An Investigation into the Site of Iatrogenic Auditory Impairment in Vestibular Schwannoma Surgery: A Pilot Study.

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> "*You have brains in your head. You have feet in your shoes. You can steer yourself any direction you choose. You're on your own. And you know what you know. And YOU are the one who'll decide where to go….*"
>
> - Oh, the places you'll go! By Dr Seuss

Abstract

During vestibular schwannoma surgery a large proportion of patients will lose their hearing. While there have been several papers investigating the mechanism behind this loss of auditory function, the exact pathophysiological mechanisms remain relatively elusive. The present study aimed to document the patterns of electrophysiological auditory responses during retrosigmoid vestibular schwannoma surgery. In particular, we aimed to determine whether the site of auditory impairment in individual cases was predominantly cochlea or neural.

Auditory function was monitored intraoperatively in two patients who underwent unilateral vestibular schwannoma surgery via the retrosigmoid approach at St George's Hospital in Christchurch, and Dunedin Public Hospital. A combination of electrocochleography and direct eighth nerve monitoring techniques were used to monitor the auditory evoked potentials from the cochlea and cochlear nerve during the course of the surgery. Auditory brainstem response recordings were obtained from the second participant due to the technical difficulties in the primary electrophysiological techniques.

Technical difficulties faced during the surgical procedure prevented the recording of both electrocochleography and direct eighth nerve monitoring potentials from each of the participants. As a consequence of this, we were unable to draw any conclusions about the site of iatrogenic injury in each surgery. Despite the insufficient recordings of auditory function, the technical and practical knowledge acquired during the course of this pilot study has established a foundation upon which the continuing research may build.

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List of Abbreviations

AAO-HNS – American Academy of Otolaryngology – Head and Neck Surgery

ABR – Auditory Brainstem Response

AC – Alternating Current

CAP – Compound Action Potential

CM – Cochlear Microphonic

CNAP – Cochlear Nerve Action Potential

CPA – Cerebellopontine Angle

CSF – Cerebrospinal Fluid

CT Scan – Computer Tomography Scan

dB – Decibels

dB HL – Decibels Hearing Level

dB nHL – Decibels normal Hearing Level

dB SL – Decibels Sensation Level

dB SPL – Decibels Sound Pressure Level

DC – Direct Current

DENM – Direct Eighth Nerve Monitoring

DPOAE – Distortion Product Otoacoustic Emission

ECochG – Electrocochleography

ENT – Ear, Nose and Throat specialty

IAA – Internal Auditory Artery

IAC – Internal Auditory Canal

IHC – Inner Hair Cell

LOC – Lateral Olivocochlear System

MGB – Medial Geniculate Body

MOC – Medial Olivocochlear System

MRI – Magnetic Resonance Imaging

NF2 – Neurofibromatosis Type II

OCB – Olivocochlear Bundle

OHC – Outer Hair Cell

PTA – Pure Tone Average

SRT – Speech Recognition Threshold

SP – Summating Potential

SPL – Sound Pressure Level

WRS – Word Recognition Score

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Chapter One: Introduction

In more recent years, the use of sophisticated diagnostic techniques, including magnetic resonance imaging (MRI), has facilitated the early diagnosis of vestibular schwannomas in a large proportion of patients. Due to the earlier stage of diagnosis, patients are presenting with smaller tumours and better preoperative hearing. In an effort to increase the postoperative rates of hearing preservation, surgeons have refined the microsurgical techniques used in vestibular schwannoma surgery. However, postoperative hearing loss is still the most prevalent complication of vestibular schwannoma surgery (Samii & Matthies, 1997a; Darwish, Bird, Goodisson, Bonkowski, & MacFarlane, 2005). A large proportion of patients who undergo vestibular schwannoma excision with attempted hearing preservation will suffer from complete anacusis on the operated side postoperatively (Samii & Matthies, 1997b).

With the use of intraoperative auditory monitoring, the pathophysiological mechanism of this hearing loss is beginning to be better understood. Postoperative hearing loss is predominantly attributed to the obstruction of the vascular blood supply to the cochlea and the cochlear nerve, or the direct mechanical damage of the cochlea or the cochlear nerve (Colletti, Fiorino, Carner, & Tonoli, 1997). While there is some understanding of the potential mechanisms, very few studies have investigated which site of the auditory system is most vulnerable to damage during the course of the surgery. In particular, the patterns of change in the auditory function at the cochlea and cochlear nerve have not been well described or investigated within the literature. An understanding the site of operative damage could significantly help elucidate the predominant mechanism of iatrogenic hearing loss, and could help shape the development of therapeutic treatments to help improve postoperative hearing outcomes in the future.

The aim of this study was to monitor the patterns of cochlear and cochlear nerve function during retrosigmoid vestibular schwannoma surgery. Documenting the changes in auditory function will provide information about the temporal change in hearing during the course of the surgery and the possible site of auditory impairment. In particular, we aimed to determine whether the site of auditory impairment during surgery was predominantly cochlear or neural.

1.1 Peripheral auditory system

A fundamental understanding of the ascending and descending pathways of the auditory system is critical in investigations of the site of auditory dysfunction during vestibular schwannoma surgery. Therefore, an overview of the functional anatomy and physiology of the peripheral auditory system will be presented here.

1.1.1 Afferent auditory pathway

The anatomy of the peripheral auditory system from the ear canal (external auditory canal) to the brainstem is presented in Figure 1. The first stage of the afferent auditory pathway involves the transmission of air particle vibrations from the external environment through the external auditory canal to the tympanic membrane. Sound waves vibrate the tympanic membrane and pass through the middle ear space via the ossicular chain, converting acoustic energy to mechanical energy. Movement of the stapes footplate against the oval window of the cochlea produces a longitudinal pressure wave in the cochlear fluids. The pressure fluctuations in the cochlear fluid compartments generates vertical displacements of the basilar membrane, which is observed as a transverse travelling wave of vibration (Von Békésy & Wever, 1960). The travelling wave propagates along the length of the basilar membrane from the base to the apex of the cochlea. The point at which maximum displacement is achieved is dependent on the frequency of the stimulus, where a high-

frequency sound will evoke maximal displacement towards the basal turn of the cochlea and a low-frequency sound will produce maximal displacement towards the apex (Musiek & Baran, 2007). This tonotopic organisation of the basilar membrane is a result of the physical characteristics of the basilar membrane as it courses through the turns of the cochlea, most notably, the stiffness gradient along the basilar membrane increasing from the apex to the base (Von Békésy & Wever, 1960).

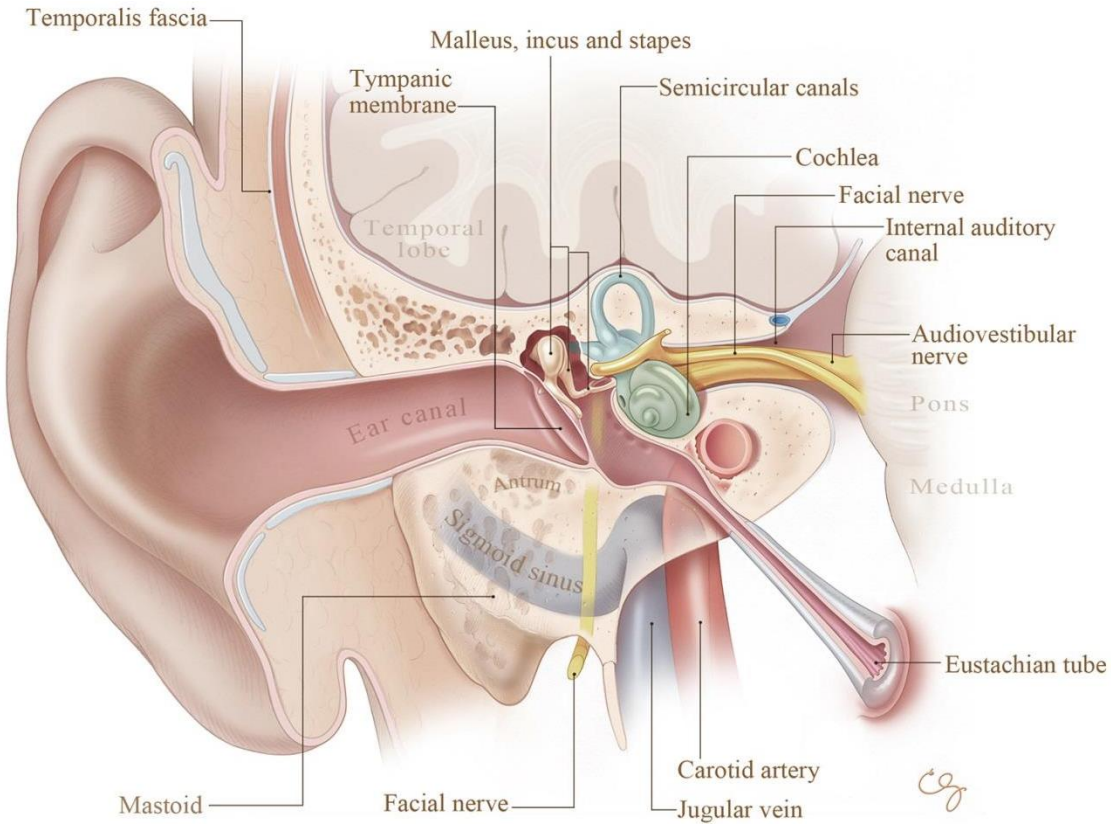

Figure 1: Coronal view of the peripheral auditory system (Jackler, 2009).

A dynamic population of sensory hair cells and support cells sit atop of the basilar membrane, forming the structure known as the organ of Corti. The organ of Corti is covered by the tectorial membrane - a gelatinous structure in which the stereocilia of the outer hair cells (OHCs) are embedded (Rask-Andersen et al., 2012). Displacement of the basilar

membrane and organ of Corti results in a radial shearing of the OHC stereocilia, which leads to a passive influx of potassium ions in to the hair cell (Gillespie & Walker, 2001). Sound waves are an alternating stimulus made up of condensations and rarefactions. The alternating polarity is reflected in the vibrations of the basilar membrane, and consequently in the influx of ions into the sensory hair cells; where the mechanically-gated ion channels on the hair cell stereocilia open and close as the basilar membrane moves up and down. The alternating current of potassium ions through the gated channels results in an alternating receptor potential, and in turn evokes a pattern of contraction and relaxation in the voltage-sensitive, electromotile structures within the OHCs (Ashmore, 1987; Santos-Sacchi & Dilger, 1988). This active process of contraction and relaxation transfers mechanical energy back in to the cochlea, which acts to partially cancel the friction of the travelling wave and therefore enhance basilar membrane vibration (Fettiplace & Hackney, 2006). This mechanism, known as the cochlear amplifier, improves hearing sensitivity and sharpens the frequency tuning of the basilar membrane, especially at low intensities (Dallos & Harris, 1978; Kim, 1986; Ryan, Dallos, & McGee, 1979). The primary driving force for auditory transduction is the + 95 mV endocochlear potential. This potential is generated and maintained by the active metabolic processes of the stria vascularis, a densely vascularised epithelia in the lateral wall of the cochlea (Wangemann, 2006).

In contrast to OHCs, the cilia of the inner hair cells (IHCs) are not embedded in the tectorial membrane; rather they are free-floating in the endolymph (Musiek & Baran, 2007). As a consequence of this, the deflection of the IHC bundles must be due to indirect forces. It is believed that the shearing of IHC hair bundles is mediated through inertial movement of the viscous cochlear fluids in the subtectorial space (Pickles, 2008). Deflection of the IHC hair bundles results in a cellular depolarisation, similar to that of the OHC, which in turn triggers the release of an excitatory neurotransmitter (glutamate). The synaptic release of

glutamate initiates an action potential in the cochlear afferent nerve fibres surrounding the IHCs (Musiek & Baran, 2007; Pickles, 2008).

The afferent innervation of the cochlea consists of two morphologically and functionally distinct types of nerve cells (Spoendlin & Schrott, 1989). The type I ganglion nerve fibres are large, myelinated fibres which constitute approximately 90 to 95% of the cochlear nerve cell population (Spoendlin & Schrott, 1989). These fibres predominantly innervate the IHCs, with each IHC receiving dense innervation from 20 to 30 type I ganglion fibres (Rask-Andersen et al., 2012). The remaining 5 to 10 % of the cochlear nerve cell population is made up of the type II ganglion nerve fibres (Spoendlin & Schrott, 1989). These fibres are relatively thin in diameter and unmyelinated, and primarily innervate the OHCs of the cochlea (Hurd, Hutson, & Morest, 1999). As there are significantly less type II fibres as compared to OHCs, the fibres tend to be distributed across a number of OHCs and will synapse with multiple OHCs (Liberman, 1980b). The nerve fibres which innervate the cochlea represent the initial bridge between the physical world of sound and the conscious perception of that sound (Nayagam, Muniak, & Ryugo, 2011).

1.1.2 Efferent auditory pathway

In addition to the afferent innervation, the cochlear hair cells receive efferent innervation from two key populations of descending auditory nerve fibres. As compared to the afferent auditory system, the anatomy of the efferent auditory system is poorly defined and its physiological function within the auditory system remains relatively ambiguous. The efferent auditory pathway originates from the primary auditory cortex and its associated areas, and courses through the medial geniculate body (MGB) - following a pathway similar to that of the afferent auditory pathway (in the opposite direction) (Huffman & Henson, 1990; Musiek & Baran, 2007). From the brainstem, the efferent fibres travel as a bundle through the

internal auditory canal (IAC) alongside the vestibular fibres, and exit into the cochlea via the habenula perforata (Musiek & Baran, 2007; Warr, Boche, & Neely, 1997). The key component of the efferent auditory system is the olivocochlear bundle (OCB), which is a complex network of descending auditory neurons which originates in the periolivary regions of the superior olivary complex (Liberman & Brown, 1986). The OCB can be split into its' two anatomically and functionally distinct subsystems (Warr & Guinan Jr, 1979):

The Lateral Olivocochlear System (LOC)

The LOC fibres are relatively thin, unmyelinated fibres which originate from the lateral superior olive and its surrounding area (Warr & Guinan Jr, 1979). From the superior olivary complex, the LOC fibres proceed laterally around the vestibular nerve root, course through the IAC and enter the cochlea in between the first and second cochlear turns (Musiek & Baran, 2007). The efferent fibres extend apically and basally, and terminate on the radial dendrites of the type I neurons which innervate the IHCs and, to a lesser extent, directly on to the base of the IHCs themselves (Liberman, 1980a; Warr & Guinan Jr, 1979; Wersinger & Fuchs, 2011). In the mammalian auditory system, the lateral fibres predominantly project to the ipsilateral cochlea (Guinan, Warr, & Norris, 1983; Wilson, Henson, & Henson, 1991).

The Medial Olivocochlear System (MOC)

The fibres of the MOC system are myelinated, and are larger in diameter than the lateral efferent fibres (Guinan Jr, 2006). The MOC fibres originate from medial periolivary regions which lie medial, ventral and anterior to the medial superior olive (Guinan et al., 1983; Warr & Guinan Jr, 1979). The MOC system is predominantly crossed, where approximately 60% - 75% of the MOC fibres cross the midline and innervate the contralateral cochlea (Thompson & Thompson, 1986; Warr, 1992).

Within the cochlea, the medial efferents directly synapse with the base of the OHC (Warr & Guinan Jr, 1979; Wilson et al., 1991).

Although very little is known about the physiological function of the auditory efferents, researchers will agree that the efferent auditory system plays a role in modulating afferent input from the periphery (Guinan Jr, 2006). Early evidence within the literature indicated that the efferent system may have only played an inhibitory role in the auditory system, down-regulating peripheral activity. More recent evidence suggests that the efferent system may also be involved in excitatory processes (Galambos, 1956; Le Prell, Halsey, Hughes, Dolan, & Bledsoe Jr, 2005; Le Prell, Shore, Hughes, & Bledsoe Jr, 2003). The current research therefore suggests that the efferent auditory system plays a role in the balance of the excitatory and inhibitory interactions within the auditory system (Musiek & Baran, 2007).

Selective activation of the medial efferent system at the OCB produces an inhibitory change in the activity of the cochlear nerve (Galambos, 1956; Gifford & Guinan, 1987). The interaction of the medial efferent system with the cochlear nerve is not, however, simply inhibitory; the relationship is more complex. Several authors have reported that the crossed MOC fibres also play an excitatory role in a phenomenon known as the 'anti-masking effect', where masking noise in the contralateral ear augments the auditory nerve responses to high-level clicks (Dolan & Nuttall, 1988; Kawase, Delgutte, & Liberman, 1993). Musiek and Baran (2007) have suggested that this anti-masking phenomenon is associated with the concept that the MOC system, when activated, can improve hearing in noise.

At the level of the cochlea, activation of the MOC system results in a frequency-specific reduction in the mechanical vibration of the basilar membrane (Cooper & Guinan, 2006; Guinan Jr & Cooper, 2008; Murugasu & Russell, 1996; Russell & Murugasu, 1997).

The suppressive effects of the efferent system at the cochlea indicate that the system may be involved in the dynamic feedback loop of the cochlear amplifier (Cooper & Guinan, 2006). From these studies, it is evident that the medial efferent system is able to differentially affect the activity of the separate portions of the peripheral auditory system.

Selective stimulation or disruption of the lateral efferent system has been significantly more difficult to achieve, which makes it more challenging to identify the exact function of the LOC fibres (Guinan Jr, 2006). More recent evidence suggests that the LOC system consists of two functional subdivisions, capable of producing slow increases or decreases in the strength of auditory nerve responses (Groff & Liberman, 2003). The most dominant effect of LOC disruption is the depression of the cochlear action potential, indicating that the LOC system predominantly plays an excitatory role in the efferent auditory system (Le Prell et al., 2005; Le Prell et al., 2003). However, Darrow et al. (2007) found the opposite effect following selective destruction of LOC fibres in mice (Darrow, Maison, & Liberman, 2007). Therefore, it can be said that the function of the LOC system is still relatively ambiguous and further research is required for us to be able to truly understand the physiological function of this system.

1.2 Vestibulocochlear nerve and internal auditory canal

The afferent nerve fibres of the auditory system exit the cochlea through a number of small openings in the osseous spiral lamina, travel through Rosenthal's canal and are bundled together along the axis of the cochlea (the modiolus) (Benoudiba, Toulgoat, & Sarrazin, 2013; Krstic, 1991; Tuncel, Sürücü, Erbil, & Konan, 2005). These bundled axons form the modiolar trunk of the cochlear nerve. Similar to the cochlea, the cochlear nerve is tonotopically organised; with low-frequency apical fibres being located within the core of the nerve and high-frequency basal fibres spiralling around the core forming the periphery (Pusz

& Littlefield, 2013). The tonotopic organisation of the cochlea and cochlear nerve persists throughout the ascending auditory system (Pantev et al., 1995; Rees & Palmer, 2010).

As the cochlear nerve exits the modiolus it is joined by the vestibular nerve which extends centrally from the vestibular apparatus. Both the cochlear and vestibular nerves extend towards the fundus of the IAC, which is located on the posterior surface of the petrous portion of the temporal bone. The vestibular nerve is composed of two distinct branches, the inferior and superior vestibular nerves, which transmit information about balance and body position from the vestibular end organs to the vestibular centres within the brain (Benoudiba et al., 2013). The two branches of the vestibular nerve converge 1 – 2 mm from the lateral fundus of the IAC to form a single vestibular nerve (Rubinstein, Sandberg, & Cajade-Law, 1996). As the vestibular and cochlear nerves course through the IAC towards the porus acousticus the two nerves fuse together to form the vestibulocochlear nerve (Spickler & Govila, 2002). This fusion occurs 3 – 4 mm from the lateral fundus of the IAC (Rubinstein et al., 1996). The efferent nerve fibres of the auditory system are also housed within the vestibulocochlear nerve; however the neural transmission along these fibres occurs in the opposite direction to that of the afferent auditory neurons.

The vestibulocochlear nerve, known as the eighth cranial nerve, is approximately 22 to 26 mm in length in adult humans, and contains just over 30, 000 auditory nerve fibres (Musiek & Baran, 2007; Spoendlin & Schrott, 1989). The vestibulocochlear nerve has been described as the bottleneck for auditory information, whereby all of the information which is coded from the cochlea must pass through the nerve to reach the central auditory centres (Musiek & Baran, 2007). As a consequence of this, any damage to the nerve may have severe consequences for auditory perception.

All peripheral nerves, including the vestibulocochlear nerve, are covered in two types of myelin. Distally, the vestibulocochlear nerve is ensheathed in a dense 'peripheral' myelin generated by the Schwann cells (Moore & Linthicum, 2001). As the nerve travels through the IAC, the myelin coating transitions to a 'central' myelin which is produced by the oligodendrocytes (Møller, 2000; Toesca, 1996). The neural sheathing of the central myelin is significantly thinner and looser than that of the peripheral myelin. The transition of peripheral to central myelin before the nerve enters the central nervous system is unique to the vestibulocochlear nerve, and is said to make the nerve more vulnerable to damage during surgeries of the IAC and cerebellopontine angle (CPA) (Battista, Wiet, & Paauwe, 2000).

The vestibular and cochlear nerves course through the IAC alongside the facial nerve and internal auditory artery (IAA). The anatomical routes of these nerves may be described by dividing the IAC into four quadrants (as seen in Figure 2). At the entrance of the IAC, the cochlear nerve sits in the anterior-inferior quadrant, just below the facial nerve (Valvassori & Palacios, 1998). The two branches of the vestibular nerve take a posterior route through the entrance of the IAC. As the nerves course through the IAC, they make a ninety-degree rotation (Silverstein, Norrell, Haberkamp, & Mcdaniel, 1986). This rotation results in a shift in the spatial relationship between the nerves where the cochlear nerve lies caudal to the inferior vestibular nerve at the porus acousticus (Rubinstein et al., 1996). As they leave the IAC, the vestibulocochlear and facial nerves cross the CPA and enter the anterolateral aspect of the brainstem at the junction between the pons and medulla (Spickler & Govila, 2002). This juncture between the vestibulocochlear nerve and the brainstem represents the point at which neural impulses from the peripheral auditory system are transferred to the central auditory system.

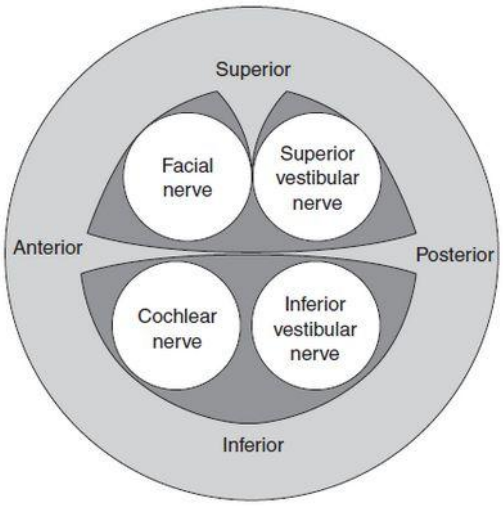

Figure 2: Schematic representation of the lateral aspect of the left internal auditory canal (Lalwani, 2008).

1.3 Blood supply of the peripheral auditory system

The blood supply to the inner ear and its respective nerves is critical for maintaining osmotic and metabolic homeostasis. Figure 3 illustrates the gross vasculature of the inner ear labyrinth. The cochlea, vestibule, their associated nerves and the facial nerve are supplied by arteries of the same source, namely, the internal auditory artery (IAA). In a majority of individuals (83 to 87%), the IAA stems from the medial loop of the anterior inferior cerebral artery; which is a branch of the basilar artery (Wende, Nakayama, & Schwerdtfeger, 1975; Zhang, Wang, Zhang, Li, & Shi, 2002). Alternatively, the IAA bypasses the anterior inferior cerebral artery and directly branches from the basilar artery; however this is more rarely reported (< 15%) (Mom, Chazal, Gabrillargues, Gilain, & Avan, 2005; Smaltino, Bernini, & Elefante, 1971). From its point of origin, the IAA exits the brainstem, transverses laterally across the CPA space, and extends into the IAC (Matsunaga, Igarashi, & Kanzaki, 1991). In the medial portion of the IAC, the IAA runs between the vestibular nerve and the facial nerve (Matsunaga et al., 1991). As the IAA extends laterally through the IAC, it branches into the anterior vestibular artery and the common cochlear artery (Matsunaga et al., 1991). The

common cochlear artery divides into the spiral modiolar artery, which ascends through the modiolus and predominantly supplies the apex, and to a lesser extent, the basal turns of the cochlea (Bachor, Selig, Jahnke, Rettinger, & Karmody, 2001). In addition to the spiral modiolar artery, the common cochlear artery gives rise to the vestibular-cochlear artery, which supplies the basal turn of the cochlea and several of the vestibular end-organs (Lysakowski, McCrea, & Tomlinson, 1998; Matsunaga et al., 1991). Branching of the spiral modiolar and vestibular-cochlear arteries forms a complex network of arterioles which supplies most of the cochlear regions (Bachor et al., 2001; Smith, 1973). These radiating arterioles emerge through Rosenthal's canal, to supply the limbus spiralis, tectorial membrane, and the organ of Corti (Musiek & Baran, 2007). In addition to this, an extensive network of arterioles courses over the scala vestibuli and supplies the stria vascularis on the lateral wall of the cochlea (Nakashima et al., 2003). Within the cochlea, the density of vascularisation increases from the apex to the base of the cochlea, which is consistent with the greater physiological activity at the basal end of the cochlea (Axelsson & Ryan, 1988). The cochlea also has a venous system for the drainage of blood from the cochlea, which is the anatomical counterpart of the arterial system described above.

