CHARACTERIZING VESTIBULAR STIMULATION IN CHILDREN WITH COCHLEAR IMPLANTS

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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Abstract

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Though vestibular impairment is highly prevalent in children with sensorineural hearing loss who use cochlear implants (CIs), improvements in balance function upon device activation have been observed in this population. The present study aimed to identify a possible mechanism by which the CI confers functional benefit. Vestibular Evoked Myogenic Potentials were employed to objectively measure current spread from the implanted device to the otoliths; cross-stimulation was recorded in 34/55 (62%) participants. Vestibular loss manifested in the form of asymmetric spatial orientation deficits, as measured by the Subjective Visual Vertical. Otolith impairment further predicted static and dynamic equilibrium [p=0.005]. Electrical pulses delivered from the implant shifted abnormal perception towards normal [p=0.007]. Similarly, device activation improved balance performance in individuals with compromised vestibular function [p=0.02]. These findings indicate that (i) current can indeed spread from a CI to the vestibular end organs, and (ii) CI stimulation can confer a functional benefit to implant users.
Acknowledgements

Writing this section has proven to be the most difficult part of putting a thesis together, simply because it is not possible to adequately thank the individuals who have been instrumental in the completion of this degree.

First, I would like to thank my supervisor, Dr. Karen Gordon, for providing expert guidance and mentorship during this phase of my academic training. Thank for you for teaching me how to ask the right questions, pushing me “into the deep end,” and patiently showing me the art of faithfully reporting results while keeping the big picture in mind. I am indebted to my advisory committee, Drs. Blake Papsin, Jennifer Campos and Sharon Cushing, for your witty remarks, tireless encouragement and devoted perseverance towards helping me grow both academically and personally; your knowledge and expertise have been invaluable.

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Contributions & Publications

This thesis is only composed of work completed during my enrollment in the Institute of Medical Science’s MSc program.

Drs. Karen Gordon, Blake Papsin, and Sharon Cushing were the vision behind this project, and provided direct, substantial and intellectual contributions to this study. Dr. William Parkes co-designed the testing protocol, aided with data collection, provided suggestions for statistical analyses, and helped prepare the manuscripts for publication. Carmen McKnight coded and programmed the acoustic and electric stimuli, in addition to aiding with data collection and manuscript preparation. Joshua Baitz assisted with extracting the muscle contraction values found in Figures 3.2 – 3.5.

Portions of this study have been published in a peer-reviewed journal:


This paper can be viewed in its published format in the Appendix. Although the respective results are cited throughout the thesis as “Parkes et al., 2016,” note that the first two authors contributed equally to the paper and, as such, are identified in the editor’s notes as co-first authors.

The results from the Subjective Visual Vertical test have been submitted for publication to *Frontiers in Integrative Neuroscience* and are currently under review.
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<tbody>
<tr>
<td>BOT-2</td>
<td>Bruininks-Oseretsky Test of Motor Proficiency</td>
</tr>
<tr>
<td>CN</td>
<td>Cranial nerve</td>
</tr>
<tr>
<td>cVEMP</td>
<td>Cervical vestibular evoked myogenic potential</td>
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<tr>
<td>IO</td>
<td>Inferior Oblique muscle</td>
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<tr>
<td>MLF</td>
<td>Medial longitudinal fasciculus</td>
</tr>
<tr>
<td>oVEMP</td>
<td>Ocular vestibular evoked myogenic potential</td>
</tr>
<tr>
<td>SCM</td>
<td>Sternocleidomastoid muscle</td>
</tr>
<tr>
<td>SNHL</td>
<td>Sensorineural hearing loss</td>
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<td>SVV</td>
<td>Subjective visual vertical</td>
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Chapter 1

Introduction

1.1 Research Questions & Hypotheses

Cochlear implantation has become a validated treatment option for patients with severe
to profound hearing loss. A complication that has been noted, however, is the spread of
the implant’s electrical energy to the anatomical structures that are in close proximity to
the auditory nerve. Our aim in the present study was to determine if vestibular potentials
could be evoked with electrical stimulation from a cochlear implant, clearly characterize
these responses, and examine whether or not this inadvertent and traditionally unwanted
stimulation has beneficial consequences for children using cochlear implants. This thesis
intends to answer the following questions:

1. What is the prevalence of vestibular reflexes in our population of pediatric cochlear
   implant users? How frequently can these reflexes be evoked with electrical pulses
   from the cochlear implant?

2. What electrical stimulation parameters are needed to elicit vestibular evoked re-
   flexes?

3. Does cochlear implant evoked stimulation of the vestibular system have an impact
   on function?
Advancements in technology and increased proficiency in implantation procedures have made the cochlear implant (CI) an exceptional treatment option for sensorineural hearing loss (SNHL) with few associated risks (Farinetti et al. 2014; for a review, see Terry, Kelt & Jeyakumar, 2015). The spread of current to extracochlear structures, nevertheless, potentially limits the functionality of the CI; a review of CI performance found that the most common reason for electrode deactivation was facial nerve stimulation (Stoddart & Cooper, 1999). It is plausible that current spread is not limited to the facial nerve, given the close proximity of the vestibular end organs and nerve branches to the implant. Cross stimulation has been shown to occur at current levels below the threshold of conscious perception (Cushing, Papsin & Gordon, 2006), and as such, self-reports cannot be relied upon to accurately reflect the occurrence of such extracochlear stimulation. Instead, vestibular evoked myogenic potentials can be utilized to objectively determine if CI current is, in fact, reaching the vestibular system.

In the present study, we first hypothesized that even when vestibular end organs are dysfunctional and do not respond to traditional testing methods, vestibular neural components remain stimulable and accessible via CI stimulation. Using the aforementioned objective measure (i.e., vestibular evoked myogenic potentials), we sought to evaluate the frequency at which electrical vestibular stimulation occurs in children with CIs. Second, various stimulus parameters were also adjusted in order to enhance our understanding of when and where current successfully activates the vestibular system. We expected that high-intensity stimulation would maximize the spread of electric current outside the cochlea, and as such, would increase the likelihood of vestibular activation. We further expected that electrodes on the basal aspect of the implanted array would more likely elicit vestibular potentials than apical electrodes, given the proximity of the former to the vestibular end organs and their innervating afferents. Third, improvements in static and dynamic equilibrium have been noted while children wear their implants (Cushing, Gordon, Rutka, James & Papsin, 2008a), and we therefore anticipated similar enhancements in function, particularly spatial orientation, while electrical pulses were provided.
Before the impact of CI stimulation on the vestibular system can be explored, one must appreciate the necessity of this sensory modality for daily function. To this end, the subsequent sections will discuss the entities that contribute to the sense of balance, investigate the methods used to assess the integrity of the peripheral vestibular system, and then examine how this system becomes compromised in children who are deaf.

1.2 Sensory components of balance

As a person navigates their constantly-changing environment, they do not often pause to consider the type of input required to maintain their equilibrium. Indeed, it is only when balance is challenged (e.g., the spatial disorientation felt by a standing passenger when a train suddenly comes to a halt) that the existence and role of this vital sensory modality are even recognized. In order for the central nervous system to counteract external forces and sustain the body’s position in space, it must receive an accurate and timely representation of the elements under its control along with the navigational challenges presented by the physical milieu. This is predominantly facilitated with information provided from the peripheral vestibular end organs, though somatosensation, vision, and audition also supply meaningful contributions. The integration and application of sensory input across these modalities takes time to develop, as exemplified by the evolution of a toddler’s uncoordinated movements into graceful strides. The following sections expound on what comprises balance, as a comprehension of the intricacies of a fully-functional system is essential before the impact of dysfunctional components can be discussed.

1.2.1 Sensory input from the vestibular system

The vestibular system is responsible for subconsciously providing awareness of spatial orientation, detection of movement, stability of images on the retinal fovea during motion, and postural control. Sensory information regarding head movement and gravitational forces is detected by the peripheral vestibular end organs, transduced into neural signals, and then relayed to centres in the central nervous system for further processing.
The bony labyrinth is a series of cavities (i.e., cochlea, vestibule, and semicircular canals) housed in the petrous region of the temporal bone. Suspended within the bony labyrinth is a collection of connected sacs and ducts, called the membranous labyrinth, in which auditory and vestibular sensory epithelia reside (Figure 1.1). The bony and membranous labyrinths are separated by perilymph – a sodium-rich, potassium-deficient fluid which is drained into the adjacent subarachnoid space via the bony cochlear aqueduct. While the source of this perilymph is unclear, a review by Sterkers and colleagues suggests that coupled endothelial and epithelial barriers play a role in filtering fluid from plasma and modifying its chemical composition (Sterkers, Ferrary & Amiel, 1998). In contrast, endolymph is a potassium-rich, sodium-deficient fluid which fills the membranous labyrinth. It is produced by the stria vascularis, located along the lateral wall of the cochlear duct, and absorbed by the endolymphatic sac. Although the cochlea and vestibular end organs serve distinct sensory purposes, the ducts of the membranous labyrinth are continuous with each other, allowing endolymph to flow between the two regions.

Figure 1.1: The peripheral vestibular apparatus, comprised of the otoliths and semicircular ducts, is located alongside the cochlea in the inner ear. Adapted from Tortora & Derrickson (2013) with permission from WILEY.
Embeded within the vestibular neuro epithelium are sensory mechanoreceptors known as hair cells. The apical aspect of these hair cells forms a large single extension, called the kinocilium, along with additional smaller processes of varying height, known as stereocilia. The stereocilia are arranged in height order, such that the tallest process is closest to the kinocilium while the shortest is furthest from the kinocilium. Extracellular filaments connect adjacent stereocilia to each other so that when they bend towards the kinocilium, potassium from the endolymph enters through cation-specific channels, and the hair cell is depolarized. The subsequent release of neurotransmitter increases the firing rate of the vestibular afferent nerve fibres. When the stereocilia are bent away from the kinocilium, the opposite occurs: ion transduction channels are closed, the cell is hyperpolarized, and the firing rate of the afferent fibres is reduced (Flock, 1965).

Two of the vestibular end organs, the saccule and the utricle, are situated at right angles to each other in the vestibule of the inner ear. Each of these organs contains a macula (neuro epithelium), in which the hair cells are found. The stereocilia and kinocilium of the hair cells project into a gelatinous mass, over which lies a fibrous membrane weighted by calcium carbonate crystals, called otoliths or otoconia. (Because the saccule and utricle both contain these crystals, they are also commonly referred to as the otoliths.) When the head moves or is tilted, the inertia of the crystals applies shearing forces on the otolithic membrane, which in turn causes bending of the hair cells and increased firing of the vestibular afferents. The hair cells are organized along curved ridges, known as striola, which divide the saccule and utricle roughly into halves. Hair cells on either side of the striola are oriented in opposite directions, so that head tilt along the striolar axis causes excitation of hair cells on one side and inhibition of cells on the other side (Spoendlin, 1966). The macula of the saccule is further oriented vertically, such that it responds to linear accelerations in the sagittal plane (i.e., up-down, forward-backward). The utricular macula, on the other hand, is positioned horizontally; its hair cells thus detect linear motion in the horizontal plane (i.e., side-to-side movements and head tilts). When the tilt stimulus is prolonged, the otoliths adapt and return to baseline firing rates, facilitating an optimal response for the next change in head position (Fernandez & Goldberg, 1976a, 1976b, 1976c).
Extending behind the vestibule are three orthogonally-positioned semicircular canals, each of which is responsible for responding to angular acceleration in a specific plane: the horizontal (lateral) duct detects movement around the vertical axis (e.g., turning the head to the left or right); the superior (anterior) duct senses rotation around the lateral axis (e.g., nodding the head); the posterior duct corresponds to motion around the anterior-posterior axis (e.g., doing a cartwheel). The base of each semicircular duct has an expansion, called the ampulla, within which hair cells of the crista ampullaris (neuroepithelium) are embedded into the cupula, a dense gelatinous mass (Brown, 1874). Unlike its otolithic analogue, the cupula is attached to the walls of the ampulla and does not allow endolymph to flow around or through it. As a result, rotational acceleration causes endolymph to distort the cupula, thus bending the hair cells and increasing neuronal firing. When the angular motion becomes constant, endolymph velocity matches that of the canal, and the cupula returns to its original position (Hillman & McLaren, 1979). Linear acceleration does not deform the cupula because the pressure exerted by the endolymph is equal on both sides of the cupula. Each semicircular canal works synergistically with its contralateral partner in the same plane. For example, a head turn to the left distorts the cupula of the left horizontal semicircular duct towards the kinocilium, depolarizing the hair cell and increasing the neural discharge of the left vestibular nerve. The same motion bends the hair cells of the right horizontal semicircular duct away from the kinocilium, concomitantly decreasing the firing rate of the right vestibular nerve. This paired excitation and inhibition of contralateral ducts allows the central nervous system to compute the direction and velocity of motion.

The hair cells of each vestibular end organ synapse onto bipolar neurons, the cell bodies of which are contained in Scarpa’s Ganglion. This vestibular ganglion is divided into two parts, a superior and inferior division, that are connected by an isthmus. The afferents from the crista ampullaris of the superior and horizontal semicircular ducts and the macula of the utricle are conducted through the superior division; a few fibres innervating the anterosuperior portion of the saccule also travel in this division. The inferior division carries sensory information from the crista ampullaris of the posterior semicircular duct and the principal part of the saccular macula. The two vestibular nerve
Chapter 1. Introduction

divisions merge to become the vestibular nerve, after which they join with the cochlear nerve to form cranial nerve (CN) VIII, the vestibulocochlear nerve. CN VIII then runs alongside the facial (VIIth) nerve before entering the internal acoustic meatus. After passing the cerebellopontine angle, CN VIII enters the brainstem at the pontomedullary junction. It is at this point that the vestibular portion of the nerve separates from the cochlear division and continues on to the ipsilateral vestibular nuclei complex, located in the rostral medulla and caudal pons. Some of the vestibular neurons also project, via the inferior cerebellar peduncle, to the flocculo-nodular lobe and vermis of the cerebellum.

The vestibular nuclear complex is made up of four major neuronal groups: the superior (Bechterew), medial (Schwalbe), lateral (Deiter’s), and inferior (descending) vestibular nuclei. The afferents from the semicircular ducts primarily synapse onto neurons in the superior and medial vestibular nuclei, although these neural groups also receive afferent fibres originating from the cerebellum. Secondary vestibular fibres arise from the superior nucleus and contribute to the medial longitudinal fasciculus (MLF), which innervates the nuclei responsible for motor control of the extrinsic eye muscles (oculomotor, trochlear, abducens and accessory oculomotor nuclei). The MLF is involved in conducting signals of the vestibulo-ocular reflex, which will be discussed subsequently. In addition to afferent input from the semicircular ducts and cerebellum, the medial vestibular nucleus receives synapses from the utricular macula. Efferent fibres from this nucleus project bilaterally to the ascending MLF and the descending vestibulospinal tracts, the latter of which innervates the cervical and thoracic spinal levels responsible for the muscles which support the head. Due to its involvement in controlling extraocular and cervical musculature, the medial nucleus plays an important role in coordinating the movements of the eyes and neck. The lateral vestibular nucleus receives afferents predominantly from the utricular macula, along with fibres from the vermis of the cerebellum. While the lateral nucleus does contribute to the MLF, it primarily sends efferents to spinal cord sections that innervate the motor neurons of the trunk and legs, making it an important centre for postural control and balance. Finally, primary afferents arriving from the saccular and utricular maculae terminate in the inferior vestibular nucleus. Efferent projections are numerous, travelling in the MLF and reticulospinal tract (which influences muscle tone),
and to the vestibulocerebellum (for precision control of posture) and the ventral posterior nucleus of the thalamus (which relays postural information to the cerebrum). To summarize rather simplistically, afferents from the semicircular ducts principally synapse on the superior and medial vestibular nuclei, with subsequent efferent projections concentrated on pathways which facilitate gaze stabilization; the otolithic afferents synapse mostly on the lateral and inferior vestibular nuclei, with efferent fibres travelling to nuclei and spinal cord areas responsible for postural control (Gacek & Lyon, 1974; for a review, see Kandel, Schwartz, Jessell, Siegelbaum & Hudspeth, 2013). It should be noted, however, that numerous fibres interconnect the vestibular nuclei, allowing these centres to integrate signals from multiple sources and influence musculature accordingly.

Sensory input provided by the vestibular end organs is used to drive three reflexes involved in stabilizing posture and vision during movement, namely, the vestibulo-ocular reflex, the vestibulospinal reflex, and the vestibulocollic reflex. The vestibulo-ocular reflex, the most well-studied reflex, is initiated when the semicircular ducts detect rotational movement of the head. In a three-neuron arc involving the medial and lateral vestibular nuclei along with the contralateral abducens and oculomotor nuclei, synergistic extraocular muscles are recruited to move the eyes in the opposite direction of head motion, thus allowing steady fixation on a target (Lorente de Nó, 1933). The simplicity of the reflex allows the system to respond to rotation in as little as 8.6 ms (Collewijn & Smeets JB, 2000). Vestibulospinal reflexes are initiated when the otoliths detect a change in centre of gravity during movement. Using the medial/lateral vestibulospinal tracts and reticulospinal tract, the vestibular nuclei and reticular formation recruit extensor and flexor limb musculature to generate the compensatory movements needed to maintain upright posture. Galvanic stimulation of vestibulospinal pathways demonstrates that this reflex occurs within 60-80 ms of stimulus onset (Britton et al. 1993; Watson & Colebatch, 1997). Although the vestibulocollic reflex is the least understood reflex of the three, it is believed to stimulate neck muscles in order to stabilize the head in space. The short-latency potentials that are recorded in response to acoustic (Bickford, Jacobson & Cody, 1964; Colebatch, Halmagyi & Skuse, 1994), galvanic (Watson & Colebatch, 1998)
and mechanic (Halmagyi, Yavor & Colebatch, 1995) stimulation are felt to be reflective of the di- or trisynaptic arc that is initiated in the otoliths (Uchino et al. 1997).

In addition to processing at the level of the vestibular nuclei, vestibular sensory input is relayed to the thalamus and then the cerebral cortex via crossed (i.e., contralateral) vestibulothalamic tracts, which run along the MLF (Dieterich & Brandt, 1993), and ipsilateral tracts, which border the medial lemniscus and synapse onto the posterolateral thalamus (Zwergal, Buttner-Ennever, Brandt & Strupp, 2008). A third, bilateral projection is believed to bypass the thalamic nuclei and terminate in the inferior insula (Dieterich et al. 2005). While the parieto-insular vestibular cortex has been characterized as a cortical processing hub in non-human primates (Guldin & Grusser, 1998), the identification of a primary vestibular cortex in humans has proven to be more challenging. The posterior insula and temporo-parietal junction have been proposed to fill this role (for a review, see Brandt & Dieterich, 1999), supported by evidence of impaired visual vertical perception (Barra et al. 2010), nystagmus (Nicita et al. 2010), vertigo (Boiten, Wilmink & Kingma, 2003) and postural instability (Cereda, Ghika, Maeder & Bogousslavsky, 2002) following lesions in this area. Vestibular projections extend to additional cortical regions, as demonstrated by neuronal activity in the somatosensory cortex (Fasold et al. 2002), premotor cortex (Lobel, Kleine, Bihan, Leroy-Willig & Berthoz, 1998), and hippocampus (Vitte et al. 1996) in response to stimulation of the vestibular end organs. Interestingly, a reduction in blood flow in the posterior cerebral artery, which supplies the occipital gyri, has been noted subsequent to vestibular stimulation (Tiecks, Planck, Haberl & Brandt, 1996; Wenzel et al. 1996). Moreover, deactivation of vestibular cortices has been reported during visual fixation and VOR habituation (Naito et al. 2003), suggesting that the occipital gyri and vestibular input processing centres might have reciprocally inhibitory influence on each other. These findings may also help to explain why fixating on an object helps to alleviate symptoms of motion sickness.

Inasmuch as the vestibular nuclei send projections up to the cortex via relay nuclei in the thalamus, the cortex mutually provides feedback to the system in a ‘top-down’ fashion. Neuronal tracing studies in animals have shown that, generally, vestibular nuclei receive
projections from diffuse regions of both cortical hemispheres (Akbarian, Grüsser & Guldin, 1993, 1994; Guldin, Mirring & Grüsser, 1993; Faugier-Grimaud & Ventre, 1989). There are some deviations from this principle, however, such as the projections from the parieto-insular vestibular cortex to ipsilateral medial and superior vestibular nuclei, especially to neural subsections involved in oculomotor control. The premotor and somatosensory cortices, on the other hand, preferentially provide input to the contralateral lateral and medial vestibular nuclei, which are involved in the vestibulospinal reflexes (Akbarian, Grüsser & Guldin, 1994). Vestibulo-ocular (gaze stability) and vestibulospinal (postural stability) thus appear to be influenced and modulated by higher cortical levels.

The design of the vestibular end organs facilitates an accurate representation of linear and rotational motion on the roll, yaw and pitch axes. The sensory input provided by these organs is then integrated and utilized by the vestibular nuclei to allow for reflexive responses to environmental changes. A cortical vestibular network further processes this sensory information and provides regulatory feedback to this system. Our sense of balance and spatial orientation is not solely dependent on vestibular end organ input, however, and the next section will describe how proprioception, vision, and audition are also involved in keeping us upright.

1.2.2 Proprioceptive, visual and auditory input

Proprioception refers to our ability to accurately identify the position of our body in space without using any of our other senses (e.g., sight, hearing, touch, etc.). Proprioceptive input extends beyond fulfilling a sensory purpose, however, in that the signals provided by specialized mechanoreceptors in muscles and joints are used to feed back to other modalities, including the vestibular system. Studies conducted in animal models have demonstrated that proprioceptive signals are integrated into the vestibular system rather quickly, even as early as at the level of first order neurons of the vestibular nuclei (Boyle & Pompeiano, 1981; Wilson, Yamagata, Yates, Schor & Nonaka, 1990). During active motion, activity in neurons of vestibular nuclei is dampened when proprioceptive input exactly matches the brain’s internal expectation of the provided motor command (Roy &
The authors suggest that this is the mechanism used by the central nervous system to distinguish between active (i.e., self-generated) and passive (i.e., externally generated) motion. Sadeghi and colleagues (2011) have further shown that following labyrinthine lesion, the vestibular nuclei compensate for the lack of vestibular input by developing an increased sensitivity to extra-vestibular input, such as proprioception. Furthermore, this re-weighting of proprioceptive input results in improved gaze stability (Sadeghi, Minor & Cullen, 2012). The impact of proprioception on balance can be observed not only at the neuronal level, but also at the gross functional level. Patients with Parkinson’s disease showed significant improvements on computerized balance and postural stability tests after receiving training sessions designed to increase awareness of body position. Notably, reductions in postural sway after training were observed during the ‘eyes-closed’ conditions of the balance tests, presumably because these tasks forced a dependence on proprioception in the absence of visual cues (Lefaivre & Almeida, 2015). Another study found that stimulation of the Achilles and Peroneus tendons, effectively perturbing proprioceptive signals from leg musculature, led to destabilization and increased postural displacement (Duclos, Maynard, Barthelemy & Mesure, 2014).

Age-related changes in balance compensation strategies have been explored, with elderly people (60-80 years of age) showing a greater dependence on proprioception rather than visual or vestibular input for postural control, especially when compared to young (20-39 years) and middle-aged (40-59 years) individuals (Wiesmeier, Dalin & Maurer, 2015). This increased reliance on internal representations of body position and movement is possibly due to the decline of exteroceptive senses, such as vision and hearing, that accompanies the ageing process.

