of the nerve then become dependent on the blood vessels within the tumour capsule and the surrounding arachnoid mater (Menovsky and van Overbeeke, 1999). In the case of patient 29 (Figure 48), the excess manipulation of the tumour capsule away from the brainstem could have compromised the nerves blood supply via the afferent and efferent vessels that supplied the oculomotor nerve on that side.

Again, with an isolated third nerve deficit, the BAEPs would be preserved and indicate adequate conduction through the pathways to the level of the midbrain. The presence of these waveforms would also give reassurance that there were no technical issues with stimulus delivery (i.e., the ear inserts becoming dislodged), avoiding potential false positives.

Ischaemic changes to cranial nerves are potentially reversible, and this may be the reason for the resolution in this particular patient's pupillary changes. Damage to a peripheral nerve can also lead to changes in the nerve cell body, due to metabolic changes that influence the microenvironment around the nerve (Engel and Kreutzberg, 1986). Microglial cells, that are usually *silent*, can be activated 4-6 days after a nerve injury that occurs in the vicinity of the cell body (Tetzlaff and Kreutzberg, 1984). These microglial cells cause displacement of the axon terminals on the surface of the cell body and can cause 80% of the synaptic connections to be lost. The resultant loss in synaptic input can be the cause of permanent functional deficit after cranial nerve dysfunction (Graeber and Kreutzberg, 1986).

Damage or compression to the central MLF fibres that is incomplete, would still enable the transmission of the nerve impulses to reach the oculomotor nuclei and elicit a response from the inferior oblique muscle. It would however be expected that as the number of recruited fibres through the MLF would be diminished there would be a corresponding decrease in the amplitude of the oVEMP (Figure 54A).

As the vestibulocochlear nerve and the third nerve would not be affected, it would be assumed that there would be no alteration in the BAEPs or neurotonic discharges seen from the extraocular muscle recording channels. This pattern of abnormality was seen in patient 16 who experienced a transient bilateral downward gaze post-operatively. The MLF and ocular nuclei are close to the mid-line and because of the crossed and partly uncrossed pathways, a lesion close to the mid-line at the level of the oculomotor nuclei would affect both of these structures. In this patient the cavernous malformation was seen to show a visible discolouration on the surface of the brainstem, and this site was used to access the malformation. The necessary surgical manoeuvres that were required to extend the cavity, that was close to the mid-line, in order to remove the lesion, were the presumed cause of the recoverable oculomotor deficits.

With a more complete and total conduction block of the conducting fibres through the MLF the lack of recruitment to the oculomotor nuclei would result in the abolition of the oVEMP. Again, the presence of the BAEPs and the absence of EMG changes would aid in the localisation of this pattern of abnormality (Figure 54B).

With more extensive exposures, and the need to remove more medially situated tumour remnants, there is an increase in the amount of traction and distortion of the brainstem structures required to access the deep-seated parts of the tumour. These manoeuvres, which are performed at the end of surgery, place the already compromised brainstem fibres and networks at increased risk of sustaining permanent damage. Patient 6 was undergoing removal of a right sided intrinsic cavernous malformation that was around the level of the trigeminal root entry zone. The malformation was accessed via a lateral pontine approach after neurophysiological mapping had identified a safe entry zone (Karakis, 2013). The lesion was described as being of a ‘firm consistency’ and was adhered to the surface of the brainstem at the medial and anterior aspects. Disruption of the microcirculation or direct trauma to the MLF pathways on the surgical side, that was unable to be compensated for, could be the likely cause of this persisting neurological deficit. This was confirmed by the loss of the oVEMP following right ear stimulation (Figure 45).

Another patient (number 27) experienced vestibulo-ocular changes that persisted post-operatively. There were no obvious alterations in the neurophysiological responses, other than a bilateral decrease in the oVEMP potentials of 50-60% of baseline (Figure 47). Again, tight adhesion to the brainstem of the meningioma could have permanently disrupted the local microcirculation when the borders of the lesion were being coagulated and removed. The preservation of the potentials could indicate the capacity for further improvement of the patient’s symptoms, although longer-term follow-up would be required to see if this is the case.

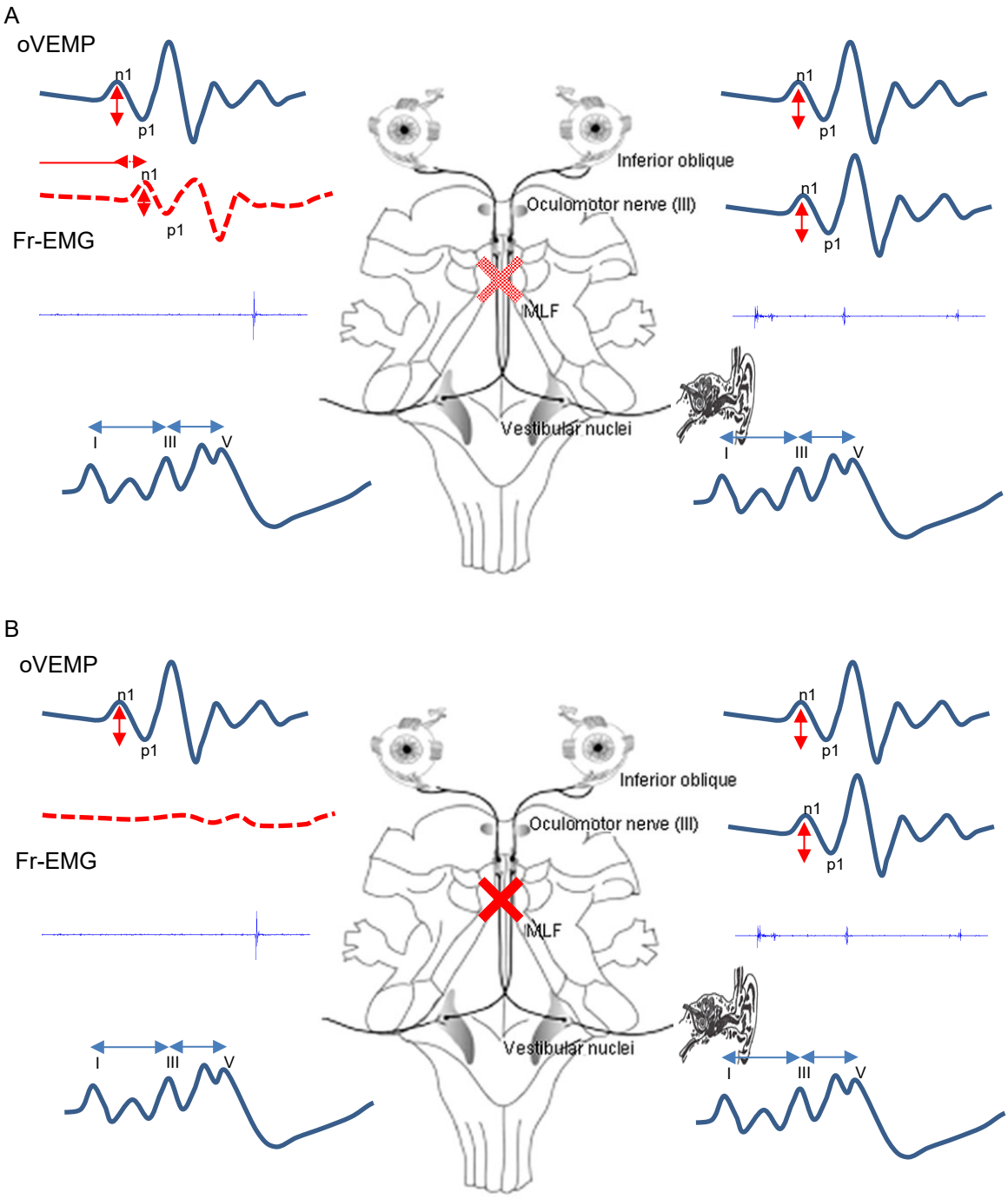


Figure 54: Central oVEMP pathway disruption.
A. Mild disruption. A partial compression or alteration in conduction of the centrally located medial longitudinal fascicule fibres would cause an alteration in the morphology of the oVEMP, with a change in latency/amplitude of the oVEMP on that side. The contralateral oVEMP and the right and left BAEPs would remain normal (indicating intact caudal pathway integrity) and the free-running EMG from the extraocular muscles would not show any spontaneous activity (indicating no rostral pathway dysfunction).
B. Severe disruption. Total conduction block to the medial longitudinal fascicules would result in an absent oVEMP being recorded on that side. The contralateral oVEMP and the right and left BAEPs would remain normal and the free-running EMG from the extraocular muscles would not show any spontaneous activity (indicating preserved caudal and rostral integrity respectively).

It is difficult to explain why the oVEMP changes that were seen in this study were confined to changes in amplitude and not latency. The peripheral portion of the eighth nerve is approximately 25mm in length (Moller et al., 1994), whilst the oculomotor nerve is approximately 45mm in length, with cisternal, cavernous and fissural-orbital portions (Iaconnetta et al., 2010). The MLF portion of the oVEMP extends from the vestibular nuclei at the level of the upper medulla and lower pons to the oculomotor nuclei in the midbrain of the brainstem and varies in length from with adult values being reached by the age of 7-8years of age. The MLF pathways that constitute the oVEMP pathways would be between 45-58mm in length (Raininko et al., 1994). The modern microscopic techniques used intraoperatively allow focal resection that is localised to discrete and specific portions of the nervous system. The smaller diameter fibres, and those fibres that are already damaged as part of the disease process, would have slower conduction velocities, and it is these fibres that are more likely to be disrupted first due to any iatrogenic mechanical or ischaemic changes, in comparison to the larger diameter healthier fibres with faster conduction velocities. The preservation of these faster conducting fibres would therefore preserve the absolute latency of n1 potential. Also, any subsequent disruption of the neural pathways would only be restricted to a small portion of the entire pathway being monitored and the normal portions of the pathway would therefore dilute any expected changes in latency.

Recent studies that have utilised other reflex testing methodologies intraoperatively have also shown results that have been confined to changes in amplitude only.

8.4.2 Other brainstem reflexes

Brainstem reflexes are designed to enable the body to adjust to sudden changes in the body's environment and are simple motor responses which are organised by the brainstem to react rapidly to external stimuli. Brainstem reflexes provide valuable information of the functional integrity of the afferent and efferent pathways and provide information about the physiology and pathophysiology of segmental and suprasegmental control mechanisms (Aramideh et al., 2002). Recording of brainstem reflexes can objectively assess functional abnormalities by detecting changes in one or more features of the recorded reflex variables (i.e., amplitude or latency). Lesions affecting the mesencephalon, pons or the medulla can cause different abnormalities. Intraoperative neurophysiological examination of brainstem reflexes and the recording of different brainstem reflexes intraoperatively may help localise more accurately impending injury within the brainstem. The mapping and monitoring of the pathways and their internuclear connections that are important for the preserved functioning of swallowing, speech coordination and gaze are only now being realised.

8.4.2.1 Blink reflex

The R1 component of the blink reflex can be recorded from the orbicularis oris in patients under general anaesthesia by using a train of repetitive stimuli delivered to the supraorbital branch of the trigeminal nerve (Deletis et al., 2009). The R1 corresponds to the oligosynaptic reflex arc that includes the afferent fibres from the ophthalmic (V1) division of the trigeminal nerve, the brainstem

connections in the lateral mid pons between the trigeminal and facial nuclei and the efferent facial nerve to the orbicularis oris (Shahani, 1970). An alteration of the R1 waveform indicates a decrease in the stimulus conduction due to an alteration in either the large myelinated afferent sensory fibres, the inter-pontine connections between the principle sensory nucleus of the trigeminal nerve and the ipsilateral facial nucleus or the afferent facial nerve fibres (Valls-Sole, 2005). In a personal study, Fernadez-Conjero and colleagues were able to elicit blink reflexes in 19 out of 21 patients undergoing a retrosigmoid approach for surgical resection of skull-based tumours (Fernandez-Conejero et al., 2014). Eight patients showed a loss of the blink reflex which subsequently recovered in five patients when the surgery was halted and none of these had any post-operative deficits. The three patients with persistent loss of amplitude all presented with a post-operative deficit. The remaining patients with blink reflexes that did not alter at the time of surgery did not show facial or trigeminal deficits post-operatively. The author concluded that the blink reflex should be incorporated in the routine recordings for intraoperative monitoring for skull-base surgery, as there is a strong correlation between the changes seen in the blink reflex intraoperatively and the function of the facial and trigeminal nerves and their brainstem reflex arc pathways post-operatively.

8.4.2.2 Masseter reflex

The masseter reflex is a monosynaptic proprioceptive trigemino-trigeminal reflex that has valuable topodiagnostic utility in clinical practice as it is strictly unilateral (Cruccu et al., 2005). Proprioceptive information from the trigeminal nerve is conducted to the mesencephalic nucleus of the trigeminal complex from which fibres descend to the mid-pons to synapse monosynaptically within the trigeminal motor nucleus. The motor neurones of the ipsilateral masseter and temporalis muscles make up the efferent limb of the reflex arc. The masseter reflex is believed to control masticatory behaviour and jaw movements during speech (Cruccu et al., 2005). The H-reflex was able to be reliable recorded intraoperatively in 70% of the patients when recorded from the masseter muscle and in 75% of the patients when recorded from the temporalis muscle (Ulkatan et al., 2017). Although the number of subjects in this study were small, the authors concluded that monitoring the H-reflex represents a simple and rapid method to assess the reflex brainstem circuitry through the midbrain and mid-pons, along with the integrity of the trigeminal nerve during surgery that involves these neurological structures (Ulkatan et al., 2017).