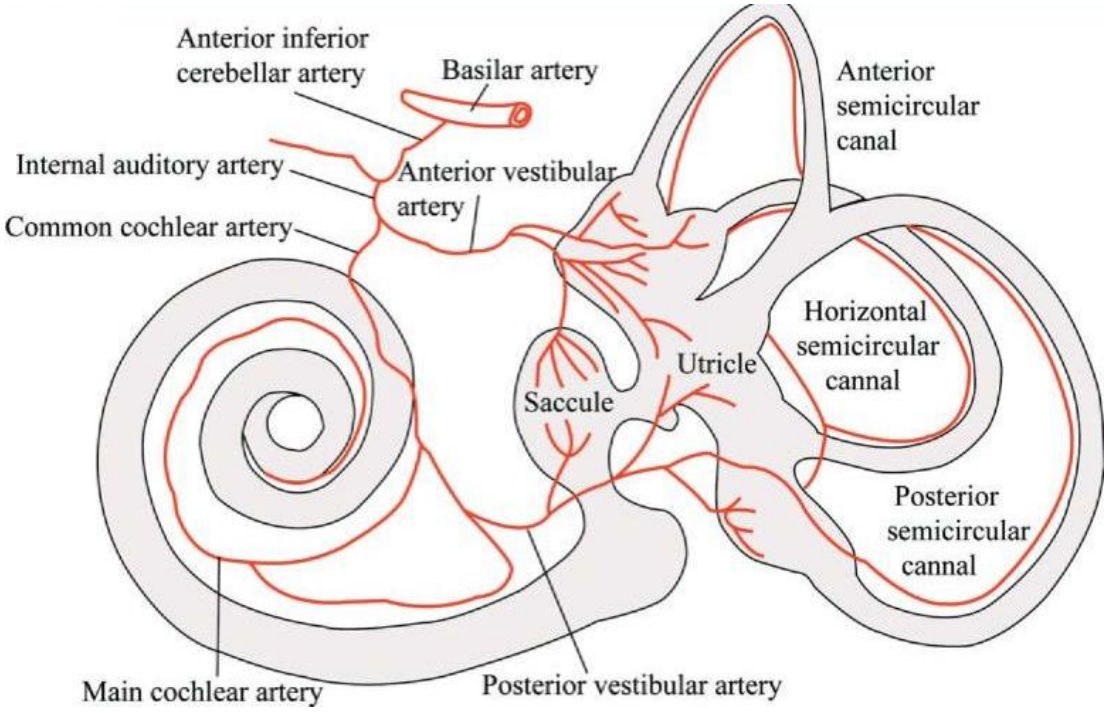

Figure 3: Schematic illustration of the vascular supply to the inner ear labyrinth (Kim & Lee, 2009).

In the IAC, the IAA appears to be tightly involved with the vestibulocochlear nerve, where the IAA and its main branches are typically found along the surface of the nerve (Fisch, Dobozi, & Greig, 1972; Matsunaga, Kanzaki, & Hosoda, 1996). The integration of the IAA and vestibulocochlear nerve is not limited to the outer surface, as the main branches of the IAA have frequently been found within the endoneurium of the nerve (Matsunaga et al., 1996). Matsunaga et al (1996) studied the ultrastructure of the eighth nerve blood supply and noted that the vasculature consists of a dual system of extrinsic vessels and intrinsic microvessels which communicate via anastomosing vessels. The extrinsic vascular supply consists of many arterioles and venules which run longitudinally along the surface of the vestibulocochlear nerve. In contrast, the intrinsic vascular supply is isolated within the endoneurium of the nerve and is composed of sparsely distributed capillaries and post-capillary venules that run parallel to the auditory nerve fibres. The microstructure of the intrinsic vascular supply, with sparse and large microvessels, represents an effective system

for maintaining the ionic and osmotic balance of the endoneurial fluid (Matsunaga et al., 1996). The balance of the endoneurial fluid is essential for both the function and metabolic nourishment of the peripheral nerve fibres (Matsunaga et al., 1996).

A disruption in the vascular blood supply of the auditory system can result in auditory dysfunction and irreversible degeneration of the cochlear tissue. The blood flow to the cochlea and cochlear nerve can be disrupted by vascular abnormalities such as vessel occlusion, vascular spasm, haemorrhage, vasculitis, or hypercoagulation. The location of this vascular disruption will dictate the nature of the auditory dysfunction. Occlusion of the IAA or one of the main branches initially results in degeneration of the membranous cochlear tissue and vestibular apparatus (Belal, 1979; Perlman, Kimura, & Fernandez, 1959). If this occlusion persists, it will eventually lead to cochlear ossification and fixation of the membranous tissue (Belal, 1979). Transient ischemia of the blood vessels supplying the cochlea and cochlear nerve will result in various degrees of peripheral hearing loss, which are dependent on the duration of ischemia and location of vascular disruption. Due to the high vascular demands of the stria vascularis, even intermittent ischemia could significantly compromise of the metabolic function of the organ of Corti (Martini & Prosser, 2003).

1.4 Vestibular schwannoma

Vestibular schwannomas (also termed acoustic neuromas) are benign tumours originating from the vestibular branch of the eighth cranial nerve. These slow-growing tumours arise from the Schwann cells in the myelin sheath surrounding the nerve (Jacob et al., 2007; Myrseth, Pedersen, Møller, & Lund-Johansen, 2007). The literature surrounding the exact nerve origins of vestibular schwannomas is divergent; however, the majority of studies have reported that the benign tumour predominantly originates from the inferior branch of the

vestibular nerve (Jacob et al., 2007; Khrais, Romano, & Sanna, 2008; Komatsuzaki & Tsunoda, 2001).

The incidence of vestibular schwannomas in the population is approximately 0.7 – 1.2 / 100, 000 per year (Babu et al., 2013; Tos, Charabi, & Thomsen, 1999), with the rates of diagnosis showing a trend of increasing incidence over the last few decades (Stangerup, Caye-Thomasen, Tos, & Thomsen, 2006). The increased incidence of vestibular schwannomas within the population may be explained by a number of factors: the use of more sensitive imaging techniques such as magnetic resonance imaging (MRI) to diagnose the tumours; an increased awareness of clinicians to the diagnosis of vestibular schwannomas; or a true increase in the incidence of these tumours (Propp, McCarthy, Davis, & Preston-Martin, 2006). The clinical presentation of patients typically occurs between the age of 45 to 60 years of age (Myrseth et al., 2007).

The majority of vestibular schwannomas (95%) are unilateral in nature (Evans et al., 2005). The exception is in patients with the rare genetic condition neurofibromatosis type II (NF2). Neurofibromatosis type II is an autosomal dominant syndrome that results from mutations in the NF2 tumour suppressor gene on the long arm of chromosome 22 (Asthagiri et al., 2009). A mutation of this gene is associated with uncontrolled cell proliferation, where patients are predisposed to develop schwannomas, meningiomas or ependymomas in young adulthood (Evans et al., 2005). In patients with NF2, the vestibular schwannomas present bilaterally and occur in patients at a much earlier age than in patients with sporadic unilateral vestibular schwannomas (Sainz et al., 1994).

In most cases, the tumour grows within the IAC, and gradually extends into the CPA as the tumour develops (Moffat, Golledge, Baguley, & Hardy, 1993). As the tumour grows within the IAC it directly compresses the surrounding neural and neurovascular structures,

resulting in degenerative changes to the nerve, impaired nerve function, and progressive signs and symptoms (Moffat et al., 1993). Involvement of the vestibulocochlear nerve is characterised by high-frequency sensorineural hearing loss, tinnitus, and disequilibrium on the affected side (Kentala & Pyykkö, 2001; Ramsden, Lye, & Dutton, 1991). In a study by Matthies and Sammi (1997) the clinical presentation of 1000 patients with vestibular schwannomas was analysed. Hearing loss was reported to be most prevalent presenting symptom in vestibular schwannomas patients (95%), followed by tinnitus (63%), vestibular disturbances (61%), and facial paresis (6%) (Matthies & Samii, 1997). In approximately 10 to 15% of patients, the hearing loss may be sudden in nature (Moffat, Baguley, von Blumenthal, Irving, & Hardy, 1994; Morrison & Sterkers, 1996). The sudden loss of hearing may result following compression of the internal labyrinthine artery in the IAC (Moffat, Hardy, & Baguley, 1989).

The natural history of the vestibular schwannoma is relatively ambiguous. The tumour may grow continuously or only to a certain size, which may be followed by a period of stagnation and even recession (Stangerup et al., 2006). In those tumours which exhibit continual growth, the rate of growth has been estimated to be within 2.4 to 10 mm/year (Charabi et al., 1998; Charabi, Tos, Thomsen, Charabi, & Mantoni, 2000; Stangerup et al., 2006). Continued growth of extracanicular tumours into the CPA can result in compression of the brainstem and obstruction of the fourth ventricle (as shown in Figure 4), which is associated with more serious morbidity and rarely, death (Moffat et al., 1989; Stangerup et al., 2006).

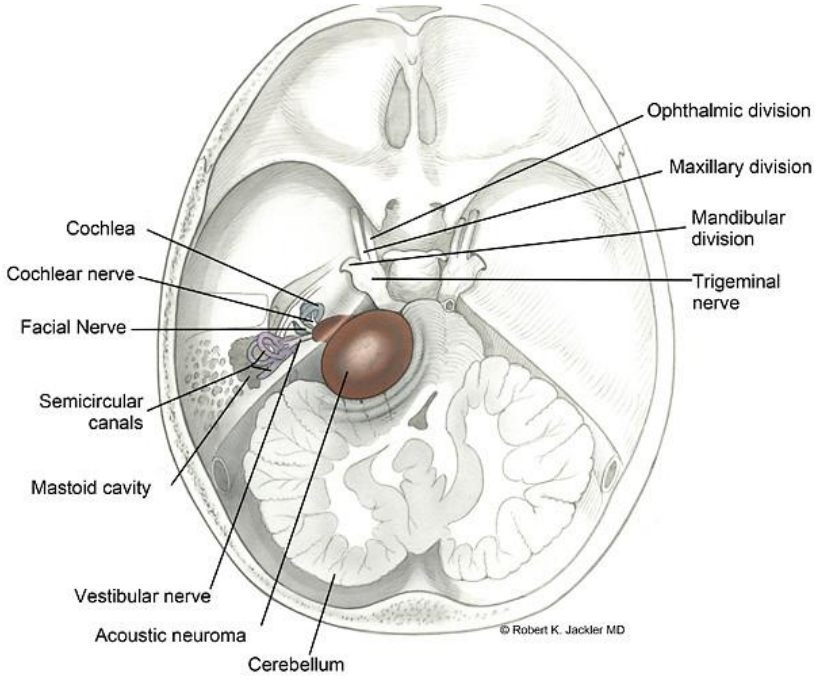

Figure 4: A trasnverse schematic depiction of an acoustic neuroma (vestibular schwannoma) growing within the internal auditory canal and extending out the cerebellopontine angle. In this diagram, the tumour is relatively large and has begun to press against the brainstem and cerebrum (Jackler, 2009).

The signs and symptoms reported by a patient at the time of presentation are not specific to vestibular schwannomas alone and can mimic those symptoms experienced by a patient with Ménière's disease or rapid sensorineural hearing loss. Consequently, the diagnosis of a patient with vestibular schwannoma must be confirmed by imaging studies such as MRI or computed tomography scanning (CT scan) to identify an intracanicular tumour consistent with a vestibular schwannoma (Kentala & Pyykkö, 2001).

Management of vestibular schwannomas can be achieved through three main treatment options: microsurgical removal of the tumour, stereotactic radiation, or conservative management with serial monitoring with outpatient consultation and contrast MRI (Myrseth et al., 2007). Within the literature, each of the treatment options has been extensively discussed and each option has its own merits in different clinical situations

(Danner, Mastrodimos, & Cueva, 2004). The choice of treatment is typically dependent on the size and location of the tumour, the degree of functional hearing loss, age of the patient, and the preference of the physician and the patient them self (Colletti et al., 2000; Myrseth et al., 2007). Advances in surgical techniques and intraoperative monitoring have allowed for complete removal of the tumour in the majority of patients undergoing microsurgery, with significantly diminished morbidity and mortality (Darrouzet, Martel, Enée, Bébéar, & Guérin, 2004). Therefore, microsurgery is often the first choice of treatment in the management of vestibular schwannomas where the patient's symptoms are significant enough that watchful waiting is unjustified.

1.5 Surgical intervention

Neurosurgical intervention remains the standard option for effective management of vestibular schwannoma cases. The surgical excision of a vestibular schwannoma may be achieved through one of three approaches; the middle cranial fossa approach, retrosigmoid (suboccipital) approach, or translabyrinthine approach. The choice of surgical approach primarily depends on the surgeon's preference and experience, with consideration to other factors, including: the patient's preoperative symptoms, the size of the tumour and the extension of the tumour within in the IAC and into the CPA (Myrseth et al., 2007; Samii & Matthies, 1997b; Sanna, Taibah, Russo, Falcioni, & Agarwal, 2004). In patients with serviceable hearing preoperatively, an approach which allows for the preservation of hearing is typically preferred (Jackler & Pitts, 1992). The two surgical approaches which facilitate the possibility of hearing preservation are the retrosigmoid and middle cranial fossa approaches. While the middle cranial fossa approach provides excellent exposure of the IAC, this approach is only suitable for the removal of smaller tumours isolated within the IAC or those with minimal extension in to the CPA (Briggs, Fabinyi, & Kaye, 2000). In contrast to this, the retrosigmoidal approach involves a posterior fossa craniotomy, which allows the

surgeons to gain panoramic visualisation of CPA and provides excellent access to the IAC through resection of its' posterior wall (Yamakami, Uchino, Kobayashi, Yamaura, & Oka, 2004). The retrosigmoidal approach can be used for the removal of various sized vestibular schwannomas (Lassaletta, Fontes, Melcon, Sarria, & Gavilan, 2003; Sanna, Taibah, et al., 2004). In patients with minimal preoperative hearing, the translabyrinthine approach is typically adopted (Day, Chen, & Arriaga, 2004). Total tumour removal is easily achieved through this approach as it allows excellent exposure of the lateral IAC and CPA with minimal retraction of the cerebellum (You, Zhang, Lu, & Liu, 2013). Access to the IAC is achieved by drilling through the structures of the inner ear labyrinth; therefore hearing is inherently sacrificed during the course of the procedure (Jackler & Pitts, 1992).

Hearing loss remains one of the most prevalent complications of vestibular schwannoma surgery, despite the significant advances in surgical techniques and the use of intraoperative auditory monitoring. Within the literature, the rates of hearing preservation have been reported to be between 31 to 67% (Arriaga, Chen, & Fukushima, 1997; Darwish, Bird et al., 2005; Glasscock III, Hays, Minor, Haynes, & Carrasco, 1993; Matthies & Samii, 1997; Maw, Coakham, Ayoub, & Butler, 2003; Samii & Matthies, 1997b; Sanna, Khrais, Piccirillo, Russo, & Augurio, 2004). However, it is difficult to make comparisons between the reported rates of hearing preservation because the size of tumours, preoperative hearing status, experience of the surgical team, and criteria used to define preserved hearing is greatly varied between the studies.

In addition to the loss of hearing, vestibular schwannoma surgery carries the risk of facial paresis or weakness (8 – 16%), leaking of cerebrospinal fluid (CSF) (2 – 4%), CPA haematoma (0.6%), and meningitis (0.14%) (Samii & Matthies, 1997b; Sanna, et al., 2004; Yamakami et al., 2004).

In the past, loss of facial nerve function was a significant postoperative complication. However, the incidence of facial nerve injury has shown a significant decline in more recent years following the use of intraoperative electromyography monitoring to detect and minimize facial nerve injury. The current rates of facial nerve preservation have been reported to be between 88% - 95% (Maw et al., 2003; Tonn et al., 2000; Youssef & Downes, 2009). Following the success of facial nerve monitoring during vestibular schwannoma surgery, researchers began to focus on monitoring of auditory function intraoperatively to improve rates of hearing preservation. Although intraoperative auditory monitoring has led to significant improvements of postoperative hearing, near complete preservation of hearing has yet to be achieved.

1.6 Electrophysiological measures of auditory function

Auditory function can be monitored throughout the surgical procedure using a number of electrophysiological techniques. In this pilot study, a combination of these electrophysiological techniques are utilised to objectively assess changes in the patient's auditory function during vestibular schwannoma surgery; therefore, a discussion of these techniques is warranted.

1.6.1 Electrocochleography (ECochG)

ECochG, first described in the 1930s, is a method of recording auditory evoked potentials from cochlea and the distal cochlear nerve (Hallpike & Rawdon-Smith, 1934; Wever & Bray, 1930). As depicted in Figure 5, the ECochG response has three primary components: the cochlear microphonic (CM), summating potential (SP), and compound action potential (CAP). These individual response components provide a wealth of information, where the first two responses reflect the function of the cochlea at the level of the hair cells, and the third response, the CAP, reflects activity from the most distal portion of

the cochlear nerve (Hall, 2006). The individual components may therefore be used to differentiate between cochlear and neural sites of impairment. However, the neural action potential component of the ECochG response only reflects the function integrity of the most distal portion of the cochlear nerve; therefore it cannot detect any disruptions which may be occurring at the proximal, intracranial portion of the cochlear nerve (Schmerber, Lavieille, Dumas, & Herve, 2004).

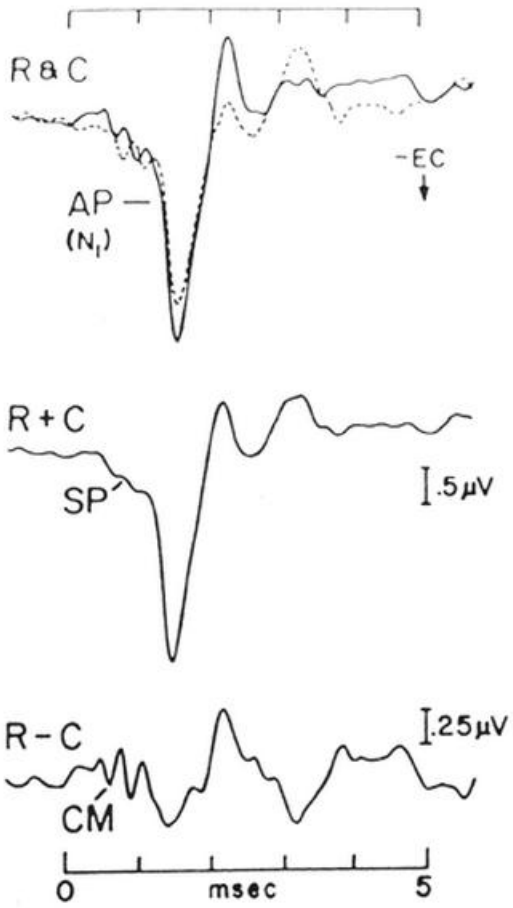

Figure 5: The components of the human electrocochleogram evoked by click stimuli. The top trace displays cochlear responses to Rarefaction (R) and Condensation (C) polarity clicks. The middle trace shows the summed responses, which enhances the Summating Potential (SP) and Action Potential (AP). Subtracting the R and C responses (bottom trace), enhances the Cochlear Microphonic (CM) component (ASHA, 1988).

Cochlear Microphonic (CM)

The cochlear microphonic is an alternating current (AC) electrical potential which reflects the instantaneous displacement of the OHC hair bundles (Dallos & Cheatham, 1976). This oscillating potential is primarily produced by the spatial summation of the OHC receptor currents, with a minimal contribution from the IHCs (Choi, Chertoff, Bian, & Lerner, 2004; Dallos & Wang, 1974; Patuzzi, Yates, & Johnstone, 1989). The frequency of the CM response mimics that of the acoustic stimulus, and the amplitude increases proportional to the stimulus intensity up to moderate intensity levels (Patuzzi et al., 1989). At high intensity levels the CM response becomes saturated and shows very little alteration (Johnstone, Patuzzi, & Yates, 1986). Due its physiological origins, the CM component of the ECochG waveform changes polarity when the phase of the stimulus is inverted (Hall, 2006). Therefore, the response will be minimized when an alternating stimulus condition is employed.

Summating Potential (SP)

The summating potential (SP) is a sustained direct current (DC) potential which reflects the non-linearity and asymmetric distortion of the hair cell response (Choi et al., 2004; Zheng, Ding, McFadden, & Henderson, 1997). The greatest contributor to this response is the IHCs of the organ of Corti, with a smaller contribution coming from the OHCs (Durrant, Wang, Ding, & Salvi, 1998; Zheng et al., 1997). Much like the CM, the SP component imitates the stimulus waveform; however in the case of the SP it is a rectified, DC version of the stimulus which reflects the temporal stimulus envelope (Dallos, 1973). The SP is observed as a unidirectional shift in the ECochG baseline preceding the CAP of the eighth nerve.

The polarity of the SP is dependent on a complex interaction between the site of the recording electrode, and the frequency and intensity of the stimulus (Davis, Deatherage, Eldredge, & Smith, 1958; Van Deelen & Smoorenburg, 1986).

Compound Action Potential (CAP)

The compound action potential (CAP) represents the summed response of the synchronous action potential firing from thousands of cochlear nerve fibres (Ferraro, 2000). The CAP is the first neural response recorded from the cochlea, and is typically characterised by a large negative peak (N1) followed by a positive peak (P1) and, in some cases, a secondary negative peak (N2) (Gibson & Beagley, 1976). In human ECochG recordings, the most dominant peak (N1) represents the activity of the most distal portion of the auditory nerve as it exits the cochlear apparatus, but not the intracranial portion of the nerve (Schlake et al., 2001).

The auditory evoked potentials generated at the cochlea and cochlear nerve dissipate as they get further from the site of generation; therefore, the location of the recording electrode is a critical factor in the measurement of the ECochG response. The recording electrode may be located in the external ear canal; against the tympanic membrane; or at the round window or promontory of the cochlea. The most frequently used electrode approach is transtympanic, where the recording electrode is passed through the tympanic membrane and placed against the promontory or round window of the cochlea. As the electrode sits adjacent to the ECochG response generators, the recordings obtained are large in amplitude (in the order of 20 to 40 μV at high stimulation intensities) (Ruth, Lambert, & Ferraro, 1988). The amplitude of the transtympanic response is almost ten-fold greater than the amplitude of the recordings obtained at the tympanic membrane (Noguchi, Nishida, & Komatsuzaki, 1999).

Rapid onset acoustic clicks are typically used in the clinical measurement of the ECochG response (Hall, 2006). The click stimulus has an almost instantaneous onset and broadband frequency response, which enables the synchronous activation of a large number of cells along the cochlear partition and within the modiolar nerve trunk (Ferraro, 2000). However, there has been increasing interest in the utility of the tone-burst ECochG in the diagnosis of Ménière's disease and intraoperative monitoring of auditory function (Conlon, 2000; Iseli & Gibson, 2010; Mandalà, Colletti, & Colletti, 2011). Tone-burst stimuli allow the clinician to obtain a more frequency-specific view of the patient's auditory function, and generate an enhanced SP which significantly increases the sensitivity of the test for diagnosing hydrops (Attias, Nageris, Ralph, Vajda, & Rappaport, 2008; Gibson, 2009).

The primary measurement parameters of the ECochG response are the amplitude and latency of the response components. The component amplitude is the most typically analysed parameter, and can be measured from a single point or a baseline reference point. Within the literature, controversy still exists in regards to which measurement technique is the best for determining the component amplitudes (Coats, 1986; Ferraro, 2000; Hall, 2006; Ruth et al., 1988). Ferraro advocates for the single point method on the basis of its simplicity. In this method, the amplitude of the response component is measured from the leading edge of the component, and from the peak to the trough.

