Interleaved Recording of the Auditory Brainstem Response in Sensorineural Hearing Loss

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Abstract

The auditory brainstem response (ABR) test is a far-field electrophysiological technique routinely used to estimate auditory thresholds, detecting auditory neuropathologies and intraoperative monitoring (Haddad et al., 2020; Hood, 1998; Jewett & Williston, 1971). Specifically, the ABR morphology and wave latencies are used as diagnostic indicators. To date, ABR is often evoked using transient acoustic stimuli (e.g., clicks and tone-burst) presented at low stimulus rate, and thousands of response averages are required to ensure adequate signal-to-noise ratio is achieved and diagnostic features of the responses are preserved. These translate to extended clinical time. Preliminary findings from the O'Beirne laboratory, using the custom-written software developed by the laboratory which delivers interleaving clicks stimuli, demonstrated that the ABR diagnostic features obtained in normal hearing (NH) participants using rapid interleaved stimuli between both ears (binaural) were of comparable quality to those recorded in current clinical setting (monaurally) (Bencito, 2020). This research aims to further investigate whether the benefits extend to adults with sensorineural (SN) hearing impairment. Specifically, whether wave V latencies obtained from rapid interleaving stimuli are significantly different from monaural conditions (slow and fast rates) in SNHI participants. The ABRs were evoked with clicks at rapid interleaving conditions which the stimulus alternate between the ears (i.e., 45.5/s to each ear, 90.9/s overall); clicks delivered monaurally at the slow rate (monaural slow; 45.5/s); and clicks delivered monaurally at the fast rate (monaural fast; 90.9/s). Our results demonstrated the benefit of the most rapid interleaving clicks paradigm used by Bencito, 2020 were translatable to the participants with SN hearing loss in this study. The rapid rate interleaved condition showed no significant change in the wave V latency compared to the conventional monaural slow paradigm. Furthermore, a significant increase in the wave V latency of monaural fast condition was shown compared to interleaved condition. The study further demonstrated the potential clinical benefit, primarily in testing time, of the use of the interleaved paradigm compared to the current conventional sequential method of auditory brainstem recording in adult population with SN hearing loss.

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List of Abbreviations/Nomenclature

ABR Auditory brainstem response

AC Air conduction

AEP Auditory evoked potential

AN Auditory nerve

ANOVA Analysis of variance

AVCN Anteroventral cochlear nucleus

BAEP Brainstem auditory evoked potentials

BEP Brainstem evoked response

BM Basilar membrane

CN Cochlear nucleus

CN VIII Cranial nerve eight (vestibulocochlear nerve)

dB HL dB hearing level

dB SL dB sensation level

dB SPL dB sound-pressure level

DCN Dorsal cochlear nucleus

HI Hearing impairment

HL Hearing loss

IC Inferior colliculus

ISI Inter-stimulus interval

ME Middle ear

MGB Medial geniculate body

NH Normal Hearing

nHL Normalised hearing level

PVCN Posteroventral cochlear nucleus

SN Sensorineural

SNR Signal-to-noise ratio

SOC Superior olivary complex

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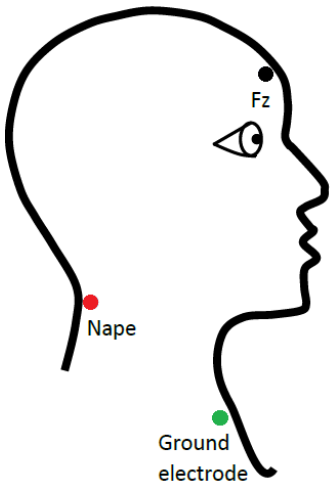
1 Literature Review

1.1 Introduction

Hearing impairment (HI) affects all age groups from new-borns to adults. HI impacts speech and language development and causes social and vocational difficulties (Olusanya et al., 2019). Early intervention is conducive for better spoken speech and language outcomes in children and improves cognitive progress in adults (Amieva & Ouvrard, 2020; Ching et al., 2014; Cullington et al., 2017; Ray et al., 2018). Subjective methods of hearing assessment (such as pure-tone audiometry) are commonly used as a front-line diagnostic tool due to their convenience and reliability in clinical settings. These methods, however, require the cooperation of the participant which can be challenging for individuals with limited physical and/or cognitive capabilities, namely infants. Thus, methods of objective assessment (such as auditory evoked response tests) that do not rely on the cooperation of the participant are invaluable tools to assess the integrity of the auditory system. Auditory evoked potentials (AEPs), including auditory brainstem response (ABR), are far-field electrical potentials emanating from the nervous system in response to an auditory stimulus and measured via surface electrodes on the scalp as shown in Figure 1.