8.4.2.3 Laryngeal adductor reflex

In comparison to other primates, the larynx in humans is situated lower in the neck so that the pharyngeal cavity is above the laryngeal cavity; this allows the characteristic resonances of vocalisation necessary for human language (Sasaki and Weaver, 1997). However, this requires an advanced laryngeal protective mechanism so that the lower airways do not become obstructed by the entry of foreign bodies. The laryngeal adductor reflex is therefore crucial for survival and is an independent self-governing motor behaviour which takes precedence over respiration and phonation (Ludlow, 2005). This reflex is triggered by stimulation of the supraglottic mucosa and

protects the tracheobronchial airway from aspiration by adducting the vocal folds and closing the laryngeal inlet (Sasaki and Weaver, 1997). The sensory information from the supraglottic mucosa ascends through the ipsilateral internal branch of the superior laryngeal nerve and vagus nerve to the nucleus of the solitary tract. Fibres then project from this nucleus ipsilaterally and contralaterally to the nucleus ambiguous on both sides where the laryngeal motor neurones are located. Effective glottis closure to protect the airways relies on bilateral vocal fold contraction that is caused by rapid contraction of the thyroarytenoid, lateral cricoarytenoid and interarytenoid muscles. These muscles are innervated by the recurrent laryngeal branch of the vagus nerve which makes up the efferent arc of the reflex (Ludlow, 2005). Recent studies have shown that the lateral adductor reflex produces early (R1) and late (R2) responses bilaterally (Tellez et al., 2018) and that these responses are able to be consistently elicited, even under differing types of anaesthesia (Sinclair et al., 2017). This has enabled the continuous monitoring of the recurrent laryngeal nerve during neck surgery for thyroidectomy and parathyroidectomy where this nerve is at risk of injury (Sinclair et al., 2017a).

However, as the laryngeal adductor reflex monitors the entire vagus nerve reflex arc, it may be applicable in other surgeries that place the sensory and motor pathways and the lower brainstem structures at risk. In a series of 53 patients undergoing cerebellar-pontine angle and brainstem surgeries, 15 or the 50 patients (30%) of the patients who were able to have the reflex monitored showed a significant change of amplitude or loss of potential (Tellez et al., 2021). The specificity of implementing either a 50% or 60% drop in amplitude as a warning criterion was 100%, although the sensitivity was higher using 50% criteria compared to a 60% loss (70% versus 40%).

Additional studies to establish the accurate warning criteria for each these reflex studies, so that they can reliably detect impending injury of their brainstem pathways and demonstrate their clinical utility need further investigation and replication in larger studies. These studies are currently on-going, but the early reports show encouraging results (Aydinlar et al., 2020, Tellez et al., 2021).

8.4.3 Strengths and limitations

One of the limitations of this study is that it is an observational study and is retrospective in nature. The patients undergoing investigation were from a heterogeneous group and further studies with larger sample size for patients presenting for specific tumour types in specific brainstem areas, as well as those undergoing the various surgical approaches should be looked at further. The patient group should also be extended into the paediatric population too, as this patient groups have a higher incidence of brainstem pathology and suffer more readily from pre- and post-operative deficits with a higher impact on their quality of life (Peeler, 2017).

The changes that are seen in the oVEMPs, in correlation with the BAEPs and the presence or absence of neurotonic discharges seen from the extraocular muscles, can give valuable localising information to the potential site of disruption. For decisions to be made intraoperatively based on the neurophysiological findings, there must be confidence in the test's ability to distinguish those patient's that are at increased risk of developing an oculomotor deficit from those that are not. The

relatively high NPV of 95.6% for the oVEMPs at follow-up is therefore meaningful in this regard. If oVEMP monitoring is to be implemented in future, then a preserved and stable oVEMP could reassure the surgeon that resection can continue. However, for this study when the oVEMPs did change, the surgeon was not informed, as this was not part of the research design. Therefore, before any alarms are raised to the surgeon that could alter the surgical outcome, the consequences of them must be put into the correct clinical context.

All of the various modalities of intraoperative monitoring have a dual function; they can be used a diagnostic tool, or they may act as surrogate endpoints. When serving as a diagnostic tool they detect the neurological injury and predict the postoperative neurological status of that nervous system pathway being monitored. When serving as a surrogate endpoint they can contribute to the prevention of neurological impairment by triggering an intervention that rescues the potential back to its baseline value to avoid the impending damage (Skinner and Holdefer, 2014).

This is now an important distinction as the surgical paradigms shift towards prioritising the preservation of neurological function over complete tumour resection. To obtain meaningful diagnostic test characteristics it is necessary to have a control group. However, there would be an ethical dilemma for the surgeons and the patients if a randomised control group were to be used, in which any adverse intraoperative monitoring changes were not reported to the surgeon or were not acted upon (Eccher et al., 2014). A proposed alternate control study is the assessment of outcome after a transient change in the monitored parameter that is reversed by a surgical intervention versus the outcome after a persistent change (Skinner and Holdefer, 2014). However, this *treatment paradox* also raises the question of how these changes should be characterised, either as a false negative or a true positive event. The rescue intervention that restores the oVEMP should be regarded as a false negative, whilst an irreversible change should be classed as a positive result. Therefore, going forward the reversible oVEMP changes should be evaluated within the context of biomarker surrogacy (Holdefer et al., 2015).

The low prevalence of post-operative deficits, with only eight of the patients showing oculomotor dysfunction, would have an impact on the positive predictive value (PPV) of the test. The low PPV of 75% and 50% at discharge and follow-up respectively (Table 15) may be accounted for by the low prevalence of patients experiencing post-operative oculomotor deficits. Further refinement of the warning criteria may alter the tests characteristics further and the construction of receiver operator curves using different amplitude cut-off points may be beneficial. Clarifying reversible from irreversible changes and correlating them with the relevant neurological changes that are transient, in both the immediate 24-48hour post-operative period and the early 2-7day post-operative period, with those with persistent and permanent, may also alter the performance of the test at different post-operative time points.

All of this information is important for surgical decision making as false positive alarms risk the patient suffering indirectly by stopping the surgery prematurely before a meaningful resection has occurred. However, with the current philosophy of surgery being aimed towards the preservation of

neurological function, and for treatment of the disease to be less harmful than the natural course of the disease, early termination of the surgical resection may be able to be compensated for with a staged reoperation - whereas a permanent neurological deficit cannot be compensated for.

8.4.4 Future directions

Studies have shown that because of their vestibular origin, vestibular evoked potentials can be recorded in patients with conductive hearing loss by using bone conducted vibration (Rosengren et al., 2019). The stimuli can be delivered via different types of transducers that include commercially available audiometric transducers (B71 or B81) or larger vibratory shakers that are adapted and used primarily in the research setting (Curthoys, 2010). However, these large vibrators are not specified as medical devices, as their original design was as accelerometers for the calibration of mechanical impedance in small devices (Frohlich et al., 2021). These devices also weigh over a kilogram and require additional amplification and mechanical supports to apply the necessary pressure to the skull, which would preclude them from use intraoperatively.

The maximum output force that is able to be generated by B71 audiometric transducer is not able to elicit oVEMPs in all subjects (Iwasaki et al., 2008). A more powerful version, based on the balanced electromagnetic separation transducer (BEST) principle, the B81, that is capable of producing higher output levels, has been proven to be able to elicit oVEMP responses in normal subjects after stimulation at the mastoid (Jansson et al., 2015, Frohlich et al., 2021). Whilst this stimulating technique would be able to be used for mid-line sub-occipital approaches to the brainstem by using a transducer on each mastoid, the placement would not be feasible for lateral approaches, as the device would either be too close or even within the sterile field. Another new prototype device, the B250, has recently been introduced which has an electrical input impedance that is compatible with the already available hardware that is used for vestibular testing (Hakansson et al., 2018). This device may prove to be sufficient to deliver a strong enough power output at the mid-frontal (Fz) region that would allow bilateral oVEMPs to be recorded simultaneously. This would allow both pathways to be assessed simultaneously and enable more rapid feedback to the surgeon. However, further clinical evaluation of this device, which is still in the research phase, would have to be established.

Bilateral oVEMPs are also able to be evoked after short duration (~1msec) electrical currents (~5mA) with the cathode on the mastoid and the anode on the forehead (Cheng et al., 2009). Using a unipolar derivation, with the C7 cervical spinal process as the anode, Rosengren was able to obtain similar results. As well as using the unipolar montage, a bipolar stimulating configuration, between the left and right mastoids, was seen to produce even higher amplitude oVEMP responses. In their study, the responses from the ipsilateral eye to the side of cathodal stimulation were seen to produces responses with an initial positive deflection, indicating other extraocular muscle excitation (Rosengren et al., 2009). The latencies of galvanic vestibular stimulation (GVS) evoked oVEMPs are shorter than those elicited by tap stimulation. This is compatible with the electrical stimulation having its effect on the otolithic afferents of vestibular nerve directly, rather

than the otolithic end organ (Goldberg et al., 1984). Therefore, for those patients with pre-existing distal vestibular dysfunction, it may mean that this modality of stimulation may offer an advantage over air-conducted stimulation.

However, due to the excessive stimulus artefact that was seen in these studies, it was necessary for the responses that were recorded following stimulation with the eyes in a downward position to be subtracted from the responses with the eyes elevated in order to reveal the final response (Watson and Colebatch, 1998). The need for these different recording conditions and eye states would preclude this exact methodology from being utilised in real time intraoperatively.

Further investigations are warranted to see if this stimulating modality is more beneficial at eliciting oVEMP responses, especially as these specific technical factors may now be able to be overcome, with modern acquisition systems which have elaborate soft-ware programmes that can be used to eliminate stimulus artefact on-line. Whilst good electrodes application is used in the first instance to avoid stimulus artefact, de-blocking capabilities which suspend the data acquisition for the duration of the stimulus artefact can be used to eliminate the artefact. The duration of the stimulus artefact can also be minimised using advances in hardware that delay the return discharge of the electrical stimulation beyond the latency of the neurophysiological potential (Sarnthein et al., 2021). Bi-phasic electrical stimulation with an alternating initial phase of delivery can also be used to cancel out the stimulus artefact. The evolution of these advances in galvanic stimulation, and the fact that the stimulus intensity and duration and phase can be altered, would mean that higher charge densities would be able to be delivered safely. Therefore, unlike bone conduction vibrator stimulators that are currently limited in their maximum output, and air conducted stimulation that is limited by the safe maximum stimulus levels over prolonged periods (Colebatch and Rosengren, 2014), electrical stimulator properties can be more easily adapted to achieve maximum stimulation.

Intraoperative monitoring techniques can be either specific for stimulation or specific for recording. Bipolar recording needle electrodes of sufficient length (i.e., 20mm) are now commercially available and are able to penetrate the muscles that control eye movement, and similar to hook wire electrodes, these can give better quality recordings with higher signal to noise ratios (Lopez, 2011). However, extraocular muscle recordings are not routinely used in many centres due to the complexity of placing the recording electrodes into the muscles through closed eyelids without direct visualisation of the muscles and the potential risk of damaging the eye and surrounding structures. These structures close to the anterior orbit include the lacrimal system and the supraorbital and supratrochlear arteries and the superior and inferior ophthalmic veins. However, whilst image guided techniques utilising ultrasound and MRI neuro-navigation may make these insertional techniques safer (Schlake et al., 1999, Alberti et al., 2001), the presence and expertise of an attending ophthalmological surgeon is often needed, especially in those patients with pre-existing deviant eye gazes. The intraoperative recording of oVEMPs using surface electrodes would potentially enable more centres to afford their patients the benefit of monitoring the oculomotor nerve function by incorporating this technique into their multi-modal recording regime. Whereas only intermittent assessment of the rostral portion of the oculomotor pathway is currently

available when the surgeon stimulates on or around the third cranial nerve, the described oVEMP recording technique offers more immediate feedback throughout the entire course of the surgery. This would be particularly beneficial during EES, where inadvertent damage to the oculomotor nerve may occur prior to its visualisation (Thirumala et al., 2013).

8.5 Conclusion

The functional and structural integrity of the vestibular pathways are at risk during surgery in and around the brainstem. The recording of ocular vestibular evoked myogenic potentials intraoperatively is a safe and effective way of monitoring the neural pathways through the vestibular nerve, vestibular nuclei, medial longitudinal fascicule and third nerve nucleus and oculomotor nerve. Changes in the n1-p1 amplitude of >50% that are correlated with a surgical event are highly correlated with a post-operative dysfunction along the oculomotor reflex pathway. When used in combination with other neurophysiological monitoring techniques, additional localising information and potential severity can be obtained. Concurrent changes in the brainstem auditory evoked potential indicate a more caudal alteration, whilst oVEMP changes accompanied with extraocular EMG activity are indicative of a potential abnormality occurring higher up along the rostral pathway (Table 16). Isolated changes to the oVEMP with preserved BAEP latencies and absent neurotonic discharges from the extraocular muscles are more indicative of a central pathway dysfunction in and around the MLF.

Table 16: Classification and localisation of neural dysfunction based on intraoperative neurophysiological changes.

Classification		**IOM changes**				
		oVEMP		BAEP		cn III
Affected site		ipsilateral	contralateral	ipsilateral	contralateral	
Caudal (cn VIII)	Mild	-	↓ amplitude	↑ I-III and ↑ I-V latency	-	-
	Severe	-	↓ amplitude/loss	↑ I-III and ↑ I-V latency	-	-
Central (MLF)	Mild	-	↓ amplitude	-	-	-
	Severe	-	↓ amplitude/loss	-	-	-
Rostral (cn III)	Mild	-	↓ amplitude	-	-	↑ EMG activity ipsilaterally
	Severe	-	↓ amplitude/loss	-	-	A-trains

- = unchanged; ↑ = increase; ↓ = decrease.

References.