It is important to note that the CM and stimulus artefact can be relatively large, and may obscure or interfere with the measurement of the CAP or SP responses within the waveform. As the CM follows the polarity of the stimulus, summing or averaging of the ECochG in response to stimuli of alternating polarity can be used to cancel out the CM and stimulus artefact and consequently eliminate the interference in the recording of the CAP and SP (Ferraro, 2000).

1.6.2 Auditory brainstem response (ABR)

The ABR was one of the first electrophysiological techniques used to monitor auditory function during vestibular schwannoma surgery, and remains common practice in surgery today. The ABR provides an objective measure of the functional integrity of the ascending auditory system from the distal cochlear nerve through to the auditory brainstem nuclei (Don, Ponton, Eggermont, & Kwong, 1998).

The typical ABR response, first described by Jewett et al. in 1970, consists of seven voltage deflections occurring within 15 ms of an abrupt acoustic stimulus (as shown in Figure 6). These deflections in the waveform represent far-field synchronous neural activity from the eighth cranial nerve through to the brainstem (Don et al., 1998). Several systems of nomenclature have been devised for the labelling of the peaks in the ABR waveform, but the most universally accepted system involves the labelling of the vertex-positive peaks with roman numerals from I to VII (Jewett, Romano, & Williston, 1970; Jewett & Williston, 1971; Roeser, Valente & Hossford-Dunn, 2000). It is generally accepted that wave I represents activity generated at the distal portion of the cochlear nerve, and wave II is generated at the proximal portion of the cochlear nerve as it enters the brainstem (Møller, Jannetta, Bennett, & Møller, 1981). Waves III to V are believed to represent a complex sum of activity from multiple neural generators in the auditory nuclei within the brainstem (Hall, 2006). Waves I, III and V are the most identifiable peaks within the waveform, with wave V being the most robust peak (Kartush, LaRouere, Graham, Bouchard, & Audet, 1991).

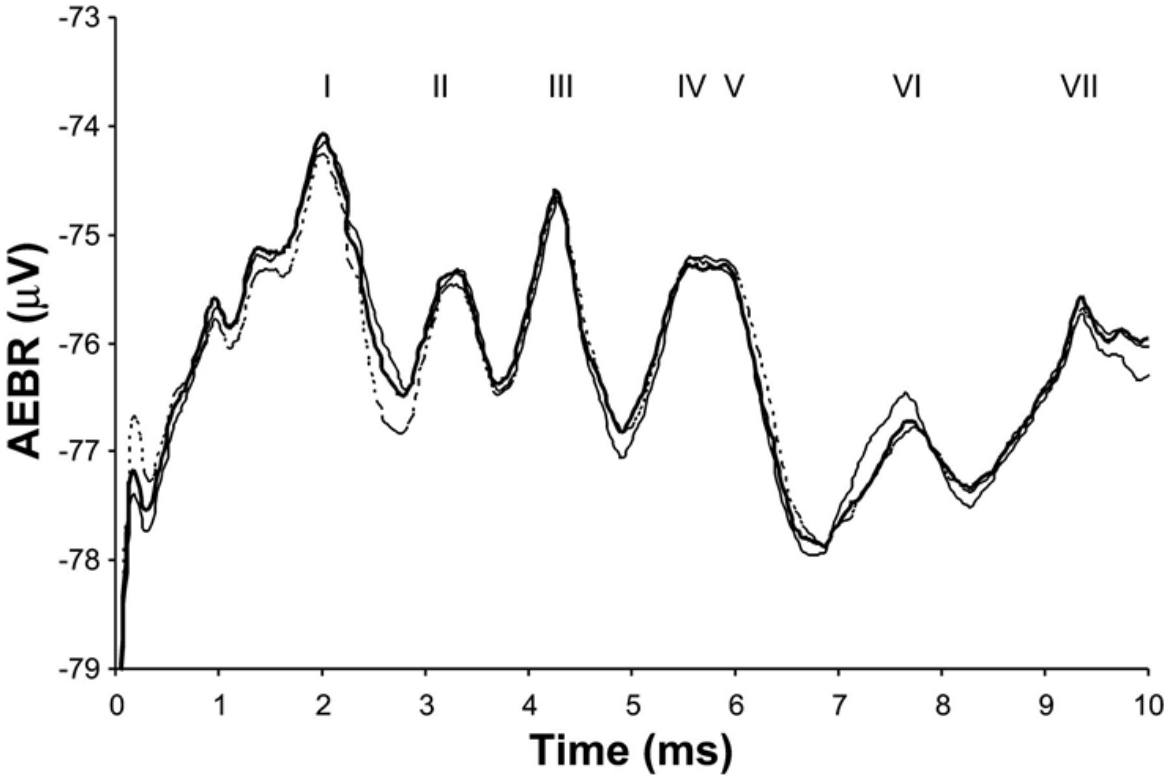

Figure 6: The auditory brainstem response in response to click stimulus (Mekjavic, Rogelj, Radobuljac, & Eiken, 2002).

Similar to the ECochG response, ABRs are best generated with transient stimuli with a rapid onset (Hall, 2006). The rapid onset of the click stimuli generates highly synchronous firing in a large population of auditory nerve fibres, resulting in a more robust recording. While the brief onset evokes a robust response from the nerve fibres, the frequency specificity of the click response is greatly impaired. The frequency spectrum of the click is vastly broader than that of the tone-burst stimuli, meaning that the click stimuli will stimulate a wider portion of the basilar membrane. Although the click is not frequency specific, it has been reported that the click ABR thresholds are highly correlated with the auditory thresholds at 2 and 4 kHz (Folsom, 1984; Gorga et al., 2006; Hyde, Riko, & Malizia, 1990). Apical regions of the cochlea are activated by the click stimuli; however the contribution from these

regions is not reflected in the ABR due to the phase cancellation of apical activity by earlier activity from the more basal, high frequency regions of the cochlea (Don & Kwong, 2009).

The primary measurement parameters of the ABR are the amplitude and latency of its waveform peaks. The absolute latency of the ABR is dictated by a number of mechanical and physiological processes within the ascending auditory system, including the travel time within the cochlea to the site of activation; the synaptic delay from the IHCs to the auditory nerve fibres; the axonal conduction time along the neural pathways; and any intervening synaptic delays within the brainstem pathways responsible for the peak activity (Don et al., 1998). Furthermore, factors such as the transducer type, participant age (developmental) or sex, body temperature and stimulus intensity can influence the latency of the ABR peaks (Fria & Doyle, 1984; Markand et al., 1987; Mochizuki, Go, Ohkubo, Tatara, & Motomura, 1982). Stimulus intensity is frequently manipulated in clinical practice to establish auditory thresholds or to plot an intensity-latency function. A reduction in stimulus intensity will be mirrored by a reduction in response magnitude, and an elongation in the latency of the response. This phenomenon is characteristic of auditory evoked potentials and reflects the decrease in neural activation with a reduction in the acoustic energy activating the cochlear partition. In normal hearing female subjects, wave I occurs approximately 1.6 ms post-stimulus, wave III is expected at approximately 3.7 ms and wave V nears 5.6 ms (Hall, 2006). Due to the effects of the previously mentioned factors which can influence the latency of the ABR, absolute latencies are not consistently accurate measurements and should be used with caution when making inter-subject comparisons (Hall, 2006). Inter-aural comparisons of the absolute peak latency and interpeak latencies are more robust measures of auditory function (Hall, 2006). Interpeak latency indicates the neural delay between the separate sites of generation. Clinically, the most analysed interpeak latency is that between waves I and V.

Prolongation of the wave I-V latency is indicative of a retrocochlear dysfunction (Coats & Martin, 1977).

The amplitude of each ABR peak is defined as the voltage difference between the peak and the subsequent trough. As the ABR is a 'far-field' technique, where the recording electrodes are far removed from the neural generators, the recorded response is small in amplitude and will rarely exceed 1.0 μV (Don & Kwong, 2009). The small amplitude of the response makes it vulnerable to inference by myogenic or electrical noise artefacts. Signal averaging is used to extract and enhance the ABR activity embedded in the background electrical and myogenic activity (Hall, 2006). Amplitude can easily be biased by a number of inter- and intra-subject factors, making it a relatively unreliable diagnostic measure. Between subjects, the amplitude may be varied by the electrode placement, EEG activity or underlying muscle artefact. In the same subject, amplitude measure may also be affected by variations in the level of electrical and myogenic noise (Don & Elberling, 1994).

1.6.3 Direct eighth nerve monitoring (DENM)

Direct eighth nerve monitoring, first introduced by Møller and Jannetta in 1983, is an electrophysiological technique which involves the recording of auditory evoked potentials directly from the vestibulocochlear nerve. The recording of these potentials requires the exposure of the proximal vestibulocochlear nerve complex within the CPA; therefore, DENM may only be used to monitor hearing during surgeries which obtain access to the CPA. In its earlier stages, DENM recordings were hindered by the lack of an electrode which could safely and consistently record the potentials. The initial DENM electrodes were custom-made and typically consisted of a Teflon-insulated wire, smooth silver ball tip, or a cotton wick connected to a very thin wire leading to an electrode box (Colletti et al., 1997; Hall, 2006; Jackson & Roberson Jr, 2000; Møller & Jannetta, 1983b). The key disadvantage of these

electrode designs is that they cannot adequately be secured to the nerve. Changes in the strength of contact between the nerve and electrode surface has the potential to significantly influence the quality of the recordings (Kartush et al., 1991). The practical limitations of these earlier electrode styles has been resolved following the development of an atraumatic, self-retaining electrode designed by Cueva and his colleagues specifically for the use in DENM. The c-like shape of this commercially available electrode allows it to be secured tightly around the nerve, while the opening ensures that the electrode can break free from the nerve in the event of an inadvertent movement (Hall, 2006).

As shown in Figure 7, the DENM response is triphasic waveform with a large positive deflection reflecting the propagation of the compound action potential along the vestibulocochlear nerve towards the brainstem (Aihara et al., 2009; Kartush et al., 1991). The cochlear nerve action potential (CNAP) is analogous to the CAP of the ECochG, differing only by the location along the cochlear nerve at which the response is recorded. The small troughs in the recorded activity which occur before and after the CNAP response are produced by the volley of neural activity travelling along the nerve towards the recording electrode and movement of the neural potentials away from the recording electrode, respectively (Roberson, Senne, Brackmann, Hitselberger, & Saunders, 1996). Similar to the ECochG and ABR, the DENM is best evoked with a transient acoustic stimulus such as the click. The brief onset of the click stimulus evokes highly synchronous firing in numerous auditory nerve fibres. To obtain more frequency-specific information about the functional integrity of the eighth nerve, tone-burst stimuli may also be used to evoke the DENM response (Jannetta, Møller, & Møller, 1984; Møller & Jannetta, 1983b).

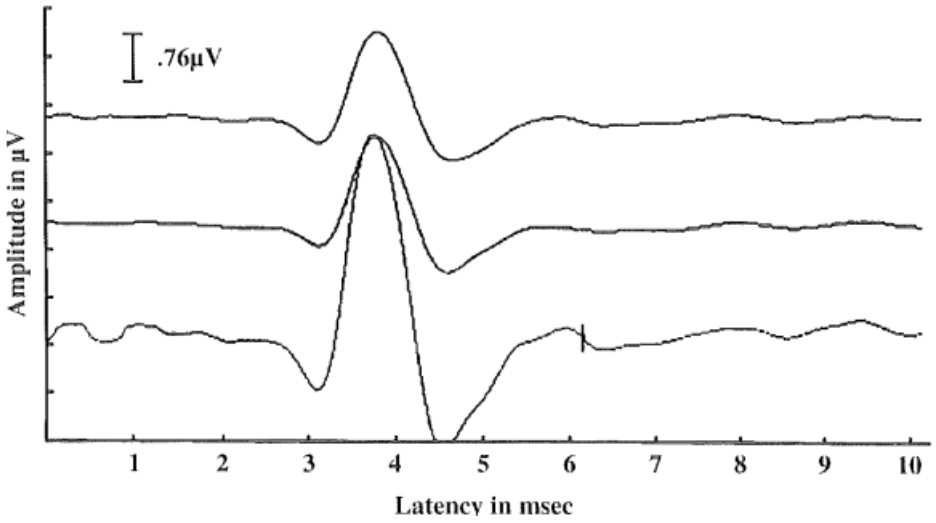

Figure 7: Direct eighth nerve monitoring (DENM) waveform obtained during vestibular schwannoma surgery. The three waveforms represent recordings from different electrode locations; with the top tracing from the internal auditory canal; middle from directly over the carotid artery; and bottom obtained alongside the eighth nerve (Roberson et al. 1996).

Measures of amplitude and latency are used in the analysis of the DENM response. The amplitude of the CNAP is measured from the leading edge of the response, and is the voltage difference between the trough and subsequent peak of the response. The amplitude of the DENM has been reported to range from 5 μV to 70 μV, depending on the patient's hearing status (Cueva, Morris, & Prioleau, 1998). As this is a very large amplitude response, very few averages are required to obtain a robust and clear waveform (Aihara et al., 2009). During surgery, DENM potentials are able to be recorded with 2 to 5 seconds, which allows for almost real-time monitoring of auditory function along the cochlear nerve (Battista et al., 2000; Danner et al., 2004). The latency of the N1 response is, in part, dependent on the location at which the recording electrode is placed along the eighth nerve. As the electrode moves further from the cochlea and towards the brainstem, the CNAP latency elongates (Battista et al., 2000). Therefore, when analysing the latency of the N1 component intraoperatively, the latency of the response must be compared against the subjects own

baseline recordings. A change in latency of 0.5 ms or greater has been used intraoperatively in vestibular schwannoma surgery as an indication of auditory dysfunction, where this change was deemed significant enough to alert the surgeon (Battista et al., 2000; Colletti et al., 1997).

1.7 Intraoperative auditory monitoring

Intraoperative monitoring of auditory function has been implemented in vestibular schwannoma surgery for a number of decades with the aim of improving rates of hearing preservation. Electrophysiological measures of auditory function, such as ABR, ECochG, or DENM, have allowed researchers and clinicians to objectively monitor the function of the ascending auditory pathway during the course of the surgical procedure. Intraoperative monitoring of auditory function provides the surgeons with real-time feedback about the functional integrity of the auditory system, allowing them to identify when operative damage has occurred and modify their techniques accordingly to prevent any further auditory damage (Colletti et al., 2000; Jackson & Roberson Jr, 2000; Silverstein, McDaniel, & Norrell, 1985). In addition to this, intraoperative monitoring has been used within the literature to investigate the potential mechanisms of hearing loss, and to identify the surgical manoeuvres that carry the greatest risk to hearing (Battista et al., 2000; Colletti et al., 1997; Colletti, Fiorino, Mocella, & Policante, 1998; Gouveris & Mann, 2009). Each of the electrophysiological techniques used in the monitoring of auditory function have their own unique advantages and disadvantages, which will be outlined below.

The ABR is the most widely used technique for intraoperative monitoring. While this electrophysiological technique does provide a non-invasive method of monitoring the integrity of a large portion of the ascending auditory pathway, the recordings are extremely vulnerable to interference from the electrical noise within the operating theatre. As the ABR

response is a far-field recording, the amplitude of the response is very small and usually requires extensive signal averaging which may extend out to 3 to 5 minutes intraoperatively (Battista et al., 2000; Gouveris & Mann, 2009). This extensive delay almost negates the usefulness of this auditory monitoring technique as the surgeon is often left guessing which surgical manoeuvre during that time had led to the aberrant change in auditory function (Danner et al., 2004; Lenarz & Ernst, 1992; Schmerber et al., 2004). In addition to this, the presence or absence of the ABR intraoperatively is poorly correlated with postoperative hearing, with reports of patients having good postoperative hearing despite the loss of the ABR response intraoperatively (Roberson, Jackson, & Mcauley, 1999). Such findings indicate that intraoperative changes in the ABR response may not truly reflect the severity of the changes of the integrity of the auditory system.

The need for more immediate information about the auditory nerve integrity led to the development of direct eighth nerve monitoring (Danner et al., 2004). As these recordings are obtained directly from the site of neural generation, the auditory evoked CNAP response is large in amplitude and requires minimal signal averaging. Robust DENM recordings may therefore be obtained within 5 s in the operating theatre environment, which provides surgeons with near real-time monitoring of the auditory system and enables them to make quick responses to these aberrant changes in hearing function (Battista et al., 2000; Cueva et al., 1998; Silverstein et al., 1985). An inherent complication of the DENM recording technique, however, is that recordings cannot be commenced until the CPA is opened and the cochlear nerve has been exposed and identified. This delayed placement of the recording electrode means that functional integrity of the auditory system cannot be monitored during the earlier stages of the surgery or in the final stages of the surgery where the electrode must be removed for closure of the surgical site. In addition to this, the placement of the electrode may interfere with the surgical site and obscure the surgeon's view of the CPA.

The final, and least utilised, method of intraoperative monitoring is ECochG. Similar to DENM, ECochG is a near-field recording of auditory evoked potentials. Consistent with this, ECochG responses are large in amplitude, which minimizes the need for extensive signal averaging. During surgery robust ECochG recordings may be obtained within a 10 s time window (Battista et al., 2000; Zappia, Wiet, O'Connor, & Martone, 1996). Although the presence or absence of the ECochG response during vestibular schwannoma surgery has been shown to be closely associated with postoperative hearing, the recorded responses are not able to reflect the function integrity of the peripheral auditory system as a whole (Attias et al., 2008). The recorded ECochG response only represents the auditory function at the cochlea and cochlear nerve; therefore the monitoring of the ECochG in isolation will be unable to detect changes in the function of the proximal portion of the cochlear nerve. In light of this, many authors have argued that the ECochG response is an inappropriate tool for intraoperative monitoring of auditory function (Attias et al., 2008; Schlake et al., 2001). However, there has been some interest in the use of ECochG for research purposes to help understand the potential mechanisms for iatrogenic injury to the auditory system during vestibular schwannoma surgery (Gouveris & Mann, 2009; Levine, Ojemann, Montgomery, & McGaffigan, 1984), as discussed below.

1.8 Potential mechanisms of iatrogenic auditory injury during vestibular schwannoma surgery

Intraoperative monitoring of auditory function has allowed researchers to investigate the stages of surgery which are critical for hearing preservation and elucidate the potential mechanisms for iatrogenic auditory injury (Colletti et al., 1997; Gouveris & Mann, 2009). The surgical manoeuvres which have been shown to carry the most risk of the loss of auditory function in the retrosigmoidal approach are: drilling of the IAC, removal of the tumour from the IAC fundus, lateral-to-medial traction of the tumour, electrocautery near the

cochlear nerve, separation of the cochlear nerve from the facial nerve, and stretching of the cochlear nerve directly (Colletti et al., 1997; Gouveris & Mann, 2009; Schmerber et al., 2004). The underlying pathophysiological mechanism for the loss of hearing during vestibular schwannoma is not fully understood; however, with the evidence from a number of animal studies, researchers have isolated the iatrogenic damage to three potential mechanisms; vascular disruption, neural injury, and/or labyrinthine damage (Colletti et al., 1997; Sekiya, Møller, & Jannetta, 1986).

1.8.1 Vascular disruption

Disruption of the blood supply to the cochlea and cochlear nerve, via vascular occlusion, rupture, or vasospasm, is believed to be the predominant cause of auditory impairment during retrosigmoid vestibular schwannoma surgery (Colletti et al., 1997). The microvessels which stem from the IAA are incredibly vulnerable during surgery as they are small in size and relatively difficult to identify (Gouveris & Mann, 2009). In addition to this, the microvasculature may be tightly involved with the tumour complex, where total removal of the tumour inevitably compromises the integrity of the branches of the IAA (Eckermeier, Pirsig, & Mueller, 1979).

In animal models of CPA surgery, manipulations of the cochlear nerve have been shown to significantly impair the microvasculature both at the site of manipulation, and at locations remote from the surgical site (Sekiya et al., 1986). Damage to the microvasculature, as identified by postoperative haemorrhages in the fixed cochlear nerve tissue, was observed in those animals which had significant reductions in the auditory evoked potentials intraoperatively (Sekiya et al., 1986). These findings indicate that there may be a strong relationship between the disruption of the microcirculation and the loss auditory function during vestibular schwannoma surgery.

The disruption of the microvessels near the cochlear nerve not only has implications for the cochlear nerve function, but may also result in injury to the cochlear apparatus. As the IAA and its respective branches provide end circulation to the inner ear, it can be expected that disruption of the IAA will produce irreversible damage to the cochlear hair cells and supporting cells, and therefore hearing (Roberson et al., 1996). The damage which occurs within the cochlear tissue in response to ischemia is said to be due to pathological changes in the cellular morphology, which is induced by a diminished metabolic activity of the cells them self (Billett, Thorne, & Gavin, 1989). As the stria vascularis is a highly vascularised structure within the cochlea, cochlear ischemia will also severely impact the metabolic function of the stria vascularis, and consequently the maintenance of the endocochlear potential (Nakashima et al., 2003). In an animal study by Sekiya et al (2000), significant deteriorations in the ECochG potentials were observed following compression of the IAA; indicating that ischemia of the cochlea can lead to a marked decline in auditory function.

1.8.2 Neural injury

Many of the surgical manoeuvres during retrosigmoidal vestibular schwannoma surgery occur within close proximity to the seventh and eighth cranial nerves in the IAC and CPA. In some instances, the nerve complexes will be directly manipulated to allow the surgeon access to the tumour or they may be manipulated during dissection of the tumour complex itself (Ojemann, 2001). Despite significant advances in microsurgical techniques and increased specialisation of the surgical team, the cochlear nerve remains highly susceptible to mechanical injury during the surgical procedure. Researchers have postulated that the mechanical injury to the cochlear nerve may be mediated through the stretching, compression, traction, or thermal insult of the nerve (Colletti et al., 1997; Gouveris & Mann, 2009; Sato et al., 2009).

As mentioned previously, as the cochlear nerve enters the CPA the myelin covering of the auditory nerve fibres changes to a oligodendrocyte-generated central myelin (Møller, 2000). In addition to this, the supporting structures which can be found within the peripheral portion of the cochlear nerve appear to be absent in the central portion of the cochlear nerve, which has significant implications for the integrity of the cochlear nerve and its susceptibility to injury during the surgical manipulations performed during vestibular schwannoma surgery (Møller, 2000). The point at which the peripheral myelin changes into central myelin (Obersteiner-Redlich zone) is reported to be the most vulnerable site along the cochlear nerve in animal models of CPA surgery (Bridger & Farkashidy, 1980; Sekiya et al., 1986). The shearing of the peripheral and central myelin cells at the junctional zone was observed in the postoperative morphological examinations, particularly in those animals who had reduced auditory evoked potentials recorded intraoperatively (Sato et al., 2009; Sekiya et al., 1986). The evidence of impaired integrity of the cochlear nerve in those animals who demonstrated reduced auditory function indicates that mechanical trauma to the cochlear nerve may, in part, be the mechanism behind the loss of hearing during vestibular schwannoma surgery.

Researchers also believed that thermal injury during electrocautery and drilling of the IAC may contribute to the loss of auditory function. In the process of electrocautery, a small electric current is used to burn and seal any exposed microvessels to control the bleeding. Experience over a number of years has demonstrated that the cochlear nerve may be severely injured when electrocoagulation is performed within close vicinity of the auditory portion of the eighth nerve (Møller, 2006). As the technique of electrocautery is based on the heating of the venous tissue to prevent excessive bleeding, this heat may spread to the nearby neural tissue. Sustained cauterisation can lead to a rise in local tissue temperature to approximately 45 to 55 °C, at which point protein and macromolecular denaturisation processes will begin to occur (Smith & Smith, 2001). In addition to this, drilling of the temporal IAC bone may

lead to an increase in the local temperature due to frictional forces. Advances in microsurgical techniques, including the use of constant artificial cerebrospinal fluid irrigation during the drilling and reducing the drilling time to short intermittent spurts, have lead researchers to believe that thermal insult from IAC drilling does not play a significant role in the iatrogenic auditory impairment during vestibular schwannoma surgery (Schmerber et al., 2004).

When discussing damage to the cochlear nerve structures, it is important to remember that the iatrogenic changes in auditory neuron function are not simply isolated to the ascending auditory pathway. Damage to the auditory neural structures will also affect the efferent auditory pathways.