Vision is another integral component of balance and postural stability, in that the sensory input provided by the eyes is used as a frame of reference to which the cerebellum compares internal expectations of motor commands. The Romberg test is often used to measure the contribution of the visual system to balance maintenance, in which an individual’s standing balance is examined under eyes-open and eyes-closed conditions (Black, Wall, Rockette & Kitch, 1982). Visual acuity is inversely proportional to postural instability, with body sway increasing by 20-70% when participants’ eyes are closed (Lord,
Clark & Webster, 1991; Magnusson, Enbom, Johansson & Pyykko, 1990; Paulus, Straube & Brandt, 1984). When static and dynamic equilibrium was assessed in children using the balance subtest of the Bruininks-Oseretsky Test of Motor Proficiency (hereafter referred to as BOT-2), all children performed worse on tasks if their eyes were closed, regardless of whether they had normal hearing or used a CI (Cushing, Gordon, Rutka, James & Papsin, 2008a). As discussed previously, the contribution of vision to equilibrium decreases in the elderly (over the age of 65) (Lord & Ward, 1994) due to the decline of sensory faculties in those populations. Barring the presence of vestibular dysfunction, one would expect that, in individuals with compromised visual systems, the eyes-closed condition of the Rhomberg test would eliminate any effect of visual acuity on balance. Indeed, Schwesig and colleagues (2011) found that on the eyes-closed, unstable-surface condition, participants with an acquired visual impairment performed equally to healthy controls with normal vision. It should also be noted that the complete removal of visual input is not always necessary to trigger postural instability; moving or misleading visual cues increase postural sway and the likelihood of falling (Borger, Whitney, Redfern & Furman, 1999; Chiarovano et al. 2015). Taken together, these findings indicate that visual cues are used by the central nervous system to detect whether we are moving or whether our environment is. The removal or distortion of these signals therefore compromises our ability to remain upright.

In addition to vestibular, proprioceptive, and visual input, auditory cues have been identified as playing a role in maintaining static equilibrium. Easton and colleagues (1998) reported improved stability, as determined by reduced centre-of-pressure deviation, when a 500 Hz square wave was binaurally presented to blind and sighted participants. The effects of auditory stimuli are small, however, when compared to visual or haptic feedback. More recently, a cross-sectional study measuring balance in bilateral hearing aid users found better performance in the aided than unaided conditions (Rumalla, Karim & Hullar, 2015). The authors suggest that using a hearing aid increases the salience of sound sources, which the nervous system then utilizes as landmarks to which its relative distance must remain constant. The presence of an auditory stimulus does not necessarily confer a benefit, however; the presence of a stationary sound field can lead to postural destabi-
lization (Raper & Soames, 1991), and a moving stimulus can cause increased deviations towards the location of the sound source (Agaeva, Al’tman & Kirillova, 2006). Performance on the Romberg test was significantly also better when conducted in a soundproof booth compared to a clinic room (Kanegaonkar, Amin & Clarke, 2012), highlighting the influence of ambience noises on postural control. As postulated by Ross & Balasubramaniam (2015), the effects of acoustic input on postural sway can be explained by the principle of stochastic resonance, whereby random noise serves to enhance central processing. Alternatively, the spatial cues offered by sound sources potentially supplement visual feedback and thus assist with maintaining static equilibrium. A contrasting theory is that the addition of sound to an environment possibly places an increased demand on cognitive resources for auditory processing, temporarily leaving fewer resources available for other functions, such as balance.

1.3 Assessing vestibular end organ function and gross balance

As discussed in the previous section, postural stability is a challenging endeavour mediated primarily via input from the vestibular system along with supplementary feedback from the proprioceptive, visual, and auditory systems. Considering the fundamental role of the vestibular system in maintaining static and dynamic equilibrium, vestibular research seeks to develop maneuvers capable of assessing the integrity of each vestibular end organ independently. The use of these focused techniques enables a clinician to potentially pinpoint the cause of a balance deficit and direct rehabilitative therapies accordingly. The following sections will thus explore a few of the methods used to objectively test function of the vestibular end organs – particularly the otoliths given their susceptibility to dysfunction in the setting of SNHL – in addition to measures of gross balance.
1.3.1 Evaluation of otolithic function

Despite early reports of myogenic potentials originating from the vestibular system in response to acoustic stimulation (Geisler, Frishkopf & Rosenblith, 1958; Bickford, Jacobson & Cody, 1964), the cervical vestibular evoked myogenic potential (cVEMP) was not accepted as a practical, clinical test until Colebatch and colleagues (1992, 1994) demonstrated that these potentials could be reliably recorded in the ipsilateral sternocleidomastoid muscle (SCM) using high-intensity, acoustic clicks. The response waveform was shown to have a biphasic morphology, with an initial positive peak (referred to as P1 or P13) followed by a negative deflection (N1 or N23). A variant of this response, the ocular vestibular evoked myogenic potential (oVEMP), has been recorded from the inferior extraocular muscles (Rosengren, McAngus & Colebatch, 2005) and has a similar waveform, but with the opposite morphology: a negative peak (N1 or N10) followed by a positive peak (P1 or P15). The numbers associated with the peak (cVEMP: P13, N23; oVEMP: N10, P15) are a reflection of the average latency of these peaks in relation to stimulus onset. In addition to acoustic stimuli, VEMPs can be elicited using bone-conducted sound presented to the mastoid bone (Sheykholeslami, Murofushi, Kermany & Kaga, 2000), although this does not allow for unilateral evaluation because the vibration travels through the skull to both ears. Galvanic stimulation can also be used to elicit VEMPs; it is unclear whether the electric current stimulates the system at the level of the hair cells (de Waele et al. 2002) or the vestibular nerve (Murofushi, Takegoshi, Ohki & Ozeki, 2002).

Although the cochlea is used for the detection of sound in humans, intracellular studies have shown that sound-sensitive fibres can arise from the saccule and utricle as well (McCue & Guinan, 1994; Murofushi & Curthoys, 1997). VEMPs are believed to be of vestibular origin because they can be elicited in patients with SNHL albeit intact vestibular function (Bickford, Jacobson & Cody, 1964), and due to the fact that these electrophysiologic responses disappear after vestibular deafferentation (Colebatch & Halmagyi, 1992). Ernst and colleagues (2006) provided additional evidence as to the saccular origin of the cVEMP when, during lateral skull-based surgery, they used needle electrodes
to directly stimulate the inferior vestibular nerve and evoke these potentials. cVEMPs were not present when the superior division of the vestibular nerve was stimulated, which is not surprising when one considers that the otolithic contributions to the superior nerve are predominantly from the utricle. It is generally felt that the close proximity of the saccule to the stapes footplate renders it susceptible to stimulation by endolymph pressure waves that are generated with a loud acoustic stimulus. This, in turn, excites the hair cells of the saccular macula and drives a derivative of the vestibulo-collic reflex. Inhibitory neurons from the vestibular nuclei project down to the ipsilateral SCM to generate this reflex, which is why the muscle must be actively contracted in order for a response to be recorded. The positive peak of the response correlates to a brief inhibition of the SCM, while the negative peak is the result of muscle excitation (Colebatch & Rothwell, 1993, 2004).

While cVEMPs are best recorded from the SCM ipsilateral to the ear being stimulated, oVEMPs are best visualized when recording electrodes are placed over the inferior oblique muscle contralateral to the stimulated ear (Rosengren, McAngus & Colebatch, 2005). The crossed nature of this vestibular response was confirmed by Iwasaki and colleagues (2007), who found present bilateral potentials in healthy subjects, but no responses contralateral to the side which had previously undergone a vestibular nerve section. While the exact origin of this response is unclear, there is evidence to suggest it is a utricular response: patients with superior vestibular neuritis have clear cVEMP responses but absent oVEMP (Manzari, Burgess & Curthoys, 2010; Shin et al. 2012), indicating that the oVEMP is dependent on the superior branch of the vestibular nerve. As mentioned previously, it is this nerve which supplies the utricle. Some afferents from the saccule do, in fact, travel through the superior vestibular nerve, yet their projections to the extraocular muscles are rather limited in comparison to utriculo-ocular projections (Isu et al. 2000). oVEMP differs from cVEMP in that they are not inhibitory potentials, however, the response amplitudes are still dependent on tonic activity of the inferior oblique muscle. When gaze is maximal in the upward direction, the inferior oblique muscle is brought closer to the recording electrodes. In addition, this maneuver increases
the tonic contraction of the muscle, resulting in larger oVEMP amplitudes (Rosengren, Colebatch, Straumann & Weber, 2013).

Clinically, VEMPs are used to assess the health of the vestibular end organs and the nerves that innervate them: absent responses have been reported in ears affected with peripheral vestibulopathies, including Ménière’s disease (de Waele, Huy, Diard, Freyss & Vidal, 1999), vestibular neuritis (Murofushi, Halmagyi, Yavor & Colebatch, 1996), and vestibular schwannoma (Patko, Vidal, Vibert, Tran Ba Huy & de Waele, 2003); decreased thresholds and abnormally large amplitudes of VEMPs are seen in patients with superior canal dehiscence (Zuniga, Janky, Nguyen, Welgampola & Carey, 2013); prolonged peak latencies are a manifestation of multiple sclerosis (Escorihuela Garcia, Llopez Carratala, Orts Alborch & Marco Algarra, 2013). The fact that bilateral VEMPs can be elicited in all normal-hearing children (Kelsch, Schaefer & Esquivel, 2006; Kastanioudakis, Saravakos, Leontis, Balatsouras & Ziavra, 2015; Pereira et al. 2015) raises the question: what does an absent response represent? Before this is answered, the methods used to elicit VEMPs must be evaluated to avoid the possibility of false negative outcomes. Firstly, the intensity of the stimulus must be high enough to evoke a clear response. The amplitude of c- and oVEMPs has been shown to decrease proportionately to decreases in stimulus intensity until the acoustic sound no longer contains sufficient energy to generate a response (Zhang, Xu, Zhang, Yang & Chen, 2014). An intensity of 95-105 decibels (dB) above normal hearing level, which corresponds to 115-130 db sound pressure level, is typically used (for a review, see Isaradisaikul, Navacharoen, Hanprasertpong & Kangsanarak, 2012). Secondly, insufficient SCM contraction increases the likelihood of a false negative result. In a report of the relationship between muscle contraction and cVEMP, Rosengren (2015) notes that although the mean electromyographic activity required for a present response was $24.8 \pm 11.4 \mu V$, some participants needed a contraction of $60 \mu V$ before a VEMP was evoked. The author suggests that confidence in the true absence of a response decreases when SCM contraction falls below $60 \mu V$. To date, the minimum contraction of the inferior oblique muscle needed to observe an oVEMP has not been investigated. Since the cVEMP and oVEMP reflect vestibulo-colic and vestibular-ocular reflex pathway function, respectively, an absent response – after controlling for the afore-
mentioned factors – thus indicates the existence of a lesion along any point of the reflex pathway.

One limitation to the VEMP is that the response is a non-physiologic reflex with a poorly understood impact on actual balance function. The static Subjective Visual Vertical (SVV) test, on the other hand, measures perceived tilt in the roll axis (i.e., spatial orientation) and therefore offers more practical insight into otolith function. The test involves manipulating a projected line until it appears to be completely vertical. Assessment is done in the dark so that external visual cues cannot be used as a frame of reference, imposing a dependence on otolithic input. Normative data collected from healthy children (Brodsky et al. 2015, 2016) and adults (Zwergal et al. 2009) demonstrate that estimation of the visual vertical is typically accurate to within 2 degrees of the true, gravitational vertical. By assessing perceived orientation of the vertical plane, the SVV test effectively evaluates for a discrepancy between the utricular input arising from each ear (Friedmann, 1971; Dieterich & Brandt, 1993; Schonfeld, Helling & Clarke, 2010; Funabashi et al. 2015). Acute unilateral peripheral vestibular hypofunction is commonly characterized by, among other symptoms, the presence of a perceptual tilt towards the compromised ear. The direction of SVV tilt has been shown to be indicative of the location of a lesion in the brainstem or cortex, in that ipsiversive tilts are manifestations of insults caudal to the upper pons, while contraversive tilts are secondary to more rostral lesions (Brandt et al. 1993, 1994). This tilt typically resolves over time as central vestibular centres compensate for the asymmetric utricular input (Vibert et al. 1996, 1999; Strupp, Arbusow, Maag, Gall & Brandt, 1998; Min et al. 2007; Kim et al. 2008; Sadeghi et al. 2010, 2011, 2012). Patients with bilateral vestibular loss score similarly to control groups (Tabak et al. 1997; Guerraz et al. 2001), although closer examination of their SVV reveals greater inter-trial variability (Funabashi et al. 2012). Even though the oVEMP and SVV both evaluate utricular function, a handful of studies (Kim, Lee & Kim, 2014; Nagai et al. 2014) investigating the relationship between the two tests found no correlation between absent oVEMPs and abnormal SVV scores. These findings can be attributed to central compensatory mechanisms that cause the SVV to return to normal after a period of time, even when the otoliths are no longer functional (Vibert et
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As this test not a reflection of peripheral vestibular function alone, the SVV should be used in conjunction with other methods of evaluating the integrity of the vestibular end organs (e.g., VEMPs).

1.3.2 Evaluation of semicircular duct function

While 'static' symptoms, such as tilt of the visual vertical or perception of linear motion, are typically indicative of otolith dysfunction, insults to the semicircular ducts are usually the cause of 'dynamic' imbalance, which manifests as rotational vertigo or nystagmus, for example. First described by Robert Bárány in 1903, caloric testing involves the use of water (or air, occasionally) to change the temperature of the middle ear, producing convection currents in the endolymph of the horizontal canal as a result. In an intact system, warm water excites hair cells of the lateral duct and mimics a head turn towards the ear being stimulated (Cawthorne & Cobb, 1954). This, in turn, generates contralateral eye movements ("slow phase") followed by corrective saccades ("fast phase") toward the stimulated side. When a cold stimulus is employed, the opposite occurs; a head turn to the opposite side is mimicked, generating slow phase eye movements towards the stimulated ear followed by corrective fast phase movements. An advantage of the caloric test is that it allows for independent evaluation of each ear and is thus highly sensitive to a unilateral deficit. The nature of the test, however, only permits assessment of the horizontal semicircular duct. Another drawback is that caloric stimuli simulate angular movements of 0.002 to 0.004 Hz, while daily rotational motion most often occurs in the range of 0.5 to 7 Hz (Hess, Baloh, Honrubia & Yee, 1985; Shepard & Telian, 1996).

Using high-acceleration movements of the head, the head-impulse test (Cremer et al. 1998; Halmagyi & Curthoys, 1988) improves on the caloric test by providing stimuli in the functional range of the vestibular system. To conduct the assessment, the subject fixates on a target while the examiner rapidly rotates the subject’s head to one side. A normally functioning vestibulo-ocular reflex enables the subject to counteract head rotation with eye movement in the opposite direction, such that ratio between head and counter-rotational eye motion is 1:1 (a “gain” of 1.0). When the semicircular ducts are
hypofunctional, the vestibular system is unable to generate the movements that keep the eyes stable in space (gain <1.0), necessitating saccades which re-acquire visual fixation on the target. These compensatory saccades can be detected through surface electrodes or high-resolution video recordings. Besides utilizing high-frequency stimuli which are more representative of physiologic conditions, the head-impulse test is advantageous over caloric stimulation due to its ability to measure superior and posterior, in addition to horizontal, duct function. It is imperative that a wide variety of evaluations are used while assessing vestibular function, as a high-frequency deficit can go undetected by the caloric test (Prepageran, Kisilevsky, Tomlinson, Ranalli & Rutka, 2005).

1.3.3 Evaluation of gross balance function

Unlike the aforementioned tests which evaluate the function of specific sensory organs, posturography measures the central nervous system’s ability to integrate input across multiple sensory modalities (vestibular, proprioceptive, visual and auditory) in order to effectively maintain an upright stance. Static posturography assesses steadiness by means of force plates which detect oscillations in body movements when a person is standing. The equipment used in dynamic posturography differs slightly, in that the force plate can be translated horizontally or rotated by electric motors that are controlled by a computer. Individuals’ responses to such regulated, reproducible external perturbations can then be recorded and compared. Sensory organization tests involve the use of dynamic visual environments which create the illusion of movement. Comparing changes in postural stability subsequent to manipulation of various senses facilitates a comprehension of the relative contributions of each modality to balance.

The Bruininks-Oseretsky Test of Motor Proficiency (Bruininks & Bruininks, 2005) is a standardized test designed to evaluate proficiency in motor and manual coordination, strength and agility. While the test may take up to 60 minutes to complete in its entirety, subsections (including the balance subtest, which will be referred to as BOT-2) can be administered as quickly as 10-15 minutes. Nine tasks evaluate a child’s ability to balance while stationary or moving while successively introducing new challenges, such
as balancing on one foot, closing the eyes, and standing on a balance beam. Normative
data collected from 1,520 children and young adults between the ages of 4 and 21 enable
the comparison of balance scores between individuals, regardless of age or sex.

1.4 Embryologic, physiologic and genetic link between
the cochlea and peripheral vestibular system

The techniques discussed in the previous section have been employed to evaluate vestibu-
lar end organ function in numerous populations, particularly with the intent of elucidating
the complex relationship between the end organs and other sensory systems. Interest-
ingly, vestibular dysfunction is overwhelmingly prevalent in children with SNHL (O’Reilly
et al. 2010), including those who qualify for cochlear implantation (Cushing et al., 2008b,
2013; Janky & Givens, 2015). Moreover, the degree of hearing loss correlates better with
otolith dysfunction in comparison to semicircular duct deficits (Tribukait, Brantberg &
Gergenius, 2004), implying a close relationship between the cochlea and otoliths.

The link between the sensory organs for hearing and balance is first seen during the em-
bryologic development of the inner ear. Around the fourth week of human development,
the otic placode arises from the ectoderm and invaginates to form the otic vesicle, the
precursor to most cell types found in the inner ear. (Incidentally, one can appreciate the
embryologic association of somatosensation with balance, in that the ectoderm gives rise
to both the inner ear and the skin [i.e., touch].) The dorsal segment of the otic vesicle
forms the utricle and the semicircular canals, or the upper portion of the vestibular end
organs. The ventral section, on the other hand, differentiates into the saccule. Around
the fifth week of development, the anterior aspect of the saccule protrudes outward in a
spiral fashion, forming the cochlea. The cochlea thenceforth remains connected to the
saccule, and thus the vestibular end organs, via the ductus reuniens.

In addition to close anatomic proximity and shared embryologic origin, the physiology
of the vestibular apparatus and the cochlea is similar, particularly in regards to their
neuroepithelium. Both systems use hair cells with stereocilia that are embedded into a mass: the organ of Corti in the cochlea, otoconia in the otoliths, and the cupula in the semicircular ducts. Disturbances in this mass cause the hair cells to bend, resulting in depolarization and increased afferent firing. Moreover, the conduction of stimuli to hair cells of the cochlea and to those of the end organs occurs through the same fluid: endolymph. The continuity of the membranous labyrinth and concurrent use of endolymph mean that physiologic perturbations can have devastating ramifications on the cochlea and vestibular apparatus. For example, the change in endolymphatic pressure and volume observed in Ménière’s disease leads to SNHL along with vestibular dysfunction (for a review, see Gürkov, Pyykö, Zou & Kentala, 2016).

The anatomic and physiologic parallels between the cochlea and vestibular end organs are presumably underpinned by similarities in their genetic makeup. Phosphatidylinositol phosphatase is a component of hair cell tip links, and deletions in the gene that encode this protein cause high-frequency deafness in mice (Goodyear et al. 2003). In a later study, Goodyear (2012) reported that although murine behaviour did not indicate vestibular deficits, objective evaluation of the vestibular maculae revealed severe dysfunction of the stereocilia. Mutations in this protein are known to cause non-syndromic deafness in humans (Schraders et al. 2010), with associated vestibular deficits and delayed motor development. Protocadherin 15 is another constituent of cochlear and vestibular hair cell stereocilia, and mutations in this gene have been associated with profound hearing and vestibular impairment in humans (Ahmed et al. 2003; Ben-Yosef et al. 2003). Genetic similarities between the cochlea and vestibular apparatus are further seen in the genes that encode for proteins, such as otoferlin, used to dock synaptic vesicles to the cell membrane and release neurotransmitter. Though the role of this protein in cochlear hair cell function is understood and mutations lead to deafness in humans (Roux et al. 2006), its function in the vestibular hair cells is unclear. Knockout mouse models exhibit vestibular evoked potentials with prolonged latencies, which are seemingly the result of delayed neurotransmitter release at the vestibular hair cell synapse (Dulon, Safieddine, Jones & Petit, 2009). Finally, SLC4A11 is a gene found in the sensory organs of the membranous labyrinth, and is believed to encode for a cotransporter responsible
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for recycling potassium and maintaining ionic homeostasis (Lopez et al. 2009). Mice with mutations in this gene have atypical auditory brainstem responses and vestibular evoked potentials (Lopez et al. 2009); SLC4A11 mutations in humans have similarly been associated with Harboyan syndrome (Desir et al. 2007), which is characterized by hearing loss and nystagmus.

The close anatomic proximity, shared embryologic development, and physiologic and genetic similarities of the cochlea and vestibular end organs conceivably increase the likelihood of concurrent insult to these sensory structures. The next section will discuss how vestibular dysfunction, as determined using the methods described in section 1.3, is highly prevalent in the context of SNHL.

1.5 Concurrent cochlear and vestibular dysfunction

A recent retrospective review of balance disorders in children (O’Reilly et al. 2010) found that while the overall prevalence of vestibular dysfunction in children was low, individuals who were diagnosed with peripheral vestibular deficits were 43 times more likely than the general pediatric population to also have SNHL. Indeed, vestibular deficits are ubiquitous in children who are profoundly deaf, with numerous studies reporting that between 20% and 91% of participants exhibit some form of impairment (Zhou, Kenna, Stevens & Licameli, 2009; Inoue et al. 2013; Xu et al. 2016; Tribukait, Brantberg & Gergenius, 2004; Cushing et al. 2013; Jacot, Van Den Abbeele, Debre & Wiener-Vacher, 2009; Shinjo, Jin & Kaga, 2007). This extensive range can be attributed to a particular study’s focused evaluation of an end organ subset (e.g., otoliths or semicircular ducts), and to the various tests used to assess the same end organ (e.g., calorics or head-impulse to evaluate semicircular duct function). Akin to the variable severity of hearing loss, vestibular deficits can be partial or complete (Rosenblut, Goldstein & Landau, 1960; Jacot, Van Den Abbeele, Debre & Wiener-Vacher, 2009) and can be unilateral or bilateral (Cushing et al. 2013).
The complex relationship between the cochlea and the end organs is made readily apparent as one appreciates the variability in vestibular function across, and even within, etiologies of SNHL. For example, it is well known that polymorphisms in the GJB2 gene cause anomalies in the gap junctions of cochlear hair cells, leading to congenital deafness. When the integrity of the end organs was assessed in individuals with a GJB2 mutation, saccular function was severely reduced while the utricles and semicircular ducts were left unscathed (Todt, Hennies, Basta & Ernst, 2005). This finding was reiterated in a second study in which children with a GJB2 polymorphism predominantly demonstrated saccular areflexia. Although horizontal canal dysfunction was observed in response to caloric and rotational stimulation, it was mild and generally unilateral (Cushing et al. 2013). The same study found that meningitis, in contrast, appears to detrimentally affect the horizontal canals, as bilateral areflexia was displayed by nearly all of the children. Saccular function, however, was intact. In support of these results, the study of human temporal bones reveals that the inflammatory response to bacterial meningitis is limited to the scala tympani, scala vestibuli, and horizontal semicircular canal (Merchant & Gopen, 1996). It is yet unclear as to why the otoliths do not succumb to the same inflammation that incapacitates the remaining sensory structures of the inner ear.