Aarsen, F.K., Van Dongen, H., Paquier, P.F., Van Mouri, M., Catsman-Berrevoets, C.E. (2004) 'Long-term sequelae in children after cerebellar astrocytoma.' *Neurology,* 62 pp. 1311-1316.

Abbott, R. (2010) 'Intraoperative neurophysiologic monitoring: its impact on the practice of a pediatric neurosurgeon.' *Childs Nerv Syst*, 16 pp. 237-240.

Adamec, I., Skoric, M.K., Handzie, J., Barusic, A.K., Bach, I., Gabelic, T. (2014) 'The role of cervical and ocular vestibular-evoked myogenic potentials in the follow-up of vestibular neuritis.' *Clinical EEG Neurosci*, 45 pp. 129-136.

Akagami, R., Dong, C.C., Westerberg, B.D. (2005) 'Localized transcranial electrical motor evoked potentials for monitoring cranial nerves in cranial base surgery.' *Neurosurgery*, 57 pp. 78–85.

Alberti, O., Sure, U., Riegel, T., Bertalnffy, H. (2001) 'Image-guided placement of eye muscle electrodes for intraoperative cranial nerve monitoring.' *Neurosurgery,* 49 pp. 660-664.

Albright, A.L., Scalbassi, R.J. (1985) 'Use of the cavitron ultrasonic aspirator and evoked potentials for the treatment of thalamic and brainstem tumours in children.' *Neurosurgery,* 17 pp. 564-568.

Aminoff, M.J., Eisen, A.E. (1998) 'AAEM Minimonograph 19: Somatosensory evoked potentials.' *Muscle Nerve,* 21 pp.277-290.

Anathanarayan, A.K., Durrant, J.D. (1991) 'On the origin of wave II of the auditory brain stem evoked response.' *Ear Hear,* 12 pp. 174-179.

Andre-Obadia, N., Zyss, J., Gavaret, M., et al. (2018) 'Recommendations for the use of electroencephalography and evoked potentials in comatose patients.' *Neuorophysiol Clin,* 48 pp. 143-169.

Aramideh, M., Ongerboer De Visser, B.W. (2002) 'Brainstem reflexes: Electrodiagnostic techniques, physiology, normative data and clinical applications.' *Muscle Nerve*, 26 pp. 14-30.

Asa, S.L., Ezzat, S. (2009) 'The pathogenesis of pituitary tumors.' *Annu Rev Pathol*, 4 pp. 97-126.

Asal, S., Sobhy, O., Salem, N. (2017) 'Study of the effect of different body positions on ocular vestibular-evoked myogenic potentials using air-conducted sound.' *Egypt J Otolaryngol*, 33 pp. 588-593.

Atcherson, S.R., Lim, T.J., Moore, P.C. Minaya, C.P. (2012) 'Comparison of auditory brainstem peak measures using ear lobe, mastoid, and custom ear canal reference electrodes.' *Audiology Research,* 2 pp. 8-11.

Atherley, G.R.C., Martin, A.M. (1971) 'Equivalent-continuous noise level as a measure of injury from impact and impulse noise.' *Ann Occup Hyg,* 14 pp. 11-28.

Aydinlar, E.I., Kocak, M., Soykam, H.O., Mat, B., Dikmen, P.Y., Sexerman, O.U., Elmaci, I., Pamir, M.N. (2020) 'Intraoperative neuromonitoring of blink reflex during posterior fossa surgeries and its correlation with clinical outcome.' *J Clin Neurophysiol,* doi: 10.1097/WNP.0000000000000777. Epub ahead of print. PMID: 33009043.

Baloh, R.W., Honrubia, V. (1990) *Clinical neurophysiology of the vestibular system*. Philadelphia: F.A. Davis.

Banoub, M., Tetzlaff, J., Schubert, A. (2003) ‘Pharmacological and physiologic influences affecting sensory evoked potentials.’ *Anesthesiology*, 99 pp. 716-737.

Barker, A.T., Freeston, I.L., Jalinous, R., Jarratt, J.A. (1987) ‘Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation.’ *Neurosurgery,* 20 pp. 100-109.

Barkhof, F. (2002) ‘The clinic-radiological paradox in multiple sclerosis revisited.’ *Curr Opin Neurol,* 15 pp. 239-245.

Barmack, N.H. (2003) ‘Central vestibular system: vestibular nuclei and posterior cerebellum’ *Brain Res Bull*, 60 pp. 511-541.

Basta, D., Todt, I., Eisenschenk, A., Ernst, A. (2005) ‘Vestibular evoked myogenic potentials induced by intraoperative electrical stimulation of the human inferior vestibular nerve.’ *Hear Res,* 204 pp. 111-114.

Bernard, J.M., Péréon, Y., Fayet, G., Guihéneuc, P. (1996) ‘Effects of isoflurane and desflurane on neurogenic motor- and somatosensory-evoked potential monitoring for scoliosis surgery.’ *Anesthesiology,* 85 pp. 1013–1019.

Binder, D.K., Sonne, D.C., Fischbein, N.J. (2010) *Cranial nerves: Anatomy, pathology, imaging*. New York, NY Thieme.

Bogle, J.M., Zapala, D.A., Burkhardt, B., Walker, K., Lundy, L., Shlefer, J., Pratt, T., Garry, M., Walker, D. (2015) ‘The effect of repetition rate on air-conducted ocular vestibular evoked myogenic potentials (oVEMPs).’ *Am J Audiol*, 24 pp. 411-418.

Bogle, J.M. (2018) ‘Clinical evaluation of the vestibular nerve using vestibular evoked myogenic potentials.’ *J Clin Neurophysiol*, 35 pp. 39-47.

Burrow, G.N., Wortzman, G., Rewcastle, N.B., Holgate, R.C., Kovacs, K. (1981) ‘Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series.’ *N Engl J Med*, 304 pp. 156-158.

Byun, J., Ahn, J.S., Park, W. (2018) ‘Microsurgical treatment outcomes of brainstem cavernous malformation: Subgroup comparison depending on application of intraoperative neurophysiologic monitoring.’ *Interdisciplinary Neurosurgery*, 13 pp. 74-81.

Caird, D., Sontheimer, D., Klinke, R. (1985) ‘Intra- and extracranially recorded auditory evoked potentials in the cat. I Source location and binaural interaction.’ *Electroencephalogr Clin Neurophysiol,* 61 pp. 50-60.

Cavallo, L.M., Somma, T., Solari, D., Iannuzzo, G., Frio, F., Baiano, C., Cappabianca, P. (2019) ‘Endoscopic endonasal transphenoidal surgery: History and evolution.’ *World Neurosurg*, 127 pp. 686-694.

Chang, M.Y., Shin, J.H., Hong, Y.H., Mun, S-K. (2017) ‘Clinical implication of vestibular evoked myogenic potentials in benign paroxysmal positional vertigo.’ *Clin Neurophysiol*, 128 pp. 351-356.

Chassard, D., Joubaub, A., Colson, A., Guiraud, M., Dubreuil, C., Banssillon, V. (1989) ‘Auditory evoked potentials during propofol anaesthesia in man.’ *Br J Anaesth*, 62 pp. 522–526.

Cheng, P.W., Chen, C.C., Wang, S.J., Young, Y.H. (2009) ‘Acoustic, mechanical and galvanic stimulation modes elicit ocular vestibular-evoked myogenic potentials.’ *Clin Neurophysiol*, 120 pp. 1841-1844.

Cheng, Y-L., Wu, H-J., Lee, G-S. (2012) 'Effects of plateau time and ramp time on ocular vestibular evoked myogenic potentials.' *J Vest Res*, 22 pp. 33-39.

Chiarovano, E., Darlington, C., Vidal, P.P., Lamas, G., de Waele, C. (2014) 'The role of cervical and ocular vestibular evoked myogenic potentials in the assessment of patients with vestibular schwannoma.' *PLoS One*, 9 e105026.

Cho, T.H., Fischer, C., Nighoghossian, N. (2005) 'Auditory and electrophysiological patterns of a unilateral lesion of the lateral lemniscus.' *Audio Neurootol,* 10 pp. 153-158.

Cochrane, D.D., Gustavsson, B., Poskitt, K.P., Steinbok, P., Kestle, J.R.W. (1994) 'The surgical and natural morbidity of aggressive resection for posterior fossa tumours in childhood.' *Pediatr Neurosurg,* 20 pp. 19-29.

Colebatch, J.G., Rothwell, J.C. (2004) 'Motor unit excitability changes mediating Vestibulocollic reflexes in the sternocleidomastoid muscle.' *Clin Neurophysiol*, 115 pp. 2567-2573.

Colebatch, J.G., Rosengren, S.M. (2014) 'Safe levels of acoustic stimulation: comments on "effects of acoustic stimuli for vestibular evoked myogenic potential studies on the cochlear function."' *Otol Neurotol*, 35 pp. 932-935.

Colebatch, J.G., Rosengren, S.M. (2019) 'Investigating short latency subcortical vestibular projections in humans: what have we learned?' *J Neurophysiol*, 122 pp. 2000-2015.

Comi, G., Filippi, M., Martinelli, V., Scotto, G. (1993) 'Brain stem magnetic resonance imaging and evoked potential studies of symptomatic multiple sclerosis patients.' *Eur Neurol*, 33 pp. 232-237.

Crnosija, L., Skoric, M.K., Gabelic, T., Adamec, I., Brinar, V., Habek, M. (2015) 'Correlation of the VEMP score, ambulation and upper extremity function in clinically isolated syndrome.' *J Neurol Sci*, 359 pp. 197-201.

Crnosija, L., Skoric, M.K., Gabelic, T., Adamec, I., Habek, M. (2017) 'Vestibular evoked myogenic potentials and MRI in early multiple sclerosis: validation of the VEMP score.' *J Neurol Sci*, 372 pp. 28-32.

Crovetto, M., Whyte, J., Rodriguez, O.M., Lecumberri, I., Martinez, C., (2010) 'Anatamo-radiological study of the superior semicircular canal dehiscence radiological considerations of superior and posterior semicircular canals.' *Eur J Radiol,* 76 pp. 167-172.

Cruccu, G., Iannetti, G.D., Marx, J.J., Thoemke, F., Truini, A., Fitzek, S. (2005) 'Brainstem reflex circuits revisited.' *Brain*, 128 pp. 386-394.

Cruccu, G., Aminoff, M.J., Curio, G., Guerit, J.M., Kakigi, R., Mauguiere, F., Rossini, P.M., Treede, R-D., Garcia-Larrea, L. (2008) 'Recommendations for the clinical use of somatosensory evoked potentials.' *Clin Neurophysiol*, 119 pp. 1705-1719.

Cullen, K.E., (2016) 'Physiology of central pathways.' *Neuro-Otology, Handbook of Clinical Neurology*, 137 pp. 17-40.

Currio, G., Oppel, F. (1988) 'Intraparenchymatous ponto-mesencephalic field distribution of brain-stem auditory evoked potentials in man.' *Electroencephalogr Clin Neurophysiol,* 69 pp. 259-265.

Curthoys, I.S., Halmagyi, G.M. (1995) 'Vestibular compensation.' *Adv Otorhinolaryngol*, 55 pp. 82-110.

Curthoys, I.S. (2010) 'A critical review of the neurophysiological evidence underlying clinical vestibular testing using sound, vibration and galvanic stimulation.' *Clin Neurophysiol*, 121 pp. 132-144.

Curthoys, I., Manzari, L. (2011) ‘Evidence missed: ocular vestibular-evoked myogenic potentials differentiate utricular from saccular function.’ *Otolaryngol Head Neck Surg*, 144 pp. 751-752.

Dai, M.J., Curthoys, I.S., Halmagyi, G.M., (1989) ‘Linear acceleration perception in the roll-plane before and after unilateral vestibular neurectomy.’ *Exp Brain Res*, 77 pp. 315-328.

Daube, J.R., Harper, C.M. (1989) ‘Surgical monitoring of cranial and peripheral nerves.’ *In* Desmedt, J.E. (ed.) *Neuromonitoring in surgery*. New York, NY: Elsevier Science Publishers, pp. 115–138.

Deletis, V., Sala, F., Morota, N. (2000) ‘Intraoperative neurophysiological monitoring and mapping during brain stem surgery: A modern approach.’ *Operative Tech Neurosurg*, 3 pp. 109-113.

Deletis, V., Urrizza, J., Ulkatan, S., Fernandez-Conejero, I., Lesser, J., Misita D. (2009) ‘The feasibility of recording blink reflexes under general anaesthesia.’ *Muscle Nerve*, 39 pp. 642-646.

Deletis, V., Fernandez-Conejero, I. (2016). ‘Intraoperative Monitoring and Mapping of the Functional Integrity of the Brainstem.’ *J Clin Neurol,* 12 pp. 262-273.

Demer, J.L., Oh, S.Y., Clark, R.A., Poukens, V. (2003) ‘Evidence for a pulley of the inferior oblique muscle.’ *Invest Ophthalmol Vis Sci,* 44 pp. 3856-3865.

Dickman, J.D. (2018) ‘The Vestibular System.’ *In* Haines, D., Mihailoff, G.A. (ed.) *Fundamental Neuroscience for Basic and Clinical Applications* 5th ed., Elsevier, pp. 320-333.

Dlugaiczyk, J. (2017) ‘Ocular vestibular evoked myogenic potentials: Where are we now?’ *Otol Neurotology*, 38 pp. 513-512.

Dlugaiczyk, J. (2020) ‘Evidence-based diagnostic use of VEMPs. From neurophysiological principles to clinical application.’ *HNO*, 68 pp. s69-78.

Dong, C.C., MacDonald, D.B., Akagami, R., (2005) ‘Intraoperative facial motor evoked potential monitoring with transcranial electrical stimulation during skull base surgery.’ *Clin Neurophysiol*, 116 pp. 588–596.