1.8.3 Labyrinthine destruction

Changes in the auditory evoked cochlear potentials during retrosigmoidal vestibular schwannoma have been well reported within the literature; indicating that the mechanism of iatrogenic auditory impairment may, in part, involve the cochlea (Colletti et al., 1998; Gouveris & Mann, 2009; Schlake et al., 2001; Zappia et al., 1996). In addition to the vascular disruption of cochlear blood flow, mechanical trauma of the labyrinth structure may severely interrupt cochlear function. Due to the close anatomical relationship of the IAC and bony labyrinth, the inner ear structures are at great risk of being damaged during the drilling procedures of retrosigmoid approach. Fenestration of the inner ear labyrinth has been reported in up to 30% of patients who underwent retrosigmoidal vestibular schwannoma surgery (Colletti et al., 1997; Tatagiba, Samii, Matthies, El Azm, & Schonmayr, 1992). The opening of the labyrinth has been correlated with varying degrees of hearing loss, with reports of up to half of the patients suffering postoperative anacusis (Colletti et al., 1997). The hearing loss experienced in patients with labyrinth fenestration is not simply limited to

sensorineural. In a recent case-series by Scarlett et al. (2008), a pseudo-conductive hearing loss was noted in four patients who had confirmed dehiscence of the labyrinthine structure. This is one of the first reports of a postoperative conductive and/or mixed hearing loss of patients who have undergone vestibular schwannoma surgery.

Drilling procedures earlier in the course of the surgery have also been associated with the loss of auditory evoked potentials (Gouveris & Mann, 2009). As this has occurred prior to the opening of the CPA, it can be said that the loss of auditory evoked potentials is not due to vascular disruption or mechanical injury to the labyrinth. Researchers have hypothesised that this loss of auditory evoked potentials in the earlier stages of the surgery is due to noise-induced cochlear damage or displacement of the ossicular chain (Gouveris & Mann, 2009).

1.9 Delayed postoperative hearing loss

Iatrogenic hearing loss is not simply isolated to the intraoperative period. Within the literature, a number of papers have reported that auditory function may further deteriorate in the early postoperative period (Fahlbusch, Neu, & Strauss, 1998; Neu, Strauss, Romstöck, Bischoff, & Fahlbusch, 1999; Strauss et al., 1991; Umezu, Aiba, Tsuchida, & Seki, 1996). Early postoperative hearing loss has been reported in approximately 10 to 26% of patients who underwent vestibular schwannoma surgery (Babbage, Feldman, O'Beirne, MacFarlane, & Bird, 2013; Neu et al., 1999; Strauss et al., 1991). In those patients, almost all suffered delayed postoperative anacusis.

Given that the hearing loss continues to deteriorate after the completion of the surgical procedure, it has been suggested that the pathological mechanism is initiated during surgery and continues thereafter (Neu et al., 1999). In a large proportion of the patients who suffered delayed anacusis, the pattern of intraoperative ABR recordings showed a gradual loss of wave V, while wave I remained relatively stable. This indicates that the initial

intraoperative damage may be isolated to the cochlear nerve. However, the eventual loss of wave I potentials during the early postoperative period suggests that gradual damage to the cochlear structures and most distal portion of the nerve may ultimately transpire.

Similar to that of the intraoperative mechanisms for hearing loss, the pathological mechanisms behind the early postoperative hearing loss are relatively unknown; however, several theories have been discussed within the literature. Specifically, researchers postulate that the delayed deterioration in hearing is due to retrograde degeneration following the disruption of the IAA microvasculature (Strauss et al., 2001); delayed excitotoxicity of the cochlear nerve fibres secondary to mechanical injury or cochlear nerve ischemia (Sekiya, Yagihashi, Asano, & Suzuki, 2002; Shimamura, Sekiya, Yagihashi, & Suzuki, 2002); or postoperative nerve oedema which may lead to secondary occlusion of the IAA due to the accumulation of fluid within the narrow IAC space (Sekiya, Suzuki, & Iwabuchi, 1990).

1.10 Site of the auditory system most vulnerable to iatrogenic injury

While researchers have begun to gain some insight to the pathophysiological mechanisms of iatrogenic hearing loss during vestibular schwannoma surgery, the portion of the auditory system which is most sensitive to this damage has yet to be investigated in depth. Such investigations may provide researchers with an indication of which portion of the auditory system is most vulnerable to injury during the surgical procedure.

In an early study by Levine et al. (1984), auditory evoked potentials were recorded intraoperatively with the aim of improving the likelihood of hearing preservation during vestibular schwannoma surgery and to gain some insight in to the mechanism of iatrogenic hearing loss. Auditory function was monitored intraoperatively using a combination of ECochG and ABR recordings. In the six cases presented, partial or total loss of the later ABR waveforms was reported in all of the cases; indicating significant damage to the neural

structures of the auditory system, proximal to the modiolar cochlear nerve trunk. In contrast, only four out of the six cases demonstrated changes in the cochlear potentials intraoperatively, where a decrease in the CM and CAP were observed in three cases, and a transient decrease of the CM and CAP was observed in one case which recovered in less than 10 minutes.

The intraoperative recordings from the patient with a transient loss of cochlear function are presented in Figure 8. The recordings outlined in this figure were obtained during the 42 minutes in which the vestibular schwannoma was being dissected off the underlying nerves in the IAC. Approximately 10 minutes into this procedure, marked changes in the ABR response were observed with the latency of the latter waves extending, and eventually the ABR disappeared entirely. During this time, the CAP response remained relatively stable. Deterioration of the CAP response was observed at a later stage (14.2 to 14.7 minutes). However, the response was recovered within 10 minutes and persisted for the duration of the surgery. From these findings, it can be predicted that iatrogenic injury predominantly occurs at the level of the cochlear nerve. The transient loss of CAP potential does however suggest minor damage to the cochlea did occur.

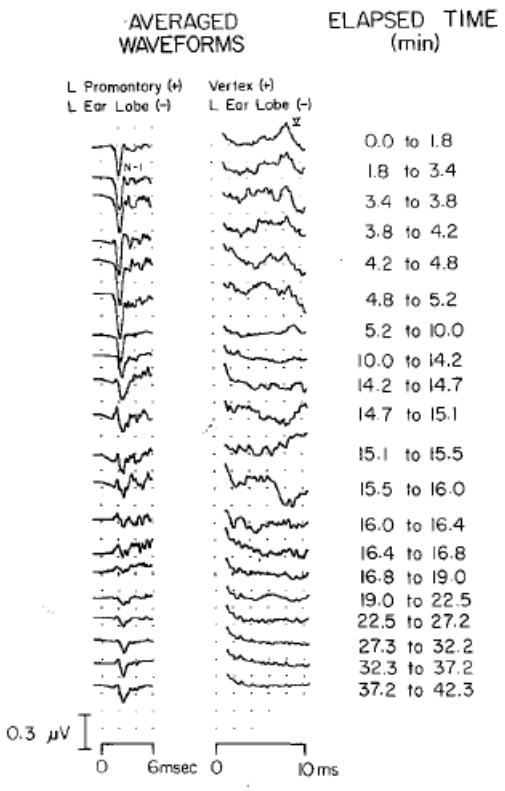

Figure 8: Intraoperative recordings of auditory function obtained during the separation of the tumour from the underlying nerve complexes. Auditory function was measured using a combination of electrocochleography and auditory brainstem response recordings (presented in the left and right panels, respectively) (Levine et al., 1984).

The patterns of auditory impairment in the study by Levine et al., (1984) suggest that the neural structures may be more vulnerable to damage than the cochlear structures. However, the small sample size of this study, and the relatively poor resolution of the auditory evoked potentials does limit the results of this study. In addition to this, significant advances in the microsurgical techniques have occurred since the 1980s. In modern vestibular schwannoma surgery, the manoeuvres which may result in damage of the auditory structures may be different to those 30 years previously.

In a more recent study by Colletti et al. (1997), which investigated the site of auditory damage during vestibular schwannoma surgery, the prevalence of iatrogenic injury at the

cochlear nerve was found to be essentially the same as that at the labyrinth (21.3% and 23.4%, respectively). These findings contradict those of the Levine et al. (1984) study and indicate that there may be no difference in the susceptibility of these two structures to iatrogenic injury. However, the methodology used by Colletti and his colleagues significantly limits the validity of these results. The prevalence of intraoperative damage to the auditory structures was determined by examining changes in the DENM response in regards to the surgical manoeuvres which preceded these changes. The conclusions about the site of damage would therefore be based on the presumption that certain surgical manoeuvres lead to dysfunction at a specific site of the auditory system. However, as discussed previously, a number of the surgical manoeuvres used in the retrosigmoidal approach carry risk to both the cochlea and cochlear nerve. To be able to differentiate between cochlea and cochlear nerve dysfunction, recordings of auditory function should be obtained at these two different portions of the auditory system. As Colletti et al (1997) only employed one modality of auditory monitoring, the loss of auditory function cannot be isolated to the cochlea or cochlear nerve.

1.11 Potential treatments for intraoperative hearing loss

Intraoperative treatment of the auditory damage which may be incurred during vestibular schwannoma surgery has received some attention in the literature over the years. Investigating the effects of pharmaceuticals on the intraoperative loss of auditory function may provide additional insight into the mechanisms and location of iatrogenic injury, and has the potential to contribute towards the goal of attaining more favourable rates of hearing preservation in the future. In the literature, researchers have predominantly focused on the intraoperative use vasoactive substances, such as *papaverine,* with the hope that it may restore vascular flow to the auditory structures in the event of decreased auditory function

(Bischoff, Romstöck, Fahlbusch, Buchfelder, & Strauss, 2008; Morawski et al., 2003; Roberson et al., 1996).

In a study by Roberson et al. (1996), topical application of papaverine on a surgical sponge (Gelfoam) directly on the contents of the IAC was completed following the deterioration of the CNAP response intraoperatively. The authors stated that the pharmalogical intervention improved waveform recovery in a number of the patients; however, they have not stated the rates of successful recovery in their cases series. Several other researchers have, however, failed to find any significant improvements in intraoperative or postoperative auditory function following the application of vasoactive substances during vestibular schwannoma surgery; indicating that the mechanism of hearing loss may not solely be attributable to vascular interruption in all patients (Bischoff et al., 2008; Scheller, Richter, Engelhardt, Köenig, & Antoniadis, 2007).

In addition to the vasoactive substances, researchers have investigated the potential benefits of a calcium channel inhibitors. Injury of the cochlear nerve and its circulation can result in a large influx of glutamate into the damaged cochlear neurons. The influx of glutamate will result in excessive activation of the excitatory neurotransmitter-gated calcium channels leading to a profound influx of extracellular calcium into the cells. An excessive build up of intracellular calcium in the auditory neurons will lead to activation of a number of calcium-activated enzymes, triggering apoptotic pathways within the cell, and eventually leading to neural cell death (Sekiya et al., 2001; Shimamura et al., 2002). Researchers hypothesise that the use of calcium channel antagonists may help reduce intracellular calcium overload which is an essential step in the prevention of further auditory nerve fibre death (Scheller et al., 2007). In support of this, Sekiya et al. (2002) noted that the perioperative administration of nidodipine, a calcium channel antagonist, to a group of rats significantly reduced traumatic impact following compression injury of the cochlear nerve within the

CPA. Consistent with this, a study by Straus (2001) which investigated the effect of postoperative nimodipine administration on the rates of hearing preservation in patients who had undergone vestibular schwannoma surgery, found that the group which had been administrated to calcium-channel antagonist had markedly improved postoperative hearing outcomes as compared to the control group (66% hearing preservation as compared to 30%, respectively).

1.12 Aims and Hypothesis

The exact mechanism and location of the iatrogenic hearing loss which may occur during vestibular schwannoma surgery is not well understood within the literature. The present study aimed to investigate the site of iatrogenic hearing loss by continuously monitoring patterns of cochlear and cochlear nerve responses during vestibular schwannoma surgery. A combination of two near-field electrophysiological techniques, ECochG and DENM, was used intraoperatively to allow the researchers to reliably monitor fine changes in the auditory function at the cochlea and the cochlear nerve. In particular, it was hypothesised that the use of these techniques would allow the researchers to determine if the site of iatrogenic hearing loss is predominantly cochlear or neural in origin. To our knowledge, this is the first study to investigate the site of operative injury during vestibular schwannoma surgery using such sensitive measures of auditory function. While Levine et al. (1984) did publish a case series investigating the mechanism and site of hearing loss, the techniques used in this study were limited in their sensitivity and the study sample was relatively small.

For the recording of auditory function during surgery, we had intended to use a newly developed, custom-made auditory evoked monitoring system. This monitoring system would allow continuous recordings of cochlear and cochlear nerve function to be obtained via ECochG and DENM simultaneously. In addition to this, the software is capable of measuring

a wide range of frequencies within a small time window. This would allow the researchers to observe changes in auditory function across a broad range of frequencies. To our knowledge, this would be the first investigation to obtain such refined information about the changes in auditory function during otologic surgeries.

Based upon the limited evidence within the literature, it is hypothesised that the site of iatrogenic injury will be predominantly isolated to the cochlear nerve. Damage of the cochlear nerve will be demonstrated by the deterioration of the DENM response in the presence of preserved ECochG potentials. However, it is expected that in a lesser portion of the participants, some deterioration in the cochlear function may also be observed as changes in the microvasculature can have significant effects at both the cochlea and cochlear nerve.

Chapter Two: Verification of Intraoperative Equipment

During the development of commercially available auditory evoked potential measurement systems, the hardware components of the system must undergo a number of calibrations. These calibrations allow the developers to quantify the acoustic and electrical output of the system and integrate these values in to the software to ensure that the intended output of the system and true acoustic output are consistent with each other. In auditory evoked potential measurement systems, one of the key elements of the system is the generation of the acoustic output. In these systems the acoustic output is generated by a sound card and is typically presented to the patient via headphones or a bone-conduction transducer.

As part of the development of the new intraoperative monitoring software, the acoustic output of the X-Fi Surround 5.1 Pro sound card in combination with two models of the Etymotic Research insert earphones (ER-2A or ER-3A) was analysed to determine the maximal acoustic output of the two different acoustic pairings across a range of frequencies.

2.1 Methods

2.1.1 Experimental Set-up

The maximal acoustic output of the X-Fi sound card and ER-3A insert earphones was compared to the output of the X-Fi sound card and ER-2A earphones. The experimental set up for the acoustic analyses is illustrated in Figure 9. The acoustic output of the two hardware systems was measured using a calibrated Axiom Audioscan test box in a manual setting. The test-box speaker was turned off to ensure that there was no extraneous output from the speaker which could have influenced the sound level recordings. The acoustic output from the acoustic hardware pairings was measured by the test box coupler microphone and filtered with an A-weighted filter. A HA1 2-cc coupler was fitted to the coupler microphone. The use

of a fixed-volume coupler ensured that the volume of the cavity between the sound source and microphone was highly consistent; whereby the apparatus is able to act as a sound pressure level meter (Dillon, 2012).

The acoustic stimuli were generated by the sound card and presented to the coupler microphone using one of the two models of Etymotic Research earphones fitted with a paediatric (10 mm) foam tip. The tip of the earphone was inserted into the entrance of the coupler at a depth of 2mm, where the depth of insertion was marked out on the foam tip to ensure consistency between trials. The coupler microphone and insert earphones were placed within the anechoic test box chamber and the chamber was sealed for the duration of testing. Care was taken during the closure of the test box to ensure that the tubing of the insert earphone was not compressed in anyway, as this would have had a significant effect on the level of the acoustic output.

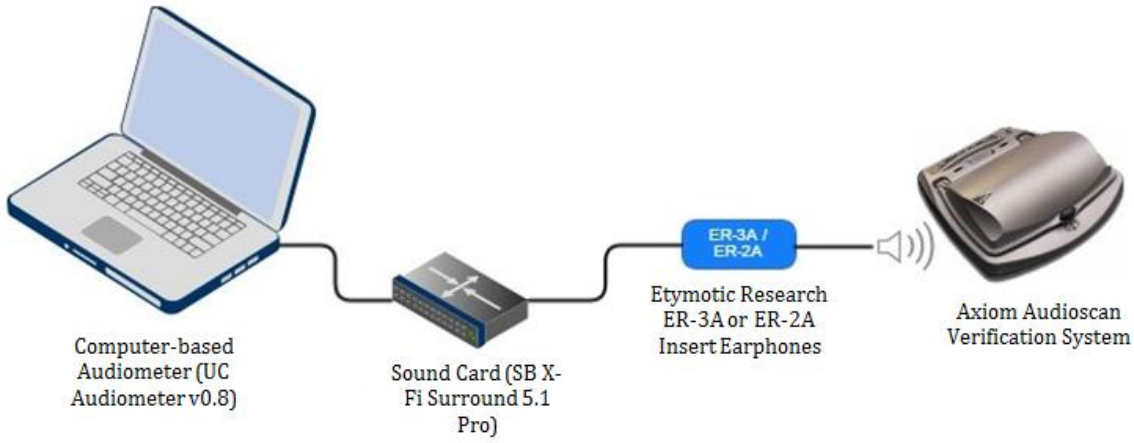

Figure 9: General experimental set-up for measurements of sound pressure level output from the SB X-Fi Surround 5.1 Pro sound card in combination with one of two models of insert earphones (Etymotic Research ER-3A and ER-2A).

2.1.2 Stimuli

A computer-based audiometer (UC Audiometer v0.8 BETA; O'Beirne, 2013) on a laptop computer (HP Elitebook Revolve 810) was used to present the pure-tone stimuli. Stimuli were presented at half-octave frequency intervals ranging from 0.125 kHz to 8 kHz at a level of 6 dB atten. re: maximal output level. The 16-bit sound card had a dynamic range of 96 dB; however the single channel output was attenuated by 6 dB to avoid any potential clipping of the signal when two signals are presented simultaneously. The left and right earphones were tested individually with a total of three trials conducted for each condition.

2.1.3 Data Analysis

The data from the three consecutive trials for each condition were averaged. A series of calculations were conducted on the raw sound pressure level data to convert the recorded output levels from dB (A) to dB SPL. To account for the initial attenuation of the sound card signal, 6 dB was added to each of the raw data points to obtain the maximal output level of an unattenuated system such as the intraoperative monitoring software. A series of frequency-specific conversion factors, outlined in Table.1, were then subtracted from these compensated data points. The resulting data points were expressed in dB SPL.

Table 1: Frequency-specific conversion factors for the conversion of dB (A) sound levels to dB SPL sound levels (IEC International Standard 61672-1, 2002).

Frequency (Hz)	***Conversion Factor (dB A to dB SPL)***
125	-16.19
250	-8.67
500	-3.25
750	-1.07
1000	0.00
1500	0.90
2000	1.20
3000	1.23
4000	0.96
6000	0.05
8000	-1.14

2.2 Results

Figure 10 illustrates the maximum acoustic output of the two models of Etymotic Research insert earphones (ER-3A and ER-2A) in combination with the X-Fi Surround 5.1 pro sound card. The difference between the left and right earphones in each condition was negligible (<0.5 dB), therefore the results from each earphone were averaged together to get a mean output for each earphone model. As shown in Figure 10, the maximum output achieved through the ER-3A earphones was markedly greater than that of the ER-2A earphones. The maximum output of the ER-3A earphones ranged from 69.8 to 118.7 dB SPL and the

maximum output of the ER-2A earphones ranged from 93.6 to 69.8 dB SPL; with the total difference of 25.1 dB between the maximal outputs of the two earphone models. Although the maximum output of the sound card with the ER-2A earphone was lower overall, the ER-2A earphone system exhibited a shallower drop-off at the high-frequency end than the ER-3A earphone system; with the total difference between the minimum and maximum outputs of the ER-2A earphones being almost half that of the ER-3A earphones (total difference in output across the frequency range of 23.8 dB compared to 48.9 dB, respectively). At 8000 Hz, the output of the two acoustic systems converged, where the maximal output was essentially the same for both. However, this convergence may be an inherent characteristic of the recording equipment or the coupler rather than a true reflection of the acoustic output of the hardware pairings at 8000 Hz.

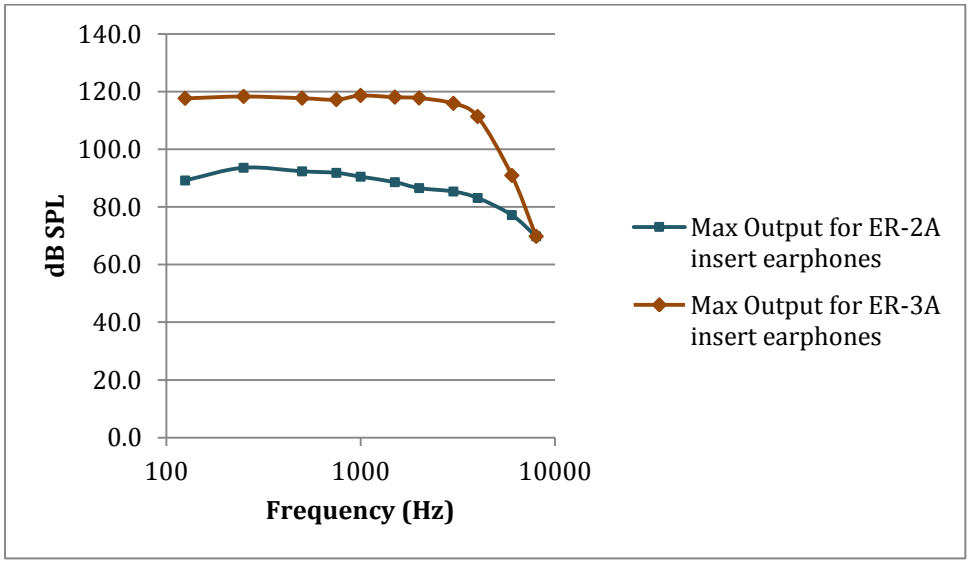

Figure 10: Maximum acoustic output for two models of Etymotic Research insert earphones; ER-2A and ER-3A. Both earphones used in combination with an X-Fi Surround 5.1 Pro sound card. Data is expressed as mean ± standard deviation, n= 3. Acoustic output was measured at half-octave frequencies from 125 Hz to 8000 Hz.

2.3 Discussion

As part of the development of a new auditory evoked potential monitoring system, the maximum output of the soundcard in combination with two models of the Etymotic Research insert earphones was measured. This analysis not only allowed us to obtain recordings of the maximum acoustic output levels to incorporate into the software, but also helped determine which model of earphone would be most suitable to use in the monitoring of auditory evoked potentials during vestibular schwannoma surgery.

In patients with vestibular schwannomas, the degree of preoperative hearing is extremely variable; however, a large proportion of patients will present with 'measureable' hearing (Matthies & Samii, 1997). While some controversy exists within the literature around the definition of 'measurable' hearing, it is most commonly defined as a pure-tone average (PTA) ≥ 50 dB HL and speech recognition scores of 50% or greater (AAO-HNS, 1995). In those patients with excellent measurable hearing, the ER-2A earphones may be used as these patients require less acoustic input to evoke a response, and the broader frequency response of the ER-2A earphones will allows researchers to investigate the changes in auditory function across a broader range of frequencies. However, in a large proportion of patients, hearing will deteriorate during the course of the surgical procedure (Sanna, Khrais, et al., 2004). As hearing thresholds decline, the intensity of the acoustic stimulus will have to be increased to ensure the level reaching the cochlea is enough to evoke a response. It can be observed in the acoustic analyses performed in this study that the maximum output that can be achieved through the ER-2A earphones is relatively low as compared to the ER-3A earphone model. Therefore, if the ER-2A were being used to monitor auditory function intraoperatively and a significant deterioration in hearing did occur, the researchers cannot determine whether the loss in auditory evoked potentials is a true reflection of the loss of auditory function, or simply due to the inability to raise the stimulus levels high enough to

evoke a response. In contrast to this, the ER-3A earphones are able to generate a much higher acoustic output. By producing a greater acoustic output, the ER-3A will be applicable to a greater proportion of the vestibular schwannoma patient population, and will allow researchers to monitor auditory function for a longer period of time if progressive hearing deterioration does occur intraoperatively. Therefore, for the purpose of this study, the combination of the X-Fi sound card and the Etymotic Research ER-3A insert earphone is preferred.

While these analyses allowed the researchers to investigate which model of earphone would be most applicable for monitoring of auditory function during vestibular schwannoma surgeries, the reliability of the sound pressure levels at the highest frequencies is questionable. The deviation of both recordings in the highest frequencies (6 kHz and 8 kHz) is most likely due to the limited frequency response of the recording equipment at high frequencies. The primary function of the Audioscan verification system is to measure the acoustic output of hearing amplification devices such as hearing aids and personal FM systems. The acoustic output of these devices is limited to approximately 6 kHz; therefore the verification system does not need to be highly sensitive to acoustic input above this. To obtain more reliable recordings of the sound pressure levels of the system, especially in the high frequencies, it may have been more preferable to use a specialised sound pressure level meter.