The vestibulo-cochlear relationship extends beyond the cause of sensory loss, such that increased impairment of auditory function is also associated with the increased likelihood of vestibular dysfunction. Tribukait and colleagues (2004) found that when a child’s pure tone average was better than 90 dB, they also demonstrated normal vestibular responses. Hearing levels greater than 100 dB were correlated with declining vestibular, particularly utricular, function. Likewise, Niu and colleagues (2016) have shown that children with profound hearing loss were more likely to report vertigo and have abnormal caloric responses, suggesting that there is a heightened risk of vestibular end organ impairment as the severity of hearing loss increases. Although correlations between hearing loss and vestibular function do appear to exist, the degree of auditory deficits cannot be reliably used to predict end organ weakness, as one study demonstrated that 16.1% of children with normal hearing thresholds had absent vestibular responses, whereas 43.3% of children with elevated hearing thresholds demonstrated normal end organ function.
(Rosenblut, Goldstein & Landau, 1960). It is also possible that structures that are anatomically closest to the cochlea are most likely to be detrimentally impacted by physiologic changes in this organ. Analysis of otolithic and semicircular duct assessment conducted in patients with idiopathic sudden SNHL revealed the greatest percentage of abnormal responses was captured by the cVEMP, followed by the oVEMP, and then the caloric test (Fujimoto et al. 2015). Citing similar findings by Iwasaki (2005), the authors surmise that the end organs adjacent to the cochlea (i.e., the saccule and utricle) are preferentially impacted by sudden SNHL compared to the semicircular ducts, which are situated farther away.

1.6 Impact of vestibular impairment on function in children with a sensorineural hearing loss

Identifying vestibular end organ dysfunction is critical in order to appreciate the various sequelae of inner ear pathologies; nevertheless, these systemic findings must also be placed in functional context. When children with a hearing loss are assessed for postural stability and balance, they are repeatedly found to perform worse than their normal-hearing peers, especially when challenges, such as a balance beam or foam pad, are introduced (Derlich, Krecisz & Kuczynski, 2011; Melo Rde, Lemos, Macky, Raposo & Ferraz, 2015; Cushing et al. 2008a; de Sousa, de Franca Barros & de Sousa Neto, 2012). Children who are deaf but have intact vestibular function perform better on balance and motor tasks than children who have auditory and vestibular impairment (Maes, de Kegel, Van Waelvelde & Dhooge, 2014). Interestingly though, they still perform worse than children who have normal hearing and vestibular responses, supporting the notion that the auditory system is instrumental in the maintenance of postural stability, as discussed in section 1.2.2.

Early efforts to identify a relationship between measures of vestibular and balance function revealed that children with reduced semicircular duct function, as evaluated by caloric testing, reached motor developmental milestones, such as sitting and head control, later in life than those with normal function (Rapin, 1974; Kaga, Suzuki, March
& Tanaka, 1981). In a more recent, comprehensive assessment of end organ function, abnormal VEMP responses or the combination of abnormal VEMPs and rotational chair assessment were better predictors of a motor developmental delay than rotational chair results alone (Inoue et al. 2013). This is likely because the otoliths send numerous projections to the musculature of the neck and limbs, so an insult to these organs has more of an impact on motor milestone achievement than injury to the semicircular ducts. Normal saccular function is further correlated with better function of static balance, particularly when the task involves standing on one foot, either on a line or on a balance beam (Jafari & Asad Malayeri, 2011). The semicircular ducts appear to play a role also in maintaining equilibrium, as the VOR gain evaluated by rotational chair technique equally predicted balance performance as the presence or absence of a VEMP (de Kegel, Maes, Baetens, Dhooge & Van Waelvelde, 2012). Furthermore, rotational testing more robustly correlates with static and dynamic equilibrium compared to caloric assessment, perhaps due to the ability of the rotational chair to identify patients with an isolated high-frequency vestibular loss (Cushing et al. 2008b). Janky and Givens have recently (2015) proposed a method of quantifying vestibular function by combining results from the cVEMP, oVEMP, and head-impulse test to account for the integrity of the saccule, utricle, and semicircular ducts, respectively. This holistic quantification of vestibular function demonstrated that children with greater degrees of end organ dysfunction performed worse on tests of dynamic visual acuity and motor function.

Though vestibular dysfunction and its effect on balance and motor abilities have been reported in this population, the impact of vestibular impairment on spatial orientation, as measured by the Subjective Visual Vertical (SVV), has not been investigated in children with SNHL. Much of the research to date has focused on visual vertical perception in adults (see section 1.3.1), yet Brodsky and colleagues (2016) have recently demonstrated that the evaluation of SVV in pediatric patients is, in fact, feasible. Moreover, the use of a smartphone application increases participant compliance without sacrificing test sensitivity for detecting peripheral vestibular loss (Brodsky et al. 2015). One of the aims of the present study is thus to evaluate vestibular function in children with SNHL who use CIs and ascertain how such deficits impact their perception of the vertical plane.
1.7 Central compensation for peripheral vestibular loss

It has been noted that despite presenting with profound vestibular deficits, children with SNHL are able to ambulate and navigate their environment quite well (Xu et al. 2016). Indeed, only when balance tasks are sufficiently challenging do performance deficits begin to emerge, differentiating these children from normal-hearing controls (Cushing et al. 2008a). The ability of children with cochleovestibular loss to operate quite normally in daily life suggests the use of compensatory strategies facilitated by the central nervous system and other sensory modalities. One way that compensation may occur following vestibular loss is through the restoration of balanced activity between the vestibular nuclei in the brainstem. At rest, the primary vestibular afferent fibres spontaneously discharge, providing tonic input to the vestibular nuclei. There are approximately 20,000 afferent fibres in non-human primates, each of which discharges at 80-100 spikes per second (Gacek & Rasmussen, 1961; Minor & Goldberg, 1991). Movement towards one side causes increased discharge of the ipsilateral fibres and decreased discharge of the contralateral fibres, allowing for the sensitive detection of movement. The partial/complete unilateral/bilateral loss of peripheral input, therefore, causes asymmetric stimulation of the vestibular nuclei, resulting in static symptoms (Smith & Curthoys, 1988), like nystagmus, skew deviation, head and body tilt. Following unilateral lesion, pre- and postsynaptic processes, such as gene expression, cell membrane modification and enhanced neurotransmitter output (Darlington & Smith, 2000), can undertake rebalancing excitatory input to the vestibular nuclei. This ‘artificial’ restoration of balanced input appears to benefit the system, as evidenced by the amelioration of vestibular symptoms (Zennou-Azogui, Borel, Lacour, Ez-Zaher & Ouaknine, 1993).

A second manner by which compensation may occur is sensory substitution for lost vestibular input. As signals from the end organs are supplemented by vision and proprioception, the central nervous system has the liberty to reweight sensory information depending on environmental context. It has been suggested that the perception of a
stable surface results in a predominant reliance on somatosensation for postural stability, while increased dependence on vestibular input is consequent to the detection of an unstable surface (Mergner & Rosemeier, 1998). Children with SNHL and associated vestibular deficits perform equivalently to normal controls on measures of postural stability when only visual input is removed (Enbom, Magnusson & Pyykko, 1991). When the participants perform the same test while standing on foam rubber, which effectively distorts proprioceptive and somatosensory input, children with vestibular loss perform significantly worse than normally-hearing controls on tasks. Furthermore, when children with SNHL who use CIs were evaluated on measures of static and dynamic equilibrium, they showed clear functional deficits when their eyes were closed. This dependence on visual input was, however, seen equally in children with SNHL and normal-hearing controls (Cushing et al. 2008a). Taken together, these studies demonstrate that, compared to their normal-hearing peers, children with a congenital cochleovestibular loss depend on exteroceptive senses due to deficient vestibular input, albeit with a preference for the somatosensory and proprioceptive modalities.

In response to the loss of sensory information from the vestibular system, compensatory mechanisms are employed by individual cells and, more globally, by the central nervous system, allowing children with cochleovestibular deficits to function daily. Moreover, many of the rehabilitative therapies made available to this pediatric subgroup focus on refining these naturally-employed strategies for more efficient performance. Recently, however, a different approach is being explored: instead of developing mechanisms of dealing with lost vestibular input, can stimulation be artificially provided to this system similarly to how a CI offers auditory rehabilitation for individuals who are deaf? If so, does supplying this stimulation confer a functional benefit to the recipient?
1.8 Electrical stimulation of the peripheral vestibular system

Considering that air-, bone-, and water-conducted stimuli can excite the maculae of the otoliths and the crista ampullaris of the semicircular ducts, it comes as no surprise that galvanic (electric) current can similarly stimulate the vestibular end organs. Using squirrel monkeys, Goldberg and colleagues (1982, 1984) demonstrated that electric current applied via electrodes bypassed the mechanical stages of sensory transduction and directly stimulated the postsynaptic trigger zone of vestibular afferents enveloping Type I cells. Hair cell afferents can be stimulated with small amounts of current (sometimes with a little as 5 µA), and irregularly-firing afferents show a heightened sensitivity to stimulus polarity as compared to regular-firing afferents (Kim & Curthoys, 2004). Early work suggested that galvanic current preferentially stimulated the otoliths. Day and colleagues (1997) demonstrated that postural tilts occur toward the anode, the electrode terminal previously shown to reduce afferent firing (Goldberg, Fernandez & Smith, 1982; Kim & Curthoys, 2004). They hypothesized that the anode unilaterally reduced otolithic activity, which was then interpreted by the central nervous system as an incline of the support surface, in turn causing postural adjustments to the ‘elevated’ side. Supporting evidence of preferential otolith stimulation was provided by Zink and colleagues (1997), who showed that tilt of the visual vertical occurred in the absence of nystagmus. In contrast, Breson (1971) and Kleine (1999) recorded nystagmus, and thus semicircular duct activity, in response to galvanic stimulation. Animal work further implied no preferential stimulation of particular sensory organs (Goldberg, Fernandez & Smith, 1982; Kim & Curthoys, 2004). It is thus apparent that galvanic current can stimulate the afferents of both the otoliths and semicircular ducts, though differences between individuals are observed (MacDougall, Brizuela, Burgess & Curthoys, 2002).

Cervical and ocular VEMPs – assessing the vestibulo-collic and vestibulo-ocular reflexes, respectively – have been evoked using transmastoid (Watson & Colebatch, 1998; Rosen gren, Jombik, Halmagyi & Colebatch, 2009) and promontory (Park, Shen & Westhofen,
galvanic stimulation. Electrically-evoked responses peak at shorter latencies than tap-evoked (Rosengren et al. 2009) or acoustically-evoked (Park et al. 2015) responses, consistent with animal work demonstrating that galvanic current stimulates the vestibular afferents or nerve fibres rather than the end organ hair cells (Goldberg et al. 1982, 1984). The amplitudes of galvanically-evoked c- and oVEMPs positively correlate with increasing stimulus intensities, though a saturation of the response is seen at high current intensities (Watson & Colebatch, 1998; Rosengren et al. 2009; Aw, Todd & Halmagyi, 2006). VEMPs elicited from the soleus muscle in response to galvanic current have larger amplitudes than acoustically-evoked VEMPs, even when these responses are normalized to pre-stimulus electromyographic activity (Bacsi, Watson & Colebatch, 2003). Bacsi and colleagues (2003) propose that this difference in amplitude is due to the differential recruitment of afferent populations in response to acoustic versus electric stimulation.

Subsequent to reports on the impact of galvanic current on postural tilt (Day, Severac Cauguil, Bartolomei, Pastor & Lyon, 1997), there has been increasing interest concerning the influence of such stimulation on spatial perception, as measured by the SVV. When the anode was placed on the left mastoid process of healthy participants, deviations of the visual vertical were biased towards the left. Likewise, when the anode was situated behind the right mastoid process, participants’ SVV shifted to the right (Tardy-Gervet & Severac-Cauguil, 1998; Volkening et al. 2014). As mentioned previously, the anode reduces vestibular afferent firing, briefly simulating in these healthy subjects the conditions of a peripheral vestibular lesion. Indeed, the perceptual tilt of healthy participants towards the anode is comparable to that of patients with peripheral vestibular impairment, who often demonstrate a baseline perceptual tilt toward their lesioned side (Dieterich & Brandt, 1993; Brandt et al. 1993, 1994; Min et al. 2007; Kim et al. 2008; Schonfeld, Helling & Clarke, 2010). Although the introduction of galvanic stimulation to healthy individuals causes an abnormal shift in perception, the opposite occurs in those with a pre-existing visual tilt. Patients with right hemispheric cortical lesions demonstrate abnormal perceptual tilts to the left during baseline testing. The application of a galvanic stimulus, however, reduces perceptual tilt error, particularly when the stimulation is pro-
vided to the left vestibular end organs (Saj, Honore & Rousseaux, 2006; Oppenlander et al. 2015).

1.8.1 Vestibular prostheses

As previously discussed, galvanic stimulation presented over the mastoid can stimulate the peripheral vestibular system, as evidenced by electrically-evoked potentials, and induce vestibular-dependent perceptual and postural changes in humans. A limitation of this technique, however, is the distance between the stimulation’s source and target, as current can potentially spread to neighbouring structures and cause unwanted effects. A device analogous to a CI is therefore being designed that captures head motion, transduces that stimulus into electrical energy, and then stimulates the vestibular afferents to provide meaningful sensory input regarding movement. In a series of experiments spearheaded by Suzuki and Cohen (Cohen, Suzuki & Bender, 1964, 1965; Suzuki, Goto, Tokumasu & Cohen, 1969), implanted electrodes were used to selectively stimulate the afferents of individual ampullae and evoke corresponding eye movements that mimicked natural responses to motion. Since then, the impact of chronically stimulating the peripheral vestibular apparatus is being investigated in animal models and a few human subjects.

One of the difficulties of implanting a vestibular prosthesis is the anatomic organization of the vestibular end organs and nerves in the inner ear. A CI that is inserted into the cochlea is simultaneously close to the hair cell afferents and, should those afferents retract following implantation, the spiral ganglion for direct cell body stimulation. The vestibular end organs, in contrast, are situated at a distance from Scarpa’s ganglion. A surgically-implanted prosthesis inserted into the semicircular duct ampullae would essentially be rendered useless if the corresponding afferents were to retract. Moreover, perforation of the membranous labyrinth can occur while inserting the electrode array and result in a hearing loss, as observed in a few rhesus monkeys (Bierer et al. 2012). Direct stimulation of Scarpa’s ganglion is also undesirable, as it would lead to a loss of vestibular sub-modality specificity and increase the likelihood of facial nerve injury.
An intermediate approach has recently been proposed (van de Berg, Guinand, Guyot, Kingma & Stokroos, 2012) that reduces invasion of the ampulla while retaining the ability to selectively activate individual ampullary nerves.

A goal of vestibular prosthetic implantation is to restore the tonic, baseline activity of the vestibular afferents without causing nystagmus and vertigo. Animal studies (Merfeld et al. 2006; Merfeld, Haburcakova, Gong & Lewis, 2007) reveal that initial activation of the implant causes nystagmus that takes a few days to subside. The exhibited behavioural response diminishes with repeated exposures, indicating an adaptation to the electric current. A follow-up study in a deaf participant receiving a modified CI showed that adaptation to continuous vestibular stimulation also occurs in humans, albeit at a faster rate; after initial activation of the implant, nystagmus was absent from tracings in under half an hour (Guyot, Gay, Kos & Pelizzone, 2012). Although repeated exposures similarly reduced the time needed to adapt to the stimulation and eliminate behavioural responses, an inter-stimulation rest period of only 18 hours was sufficient to extinguish the adaptation phenomenon. Once the vestibular system had acclimatized to chronic stimulation, modulation of the electric stimulation induced smooth, oscillating eye movements.

Initial efforts to optimize stimulus parameters determined that current pulse frequency and intensity increased evoked eye movement response amplitudes, though the latter also shifted the axis of movement, presumably due to the spread of current to the adjacent semicircular organs (Davidovics, Fridman, Chiang & Della Santina, 2011). Changing the interphase gap had no effect on responses, but shorter pulse durations (less than 340 µs) more effectively elicited response amplitudes without shifting movement axes due to the use of lower amounts of electric charge. A second study found that, once non-human primates had habituated to electrical stimulation, co-modulation of the current pulse rate and intensity was most successful at evoking a wide range of vestibulo-ocular reflex amplitudes compared to modulation of either pulse frequency or intensity alone (Davidovics et al. 2013). Vestibular prostheses have recently been implanted in patients with Ménière’s disease (Phillips et al. 2015) and bilateral vestibular loss (Guinand et al.
2015), and are well-tolerated while being used to evoke robust eye movements. Unlike prior animal studies, pulse rate was less effective than current amplitude at modulating slow phase velocity movements (Phillips et al. 2015), a surprising result in light of the fact that the vestibular system uses afferent firing rate to encode for head movements. The authors postulate that the effect of current intensity on slow phase velocity is due to the recruitment of a greater number of afferents and is nonphysiologic. Patients further reported perceived motion in the same direction as their slow phase eye movements, indicating a consistent effect of electrical stimulation on vestibular processing centres in the brainstem and cortex. In addition to vestibulo-ocular reflexes and perceived motion, electrical stimulation from a vestibular implant is known to induce postural responses that are specific to the semicircular duct that is stimulated (Phillips et al. 2013). For example, stimulation of the right posterior semicircular duct results in forward and leftward postural deviations, a typical reflexive response that is initiated when this duct senses accelerations around the anterior-posterior axis.

A vestibular implant, though an effective means of restoring lost vestibular input to a heterogeneous group of patients (Guinand et al. 2015), can unfortunately come at a cost to hearing and residual end organ function, possibly as a result of the implantation procedure (Phillips et al. 2015). Furthermore, vestibular prostheses are presently programmed to provide focused stimulation to the semicircular ducts, leaving the saccule and utricle largely ignored. Given its close proximity to the otoliths, current from a CI could potentially spread to stimulate the vestibular apparatus in individuals who suffer with concurrent cochlear and vestibular dysfunction. The next section will therefore explore the concept of extracochlear current spread to determine if vestibular stimulation by a CI is, in fact, a possibility.

1.8.2 Spread of electric current from a cochlear implant

A CI can rehabilitate auditory dysfunction in the setting of SNHL because of its ability to bypass the cochlea and directly stimulate the primary auditory afferents located in the osseous spiral lamina (Djourno, Eyries & Vallancien, 1957). The device itself is a
conglomerate of components that work synergistically to convert sounds into electrical impulses which can, in turn, be relayed to the brain via the cochleovestibular nerve (CN VIII). Acoustic input is captured by a microphone and subsequently filtered into frequency bands by a speech processor. The processor then uses an external transmitter to send this analysis to a surgically-implanted, subcutaneous receiver-stimulator. This last component is directly connected to an intracochlear electrode array and is thus responsible for converting the processed input into electrical pulses. In an effort to mimic the tonotopic organization of a functioning cochlea, the receiver-stimulator uses electrodes located at the base of the cochlea to represent high frequency bands, while more apical electrodes are utilized for lower frequencies. In addition to frequency, a CI can portray sound intensity due to the ability of each electrode to deliver electrical pulses of varying current amplitudes. A ‘dynamic range’ can therefore be programmed for each electrode, such that the amplitude of the delivered electric pulses is representative of the acoustic stimuli’s intensity.

The facial nerve courses alongside the cochlear and vestibular nerves prior to entering the internal auditory canal, and as a result, can be inadvertently stimulated by electric current from a CI. While certain conditions such as otosclerosis and otosyphilis may predispose CI users to facial nerve stimulation, it is generally felt that reduced impedance of the bone between the cochlea and facial nerve canal allows current to be shunted to this nerve (Seyyedi, Hermann, Eddington & Nadol, 2013). Symptoms of facial nerve stimulation include involuntary movements of facial musculature, twitching, and pain. Extra-cochlear current spread limits the functionality of a CI, as electrode deactivation, reduced usable current ranges, and sometimes explantation of the device are necessary to alleviate symptoms of facial nerve stimulation.

The spread of current to the facial nerve is a commonly reported side effect of cochlear implantation, and is observed in 1 to 14.9% of CI users (Kelsall, Shallop, Brammeier & Prenger, 1997; Kempf, Tempel, Johann & Lenarz, 1999; Rayner, King, Djallilian, Smith & Levine, 2003; Smullen et al. 2005). Using electromyographic techniques to objectively capture nerve stimulation in children who use CIs, Cushing and colleagues (2006) demon-
strated that the prevalence of this aberrant stimulation is actually much higher (34% in a retrospective group; 59% in a prospectively-tested group). Facial nerve responses, recorded using a combination of midline recording channels and surface electrodes placed on the facial musculature, peaked at a latency of 3 ms following stimulus onset. Stimulus intensities of $224 \pm 13$ clinical units (manufacturer-defined units of current) were sufficient to evoke these potentials, while an increase of 16.4 clinical units above those thresholds was required to produce a perceptible response that was reported by the children. When the stimulation was further increased by 6.3 units, facial movements could be visually observed. These results indicate that facial nerve stimulation occurs at current intensity levels far below those required to produce the perception of facial muscle movement. Moreover, the intensities used to elicit responses were within the current range used daily by some of the participants. While increasing current intensities produced potentials with larger peak-to-peak amplitudes (Cushing et al. 2009), the likelihood of evoking a facial response was equivalent regardless of whether an apical, midline, or basal CI electrode was used to deliver the stimulus (Cushing et al. 2006).

Accounts of vestibular symptoms (e.g., nystagmus, perception of motion) reported during and after implant activation (Bance, O’Driscoll, Giles & Ramsden, 1998; Black, Lilly, Peterka, Fowler & Simmons, 1987; Wong, See & Yu, 2000) have prompted investigations into whether a CI can also stimulate the vestibular system. It has also been demonstrated that children perform better on measures of static and dynamic equilibrium (Cushing et al. 2008a) and adults show improvements in postural stability (Buchman, Joy, Hodges, Telischi & Balkany, 2004) while using their CI. Although these reports suggest that the implant has some influence on the vestibular system, the mechanism of this effect is still unclear. Jin and colleagues (2006) demonstrated that although acoustically-evoked VEMPs were lost subsequent to cochlear implantation, activation of the CI restored these responses. This group then postulated that the restoration of these responses was due to CI-mediated stimulation of the vestibular nerves. There are two methodological shortcomings, however, that undermine confidence in this presupposition. First, the study does not appear to control for tonic contraction of the SCM; the absence of VEMPs might therefore be the result of insufficient muscle contraction. Second, while the child’s
activated CI was introduced in the experimental condition, an acoustic stimulus was used in conjunction with the CI, making it difficult to isolate electric current (as opposed to inter-test variability) as being solely responsible for restoring the recorded VEMP responses. Thus until now, the method by which CI stimulation impacts vestibular function has not been clearly established.

1.9 Summary

An unfortunate consequence of the close link between the cochlea and peripheral vestibular system is that SNHL is often accompanied by concurrent vestibular dysfunction. End organ deficits, in turn, translate into balance and functional impairment, including an abnormal tilting of the visual environment toward the compromised ear. This impaired spatial orientation has not been previously investigated in children who receive CIs despite evidence that vestibular dysfunction is highly prevalent in this pediatric group. Moreover, enhanced performance on vestibular-dependent tasks has been observed while individuals use their CI, though the mechanism by which this device improves function is unknown. In this study, we aimed to determine whether or not CI stimulation could evoke vestibular responses, and if so, whether such stimulation conferred a functional benefit to the recipient. We chose the otoliths to be the focus of our investigation due to their close proximity to the cochlea and, therefore, a CI when present. We specifically set out to answer the following questions:

1. What is the prevalence of vestibular reflexes in our population of pediatric cochlear implant users? How frequently can these reflexes be evoked with electrical pulses from the cochlear implant?