Eccher, M.A., Ghogawala, Z., Steinmetz, M.P. (2014) ‘The possibility of clinical trial in neurophysiological intraoperative monitoring: a review.’ *J Clin Neurophysiol*, 31 pp. 106-111.

Eldridge, R., Parry, D. (1992) ‘Vestibular schwannoma (acoustic neuroma). Consensus development conference. *Neurosurgery,* 30 pp. 962-964.

Engel, A.K., Kreutzberg, G.W. (1986) ‘Changes of acetylcholinesterase molecular forms in regenerating motor neurons.’ *Neuroscience,* 18 pp. 467-473.

Ernst, A., Todt, I., Seidle, R.O., Eisenschenk, A., Blodow, A., Basta,D. (2006) ‘The application of vestibular-evoked myogenic potential in otoneurosurgery’. *Otolaryngol Head Neck Surg*, 135 pp. 286-290.

Evans, D.G., Moran, A., King, A., Saeed, S., Gurusinghe, N., Ramsden, R. (2005) ‘Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought.’ *Otol Neurotol,* 26 pp. 93-97.

Ezzat, S., Asa, S.L., Couldwell, W.T. (2004) ‘The prevalence of pituitary adenomas: a systematic review.’ *Cancer*, 101 pp. 613-619.

Fahlbusch, R., Strauss, C. (1991) ‘Surgical significance of cavernous hemingioma of the brainstem.’ *Acta Neurochir*, 52 pp. 25-32.

Fernandez-Conejero, I., Ulkatan, S., Sen, C., Deletis, V. (2012) 'Intra-operative neurophysiology during microvascular decompression for hemifacial spasm.' *Clin Neurophysiol,* 123 pp. 78-83.

Fernandez-Conejero, I., Torres, A., Gabarros, A., Deletis, V. (2014) 'Correlation between blink reflex (br) and corticobulbar motor evoked potentials (comeps) in skull base surgery and role as a predictor of clinical outcome.' *Clin Neurophysiol*, 125 pp. e19.

Fetter, M. (2000) 'Assessing vestibular function: which tests, when?' *J Neurol*, 247 pp. 335-342.

Fife, T.D. (2010) 'Overview of anatomy and physiology of the vestibular system.' *In* Eggers, S.D., Zee, D. (ed.) *Vertigo and Imbalance: Clinical Neurophysiology of the Vestibular System*. 1st ed., Elsevier, pp 5-27.

Fife, T.D., Colebatch, J.G., Kerber, K.A. et al. (2017) 'Practice guideline: Cervical and ocular vestibular evoked myogenic potential testing. Report of the guideline development, dissemination and implementation subcommittee of the American Academy of Neurology.' *Neurology*, 89 pp. 1-9.

Flock., A. (1965) 'Transducing mechanisms in the lateral line canal organ receptors.' *Cold Spring Harbour Symp Quant Biol*, 30 pp. 133-145.

Flock, A., Orman, S. (1983) 'Micromechanical properties of sensory hairs in receptors cells of the inner ear.' *Hear Res*, 11 pp. 249-260.

Frazier, J.L., Lee, J., Thomale, U.W., Noggle, J.C., Cohen, K.J., Jallo, G.I. (2009) 'Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies.' J Neurosurg. Pediatr, 3 pp. 259-269.

Frohlich, L., Wolke, M., Plontke, S.K., Rahne, T. (2021) 'Influence of bone conductor transducer type and placement on ocular and cervical vestibular evoked myogenic potentials.' *Sci Rep*, 11 pp. 1-8.

Fukaya, C., Katayama, y., Kasai, M (1999) 'Intraoperative electrooculographic monitoring of oculomotor nerve function during skull base surgery.' *J Neurosurg*, 91 pp. 157-159.

Fukuoka, T., Takeda, H., Dembo, T., Nagoya, H., Kato, Y., Deguchi, I. (2012) 'Clinical review of 37 patients with medullary infarction.' *J Stroke Cerebrovasc Dis*, 21 pp. 594-599.

Gabelic, T., Krbot, M., Sefer, A.B., Isgum, V., Adamec, I., Habek, M. (2013) 'Ocular and cervical vestibular evoked myogenic potentials in patients with multiple sclerosis.' *J Clin Neurophysiol*, 30 pp. 86-91.

Gabelic, T., Skoric, M.K., Adamec, I., Barun, B., Zadro, I., Habel, M. (2015) 'The vestibular evoked myogenic potential (VEMP) score: a promising tool for evaluation of brainstem involvement in multiple sclerosis' *Eur J Neurol*, 22 pp. 261-269.

Gan, R., Noronha, A. (1995) 'The medullary vascular syndromes revisited.' *J Neurol*, 242 pp. 195–202.

Gazioglu, S., Boz, C. (2012) 'Ocular and cervical vestibular evoked myogenic potentials in multiple sclerosis patients.' *Clin Neurophysiol*, 123 pp. 1872-1879.

Gersdorff, M.C.H. (1982) 'Simultaneous recordings of human auditory potentials: transtympanic electrocochleography (ECochG) and brainstem-evoked responses (BER).' *Arch Otorhinolarygol,* 234 pp. 15-20.

Gianoli, G.J., Soileau, J.S. (2012) 'Acoustic neuroma neurophysiologic correlates: vestibular-preoperative, intraoperative and postoperative.' *Otolaryngol Clin N Am,* 45 pp. 307-314.

Giliberto, G., Lanzino, D.J., Diehn, F.E., Factor, D., Flemming, K.D., Lanzino, G. (2010) 'Brainstem cavernous malformations: anatomical, clinical, and surgical considerations.' *Neurosurg Focus*, 29 E9.

Goebel, J.A., O'Mara, W., Giannoli, G. (2001) 'Anatomic considerations in vestibular neuritis.' *Otol Neurotol*, 22 pp. 512-518.

Goldberg, J.M., Fernandez, C. (1980) 'Efferent vestibular system in the squirrel monkey: anatomical location and influence on afferent activity.' *J Neurophysiol,* 43 pp. 986-1025.

Goldberg, J.M., Smith, C.E., Fernandez, C. (1984) 'Relationship between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey.' *J Neurophysiol*, 51 pp. 1236-1256.

Goldberg, J.M. (2000) 'Afferent diversity and the organization of central vestibular pathways.' *Exp Brain Res*, 130 pp. 277-297.

Govender, S., Rosengren, S.M., Colebatch, J.G. (2009) 'The effect of gaze direction on the ocular vestibular evoked myogenic potential produced by air-conducted sound.' *Clin Neurophysiol*, 120 pp. 1386-1391.

Govender, S., Cheng, P.Y., Dennis, D.L., Colebatch, J.G. (2016) 'Electrode montage and gaze effects on ocular vestibular evoked myogenic potentials.' *Clin Neurophysiol*, 127 pp. 2846-2854.

Gozke, E., Erdal, N., Ozkarakas, H. (2010) 'Ocular vestibular evoked myogenic potentials in patients with migraine.' *Acta Neurol Belg*, 110 pp. 321-324.

Graeber, M.B., Kreutzberg, G.W. (1986) 'Astrocytes increase in glial fibrillary acidic proteins during retrograde changes of facial motor neurons.' *J Neurocytol*, 15 pp. 363-373.

Gross, B.A., Lin, N., Du, R., Day, A.L. (2011) 'The natural history of intracranial cavernous malformations.' *Neurosurg Focus,* 30 pp. E24.

Gurkov, R., Katner, c. (2013) 'Modulation of oVEMP amplitudes by lateral head tilts.' *Clin Neurophysiol*, 124 pp. 1911-1912.

Habek, M. (2013) 'Evaluation of brainstem involvement in multiple sclerosis.' *Expert Rev Neurother*, 13 pp. 299-311.

Haines, D., Mihailoff, G.A. (2018) *Fundamental Neuroscience for Basic and Clinical Applications*. 5th ed., Elsevier.

Hakansson, B., Jansson, K.L., Tengstrand, T., Johannsen, L. (2018) 'VEMP using a new low-frequency bone conduction transducer.' *Med Devices Evid Rep*, 11 pp. 301-312.

Halonen, J.P., Jones, S., Shawkat, F. (1988) 'Contribution of cutaneous and muscle afferents fibres to cortical SEPs following median and radial nerve stimulation in man.' *Electroencephalogr Clin Neurophysiology*, 71 pp. 331-335.

Harbert, M.J., Yeh-Nayre, L.A., O'Halloran, H.S. (2012) 'Unrecognised visual field deficits in children with primary central nervous system brain tumours.' *J Neurooncol*, 107 pp. 545-549.

Hariharan, P., Balzer, J.R., Anetakis, K., Crammond, D.J., Thirumala, P.D. (2018) 'Electrophysiology of extraocular cranial nerves: Oculomotor, trochlear and abducens nerve.' *J Clin Neurophysiol*, 35 pp. 11-15.

Hashimoto, I., Ishiyama, Y., Yoshimoto, Y., Nemoto, S. (1981) 'Brainstem auditory evoked potentials recorded directly from human brainstem and thalamus.' *Brain,* 104 pp. 841-859.

Health and Safety Executive 2005 'Final regulatory impact assessment of the control of noise at work regulations 2005.'

Heidenreich, K.D., Kileny, P.R., Ahmed, S. (2017) 'Superior canal dehiscence syndrome affecting 3 families.' *JAMA Otolaryngol Head Neck Surg*, 143 pp. 656-662.

Heneghan, C.P., Thornton, C., Navaratnarajah, M., Jones, J.G. (1987) 'Effect of isoflurane on the auditory evoked response in man.' *Br J Anaesth,* 59 pp. 277–282.

Hirsch, B.E., Durrant, J.D., Yetiser, S. (1996) 'Localising retro-cochlear hearing loss.' *Am J Otol,* 17 pp. 537-546.

Hizli, O., Cureoglu, S., Kaya, S., Schachern, P.A., Paparella, M.M., Adams, M.E., (2016) 'Quantitative vestibular labyrinthine otopathology in temporal bones with vestibular schwannoma.' *Otolaryngol Head Neck Surg*, 154 pp. 150-156.

Ho, R-W., Huang, H-W, Ho, J-T (2015) 'The influence of pituitary adenoma size on vision and visual outcomes after trans-sphenoidal adenectomy: A report of 78 cases.' *J Korean Neurosurg Soc,* 57 pp. 23-31.

Holdefer, R.N., Kinney, G.A., Robinson, L.R., Slimp, J.C. (2013) 'Alternative sites for intraoperative monitoring of cranial nerves X and XII during intracranial surgeries.' *J Clin Neurophysiol,* 30 pp. 275-279.

Holdefer, R., MacDonald, D., Skinner, S. (2015) 'Somatosensory and motor evoked potentials as biomarkers for post0operative neurological status.' *Clin Neurophysiol,* 126 pp. 857-865.

Horn, A.K.E., Leigh, R.J. (2011) 'The anatomy and physiology of the ocular motor system' Ch2. *In* Handbook of Clinical Neurology, Vol 82, Kennard, C., Leigh, R.J. *Elsevier*.

Huang Y-C., Tsung, T.L., Young, Y.H. (2012) 'Feasibility of ocular vestibular-evoked myogenic potentials (oVEMPs) recorded with eyes closed.' *Clin Neurophysiol*, 123 pp. 376-381.

Iaconetta, G., de Notaris, M., Cavallo, L.M., Benet, A., Ensenat, J. (2010) 'The oculomotor nerve: microanatomical and endoscopic study.' *Neurosurgery,* 66 pp. 593-601.

Indaram, M., Edmund, J., Guo, Y., Peeler, C., Hollander, J., Heidary, G. (2017) 'Oculomotor outcomes in children treated for brain tumors of the posterior fossa.' *J of American Assoc for Pediatr Ophthalmol Strabismus*, 21 pp. e16.

Inoue, A., Egami, N., Fujimotor, C., Kinoshita, M., Yamasoba, T., Iwasaki, S. (2016) 'Vestibular evoked myogenic potentials in vestibular migraine. *Ann Otol Rhinol Laryngol*, 125 pp. 931-937.

Invernizzi, P., Bertolasi, L., Bianchi, M.R., Turatti, M., Gajofatto, A., Benedetti, M.D. (2011) 'Prognostic value of multimodal evoked potentials in multiple sclerosis: the EP score.' *J Neurol*, 258 pp. 1933-1939.

Ivankovic, A., Madaric, V.N., Starcevic, K., Skoric, M.K., Gabelic, T., Adamec, I., Habek, M. (2013) 'Auditory evoked potentials and vestibular evoked myogenic potentials in evaluation of brainstem lesions in multiple sclerosis.' *J Neurol Sci*, 328 pp. 24-27.

Iwasaki, S., McGarvie, L.A., Halmagyi, G.M. (2007) 'Head taps evoke a crossed vestibulo-ocular reflex.' *Neurology*, 68 pp. 1227-1229.

Iwasaki, S., Smulders, Y.E., Burgess, A.M., McGarvie, L.A., MacDougal, H.G., Halmaygi, G.M. (2008) 'Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects.' *Clin Neurophysiol*, 119 pp. 2135-2147.

Iwasaki, S., Chihara, y., Fujimoto, C., Murofushi, T., Yamasoba, T. (2012) 'Different effects of head tilt on ocular vestibular-evoked myogenic potentials in response to bone-conducted vibration and air-conducted sound.' *Exp Brain Res,* 223 pp. 389-396.

Janky, K.L., Nguyen, K.D., Welgampola, M., Zuniga, M.G., Carey, J.P. (2013) 'Air-conducted oVEMPs provide the best separation between intact and superior canal dehiscent labyrinths.' *Otol Neurotol*, 34 pp. 127-134.

Jansson, K.F., Hakansson, B., Johannsen, L., Tengstrand, T. (2015) 'Electro-acoustic performance of the new bone vibrator Radioear B81: A comparison with the conventional Radioear B71.' *Int J Audiol*, 54 pp. 334-340.