Chapter Three: Investigations into the Site of Iatrogenic Auditory Impairment during Vestibular Schwannoma Surgery

In a 2-month period from December 2014 to January 2015, two patients underwent surgical removal of a vestibular schwannoma via the retrosigmoidal approach at St George's Private Hospital and Dunedin Public Hospital. Both of these participants were undergoing unilateral removal of a vestibular schwannoma and neither of the participants had been diagnosed with Neurofibromatosis II (NF2).

Surgeons operating at both Dunedin Public Hospital and St George's Hospital employ either the translabyrinthine or the retrosigmoidal surgical approach for vestibular schwannoma excision. Candidacy for the retrosigmoidal approach is determined by the location and size of the tumour, and the possibility of residual hearing preservation. Postoperative hearing preservation cannot be achieved through the translabyrinthine approach as this approach results in complete destruction of the cochlear structures. Irrespective of the preoperative hearing thresholds and the possibility of hearing preservation, a number of surgeons have expressed a preference for the retrosigmoidal approach as it enables panoramic visualisation of the CPA and higher rates of facial nerve preservation in large tumours (You et al., 2013). All participants were recruited on the basis that they had some degree of measurable hearing preoperatively and were undergoing vestibular schwannoma surgery via the retrosigmoid approach.

3.1 Participants

The demographic characteristics of the two participants are detailed in Table 2. One participant was male and the other participant was female, aged 47 and 69 years old, respectively. Tumour size was classified based upon the maximal diameter of the extracanicular portion of the vestibular schwannoma on the MRI. Tumours were classified as

being ‘small’ when the maximal extracanicular diameter was less than 15 mm, ‘medium’ when diameter was between 15 mm – 29 mm, and tumours greater than 30 mm in diameter were classed as being ‘large’ (Hara & Kusakari, 2003). Based on this classification, both of the participants’ tumours were classified as being medium in size. All tumours were determined to be histologically benign.

Table 2: Participant demographic characteristics and tumour size

Case	***Sex***	***Age (years)***	***Tumour Side***	***Maximum Tumour Diameter (mm)***	***Tumour Size Classification***
1	M	47	L	25	Medium
2	F	69	R	16	Medium

3.2 Ethical Considerations

Ethical approval from the Southern Health and Disability Ethics Committee was granted on 18th July 2014 (Ethics Ref: 14/STH/92, see Appendix A). Written informed consent was obtained from each participant prior to testing (Appendix B), and participant confidentiality was strictly maintained in accordance with the conditions outlined in the ethics application.

3.3 Outline of General Procedure

All participants had previously undergone MRI examination(s) to confirm the presence of a suspected vestibular schwannoma and to determine the size of the tumour. Audiometric testing had previously been conducted with both of the participants to determine the presence of measurable hearing on the tumour side preoperatively, and consequently the candidacy for attempted hearing preservation via the retrosigmoidal approach.

The testing procedure for this study consisted of three phases: pre- and postoperative audiological assessments, and intraoperative monitoring of auditory function. To ensure consistency, all testing was performed by the author. Placement of equipment within the surgical field was completed by the lead Ear, Nose and Throat (ENT) surgeon and neurosurgeon.

Pre- and Postoperative Audiological Assessments

The participants underwent preoperative audiological assessments within the week prior to their surgery. The postoperative audiological assessments were completed on the day of the participant's discharge from hospital (3 to 5 days postoperative). Both of these audiological assessments were completed in a sound-treated room at the University of Canterbury Speech and Hearing Clinic or at the Audiology Department of Dunedin Public Hospital. The pre- and postoperative test battery included: otoscopy, pure-tone audiometry, speech audiometry, distortion product otoacoustic emissions (DPOAEs), and tympanometry (only preoperatively).

Intraoperative Monitoring of Auditory Function

Intraoperative measurements of the participant's auditory function were recorded throughout the surgical procedure, where practically possible. A combination of ECochG, DENM, and ABR recordings were measured during the surgery to assess the intraoperative patterns of hearing loss and gain some insight into the predominant site of auditory damage during vestibular schwannoma surgery. It had been intended that our newly-developed intraoperative software would be used to record these potentials; however, due to unforeseen technical difficulties it could not be used for the testing of either participant.

Due to the differences in the methodologies used in each case, the cases will be presented individually. A detailed description of the protocols used, and the participant's results will be presented and discussed in each case.

3.4 Case One

The first case of this series was a 47- year old male who was admitted to St George's Hospital for unilateral removal of a left-sided medium vestibular schwannoma via the retrosigmoid approach. The patient was referred to an otolaryngologist following the identification of a significant asymmetry in his hearing sensitivity and reports of unilateral 'ringing' tinnitus in the ear with the poorer hearing sensitivity (left ear). Imaging studies revealed a suspected vestibular schwannoma on the left side with a diameter of 25 mm. The patient decided to have the tumour surgically removed via the retrosigmoid approach to attempt hearing preservation.

3.4.1 Pre- and Postoperative Audiological Assessment

3.4.1.1 Otoscopy

Otoscopic examination of the tympanic membrane, external auditory canal and external auditory structures was conducted to rule out the presence of any pathological conditions which may affect further audiological examinations.

3.4.1.2 Pure-tone and Speech Audiometry

Pure-tone hearing thresholds were measured (in dB HL) using the modified Hughson-Westlake procedure with a calibrated diagnostic audiometer (Grayson-Stadler GSI 61 Two-Channel Clinical Audiometer). Signals were presented to the participant using Etymotic Research ER-3A insert earphones or a Radioear B-71 bone conduction vibrator. Sennheiser HDA 200 circum-aural headphones were used for extended high frequency audiometry. Air

conduction thresholds were measured in 5 dB steps at half-octave frequencies from 0.25 kHz to 8 kHz across the conventional audiometric frequency range and at sixth-octave intervals in the extended high-frequencies (9 kHz to 16 kHz). Where air conduction thresholds of 20 dB HL or greater existed at any octave frequency(s) between 0.5 kHz and 4 kHz, bone conduction thresholds were measured at the respective frequency(s). Contralateral air-conduction masking was applied using the step masking method when the difference in thresholds between the test ear and the non-test ear was equal to or exceeded the minimum interaural attenuation difference. The minimum interaural attenuation value for insert earphones is 75 dB at 1 kHz and below, and 50 dB at frequencies above 1 kHz for deeply-seeded insert ear phones (Sklare & Denenberg, 1987; Yacullo, 2009). For circum-aural and supra-aural headphones, the minimum interaural attenuation value is 40 dB across the audiometric and extended high frequencies (Snyder, 1973; Yacullo, 2009). Bone-conduction masking was also applied to the non-test ear via the step masking method when the air-bone gap was 15 dB or greater (ASHA, 2005).

Speech Audiometry was conducted using the New Zealand recording of the Consonant Vowel Consonant (revised AB) Word Lists (National Audiology Centre, Auckland, New Zealand). Word lists were presented to each ear via ER-3A insert earphones using a disc player (Phillips PD9030/79) and a calibrated diagnostic audiometer (Grayson-Stadler GSI 61 Two-Channel Clinical Audiometer). The maximal speech recognition threshold was established by determining the percentage of words correctly repeated back when the speech stimuli was presented to the participant at a level 40 dB above their PTA. The PTA was calculated as the average of the air-conduction thresholds at 0.5, 1 and 2 kHz if the configuration of the audiogram was relatively flat, or the average of the two best thresholds at these frequencies for a steeply sloping audiogram. If the participant scored lower than 90%, the presentation level is increased by 10 dB. It is recommended that speech

presentation levels should not exceed 90 dB as this may lead to distortion of the speech signal and can be uncomfortable for the patient (NZAS, 2007). If no improvement in the speech score was observed following an increase in the presentation level, or if the 'rollover' effect was observed, the highest percentage of words correct was accepted as the maximal speech recognition score. Once the maximal speech recognition threshold was established, the presentation level was lowered in 10 to 15 dB steps to establish a performance-intensity function. From this function, the speech recognition threshold (SRT) can be calculated. The SRT is defined as the lowest presentation level at which 50% of the spondaic words could be identified. Speech masking noise was presented to the contralateral ear when the presentation level of the speech stimuli exceeds that of the best bone conduction threshold of the non-test ear by 60 dB or greater for insert earphones, or by 40 dB or greater for supra-aural headphones (Sklare & Denenberg, 1987; Yacullo, 1999).

The participant's preoperative and postoperative hearing was classified using the guidelines for evaluation of hearing preservation in acoustic neuroma surgery set forth by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS, 1995). Under these guidelines, hearing classifications are based on the PTA of the hearing thresholds at 0.5, 1, 2 and 3 kHz in the ear ipsilateral to the tumour, and the maximum speech discrimination score in that ear at a presentation level no greater than 40 dB SL or at the participant's maximal comfort level (whichever is less). As outlined in Table 3, hearing was classified within the A class if the participant has a PTA less than or equal to 30 dB HL and the speech discrimination 70% or greater; class B if the PTA was between 31 dB HL and 50 dB HL, and speech discrimination was 50% or greater; class C if the PTA was greater than 50 dB HL and speech discrimination was 50% or higher; and class D includes PTAs at any level, with a speech discrimination score of less than 50%.

Hearing which fell within Class A or B is classified under these guidelines as being 'serviceable' hearing.

Table 3: AAO-HNS guidelines for reporting hearing in cases of vestibular schwannomas.

Class	***PTA (dB HL)***	***Word Recognition Score (%)***
A	≤ 30	≥ 70
B	31 - 50	≥ 50
C	> 50	≥ 50
D	Any Level	< 50

3.4.1.3 Tympanometry

Tympanometry was performed preoperatively using a Grayson-Stadler GSI Tympstar tympanometer. The purpose of conducting preoperative tympanometry in this study was to assess the participant's middle ear status. The presence of middle ear effusion may result in a conductive hearing loss, which would significantly affect the behavioural and electrophysiological measures. Tympanometry was performed using a 226 Hz probe tone, at a sweep rate of 200 daPa/s. The recorded tympanograms were compared to the adult normative data from ASHA (1990). A type 'A' tympanogram, consistent with normal middle ear function, was classified as a trace with a peak pressure between -100 and +100 daPa, a static compliance between 0.3 and 1.4 mmho, and an ear canal volume at +200 daPa between 0.6 and 1.5 cm^3. Traces with a normal peak pressure and volume, but a static compliance above or below the normative range were classified as being A_d or A_s, respectively. A trace with a low peak pressure value, less than -100 daPa, is indicative of tympanic membrane retraction and is classified as a type C tympanogram. If no identifiable peak was identified, but the ear canal volume fell within the normative range, the recording was classified as a type B tympanogram and is consistent with middle ear effusion. A flat trace with a high ear

canal volume suggests the presence of a tympanic membrane perforation and flat traces with a low ear canal volume indicate a wax blockage or that the probe tip is positioned against the ear canal wall.

3.4.1.4 DPOAEs

Otoacoustic emissions were evoked and recording using commercially-available otoacoustic emission recording equipment (Scout Diagnostic Otoacoustic Emission System, Biologic Systems). The stimuli consisted of two primary pure-tones; f_1 and f_2, where the ratio of frequency f_1:f_2 was held constant at 1.22 – the frequency ratio that has been shown to give the largest amplitudes DPOAEs (Dhar, Long, Talmadge, & Tubis, 2005; Gaskill & Brown, 1990). The intensity of the primary tones was maintained at 65 dB SPL and 55 dB SPL for f_1 and f_2, respectively. Maintaining the intensity of f_1 greater than f_2 has been shown within the literature to result in a modest increase in the emission amplitude (in the order of approximately 3 dB) (Gaskill & Brown, 1990; Hauser & Probst, 1991).

DPOAE emissions were recorded in descending order from 8 kHz to 2 kHz, with the frequency of f_2 decreasing in half-octave steps. Graphic plots of the intensity of the primary tones, the noise floor and the averaged amplitude of the DPOAE emission ($2f_1$-f_2) were visualised following the completion of each condition. The DPOAE amplitude and signal-to-noise ratio at each frequency were calculated based on a minimum of 50 samples, from a total sample of 1024. The stopping criterion for each recorded condition was a minimum DPOAE amplitude of -5 dB and a maximum noise floor of -17 dB, or a maximum recording time of 20 seconds. Emissions were defined as being present when the signal-to-noise ratio was greater than 5 dB and the absolute amplitude of the DPOAE emission exceeded -10 dB SPL (Hall, 2000).

3.4.2 Intraoperative Auditory Monitoring

All intraoperative recordings of auditory function were performed using the commercially-available Interacoustics Eclipse 772550sw Equinox recording unit connected to a laptop computer (Levono Thinkpad T420s) via a USB connection. All electrodes, with the exception of the DENM electrode, were positioned immediately after the participant had been placed under general anaesthesia.

The air-conducted stimuli for each of the intraoperative recording techniques were presented monaurally to the ear ipsilateral to the tumour using Etymotic Research ER-3A insert earphones. Insert earphones separate the transducer box from the electrode site, adding a delay between the stimulus production and the delivery of sound to the auditory system. This delay is significant enough that the stimulus artefact will have occurred before the recording of the electrode activity has begun (Hall, 2006). The recording software will account for this delay, and exclude the stimulus artefact from the final recording trace.

The auditory responses were recorded periodically during the surgical procedure when practically possible. Recordings were paused during surgical procedures which could produce significant acoustic or electrical noise. These procedures included: drilling of the IAC or skull, monopolar electrosurgical coagulation, ultrasonic aspiration of the tumour, or facial nerve stimulation. When recordings could not be obtained, the surgical procedure was paused briefly (at the discretion of the surgeon) to allow a set of recordings to be made. The timing of the recordings and the stage of the surgical procedure was documented so that any changes in the auditory potentials could be interpreted with regards to the surgical procedure which preceded that change.

3.4.2.1 ECochG

Apparatus

ECochG recordings were recorded differentially between a sterilised tympanic electrode and a subdermal needle electrode on the contralateral mastoid. The placement of the non-inverting electrode at the contralateral mastoid, as shown in Figure 11, has been recommended by the electrode manufacturers and has previously been used by a number of authors for the recording of ECochG potentials intraoperatively (McClellan et al., 2014; Shallop & Arenberg, 1993). The contralateral mastoid electrode placement offers two key advantages; the electrode does not interfere or obstruct the surgical field, and the risk of the electrode being accidentally disconnected during the procedure is significant reduced. Two additional electrodes were positioned on the participant's lower cheek to act as a ground electrode and an additional reference electrode. Initial ECochG recordings using the standard three-electrode montage (inverting, non-inverting and ground) were contaminated with a significant degree of extraneous noise. Therefore a fourth electrode was placed on the participant's face to reduce the noise floor through common-mode rejection. The placement of this fourth electrode significantly reduced the amount of artefact rejection, and allowed subsequent recordings to be obtained.

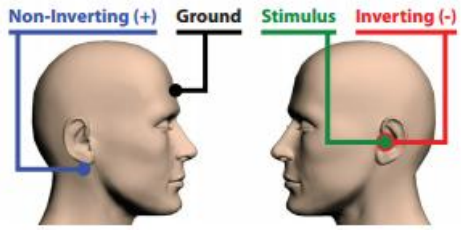

Figure 11: Suggested electrode montage for tympanic electrocochleography recordings (Intelligent Hearing Systems, 2005).

Sterile, stainless-steel, subdermal electrodes (Ambu, Denmark) were used for the non-inverting, ground and reference electrodes. The 12 mm needle electrodes were inserted under the skin by the lead ENT surgeon, and the electrode and electrode leads were secured against the participant's skin with surgical tape. Subdermal electrodes were chosen over the standard self-adhesive Ag/AgCl- electrodes as they provide a more consistent, low-impedance connection. The subdermal electrodes offer additional advantages in that they are able to be placed quickly and securely, they do not require any additional preparation of the skin, and they take up very little space on the skin surface (Hall, 2006). The electrode leads for the reference electrodes and inverting electrode were connected to the bio-amplifier, which in turn was connected to the Eclipse system through a long cable lead.

Placement of the Inverting Electrode

As discussed previously, the location of the ECochG electrode can significantly influence the quality of the recordings. While the transtympanic placement is able to record robust, high-amplitude potentials, this approach is relatively invasive and carries a slight risk (0.5%) of persistent tympanic membrane perforation (Ng, Srireddy, Horlbeck, & Niparko, 2001). For this reason, the non-invasive tympanic electrode was trialled during the testing of participant one. Prior to the placement of the inverting electrode, the ear canal was visually inspected under the operating microscope. Any debris or wax which may have interfered with the placement of the electrode or insert earphone within the ear canal was extracted with a sterilised curette tool.

A soft-tipped, silver tympanic electrode (Sanibel, Denmark) was used as the inverting electrode for the tympanic membrane ECochG recordings. Under microscopic guidance, the lead ENT surgeon gently inserted the electrode down the ear canal until it made a soft contact with the tympanic membrane. The electrode lead was held in place as a compressed ER-3A

foam insert earphone was placed alongside the electrode lead in the ear canal. Placement of the foam insert earphone within the ear canal serves two key purposes; the earphone delivers acoustic stimuli to the ear ipsilateral to the tumour and the expansion of the foam plug within the ear canal helps secure the inverting electrode. The electrode lead and earphone tubing were secured against the side of the participant's face with surgical tape to prevent any movement or displacement of the equipment during surgery.

Acoustic Stimuli

ECochG potentials were evoked using 4 kHz tone-bursts presented at a rate of 11.3 stimuli per second. As discussed previously, click stimuli are the most commonly used stimulus to elicit ECochG responses as the abrupt onset of the stimuli results in greater synchronous firing of the auditory fibres and therefore larger responses (Ferraro, 2000). However for the purpose of this study, tone-burst stimuli were used with the aim of monitoring fine changes in auditory function. Tone-bursts were presented with an alternating polarity to eliminate the stimulus artefact and cochlear microphonic, both of which are dependent on the phase of the stimulus. The low stimulus rate of 11.3/s was selected to avoid any adaptation of the CAP response which may occur at higher stimulation rates (Wilson & Bowker, 2002).

Recording Procedure

All tone-burst stimuli were presented at 95 dB nHL to establish a near-maximal amplitude response, and to obtain robust responses from which any adverse change in amplitude or latency may be tracked. The raw recordings were amplified (x 100 000), filtered and sampled within an 8 ms time window after the stimulus onset. A band-pass filter from 10 Hz to 1500 Hz (with a slope of 6 dB per octave) was applied to the raw samples to minimise the stimulus artefact or any extraneous noises which may be sampled by the recording

electrodes. An additional notch filter at 50 Hz was applied to eliminate mains interference. The high-pass filter cut-off frequency must be maintained at a relatively low frequency to ensure that the morphology of the DC summating potential could be preserved (Durrant & Ferraro, 1991).

The responses were averaged over a total of 1000 sweeps. Signal averaging was optimised with the use of Bayesian weighting. Bayesian weighting is a variation on the traditional averaging technique which uses statistical models to reduce the destructive effects of intermittent noise artefacts (Sanchez & Gans, 2006). By reducing the effects of artefact noise, a more favourable signal-to-noise ratio is achieved and fewer averages are required. Two averaged responses were obtained for each condition to ensure a repeatable response was present.

Analysis

The recorded traces were saved to the laptop computer and analysed in more detail following the completion of the surgery. The waveforms were visually inspected and evaluated by the author of this study to determine whether a response was present or absent. A response was defined as present if two repeatable waveforms were identified for each condition. The amplitude and latency of the confirmed CAP responses were analysed and the responses from the two duplicates at each condition were averaged. The SP could not be identified in any of the recorded waveforms and the use of alternating polarity stimuli eliminated the CM response; therefore, only the CAP response was analysed.

3.4.2.2 DENM

The researchers in this study endeavoured to obtain measures of cochlear function via DENM in all participants. In the present case, however, the cochlear nerve could not be

identified following the opening of the CPA. The absence of a distinct cochlear nerve meant that the recording electrode could not be positioned, and therefore DENM recordings could not be obtained from this participant.

3.4.3 Results

The preoperative audiological results for participant one are presented in Figure 12. Preoperative audiometry revealed normal hearing thresholds in the low-frequencies steeply sloping to a moderately-severe hearing loss at 2 kHz, rising to a mild hearing loss at 3 kHz, and sloping back to a moderately-severe hearing loss at the high frequencies in the left ear (ipsilateral to the tumour) (PTA = 32.5 dB HL). The hearing loss was sensorineural in nature. Extended high-frequency audiometry revealed a moderate sloping to moderately severe hearing loss, with no responses at the highest frequencies (14 kHz and 16 kHz). Pure-tone thresholds for the right ear revealed normal hearing sloping to a moderate hearing loss at the highest extended frequencies (14 kHz and 16 kHz) (PTA = 5 dB HL). Speech audiometry was consistent with the pure-tone audiogram for both ears (left: WRS of 100% at 70 dB HL, and right: WRS of 100% at 30 dB HL). According to the AAO-HNS classifications of hearing, the preoperative hearing for this participant falls within class B, representing serviceable hearing. Objective measures of OHC function via DPOAEs yielded reliable emissions at 3 kHz in the left ear and from 2 kHz to 4 kHz in the right ear. The absence of almost all of the DPOAE emissions in the ear ipsilateral to the tumour suggests a degree of cochlear involvement in the preoperative hearing loss.

Intraoperative ECochG recordings were initiated once the dura mater was opened, and were recorded intermittently throughout the surgical procedure. The ECochG traces obtained during surgery are shown in Figure 13, and the averaged CAP amplitude and latency values are detailed in Table 4. Tympanic ECochG recordings obtained from the left ear

intraoperatively provided evidence of cochlear function during cerebellar retraction and the debulking of the tumour. During the retraction of the cerebellum, a series of replicable tone-burst evoked CAPs were recorded with an average amplitude of 0.024 μV and latency of 2.21 ms. Subsequent recordings of auditory function obtained during the debulking of the tumour showed a slight shift in the CAP latency as compared to the earlier recordings (2.67 ms as compared to 2.21 ms, respectively). While this change in latency may be indicative of cochlear injury, the variation in latency may also simply be inherent to the poor quality recordings. Following the dissection of the eighth cranial nerve, no further ECochG recordings could be identified.

Continuous monitoring of cochlear function was made difficult by the poor quality of the recordings. The extraneous noise and artefact levels within the operating theatre obscured the relatively small amplitude responses, where reliable responses could only be recorded when the surgery was briefly paused (at the discretion of the operating personnel). Pausing of the operation can however be disruptive to the surgical procedure and extend the time that the patient is under general anaesthesia; therefore very few recordings were obtained during this operation. DENM could not be conducted during this surgery as the cochlear nerve could not be identified following the opening of the CPA. Therefore, conclusions about the site of auditory function could not be made from this case as responses could only be obtained from the cochlea.

Postoperative audiological assessments were performed five days postoperative. The patient reported no apparent hearing sensitivity in the operated ear (left ear). Pure-tone audiometry confirmed the patient's self-report of anacusis in the left ear, where there were no responses to pure-tone stimuli presented at the limits of the audiometer; indicating class D hearing postoperatively (as shown in Figure 12). All DPOAEs were absent from 2 kHz to 8 kHz in

the operated side. No significant changes in the auditory function of the contralateral ear were noted postoperatively.