Figure 1

Surface Electrode Placements for ABR.



Note. Vertical montage is depicted here with active electrode (black) placed on forehead, ground electrode (green) placed on clavicle, and negative electrode (red) placed on nape. Adapted from 'Interleaved Recording of the Auditory Brainstem Response' by S. Bencito, 2020) (Bencito, 2020)

ABR is one of the early-latency AEPs (within 10ms after stimulus onset) generated by serial and parallel synchronised activations of the auditory pathway, beginning at the distal vestibulocochlear nerve, and terminating at the medial geniculate nucleus of the thalamus, depicted in Figure 2. Since its first description in 1971 by Jewett & Williston correlating components of ABRs with a range of physiological functions, ABR has been commonly used as a tool to estimate hearing thresholds, monitor auditory function intra-operationally, screen for hearing loss in new-borns, and diagnose peripheral injuries and lesions along the auditory pathway (Haddad et al., 2020; Hood, 1998; Jewett & Williston, 1971).

At present, clinical ABR is performed by delivering transient auditory stimuli, such as tone burst or clicks, sequentially to one ear and adjusting one parameter (e.g., intensity or frequency) at a time (Kelly et al., 2016). Due to the nature of far-field recording, averages of several hundreds to thousands of responses are required in order to extract the small amplitude ABRs from the surrounding unwanted physiological and electrical noises. Conventional ABR at levels close to auditory threshold requires at least an average of 2000 sweeps to reach an acceptable signal-to-noise ratio (SNR). This translates to a lengthy acquisition time, which has significant impact not only on patient comfort but also on the feasibility of obtaining sufficient diagnostic information from ABR in practice where clinical time is limited. Increasing the number of elicited responses by increasing stimulus presentation rate can reduce the acquisition time to a certain extent; however, a higher rate (e.g., more than 50/s) leads to the change of overall ABR waveform morphology and alteration of the characteristics of ABR components, such as wave amplitude and latency (Mouney et al., 1976; Paludetti et al., 1983). This rate effect (discussed further in Section 1.5) has been proposed to be caused by neural adaptation and fatigue of the auditory system to repeated stimulation, thus limiting the rate in conventional ABR to as low as 10 presentations per second (Don et al., 1977). Furthermore, as increasing stimulus repetition rate shortens the inter-stimulus interval (ISI), the ISI is limited by the averaging window to circumvent overlapping ABRs (Kjaer, 1980). The trade-off between reducing acquisition time and minimising the effect of neural fatigue evoked by high stimulus rate has long been a challenge in AEP studies. The rate-induced adaptation and fatigue has been proposed to originate from the peripheral auditory nervous system (Don et al., 1977). Since ABR is mostly generated from the neuronal populations of the central auditory system, an interleaving stimulus paradigm where auditory presentation alternates between the ears

should allow the peripheral site of fatigue and adaptation to recover and maintain evoking ABR at a higher rate (Bencito, 2020).