Jellinek, D., Jewkes, D., Symon, L. (1991) 'Noninvasive intraoperative monitoring of motor evoked potentials under propofol anesthesia: effects of spinal surgery on the amplitude and latency of motor evoked potentials.' *Neurosurgery,* 29 pp. 551-557.

Jeong, S.H., Kim, H.J., Kim, S.J. (2013) 'Vestibular neuritis.' *Semin Neurol*, 33 pp. 185-194.

Jewett, D.L., Romano, M.N., Williston, J.S. (1970) 'Human auditory evoked potentials: possible brainstem components detected on the scalp.' *Science,* 167 pp. 1517-1518.

Jewett, D.L., Williston, J.S. (1971) 'Auditory-evoked far fields averaged from the scalp of humans.' *Brain*, 94 pp. 681-696.

Johnston, P.C., Hamrahian, A.H., Weil, R.J., Kennedy, L. (2015) 'Pituitary tumor apoplexy.' *J Clin Neurosci*, 22 pp. 939-144.

Jones, S.M., Subramanian, G., Avniel, Y., Guo, Y., Burkard, R.F., Jones, T.A. (2002) 'Stimulus and recording variables and their effects on mammalian vestibular evoked potentials.' *J. Neurosci Methods*, 118 pp. 23-31.

Kalkman, C.J., ten Brink, S.A., Been, H.D., Bovill, J.G. (1991) 'Variability of somatosensory cortical evoked potentials during spinal surgery: Effects of anesthetic techniques and high-pass digital filtering.' *Spine*, 16 pp. 924–929.

Kantner, C., Hapfelmeier, A., Drexl, M. (2014) 'The effects of rise/fall time and plateau time on ocular vestibular evoked myogenic potentials.' *Eur Arch Otorhinolaryngol*, 271 pp. 2401-2407.

Karakis, I. (2013) 'Brainstem mapping.' *J Clin Neurophysiol*, 30 pp. 597-603.

Karatas, M. (2009) 'Internuclear and supranuclear disorders of eye movements: clinical features and causes.' *Eur J Neurol,* 16 pp. 1265-1277.

Keane, J.R. (2005) 'Internuclear ophthalmoplegia: unusual cases in 114 of 410 patients.' *Arch Neurol*, 62 pp. 714-717.

Keenan, K.G., Farrina, D., Maluf, K.S., Merlettis, R., Enoka, R.M. (2005) 'Influence of amplitude cancellation on the simulated surface electromyogram.' *J Appl Physiol*, 98 pp. 120-131.

Kenatala, E., Pyykko, J. (2001) 'Clinical picture of vestibular schwannoma.' *Auris Nasus Larynx,* 28 pp. 15-22.

Khan, S., Chang, R. (2013) ‘Anatomy of the vestibular system: a review.’ *Neuro Rehabilitation* 32 pp. 437-443.

Kim, H.A., Lee, H.Y., Yi, H.A., Lee, S.R., Lee, S.Y., Baloh, R.W. (2009) ‘Pattern of otolith dysfunction in posterior inferior cerebellar artery territory cerebellar infarction.’ *J Neurol Sci*, 280 pp. 65-70.

Kim, H.J., Lee, H.J., Kim, J.S. (2014) ‘Ocular vestibular evoked myogenic potentials to head tap and cervical vestibular evoked myogenic potentials to air-conducted sounds in isolated internuclear ophthalmoplegia.’ *Clin Neurophysiol*, 125 pp. 1042-1047.

Kim, C.H., Jang, M.U., Choi, H-C., Sohn, J-H. (2015) ‘Subclinical vestibular dysfunction in migraine patients: a preliminary study of ocular and rectified cervical vestibular evoked myogenic potentials.’ *J Headache Pain*, 16 pp. 93-112.

Kinoshita, M., Iwasaki, S., Fujimoto, C., Inoue, A., Egami, N., Chihara, Y., Ushio, M., Yamasoba, T. (2013) ‘Ocular vestibular evoked myogenic potentials in response to air-conducted sound and bone-conducted vibration in vestibular schwannoma.’ *Otol Neurotol*, 34 pp. 1342-1348.

Kodama, K., Javadi, M., Seifert, V., Szelenyi, A. (2014) ‘Conjunct SEP and MEP monitoring in resection of infratentorial lesions: lessons learned in a cohort of 210 patients.’ *J Neurosurg*, 121 pp. 1453-1461.

Kondziolka, D., Monaco, E.A., Lunsford, L.D. (2013) ‘Cavernous malformations and hemorrhage risk.’ *Prog Neurol Surg,* 27 pp. 141-146.

Koos, W.T., Day, J.D., Matula, C., Levy, D.I. (1998) ‘Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas.*’ J Neurosurg,* 88 pp. 506-512.

Krasnianski, M., Neudecker, S., Zierz, S. (2004) ‘Classical crossed pontine syndromes.’ *Neurol Psychiatr,* 72 pp. 460-468.

Krisht, A., Barnett, D.W., Barrow, D.L., Bonner, G. (1994) ‘The blood supply of the intracavernous cranial nerves: an anatomical study.’ *Neurosurgery,* 34 pp. 275-279.

Krause, E., Mayerhofer, A., Gurkov, R. (2013) ‘Effects of acoustic stimuli used for vestibular evoked myogenic potential studies in cochlear function.’ *Otol Neurotol*, 34 pp. 1186-1192.

Kugelberg, E. (1946) ‘Injury activity and trigger zones in human nerves.’ *Brain,* 69 pp. 310–324.

Kugelberg, E., Cobb, W. (1951) ‘Repetitive discharges in human motor nerve fibers during the post-ischaemic state.’ *J Neurol Neurosurg Psychiatry*, 14 pp. 88–94.

Lacowska, M., Glinka, P., Niemczyk, K. (2003) ‘Air-conducted and skull-tap cervical vestibular evoked myogenic potentials in determining nerve division involvement in vestibular schwannoma patients.’ *Adv Clin Exp Med*, 27 pp. 335-341.

Lang, J. (1981) ‘Neuroanatomy of the optic, trigeminal, facial, glossopharyngeal, vagus, accessory and hypoglossal nerves.’ *Arch Otorhinolaryngol*, 231 pp. 1-69.

Lang, J. (1982) ‘Anatomy, length and blood vessel relations of “central” and “peripheral” paths of intracisternal cranial nerves.’ *Neurochir*, 43 pp. 217-258.

Langman, A.W., Jackler, R.K., Althaus, S.R. (1990) ‘Meningioma of the internal auditory canal.’ *Am J Otol,* 11 pp. 201-204.

Lee, W.Y., Hou, W.Y., Yang, L.H., Lin, S.M. (1995) 'Intraoperative monitoring of motor function by magnetic motor evoked potentials.' *Neurosurgery,* 36 pp. 493-500.

Lee, H., Baoh, R.W. (2005) 'Sudden deafness in vertebrobasilar ischemia: clinical features, vascular topographical patterns and long-term outcome.' *J Neurol Sci*, 228 pp. 99-104.

Lee, J.D., Park, M.D., Lee, B.D., Lee, T.K., Sung, K.B., Park, J.Y. (2013) 'Abnormality of cervical vestibular-evoked myogenic potentials and ocular vestibular-evoked myogenic potentials in patients with recurrent benign paroxysmal positional vertigo.' *Acta Otolaryngol,* 133 pp. 150-153.

Lee, S.H., Kim, H.J., Kim, J.S. (2018) 'Ocular motor dysfunction due to brainstem disorders.' *J Neuroophthalmol*, 38 pp. 393-412.

Legatt, A.D., Arezzo, J.C., Vaughan, H.G. (1988) 'The anatomic and physiologic bases of brain stem auditory auditory-evoked potentials.' *Neurol Clin*, 6 pp. 681-704.

Legatt, A.D. (2002) 'Mechanisms of intraoperative brainstem auditory evoked potential change.' *J Clin Neurophysiol,* 19 pp. 396-408.

Legatt, A.D. (2018) 'Electrophysiology of cranial nerve testing: Auditory nerve.' *J Clin Neurophysiol*, 35 pp. 25-38.

Leyssens, L., Heinze, B., Vinck, B., van Ombergen, A., Vanspauwen, R., Wuyts, F.L., Maes, L.K. (2017) ''Standard' versus 'nose reference' electrode placement for measuring oVEMPs with air-conducted sound: Test-retest reliability and preliminary patient results.' *Clin Neurophysiol*, 128 pp. 312-322.

Li, Z-Y., Li, M., Liang, J-T., Bao, Y.H., Chen, G., Guo, H-C, Ling, F. (2017) 'Usefulness of intraoperative electromyographic monitoring of oculomotor and abducens nerves during skull base surgery.' *Acta Neurochir (Wien)*, 159 pp. 1925-1937.

Lim, L.J., Dennis, D.L., Govender, S., Colebatch, J.G. (2013) 'Differential effects of duration for ocular and cervical vestibular evoked myogenic potentials evoked by air- and bone-conducted stimuli.' *Exp Brain Res*, 224 pp. 437-445.

Lin, M.C., Chen, C.M., Tseng, H.M., Xiao, F., Young, Y.H. (2013) 'A proposed method to comprehensively define outcomes in acoustic tumor patients undergoing cyberknife management.' *Stereotact Funct Neurosurg*, 91 pp. 177-185.

Lin, K.I., Chen, C.M., Wang, S.J., Young, Y.H. (2014) 'Correlating vestibular schwannoma size with vestibular-evoked myogenic potential results.*' Ear Hear*, 35 pp. 571-576.

Lindeman, H. (1973) 'Anatomy of the otolith organs.' *Adv Oto-Rhino-Laryngology*, 20 pp. 405-433.

Liu, Z., Feng, S., Li, J., Cao, H., Huang, J., Fan, F., Cheng. L., Liu, Z., Cheng, Q. (2020) 'The epidemiological characteristics and prognostic factors of low-grade brainstem glioma: A real-world study of pediatric and adult patients.' *Front Oncol* 10 pp. 391-402.

Lopez, I., Honrubia, V., Baloh, R. (1997) 'Aging and the human vestibula nucleus.' *J Vest Res*, 7 pp. 77-85.

Lopez, J.R. (2011) 'Neurophysiologic intraoperative monitoring of the oculomotor, trochlear and abducens nerves.' *J Clin Neurophysiol*, 28 pp. 543-550.

Lopez-Escamez, J.A., Carey, J., Chung, W.H., Goebel, J.A., Magnusson, M. (2015) 'Diagnostic criteria for Menieres disease.' *J Vestib Res*, 25 pp. 1-7.

Lotto, M.L., Banoub, M., Schubert, A. (2004) ‘effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials.’ *J Neurosurg Anesthesiol,* 16 pp. 32-42.

Louis, D.N., Perry, A., Reifenberger, G., et al., (2016) ‘The World Health Organization Classification of Tumours of the Central Nervous System: a summary.’ *Acta Neuropathol*, 131 pp. 803-820.

Lubicky, J.P., Spadaro, J.A., Yuan, H.A., Fredrickson, B.E., Henderson, N. (1989) ‘Variability of somatosensory cortical evoked potential monitoring during spinal surgery.’ *Spine,* 14 pp.790–798.

Luders, H (1988) ‘Surgical monitoring with auditory evoked potentials.’ *J Clin Neurophysiol,* 5 pp. 261-285.

Ludlow, C.L. (2005) ‘Central nervous system control of the laryngeal muscles in humans.’ *Respir Physiol Neurobiol*, 147 pp. 305-322.

Lynn, S.G., Driscoll, C.L., Harner, S.G., Beatty, C.W., Atkinson, E.J. (1999) ‘Assessment of disequilibrium after acoustic neuroma removal.’ *Am J Otol,* 20 pp. 484-494.

MacDonald, D.B., Al-Zayed, Z., Stigsby, B., Al-Homoud, I. (2009) ‘Median somatosensory evoked potential intraoperative monitoring: Recommendations based on signal-to-noise ratio analysis.’ *Clin Neurophysiol*, 120 pp. 315-328.

MacDonald, D.B., Skinner, S., Shils, J., and Yingling, C. (2013). ‘Intraoperative motor evoked potential monitoring – A position statement by the American Society of Neurophysiological Monitoring.’ *Clinical Neurophysiology,* 124 pp. 2291-2316.

MacDonald, D.B., Dong, C., Quatrale, R., Sala, F., Skinner, S., Soto, F., Szelenyi, A. (2019) ‘Recommendations of the International Society of Intraoperative Neurophysiology for intraoperative somatosensory evoked potentials.’ *Clin Neurophysiol*, 130 pp. 161-179.

Magill, S.T., Young, J.S., Chae, R., Aghi, M.K., Theododopoulos, P.V., McDermott, M.W. (2018) ‘Relationship between tumour location, size, and WHO grade in meningioma.’ *Neurosurg Focus*, 44 pp. E4.

Magliulo, G., Gogliardi, S., Cingilio Appriani, M., Iannella, G., Re, M. (2014) ‘Vestibular neurolabyrinthitis: a follow up study with cervical and ocular vestibular evoked myogenic potentials and the video head impulse test.’ *Ann Otol Rhinol Laryngol*, 123 pp. 162-173.

Makowiec, K.F., Piker, E.G., Jacobson, G.P., Ramadan, N.M., Roberts, R.A. (2018) ‘Ocular and cervical vestibular evoked myogenic potentials in patients with vestibular migraine.’ *Otol Neurotology*, 39 pp. 561-567.

Mallinson, A., Kuijpers, A., Longridge, N. (2018) ‘Optimum number of sweeps in clinical oVEMP recording; how many sweeps are necessary?’ *J Int Adv Otol*, 14 pp. 72-76.