2. What electrical stimulation parameters are needed to elicit vestibular evoked reflexes?

3. Does cochlear implant evoked stimulation of the vestibular system have an impact on function?
Chapter 2

Methods

This study was approved by an institutional research ethics board (Study No. 7266), which adheres to the Tri-council Policy Statement: Ethical Conduct for Research Involving Humans. Written consent was obtained from all subjects (or from parents/guardians on their behalf) prior to participation in the study.

2.1 Participants

Pilot data were collected from a group of adults in our laboratory with normal hearing and otolith function (n=9; 6 females; 28.8 ± 7.7 [mean ± standard deviation] years of age). Review of a pre-existing research database identified 220 children and young adults with CIs who had previously undergone vestibular testing as part of their clinical work-up. Initial recruitment efforts focused on this pediatric group due to their prior exposure to vestibular testing methods, which we expected would increase compliance with our assessment protocol. As the study progressed, participant sampling criteria expanded to include any child or young adult with a CI who was willing and able to follow simple instructions during testing. Children under the age of 7 were excluded from recruitment given the length of the testing protocol for this study and the effort-related difficulties with repetitive VEMP testing in this age group reported by Kelsch

36
and colleagues (2006). We also anticipated that vestibular evaluation would be difficult in individuals with developmental challenges. There were no exclusions based on etiology of hearing loss, sidedness of implant or duration of implant use.

Fifty-five children and young adults with CIs were ultimately recruited for participation. The 33 males and 22 females were $15.1 \pm 4.0$ (range $= 7.9 - 27.0$) years of age at the time of testing and had $10.1 \pm 4.3$ years of experience with their implants. Ten participants were unilaterally implanted on the right and used either a hearing aid ($n = 7$) or no device ($n = 3$) for their left ear. These children were, on average, $7.8 \pm 4.1$ years of age when they received their implant. Of the 45 bilaterally implanted participants, 7 received both implants in the same surgery at age $8.0 \pm 4.3$. The other 38 CI users received their devices in a sequential fashion, such that they underwent their first implantation at $3.6 \pm 2.9$ years of age and their second at $9.6 \pm 3.7$ years (inter-implant delay of $6.1 \pm 3.1$ years). One child had recently been reimplANTED on the left side, so this ear was not tested. The total number of ears tested was 99. Though VEMP assessment was conducted in all participants, 2 children could not complete SVV testing. Thirty-five participants completed BOT-2 evaluation.

The participant sample was heterogeneous with respect to etiology of deafness, as detailed in Table 2.1. The 13 children with cochleovestibular malformations were further subdivided into four groups according to the type of anomaly, namely, incomplete partition type II, including the classic Mondini deformity (8 participants, one of whom had genetic confirmation of Pendred Syndrome); hypoplastic cochlea (1 participant); dilated vestibular aqueduct (3 participants); posterior semicircular canal dysplasia as a symptom of Waardenburg Syndrome (1 participant).
### Etiology of hearing loss

<table>
<thead>
<tr>
<th>Etiology of hearing loss</th>
<th>No. (%) of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochleovestibular anomalies</td>
<td>13(24)</td>
</tr>
<tr>
<td>IP type II</td>
<td>8(62)</td>
</tr>
<tr>
<td>Pendred Syndrome</td>
<td>1(13)</td>
</tr>
<tr>
<td>Hypoplastic cochlea</td>
<td>1(8)</td>
</tr>
<tr>
<td>EVA</td>
<td>3(23)</td>
</tr>
<tr>
<td>Posterior SCC dysplasia</td>
<td>1(8)</td>
</tr>
<tr>
<td>Connexin 26 mutation</td>
<td>11(20)</td>
</tr>
<tr>
<td>Usher Syndrome</td>
<td>7(13)</td>
</tr>
<tr>
<td>Congenital CMV infection</td>
<td>6(11)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5(9)</td>
</tr>
<tr>
<td>ANSD</td>
<td>2(4)</td>
</tr>
<tr>
<td>Noonan Syndrome</td>
<td>1(2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10(18)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>55</strong></td>
</tr>
</tbody>
</table>

Table 2.1: Etiology of hearing loss in participants. IP=Incomplete partition; EVA=Enlarged vestibular aqueduct; SCC=Semicircular canal; CMV=Cytomegalovirus; ANSD=Auditory neuropathy spectrum disorder.

### 2.2 Otolith and gross balance assessment

#### 2.2.1 Assessment of saccular and utricular function

VEMP recordings were collected and analyzed using a two-channel surface electrode montage and Neuroscan Synamps 2™ (Compumedics Neuroscan, El Paso, TX, USA) recording platform. For cVEMP recordings, the non-inverting (active) electrode was placed over the midpoint of the SCM ipsilateral to the stimulated ear and referenced to the sternum. For oVEMP testing, the non-inverting electrode was placed over the mid-infraorbital rim contralateral to the stimulated ear and referenced to the cheek approximately 2 cm inferiorly. The montage ground electrode was placed on the mid-forehead. See Figure 2.1 for an illustration of electrode placement. Impedance was kept below 5 kΩ. The stimuli used to elicit VEMP recordings were monoaural stimulation; if the participant was a bilateral implant user, testing was completed on one side and then repeated on the other side.
After placing the electrodes, participants were instructed to lie supine. During cVEMP testing, a simultaneous head lift and contralateral turn was employed to bring the SCM into a state of tonic contraction. Electromyogram (EMG) activity was monitored throughout data acquisition, and appropriate feedback was provided in real time to ensure that sufficient muscular contraction was sustained. Occasionally, younger children needed to prop themselves onto their elbows, a maneuver that has been previously shown to reduce fatigue without compromising test sensitivity (Kelsch, Schaefer & Esquivel, 2006). During oVEMP testing, participants were asked to keep their head in a neutral position while lying supine. Maximal up-gaze was achieved by directing participants to look at a fixed target above and behind them. This maneuver was used to both induce contraction of the inferior oblique muscle and bring the muscle closer to the recording electrode (Rosen gren, Colebatch, Straumann & Weber, 2013). VEMP tests were performed sequentially (i.e., cVEMP first, oVEMP second) to avoid confusion with simultaneous positioning.

EMG signals were bandpass filtered (1-3000 Hz) and recorded in a -5 to 50 ms window relative to the onset of the stimulus. Responses were collected at a sampling rate of 20,000 Hz, and no on-line artifact rejection was used. The software display was configured such that the continuous EMG activity and the averaged waveform could be viewed simultaneously. For all VEMP tests, at least 2 trials (100 sweeps each) were performed. Averaged waveforms were scanned online for the presence of myogenic responses with biphasic morphology (P1/N1 for cVEMPs, N1/P1 for oVEMPs). If no such responses were identified after 2 trials, testing was concluded. Likewise, when replicating responses were observed, testing was concluded. When there was discordance between the online observations of the two trials, a third trial was completed.
2.2.2 Subjective Visual Vertical assessment

Static SVV was measured using the Visual Vertical™ (Clear Health Media, Wonga Park, Australia) application on an iPod (Apple, Cupertino, USA) fastened to the bottom of a bucket, a technique previously shown to reliably evaluate perceptual tilt without sacrificing the sensitivity of the test to peripheral vestibular loss (Zwergal et al. 2009; Brodsky, Cusick, Kawai, Kenna & Zhou, 2015). Testing was done in the dark, and the bucket completely filled the field of view, eliminating external visual cues. Participants sat upright with a neutral head position (Figure 2.2). The bucket was rotated such that the red line presented by the application was oriented to the left (counter-clockwise; referred to as “left trials”) or right (clockwise; referred to as “right trials”) of the true vertical. Participants were then instructed to rotate the bucket until the linear marker was congruent with their perception of vertical. After 10s, the application calculated the difference between true and perceived vertical with an accuracy of 0.1 degrees, representing rightward and leftward deviations with positive and negative values, respectively. A few practice trials (1–3, as needed) were conducted to ensure participants’ familiarity with the protocol, after which SVV measurements were recorded while subjects had their implants off or received unilateral electric stimulation. Six trials per condition were completed in a random order, with the bucket initially oriented to the left or right of true vertical for an equal number of trials.
2.2.3 Static and dynamic balance

Static and dynamic equilibrium were evaluated using the balance subtest (hereafter referred to as the BOT-2) of the Bruininks-Oseretsky Test of Motor Proficiency (Bruininks & Bruininks, 2005). The test involved nine tasks that challenged balance function by successively introducing new challenges, such as walking forward on a line or balancing on one foot on a balance beam (Figure 2.3). If participants reached the target (e.g., standing on one leg for 10 seconds) on their first attempt, they continued on to the next task. If they could not achieve the target, they were allowed to try again for a maximum of two attempts. The better of the two attempts was used to calculate their point score for that task. A point score was calculated based on ability to reach the target (Table 2.2), and the point scores of the nine tasks were summed to yield a total point score, which could range from 0 to 37 points. An age- and sex-matched scale score was then obtained using normative data provided by the test. Participants completed each task with the external component of their CI equipment turned on, and again with the CI processors turned off (i.e., no input from the implant). The order in which they performed the task with their processors “on” or “off” was randomized to control for a learned effect.
### Chapter 2. Methods

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Target</th>
<th>Maximum point score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing with feet apart on a line – eyes open</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Walking forward on a line</td>
<td>6 steps</td>
<td>4</td>
</tr>
<tr>
<td>Standing on one leg on a line – eyes open</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Standing with feet apart on a line – eyes closed</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Walking forward heel-to-toe on a line</td>
<td>6 steps</td>
<td>4</td>
</tr>
<tr>
<td>Standing on one leg on a line – eyes closed</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Standing on one leg on a balance beam – eyes open</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Standing heel-to-toe on a balance beam</td>
<td>10 seconds</td>
<td>4</td>
</tr>
<tr>
<td>Standing on one leg on a balance beam – eyes closed</td>
<td>10 seconds</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2.2: Bruininks-Oseretsky Test of Motor Proficiency Balance Subtest (BOT-2) tasks description, targets and maximum score.

## 2.3 Stimuli

### 2.3.1 Acoustic

A 500 Hz, Blackman-windowed tone burst stimulus with a duration of 4 ms (2 ms rise/fall time, no plateau) was presented at 124 dB sound-pressure-level to elicit myogenic responses. These parameters were chosen due to their predominant use in clinical settings and their validated ability to produce robust, large-amplitude responses (de Oliveira Barreto, Colafemina & de Lemos Menezes, 2011; Wu & Murofushi, 1999; Singh, Kumar, Aparna & Barman, 2014). The stimulus was generated by MATLAB® (MathWorks Corporation, Natick, MA, USA) and then delivered monaurally via an E–A–RTONE™ 3A insert (3M Company, Indianapolis, IN, USA). For each trial, the tone burst was presented at 5.1 Hz for 20 s, yielding 100 sweeps.

Prior to commencing the study, a sound level meter with a 2cc coupler (Larson Davis, Depew, NY, USA) was used to verify the intensity of the stimulus. The stimulus waveform was also verified using an oscilloscope (Pico Technology Ltd®, St Neots, Cambridgeshire, UK). Figure 2.4 illustrates the acoustic stimulus waveform (A) and the presentation frequency (B). While verifying the stimulus waveform, a delay of 1.3 ms was observed between the stimulus trigger and the actual presentation of stimuli to the ear (C). A cor-
rection factor was thus applied when measuring VEMP peak latencies offline to account for this delay.

Figure 2.4: The acoustic stimulus had a duration of 4 ms (A) and was presented at 5.1 Hz (i.e., every 196 ms) (B). A delay of 1.3 ms (C) was observed between the trigger (red tracing) and actual presentation of sound to the ear (blue tracing).

2.3.2 Electric

To elicit VEMPs with electric stimulation, the ear insert used to deliver acoustic stimuli was eliminated and replaced with a Nucleus Freedom processor (Cochlear Corporation,
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Sydney, Australia), which interfaced between the programming software and the participant’s device. An electrical stimulus was generated by Custom Sound EP™ software (Cochlear Corporation, Sydney, Australia) and delivered to the participant’s CI directly. Maximally tolerated intensity levels were first determined for both single 57 µs biphasic electrical pulses (25 µs/phase with a 7 µs interphase gap) (Figure 2.5A) and trains of these same pulses delivered at 900 pulses/s for 4.4 ms (B). The waveforms of the electric stimuli were verified using an oscilloscope. Similarly to the acoustic stimuli, there was a delay between the trigger and actual onset of stimulus, though this delay was much shorter and only 6.3 µs (C). An appropriate correction factor was therefore applied to electrically-evoked VEMP peak latencies.

When both stimuli were tolerated equally by a participant, the pulse train was selected for VEMP testing because its duration approximated that of the tone burst used in the acoustic protocol. At times, though, the pulse train was uncomfortable for the participants, so a single pulse was used. The electrical stimulus was delivered at 5.1 Hz over 20 s for each VEMP trial. VEMP tests were conducted initially with basal stimulation at electrode 3 (E3) and then repeated with apical stimulation at electrode 20 (E20).

Figure 2.5: Electric stimuli were comprised of either a single pulse (A) or a pulse train (B). A minimal delay of 6.3 µs (C) was observed between the trigger (blue tracing) and actual presentation of stimuli (red tracing).
2.4 Data analysis

Statistical analyses were conducted using RStudio Version 0.98 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics 23 (IBM Corporation, Armonk, USA).

2.4.1 Vestibular Evoked Myogenic Potentials

A VEMP was ultimately judged to be positive or negative offline. A positive cVEMP response was defined as a reproducible, biphasic waveform with an initial positive (P1) peak followed by a negative (N1) peak occurring within an acceptable latency range, defined below, and with a peak-to-peak amplitude $>20 \mu V$. Based on the mean latencies $\pm 2$ standard deviation units determined by recent studies of VEMPs in children with sensorineural hearing loss, the acceptable latency range for acoustic cVEMP responses was defined as 12.10 – 18.06 ms for P1 and 17.75 – 24.63 ms for N1 (Xu et al. 2015a, b). A positive oVEMP response was defined as the presence of a reproducible, biphasic waveform with an initial N1 peak followed by a P1 within an acceptable latency range. The acceptable latency range for acoustic oVEMP responses extrapolated from the literature as aforementioned for the cVEMP, was defined as 8.13 – 11.73 ms for N1 and 11.15 – 17.23 ms for P1 (Xu et al. 2015a, b). As the technique for electrical stimulation was novel, specific latencies could not be referenced, so responses were judged on morphology. As a framework, however, our expectation was that latencies for electrical stimulation would be shorter by a relatively consistent amount based on our experience with electrically evoked auditory brainstem responses. To quantify stenocleidomastoid and inferior oblique muscle activity offline, EMG tracings were first rectified and then averaged in a 50 to 190 ms epoch window relative to stimulus onset. This epoch window was employed to evaluate muscle contraction alone without interference of a vestibular potential, when present.

Simple linear regression models were used to predict the amplitude of a VEMP based on the tonic activity of the sternocleidomastoid or inferior oblique muscle. Fisher’s exact
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tests compared the proportions of ears in which a VEMP could be elicited using single pulse or pulse train stimuli delivered using the basal or apical aspects of the implanted electrode array. Logistic regression analysis predicted the odds of eliciting a VEMP with increasing electric stimulus intensities. In participants with both acoustically- and electrically-evoked responses, paired samples $t$-tests compared peak latencies and amplitudes.

2.4.2 Subjective Visual Vertical

When compared to the arithmetic mean of SVV trials, the mean of absolute SVV values more accurately reflects the perceptual abnormalities of patients with bilateral vestibular dysfunction (Funabashi et al. 2012). We expected to find abnormalities in SVV given that vestibular dysfunction is common in children with CIs (Cushing et al. 2013). The numeric component of a participant’s SVV score in each condition was thus calculated by averaging the absolute values of the 6 trials. To allow for direction-specific analyses, however, the calculated SVV score retained the arithmetic sign (positive or negative) of the sum of the trials. The normal range of deviation was set to be 2 degrees in either direction of the true vertical, based on normative data in children (Brodsky et al. 2015, 2016) and adults (Zwergal et al. 2009). The root-mean-square error was used as an indicator of spatial orientation precision. To calculate this value, the squares of the differences between the SVV measured at each trial and the overall calculated SVV score were summed and then divided by the number of trials (i.e., six). The square root of this number yielded the root-mean-square error. This calculation can be summarized using the following formula:

$$\text{Root-mean-square error} = \sqrt{\frac{\sum_{n=1}^{6}(SVV_n - SVV_{\text{calculated}})^2}{6}}$$

where $n$ is the trial number.

Repeated Measures ANOVAs were used to determine the effect of trial and initial orientation of the linear marker on SVV score and to assess the effects of electric stimulation
on perception in bilaterally implanted participants. The latter analysis excluded 1 reimplanted and 10 unilaterally implanted participants, as they did not receive stimulation on their left side. Bonferroni-corrected $t$-tests were used to compare subgroups post hoc. A Multiple Linear Regression model was also used to identify predictors of all participants’ SVV score change while receiving stimulation.

2.4.3 BOT-2

Shapiro-Wilks tests of normality were used to identify deviations from normal distributions, and Wilcoxon signed rank tests compared participants’ scores during the two conditions (CI ‘off’ vs. ‘on’). Simple and multiple linear regression models were employed to identify predictors of balance performance and the amount of score change between the two conditions.
Chapter 3

Results

This study sought to examine whether or not electric current from a CI can spread to stimulate the nearby peripheral vestibular system. As outlined in Chapter 2, vestibular evoked potentials were utilized to objectively capture current spread to the otoliths, the end organs situated closest to the cochlea and, by extension, CI. We further sought to characterize the implant stimulation needed to successfully drive otolith reflexes by manipulating the type of delivered stimulus (single pulse versus train of pulses) and location of delivery (apical versus basal ends of the implant array). We were interested in the prevalence of vestibular stimulation in our sample of CI users, and hypothesized that even when the otoliths were shown to be dysfunctional, the vestibular system would still respond to stimulation from an implant array. The second part of our study investigated whether or not the spread of CI current to the otoliths translated into an improvement on tasks that evaluated spatial orientation and the maintenance of equilibrium. Based on prior work from our group, we expected that children with SNHL who use CIs would show impairments on such tasks, but also anticipated that providing electrical input to the system would enhance performance on balance and perceptual measures.

This chapter will describe the results of these endeavours using the methods outlined in the previous chapter. The study’s findings will be discussed with the intent of answering the three original research questions:
1. What is the prevalence of vestibular reflexes in our population of pediatric cochlear implant users? How frequently can these reflexes be evoked with electrical pulses from the cochlear implant?

2. What electrical stimulation parameters are needed to elicit vestibular evoked reflexes?

3. Does cochlear implant evoked stimulation of the vestibular system have an impact on function?

In addition, correlations between electrically-evoked potentials (i.e., VEMPs) and functional tests (i.e., SVV, BOT) will be examined, as a relationship between these measures would support the notion that the benefit of cochlear implantation can extend beyond the auditory system to include that of the peripheral vestibular apparatus as well.

### 3.1 Stimulation of the vestibular end organs with a cochlear implant

Cervical and ocular VEMPs were elicited in response to acoustic and electric stimuli. Representative waveforms are displayed in Figure 3.1. No other vestibular responses to the stimuli (e.g., nystagmus) were observed while subjectively monitoring the participants. The children and young adults also did not report symptoms of vertigo, sensations of movement, dizziness or disorientation while being stimulated.

In our discussion of VEMPs in section 1.3.1, we noted that these potentials provide invaluable insight into the functionality of the otoliths and their corresponding reflex pathways. Since an absent response is indicative of an otolithic or neural lesion, painstaking efforts must be put forth by both the subject and evaluator to reduce the risk of false negatives. Hence before describing the prevalence of vestibular dysfunction in children with CIs, we assessed our electromyographic data to ensure it was a robust, accurate reflection of end organ integrity.
Figure 3.1: Reproducible cervical and ocular vestibular potentials were evoked using acoustic and electric stimuli. Reproduced from Parkes et al. (2016) with permission from WILEY.

3.1.1 Reliability of VEMPs as a measure of otolith activity

The average SCM contraction during cVEMP testing with acoustic stimuli was $151.44 \pm 63.46 \mu V$. The range of tonic contraction across all participants during this condition was 48.09 to 333.21 \mu V. Similarly, the average SCM contraction while eliciting cVEMPs with electric stimuli was $160.91 \pm 73.73 \mu V$, ranging from 48.68 to 436.75 \mu V. During oVEMP testing with acoustic stimuli, the average inferior oblique (IO) muscle contraction was $6.95 \pm 4.37 \mu V$ (range: 1.11 – 26.18 \mu V). During testing with electric stimuli, the recorded IO contraction was, on average, $14.99 \pm 21.42 \mu V$ (median: 8.50 \mu V; range: 1.01 – 147.52 \mu V).

The waveforms depicted in Figure 3.1 are typically seen on clinical recording platforms. These responses are obtained by presenting the stimulus repeatedly and then averaging the post-stimulus activity of the SCM and IO across these trials. In addition to this averaged waveform, we plotted EMG activity on a trial-by-trial basis to confirm that participants maintained tonic contraction throughout the duration of the recording window. Examples of these plots are shown in Figures 3.2 and 3.3. The amplitude peaks of the averaged VEMP waveform that result from inhibition or excitation of the muscle can
Chapter 3. Results

Figure 3.2: cVEMP event-related potentials across trials in response to acoustic (A, B) and electric (C, D) stimuli. Red bands represent EMG amplitude peaks and are averaged to yield the cVEMP P1 peak. Blue bands represent amplitude troughs and, when averaged, form cVEMP N1. The averaged waveform is shown below each plot.
Chapter 3. Results

(a) Present acoustically-evoked oVEMP
(b) Absent acoustically-evoked oVEMP
(c) Present electrically-evoked oVEMP
(d) Absent electrically-evoked oVEMP

Figure 3.3: oVEMP event-related potentials across trials in response to acoustic (A, B) and electric (C, D) stimuli. Blue bands represent amplitude troughs and, when averaged, form oVEMP N1. Red bands represent EMG amplitude peaks and are averaged to yield the oVEMP P1 peak. The averaged waveform is shown below each plot.
be visualized in these trials as bands of increased or decreased EMG activity. As seen in parts (B) and (D) of Figures 3.2 and 3.3, some participants did not have a VEMP response despite a sustained tonic contraction. The absence of vestibular potentials thus appears to be a reflection of otolithic dysfunction, and is not the mere result of insufficient muscle activity.

It is known that the peak amplitude of the cVEMP is dependent on the amount of tonic muscle contraction, however, we were interested in quantifying this relationship further and thus used a simple linear regression to predict VEMP amplitude based on SCM (Figure 3.4) or IO muscle contraction (Figure 3.5). The statistics of each model are described in the captions of their respective figures. With the exception of electrically-evoked oVEMPs \( p = 0.078 \), the amplitude of vestibular evoked potentials could be reliably predicted based on the amount of muscle contraction. Figures 3.4 and 3.5 demonstrate that though a group of participants achieved muscle activity that was comparable to participants with VEMPs, the former group did not have an observable response, presumably due to the compromised integrity of their vestibular end organs.

Descriptive statistics of SCM and IO activity in children with and without VEMPs are outlined in Table 3.1. Mann-Whitney U comparisons indicated that SCM tonic contraction in ears with an acoustically-evoked cVEMP (Median = 156.67 µV) was not significantly greater than SCM contraction when a response was not seen (Md = 132.71 µV) \( [U = 1468, p = 0.053] \). The test did, however, reveal a significant difference between contraction in those with (Md = 158.15 µV) and without (Md = 134.91 µV) an electrically-evoked cVEMP \( [U = 6260, p = 0.009] \). A similar trend was seen with IO activity for oVEMPs. Mann-Whitney U comparisons did not indicate significant differences between IO contraction in those with (Md = 5.72 µV) or without (Md = 6.55 µV) acoustically-evoked oVEMPs \( [U = 850, p = 0.434] \), though a difference was revealed in IO activity between those with (Md = 10.17 µV) and without (Md = 8.24 µV) an electrically-evoked oVEMP \( [U = 4370, p = 0.037] \).