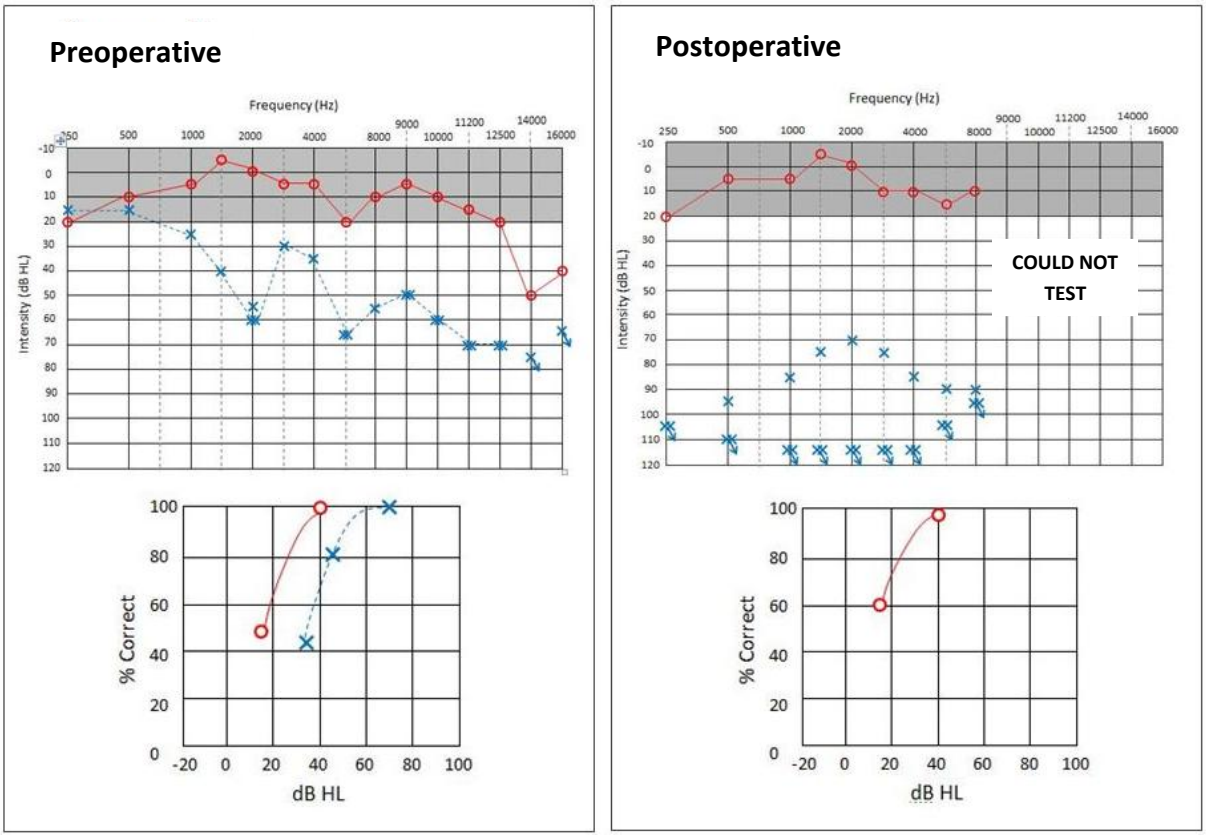

Figure 12: Behavioural thresholds from participant one collected before and after vestibular schwannoma surgery. The top panels show the pure-tone audiograms and the bottom panels show the participant's performance during speech audiometry. The left and right ears are represented by crosses and circles respectively (double crosses and filled circles indicate the use of contralateral masking).

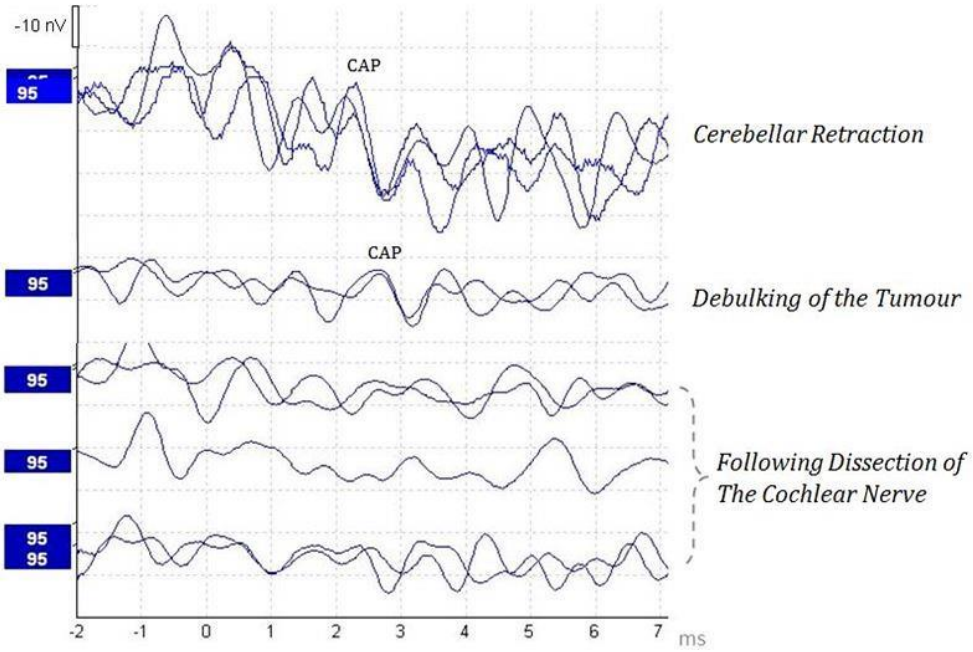

Figure 13: Tone-burst electrocochleography recordings obtained during vestibular schwannoma surgery in participant one. The electrocochleography traces are presented in the temporal order at which they were recorded intraoperatively. A compound action potential (CAP) was marked as being present when more than two replicable waveforms were obtained at one condition.

Table 4: Electrocochleography recordings of auditory function obtained during participant one's surgical procedure. The recordings are temporally sequenced in accordance with the stages of the surgery at which they were recorded. The type of stimuli, stimulus intensity and averaged compound action potential (CAP) amplitude and latency are included.

Stage of Operation	***Stimulus***	***Intensity (dB nHL)***	***CAP Amplitude (µV)***	***CAP (ms)***	***Latency***
Cerebellar retraction	4 kHz TB	95	0.024	2.21	
Debulking of the tumour	4 kHz TB	95	0.021	2.67	
Following eighth nerve dissection	4 kHz TB	95	*No identifiable waveforms*		

3.4.4 Discussion

The aim of this study was to evaluate the site of iatrogenic injury in patients undergoing vestibular schwannoma surgery via the retrosigmoid approach. By using two electrophysiological modalities which measure the function at the cochlea and cochlear nerve it was hoped that we may determine whether the injury to the auditory system was predominantly of a cochlear or cochlear nerve origin. Unfortunately, in this first case we were unable to draw any conclusions about the site of injury as DENM recordings could not be obtained intraoperatively.

3.4.4.1 Inability to record DENM intraoperatively

Following the opening of the CPA during surgery, the cochlear nerve could not be identified as a separate entity from the tumour complex. As the surgeons were unable to isolate a separate portion of the cochlear nerve, DENM recordings could not be obtained in this case. The inability to identify the cochlear nerve within the CPA appears to be an inherent disadvantage of the DENM recording technique as the placement of the recording electrode is entirely reliant on the differentiation of the cochlear nerve from the tumour complex. While this disadvantage has rarely been discussed within the literature, it has been reported by a small number of authors (Aihara et al., 2009; Colletti et al., 1997; Jacob et al., 2007). In a study by Aihara et al. (2009), which investigated the potential benefits of intraoperative DENM monitoring on postoperative hearing outcomes, the authors noted that they were unable to correctly isolate the cochlear nerve when the tumour being operated on was large in size. While the classification system used in this study does not specify the size of large tumours, the more commonly used definition of large tumours is <26 to 30 mm (Godefroy, van der Mey, de Bruine, Hoekstra, & Malessy, 2009; Hara & Kusakari, 2003). Consistent with this, Jacob et al. (2007) reported significant difficulty in identifying the

eighth nerve, especially in cases where the extrameatal tumour size was 2mm or greater. Although the study by Jacob and his colleagues was primarily investigating the vestibular nerve of origin in vestibular schwannoma cases, the cochlear and vestibular nerves form a single nerve complex within the CPA; therefore, any difficulties in the isolation of the vestibular nerve in patients with large extrameatal tumours can be expected to translate to difficulties in the identification of the cochlear nerve. The experimental observations from these studies suggest that the extrameatal size of the tumour has significant implications on the surgeon's ability to identify the cochlear nerve during the early stages of the surgery, and therefore ability to make DENM recordings. Consistent with this, the vestibular schwannoma in participant one was 25 mm in size. While this may not be classified as a 'large' tumour, the tumour complex appears to have been significantly large enough to obscure the eighth nerve.

In the study by Aihara et al. (2009), the authors suggested possible modifications in the recording protocols which may allow the recording of DENM potentials to occur in the absence of an identifiable cochlear nerve; the first of which involves the placement of a recording electrode against the lateral recess of the forth ventricle. The floor of the fourth ventricle is the location of the dorsal surface of the cochlear nucleus. Placement of an electrode against this structure allows the recording of auditory evoked potentials from a large portion of the cochlear nucleus (Colletti et al., 1997; Møller, 1996; Møller & Jannetta, 1983a; Møller, Jannetta, & Jho, 1994; Wazen, 1994). As the cochlear nucleus sits proximal to the tumour complex, recordings from the cochlear nucleus will still allow researchers to monitor any changes in auditory function which may occur due to manipulations of the tumour or the cochlear nerve directly. Although this method may present a practical alternative for the recording of auditory evoked potentials in the absence of an identifiable cochlear nerve, the placement of the recording electrode has the potential to cause irreversible damage of the brainstem.

The second alternative for the recording of near-field auditory evoked potentials within the CPA in the absence of an identifiable cochlear nerve is to perform internal compression and dissection of the tumour complex until the cochlear nerve is able to be identified (Aihara et al., 2009). Once the cochlear nerve is identified, the DENM electrode can be positioned around the cochlear nerve and recordings can be initiated. However, this method of delayed DENM recordings is not appropriate for the monitoring of trauma-induced changes in auditory function. In a number of studies, it has been documented that tumour dissection is one of the more critical stages of surgery for the preservation of hearing (Colletti et al., 1997; Gouveris & Mann, 2009). Therefore, a large proportion of the auditory damage may occur prior to the placement of the DENM recording electrode.

Finally, it is important to remember that the absence of an identifiable cochlear nerve does not necessarily mean that the cochlear nerve is not functionally intact. The functional integrity of the cochlear nerve and ascending auditory pathways can be monitored during the surgical procedure using ABR recordings. Although the ABR technique is associated with poor quality recordings within the operating theatre, it does not rely on the placement of a recording electrode in the operating field and may be used as a viable back up recording technique if the cochlear nerve cannot be identified during the surgical procedure.

3.4.4.2 Interpretation of ECochG recordings

Despite the lack of DENM recordings, several tympanic ECochG recordings of cochlear function were obtained during the first participant's surgery. In the early stages of the surgical procedure, reliable and repeatable CAP responses were recorded; indicating the functional integrity of the cochlea and most distal portion of the cochlear nerve remained relatively unchanged. During the course of the surgical procedure, the eighth nerve was sectioned to facilitate total removal of the tumour. Following this, ECochG recordings of

cochlear function were absent; suggesting that the functional integrity of the cochlea was severely impaired. The loss of cochlear function following the transection of the tumour complex has been reported in a number of other studies (Babbage et al., 2013; Gouveris & Mann, 2009; Wazen, 1994). In particular, a study by Babbage et al. (2013) which investigated the possible mechanisms for delayed postoperative hearing loss in patients undergoing vestibular schwannoma surgery observed the loss of cochlear responses in three out of the seven patients in whom the cochlear nerve could not be preserved. The loss of cochlear function following transection of the eighth nerve is most likely a result of injury to the IAA or one of its key branches (Konishi, Butler, & Fernandez, 1961; Sekiya, Iwabuchi, Kamata, & Ishida, 1985). The tight integration of the IAA and eighth cranial nerve makes complete preservation of the arterial blood supply extremely difficult when the whole nerve is severed during tumour removal.

While these recordings are consistent with severe damage of the cochlear blood supply, we cannot confidently state that the loss of cochlear function is a consequence of the sectioning of the eighth nerve complex as we were only able to obtain a limited number of recordings throughout the surgical procedure. The temporal spacing between these recordings makes it significantly more challenging to determine which manoeuvre during that time window led to the aberrant change in auditory function. More continuous monitoring of auditory function is required to allow us to draw sound conclusions about the surgical manoeuvre which results in the change in auditory function.

3.4.4.3 Reliability of tympanic membrane ECochG recordings

In the present study, a minimally invasive ECochG electrode placement was trialled with the hope that we may be able to reliably record ECochG potentials during vestibular schwannoma surgery with a technique that carries very minimal risk to the study participants.

While the tympanic membrane wick electrode was easy to position and did not result in any traumatic insult of the tympanic membrane, the magnitude of the recordings was very small (0.021 – 0.024 μV). Due to the miniscule amplitude of these responses, a significant amount of signal averaging was required. In addition to this, the recordings were highly susceptible to the extraneous noise within the operating theatre, where reliable recordings could only be obtained when the surgical procedure was paused. The need to pause the operating procedure to acquire ECochG recordings meant that very few recordings could be acquired during the time-course of the procedure. The difficulties faced with the recording of ECochG potentials during surgery highlights the limitations of recording at more far-field locations in such a hostile recording environment. Although we had difficulty obtaining reliable and robust ECochG potentials from the tympanic membrane, the tympanic and extra-tympanic electrode placements have been successfully used by a number of authors in both vestibular schwannoma and vestibular nerve sectioning surgeries (Attias et al., 2008; Winzenburg, Margolis, Levine, Haines, & Fournier, 1993). In particular, Attias et al. (2008) reported that the tympanic ECochG potentials recorded during vestibular schwannoma surgery were large in amplitude, and the presence or absence of these potentials intraoperatively was an excellent predictor of postoperative hearing function.

Although there is some evidence that the tympanic electrodes can be successfully used to record ECochG potentials during vestibular schwannoma surgery, the transtympanic electrode placement is most commonly used within the literature (Battista et al., 2000; Colletti et al., 1998; Winzenburg et al., 1993; Zappia et al., 1996). The placement of the recording electrode against the cochlea results in an almost ten-fold increase in the amplitude of the ECochG response (Hall, 2006; Winzenburg et al., 1993). The recording of more robust potentials during surgery will decrease the amount of signalling averaging, and therefore acquisition time required. In light of the small amplitude responses obtained during this case

with the tympanic membrane electrode placement, it is recommended that in future research the transtympanic electrode placement should be adopted to allow for more robust responses to be recorded.

3.5 Case Two

Participant two was a 70-year old female who underwent unilateral excision of a right-sided medium vestibular schwannoma at Dunedin Public Hospital. She was referred to an otolaryngologist following the identification of a significant asymmetry in her hearing sensitivity and reports of an intermittent shooting pain, just anterior to the right mastoid. Imaging studies performed two years previously revealed a small suspected vestibular schwannoma on the right side which was determined to have a very slight chance of growing (approximately 10%). Given the minimal chance of further tumour progression, a wait-and-see approach was adopted. A follow-up MRI revealed that the tumour had grown; therefore the patient opted to have the tumour surgically removed.

3.5.1 Pre- and Postoperative Audiological Assessment

The pre- and postoperative audiological assessments for patient two were conducted under the same protocols described in participant one, with the exception of type of headphones used during preoperative audiometry. Preoperative otoscopic examination revealed significant, non-occluding wax within the ear canal of the right ear which contraindicated the use of insert earphones. Accordingly, TDH-39 supra-aural headphones were used to present the air-conducted acoustic stimuli for the audiometric assessments.

Intraoperatively, this wax was removed by the ENT surgeon under microscopic guidance to allow for clear visualisation of the tympanic membrane. The tympanic membrane was also visually examined postoperatively to ensure the perforation caused by the placement

of the ECochG through the tympanic membrane had spontaneously healed and did not require any medical intervention. Due to the intraoperative removal of the wax, insert earphones were employed in the postoperative audiological assessments.

3.5.2 Intraoperative monitoring of auditory function

A combination of ECochG, DENM and ABR recordings were used during the course of the surgery to monitor the participant's auditory function. The ABR was set-up as an alternative method of recording auditory function if any complications, similar to that in the first case, were encountered with the primary recording techniques.

3.5.2.1 ECochG

ECochG recordings were carried out under the same protocols as those described in the first case, with the exception of the inverting electrode location. In the first case, the tympanic membrane placement of the inverting electrode did not yield robust or reliable recordings during the course of the surgery. To obtain more reliable ECochG recordings, the author of this study opted for a more invasive, transtympanic electrode placement.

The methodology for the placement of the transtympanic ECochG electrode was based upon the technique previously described by Schwaber and Hall III (1990). A sterile, subdermal needle electrode (Ambu, Denmark) was used as the inverting electrode for transtympanic recordings. In earlier transtympanic studies, a long (> 50 mm) needle electrode which extended from the promontory to past the pinna was employed for ECochG recordings. The length of these electrodes presented a significant challenge for surgeons in terms of the atraumatic securing of the electrode throughout the surgical procedure. In contrast to this, the shorter subdermal electrode offers a number of clinical advantages over the longer needle

electrodes in regards to the ease of insertion and simplicity of electrode stabilisation within the ear canal (Schwaber & Hall III, 1990).

The placement of the transtympanic electrode was completed by the lead ENT surgeon under the view of the operating microscope. Using bayonette forceps, the electrode was guided through the external auditory canal, inserted through the inferior portion of the tympanic membrane and placed against the promontory of the cochlea. The electrode was held in place and a compressed ER-3A foam insert was positioned alongside the electrode within the external auditory canal, as displayed in Figure 14. The electrode lead and the tubing of the ER-3A insert earphones were secured against the participant's skin using a surgical tape to ensure that the equipment remained stable and did not obscure access to the operating site.

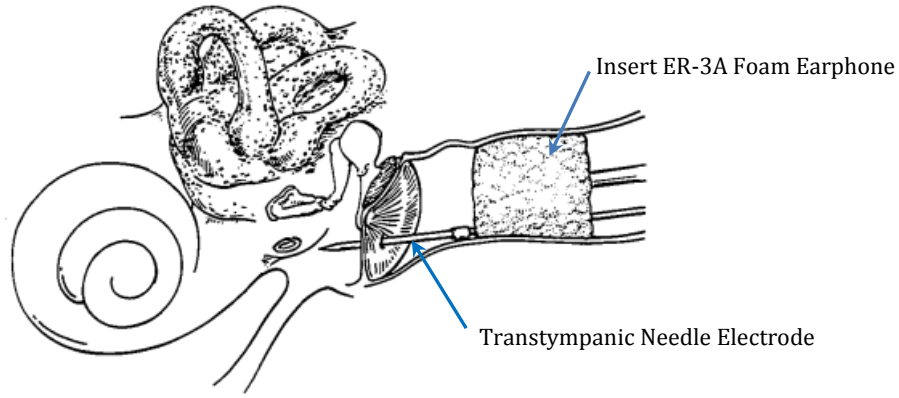

Figure 14: Illustration of the simplified transtympanic technique for placement of a subdermal needle electrode on the promontory. The electrode is secured within the external auditory canal by an insert ER-3A foam earphone (adapted from Schwaber & Hall III, 1990).

3.5.2.2 DENM

Apparatus

The electrode montage used in ECochG recordings was repeated for the DENM recordings, with the exception of the inverting electrode which was placed against the eighth cranial nerve (cochlear nerve). An atraumatic, Cueva 2 mm self-retaining electrode (Ad-Tech Medical, USA) was used as the inverting electrode for DENM recordings. As shown in Figure 15, the Cueva electrode consists of a c-shaped electrode with a silicone-coated platinum wire which extends distally to an electrode pin connector. The inner surface of the c-shaped electrode component contains a platinum surface which is left exposed so that it can be in direct contact with the nerve (Ruckenstein, Cueva, & Prioleau, 1997). The c-shaped portion is flexible, which allows for fine manipulation of its shape to ensure it is attached to the nerve with an appropriate amount of tension. The tensile strength of the electrode is designed to be lower than that of the nerve so that any accidental traction of the electrode will result in an opening of the c-shaped component and dislodgement of the electrode, rather than causing any traumatic damage to the nerve.

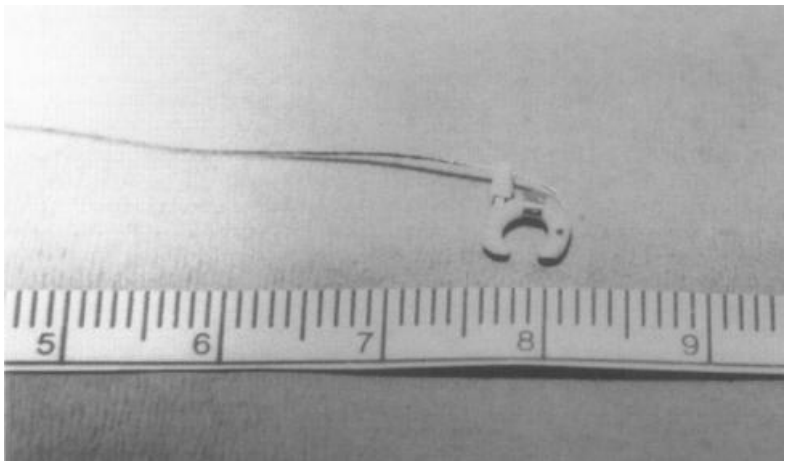

Figure 15: Cueva, self-retaining electrode design. The c-shaped portion of the electrode is applied to the nerve (Ruckenstein et al., 1997).

Placement of the Inverting Electrode

Placement of the Cueva DENM electrode could only be completed once the CPA had been opened and a portion of the tumour had been debulked. The cochlear nerve was identified based upon its anatomical location and gross appearance. The Cueva electrode was loaded into a specially-designed applicator wand which allowed for fine control of the expansion and compression of the c-shaped component, and the precise placement of the electrode along the nerve. Under the view of the operating microscope, the neurosurgeon used the applicator wand to position the electrode around the cochlear nerve, proximal to the tumour. The c-shaped portion of the electrode was fastened around the nerve and the electrode cable was detached from the applicator wand (displayed in Figure 16). The insulated electrode wire was directed away from the operating site and secured to the surrounding surgical drapes with surgical staples. Once the electrode had been secured in place the electrode pin was connected to the bioamplifier of the recording equipment.

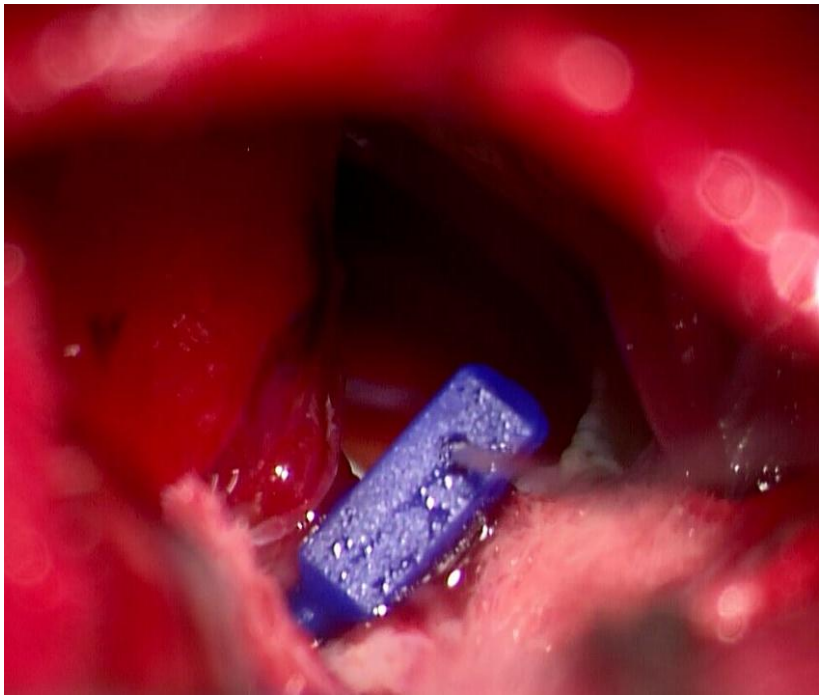

Figure 16: The placement of the Cueva electrode around the cochlear nerve during surgery in participant two.

Stimuli

The stimulus parameters which were used for the intraoperative ECochG recordings were also used for the DENM recordings.

Procedure

DENM recordings were obtained following the placement of the Cueva electrode around the cochlear nerve. The electrode remained in place until the surgeons began to drill away the IAC to access the intracanicular portion of the tumour. The electrode was removed for the duration of IAC drilling to ensure that the electrode was not damaged and did not obscure the surgical field. Once the drilling was complete, the electrode was reattached to the cochlear nerve proximal to the tumour and recordings continued.

All tone-burst stimuli were presented at 125 dB nHL to elicit a maximum amplitude response from which any changes in amplitude or latency may be tracked. The raw recordings were amplified (x 100 000), filtered and sampled within an 8 ms time window after the stimulus onset. Responses were filtered with a band-pass filter with a bandwidth of 100 Hz to 1500 Hz and a slope of 6 dB per octave. An additional notch filter at 50 Hz was applied to eliminate mains interference. The high-pass filter was set at a higher cut-off frequency than that used for ECochG recordings because the DENM waveform does not contain any DC potentials like the SP.

The responses were averaged over a total of 500 sweeps using Bayesian weighted signal averaging. Two averaged responses were obtained for each condition to ensure that a repeatable response was present.