Manninen, P.H., Lam, A.M., Nicholas, J.F. (1985) ’The effects of isoflurane-nitrous oxide anesthesia on brainstem auditory evoked potentials in humans.’ *Anesth Analg*, 64 pp. 43–47.

Manzari, L., Burgess, A.M., McGarvie, L.A., Curthoys, I.S. (2013) ‘An indicator of probable semicircular canal dehiscence: ocular vestibular evoked myogenic potentials to high frequencies.’ *Otolaryngol Head Neck Surg*, 149 pp. 142-145.

Markand, O.N., Farlow, M.R., Stevens, J.C., Edwards, M.K. (1989) ‘Brainstem auditory potential abnormalities with unilateral brainstem lesions demonstrated by magnetic resonance imaging.’ *Arch Neurol,* 46 pp. 295-299.

Matthies, C., Samii, M. (1997) ‘Management of 1000 vestibular schwannomas (acoustic neuromas).’ *Neurosurgery,* 40 pp. 1-9.

Mattingly, J.K., Portnuff, C.D., Hondorp, B.M., Cass, S.P. (2015) ‘Sudden bilateral hearing loss after cervical and ocular vestibular evoked myogenic potentials.’ *Otol Neurotol*, 36 p. 961-964.

Mazzoni, A. (1990) ‘The vascular anatomy of the vestibular labyrinth in man.’ *Acta Otolaryngol,* 472 pp. 1-83.

McDonald, W.I., Sears, T.A. (1970) ‘The effects of experimental demyelination on conduction in the central nervous system.’ *Brain*, 93 pp. 583-598.

McLaren, J.W., Hillman, D.E. (1979) ‘Displacement of the semicircular canal cupula during sinusoidal rotation.’ *Neuroscience*, 4 pp. 2001-2008.

McPherson, D.R. (2018) ‘Sensory hair cells: An introduction to structure and physiology.’ *Integrat Comp Biol*, 58 pp.282-300.

Melmed, S. (2011) ‘Pathogenesis of pituitary tumors.’ *Nat Rev Endocrinol*, 7 pp. 256-266.

Menovsky. T., van Overbeeke, J.J. (1999) ‘On the mechanism of transient postoperative deficit of cranial nerves.’ *Surg Neurol*, 51 pp. 223-226.

Merletti, R., Aventaggiato, M., Botter, A., Holobar, A., Marateb, H., Viera, T.M. (2010) ‘Advances in surface EMG: recent progress in detection and processing techniques.’ *Crit Rev Biomed Eng,* 38 pp. 305-345.

Merlo, K., Campanini, I. (2010) ‘Technical aspects of surface electromyography for clinicians.’ *Open Rehabil J,* 3 pp. 98-109.

Merton, P.A., Morton, H.B. (1980) ‘Stimulation of the cerebral cortex in the intact human subject.’ *Nature,* 285 pp. 227.

Mikulec, A.A., McKenna, M.I., Ramsey, M.J., Rosowski, J.J. Hermann, B.S., Rauch, S.D. (2004) ‘Superior semicircular canal dehiscence presenting as conductive hearing loss without vertigo.’ *Otol Neurotol*, 25 pp. 121-129.

Minahan, R.E., Mandir, A.S. (2011) ‘Neurophysiologic intraoperative monitoring of the trigeminal and facial nerves.’ *J Clin Neurophysiol*, 28 pp. 551-565.

Minor, L.B., Solomon, D., Zinreich, J.B., Zee, D.S. (1998) ‘Sound- and/or pressure induced vertigo due to bone dehiscence of the superior semicircular canal.’ *Arch Otolaryngol Head Neck Surg*, 124 pp. 249-258.

Moller, A.R., Jannetta, P., Bennett, M., Moller, M.B. (1981) ‘Intracranially recorded responses from the human auditory nerve: new insights into the origin of the brainstem evoked potentials (BAEPs).’ *Electroencephalogr Clin Neurophysiol,* 52 pp. 18-27.

Moller, A.R., Jannetta, P.J. (1982a) ‘Evoked potentials from the inferior colliculus in man.’ *Electroencephalogr Clin Neurophysiol,* 53 pp. 612-620.

Moller, A.R., Jannetta, P., Moller, M.B. (1982b) ‘Intracranially recorded auditory nerve response in man: New interpretations of BSER.’ *Arch Otolaryngol,* 108 pp. 77-82.

Moller, A.R., Jannetta, P.J. (1983) ‘Interpretation of brainstem auditory evoked potentials: results from intracranial recordings in humans.’ *Scand Audiol,* 12 pp. 125-133.

Moller, A.R., Colletti, V., Fiorini, F.G. (1994) 'Neural conduction of the human auditory nerve: bipolar recordings from the exposed portion of the intracranial portion of the eight nerve during vestibular nerve section.' *Electroencephalogr Clin Neurophysiol,* 92 pp. 316-320.

Morota, N., Ihara, S., Deletis, V. (2010) 'Intraoperative neurophysiology for surgery in and around the brainstem: Role of brainstem mapping and corticobulbar tract motor-evoked potential monitoring.' *Childs Nerv Syst*, 26 pp. 513-521.

Muller, H.L. (2014) 'Craniopharyngioma.' *Endocr Rev*, 25 pp. 513-543.

Murnane, O.D., Akin, F.W., Kelly, J.K., Byrd, S. (2011) 'Effects of stimulus and recording parameters on the air conduction ocular vestibular evoked myogenic potential.' *J Am Acad Audiol,* 22 pp. 469-480.

Murofushi, T., Shimizu, K., Takegoshi, H., Cheng, P.W. (2001) 'Diagnostic value of prolonged latencies in the vestibular evoked myogenic potential.' *Arch Otolaryngol Head Neck Surg,* 127 pp. 1069-1072.

Murofushi, T., Ozeki, H., Inoue, A., Sakata, A. (2009) 'Does migraine associated vertigo share a common pathophysiology with Menieres disease? Study with vestibular evoked myogenic potential.' *Cephalgia*, 29 pp. 1259-1266.

Murofushi, T., (2016) 'Clinical application of vestibular evoked myogenic potential (oVEMP)'. *Auris Nasus Larynx*, 43 pp.367-376.

Myrseth, E., Moller, P., Goplen, F., Wentzel-Larsen, T., Lund-Johansen, M. (2006) 'Untreated vestibular schwannoma: vertigo is a powerful predictor for health-related quality of life.' *Neurosurgery*, 59 pp. 67-76.

Myrseth, E., Pedersen, P.-H., Moller, P., Lund-Johansen, M. (2007) 'Treatment of vestibular schwannomas. Why, when and how?' *Acta Neurochir (Wein),* 149 pp. 647-660.

Naito, Y., Newman, A., Lee, W., Beykirch, K., Honrubia, V. (1995) 'Projection of the individual vestibular end-organs in the brainstem of the squirrel monkey.' *Hearing Res*, 87 pp. 141-155.

Nakahara, H., Yoshimura, E., Tsuda, Y., Murofushi, T. (2013) 'Damaged utricular function clarified by oVEMP in patients with benign paroxysmal positional vertigo.' *Acta Otolaryngol*, 133 pp.144-149.

Nathan, N., Tabaraud, F., Lacroix, F., Moulies, D., Viviand, X., Lansade, A. (2003) 'Influence of propofol concentrations on multipulse transcranial motor evoked potentials.' *Br J Anaesth,* 91 pp. 493–497.

Nerrant, E., Tilikete, C. (2017) 'Ocular manifestations of multiple sclerosis.' J *Neuroopthalmol*, 37 pp. 332-340.

Nichols, G.S., Manafov, E. (2012) 'Utility of Electromyography for nerve root monitoring during spinal surgery.' *J Clin Neurophysiol*, 29 pp.140-148.

Nuwer, M.R., Dawson, E. (1984) 'Intraoperative evoked potential monitoring of the spinal cord: Enhanced stability of cortical recordings.' *Electroencephalogr Clin Neurophysiol,* 59 pp. 318–327.

Nuwer, M.R., Emerson, R.G., Galloway, G., Legatt, A.D., Lopez, J., Minahan, R. (2012) 'Evidence based update: intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials.' *Neurology*, 78 pp. 585–589.

Oh, S.Y., Kim, J.S., Lee, J.M., Shin, B.S., Hwang, S.B., Kwak, K.C., Kim, C., Jeong, S.K., Kim, T.W. (2013) 'Ocular vestibular evoked myogenic potentials induced by air-conducted sound in patients with acute brainstem lesions.' *Clin Neurophysiol*, 124 pp. 770-778.

Oh, S.Y., Kim, H.J., Kim, J.S. (2016) 'Vestibular-evoked myogenic potentials in central vestibular disorders.' *J Neurol*, 263 pp. 210-220.

Okuno, T., Sando, I. (1987) 'Localization, frequency and severity of endolymphatic hydrops and the pathology of the labyrinthine membrane in Menieres disease.' *Ann Otol Rhinol Laryngol*, 96 pp. 438-445.

Paez, J.H., Isenberg, S., Apt, L. (1984) 'Torsion and elevation under general anesthesia and during voluntary eyelid closure (Bell phenomena).' *J Pediatr Ophthalmol Strabismus*, 21 pp. 22-24.

Papathanasiou, E.S., Murofushi, T., Akin, F.W., Colebatch, J.G. (2014) 'International guidelines for the clinical application of cervical vestibular evoked myogenic potentials: an expert consensus report.' *Clin Neurophysiol*, 125 pp. 658-666.

Park, H.J., Lee, I., Shin, Y.J., Park, M.S. (2010) 'Frequency-tuning characteristics of cervical and ocular vestibular evoked myogenic potentials by air-conducted tone bursts.' *Clin Neurophysiol*, 121 pp. 85-89.

Pathak, K.S., Amaddio, B.S., Scoles, P.V., Shaffer, J.W., Mackay, W. (1989) 'Effects of halothane, enflurane, and isoflurane in nitrous oxide on multilevel somatosensory evoked potentials.' *Anesthisiol,* 70 pp. 207–212.

Pearce, J.M.S. (2000) 'Wallenberg's syndrome.' *J Neurol Neurosurg Psychiatr*, 68 pp. 570-571.

Pechstein, U., Cedzich, C., Nadstawek, J., Schramm, J. (1996) 'Transcranial high-frequency repetitive electrical stimulation for recording myogenic motor-evoked potentials with the patient under general anesthesia.' *Neurosurgery*, 39 pp. 335-344.

Pechstein, U., Nadstawek, J., Zentner, J., Schramm, J. (1998) 'Isoflurane plus nitrous oxide versus propofol for recording of motor evoked potentials after high frequency repetitive electrical stimulation.' *Electroencephalogr Clin Neurophysiol,* 108 pp.175–181.

Peeler, C.E. (2017) 'A review of visual and oculomotor outcomes in children with posterior fossa tumors.' *Semin Pediatr Neurol*, 24 pp. 100-103.

Pelosi, L., Stevenson, M., Hobbs, G.J., Jardine, A., Webb, J.K. (2001) 'Intraoperative motor evoked potentials to transcranial electrical stimulation during two anaesthetic regimens.' *Clin Neurophysiol,* 112 pp. 1076–1087.

Perlman H.B., Kimura, R., Fernandez, C. (1959) 'Experiments on temporary obstruction of the internal auditory artery.' *Laryngoscope*, 69 pp. 591-613.

Peterson, D.O., Drummond, J.C., Todd, M.M. (1986) 'Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans.' *Anesthisiol,* 65 pp. 35–40.

Piker, E.G., Jacobson, G.P., McCaslin, D.L., Hood, L.J. (2011) 'Normal characteristics of the ocular vestibular evoked myogenic potential.' *J Am Acad Audiol*, 22 pp. 222-230.

Polman, C.H., Rudick, R.A. (2010) 'The multiple sclerosis functional composite: a clinically meaningful measure of disability.' *Neurology*, 74 pp. s8-15.

Porkkala, T., Jäntti, V., Kaukinen, S., Häkkinen, V. (1997) 'Nitrous oxide has different effects on the EEG and somatosensory evoked potentials during isoflurane anaesthesia in patients.' *Acta Anaesthesiol Scand*, 41 pp. 497–501.

Portnuff, C.D.F., Kleindienst, S., Bogle, J.M. (2017) ‘Safe use of acoustic vestibular-evoked myogenic potential stimuli: Protocol and patient specific considerations.’ *J Am Acad Audiol*, 28 pp. 708-717.

Prass, R.L., Lüders, H. (1986) ‘Acoustic (loudspeaker) facial electromyographic monitoring: part 1. Evoked electromyographic activity during acoustic neuroma resection.’ *Neurosurgery,*19 pp. 392–400.

Procaccio, F., Gambin, R., Gottin, L., Bricolo, A. (2000) ‘Complications of brainstem surgery; prevention and treatment.’ *Oper Tech Neurosurg*, 3 pp. 155-157.

Pullicion, P.M. (1993) ‘Diagrams of perforating artery territories in axial, coronal and sagittal planes.’ *Neurology*, 62 pp. 41-73.

Rahne, T., Plobi, S., Plontke, S.K., Strauss, C. (2018) ‘Preoperative determination of nerve of origin in patients with vestibular schwannoma.’ *HNO,* 66 pp. 16-21.

Raininko, R., Autti, T., Vanhanen, S.L., Ylikoski, A., Erkinjuntti, T., Santavuori, P. (1994) ‘The normal brain stem from infancy to old age’ A morphometric MRI study.’ *Neuroradiology*, 36 pp. 364-368.

Rhoton, A.L. (1994) ‘Meningiomas of the cerebellopontine angle and foramen magnum.’ *Neurosurg Clin N Am,* 5 pp. 349–364.

Richard, C.D. (1983) ‘Actions of general anaesthetics on synaptic transmission in the CNS.’ *Br J Anaesth,* 55 pp. 201–207.