We realized that the presence of a VEMP is contingent on three factors, namely otolith integrity, sufficient muscle contraction and a high-intensity stimulus. Based on the opti-
Figure 3.4: Linear regression models were used to predict the amplitude of acoustically- and electrically-evoked cVEMPs based on SCM tonic contraction. The shaded regions represent the 95% confidence intervals of the regression slope. (a) $F[1, 44] = 10.22, p = 0.003$ with an $R^2$ of 0.17. (b) $F[1, 50] = 47.99, p<0.0001$ with an $R^2$ of 0.48.
Figure 3.5: Linear regression models were used to predict the amplitude of acoustically- and electrically-evoked oVEMPs based on IO tonic contraction. The shaded regions represent the 95% confidence intervals of the regression slope. (a) $F[1, 24] = 14.89$, $p<0.001$ with an $R^2$ of 0.36. (b) $F[1, 31] = 3.332$, $p = 0.078$ with an $R^2$ of 0.07.
Table 3.1: SCM and IO activity of participants with and without acoustically- and electrically-evoked cVEMPs and oVEMPs. Muscle activity given in units of µV.

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Mean Contraction</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present acoustic cVEMP</td>
<td>164.58</td>
<td>67.24</td>
<td>156.67</td>
<td>48.09 – 320.60</td>
</tr>
<tr>
<td>Absent acoustic cVEMP</td>
<td>139.81</td>
<td>58.11</td>
<td>132.71</td>
<td>51.52 – 333.21</td>
</tr>
<tr>
<td>Present electric cVEMP</td>
<td>186.39</td>
<td>81.86</td>
<td>158.15</td>
<td>72.35 – 385.56</td>
</tr>
<tr>
<td>Absent electric cVEMP</td>
<td>154.11</td>
<td>70.07</td>
<td>134.91</td>
<td>48.68 – 436.75</td>
</tr>
<tr>
<td>Present acoustic oVEMP</td>
<td>6.20</td>
<td>3.06</td>
<td>5.72</td>
<td>1.19 – 13.69</td>
</tr>
<tr>
<td>Absent acoustic oVEMP</td>
<td>7.21</td>
<td>4.74</td>
<td>6.55</td>
<td>1.11 – 26.18</td>
</tr>
<tr>
<td>Present electric oVEMP</td>
<td>15.40</td>
<td>18.31</td>
<td>10.17</td>
<td>2.39 – 103.34</td>
</tr>
<tr>
<td>Absent electric oVEMP</td>
<td>14.93</td>
<td>21.89</td>
<td>8.24</td>
<td>1.01 – 147.52</td>
</tr>
</tbody>
</table>

mal recording conditions (stimulus and EMG activity), it is reasonable to conclude that VEMP absence reflects vestibular dysfunction.

As outlined at the beginning of this chapter, our first research objective was to quantify vestibular (specifically otolith) dysfunction in children with SNHL who have been rehabilitated with CIs. We also aimed to elicit VEMPs using electric pulses from the CI, which would provide evidence to support the spread of current from the implanted device to the peripheral vestibular system. We hypothesized that sending an electrical stimulus via the CI would generate a vestibular response, even if the vestibular end organs were compromised. The next section will describe the results of these endeavours.

### 3.1.2 Prevalence of vestibular dysfunction in children with cochlear implants

A cervical or ocular VEMP in at least one ear could be elicited with acoustic stimulation in 32 participants (58%) and with electric stimulation through the CI in 34 participants (62%) (Figure 3.6a). A cVEMP was present in 46 of the 99 ears (46%) tested acoustically and in 35 ears (35%) stimulated electrically. An oVEMP was evoked acoustically in 26 ears (26%), and electrically in 26 ears (26%) (Figure 3.6b).

Of 99 ears tested for cVEMPs, 38 (38%) were non-responsive to acoustic and electric stimuli, 20 (20%) were responsive to both acoustic and electric stimuli, and 26 (26%)
were responsive to acoustic stimulation alone. In the 53 ears without acoustic cVEMPs, an electric cVEMP was present in 15 (28%) (Figure 3.7a).

Of 99 ears tested for oVEMPs, 54 (55%) were non-responsive to acoustic and electric stimuli, 7 (7%) were responsive to both acoustic and electric stimuli, and 19 (19%) were responsive to acoustic stimulation alone. In the 73 ears without acoustic oVEMPs, an electric oVEMP was present in 19 (26%) (Figure 3.7b).

(a) Vestibular potentials were evoked with acoustic and electric stimulation in 58% and 62% of participants, respectively.

(b) Proportion of VEMPs in response to acoustic (cVEMP=46%, oVEMP=26%) and electric (cVEMP=35%, oVEMP=26%) stimuli.

Figure 3.6: Prevalence of VEMPs in children with CIs. Adapted from Parkes et al. (2016) with permission from WILEY.

(a) eVEMPs
(b) oVEMPs

Figure 3.7: In a proportion of ears which did not respond to the acoustic VEMP stimulus, electrical current stimulated the vestibular neural elements and evoked cervical (a) and ocular (b) VEMPs. Adapted from Parkes et al. (2016) with permission from WILEY.
3.1.3 Impact of stimulus parameters on VEMP prevalence and morphology

Having obtained objective evidence of electric current spread to the vestibular system, we changed stimulus parameters in an effort to understand more of what type of stimulation to which the vestibular best responds. We expected that high intensity stimuli would maximize extracochlear current spread and, therefore, increase the odds of eliciting vestibular reflexes. We also predicted that basal electrodes would more likely drive these responses, given their close proximity to the end organs and their afferents. This section will explore the impact of stimulus duration (single pulses vs. trains of these pulses) and location of delivery (apical vs. basal electrodes) on VEMP prevalence and waveform characteristics.

Single pulse vs. pulse train stimuli

During initial stages of the study, both single pulse and pulse train stimuli were used to elicit VEMPs. cVEMP testing using both stimulus types delivered from basal (E3) and apical (E20) electrodes was conducted in 27 ears; in 1 ear, single pulse versus pulse train testing could only be completed at E20. oVEMP testing using these parameters was completed in 26 ears. In the tested ears, a cVEMP was evoked in 13% of these conditions (Present = 7; Absent = 46) using single pulse stimuli and in 19% (Present = 10; Absent = 43) with pulse train stimuli. Comparisons of these proportions using a Fisher’s exact test revealed no difference \( p = 0.598 \) in the prevalence of VEMPs with pulse trains as compared to single pulse stimuli. Similarly, oVEMPs were elicited in 10% of these conditions (Present = 5; Absent = 47) with single pulse stimuli and in 12% (Present = 6; Absent = 46) using pulse train stimuli. Fisher’s exact comparisons again revealed that neither stimulus was more effective than the other at eliciting these potentials \( p > 0.99 \).

In 7 ears, cVEMPs were elicited using both types of stimuli at the same electrode in the CI array, allowing for peak latency and amplitude comparisons. A paired samples \( t \)-test indicated that the P1 latency of pulse train evoked cVEMPs \( (12.4 \pm 1.5 \text{ ms}) \) was 1.2 ms greater than that of single pulse evoked cVEMPs \( (11.2 \pm 0.8 \text{ ms}) \) \( t(6) = -3.387, p \)
Chapter 3. Results

The N1 peak latency of pulse train evoked cVEMPs (19.6 ± 2.8 ms) was, on average, 0.7 ms greater than that of single pulse evoked cVEMPs (18.9 ± 2.6), though this difference was not statistically significant \([t(6) = -1.680, p-value = 0.144]\). Since only the latency of the P1 peak increased while using pulse train stimuli while the N1 peak latency remained consistent, the intra-peak latency (i.e., between P1 and N1 of the same waveform) was compared to determine if pulse train stimuli caused a ‘compression’ of VEMP waveforms. Intra-peak latency was found to be equivalent for single pulse (7.7 ± 1.9 ms) and pulse train (7.2 ± 1.6 ms) evoked VEMPs \([\text{paired } t\text{-test}; t(6) = 1.069, p-value = 0.326]\). Peak-to-peak amplitude, which was normalized to SCM tonic activity, was equivalent for single pulse (1.08 ± 0.49) and pulse train (1.30 ± 0.70) evoked cVEMPs \([\text{paired } t\text{-test}; t(6) = -1.179, p-value = 0.283]\). oVEMPs were elicited using both stimuli in only 2 ears, precluding analyses of latency or amplitude differences in these responses.

*Basal vs. apical stimulation*

Stimulation was delivered to the peripheral vestibular system using the basal (E3) and apical (E20) aspects of the CI electrode array. As indicated in Figure 3.8, basal stimulation generated cVEMPs in 28 of the 99 tested ears (28%), and apical stimulation evoked cVEMPs in 18 of the 98 tested ears (18%). A Fisher’s exact comparison indicated that cVEMPs were equally prevalent using either electrode \([p = 0.129]\). Likewise, oVEMPs were not preferentially elicited using the basal or apical ends of the array \([p = 0.435]\). Basal stimulation generated oVEMPS in 13 of the 99 tested ears (13%), and apical stimulation evoked these potentials in 17 of the 98 tested ears (17%).

In 15 ears, cVEMPs were present in response to stimulation from both electrodes, allowing for evaluation of the impact of stimulation location on VEMP latency and amplitude. P1 latency did not significantly differ when the cVEMP was generated using E3 (12.1 ± 1.8 ms) or E20 (11.6 ± 0.8 ms) \([\text{paired } t\text{-test}; t(14) = 1.322, p = 0.207]\). N1 latency was also comparable when eliciting the cVEMP using E3 (18.9 ± 1.8 ms) or E20 (18.2 ± 1.4 ms) \([\text{paired } t\text{-test}; t(14) = 1.367, p = 0.193]\). Location of stimulation seemingly did not affect cVEMP amplitude (normalized to SCM contraction) either, with E3 (1.00 ± 0.58
µV) and E20 (0.79 ± 0.48 µV) generating equally large responses [paired t-test; t(14) = 1.08, p = 0.298].

Figure 3.8: VEMP prevalence proportions did not differ significantly in response to basal (Electrode 3) or apical (Electrode 20) stimulation [p > 0.05]. Adapted from Parkes et al. (2016) with permission from Wiley.

In 4 ears, oVEMPs were present in response to both basal and apical stimulation. Given the small sample size, Shapiro-Wilk normality tests were conducted to determine whether the differences were normally distributed. When this stipulation was true, a paired t-test was used to compare the differences; if not, a Wilcoxon test was conducted. N1 latency did not significantly differ when the response was elicited using E3 (6.8 ± 1.4 ms) or E20 (6.9 ± 0.3 ms) [paired t-test; t(3) = -0.085, p = 0.938]. P1 latency was also comparable when generating the oVEMP from E3 (8.4 ± 1.0 ms) or E20 (8.7 ± 0.4 ms) [paired t-test; t(3) = -0.463, p = 0.675]. Location of stimulation also did not impact oVEMP amplitude (normalized to IO contraction), with E3 (0.36 ± 0.14 µV) and E20 (0.21 ± 0.08 µV) generating equally large responses [paired t-test; t(3) = 1.972, p = 0.143].

Stimulation intensity

Although stimulation was delivered at individualized maximum comfort levels, Figure 3.9 demonstrates an increased prevalence of VEMP responses in individuals who could tolerate higher levels of stimulation, measured in manufacturer-defined clinical programming units (CU). Logistic regression analyses confirmed this trend (p < 0.0001 for both
c- and oVEMPs). More specifically, the regression model predicts that for every 10 CU increase in stimulus intensity, the odds of eliciting a c- and oVEMP increase by 1.66 and 1.82, respectively.

Figure 3.9: The odds of eliciting a VEMP increased in individuals who could tolerate higher stimulus intensities. Adapted from Parkes et al. (2016) with permission from WILEY.

In participants with positive electric VEMPs, stimulation intensity was normalized by subtracting individual hearing thresholds (Figure 3.10). The lowest intensity level used to elicit a VEMP was 60 CU above hearing threshold. The largest proportion of positive electrically-evoked cVEMPs was obtained at stimulation levels between 80 and 99 CU above hearing threshold. The largest proportion of positive electrically-evoked oVEMPs was obtained at stimulation levels between 100 and 119 CU above hearing threshold.

Figure 3.10: The stimulus intensities used to successfully elicit VEMPs were normalized to individual hearing thresholds. The largest proportion of c- and oVEMPs were obtained at levels between 80-99 CU and 100-119 CU above hearing threshold, respectively. Adapted from Parkes et al. (2016) with permission from WILEY.
3.1.4 Impact of stimulus medium on VEMP characteristics

**Latencies of VEMPs evoked with acoustic vs. electric stimuli**

As demonstrated in Figure 3.11, electrically-evoked responses occurred at shorter latencies compared to acoustically evoked responses: \( cVEMP \text{ P1: } 11.6 \pm 1.1 \text{ ms vs. } 13.7 \pm 1.3 \text{ ms} \); \( cVEMP \text{ N1: } 18.5 \pm 1.2 \text{ ms vs. } 21.1 \pm 2.0 \text{ ms} \); \( oVEMP \text{ N1: } 7.2 \pm 1.6 \text{ ms vs. } 8.6 \pm 1.4 \text{ ms} \); \( oVEMP \text{ P1: } 9.2 \pm 2.2 \text{ ms vs. } 11.7 \pm 2.1 \text{ ms} \). Both acoustically- and electrically evoked responses were recorded in 20 ears during cVEMP testing and in 7 ears during oVEMP testing, allowing for paired analyses. The peak latencies for this sub-group are outlined in the caption of Figure 3.11. Paired \( t \)-tests indicated that the P1 peak of electrically-evoked cVEMPs was 1.9 ms shorter than acoustically-evoked responses \( [t(19) = 7.236, p < 0.0001] \). The N1 peak of electrically-evoked cVEMPs was, on average, 2.6 ms shorter \( [t(19) = 6.298, p < 0.0001] \). Similarly, the N1 peak of electrically-evoked oVEMPs was 2.0 ms shorter than acoustically-evoked responses \( [t(6) = 4.596, p = 0.004] \). A 3.4 ms difference was noted between the P1 peaks of electrically- and acoustically-evoked oVEMPs \( [t(6) = 5.444, p = 0.002] \).

**Amplitudes of VEMPs evoked with acoustic vs. electric stimuli**

Since the amplitude of a VEMP is highly dependent on the contraction of the muscle from which it is being recorded, amplitude comparisons between acoustically- and electrically-evoked VEMPs must control for variability in SCM and IO tonic activation. Thus, a ’normalized’ amplitude was calculated by dividing the recorded VEMP amplitude by the muscle contraction. It should be noted that this normalized amplitude is actually a ratio and is therefore dimensionless (i.e., unitless). Both acoustic and electric stimuli generated cVEMPs in 20 ears, however, SCM contraction was not available for one of these recordings; this ear was excluded from the analysis. oVEMPs were elicited by both acoustic and electric stimuli in 7 ears. Acoustic stimuli evoked cVEMPs with an average normalized amplitude of 2.03 ± 1.24, while electric stimuli elicited responses with an average normalized amplitude of 0.81 ± 0.43 [mean difference = 1.21; paired \( t \)-test; \( t(18) = 4.49, p < 0.001 \)]. In the same manner, acoustically-evoked oVEMP normalized
amplitudes $(0.93 \pm 0.80)$ were larger than those evoked with electric stimuli $(0.18 \pm 0.12)$ [mean difference $= 0.74$; $t(6) = 2.526$, $p = 0.045$].

P1 and N1 amplitude peaks of cervical VEMPs

![Graph showing amplitude peaks of cervical VEMPs](image)

N1 and P1 amplitude peaks of ocular VEMPs

![Graph showing amplitude peaks of ocular VEMPs](image)

Figure 3.11: Electrically-evoked VEMPs occurred at shorter latencies compared to acoustically-evoked responses at each peak. Both acoustically and electrically evoked potentials were present in 20 and 7 ears during cVEMP and oVEMP testing, respectively. Peak latencies (electric vs. acoustic) of this subgroup were as follows: (top left) $11.4 \pm 1.0$ ms vs. $13.3 \pm 0.9$ ms; (top right) $18.2 \pm 1.8$ ms vs. $20.8 \pm 2.0$ ms; (bottom left) $7.1 \pm 0.7$ ms vs. $9.0 \pm 1.2$ ms; (bottom right) $8.6 \pm 0.5$ ms vs. $12.0 \pm 1.6$ ms. From Parkes et al. (2016) with permission from WILEY.

3.1.5 Influence of hearing loss etiology on otolith function and responsiveness to electric stimulation

As demonstrated in Table 3.2, all children with SNHL due to a nonfunctional connexin protein retained otolithic function. Electric pulses from a CI stimulated the peripheral vestibular end organs in 9 children (82%), with electrically-evoked cVEMPs and
oVEMPs recorded in 8 (73%) and 5 (45%) participants, respectively. Seven out of 13 children (54%) who had lost their hearing due to cochlear and/or vestibular malformations demonstrated positive VEMP responses. Over half of this group (7/13 [54%]) also responded to electric stimulation: 5 had an electrically-evoked cVEMP, and 7 had an electrically-evoked oVEMP. Amongst the group diagnosed with Usher syndrome (n = 7), none had intact otolithic function in either ear, yet responses to electric current were recorded in 4 (57%) (cVEMPs = 4/7 [57%]; oVEMPs = 1/7 [14%]). Similarly, the group of children with hearing loss due to meningitis exhibited bilateral vestibular dysfunction. Current from their CI was able to access the vestibular system in all but one individual, with electrically-evoked cVEMPs recorded in 3 (60%), and oVEMPs observed in 2 (40%).

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<th>Acoustic VEMP</th>
<th>Electric VEMP</th>
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<td>8</td>
<td>5 (63%)</td>
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<td>0 (0%)</td>
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<td>Connexin 26 mutation</td>
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<td>Noonan Syndrome</td>
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<tr>
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<td>10</td>
<td>8 (80%)</td>
<td>7 (70%)</td>
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Table 3.2: Distribution of VEMPs in at least one ear in response to acoustic and electric stimulation amongst children grouped by etiology of hearing loss. IP=Incomplete partition; EVA=Enlarged vestibular aqueduct; SCC=Semicircular canal; CMV=Cytomegalovirus; ANSD=Auditory neuropathy spectrum disorder.

3.2 Perception of the visual vertical in children with cochlear implants

Sections 3.2 and 3.3 will describe the experimental results of our third research question: does CI stimulation improve performance on tests that are dependent on vestibular func-
tion? We hypothesized that children with cochleovestibular deficits would demonstrate enhanced performance on the SVV and BOT-2 tests while receiving electrical stimulation from their CIs.

Prior to commencing SVV testing, participants were given a few practice trials (1-3, as needed) to ensure that they were familiar with the protocol and could confidently make their decisions in the time allotted. In addition, the within-subject variability of SVV scores was assessed to confirm that this measure accurately reflected the perception of visual vertical in the 53 tested individuals. Figure 3.12 demonstrates that participants who achieved a normal SVV score overall (i.e., an averaged SVV score <2 degrees in either direction) in the absence of CI stimulation were also more consistent across the 6 trials (i.e., low root-mean-square error). On the other hand, individuals who scored abnormally on the SVV also exhibited more variability in their estimation of the visual vertical on a trial-to-trial basis.

![Figure 3.12: The error around each participant’s baseline SVV score is plotted with the x-coordinate of each point indicating an individual’s (averaged) SVV score, and the y-coordinate denoting the participant’s variability across the 6 trials. Individuals with a normal SVV score (shaded region) were also more consistent in their responses across the 6 trials.](image-url)
Having been made aware that children with SNHL can have an abnormal perception of vertical while their CIs are turned off, the subsequent sections will outline the prevalence of this abnormal perception in our sample, explore specific contexts in which this abnormality surfaces, and evaluate the impact of electric stimulation on visual vertical estimation.

### 3.2.1 Contextual perceptual deficits in the absence of cochlear implant stimulation

In the group of adults with normal otolith function, all individuals achieved an SVV score within the normal range of deviation (i.e., perceptual tilt <2 degrees to the left [negative] or right [positive] of zero; 0.5 ± 0.9 degrees). In the absence of stimulation (CI processor switched off), only 29 children who use CIs (55%) had a normal SVV score (-0.3 ± 1.4 degrees); the remaining 24 (45%) had a score outside the normal range of deviation. In the latter group of 24, 13 participants (54%) showed a perceptual tilt to the left (-2.9 ± 0.4 degrees) and 11 (46%) demonstrated a rightward tilt (3.6 ± 1.2 degrees). SVV measurements from the cochlear-implanted participants are shown in Figure 3.13 along with data from normal hearing adults for reference.

While trial number was not a significant predictor of SVV measurement variability \( F(2, 116) = 0.364, p = 0.696 \), the perception of the visual vertical in the absence of stimulation was biased towards the initial direction of the linear marker \( F(1, 58) = 59.781, p<0.001 \). As shown in Figure 3.14, there was a significant effect of direction on initial tilt \( F(3, 58) = 6.253, p = 0.001 \): those children with an abnormal perceptual tilt to the left demonstrated an exaggerated deviation when the linear marker was initially oriented to the left (-3.5 ± 0.8 degrees) compared to the right (-1.4 ± 1.8 degrees) [paired \( t \)-test, \( p = 0.004 \)], and individuals with an abnormal rightward perceptual tilt showed an exaggerated deviation when the linear marker was initially oriented to the right (4.6 ± 2.8 degrees) compared to the left (-0.3 ± 2.1 degrees) [paired \( t \)-test, \( p<0.001 \)]. Furthermore, abnormalities relative to the CI group with a normal SVV (Left trials: -1.0 ± 1.1 degrees;
Figure 3.13: SVV measurements while participants had their implants turned off. Positive scores indicate a perceptual tilt to the right, while negative scores represent a tilt to the left. Each line illustrates a participant’s SVV across the six trials, and the general trend for each group is shown with the darker line. (A) In all of the normal-hearing adults, the SVV remained within the normal range of deviation, represented with the grey bar. (B) The same is not true of children with CIs, of whom only 55% had a normal SVV score. In the remaining group with an abnormal SVV, 54% showed a perceptual tilt to the left (C) and 46% demonstrated a rightward tilt (D).

Right trials: 0.3 ± 1.3 degrees) were found for both initial tilt directions in children with left [independent $t$-tests; Left trials: $p<0.001$; Right trials: $p = 0.03$] and right tilts [independent $t$-tests; Right trials: $p<0.001$; Left trials: $p = 0.358$]. Though the tested adults with normal otolith function were not age-matched to our participants with CIs, SVV score comparisons between these groups were used to confirm the enhanced bias of the linear marker’s starting position on visual vertical estimation in children with CIs. Abnormalities relative to this control group were indeed noted for both initial tilt directions in children with left [independent $t$-tests; Left trials: $p<0.001$; Right trials: $p$
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= 0.01] and right tilts [independent t-tests; Right trials: p<0.001; Left trials: p>0.99]. There were no differences between children using CIs who achieved a normal SVV score and the control group for left [independent t-test; p>0.99] or right [independent t-test; p>0.99] trials.