Analysis

The recorded traces were saved to the laptop computer so that they could be analysed in more detail following the completion of the surgery. The waveforms were visually inspected and evaluated by the author to determine whether a response was present or absent. The amplitude and latency of the confirmed CNAP responses were analysed and the responses from the two duplicates at each condition were averaged.

3.5.2.3 ABR

Apparatus

The ECochG electrode array was modified for the recording of the ABR. Responses were differentially recorded between subdermal electrodes positioned on the midline forehead (Fzp) and contralateral mastoid (M_1). While conventional ABR protocols dictate that the differential recording is made between an electrode placed at the vertex or forehead and an electrode placed near the ipsilateral ear, the placement of an electrode on the ipsilateral mastoid is not practically possible during vestibular schwannoma surgery via the retrosigmoid approach. In addition to this, the ABR component which is of greatest interest during intraoperative monitoring (wave V) is generated within the brainstem. As the brainstem sits along the sagittal midline of the head, an electrode placed at the contralateral mastoid will be approximately equidistant to the brainstem as an electrode placed at the ipsilateral mastoid. Therefore, the side that the mastoid electrode is placed on should have little effect on wave V.

Acoustic Stimuli

The ABR was generated using 100 μs rarefaction clicks presented at a rate of 44.1 per second. As the ABR response is recorded from a far greater distance to the neural generators than the near-field ECochG and DENM techniques, the strength of the response must be optimised as much as possible. The click stimulus activates of a large portion of the cochlea

within a small temporal window, which results in greater neural synchronicity and a more robust response than that generated with a tone-burst. The stimulus rate was chosen to allow for the collection of clear responses within a small time period. While it has been reported that stimulus rates greater than 20 per second may have detrimental effects on the latency and amplitude of the ABR components, the effect is significantly less for the later wave V component (Chiappa, Gladstone, & Young, 1979). In addition to this, the effect of stimulus rate is weaker in ears with cochlear or retrocochlear pathologies (Møller, 1996). For these reasons, it has been recommended that stimulation rates of 40 to 70 per second be used intraoperatively to ensure recordings can be obtained efficiently during surgical procedures (Møller, 1996).

Procedure

Recordings of the ABR potential were made periodically throughout the surgical procedure until the cochlear nerve was dissected. The first recordings were not initiated until the electrode montage could be modified from the ECochG montage to the ABR montage, which occurred following the opening of the dura mater. When DENM recordings were being obtained during surgery the ABR recordings had to be paused as the recording equipment was only capable of recording potentials from one electrophysiological technique at a time.

The ABR response was obtained using acoustic stimuli presented at 90 dB nHL. Following the intermittent loss of a clear waveform at 90 dB nHL, the stimulus intensity was raised to 95 dB nHL (at the limit of the equipment). The raw activity was amplified (x 100 000), filtered and sampled in a time window of 22 ms after the stimulus onset. An extended time window was required for the ABR as the response latency may extend out to 11 to 15 ms. Responses were filtered using a band-pass filter with a bandwidth of 33 – 1500 Hz and a slope of 6 dB per octave. An additional notch filter at 50 Hz was applied to eliminate mains

interference. These filter settings were selected to minimise the influence of extraneous noise on the response while maintaining the morphological integrity of the waveform.

The responses were averaged over a total of 4000 sweeps using Bayesian weighted signal averaging to ensure optimal signal averaging was achieved. Two averaged responses were obtained for each condition to ensure that a repeatable response was present.

Analysis

The recorded traces were saved to the laptop computer so that they could be analysed in more detail following the completion of the surgery. The waveforms were visually inspected and evaluated by the researchers to determine whether a response was present or absent. A response was classified as being present when the peak(s) were identified in the two traces collected for each condition. Where individual peak(s) were identified, the absolute latency and intensity of these peak(s) were determined from the average of the peak(s) over the two replicate waveforms at each condition.

3.5.3 Results

The results from the preoperative audiological assessment are detailed in Figure 17. Preoperative audiometry revealed a mild, steeply sloping to severe sensorineural hearing loss at 1.5 kHz, rising to a moderately-severe sensorineural hearing loss in the right ear (ipsilateral to the tumour) (PTA = 46 dB HL). In the extended high frequencies, a profound hearing loss was observed at 9 kHz, with no further responses being present at 10 kHz and above. Speech discrimination was poorer in the right ear than expected based upon the pure-tone audiogram, with a maximum word recognition score of 36% being obtained at 75 dB HL. At higher presentation levels a rollover effect was observed. The rollover effect is defined as the paradoxical decrease in speech recognition with increasing presentation levels at high-

intensity levels, consistent with a retrocochlear pathology (Stach, 2003). In accordance with the AAO-HNS guidelines the preoperative hearing for participant two falls within class D, which is defined as being non-serviceable hearing. Pure-tone thresholds obtained for the left ear revealed normal hearing across the conventional audiometry frequency range, with a mild hearing loss at 8 kHz (PTA = 10 dB HL). In the extended high frequencies, the thresholds in the left ear sloped from a mild hearing loss to a moderately severe hearing loss in the highest frequencies. Speech discrimination results were consistent with normal speech recognition in the left ear (WRS of 100% at 40 dB). Objective measures of OHC function via DPOAEs yielded reliable emissions at 1.5 kHz and 2 kHz in the right ear and across the frequency range (1.5 kHz to 6 kHz) in the left ear. The absence of almost all DPOAE emissions is indicative of cochlear involvement in the loss of hearing. More specifically, the deterioration of high-frequency cochlear function is consistent with the notion that the basal end of the cochlea is more vulnerable to damage than the apical, low-frequency regions.

A combination of ECochG, ABR and DENM recordings were obtained intraoperatively. The amplitude and latency measures of the recordings are detailed in Table 5 and the averaged waveforms of these recordings are presented in their temporal order in Figure 18. Transtympanic ECochG recordings of cochlear function were found to be completely absent in the initial stages of the surgical procedure. While this could indicate a loss of cochlear function, the total absence of the ECochG response towards the beginning of the surgery most likely indicates that the transtympanic electrode had not made adequate contact with the promontory of the cochlea. For the remainder of the surgical procedure, a combination of ABR and DENM recording techniques was used. ABR recordings obtained during the opening of the dura mater and cerebellar retraction provided evidence of ascending auditory function in response to 90 dB nHL clicks presented to the operated side (right ear). As shown in Figure 18, the ABR waveform had a clear and repeatable wave V deflection;

however none of the other waves could be identified. This was true for all of the subsequent recordings of the ABR response. To investigate the characteristics of the wave V response, the stimulus intensity was reduced to 80 dB nHL in the early stages of the surgery. At lower stimulation levels the ABR demonstrated a reduction in amplitude and elongation in latency which is characteristic of an auditory evoked response; with a drop in amplitude from 0.123 µV and 0.056 µV and shift in latency from 7.77 ms and 8.30 ms, for the 90 dB nHL and 80 dB nHL conditions.

Direct recordings of cochlear nerve function could only be initiated once the surgeons had obtained adequate access to the cochlear nerve, and were able to position the DENM recording electrode on the cochlear nerve. As shown in Figure 18, the DENM response remained relatively stable during the debulking of the tumour. When tension was applied to the cochlear nerve during the debulking of the tumour, however, a distinct change in the CNAP was observed. The amplitude of the CNAP response was markedly reduced from 0.035 µV to 0.018 µV, and the latency of the response extended out to 1.83 ms as compared to the previous recording at 1.60 ms, indicating an adverse change in the neural function of the cochlear nerve. Once a significant portion of the tumour had been debulked, the bone of the IAC was drilled down to gain access to the intracanicular portion of the tumour. The DENM electrode was removed during the drilling of the IAC to ensure that the electrode would not be damaged and that it did not obscure the surgical field and the recording equipment was converted back to the ABR setting.

During the drilling of the IAC, the click-evoked ABR was intermittently lost. The brief absence of the response during the drilling procedure is most likely a reflection of the high noise and artefact levels during this procedure masking the response, rather than a true loss in auditory function. Consistent with this, the ABR response recovered following an increase in the stimulus intensity to 95 dB nHL and the response persisted when the intensity

was reduced back to 90 dB nHL. Once the IAC drilling was completed, a final ABR was recorded at 90 dB nHL before the DENM recording electrode was repositioned. A repeatable wave V response was observed at this point of the surgery with an amplitude of 0.109 µV and latency of 7.50 ms. The DENM electrode was repositioned against the cochlear nerve, however no reliable responses could be obtained in response to the 125 dB nHL tone-burst stimuli. This may indicate a loss of nerve function during the drilling procedure. As no further CNAPs could be obtained, the recording electrode was removed from the nerve.

At the later stages of the surgery, the vestibulocochlear nerve had to be sacrificed for the surgeons to be able to achieve complete removal of the tumour complex. To confirm the loss of auditory function at the level of the cochlear nerve a series of ABR recordings were made. Interestingly, the ABR responses persisted following the complete dissection of the vestibulocochlear nerve. A no-stimulus trial was conducted to see whether any activity would be present in the absence of acoustic stimuli, and no repeatable waveforms were recorded under this condition; indicating that the persistent ABR response was an auditory evoked response, most likely from the contralateral ear. The persistence of this response and the potential contributions from the contralateral ear will be discussed further in the following section.

The postoperative audiological assessment was performed three days postoperative. The patient reported that she had no hearing sensitivity in the operated ear (right ear), which was confirmed by the pure-tone audiogram. As shown in Figure 17, no responses were recorded in the right ear at the limits of the audiometer across the audiometric frequency range (class D hearing). Complete anacusis in the operated ear was anticipated given that the cochlear nerve was completely severed to achieve total tumour removal intraoperatively. All DPOAEs were absent from 2 kHz to 8 kHz in the operated side. No significant changes in the auditory function of the contralateral ear were noted postoperatively.

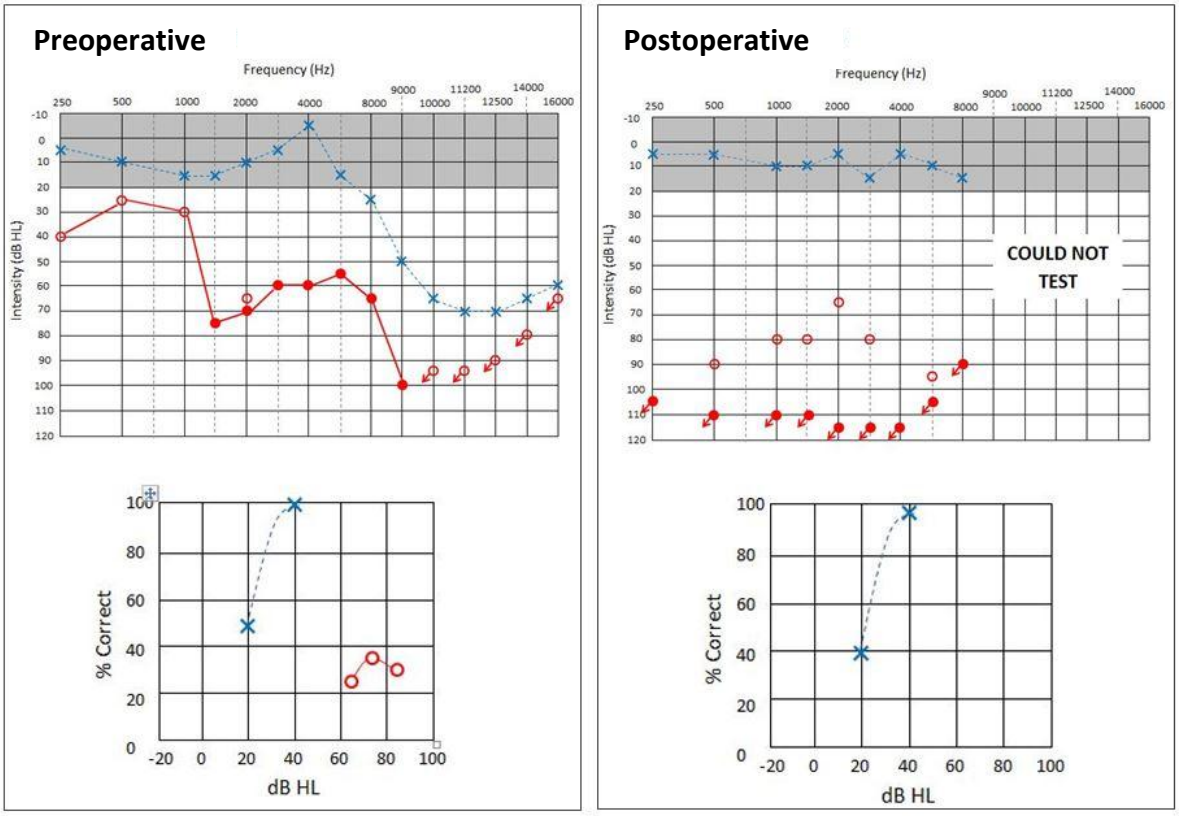

Figure 17: Behavioural thresholds from participant two collected before and after vestibular schwannoma surgery. The top panels show the pure-tone audiograms and the bottom panels show the participant's performance during speech audiometry. The left and right ears are represented by crosses and circles respectively (double crosses and filled circles indicate the use of contralateral masking).

Table 5: Electrophysiological measures of auditory function obtained during participant two's surgical procedure. The recordings of auditory function are temporally sequenced in accordance with the stages of the surgery at which they were recorded. The type of stimuli, stimulus intensity and averaged amplitude and latency of the recorded responses is included.

Stage of Operation	***Type of Recording***	***Stimuli***	***Intensity (dB nHL)***	***Wave V Amplitude (µV)***	***Wave V Latency (ms)***	***CNAP Amplitude (µV)***	***CNAP Latency (ms)***
Dura opening	ABR	Click	90	0.123	7.77	-	-
	ABR	Click	80 *	0.056	8.30	-	-
Cerebellar retraction	ABR	Click	90	0.142	7.78	-	-
DENM electrode placed on nerve	*No recordings were obtained during this stage of surgery*						
Debulking of the tumour	DENM	4 kHz TB	125	-	-	0.046	1.27
Debulking of the tumour	DENM	4 kHz TB	125	-	-	0.035	1.6
Stretching of the nerve	DENM	4 kHz TB	125	-	-	0.018	1.83
Debulking of the tumour	ABR	Click	90	0.086	7.67	-	-
Drilling of the IAC	ABR	Click	95 **	0.127	7.30	-	-
	ABR	Click	90	0.073	7.97	-	-
End of IAC drilling	ABR	Click	90	0.109	7.50	-	-
DENM repositioned on the nerve	*No recordings were obtained during this stage of surgery*						
	DENM	4 kHz TB	125	-	-	*No identifiable waveform*	
After dissection of cochlear nerve	ABR	Click	95	0.130	7.37	-	-
No-stimulus trial	ABR	Click	95	*No identifiable waveform*		-	-
Tumour dissection	ABR	Click	95	0.093	7.6	-	-
	ABR	Click	95	0.136	7.34	-	-

* A trial at 80 dB nHL was conducted to check that the response showed the characteristic decrease in amplitude and increase in latency with a reduction in the stimulus intensity.

** Stimulus intensity was raised to the maximum intensity of the equipment (95 dB nHL) to check for the presence of a response following the loss of a response at 90 dB nHL.

ABR = Auditory Brainstem Response CNAP = Cochlear Nerve Action Potential DENM = Direct Eighth Nerve Monitoring

IAC = Internal Auditory Canal TB = Tone-burst stimuli

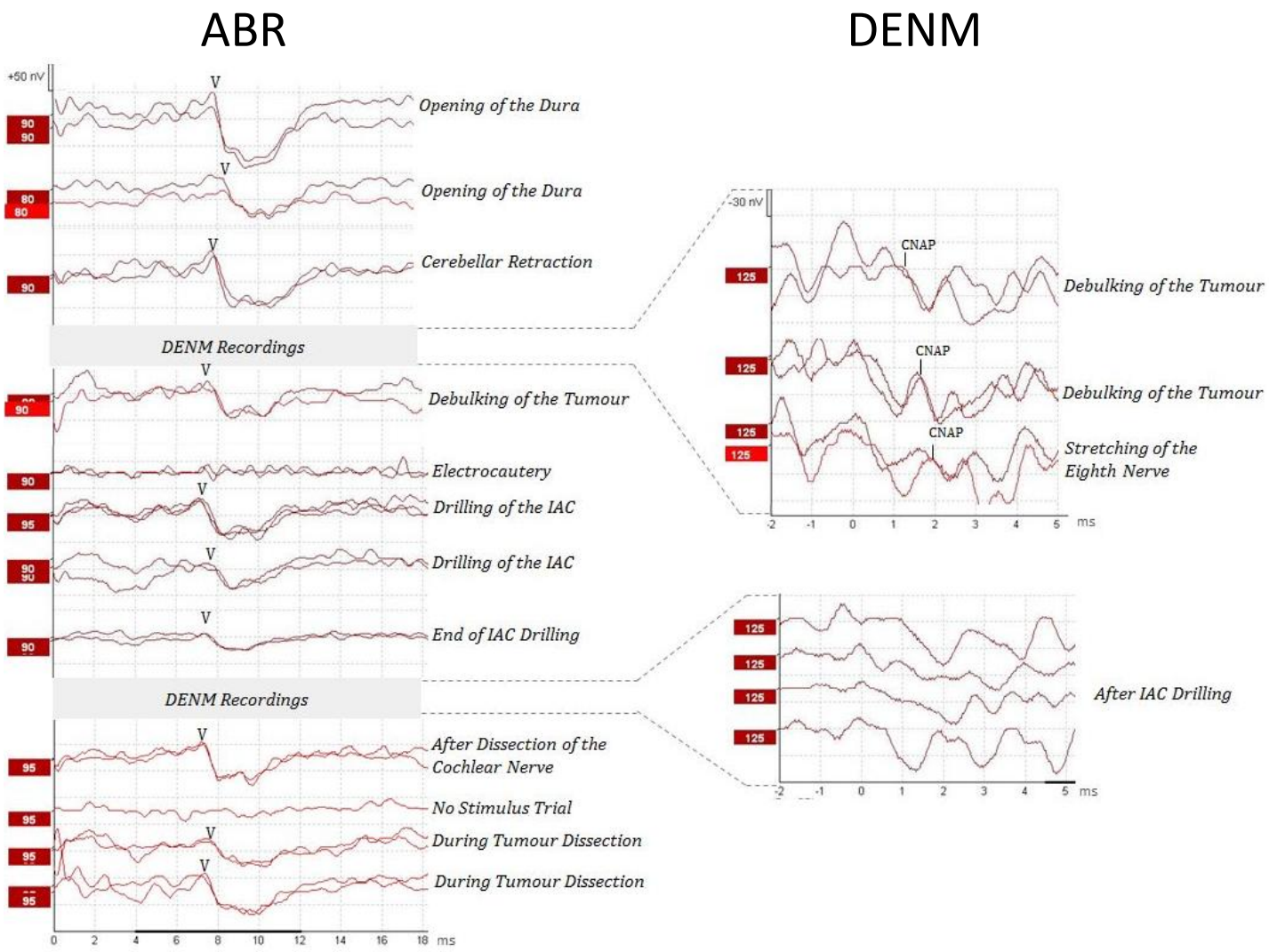

Figure 18: Electrophysiological recordings of auditory function obtained during vestibular schwannoma surgery in participant two. The averaged waveforms are presented in the temporal order at which they were recorded intraoperatively, with the auditory brainstem response (ABR) traces detailed in the left panel and the direct eighth nerve monitoring (DENM) traces in the right panel. A response (wave V or cochlear nerve action potential (CNAP)) was marked as being present when more than two replicable waveforms were obtained at one condition.

3.5.4 Discussion

To investigate the site of auditory impairment in the second participant, the researchers employed three electrophysiological techniques to monitor auditory function intraoperatively; ECochG, DENM, and ABR. While the researchers were able to achieve recordings of cochlear nerve function via DENM and ABR, transtympanic ECochG recordings of cochlear function could not be obtained. Therefore, in the second case of this series no conclusions about the site of auditory injury could be drawn. The data obtained during this case, in addition to the technical difficulties, will be discussed in the following sections.

3.5.4.1 No attainable ECochG recordings

At the beginning of the surgery, a subdermal transtympanic electrode was positioned against the cochlear promontory to allow for near-field measures of cochlear function to be obtained during the course of the surgery. Once the surgery had begun, attempts were made to record ECochG potentials; however, no repeatable or reliable ECochG waveforms could be recorded. The complete absence of ECochG potentials may indicate severe damage of the cochlea and its supporting structures, however, as these recordings were obtained relatively early in the surgical procedure and no recordings had been obtained previously, the absence of recordings most likely indicates that the electrode was not in direct contact with the cochlear promontory. In addition, the loss of cochlear potentials at such an early stage of the surgical procedure has not previously been reported within the literature. The earliest reported losses of ECochG potentials during vestibular schwannoma surgery have occurred during the stages of squamous drilling, just prior to the opening of the dura mater (Gouveris & Mann, 2009). In these cases, the authors believed that the loss in auditory function was a result of noise-induced cochlear damage. In the present study, the absence of ECochG

recordings prior to squamous drilling further supports the theory that the absence of the ECochG at such an early stage of the surgery reflects a technical fault rather than a true loss in the auditory function.

The complete absence of the ECochG response is most likely due to insufficient contact of the electrode with the promontory. Although the lead surgeon was confident with the placement of the recording electrode, the electrode may have shifted into the middle ear space during the re-positioning of the patient or it may have not truly made contact with the promontory at the time of placement. During the placement of the ECochG electrode, it has been recommended that the electrical impedance of the differential pair, and the recording electrode itself, be analysed to ensure sufficient electrode contact has been achieved (Hall, 2006; Sass, Densert, & Arlinger, 1998; Schlake et al., 2001). High electrode impedance can provide an indication that the recording electrode has not made a sufficient contact with the cochlea (Schwaber & Hall III, 1990). In future research, it is suggested that electrode impedance testing be incorporated into the ECochG test protocols to ensure that an adequate contact between the electrode and the promontory has been achieved. In addition to this, researchers should attempt to obtain a baseline ECochG recording immediately after the placement of the electrode to ensure the electrode has been positioned correctly and that the ECochG recordings are clear and reliable. The identification of a poor electrode placement is essential during the early stages of the surgical set-up, as the surgeon will be able to reposition the transtympanic electrode before the start of the surgical procedure. Repositioning of the transtympanic electrode during the surgical procedure will not be possible, as the ipsilateral ear canal must remain under sterile surgical drapes during the retrosigmoid surgical approach.

The technique of electrode stabilisation within the external auditory canal may have contributed to the movement of the electrode during the surgical procedure. Although a

number of authors have successfully used the technique of inserting the ER-3A foam earphone alongside the transtympanic electrode to stabilise the electrode, several authors have expressed a preference for the more invasive, transtragal stabilisation technique (Gouveris & Mann, 2009; Lenarz & Ernst, 1992; Prass, Kinney, & Lüders, 1987). The transtragal placement of the transtympanic electrode involves the passing of the recording electrode through the anterior portion of the tragus and extending it down the ear canal towards the tympanic membrane (H Gouveris, personal communication, 12th December, 2014). The electrode is then inserted through the posterior-inferior portion of the tympanic membrane and placed against the promontory of the cochlea. Following the placement of the electrode, the electrode is temporarily held in place and an insert earphone is positioned in the ear canal alongside the recording electrode. The authors who have employed this technique state that it provides a more reliable and secure placement of the recording electrode, where the electrode will maintain a stable contact with the cochlea throughout the surgical procedure. While this electrode placement has been favoured by several authors, the procedure is significantly more invasive than the conventional transtympanic electrode placement described by Schwaber and Hall III (1990). In participant-based research projects a balance between the potential benefits and risks for the participant is essential. In the present pilot study, the recording of auditory function during the participant's surgery was conducted to help develop a greater understanding of the auditory damage which may occur during vestibular schwannoma surgery. As the findings of this study will not directly benefit the participants themselves it was important that we used techniques which were minimally invasive but allowed us to record sufficient data. While the transtympanic ECochG recordings were absent in the present case, it is suggested that future research should persist with this electrode placement as it has been shown within the literature to produce

significantly larger response amplitudes than can be achieved through any other electrode placement and is markedly less invasive than the transtragal, transtympanic placement.