Richards, B.W., Jones, F.R., Younge, B.R. (1992) ‘Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves.’ *Am J Ophthalmol*, 113 pp. 489-496.

Rodriguez, A.I., Thomas, M.L.A., Fitzpatrick, D. Janky, K.L. (2018) ‘Effects of high sound exposure during air-conducted vestibular evoked myogenic potential testing in children and young adults.’ *Ear Hear*, 39 pp. 269-277.

Romstock, J., Strauss, C., Fahlbusch, R. (2000) ‘Continuous electromyography monitoring of motor cranial nerves during cerebellopontine angle surgery.’ *J Neurosurg*, 93 pp. 586–593.

Rosengren, S.M., Todd, N.P., Colebatch, J.G. (2005) ‘Vestibular evoked extraocular potentials produced by stimulation with bone-conducted sound.’ *Clin Neurophysiol*, 116 pp. 1938-1948.

Rosengren, S.M., Jombik, P., Halmagyi, G.M., Colebatch, J.G. (2009) ‘Galvanic ocular vestibular evoked myogenic potentials provide new insight into vestibulo-ocular reflexes and unilateral vestibular loss.’ Clin Neurophysiol, 120 pp. 569-580.

Rosengren, S.M., Govender, J.G., Colebatch, J.G. (2009a) ‘The relative effectiveness of different stimulus waveforms in evoking VEMPs: significance of stimulus energy and frequency.’ *J Vestib Res*, 19 pp. 33-40.

Rosengren, S., Welgampola, M., Colebatch, J. (2010) ‘Vestibular evoked myogenic potentials: past, present and future.’ *Clin Neurophysiol*, 121 pp. 636-651.

Rosenberg, S.M., Colebatch, J.G. (2011) ‘Ocular evoked myogenic potentials are abnormal in internuclear ophthalmoplegia’. *Clin Neurophysiol*, 122 pp. 1264-1267.

Rosengren, S.M., Colebatch, J., Straumann, D., Weber, K.P. (2013) ‘Why do oVEMPs become larger when you look up? Explaining the effect of gaze elevation on the ocular vestibular evoked myogenic potential.’ *Clin Neurophysiology*, 124 pp. 785-791.

Rosengren, S.M., Colebatch, J.G., Young, A.S., Govender, S., Welgampola, M.S (2019) 'Vestibular evoked myogenic potential in practice: Methods, pitfalls and clinical applications.' *Clin Neurophysiol Prac*, 4 pp.47-68.

Ross, M.D., Komorowski, T.E., Donovan, K.M. Pote, K.G. (1987) 'The suprastructure of the saccular macula.' *Acta Otolaryngol*, 103 pp. 56-63.

Rossiter, J., Wood, M., Lockwood, A. (2006) 'Operating conditions for ocular surgery under general anesthesia: an eccentric problem.' *Eye*, 20 pp. 55-58.

Sala, F., Manganotti, P., Tramontano, V., Bricolo, A., Gerosa, M. (2007) 'Monitoring of motor pathways during brainstem surgery: what we have achieved and what we are still miss?' *Neurophysiol Clin*, 37 pp. 399-406.

Sala, F., Coppola, A., Tramontano, V. (2015) 'Intraoperative neurophysiology in posterior fossa tumor surgery in children.' *Childs Nerv Syst*, 31 pp. 1791-1806.

Saman, Y., Barniou, D.E., Gleeson, M. (2009) 'A contemporary review of balance dysfunction following vestibular schwannoma surgery.' *Laryngoscope,* 119 pp. 2085-2093.

Samii, M., Matthies, C. (1997) 'Management of 1,000 vestibular schwannomas (acoustic neuromas): hearing function in 1,000 tumor resection.' *Neurosurgery*, 40 pp. 248–260.

Samra, S.K., Lilly, D.J., Rush, N.L., Kirsh, M.M. (1984) 'Fentanyl anesthesia and human brainstem auditory evoked potentials.' *Anesthisiol*, 1984; 61 pp. 261–265.

Sandhu, J.S., George, S.R., Rea, P.A., (2013) 'The effect of electrode positioning on the ocular vestibular evoked myogenic potential to air-conducted sound.' *Clin Neurophysiol,* 124 pp. 1232-1236.

Sarnthein, J., Tomiliv, M., Baag, M., Regli, L. (2021) 'Improving intraoperative evoked potentials at short latency by novel neuro-stimulation technology with delayed return discharge.' *Clin Neurophysiol*, 132 pp. 1195-1199.

Sasaki, C.T., Weaver, E.M. (1997) 'Physiology of the larynx.' *Am J Med*, 103 pp. 9-18.

Scheepstra, G.L., deLange, J.J., Booij, L.H., Ross, H.H. (1989) 'Median nerve evoked potentials during propofol anaesthesia.' *Br J Anaesth,* 62 pp. 92–94.

Scherg, M., von Cramon, D. (1985) 'A new interpretation of the generators of BAEP waves I-V: Results of a spatio-temporal dipole model.' *Electroencephalogr Clin Neurophysiol,* 62 pp. 290-299.

Schindler, E., Muller, M., Zickmann, B., Osmer, C., Wozniak, G., Hempelmann, G. (1998) 'Modulation of somatosensory evoked potentials under various concentrations of desflurane with and without nitrous oxide.' *J Neurosurg Anesthesiol*, 1998; 10 pp. 218–223.

Schlake, H.P., Goldrunner, R., Mileswski, C., Siebert, M., Behr, R., Riemann, R., Helms, J., Roosen, K. (1999) 'Technical developments in intra-operative monitoring for the preservation of cranial motor nerves and hearing in skull base surgery.' *Neurol Res*, 21 pp. 11-24.

Schlake, H.P., Goldrunner, R., Siebert, M., Behr, R., Roosen, K. (2001) 'Intraoperative electromyographic monitoring of extra-ocular motor nerves (cn, III, VI) in skull base surgery.' *Acta Neurochir (Wien),* 143 pp. 251-261.

Schmidt, R.F., Boghami, Z., Choudhry, O.J., Eloy, J.A., Jyung, R.W., Liu, J.K. (2012) 'Incidental vestibular schwannomas: a review of prevalence, growth rate, and management challenges.' *Neurosurg Focus*, 3 E4.

Schwartz, D.M., Morris, M.D., Spydell, J.D., Brink, C.T., Grim, M.A., Schwartz, J.A. (1990) 'Influence of click polarity on the brain-stem auditory evoked response (BAER) revisited.' *Electroencephalography Clin Neurophysiol*, 77 pp.445–457.

Seidel, K., Bliner, M.S., Zubak, I., Rychen, J., Beck, J., Raabe, A. (2020) 'Continuous dynamic mapping to avoid accidental injury to the facial nerve during surgery for large vestibular schwannomas.' *Neurosurg Res*, 43 pp. 241-248.

Sekhar, L.N., Janetta, P.J. (1984) 'Cerebellopontine angle meningiomas. Microsurgical excision and follow-up results.' *J Neurosurg,* 60 pp. 500-505.

Sekhar, L.N., Moller, A.R. (1986) 'Operative management of tumors involving the cavernous sinus.' *J Neurosurg,* 64 pp. 879-889.

Sekiya, T., Iwabuchi, T., Okabe, S. (1990) 'Occurrence of vestibular and facial nerve injury following cerebellopontine angle operations.' *Acta Neurochir (Wein),* 102 pp. 108-113.

Sekiya, T., Hatayama, T., Iwabuchi, T., Maeda, S. (1993) 'Intraoperative recordings of evoked extraocular muscle activities to monitor ocular motor nerve function.' *Neurosurgery*, 32 pp. 227-235.

Selesnick, S.H., Jackler, R.K., Pits, L.W. (1993) 'The changing clinical presentation of acoustic tumors in the MRI era.' *Laryngoscope*, 103 pp. 431-436.

Seltzer, J., Wedemeyer, M.A., Bonney, P.A., Carmichael, J.D., Weiss, M., Zada, G. (2019) 'Outcomes following transsphenoidal surgical management of incidental pituitary adenomas: a series of 52 patients over a 17year period.' *J Neurosurg*, 130 pp. 1548-1592.

Shahani, B. (1970) 'The human blink reflex.' *J Neurol Neurosurg Psychiatr*, 33 pp. 792-800.

Shannon, R.V., Moore, J.K., McCreery, D.B., Portillo, F. (1997) 'Threshold-distance measures from electrical stimulation of human brainstem.' *IEEE Trans. Rehab. Eng.*, 5 pp. 70-73.

Shepard, N.T. (2006) 'Differentiation of Meniere's disease and migraine associated dizziness: a review.' *J Am Acad Audiol*, 17 pp. 69-80.

Shojaku, H., Watanabe, Y., Tsubota, M., Katayama, N. (2008) 'Evaluation of the vestibular evoked myogenic potential during parabolic flight in humans.' *Exp Brain Res*, 187 pp. 477-481.

Silwinska-Kowalska, M., Davis, A. (2012) 'Noise-induced hearing loss.' *Noise Health*, 14 pp. 274-280.

Simon, M. (2011) 'Neurophysiologic intraoperative monitoring of the vestibulocochlear nerve.' *J Clin Neurophysiol*, 28 pp. 566-581.

Sinclair, C.F., Tellez, M.J., Tapia, O.R., Ulkatan, S. (2017) 'Contralateral R1 and R2 components of the laryngeal adductor reflex in humans under general anesthesia.' *Laryngoscope*, 127 pp. 443-448.

Sinclair, C.F., Tellez, M.J., Tapia, O.R., Ulkatan, S. (2017a) 'A novel methodology for assessing laryngeal and vagus nerve integrity in patients under general anesthesia.' *Clin Neurophysiol,* 128 pp. 1399-1405.

Sindou, M., Mercier, P. (2018) 'Microvascular decompression for hemifacial spasm: Outcome on spasm and complications. A review.' *Neurochirugie*, 64 pp. 106-116.

Singh, R., Husain, A.M. (2011) ‘Neurophysiologic intraoperative monitoring of the glossopharyngeal and vagus nerves.’ *J Clin Neurophysiol*, 28 pp. 582-586.

Singh, N.K., Barman, A. (2014) ‘Efficacy of ocular vestibular evoked myogenic potentials in identifying posterior semicircular canal benign paroxysmal vertigo.’ *Ear Hear*, 36 pp. 261-268.

Singh, N.K., Kadisonga, P., Ashitha, P. (2014a) ‘Optimizing stimulus repetition rate for recoding ocular vestibular evoked myogenic potential elicited by air-conduction tone bursts of 500Hz.’ *Audiol Res*, 4 pp. 14-20.

Singh, H., Vogel, R.W., Lober, R.M., Doan, A.T., Matsumoto, C.I., Kenning, T.J., Evans, J.J. (2016) ‘Intraoperative neurophysiological monitoring for endoscopic endonasal approaches to the skull base: a technical guide.’ *Scientifica,* 6 pp. 1-20.

Singh, N.K., Thirunavukkarasu, K., Barman, A. (2019) ‘Optimum response filter setting for air conduction-induced ocular vestibular evoked myogenic potential.’ *J Am Acad Audiol*, 30 pp. 753-763.

Skinner, S.A. (2011) Neurophysiologic monitoring of the spinal accessory nerve, hypoglossal nerve, and the spinomedullary region.’ *J Clin Neurophysiol*, 28 pp.587-598.

Skinner, S.A., Holdefer, R.N. (2014) ‘Intraoperative neuromonitoring alerts that reverse with intervention: treatment paradox and what to do about it.’ *J Clin Neurophysiol*, 31 pp. 118-126.

Sloan, T.B. (2010) ‘Anesthesia and intraoperative neurophysiological monitoring in children.’ *Childs Nerv System*, 26 pp. 227-235.

Sloan, T.B. (2013) ‘Muscle relaxant use during intraoperative neurophysiologic monitoring.’ *J Clin Monit Comput*, 27 pp. 35-46.

Slotty, P.J., Abdulazim, A., Kodama, K., Javadi, M., Hanggi, D., Seifert, V., Szelenyi, A. (2017) ‘Intraoperative neurophysiological monitoring during resection of infratentorial lesions: the surgeons view.’ *J Neurosurgery*, 126 pp. 281-288.

Smith, C., Lowry, O., Wu, M. (1965) ‘The electrolytes of the labyrinthine fluids.’ *Laryngoscope*, 64 pp. 141-153.

Stangerup, S, E., Caye-Thomasen, P. (2012) ‘Epidemiology and natural history of vestibular schwannomas.’ *Otolaryngol Clin N Am,* 46 pp. 257-268.

Strauss, C., Romstock, J., Fahlbusch, R. (1994) ‘Intraoperative monitoring of the floor of the fourth ventricle.’ *J Neurosurg,* 80 pp. 213-220.

Strauss, C., Romstock, J., Fahlbusch, R. (1999) ‘Pericollicular approaches to the rhomboid fossa. Part II. Neurophysiological basis.’ *J Neurosurg*, 91 pp. 768-775.

Stromberg, A.K., Olofsson, A., Westin, M., Duan, M., Stenfelt, S. (2016) ‘Changes in cochlear function related to acoustic stimulation of cervical vestibular evoked myogenic potential stimulation.’ *Hear Res*, 340 pp. 43-49.

Strupp, M., Kremmyda, O., Asamczyk, C., Bottcher, N., Muth, C., Yip, C.W., Bremova, T. (2014) ‘Central ocular motor disorder, including gaze palsy and nystagmus.’ *J Neurol*, 261 (suppl 2) pp. S542-558.

Su, C.H., Young, Y.H. (2011) ‘Differentiating cerebellar and brainstem lesions with ocular vestibular-evoked myogenic potential test.’ *Eur Arch Otorhinolaryngol*, 268 pp. 923-930.