![Graph showing subjective visual vertical (SVV) for normal-hearing adults and groups of participants with CIs.](image)

Figure 3.14: The initial orientation of the SVV linear marker influenced estimation of the visual vertical. Positive values represent deviations to the right, and negative values indicate deviations to the left. The grey bar marks the normal range of deviation. In cochlear-implanted participants with a left perceptual tilt, exaggerated deviations to the left were observed on left-oriented trials (mean ± SE). Conversely, participants with a rightward tilt demonstrated exaggerated deviations to the right on right-oriented trials. SVV scores of normal-hearing adults in left- and right-oriented trials are shown for reference.

3.2.2 Electric stimulation shifts perception toward normal

Electric stimulation from a CI shifted the perception of visual vertical toward centre [F(4,78) = 3.791, p = 0.007]. As shown in Figure 3.15, the proportion of participants with normal scores while being stimulated from either ear improved to 74% (39/53) [Fisher’s exact test, p = 0.068]. Specifically, stimulation shifted initially abnormal SVV scores into the normal range of deviation in 14/24 participants (58%). Twenty-five of 29 (86%) participants maintained a normal SVV score while being stimulated, while the
electric current resulted in abnormal tilts in 4 (14%). Post hoc analysis with Bonferroni correction further confirmed that the score of bilaterally-implanted participants with an initial normal SVV (-0.5 ± 1.3 degrees) did not significantly differ while receiving stimulation from the left (-0.4 ± 1.5 degrees) [paired t-test, p>0.99] or right CI (-0.7 ± 1.2 degrees) [paired t-test, p>0.99]. Individuals with a left tilt (-2.9 ± 0.4 degrees) showed a trend toward improvement while being stimulated from their left CI (-2.0 ± 1.9 degrees) [paired t-test, p = 0.177], with no clear effects from right CI stimulation (-2.4 ± 1.5 degrees) [paired t-test, p>0.99]. Participants with a rightward tilt (3.7 ± 1.4 degrees), in contrast, greatly benefited from stimulation via their left implant (2.1 ± 1.0 degrees) [paired t-test, p = 0.017], and even more so with right CI stimulation (1.4 ± 1.8 degrees) [paired t-test, p = 0.002].

Figure 3.15: (A) The SVV scores across six trials of bilaterally-implanted participants demonstrate that electric stimulation from a CI shifted the perception of visual vertical toward centre. (B) Stimulation was most beneficial when provided from the ear ipsilateral to the tilt. Each bar represents the group mean ± SE for each experimental condition.
In bilaterally-implanted participants with either a normal or abnormal SVV score, electric current also reduced concordance of SVV with the linear marker’s initial orientation \[F(2,38) = 3.422, p = 0.043\]. As shown in Figure 3.16, CI users were better able to compensate while receiving stimulation from their right CI (0.05 ± 1.8 degrees) [paired t-test, \(p = 0.034\)] compared to no stimulation (0.7 ± 2.9 degrees) during trials with an initial rightward orientation. Left CI stimulation did not significantly improve perception during these trials (0.5 ± 2.1 degrees) [paired t-test, \(p = 0.148\)]. During the left-oriented trials, electric current from the right (-1.6 ± 1.8 degrees) [paired t-test, \(p > 0.99\)] or left (-1.1 ± 1.7 degrees) [paired t-test, \(p = 0.302\)] CI did not confer a significant benefit compared to no stimulation (-1.7 ± 1.7 degrees). The linear marker’s biasing effect was not reduced to a greater extent in participants with a left- or rightward abnormal tilt compared to individuals with a normal SVV \[F(4,76) = 0.66, p = 0.622\].

Figure 3.16: Electric stimulation from a CI reduced the biasing effect of the marker’s initial orientation on SVV score (mean ± SE). This reduction of bias was seen equally in groups with normal SVV or a left/rightward abnormal tilt. Positive values represent deviations to the right, and negative values indicate deviations to the left.

As illustrated in Figure 3.12, participants who scored overall within the normal range of deviation also tended to be more precise (i.e., low root-mean-square error) across the 6 trials. Conversely, participants with an abnormal SVV score tended to have a large
root-mean-square error. To ensure that the observed benefit of CI stimulation was actually due to improvement in function and not the mere result of inter-trial variability, we compared participants’ root-mean-square error in the absence of stimulation to their root-mean-square error while being stimulated. As Figure 3.17 demonstrates, participants’ estimations of the visual vertical were more precise while receiving CI stimulation, as evidenced by reduced inter-trial variability. In comparison to their root-mean-square error in the absence of CI stimulation (2.04 ± 1.47 degrees), inter-trial variability decreased while receiving right CI stimulation (1.43 ± 0.90 degrees) [paired $t$-test, $t(52) = 3.281, p = 0.002$]. Inter-trial variability did not significantly change while individuals were stimulated from their left CI (2.16 ± 1.10 degrees) [paired $t$-test, $t(41) = -0.229, p = 0.82$].

Figure 3.17: Participants’ root-mean-square error decreased while they received CI stimulation. Red and blue dots indicate root-mean-square error while being stimulated from the right or left CI, respectively. The diagonal black line represents no change in error in the absence vs. presence of stimulation. Data points under the line represent individuals with a lower root-mean-square error while being stimulated, while points over the line indicate increased inter-trial variability while receiving stimulation.
3.2.3 Predictors of perceptual tilt and SVV score change

Participants’ age \( [p = 0.627] \), sidedness of first implant \( [p = 0.509] \), and the presence of an acoustically-evoked cVEMP \( [p = 0.71] \) or oVEMP \( [p = 0.053] \) (i.e., residual saccular or utricular function, respectively) did not predict the degree or direction of initial SVV tilt [Multiple linear regression; \( F(4,48) = 1.865, p = 0.132 \), adjusted \( R^2 = 0.0624 \)]. There was no difference between the absolute degree of SVV tilt in participants with (median = 1.7, 95% Confidence Interval = 1.3-2.7) and without (median = 2.0, 95% Confidence Interval = 1.3-2.7) oVEMPs [Mann-Whitney-Wilcoxon, \( W = 300.5, p = 0.594 \)]. There were no clear differences in the distribution of otolith function amongst individuals with a normal SVV \( (cVEMP: \text{Present} = 19, \text{Absent} = 10; \ oVEMP: \text{Present} = 12, \text{Absent} = 17) \) or abnormal SVV \( (cVEMP: \text{Present} = 10, \text{Absent} = 14; \ oVEMP: \text{Present} = 8, \text{Absent} = 16) \) [Fisher’s exact tests; cVEMP: \( p = 0.102 \); oVEMP: \( p = 0.582 \)].

The proportions of participants with a normal or abnormal SVV score in the absence of stimulation are given in Table 3.3 according to etiology of hearing loss. Most children with a Connexin 26 mutation (70%) or cochleovestibular malformation (62%) were able

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<th>Etiology</th>
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<th>Abnormal SVV</th>
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<th>Right Tilt</th>
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<td>1 (50%)</td>
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Table 3.3: Proportions of participants with a normal or abnormal SVV in the absence of stimulation are described for each etiologic group. Individuals with an abnormal SVV are further subdivided according to the direction of perceptual tilt. IP=Incomplete partition; EVA=Enlarged vestibular aqueduct; SCC=Semicircular canal; CMV=Cytomegalovirus; ANSD=Auditory neuropathy spectrum disorder.
to accurately estimate the visual vertical. Most of the participants with SNHL due to Usher syndrome (83%) or meningitis (80%), on the other hand, exhibited perceptual deficits, with a majority of that subgroup demonstrating a rightward perceptual tilt (80% and 75%, respectively). Four of the five individuals with Usher syndrome who scored abnormally in the absence of stimulation were able to accurately estimate the visual vertical while receiving stimulation from their CI. Thus, while only 1/6 (17%) individuals with this syndrome achieved a normal score in the absence of stimulation, there was a trend toward improvement in this group, such that 5/6 (83%) could accurately estimate the visual vertical with CI stimulation [Fisher’s exact test, p = 0.08]. The proportions of individuals by etiologic group who demonstrated normal SVV scores while receiving CI-mediated vestibular stimulation are outlined in Table 3.4.

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<th>Etiology</th>
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Table 3.4: Proportions of participants with a normal or abnormal SVV while receiving stimulation are described for each etiologic group. IP=Incomplete partition; EVA=Enlarged vestibular aqueduct; SCC=Semicircular canal; CMV=Cytomegalovirus; ANSD=Auditory neuropathy spectrum disorder.

As shown in Figure 3.18, the degree and direction of initial tilt from centre significantly predicted the degree and direction of SVV shift produced with right CI stimulation [p<0.0001]. There were no clear effects of stimulation intensity normalized to hearing thresholds [p = 0.975], stimulation from the ear implanted first [p = 0.67], or the presence of an electrically-evoked cVEMP [p = 0.872] or oVEMP [p = 0.431] on SVV score change [F(5,45) = 5.405, p<0.001, adjusted $R^2 = 0.306$]. The degree and direction of
initial tilt similarly predicted the degree and direction of SVV shift produced with the left CI \( p < 0.001 \), with no clear effects of normalized stimulation intensity \( p = 0.293 \), stimulation from the ear implanted first \( 0.395 \), or the presence of an electrically-evoked VEMP \( p = 0.342 \) on SVV score change \( F(4,35) = 5.912, p < 0.001, \text{adjusted } R^2 = 0.335 \).

Figure 3.18: Electric stimulation from a CI shifted perception of visual vertical towards normal. The x-coordinate of each data point represents a participant’s SVV score in the absence of stimulation, with negative values indicating a leftward perceptual tilt and positive values indicating a rightward tilt. The y-coordinate of each point represents the change in SVV score, with positive and negative values representing rightward and leftward shifts, respectively. Bilaterally-implanted participants are represented by two dots, illustrating the change while being stimulated from their right (red) and left (blue) CI. Unilaterally-implanted individuals are represented by a red dot due to stimulation from the right side alone. The grey bar marks the amount of change from baseline SVV (no stimulation) needed to achieve a normal SVV score.
3.3 Impact of cochlear implant stimulation on static and dynamic equilibrium

Static and dynamic equilibrium, as approximated by the BOT-2, were evaluated while participants used their CIs and while the implant’s external processors were turned off. Initial analyses of data distributions indicated significant deviations from normality [Shapiro-Wilk normality test; BOT score, CI Off: $W = 0.801$, $p<0.001$; BOT score, CI On: $W = 0.822$, $p<0.001$]; thus, a Wilcoxon signed rank test with continuity correction was used to evaluate the differences in BOT-2 score with the CI ‘on’ versus ‘off.’ Participants, on average, did not significantly improve on the BOT-2 while using their CIs (median = 7 points; 95% Confidence Interval = 6-9) as compared to when their CIs were off (median = 6 points; 95% Confidence Interval = 5-9) [$W = 137$, $p = 0.495$]. Linear regression analysis plotted in Figure 3.19, however, indicated that change in score was predicted by CIs-off BOT-2 score, such that participants with poor balance were more likely to improve, while children with relatively better balance achieved the same or lower score when the CI external processor was switched on [coefficient = -0.229, $p = 0.0081$; $F(2,32) = 0.199$, $p = 0.029$, adjusted $R^2 = 0.149$]. We thus investigated how participants with ($n = 19$) and without ($n = 16$) acoustic VEMPs performed with their CIs on as compared to off. As illustrated in Figure 3.20, participants without an acoustic VEMP tended to have poorer balance overall than individuals with residual otolith function. Interestingly, acoustic non-responders demonstrated a small, yet consistent, improvement in balance function when their CIs were being used (median = 5 points; 95% Confidence Interval = 4-6) compared to when the CI processors were switched off (median = 4.5 points; 95% Confidence Interval = 3-5) [Wilcoxon signed rank test; $W = 4.5$, $p = 0.015$]. BOT-2 performance of individuals with present acoustic VEMPs did not change whether their implants were switched off (median = 10 points; 95% Confidence Interval = 6-12) or on (median = 9 points; 95% Confidence Interval = 7-12) [Wilcoxon signed rank test; $W = 67.5$, $p = 0.689$].
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Figure 3.19: The amount of BOT-2 change upon CI activation was predicted based on balance performance, in that participants with poor balance were more likely to improve compared to individuals with relatively better balance. Note: random noise (“jitter”) was added to the data points to allow for viewing of overlapping symbols.

Figure 3.20: Whereas BOT-2 performance did not differ when individuals with otolith function had their CIs on versus off, balance gains were observed in acoustic non-responders who activated their devices (median ± 95% Confidence Intervals).
As Figure 3.21a illustrates, the presence of an acoustically-evoked VEMP – indicating residual otolith function – predicted BOT-2 score [coefficient = 5.05; F(1,33) = 8.984, p = 0.005, adjusted $R^2 = 0.19$]. A bonferroni-corrected post hoc pairwise comparison using a Wilcoxon rank sum test revealed a significant difference between the BOT-2 scores of those with and without acoustic VEMP (p<0.001). Figure 3.21b highlights the distribution of electrically-evoked VEMP among participants who showed balance improvement with their CIs switched on and individuals who did not. Unlike acoustically-evoked VEMP, the presence of an electrically-evoked potential did not predict a participant’s performance on the BOT with their implants on [coefficient = 0.857; F(1,33) = 0.246, p = 0.623; adjusted $R^2 = -0.023$]. Adjusting for the aforementioned effect of ‘CI-off’ BOT-2 score on ‘CI-on’ score, the presence of an electrically-evoked VEMP further did not prognosticate the amount of BOT score change between the two conditions [coefficient = 0.251, p = 0.782; F(2,32) = 3.985, p = 0.029, adjusted $R^2 = 0.149$]. Tasks 4, 6, and 9 of the BOT-2 involved completing balance activities in the absence of vestibular cues, presumably imposing a dependence on vestibular input for the maintenance of postural stability. The presence of an electric VEMP did not, however, predict the amount of change on these tasks with the CIs turned off versus on: Task 4 (coefficient = -0.262, F(1,33) = 0.539, p = 0.468, adjusted $R^2 = -0.014$); Task 6 (coefficient = 0.238, F(1,33) = 1.602, p = 0.215, adjusted $R^2 = 0.017$); Task 9 (coefficient = -0.143, F(1,33) = 0.155, p = 0.697, adjusted $R^2 = -0.026$).
(a) Impact of residual otolith function (i.e., acoustically-evoked VEMPs) on balance

(b) Electrically-evoked VEMPs did not predict enhanced balance performance

Figure 3.21: (A) Participants with residual otolith function (i.e., acoustically-evoked cVEMPs and/or oVEMPs) performed better on the BOT-2 than individuals without these evoked responses. (B) The presence of electrically-evoked VEMPs did not predict balance or the change in BOT-2 score when the implants were switched on. The presence or absence of a cVEMP is represented by symbol colour, while that of the oVEMP is illustrated by symbol shape. For example, an individual with an absent c- and oVEMP would be depicted by a purple circle. The diagonal black line represents no change in BOT-2 score in the CI off vs. on conditions. Data points under the line represent individuals with reduced performance while using their implants, and points over the line indicate enhanced performance. Note: random noise (“jitter”) was added to the data points to allow for viewing of overlapping symbols.
As outlined in Table 3.5, 80% of children with Usher syndrome and 100% of participants with meningitis showed equivalent or improved equilibrium while using their implants compared to when their implants were turned off. The four individuals with a Connexin polymorphism who showed reduced BOT-2 performance with their implants turned on had an averaged score decrease of $2.75 \pm 0.5$ points from their ‘CI-off’ score of $14.75 \pm 5.25$ points.

<table>
<thead>
<tr>
<th>Etiology</th>
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<th>Equivalent</th>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>4 (80%)</td>
</tr>
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</tr>
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<tr>
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<td>4 (50%)</td>
<td>4 (50%)</td>
<td>0</td>
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</table>

Table 3.5: The proportions of participants who had improved, equivalent or lower BOT-2 scores for the ‘CIs-on’ (compared to ‘CIs-off’) condition are described for each etiologic group. IP=Incomplete partition; EVA=Enlarged vestibular aqueduct; CMV=Cytomegalovirus; ANSD=Auditory neuropathy spectrum disorder.
Chapter 4

Discussion

Though the CI is a well-established means of restoring input to the auditory system, its effects on the vestibular portion of the inner ear are unclear. Histopathologic studies of adult cadaveric temporal bones after cochlear implantation have demonstrated vestibular damage including fibrosis or ossification of vestibular components (Tien & Linthicum, 2002) and collapse of the saccular membrane (Handzel, Burgess & Nadol, 2006). The negative impact of the intervention may be attributed to iatrogenic injury or inflammation subsequent to the surgical procedure. In contrast, improved balance function following CI activation has been reported (Eisenberg, Nelson & House, 1982; Buchman et al. 2004; Cushing et al. 2008a), suggesting that the benefits of the implanted device might extend beyond the auditory system to include that of the vestibular system as well. Similar to how CI current can spread from the implant array to the facial nerve (Cushing et al. 2006, 2009), it has been proposed that the CI can directly stimulate the peripheral vestibular apparatus (Jin et al. 2006); until now, however, this phenomenon has not been objectively demonstrated. In this study, we hypothesized that vestibular potentials could be evoked using CI stimulation, thereby providing preliminary evidence supporting direction stimulation as a mechanism by which the CI improves balance. In an effort to identify the ramifications of CI current spread on function, we measured participants’ performance on an otolithic-dependent task both in the absence and presence of stimulation. We were further interested in investigating the relationship between otolith
function and gross balance. In this chapter, the results of the aforementioned endeavours presented in Chapter 3 will be discussed in light of the specific research questions, namely:

1. What is the prevalence of vestibular reflexes in our population of pediatric cochlear implant users? How frequently can these reflexes be evoked with electrical pulses from the cochlear implant?

2. What electrical stimulation parameters are needed to elicit vestibular evoked reflexes?

3. Does cochlear implant evoked stimulation of the vestibular system have an impact on function?

4.1 What is the prevalence of vestibular reflexes in pediatric cochlear implant users? How frequently can these reflexes be evoked with electrical pulses from the cochlear implant?

Reliability of VEMPs as an indicator of vestibular function

The aims of the present study included evaluating vestibular dysfunction in children with CIs and determining the prevalence of CI-mediated vestibular responses in this population irrespective of end organ function. The otoliths were chosen to be the focus of our investigation due to their closer anatomic proximity to the cochlea (and CI) and because their function better predicts motor development and static balance as compared to the semicircular ducts (Inoue et al. 2013; Fujimoto et al. 2015; Iwasaki et al. 2005; Jafari & Asad Malayeri, 2011). VEMPs were particularly appealing for vestibular end organ assessment because they do not produce unpleasant vestibular symptoms, such as dizziness and vertigo. Furthermore, the effects of acoustic and electric stimuli on the response could be independently evaluated without additional compounding factors, such as mechanical and thermal stimuli that are used for rotational chair and caloric testing, respectively.
Since the presence of a VEMP is contingent on stimulus energy (intensity) and muscle contraction, efforts were made to ensure that these components were optimal in order to make reasonable conclusions regarding end organ integrity. Acoustic stimulus parameters were chosen that would increase the likelihood of eliciting a response, if present. Individualized, maximally-tolerable CI stimulus intensities were then utilized to facilitate the spread of current outside the cochlea. We recruited an older sample of pediatric CI users, given the effort-related difficulties reported in children under 7 years of age (Kelsch, Schaefer & Esquivel, 2006). We further monitored SCM and IO contraction during testing and provided feedback to the participants in real time so that they could sustain a consistent peak-to-peak amplitude. Despite offering continued guidance throughout the assessment, some younger participants could not consistently maintain up-gaze during oVEMP testing, which may have impacted the sensitivity of the test. To mitigate this, recordings were repeated to reproduce the presence or absence of the VEMP. One limitation of the study protocol was the absence of middle ear evaluation, as a conductive loss can lead to a false negative response. While there is no better method than to have actually measured middle ear function prior to testing, one would predict a rather low prevalence of middle ear dysfunction in this sample given the age of the children (>7 years) and the fact that they had undergone a mastoidectomy during cochlear implantation.

A limitation of the recording software was that only the unrectified EMG activity could be monitored during VEMP testing. Offline rectification and averaging was thus conducted to quantify the actual magnitude of muscle contraction in each individual. The range of tonic SCM contraction across all participants was 48.1 - 436.7 µV. Rosengren (2015) reports that in participants with normal vestibulocochlear function, the mean rectified minimum contraction required to record a cVEMP was 24.8 ± 11.4 µV; while a response was seen with a contraction as small as 6.6 µV, EMG activity of 60 µV was required in other participants before a response appeared. The author thus notes that while cVEMPs may be present with EMG levels <60 µV, there is an elevated risk of a Type I error with lower muscle activity levels, i.e., a missed response when the system is, in fact, normal. As seen in Figure 3.4, almost all of the rectified mean EMG recordings in
the present study – particularly those in which cVEMPs were not observed – surpassed this 60 µV threshold. To date, the minimum contraction required to record an oVEMP has not been investigated. Given that the IO muscle is significantly smaller than the SCM, it was surprising to record rectified EMG levels as large as 100 µV during oVEMP testing (Figure 3.5). These large values seem to indicate that the recorded activity was not reflective of the IO muscle alone. In contrast to the active electrode for cVEMP testing, which is directly placed over the large SCM, the recording electrode for oVEMP evaluation tends to overlie a number of smaller extraocular muscles in addition to the IO. Thus, while the oVEMP response is generated by the IO, it remains unclear how much of the recorded tonic contraction can be attributed directly to this small muscle.

Rectified mean EMG comparisons showed that there were no differences in the amount of SCM and IO contraction between the ears with and without acoustically-evoked VEMPs. There were many more conditions involving electric stimuli (e.g., E3 vs. E20, single pulse vs. pulse train) compared to those involving acoustic stimuli, which is likely why a difference was noted in muscle activity when an electrically-evoked VEMP was present or absent; there was simply more power in that model to detect a statistical, but not clinically meaningful, difference. Comparison of rectified mean EMG activity to that of normal-hearing and cochlear-implanted participants with VEMPs increased our confidence that an absent response was truly reflective of end organ dysfunction and not mere inadequate muscle contraction.

_Vestibular stimulation with a CI_

Figure 3.6a demonstrates that 58% of participants with CIs had a VEMP in at least one ear in response to acoustic stimulation. Conversely, 23 of the 55 (41%) children did not have residual vestibular function in the tested ears. The proportions of acoustically-evoked cVEMPs (46%) and oVEMPs (26%) in this sample correspond to percentages (61% and 59% respectively) reported by Xu and colleagues (2015), who evaluated end organ function in children with a profound hearing loss. Whereas the children in Xu’s study seemingly did not use a CI, each of the participants in the present study had received this intervention. The elevated prevalence of vestibular dysfunction in our sample
might therefore be the consequence of increased cochleo-vestibular dysfunction, which necessitated cochlear-implantation, or is a result of the surgical procedure itself.

We hypothesized that electrical stimulation from a CI would elicit VEMP s, confirming the spread of electric current from the intra-cochlear device to the vestibular end organs. Indeed in 62% of participants assessed with our novel technique, current spread to the vestibular system was evidenced by the presence of an electrically-evoked VEMP in at least one ear. This finding suggests that the prevalence of vestibular cross-stimulation has been understated in the literature until now. As noted in studies of CI-mediated facial nerve activity (Cushing et al. 2006, 2009), electrophysiologic recordings are more sensitive to cross-stimulation – and are thus more representative of its prevalence – compared to self-reporting measures or patient observation. This is because nerve activity facilitated by electrical stimulation can often occur below the stimulus intensity levels required for observable symptoms, such as muscle twitching.