3.5.4.2 Interpretation of the DENM recordings

During the surgical procedure, successful identification of the cochlear nerve allowed for the DENM electrode to be positioned and subsequent recordings of the CNAP to be obtained throughout the operation. The functional integrity of the cochlear nerve remained intact during the early stages of tumour debulking, as demonstrated by stable serial DENM recordings. However, during the manipulation of the tumour complex, definite changes in the auditory function of the nerve were observed. Stretching of the nerve and tumour complex to allow the surgeon to gain better access to the tumour resulted in a distinct shift in the CNAP amplitude and latency; indicating significant impairment to the functional integrity of the cochlear nerve. The deterioration of the cochlear nerve response following surgical manipulations of the nerve has frequently been reported within the literature (Sekiya et al., 1986; Colletti et al., 1997). It is believed that stretching of the eighth nerve results in disturbances in the neural microcirculation or damage of the neural axons directly. Consistent with this, a series of animal studies by Sekiya and his colleagues (1985, 1986, & 1987) observed haemorrhaging of the microvessels along the cochlear nerve and shearing of the neural axons within the IAC following surgical manipulations within the CPA space. In these studies, the anatomical changes of the integrity of the cochlear nerve were closely associated with distinct changes in the auditory evoked potentials recorded from the cochlear nerve; which is similar to that observed in participant two.

It is important to note, however, that not all changes in the DENM response are permanent. Several authors have reported a phenomenon known as *conduction block* in which the changes in neural auditory function may recover in patients several months after

the surgery (Colletti et al., 1997; Kveton, Tarlov, Drumheller, Katcher, & Abbott, 1989; Kveton, 1990). As its name suggests, conduction block involves the inhibition of neural transmissions from the cochlea up to the auditory brainstem centres. This impaired neural function may be mediated through vascular compromise or neural compression, similar to that of the permanent loss of auditory function; however, the loss of hearing is reversible. In cases of conduction block, the pattern of changes in the CNAP response may differ from the usual pattern of CNAP deterioration where the amplitude of the CNAP will be attenuated but the latency remains relatively unchanged (Colletti et al., 2000; Sekiya & Møller, 1987). In addition to this, the deflection just prior to the CNAP has been reported to remain unaffected in cases of conduction block, which leads to the DENM waveform being dominated by the first deflection of the waveform rather than the distinct CNAP component (Colletti, Bricolo, Fiorino, & Bruni, 1994). While this pattern of evoked potential changes following surgical manipulations of the eighth nerve was not observed in this case, it is important for researchers to be aware of the differences in CNAP patterns and to be able to differentiate between conduction block and total neural impairment.

3.5.4.3 Quality of the DENM recordings

In the field of intraoperative monitoring, DENM has been described as the most optimal technique of recording auditory function during vestibular schwannoma surgery, as the placement of the recording electrode directly against the eighth nerve allows for large amplitude responses to be obtained within a very short period of time. Within the literature, the amplitude of the CNAP has been reported to be up to 2 to 70 μV (depending on the degree of residual hearing) (Colletti et al., 1998; Cueva et al., 1998; Silverstein et al., 1985). The magnitudes of the DENM recordings obtained in the present case were significantly less than the DENM amplitudes reported within the literature, where the maximal amplitude of the recordings from participant two ranged between 0.042 and 0.049 μV. The marked

difference between the DENM recording amplitudes in the present case may have been due to insufficient contact between the recording electrode and the eighth nerve.

The recording of robust auditory evoked neural activity from the nerve directly is dependent on the strength of contact between the electrode interface and the eighth nerve. During the surgical procedure, fluid within the CPA space may have inferred with the contact of the electrode with the eighth nerve. Consistent with this, Cueva (2012) observed a drop in the amplitude of the DENM recordings with no shift in latency when the area surrounding the electrode contact was bathed in an excess of blood or artificial CSF. The presence of fluid between the electrode and the neural generators produces greater resistance for the electrical activity, which results in a diminished response at the electrode interface. In the present case, the surgical staff regularly irrigated the surgical site surrounding the electrode interface. This irrigation may, in part, explain the small amplitude of the DENM recordings.

Another possible explanation for the small amplitude of the DENM recordings is the lack of prior experience of the surgical staff with this technique of auditory monitoring. While the lead surgeons of this project have regularly practiced ECochG and facial nerve monitoring in clinical practice and during vestibular schwannoma surgery, this case represents their first experience with the DENM recording technique. Placement of the DENM recording electrode involves the positioning of the electrode against nerve, followed by the closure of the c-shaped contact around the nerve to ensure adequate pressure is achieved around the nerve. Due to the surgeons' inexperience with the application of this recording electrode, adequate contact of the electrode against the nerve may have not been achieved. The tight contact between the electrode and neural generators is essential for recording robust potentials, where an increase in the distance between the electrode and nerve will result in greater electrical impedance and therefore reduced amplitude of the response. In many of the studies within the literature, the surgeons have routinely used DENM as part of

clinical practice or as part of a large-scale research project which has allowed them to develop a wealth of experience in the technique of placing the recording DENM electrode. This demonstrates the significant learning curve faced by all of the researchers involved in a pilot study.

3.5.4.4 Persistence of the ABR response following nerve transection

During the course of the surgical procedure, the eighth nerve was sacrificed to allow the surgeons to achieve total removal of the tumour complex. Given that the cochlear nerve is the bottleneck for the neural transmission of auditory information, it can be expected that any auditory evoked recordings proximal to the point of transection would be absent after the nerve had been severed. However, repeatable ABR recordings were observed following the transection of the nerve. The persistence of the ABR indicates a paradoxical preservation of auditory function in the absence of an anatomically intact cochlear nerve. The presence of the ABR waveform following nerve transection is believed to be due to cross-over hearing at the contralateral ear where the auditory evoked potentials are generated by the contralateral auditory system.

When a high-intensity auditory stimulus is presented monaurally, some of the acoustic energy at the ipsilateral ear may be transferred to the contralateral ear via bone vibration of the skull in a process termed ‘cross-over hearing’. The acoustic energy which reaches the contralateral ear is, however, significantly attenuated. This reduction of the acoustic energy between the ears is termed the interaural attenuation and is dependent on: the type of transducers used, the frequency spectrum of the stimuli, and the individual patients (Yacullo, 2009). While a large degree of variability exists between individual patients, researchers have established a set of averaged interaural attenuation values in which the interaural attenuation for supra-aural headphones is 40 dB for all conventional audiometric frequencies, and is 75

dB at 1000 Hz and below and 50 dB for frequencies above 1000 Hz for insert earphones. In the present case, the click stimuli were presented in the ipsilateral ear at 95 dB nHL with insert earphones; therefore, it is possible that 20 to 45 dB crossed over and activated the contralateral cochlea, resulting in the generation of auditory evoked neural potentials. Provided that the contralateral auditory pathway is intact, these neural potentials will be transmitted along the contralateral cochlear nerve and ascend through the auditory nuclei of the brainstem whereby the contralateral neural activity may potentially be detected as a wave V component in the ABR waveform. The presence of contralateral contributions to the ABR waveform does, however, put the reliability of the earlier ABR recordings prior to nerve transection into question.

Within the literature, there are a number of earlier studies which have observed an ABR pattern similar to that of the present case in patients with severe-to-profound unilateral hearing losses when contralateral masking is not applied (Chiappa et al., 1979; Humes & Ochs, 1982; Smyth, 1985). In these cases, the authors found that the ABR waveform has the potential to demonstrate near-normal ABR waveform morphology; consistent with that observed in participant two. The presence of a near-normal ABR response in patients with a severe unilateral hearing loss presents a major hazard in clinical practice as this response may be perceived as evidence of sufficient auditory function in an ear which is significantly impaired. While the ABR response will appear normal upon visual inspection, the latency of the wave V component is abnormally delayed. The delayed latency of the ipsilateral wave V component is said to be equivalent to the latency values of the contralateral ear in response to the attenuated acoustic signal (Smyth, 1985).

The possibility that there may be contributions from the contralateral ear in the ABR response of patients with a significant asymmetric hearing loss emphasises the need for contralateral masking in ABR testing. The use of masking noise in the contralateral ear helps

eliminate the degree of cross-over hearing and ensures that the recorded response is a true reflection of the function integrity of the ipsilateral auditory system. In a study by Humes and Ochs (1982), the use of contralateral masking was examined in both normal hearing patients and a small number of patients with a profound unilateral sensorineural hearing loss. A crossed ABR response, similar to that of the present case was observed in all of the patients with a unilateral hearing loss when a high-intensity click stimulus was presented in the absence of contralateral masking. Following the application of masking noise at the contralateral ear, this crossed-ABR response was completely absent where the ABR recordings reflected the true auditory function in the ipsilateral ear. Some researchers have, however, questioned whether the application of contralateral masking in ABR testing will result in a central masking dilemma (Humes & Ochs, 1982). Central masking occurs when the hearing threshold of one ear is elevated with the presentation of masking noise, even at low intensity levels, to the contralateral ear (Hall, 2006). However, it has been well documented that the presence of contralateral masking noise does not significantly affect the amplitude or latency of the ABR response from the ipsilateral auditory pathways (Humes & Ochs, 1982; Reid, Birchall, & Moffa, 1984).

In the testing of participant two, contralateral masking was not employed as we had intended to only use ECochG and DENM recordings to assess auditory function during the course of the surgery. The equipment for ABR recordings was only set up on the patient as a back-up recording method if the other electrophysiological techniques could not obtain reliable recordings. Near-field techniques such as ECochG and DENM do not require masking as the electrical activity is measured close to the neural generators, and the recording sites for both techniques occur prior to the convergence of the ascending auditory system; therefore there is very little chance of recording a contralateral response (Hall, 2006). We have, however, learnt from this case that if there is the potential that ABR recordings will be

recorded intraoperatively, it is important to set up the contralateral ear with an insert earphone for the application of contralateral masking to ensure that the ABR response is a true reflection of the ipsilateral auditory function.

Chapter Four: Discussion

In the present study, intraoperative monitoring of auditory function with ECochG and DENM was attempted in two patients undergoing retrosigmoid vestibular schwannoma surgery with the aim of investigating the site of iatrogenic auditory impairment. By using two electrophysiological modalities which measure the function at the cochlea and cochlear nerve it was hoped that we would determine whether the origin of the intraoperative hearing losses was predominantly cochlea or neural. However, as discussed in the previous chapter, a number of technical difficulties meant that recordings of both cochlear and cochlear nerve function could not be obtained in either of the participants in this study. As a consequence of this, we could not draw any conclusions about the site iatrogenic injury in the participants of this study. The limitations of this study, the future research directions and clinical implications of this study will be discussed in the following sections.

4.1 Limitations

The predominant limitation of this study was the inability to obtain reliable or robust recordings from both the cochlea and the cochlea nerve in either of the participants. The difficulty of recording auditory evoked potentials during surgical procedures has been well documented within the literature. As this was the first study of its kind in this research centre, it can be expected that some time will be spent refining the electrophysiological techniques and protocols. While the difficulties faced with the electrophysiological techniques limited the strength of our results, the techniques practiced and information learnt from this study establishes a basis from which subsequent research can build.

The inherent limitations of the pilot study were not only limited to the refinement of the recording techniques. To establish this pilot study, the early stages of the research project were spent obtaining ethical approval, establishing evidence-based test protocols based upon

the literature, and sourcing the recording equipment. These stages of the research project significantly delayed the date from which the testing could be commenced. In addition to this, a number of technical delays were encountered in the development of the custom-built auditory evoked potential recording software. It was decided that the testing would be delayed until the completion of the custom-made monitoring software as the software would allow for continuous monitoring of ECochG and DENM potentials across a broader range of frequencies. Such acute monitoring of auditory function has yet to be described within the literature. Unfortunately, the custom-made software could not be completed within time; therefore, the author had to revert to commercially-available auditory evoked monitoring software.

The delay in the testing of the participants was compounded by the low frequency of vestibular schwannoma cases undergoing surgical excision via the retrosigmoid approach. The recruitment of the participants was entirely dependent on the surgical schedule of the lead ENT surgeon in the two localities. In the South Island of New Zealand, vestibular schwannoma surgeries are relatively infrequent; whereby there may only be a case every three to four weeks. As a consequence of this, only two participants could be tested within the time period of this thesis project. Such a small sample size is relatively unavoidable for a pilot study of this complexity. The sample size of two participants is not sufficient enough to draw any conclusions about the site of auditory impairment even if recordings of both cochlear and cochlear nerve function had been obtained. Within the literature, the smallest series in which the patterns of auditory function at the cochlea and cochlear nerve have been documented is that by Levine et al. (1984), which involved 6 participants. In a large proportion of intraoperative auditory monitoring studies, however, the sample size may extend up to 420 participants. A larger sample size of participants would allow researchers to establish a more succinct picture of the trends and patterns of iatrogenic auditory impairment

at the two levels of the auditory system. As this pilot study is part of an ongoing research project, it is anticipated that the inclusion of more participants to the study sample size will overcome this limitation and allow researchers to establish an understanding of the patterns of hearing loss during vestibular schwannoma surgery.

4.2 Directions for Future Research

4.2.1 Further investigations into the site of iatrogenic injury during vestibular schwannoma surgery

As we were unable to monitor both ECochG and DENM recordings during the course of the surgery, the objective of investigating the site of auditory injury remains elusive. Continuation of this research is required to establish the patterns of auditory impairment which may occur during vestibular schwannoma surgery and determine where along the auditory pathway the damage is predominantly occurring. If the site of auditory damage can be elucidated, it will provide researchers a greater understanding of the pathophysiological mechanisms behind the iatrogenic hearing loss. Creating a better understanding of the hearing loss which may occur during vestibular schwannoma surgery is an essential step in the development of targeted therapeutics and further modification of the microsurgical techniques with the aim of improving postoperative hearing outcomes in this patient population.

In future research, it may also be important to maintain a detailed history of the surgical manoeuvres occurring at the time of deterioration in auditory function. A detailed temporal history of the surgical manoeuvres will allow the researchers to identify the surgical procedures most likely to produce these aberrant changes in the auditory function. While a number of studies have investigated the stages of surgery which carry the greatest risk of hearing loss, there are no known studies within the literature which have examined the

changes in auditory function at both the cochlea and cochlear nerve in relation to the surgical manoeuvres (Colletti et al., 1997; Gouveris & Mann, 2009). This information may provide greater insight into the underlying mechanism of the operative trauma to the auditory system and could be used by the surgeons to guide the modification of the surgical procedures.

Finally, in the continuation of this research the custom-made auditory evoked software should be utilised to allow for a more acute monitoring of auditory function during the course of the surgery. As mentioned previously, such fine monitoring of auditory function intraoperatively has yet to be reported within the literature. Due to the tonotopic structure of the auditory nerve, it is presumed that damage of the nerve will predominantly affect the high frequency fibres. By monitoring the function of the cochlear nerve, and the cochlea, across a broader range of frequencies the researchers may be able to document the true frequency patterns of the hearing loss during vestibular schwannoma surgery, across a range of participants.

4.2.2 Establishment of an intraoperative auditory monitoring program in New Zealand

The developments made on the intraoperative monitoring procedures and the calibration of the acoustic equipment of intraoperative monitoring system may also be useful for the establishment of an intraoperative monitoring program in New Zealand. At present, intraoperative monitoring of auditory function during vestibular schwannoma surgery is not commonplace in New Zealand. Around the world, a number of countries have adopted intraoperative monitoring as part of everyday clinical practice with the aim of improving the rates of postoperative hearing preservation (P Bird, personal communication, 13th February 2015). Over the past few decades, intraoperative monitoring of auditory function has gained a wealth of interest. Following the success of facial nerve monitoring in increasing the rates of functional preservation, researchers began to focus on the use of auditory monitoring to

improve hearing preservation. Intraoperative auditory monitoring allows the clinician to advise the surgeon of any significant changes in the auditory function and enables the surgeons to modify their technique to prevent further deterioration of the hearing. Within the literature, it has been shown that the addition of intraoperative auditory monitoring during the surgical procedure has led to a significant increase in the rates of hearing preservation (Attias et al., 2008; Colletti et al., 2000; Lenarz & Ernst, 1992). In particular, a study by Tonn et al. (2000) which examined the effect of intraoperative monitoring on the functional outcomes in patients who underwent vestibular schwannoma surgery found that hearing preservation rose from 8.8% to 26.8% with the use of intraoperative auditory monitoring.

In New Zealand, the rates of hearing preservation are not readably available. However, in a study by Darwish et al. (2005) the facial nerve function and hearing preservation rates were reported for those patients who underwent retrosigmoid vestibular schwannoma surgery in the Christchurch area over a 17 year period. In this study, the rates of measurable hearing preservation have been reported to be 21% over the entire study, with rates of 32% hearing preservation occurring within the last five years of the study. Consistent with this, a study by Babbage et al. (2013) which examined the patterns of postoperative hearing loss in patients undergoing vestibular schwannoma surgery in Christchurch noted that hearing was preserved postoperatively in 30% of the participants. As mentioned previously, the use of intraoperative auditory monitoring during surgery has been reported to increase rates of hearing preservation to 31 to 67% (Arriaga et al., 1997; Darwish et al., 2005; Glasscock III et al., 1993; Samii & Matthies, 1997b; Sanna et al., 2004). Therefore, it can be said that establishing an intraoperative monitoring program for New Zealand may have significant implications on the rates of hearing preservation in patients undergoing vestibular schwannoma surgery. The preservation of hearing not only has implications on the patient's

ability to hear or perceive sounds, but has been found to play a significant role in the patient's postoperative quality of life (Inoue, Ogawa, & Kanzaki, 2001; Tufarelli et al., 2006).

4.3 Clinical Implications

As no conclusions about the sites of iatrogenic injury could be drawn from this study, the findings do not have any immediate clinical implications. However, with the continuation of this research it is anticipated that future findings will help increase our understanding of the auditory impairment and help refine the surgical techniques and pharmaceutical treatments used in modern vestibular schwannoma surgery. The increased understanding of the mechanisms of damage and development of preventative measures may have a distinct effect on the postoperative outcomes for patients undergoing vestibular schwannoma surgery.

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Appendix A: Ethical approval letter from the Southern Health and Disability Ethics Committee.

Health and Disability Ethics Committees
C/- MEDSAFE, Level 6, Deloitte House
10 Brandon Street
PO Box 5013
Wellington

0800 4 ETHICS
hdecs@moh.govt.nz

18 July 2014

Mr Philip Bird
Private Bag 4710
Christchurch 8140

Dear Mr Bird

Re:	**Ethics ref:**	**14/STH/92**
	Study title:	SITE OF AUDITORY IMPAIRMENT DURING VESTIBULAR SCHWANNOMA SURGERY: A study of intraoperative auditory function via direct eighth nerve monitoring and electrocochleography.

I am pleased to advise that this application has been *approved* by the Southern Health and Disability Ethics Committee. This decision was made through the HDEC-Expedited Review pathway.

The main issues considered by the HDEC in giving approval were as follows.

- Please change "asked" to "invited" in first paragraph of Patient Information Sheet
- Interpreter box can be removed and only have yes no tick box for GP question - the rest just require a tick.
- Please include 1:200 risk of persistent perforation of the eardrum as a potential rare complication of the monitoring for this study in the Patient Information Sheet.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Southern Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
2. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

3. Make suggested changes to Patient Information Sheet

Non-Standard conditions must be completed before commencing your study. Non-standard conditions do not need to be submitted to HDEC before commencing your study.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

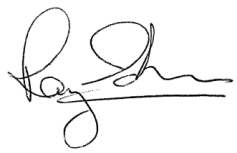
Your next progress report is due by 18 July 2015.

Participant access to ACC

The Southern Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,



Ms Raewyn Idoine
Chairperson
Southern Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	*Version*	*Date*
CV for CI: CV for Assoc Prof Philip Bird, the co-coordinating investigator for this study	1	01 June 2014
PIS/CF	1	30 May 2014
Approval of research from Maori Research Advisory Group, University of Canterbury.	1	26 June 2014
Protocol: Protocol for present study.	1	19 June 2014
Evidence of scientific review: Evidence of favourable Peer review. This study was peer reviewed by Prof Peter Thorne, University of Auckland.	1	30 June 2014
Application	1	

Appendix B
Statement of compliance and list of members

Statement of compliance

The Southern Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008713) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Ms Raewyn Idoine	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Mrs Angelika Frank-Alexander	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Dr Sarah Gunningham	Non-lay (intervention studies)	01/07/2012	01/07/2015
Ms Gwen Neave	Lay (consumer/community perspectives)	01/07/2012	01/07/2014
Dr Nicola Swain	Non-lay (observational studies)	01/07/2012	01/07/2015
Dr MARTIN THAN	Non-lay (intervention studies)	01/07/2012	01/07/2015
Dr Devonie Waaka	Non-lay (intervention studies)	01/07/2013	01/07/2016
Dr Mathew Zacharias	Non-lay (health/disability service provision)	01/07/2012	01/07/2015

http://www.ethics.health.govt.nz

Appendix B: Patient Information and consent form

INFORMATION FORM

Site of auditory impairment during vestibular schwannoma surgery

September 2014

Introduction

You are asked to take part in a study investigating monitoring of hearing during vestibular schwannoma surgery. Your participation in this study is entirely voluntary. You do not have to take part, and if you choose not to you will receive the standard care available. If you do choose to participate, you are free to withdraw at any time. All patients having this surgery are currently being asked to participate in this study.

Why is this study being done?

Unfortunately, one of the risks of vestibular schwannoma surgery is hearing loss. This study will monitor each patient's hearing during surgery to investigate where in the hearing system damage is occurring (if at all). The results of this study will be used to help surgeons understand which parts of the auditory system are most at risk during the surgery. This information may help guide the development of future treatments to reduce the risk of hearing loss in this type of surgery.

What does this study involve if I choose to participate?

Prior to surgery your hearing will be tested. These tests will not cause you any discomfort. The hearing test will be the same as you would usually have prior to surgery, except that hearing at higher frequencies will also be tested. We will also do a short test which tests your inner ear function by playing sounds into your ear and measuring an "echo" response back. You do not have to provide a response in this test.

During the surgery your brain will respond to a sound in the same way as when you are awake. We can measure this activity by using "electrodes". Electrodes are wires that are connected from a computer to sensors placed on your skin and the ear by the surgeon. A tiny needle electrode will be inserted into the eardrum (after you are asleep) which will allow us to measure responses from your inner ear. A special electrode will also be placed on your hearing nerve so we can record any changes in how this nerve responds during surgery. We

will use the electrodes to monitor your responses to the sounds throughout the surgery. The recording does not require you to give any response and will not affect the rest of the surgery. This technique of testing hearing is not usually used in this type of surgery at this hospital; however, it is often performed at other hospitals worldwide.

Following the surgery, you will have another hearing test (similar to the one before surgery). This would be done regardless of your involvement in this study. The hearing test will be done towards the end of your hospital stay. It will not delay your recovery or discharge from hospital. Your hearing will be tested by Ms Harriet Apthorp, a Masters of Audiology student.

Is there any risk to me by being involved in this study?

We do not expect any increased risk from being involved in this study beyond the risks involved with the surgery. There is a very slight risk that one of the electrodes could leave a tiny hole in the ear drum, however this is an extremely rare complication (0.5%). Every participant will be tested for this complication, and if present, they will be treated accordingly by their doctor. You can withdraw from the study at any time and this will have no effect on your care after surgery.

Will this study help me?

This study will not directly help you, but may help preserve hearing for people undergoing a similar operation in the future. If we can detect where hearing loss occurs, methods may be developed to prevent it from occurring in the future.

Important information

If you take part in the study your privacy and confidentiality will be protected. No information will be shown to people outside the study staff that could be identified to you. No material that could personally identify you will be used in any reports on this study.

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact an independent health and disability advocate:

Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

This study has received ethical approval from the Southern Regional Ethics Committee (ethics reference 14/STH/92).

If you have further questions or would like to discuss the research further, please do not hesitate to contact the researchers

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Consent Form

Site of auditory impairment during vestibular schwannoma surgery

May 2014

Request for Interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

Please read and tick the appropriate box:

- I have read and I understand the information sheet *"Site of auditory impairment during vestibular schwannoma surgery*" ☐
- I have had the opportunity to discuss this study and have had any questions answered satisfactorily ☐
- I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study ☐
- I have had this project explained to me by one of the investigators ☐
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and that this will in no way affect my future/continuing health care. ☐
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports in this study ☐
- I understand that the investigation will be stopped if it should appear to be harmful to me. ☐
- I have had time to consider whether to take part in this study ☐
- I know who to contact if I have any questions about the study ☐
- I know who to contact if I have any side effects to the study ☐

	Yes	No
• I agree to my GP or other current provider being informed of my participation in this study	☐	☐
• I would like a copy of the summarised results at the completion of the study	☐	☐

Participant to sign:

I …….....
(full name) hereby consent to take part in this study to investigate the site of impairment during vestibular schwannoma surgery

Signature..... Date.....

Researcher to sign:

I.....
(full name) believe that consent was given freely by the participant and have witnessed the signing of the consent form above

Signature..... Date.....