Su, C.H., Chen, C.M., Young, Y.H., (2013) 'Differentiating cerbellopontine angle meningioma from schwannoma using caloric testing and vestibular-evoked myogenic potentials.' *J Neurol Sci*, 335 pp. 155-159.

Sung, P.H., Chang, C.M., Young, Y.H., Jaw, F.S., Cheng, P.W. (2014) 'Optimal stimulation mode for obtaining galvanic ocular vestibular-evoked myogenic potentials: Our experience.' *Clin Ololaryngol*, 39 pp. 240-245.

Takagi, M., Abe, H., Hasegawa, S., Usui, T. (1992) 'Reconsideration of Bell's phenomena using a magnetic search coil method.' *Doc Opthalomol*, 80 pp. 343-352.

Taniguchi, M., Cedzich, C., Schramm, J. (1993) 'Modification of cortical stimulation for motor-evoked potentials under general anesthesia; technical description.' *Neurosurgery,* 32 pp. 219-26.

Tascioglu, A.B. (2005) 'Brief review of vestibular anatomy and its higher order projections.' *Neuroanatomy*, 4 pp. 24-27.

Tatu, L., Moulin, T., Bogousslavsky, J., Duvennoy, H. (1996) 'Arterial territories of human brain: brainstem and cerebellum. *Neurology,* 47 pp. 1125-1135.

Taylor, R.L., Zagami, A.S., Gibson, W.P., Black, D.A. Watson, S.R. (2012) 'Vestibular evoked myogenic potentials to sound and vibration: characteristics in vestibular migraine that enable separation from Meniere's disease.' *Cephalgia,* 32 pp. 213-225.

Taylor, R.L., Bradshaw, A.P., Halmagyi, G.M., Welgampola, M.S. (2012a) 'Tuning characteristics of ocular and vestibular evoked myogenic potentials in intact and dehiscent ears.' *Audiol Neurootol*, 17 pp. 207-218.

Taylor, R.L., Xing, M., Black, D.A., Halmagyi, G.M. (2013) 'Ocular vestibular evoked myogenic potentials: the effect of head and body tilt in the role plane.' *Clin Neurophysiol*, 125 pp. 627-634.

Taylor, R.L., Schulin, M., Goonetilleke, S., Welgampola, M.S. (2014) 'Does electrode impedance affect the recording of ocular vestibular-evoked myogenic potentials?' *J Am Acad Audiol*, 25 pp. 969-974.

Taylor, R.L., Welgampola, M.S., Nham, B., Rosengren, S.M. (2020) 'Vestibular evoked myogenic potential testing in vestibular localization and diagnosis.' *Semin Neurol*, 40 pp. 18-32.

Tellez, M.J., Ulkatan, S., Blitzer, A., Sinclair, C.F. (2018) 'Unearthing a consistent bilateral R1 component of the laryngeal adductor reflex in awake humans.' *Laryngoscope*, 128 pp. 1581-1587.

Tellez, M.J., Mirallave-Pescador, Seidel, K., Urriza, J., Shoakazemi, A., Raabe, A., Ghatan, S., Deletis, V., Ulkatan, S. (2021) 'Neurophysiological monitoring of the laryngeal adductor reflex during cerebellar-pontine angle and brainstem surgery.' *Clin Neurophysiol*, 132 pp. 622-631.

Tetzlaff, W., Kreutzberg, G.W. (1984) 'Enzyme changes in the rat facial nucleus following a conditioning lesion.' *Exp Neurol*, 85 pp. 547-564.

Theodros, D., Pateal, M., Ruzevick, J., Lim, M., Bettegowda, C. (2015) 'Pituitary adenomas: historical prospective, surgical management and future directions.' *CNS Oncol,* 4 pp. 411-429.

Thirumala, P.D., Mohanraj, S.K., Habeych, M., Wichman, K., Chang, Y., Gardner, P., Snyderman, C., Crammond, D.J., Balzer, J. (2013) 'Value of free-running electromyographic monitoring of extraocular cranial nerves during expanded endonasal surgery (EES) of the skull base.' *J Neurol Surg Rep*, 74 pp. 43-50.

Thomas, M.L.A., Fitzpatrick, D., McCreery, R., Janky, K.L. (2017) 'Big stimulus, little ears: Safety in administrating vestibular-evoked myogenic potentials in children.' *J Am Acad Audiol,* 28 pp. 395-403.

Thompson, A.J., et al., (2017) 'Diagnosis of multiple sclerosis:2017 revisions of the McDonald criteria.' *Lancet Neurol*, 17 pp. 162-173.

Tintore, M., Rovira, A., Arrambide, G. (2010) 'Brainstem lesions in clinically isolated syndromes.' *Neurology*, 75 pp. 1933-1938.

Tjernstrom, F., Fransson, P.A., Kahlon, B. (2016) 'Hearing and vestibular function after preoperative intratympanic gentamicin therapy for vestibular schwannoma as part of vestibular prehab.' *Ear Hear*, 37 pp. 744-750.

Todd, N.P., Rosengren, S.M., Aw, S.T., Colebatch, J.G. (2007) 'Ocular vestibular evoked myogenic potentials (OVEMPS) produced by air- and bone-conducted sound.' *Clin Neurophysiol*, 118 pp. 381-390.

Todd, N.P., Rosengren, S.M., Colebatch, J.G. (2008) ''Ocular vestibular evoked myogenic potentials (OVEMPs) produced by impulsive transmastoid acceleration.' *Clin Neurophysiol*, 119 pp. 1638-1681.

Toleikis, J.R. (2005). 'Intraoperative monitoring using somatosensory evoked potentials. A position statement by the American Society of Neurophysiological Monitoring.' *J Clin Comput Mon,* 19 pp. 241-258.

Tufarelli, D., Meli, A., Labini, F.S. (2007) 'Balance impairment after acoustic neuroma surgery.' *Otol Neurotol*, 28 pp. 814-821.

Uchino, Y., Kushiro, K. (2011) 'Differences between otolith and semicircular canal activated circuitry in the vestibular system.' *Neuroscience Res*, 71 pp. 315-327.

Ulkatan, S., Jaramillo, A.M., Tellez, M.J., Goodman, R.R., Deletis, V. (2017) 'Feasibility of eliciting the H-reflex in the masseter muscle in patients under general anesthesia.' *Clin Neurophysiol*, 128 pp.123-127.

Valls-Sole, J. (2005) 'Neurophysiological assessment of trigeminal reflexes in disorders of central and peripheral nervous systems.' *Clin Neurophysiol*, 116 pp. 2255-2265.

Venhovens, J., Meulstee, J., Verhagen, W.I.M. (2016) 'Vestibular evoked myogenic potentials (VEMPS) in central neurological disorders.' *Clin Neurophysiol*, 127 pp. 40-49.

Virgo, J.D., Plant, G.T. (2017) 'Internuclear ophthalmoplegia.' *Prac Neurol*, 17 pp. 149-153.

Voss, S.E., Adegoke, M.F., Horton, N.J., Sheth, K.N., Rosand, J., Shera, C.A. (2010) 'Posture systematically alters ear-canal reflectance and DPOAE properties.' *Hear Res*, 263 pp. 43-51.

Voss, N.F., Vrionis, F.D., Heilman, C.B., Robertson, J.H. (2000) 'Meningiomas of the cerebellopontine angle.' *Surg Neurol*, 53 pp. 439-447.

Wada, S.I., Starr, A. (1983) 'Generation of auditory brain stem responses (ABRs). III. Effects of lesions of the superior olive, lateral lemniscus and inferior colliculus on the ABR in guinea pig.' *Electroencephalogr Clin Neurophysiol,* 56 pp. 352-366.

Walsh. P., Kane, N.M., Butler, S. (2005) 'The clinical role of evoked potentials.' *J Neurol Neurosurg Psychiatr,* 76 (suppl 2) pp.16-22.

Walther, L.E., Rogowski, M., Hormann, K., Schaf, H., Lohler, J. (2011) 'Ocular vestibular evoked myogenic potentials to air conduction (AC oVEMP): useful in clinical practice. *Otolaryngol Pol*, 65 pp. 333-338.

Walther, L.E., Blodow, A., (2013) 'Ocular vestibular evoked myogenic potential to air conducted sound stimulation and video head impulse test in acute vestibular neuritis.' *Otol Neurotol*, 34 pp. 1084-1089.

Walther, L., Wenzel, A., Buder, J., Bloching, M., Kniep, R., Blodow, A. (2014) 'Detection of human utricular otoconia degeneration in vital specimen and implications for benign paroxysmal vertigo.' *Euro Arch Oto-Rhino-Laryngology*, 271 pp. 3133-3188.

Wang, A.C., Than, K.D., Etame, A.B., LaMarca, F., Park, P. (2009) 'Impact of anesthesia on transcranial electrical motor evoked potential monitoring during spine surgery: a review of the literature.' *Neurosurg Focus*, 27 E7.

Wang, S-J., Jaw, F.S., Young, Y-H. (2013) 'Optimizing the bandpass filter for acoustic stimuli in recording ocular vestibular-evoked myogenic potentials.' *Neurosci Letters*, 542 pp. 12-16.

Wang, S.I., Tseng, C.C., Young, Y.H. (2013a) 'Selective effects of head posture on ocular vestibular-evoked myogenic potential (oVEMP) by bone-conducted vibration.' *Clin Neurophysiol*, 125 pp. 621-626.

Ward, B.K., Wenzel, A., Ritzl, E.K. (2013) 'Near-dehiscence: clinical findings in patients with thin bone over the superior semicircular canal.' *Otol Neurotol*, 34 pp. 1421-1428.

Ward, B.K. Carey, J.P., Minor, L.B. (2017) 'Superior canal dehiscence syndrome: lessons from the first 20 years.' *Front Neurol*, 8 pp. 177.

Washington, C.W., McCoy, K.E., Zipfel, G.J. (2010) 'Update on the natural history of cavernous malformations and factors predicting aggressive clinical presentation.' *Neurosurg Focus,* 29 pp. E7.

Watson, S.R., Colebatch, J.G. (1998) 'Vestibulocollic reflexes evoked by short duration galvanic stimulation in man,' *J Physiol*, 513 pp. 587-597.

Watson, S.R.D., Halmaygi, G.M., Colebatch, J.G. (2000) 'Vestibular hypersensitivity to sound (Tullio phenomena): Structural and functional assessment.' *Neurology*, 54 pp. 722-728.

Weber, K., Rosengren, S., Michels, R., Strum, V., Straumann, D., Landau, K. (2012) 'Single motor unit activity in human extraocular muscles during the vestibulo-ocular reflex.' *J Physiol*, 590 pp. 3091-3101.

Weber, K.P., Rosengren, S.M. (2015) 'Clinical utility of ocular vestibular-evoked myogenic potentials (oVEMPs).' *Curr Neurol Neurosci Rep*, 15 pp 22-31.

Welgampola, M.S. (2008) 'Evoked potential testing in neuro-otology.' *Curr Opin Neurol*, 21 pp. 29-35.

Welgampola, M.S., Migliaccio, A.A., Myrie, O.A., Minor, I.B., Carey, J.P. (2009) 'The human sound-evoked vestibular ocular reflex and its electromyographic correlate.' *Clin Neurophysiol*, 120 pp. 158-166.

Welniarz, Q., Dusart, I., Roze, E. (2017) 'The corticospinal tract: evolution, development, and human disorders.' *Dev Neurobiol*, 77 pp. 810–29.

Wen, M.H., Cheng, P.W., Young, Y.H. (2012) 'Augmentation of ocular vestibular-evoked myogenic potentials via bone-conducted vibration stimuli in Meniere disease.' *Ololaryngol Head Neck Surgery,* 146 pp. 797-803.

Weng, Y-C., Young, Y. (2014) ‘Mapping affected territory of anterior/posterior inferior cerebellar artery infarction using a vestibular test battery.’ *Acta Oto-Laryngologica*, 134, pp. 268-274.

Whitmore, R.G., Urban, C., Church, E., Ruckenstein, M., Stein, S.C., Lee, J.Y. (2011) ‘Decision analysis of treatment options for vestibular schwannoma. Clinical article.’ *J Neurosurg,* 114 pp. 400–413.

Wiegand, D.A., Fickel, V. (1989) ‘Acoustic neuroma – the patient’s perspective: subjective assessment of symptoms, diagnosis, therapy, and outcome of 541 patients.’ *Laryngoscope,* 99 pp. 179-187.

Winters, S.M., Campschroer, T., Grolman, W., Klis, S.F. (2011) ‘Ocular vestibular evoked myogenic potentials in response to air-conducted sound in Meniere’s disease.’ *Ololaryngol Head Neck Surgery*, 32 pp. 1273-1280.

Yamada, T.H., Tranfedt, E.E., Tamaki, T., Torres, F., Iaizzo, P.A. (1994) ‘The effects of volatile anesthetics on the relative amplitudes and latencies of spinal and muscle potentials evoked by transcranial magnetic stimulation.’ *Spine,* 19 pp. 1512-1517.

Zimmerman, R.S., Spetzler, R.F., Lee, K.S., Zabramski, J.M., Hargraves, R.W. (1991) ‘Cavernous malformations of the brain stem.’ *J Neurosurg,* 75 pp. 32-39.

Zuniga, M.G., Janky, K.L., Nguyen, K.D., Welgampola, M., Carely, J.P. (2012a) ‘Ocular versus cervical VEMPs in the diagnosis of superior semicircular canal dehiscence syndrome.’ *Otol Neurotol*, 34 pp. 121-126.

Zuniga, M.G., Janky, K.L., Schubert, M.C., Caret, J.P. (2012) ‘Can vestibular evoked myogenic potentials help differentiate Meniere disease for vestibular migraine?’ *Otolaryngol Head Neck Surg*, 146 pp. 788-796.