There are a few reports of vestibular nerve stimulation after cochlear implantation, most of which cast it in a negative light. Using infrared videonystagmography, Bance and colleagues (1998) determined that 5.9% of cochlear-implanted patients exhibited nystagmus while receiving stimulation from their device. This study was prompted by a single patient who had become a non-user after developing violent nystagmus upon CI activation that could not be resolved with programming modifications. Shortly thereafter, Ito (1998) surmised that the spread of current to the vestibular nerve was responsible for post-operative dizziness that developed secondary to implant use. Whereas these prior reports described aberrant current spread that translated into unpleasant symptoms, the present study has shown that a percept does not necessarily accompany vestibular cross-stimulation. With this in mind, it should not be assumed that this phenomenon is invariably detrimental.

Though end organ dysfunction was common in this sample of implanted children, we hypothesized that electric current would drive these reflexes in participants with absent acoustic VEMP s. As seen in Figure 3.7, electric VEMP s were obtained in 28% of ears non-responsive to acoustic cVEMP testing and in 25% of ears non-responsive to acoustic
oVEMP testing. This finding brings the concept of vestibular areflexia into question. Though their otolithic end organs were shown to be dysfunctional, these participants’ vestibular systems remained stimulable. Akin to the CI bypassing dysfunctional hair cells to stimulate the cochlear nerve, electrical current was seemingly able to bypass dysfunctional otoliths to more directly stimulate the vestibular neural elements. Of the 99 ears tested for cVEMPs and oVEMPs, 38 and 54 ears did not respond to acoustic and electric stimuli. It presently remains unclear whether this non-responsiveness is due to limited extracochlear current spread or is indicative of the functionality of the vestibular afferents.

**Hearing loss etiology and peripheral vestibular stimulation**

Electric pulses from a CI stimulated the vestibular system in 63% of participants with an anomalous cochlea. Compared to children with normal cochleae, individuals with cochlear abnormalities are susceptible to facial nerve stimulation (Cushing et al. 2006), which significantly interferes with CI programming strategies (Papsin, 2005). Facial nerve stimulation in this population is thought to be the result of abnormal facial nerve anatomy (Hoffman, Downey, Waltzman & Cohen, 1997; Graham, Phelps & Michaels, 2000) or incomplete device insertion in the shortened cochlear ducts (Maas, Bance, ODriscoll, Mawman & Ramsden, 1996). The presence of an inner ear deformity might then elevate the risk of extracochlear stimulation, including that of the vestibular nerve. Although the Cushing (2006) study demonstrated that facial nerve stimulation was less prevalent in children who received a CI secondary to meningitis, the majority of this group in the present study (80%) exhibited current spread to the vestibular system. Notably, these responses were evoked despite the fact that all 5 participants had dysfunctional end organs. The spread of current to the vestibular nerve in these patients was possibly facilitated by ossification that follows meningitic infection of the inner ear.
### 4.2 What electrical stimulation parameters are needed to elicit vestibular evoked reflexes?

*Effect of single pulse vs. pulse train stimuli on VEMP prevalence and morphology*

Since a train of electric pulses presumably delivers more charge to the vestibular system than single pulses, one would predict a higher prevalence of VEMPs with pulse trains than single pulses. In the ears tested with single pulse and pulse train stimuli however, the prevalence of cVEMPs and oVEMPs was equivalent. As will be discussed later, the use of greater stimulus intensities – and thus greater charge delivered to the system – increased the likelihood of eliciting these vestibular responses. It should be noted that, in order to maximize the odds of eliciting an electrical VEMP, highest tolerable intensity levels for each of the stimuli were used. We subjectively noted that children could, at times, tolerate higher intensity levels for the single pulses than the pulse trains. Increased stimulus intensities for single pulses may have therefore been a compounding factor in this analysis. VEMP testing using both types of stimuli was administered only during initial stages of the study given the length of protocol and participants’ reports of muscle fatigue with repetitive testing across multiple conditions (single pulse vs. pulse train using E3 and E20 in each ear).

The duration of acoustic stimuli has been shown to impact VEMP latency: average P1 and N1 peaks have a greater latency when evoked with tone bursts compared to clicks (Welgampola & Colebatch, 2001). The same study demonstrated that peak latency increased with increasing tone-burst duration, though this increase was not directly proportional to stimulus duration. Likewise in the present study, electrically-evoked cVEMP P1 latencies increased by 1.2 ms when evoked with pulse trains as compared to single pulses. It is worthwhile to note that this latency shift corresponds to the time interval between pulses of the train stimulus, as seen in Figure 2.5b. Though it is unclear why the response would lock to the second pulse in a train of stimuli, it is possible that the vestibular system recognizes the pulse train as a series of single pulses as opposed to a cohesive, 4.4 ms unit. As the present study focused on determining whether or not
vestibular potentials could be evoked with a CI, a short duration stimulus was chosen to avoid masking the presence of an oVEMP, which has a shorter peak latency than the cVEMP. Future endeavours might therefore extend the duration of the pulse train to further elucidate the impact of electric stimulus duration on the cVEMP.

**Basal vs. apical stimulation**

Apart from highlighting a high prevalence of asymptomatic current spread from the CI to the vestibular system, the present data additionally offer insight into characterizing the nature of such cross-stimulation. As basal electrodes are nearer anatomically to the afferents innervating the otoliths, one might hypothesize that vestibular activation would be more likely with basal (E3) stimulation compared to apical (E20) stimulation. VEMPs were not, however, preferentially evoked using the basal or apical ends of the implant array. Moreover, there were some participants in whom basal stimulation did not generate a VEMP, but apical stimulation did. There were additionally no clear differences in peak latencies of apically- versus basally-elicited VEMPs. A previous study determined that myogenic responses to facial nerve stimulation were equally prevalent with apical (E20), midpoint (E9), and basal (E3) stimulation (Cushing et al. 2006). The exact path of extracochlear current spread from an implant to the vestibular system is as of yet unknown and may vary depending on the etiology of deafness and the physical milieu of the implant.

**Stimulation intensity**

Electric stimulation in our protocol was purposefully delivered at the highest comfortable intensity in an effort to maximize extracochlear current spread. As expected, a higher rate of vestibular cross-stimulation was noted as current level increased. Interestingly though, VEMPs were also produced with stimulation as low as 200 CU. Since threshold testing was not performed, it is certainly plausible that VEMPs could have been obtained at even lower levels of stimulation. Furthermore, Rosengren (2015) notes that while it is theoretically possible to record a VEMP as soon as muscle units are active, a minimum number of units may need to be synchronously recruited in order for a response to be detected. By extension then, vestibular stimulation may have occurred in our children
with absent electrically-evoked VEMPs, albeit below the vestibular afferent recruitment threshold required to record a VEMP. Combined with the fact that none of the electrical stimulation was perceived to be uncomfortably loud by the participants, this would suggest that vestibular cross-stimulation can occur within the clinical map ranges of many users.

*Impact of stimulus medium on VEMP characteristics*

As previously discussed, electric current from the CI was able to bypass dysfunctional otoliths and directly stimulate vestibular neural components. The peak latency data further support this notion. Electrically-evoked VEMPs obtained via CI stimulation were faster in onset than acoustically-evoked VEMPs and comparable to the responses obtained by Park and colleagues (2015) after direct promontory stimulation. This observation implies that the site of activation differs between the two stimuli. Whereas acoustically-evoked responses are dependent upon mechanical stimulation of the vestibular end organs via a travelling fluid wave, the shorter latencies of the electrically-evoked responses suggest a more direct path of neural stimulation.

Acoustic stimuli evoked larger cVEMPs and oVEMPs than electric stimuli, even when peak-to-peak amplitude was normalized to tonic EMG activity. In contrast, Bacsı and colleagues (2003) found that when measuring these potentials from the soleus muscle, amplitudes of acoustically-evoked VEMPs were smaller than that of galvanically-evoked responses. While differing strategies may be employed by the central nervous system to recruit the SCM and soleus, a more likely explanation is that the electric stimuli used in this study were presented at maximally tolerable levels and were thus not intensity-matched to the acoustic stimuli. Single pulse stimuli were also used at times, so the shorter duration of electric compared to acoustic stimuli may have contributed to this amplitude difference. Furthermore, fibrosis occurs in the inner ear secondary to cochlear implantation, effectively increasing electrical resistance. The smaller amplitudes of electric VEMPs in the present study might also then be attributed to restricted current flow in the inner ears of CI users compared to the healthy participants tested in the Bacsı (2003) study.
4.3 Does cochlear implant evoked stimulation of the vestibular system have an impact on function?

The present study used the SVV test to investigate how children with CIs perceive the vertical plane and to determine if CI stimulation affects their perception of the visual vertical. We found that a large proportion of CI users have an asymmetric weakness that is augmented by visual tilts in the direction of their abnormality. Electric current from the implant helps to correct this abnormal perception, especially when the stimulated ear is ipsilateral to the visual tilt.

Abnormal perception of the visual vertical in CI users

Given the high prevalence of vestibular dysfunction in children with SNHL who use CIs, we expected that a large percentage of participants would demonstrate abnormal scores on the SVV test. Indeed, 24% of subjects had an abnormal leftward tilt, and 20% showed a tilt to the right. The degree of tilt in these groups (Left tilt: -2.9 ± 0.4 degrees; Right tilt: 3.6 ± 1.2 degrees) is comparable to SVV scores of children with peripheral vestibular loss (Brodsky et al. 2015, 2016), providing evidence of vestibular dysfunction in children with CIs in addition to previous reports (Parkes et al. 2016; Cushing et al. 2013; Thierry et al. 2015; Xu et al. 2015b). Figure 3.13 (“(b) CI Participants: Normal SVV”) further demonstrates that even when CI users achieved normal overall SVV scores, there was a large amount of trial-to-trial variability in their perception of vertical. A normal score in these participants, then, would not necessarily equate to normal function (Funabashi et al. 2012), but rather increased central compensation in response to reduced vestibular integrity (Vibert et al. 1996, 1999).

Although visual cues are removed during SVV testing to impose dependence on otolithic input, the linear marker has been shown to bias the SVV towards the direction of initial presentation (Pagarkar et al. 2008; Toupet et al. 2015). Pagarkar and colleagues (2008) found this effect was enhanced in participants with unilateral peripheral vestibular deficits, and supposed that this bias was equally distributed between left and right trials. Our data suggest, however, that deficits were truly brought out when the marker was
oriented in the same direction as the perceptual deficit (Figure 3.14). The present study furthermore highlights the importance of including left and right start positions when measuring the SVV; a participant with a right perceptual tilt could theoretically have demonstrated a normal SVV if only left-oriented trials were presented, and vice versa.

The presence of a perceptual abnormality in our participants coincides with other reports of vestibular and functional deficits in children with a profound hearing loss. Amongst young children (20-97 months of age) who underwent vestibular assessment before cochlear implantation, those with vestibular end organ dysfunction were more likely to acquire gross motor skills, such as head control and independent walking, at a later age than those with functional systems (Inoue et al. 2013). This developmental delay can persist or even worsen with time (Rine et al. 2000). As the interchange between visual, vestibular and somatosensory modalities can facilitate the development of compensatory mechanisms for daily function, appropriately difficult balance tasks must sometimes be administered before performance deficits are observed (Cushing et al. 2008). Similarly, the participants of the present study did not anecdotally complain of a perceptual tilt; deficiencies did emerge nonetheless, especially in certain visual contexts.

Perceptual accuracy improves with CI stimulation

Children were able to more accurately estimate the gravitational vertical while being stimulated via their CI compared to no stimulation, as shown in Figure 3.15. This finding is in accordance with numerous reports of improved balance while using a CI (Eisenberg et al. 1982; Buchman et al. 2004; Cushing et al. 2008). Figure 3.15 (“Normal SVV” group) demonstrates that when peripheral vestibular function is intact or central perceptual centres have adequately compensated for the deficit, CI stimulation does not adversely affect the perception of vertical. Data plotted in Figure 3.16 indicate that although participants with a normal or abnormal SVV score were biased towards the linear marker’s initial orientation, this effect was reduced while electric stimulation was provided. It has been proposed that the biasing effect is due to the incorporation of the marker’s position into short-term visual memory, which then influences the estimation of vertical (Toupet et al. 2015). Figure 3.14 reveals that CI users are not immune to
this effect and may, in fact, rely more heavily on visual memory during these tasks, as exemplified in participants with an abnormal perceptual tilt. The reduction of this bias while receiving stimulation suggests that electric current recalibrates the internal perception of gravitational vertical in CI users, enhancing their ability to estimate the vertical independently of external cues.

This study has shown that even when the otoliths themselves are non-functional, the neural components of the vestibular system remain responsive to external stimuli. This was objectively demonstrated using current from a CI to elicit VEMPs from areflexic vestibular end organs (Parkes et al. 2016). Sadeghi and colleagues further revealed that after a labyrinthine insult in nonhuman primates, neurons of the vestibular nuclei compensated for sensory loss by developing a greater sensitivity to extra-vestibular input (Sadeghi et al. 2010, 2011, 2012). These findings of vestibular cross-stimulation with a CI, integration of external input by vestibular nuclei, and improved perception with stimulation collectively imply that the central nervous system is able to utilize electric stimulation from a CI as a supplement to, or in lieu of, otolith input. Improved spatial perception might alternatively be explained in part by the phenomenon of stochastic resonance, by which the deliberate introduction of noise into a system can enhance signal processing (McDonnell & Abbott, 2009.) A third possible explanation is that although the stimulus itself does not provide meaningful input for one specific sensory modality (auditory or vestibular), multisensory integration facilitates a gestalt-like interpretation of the CI stimulation.

Data shown in Figures 3.15 and 3.18 illustrate that while electric current from either ear improved perceptual accuracy, stimulation from the side ipsilateral to the tilt conferred an even greater advantage. Improvements in vertical perception have also been observed in patients with right-hemisphere stroke who received galvanic vestibular stimulation, although these patients were more accurate with contralateral stimulation (i.e., from their left side) (Saj et al. 2006; Oppenlander et al. 2015). Inasmuch as SVV tilt manifestation is representative of lesion location in the vestibular pathway (Dieterich & Brandt 1993; Brandt et al. 1994; Yang et al. 2014), the most beneficial site of stimulation is potentially
dependent on where input is needed: peripheral vestibular dysfunction requires ipsilateral stimulation, while contralateral stimulation restores input to more rostral deficiencies.

**Predictors of perceptual tilt and SVV score change**

As outlined in section 3.2.3, the direction or severity of perceptual tilt could not be predicted based on participants’ age, first implanted ear, or residual otolith function. A previous investigation into the relationship between bone-conducted oVEMPs and the Subjective Visual Horizontal test, another functional measure of utricular health, found that rates of abnormality correlated between the two assessment methods in patients with Meniere’s disease (Lin & Young, 2011). Whereas congruence between the SVV and oVEMP tests might be expected during the acute phases of vestibular impairment, improvement in SVV performance has been reported in the weeks following the onset of vestibular dysfunction (Vibert et al. 1996, 1999; Min et al. 2007), presumably due to compensatory mechanisms initiated by vestibular processing centres. Central compensation subsequent to compromised otolith function might then explain the lack of consistency noted here between abnormal oVEMP and SVV results. Consequently, in individuals with chronic vestibular loss, such as the participants in the present study, oVEMP evaluation may perhaps be more sensitive and/or specific to end organ impairment than SVV (Valko et al. 2011).

Linear regression analysis of data shown in Figure 3.18 indicated a significant correlation between the degree of abnormality and the amount of SVV score change, which is perhaps why statistically significant improvements were detected in those with a right perceptual tilt but not those with a left tilt; the group with a right deficit exhibited more change because they had more of an initial abnormality. The intensity of stimulation seemingly does not dictate the amount of gained perceptual benefit, as indicated by the linear regression. Although all participants received a comfortably loud stimulus, those who tolerated higher intensity levels did not show a greater shift in SVV score. Moreover, the aforementioned study of galvanic vestibular stimulation reported improved vertical estimation while using a subthreshold stimulus (Oppenlander et al. 2015). These findings imply that the perceptual benefit is contingent on the successful stimulation of the
vestibular system rather than being a function of the magnitude of stimulation provided. As such, it is conceivable that the current levels used daily by children with CIs may be sufficient to cross-stimulate the vestibular system and confer functional benefit.

**Impact of CI stimulation on balance function**

To further elucidate the effect of CI-mediated vestibular stimulation on function, tasks evaluating static and dynamic equilibrium were administered while participants’ devices were switched off and while they were activated in ambient noise. For the purposes of this test, electrical stimulation was purposefully not delivered at high intensities, as was done for VEMP and SVV assessment. Instead, participants completed each task using the current levels that had been individually programmed by their audiologist for their daily use. These levels were used with the intent of investigating whether or not the presence of electrically-evoked VEMPs correlates with CI-facilitated balance improvement, and by extension, whether vestibular cross-stimulation can occur at levels within the clinical map ranges of CI users.

CI users demonstrated postural instability while performing balance tasks with their devices switched off, evidenced by an average scale score of 8 ± 6 points. In conjunction with the fact that 42% of this tested sample was areflexic in response to acoustic stimuli, the present study provides further evidence that the balance impairment noted in this population of children is likely due to their vestibular dysfunction. Indeed, a previous investigation of equilibrium in children found that while normal-hearing participants could achieve BOT-2 scores of 17 ± 5 points, the implanted group obtained scores of only 12 ± 6 points, on average (Cushing *et al.* 2008a). Another comparison between children with SNHL who received unilateral CI, bilateral CI, or no intervention revealed no significant difference in BOT-2 score among the three groups (Eustaquio, Berryhill, Wolfe & Saunders, 2011), suggesting that balance impairment is a sequela of cochleovestibular dysfunction and is not necessarily secondary to surgical trauma. Furthermore, the presence of an acoustic VEMP in the present study prognosticated BOT-2 score, such that individuals with a present response performed significantly better than those from whom VEMPs were not recorded. This finding is consistent with previous reports of
the relationship between otolith integrity and balance function. De Kegel and colleagues (2012) observed that deaf children who had bilaterally intact otolith function exhibited reduced mean sway velocity compared to children with unilateral or bilateral saccular dysfunction. Another study found that children with a congenital or early-acquired hearing loss who had intact saccular function showed enhanced performance on two static balance tests (i.e., standing on one foot on a line or a balance beam) compared to children without these responses (Jafari & Asad Malayeri, 2011). The present study confirms this finding, noting the contributions of both the saccule (cVEMP) and utricle (oVEMP) while maintaining equilibrium in a fixed position and while moving (complete BOT-2 scale score).

Participants with compromised otolith integrity showed a small, yet consistent, improvement in balance performance while using their implants compared to while their devices were switched off. Linear regression analysis revealed that the change in BOT-2 score could be predicted by ‘CIs-off’ BOT-2 performance, such that individuals with poor balance were likely to improve when their CIs were activated, while the addition of a CI did not confer any clear benefit to those with relatively better balance. The reduced impact of CI use on performance in this latter group might be explained by the fact that these individuals had residual otolith function, which may have been deemed by the central nervous system as more reliable than electrical stimulation from the CI. These results may alternatively be attributed to ceiling effects of the test.

The effect of a single-electrode CI on equilibrium was first described by Eisenberg and colleagues (1982), who noted that postural stability – as measured by a postural test that had been adapted from the Ataxia Test Battery – improved with device activation. Later, Buchman and colleagues (2004) reported that device activation in music seemed to confer an additional advantage when computerized dynamic posturography was performed. Finally, Cushing and colleagues (2008a) demonstrated a statistically significant improvement in scores on the BOT-2 when children completed tasks with their implants on versus off. One possible explanation for this constellation of findings is that extracochlear spread of current to the vestibular system with implant use may
provide a usable vestibular cue in the form of background activation. As demonstrated by the present study, electric stimulation can spread to vestibular neural components, both in the presence and absence of functional otolith organs (Parkes et al. 2016). This low-level activation may theoretically serve to boost weak but intact residual vestibular function through the principle of stochastic resonance, whereby random noise (i.e., stimulation) may counterintuitively serve to enhance central signal processing (for a review, see McDonnell & Abbott, 2009). The absence of a correlation between electrically-evoked VEMPs and balance improvement with the CI was a surprising result, but may nonetheless be reflective of the dependence of the central nervous system on multiple sensory modalities besides vestibular input for bipedal stance. Electrotactile tongue (Barros, Bittar & Danilov, 2010) and auditory (Cushing et al. 2012) feedback on head position has been shown to improve postural control and reduce sway, even when conventional rehabilitative methods are ineffective. The improvement in BOT-2 score when our sample used their CI might then be due to the combination of vestibular and auditory cues that are afforded to them by their device.

Etiology of hearing loss appears to play a role in a child’s ability to maintain equilibrium, given that superior balance performance is observed when the cause of deafness is genetic as opposed to idiopathic (Butterfield & Ersing, 1986). Moreover, patients who develop vestibular dysfunction in infancy demonstrate enhanced head stabilization following postural perturbations compared to patients who acquire vestibular loss in adulthood (Shupert & Horak, 1996). Buchanan and Horak (2001) note that the duration of vestibular loss might also have implications on postural control, as an extended period of time facilitates the development and honing of compensatory strategies by the central nervous system. In support of this notion, another study found that, though there was a wide spectrum of balance function in this group, cochlear-implanted children with a GJB2 mutation tended to perform better than children who had lost their hearing secondary to other causes, such as meningitis and cochleovestibular anomalies (Cushing et al. 2008b). The present study found that in this group with a Connexin polymorphism, 92% retained otolith function (Table 3.2), only 33% demonstrated an abnormal SVV score in the absence of stimulation (Table 3.3), and none exhibited improved BOT-2 performance
with their CIs on (Table 3.5). Although the small sample size of each etiologic group precludes definitive conclusions, these results suggest that children with the Connexin mutation may have an internally-referenced, vestibular-dependent sense of equilibrium. As such, balance maintenance in this group is fairly consistent regardless of whether or not the implant is used. On the other hand, of the children who had acquired SNHL secondary to Usher syndrome or meningitis, none had otolith function (Table 3.2), and 83% and 80%, respectively, obtained an abnormal SVV score (Table 3.3). When receiving stimulation from their CIs, however, the proportions of individuals with a normal SVV score in these groups increased to 83% and 60% (Table 3.4). Similarly, 40% and 75% demonstrated improved balance performance while using their devices (Table 3.5). The conferred benefit of the implant in these children might be attributed to the delayed onset and progression of their cochleovestibular deficits, which may allow the central nervous system to incorporate CI stimulation into compensatory strategies as the child develops. As a result, the removal of an input source (i.e., their CI) potentially leads to a reduction in both auditory and vestibular function.

### 4.4 Future directions

While the results of this study – namely, the beneficial impact of CI stimulation on the vestibular system – are encouraging, they also open the door to a plethora of ensuing research questions. The ability to record VEMPs as objective evidence of current spread to the peripheral vestibular organs provides one with a window into the dynamic milieu of the inner ear following cochlear implantation. In the initial months after activation of the device, low current levels are typically employed in an effort to allow the auditory system to adapt to a novel stimulus, that is, electrical current. Whereas the spiral ganglion cell bodies are targeted and engaged, the purposeful minimization of current spread conceivably leaves the vestibular afferents largely unstimulated, which may in turn lead to synaptic pruning. The fibrosis that occurs subsequent to surgical invasion of the inner ear might further hinder the spread of current to the vestibular end organs.
Therefore, longitudinal VEMP testing using both acoustic and electric stimulation may provide insight into the health and development of the vestibular end organs and neural elements after cochlear implantation. Furthermore, SVV assessment in the present study was administered in participants who had years of experience with their devices. Pre- and postoperative longitudinal SVV evaluation would thus presumably clarify whether perceptual abnormalities are a sequela of cochleovestibular pathology or are the result of surgical trauma.

In this study, CI stimulation was deliberately provided at comfortably loud intensities in order to maximize extracochlear current spread and evoke vestibular potentials. Gains in perceptual accuracy were observed in most participants, however, irrespective of whether or not a VEMP elicited. The improvement in balance function while participants used their devices also suggests that vestibular cross-stimulation may be occurring at lower intensity levels. Further investigation is thus needed to compare the amount of stimulation necessary to observe balance or perceptual improvement with the threshold of current required to evoke a vestibular reflex. Due to software limitations, the present study protocol was restricted to examining the impact of unilateral electric stimulation on perceptual tilt. As the majority of children with bilateral SNHL seen at our institution receive two implants, it would be worthwhile to explore how the vestibular system responds to the simultaneous delivery of bilateral stimulation, particularly if this confers a greater benefit in comparison to unilateral input. Though the children assessed in the present study were physically able to complete the testing protocol, one can imagine the challenges associated with the use of this ‘bucket’ technique in younger children, who have not yet developed the strength needed to support the bucket’s weight. Future studies should therefore explore the efficacy of a commercially-available goggle system for SVV evaluation, which might then aid with extending the applicability of this test to a younger population.

As this is the first endeavour to objectively capture current spread to the otoliths, future studies should investigate whether CI stimulation also reaches the semicircular canals, as evidenced by evoked vestibulo-ocular reflexes or nystagmus. Doing so would encourage
discussion regarding the therapeutic potential of the CI beyond the auditory system. The exact mechanism by which the vestibular processing centres use electric pulses to enhance visual vertical perception is beyond the scope of this thesis. Presumably though, the delivery of meaningful information regarding head position via the CI would further improve balance function. Indeed, initial attempts at using auditory cues to provide stabilizing cues have been successful (Cushing et al. 2012). So as not to interfere with auditory processing, the presentation of ‘inaudible,’ focused current to the vestibular end organs may, in the future, bestow the implant with two purposes: auditory and vestibular rehabilitation.
Chapter 5

Conclusions

Although it is well-established that children with a profound hearing loss also have associated vestibular and balance deficits, the means by which the CI can improve vestibular function must be investigated. The results presented in this thesis provide preliminary evidence supporting direct vestibular stimulation as a possible mechanism by which a CI enhances balance performance. VEMP testing using CI stimulation provides a new method of objectively measuring current spread from an intracochlear electrode array to the vestibular system. Vestibular cross-stimulation does not invariably produce perceptible symptoms, and as such, likely occurs in a much higher proportion of implant users than previously thought. Moreover, while higher current intensities increase the likelihood of stimulating the end organs, none of the stimulation was perceived to be uncomfortably loud by participants. Combined with the fact that stimulation was presented at the highest tolerable intensity and VEMP threshold testing was not conducted, it is plausible that cross-stimulation occurs at levels within the dynamic current ranges used daily by CI users. Vestibular activation is not limited to stimulation from one end of the intracochlear array; vestibular potentials were evoked equally with electric current delivered using basal and apical electrodes. Though the exact site of vestibular excitation remains unknown, the data described in earlier chapters indicate that electric current can bypass the otoliths to directly stimulate vestibular afferents. Importantly, even when
these end organs are compromised, vestibular reflex pathways remain stimulable and can be accessed via a CI.

In an alarming large proportion of CI users, vestibular loss manifests in the form of abnormal spatial orientation characterized by an abnormal tilting of the visual environment. CI users’ asymmetric perceptual deficits are augmented in specific visual contexts, resulting in an inability to compensate from visual tilts in the direction of their abnormality. Effects of CI stimulation are encouraging, as abnormal perception perception shifts towards normal once electrical pulses are provided from the implant. Despite concerns that current spread from an implant might cause deleterious effects, these findings indicate a functional benefit of the deliberate spread of electric current to extracochlear structures, including the peripheral vestibular end organs. Notably, this benefit is realized regardless of which ear is stimulated. The ability of children with SNHL using CIs to ambulate well despite having vestibular anomalies is a testament to the remarkable capacity of the central nervous system to compensate for lost sensory input. It is only when vestibular-dependent tests are administered that the deficits of these children begin to emerge. Indeed, the lack of correlation between an objective measure of vestibular end organ integrity (i.e., VEMP) and a vestibular-reliant functional task (i.e., SVV) is likely indicative of the central compensatory mechanisms that are employed by children with SNHL in order to navigate their environment.

In accordance with previous work, impairment in static and dynamic equilibrium was observed in children with SNHL treated with CIs. The presence of otolith function prognosticated balance performance, such that individuals with absent otolith input had worse balance than those with intact unilateral or bilateral function. In this former group, however, the use of their device(s) mediated small, yet consistent, improvements in balance performance. The presence of an electrically-evoked VEMP did not clearly correlate with balance improvement upon CI activation. Like the SVV, this finding may reflect the dependence of the central nervous system on multiple sensory modalities beside vestibular input for bipedal stance.
The results shown in this thesis demonstrate that electric current from a CI can spread beyond its primary auditory targets to also activate peripheral components of the vestibular system. It is our hope that in addition to raising awareness of vestibular and balance dysfunction that impedes normal function in children with SNHL rehabilitated with CIs, these findings will encourage future research on harnessing extracochlear current and directing it towards the vestibular system in the form of meaningful postural input. The realization of this goal would be a major step towards restoring necessary sensory input in this population with concurrent auditory and vestibular loss.
Chapter 6

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Vestibular Evoked Myogenic Potential Testing as an Objective Measure of Vestibular Stimulation With Cochlear Implants

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Objectives/Hypothesis: To determine if vestibular potentials could be elicited with electrical stimulation from cochlear implants. Study Design: Prospective cohort study. Methods: Vestibular responsiveness to electrical stimulation from cochlear implants was assessed via vestibular evoked myogenic potential (VEMP) testing in 53 pediatric and young adult patients. Results: Thirty-one participants (56%) showed at least one vestibular potential in response to acoustic stimulation; 33 (62%) had an electrically evoked vestibular response. A cervical VEMP (cVEMP) was present in 45 of the 96 tested ears (47%) in response to acoustic stimulation, and in 34 ears (35%) with electrical stimulation. An ocular VEMP (oVEMP) was elicited acoustically in 25 ears (26%) and electrically in 34 (35%) ears. In the ears with absent responses to acoustic stimuli, electrically evoked cVEMPs and oVEMPs were present in 14 (27%) and 18 (25%) ears, respectively. Electric VEMPs demonstrated shorter latencies than acoustic VEMPs (P < .01). Whereas an increased prevalence of VEMPs was seen at high stimulation levels (P < .01), there was no difference between prevalence proportions with basal (electrode 3) or apical (electrode 20) stimulation (P > .05). Conclusions: VEMPs can be elicited with electrical stimulation in a proportion of children with cochlear implants, demonstrating current spread from the cochlea to the vestibular system. The presence of electric VEMPs in acoustically nonresponsive ears, along with the shorter latencies of electrically driven VEMPs, suggests that electrical current can bypass the otoliths and directly stimulate vestibular neural elements.

Key Words: Vestibular, cochlear implant.

Level of Evidence: 4.

Laryngoscope, 00:000–000, 2016

INTRODUCTION

Although cochlear implantation (CI) has provided auditory rehabilitation for children who are deaf, the effects of this intervention on the vestibular portion of the inner ear remain unclear. Histopathologic study of cadaveric temporal bones after CI demonstrated vestibular damage in some cases evidenced by fibrosis of the vestibule and distortion of the saccular membrane. Conversely, reports of improved balance function with cochlear implant activation suggest that CI can also positively impact the vestibular system. Given that children with congenital deafness have a high prevalence of concurrent vestibular dysfunction, the therapeutic implications of the latter findings are intriguing. Whereas the negative impact of CI on the vestibular system can be attributed to direct injury and inflammation, the mechanisms by which CI might enhance vestibular function have yet to be investigated. Rumalla et al. have recently demonstrated enhanced postural stability with hearing aid use. They proposed that this could be explained by the gain in spatial cues conferred by increased auditory stimulation and suggested that a similar benefit might be possible with cochlear implant use. An alternative mechanism by which CI may positively impact balance function is via direct stimulation of the vestibular nerves. Even in the face of end organ trauma, evidence suggests that peripheral vestibular afferents are preserved after CI. Just as current can spread from an intracochlear electrode array to the facial nerve, one must also consider the possibility of vestibular cross-stimulation.
In the present study, we aimed to determine whether or not cochlear implant stimulation can evoke vestibular responses. If possible, this would provide preliminary evidence supporting direct stimulation as a mechanism by which CI improves balance. Reliable objective measures of vestibular responsiveness are well known. Cervical and ocular vestibular evoked myogenic potentials (VEMPs) are reflexes mediated by the saccule and utricle, respectively, that can be elicited by air-conducted sound, bone-conducted vibration, and galvanic stimulation. Though the functional significance of these reflexes remains ill-defined, VEMPs can be used to assess otolithic integrity, as well as vestibulocollis and vestibulo-ocular pathways.\(^6\)

Clinically, high-intensity acoustic stimuli are used to generate VEMPs. It has been previously demonstrated that a functional cochlea is not necessary to evoke VEMPs acoustically.\(^6\) Transmastoid galvanic stimulation can elicit the same myogenic responses, but activates the vestibular system more broadly at the distal vestibular nerves.\(^11,12\) Recently, VEMPs have been produced with direct premyotome stimulation, suggesting that there is a real possibility of generating electrically evoked VEMPs with the implanted device.\(^13\)

Our study tested the hypotheses that: 1) electric stimulation from a cochlear implant would elicit VEMPs, thereby indicating extracochlear spread of current to the vestibular system and 2) VEMPs could be evoked via electric stimulation in children who are afebrile to acoustic stimulation.

**MATERIALS AND METHODS**

This prospective cohort study was approved by an independent research ethics board (REB#1000007266). Written consent was obtained for all subjects. Review of a prospecting research database identified 220 children and young adults with cochlear implants who had previously undergone VEMP testing during their clinical workup. Children under 7 years old were excluded given the lengthy testing protocol and the effort-related difficulties with repetitive VEMP testing in this age group.\(^11\) There were no exclusions based on etiology of hearing loss, implanted side, or duration of implant use.

**VEMP Testing**

Responses were collected and analyzed using a two-channel surface electrode montage and Neuralcon Synamps 2 (Compumedics Neuroscan, El Paso, TX; recording platform. For cervical VEMP (cVEMP) recordings, the noninverting electrode was placed over the midpoint of the sternocleidomastoid (SCM) muscle ipsilateral to the stimulated ear and referenced to the sternum. For ocular VEMP (oVEMP) testing, the noninverting electrode was placed over the midinfraorbital rim contralateral to the stimulated ear and referenced to the cheek 2 cm inferriorly. The montage ground electrode was placed on the midforehead. Impedance was kept below 5 kΩ.

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Participants were positioned supine. During eVEMP testing, a simultaneous head lift and contralateral turn were employed to achieve tonic SCM contraction. The nonrectified electromyogram (EMG) was monitored throughout data acquisition, and appropriate feedback was provided in real time to ensure sufficient muscular contraction was sustained. Occasionally, younger children needed to prop themselves onto their elbows, a maneuver that reduces fatigue without compromising sensitivity.\(^11\) During eVEMP testing, participants kept their head in a neutral position while lying supine. Maximal up-gaze was achieved by directing participants to look at a fixed target above and behind them. This maneuver both induces contraction of the inferior oblique muscle and brings the muscle closer to the recording electrode.\(^12\) VEMP tests were performed sequentially (eVEMP first, oVEMP second) to avoid confusion with simultaneous positioning.

EMG signals were bandpass filtered (1 to 3,000 Hz) and recorded in a ~5 to 50-ms window relative to stimulus onset. The software display was configured for simultaneous viewing of continuous EMG activity and the averaged waveform. No online artifact rejection was used. For all VEMP tests, at least two trials (100 sweeps each) were obtained. Averaged waveforms were scanned online for the presence of myogenic responses with biphasic morphology. If no such responses were identified after 2 trials, testing was terminated. Likewise, testing concluded once two replicating responses were obtained. When there was discordance between online observations of two trials, a third trial was collected.

**Acoustic Stimulus**

Myogenic responses were elicited by a 500-Hz, Blackman-windowed tone-burst of 4-ms duration (~2 ms rise/fall time, no plateau), presented at 124 dB SPL and a rate of 5.1 Hz for 20 seconds. The stimulus was generated by MATLAB (MathWorks Corp., Natick, MA) and delivered monaurally via a E-A-Rtone 3A insert earphone (3M Company, Indianapolis, IN).

**Electric Stimulus**

The insert earphone was removed and replaced with a Nucleus Freedom processor (Cochlear Corp., Sydney, Australia), which delivered an electric stimulus directly to the participant’s cochlear implant, using Custom Sound EP software (Cochlear Corp.). Maximal tolerated intensity levels were first determined for both single 57-μs biphasic electric pulses (25 μs/phase with a 7-μs interphase gap) and trains of these same pulses delivered at 900 pulses/s for 4 ms. When both stimuli were tolerated equally, the pulse-train was selected due to its comparable duration to the acoustic stimulus. Otherwise, the stimulus with the greater intensity level was used. The stimulus was also delivered at 5.1 Hz over 20 seconds. VEMP tests were conducted initially with basal stimulation at electrode 3 (E3) and then repeated with apical stimulation at electrode 20 (E20).

**Data and Analysis**

A VEMP was ultimately judged as present or absent offline. A cVEMP was defined as a reproducible, biphasic waveform with an initial positive (P1) peak followed by a negative (N1) peak, and a peak-to-peak amplitude >20 μV. For acoustic cVEMPs, acceptable latency ranges of P1 and N1 peaks were 12.10 to 18.06 ms and 17.75 to 24.63 ms, respectively. These were based on mean latencies ± 2 standard deviations (±SD) determined by a recent study of VEMPs in children with sensorineural hearing loss.\(^16\) An oVEMP was defined as a reproducible, biphasic waveform with an initial N1 peak followed by a P1 peak. Acceptable peak latencies for the acoustic oVEMPs were determined similarly, and ranged from 4.13 to 11.73 ms and 11.15 to 17.23 ms for P1 and N1, respectively.\(^16\) As the technique for electric stimulation was novel, specific latencies could not be referenced; however, we expected these latencies to be shorter based on our experience with electrically evoked...
auditory brainstem responses. To quantify SCM contraction off-line, the EMG tracing was rectified and averaged. RStudio Version 0.98 (R Foundation for Statistical Computing, Vienna, Austria) was employed for all statistical analyses.

RESULTS
Fifty-three children and young adults with cochlear implants participated. The 32 males and 21 females ranged in age from 7 to 27 years, with a mean age of 15.1 ± 4.0 years. The group was heterogeneous with respect to etiology of deafness (Table I). Eight underwent unilateral CI at 8.3 ± 4.1 years, seven were bilaterally implanted simultaneously at 8.0 ± 4.3 years, and 38 received bilateral CI sequentially, with their first CI at 3.6 ± 2.9 years and their second CI 6.1 ± 3.1 year later. One of the sequentially implanted children was recently reimplanted on one side; this new device was not tested. Another child was fatigued and unwilling to be tested on one side. Thus, a total of 96 ears were assessed.

Average SCM contraction during cVEMP testing was 157.8 ± 71.3 μV. The range of tonic SCM contraction across all participants was 48.1 to 436.7 μV. Representative c/oVEMPs evoked by acoustic and electric stimulation are displayed in Figure 1. No vestibular symptoms were experienced during testing. Prevalence data are summarized in Figure 2.

Of 96 ears tested for cVEMPs, 37 (39%) were non-responsive to acoustic and electric stimuli, 20 (21%) were responsive to both acoustic and electric stimuli, and 25 (26%) were responsive to acoustic stimulation alone. In the 51 ears without acoustic cVEMPs, an electric cVEMP was present in 14 (27%) (Fig. 3).

Of 96 ears tested for oVEMPs, 53 (55%) were non-responsive to acoustic and electric stimuli, seven (7%) were responsive to both acoustic and electric stimuli, and 18 (19%) were responsive to acoustic stimulation alone. In the 71 ears without acoustic oVEMPs, an electric oVEMP was present in 18 (25%) (Fig. 3).

Electrically evoked responses occurred at shorter latencies than acoustically evoked responses at each peak (P < .01, 2-tailed paired t test): cVEMP P1: 11.6 ± 1.1 vs. 13.7 ± 1.3 ms; cVEMP N1: 18.4 ± 1.9 vs. 21.1 ± 2.0 ms; oVEMP N1: 7.1 ± 1.9 vs. 8.6 ± 1.4 ms; oVEMP P1: 9.0 ± 2.2 vs. 11.6 ± 2.1 ms (mean ± SD; Fig. 4). Amplitude differences between electrically and acoustically evoked responses were not compared given the dependence on variable tonic contraction.

Electric VEMPs were equally prevalent (P > .05, Fisher exact test) along the electrode array. Basal (E3) and apical (E20) stimulation generated cVEMPs in 27 (28%) and 18 (19%) ears, respectively, and oVEMPs in 12 (13%) and 17 (18%) ears, respectively. Although stimulation was delivered at individualized maximum comfort level, likelihood of eliciting a c/oVEMP significantly increased in individuals with higher tolerance levels (P < .01, logistic regression; Fig. 5A). More specifically, the model predicted that for every 10 clinical unit (CU) increase in stimulation intensity, the odds of eliciting a c/oVEMP increased by 1.65 and 1.77, respectively.

In participants with electric VEMPs, stimulation intensity was normalized to individual hearing thresholds (Fig. 5B). The lowest stimulation used to elicit a VEMP was 60 CU above hearing threshold. The largest proportion of electric c/oVEMPs were obtained at stimulation levels between 80 and 99 CU and 100 and 119 CU above hearing threshold, respectively.
DISCUSSION
We hypothesized that electric stimulation from a cochlear implant could elicit VEMP responses, which would confirm spread of electric stimulation from the intracochlear electrode array to the vestibular system. In 62% of participants, spread of current to the vestibular system was evidenced by a VEMP response in at least one ear. This finding suggests that the prevalence of vestibular cross-stimulation from cochlear implants has been significantly understated in the literature until now.

Cross-stimulation of the vestibular nerve after CI has been studied only sparingly and mostly in a negative light. Bance et al. used videonystagmography to assess 17 patients for nystagmus during implant stimulation and found a prevalence of 5.9%. This study was prompted by a single patient who developed violent nystagmus upon activation that could not be resolved with programming modifications. Shortly after, Ito surmised that extracochlear spread of current was responsible for prolonged postoperative dizziness with implant use in two of 11 patients. Where these prior reports described aberrant current spread translating into unpleasant symptoms, the present study has shown that cross-stimulation can also occur in the absence of a vestibular percept. With this in mind, one should not assume that this phenomenon is necessarily a negative event.

The high percentages of absent acoustically evoked VEMPs demonstrate the prevalent end organ dysfunction in this sample of implanted children. One limitation of the study protocol was the absence of a middle ear assessment, as abnormal anatomy that would impair sound conduction can lead to a false negative VEMP. However, all participants were older than age 7 years and had undergone a mastoidectomy to facilitate CI, so one would predict a rather low prevalence of middle ear dysfunction in this cohort. The sensitivity of oVEMP testing may also have been reduced by variability in the maintenance of up-gaze that inevitably occurred at times while testing pediatric participants. Though the possibility of false negatives remains, efforts were made to optimize test sensitivity. Specifically, the stimulus intensity was maximal and the measures were repeated. Furthermore, the degree of tonic SCM contraction during cVEMP testing was closely monitored given that amplitude of the inhibitory cVEMP response is largely dependent upon underlying contraction. All patients with absent cVEMP responses produced a contraction of at least 60 μV as per mean rectified EMG, thereby exceeding the minimum contraction reported to be required to produce a response in normal subjects.

Secondarily, we hypothesized that electric VEMPs would be attainable in children with absent acoustic VEMPs. Indeed, electric VEMPs were obtained in ears that were nonresponsive to acoustic stimuli. Remarkably, though the otoliths in these children were shown to be dysfunctional, their vestibular systems remained stimulable. Akin to the cochlear implant bypassing dysfunctional hair cells to stimulate the cochlear nerve, electric current was seemingly able to bypass dysfunctional otoliths to more directly stimulate the vestibular neural elements. Latency data further support this
notion. VEMPs evoked electrically via cochlear implant stimulation were faster in onset than acoustically evoked VEMPs and comparable to the responses obtained with direct promontory stimulation. This observation implies that the site of activation differs between the two stimuli. Whereas acoustically evoked responses are

Fig. 4. In participants with both acoustic and electrical responses, the amplitude P1 (top left) and N1 (top right) peaks of cervical VEMPs (cVEMPs) occurred at shorter latencies when evoked with electrical stimulation (P1: 11.4 ± 1.0 ms; N1: 16.2 ± 1.8 ms) in comparison to acoustic stimulation (P1: 13.3 ± 0.9 ms; N1: 20.8 ± 2.0 ms) (P < .01). The same was true of the N1 (acoustic: 9.0 ± 1.2 ms; electric: 7.1 ± 0.7 ms) (bottom left) and P1 (acoustic: 12.0 ± 1.6 ms; electric: 8.5 ± 0.5 ms) (bottom right) peaks of the ocular VEMPs (oVEMPs) (P < .01). N1 = biphasic waveform with an initial negative peak; P1 = biphasic waveform with an initial positive peak; VEMP = vestibular evoked myogenic potential. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Fig. 5. (A) Cervical VEMPs (cVEMPs) and ocular VEMPs (oVEMPs) were more frequently evoked (P < .01 for both tests) with higher stimulus intensities, given in manufacturer-defined units of current. (B) The stimulus intensities used to elicit VEMPs were normalized to the participants’ hearing thresholds. VEMP = vestibular evoked myogenic potential. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
dependent upon mechanical stimulation of vestibular end organs via a travelling fluid wave, the shorter latencies of electrically evoked responses suggest a more direct path of neural stimulation.

As basal electrodes are anatomically closer to the most distal afferents innervating the otoliths, one might hypothesize that vestibular activation would be more likely with basal stimulation compared to apical stimulation. However, the difference in the proportion of electrically evoked VEMPs in response to basal versus apical stimulation was not statistically significant. Furthermore, there were some participants in whom basal stimulation did not generate a VEMP, but apical stimulation did. The fact that vestibular cross-stimulation is not restricted to either end of the electrode array is consistent with prior work that drew the same conclusion for facial nerve stimulation.\(^9\) The exact path of extracochlear current spread from an implant to the vestibular system is yet unknown and may vary depending on etiology of deafness or the specific environment surrounding the electrode. Heterogeneity of the present sample precluded any comparative analyses across etiologies.

Implant stimulation in our protocol was purposefully delivered at the highest comfortable intensity to maximize extracochlear current spread. As expected, a higher rate of vestibular cross-stimulation was noted as current level increased. VEMPs were, however, also produced with stimulation as low as 200 CU. Because threshold testing was not performed, it is certainly plausible that VEMPs may be obtainable at even lower levels of stimulation. Combined with the fact that none of the electric stimulation was perceived as uncomfortably loud by the participants, this would suggest that vestibular cross-stimulation can occur at levels within the clinical map ranges of many users.

Improved postural stability with implant activation was first described by Eisenberg et al. in 1982.\(^2\) Later, Buchanan et al. reported that device activation in music seemed to confer an additional advantage when computerized dynamic posturography was performed.\(^3\) Finally, Cushing et al. demonstrated a statistically significant improvement in scores on the Brunnings-Oserskey Test of Motor Proficiency 2 (BOT-2) when children completed tasks with their implants “on” versus “off.”\(^4\) One possible explanation for this constellation of findings is that extracochlear spread of current to the vestibular system with implant use may provide a usable vestibular cue in the form of background activation. This low-level activation may theoretically serve to boost weak but intact neural hearing loss using cochlear implants. Laryngoscope 2008;118:1514-1523.

Bibliography


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