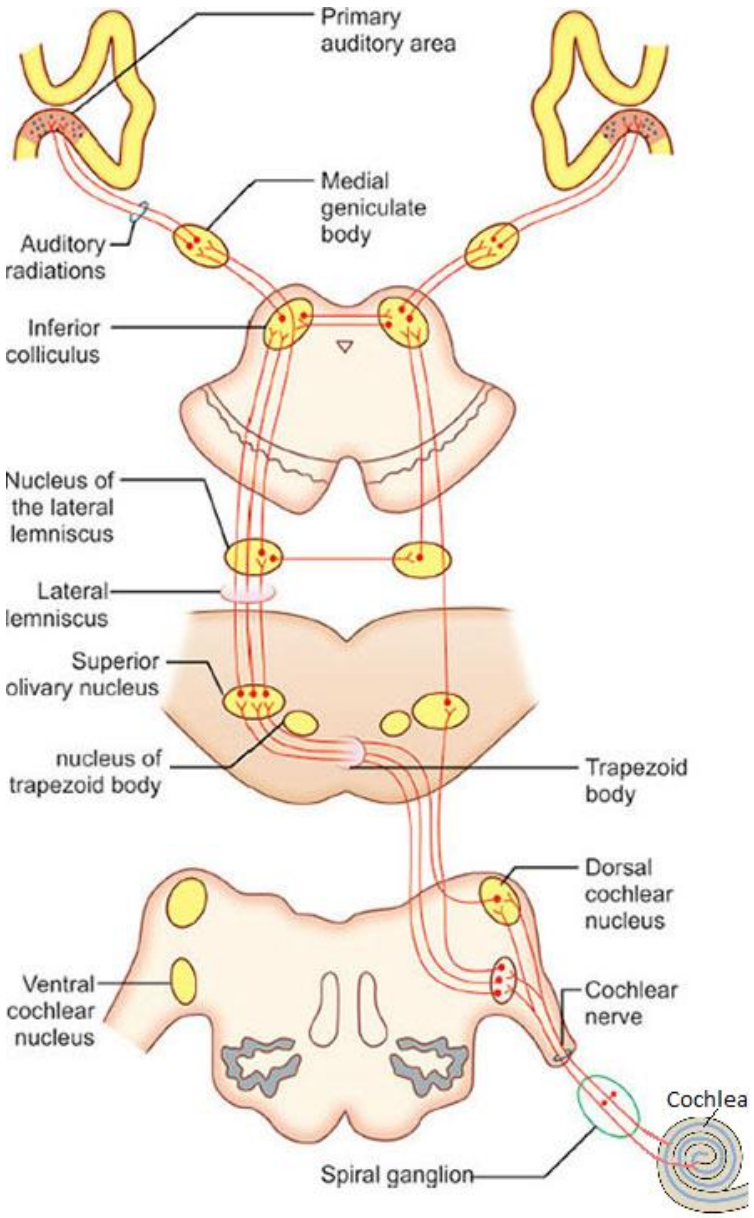
Preliminary data from the O'Beirne group has recently demonstrated that the use of interleaving clicks stimuli shortens the acquisition time whilst preserving diagnostic values of ABR such as the wave V latency (Bencito, 2020). The ABRs evoked with interleaving paradigm (binaural stimulation at a fast rate) was also shown to be comparable in overall morphology to the conventional ABR (monaural stimulation at a slow rate) in normal hearing (NH) individuals (Bencito, 2020). Hence, the purpose of this study is to investigate the effect of abovementioned interleaving clicks strategy in the sensorineural hearing loss (SNHL) population using the latency and amplitude of wave V to compare the response quality. This review aims to provide:

1) An overview of the anatomical and physiological basis of ABR
2) An outline of the conventional ABR procedure
3) A discussion on the subject factors, recording parameters, and stimulus parameters affecting the ABR waveform morphology
4) A discussion on the stimulus rate effect on ABR and the proposed mechanisms

Note that ABR is also referred to as brainstem auditory evoked potentials (BAEP), auditory evoked potential (AEP), and brainstem evoked response (BEP) in the literature. Thus, for the ease of understanding and coherence, the term ABR will be used throughout this review.

Figure 2

Central Auditory Pathway.



Note. Auditory portion of the eighth cranial nerve (CN VIII; cochlear nerve) terminates in various portions (dorsal and ventral) cochlear nucleus (CN) at the pontomedullary junction with topographic organization of acoustic frequency. Sequential activation involves the superior olivary complex (SOC) in the caudal to mid-pons with some decussate via the trapezoid body, the lateral lemniscus in mid-pons, the inferior colliculus (IC) in caudal midbrain, up to the medial geniculate body as part of the metathalamus, and projects to the auditory cortex in the temporal lobe. Adapted from 'Comprehensive Textbook of Medical Physiology (Volume 2)' by Pal et al., 2017 (Pal et al., 2017).

1.2 Neural generators of the ABR

In normal hearing (NH) individuals, the ABR waveform consists of five to seven positive peaks, which are conventionally labelled with Roman numerals I to VII. Each peak (or wave) has been proposed to correspond to activity from specific neuronal population(s) along the auditory pathway (Hall, 2007; Jewett & Williston, 1971). ABR parameters that are of clinical and physiological relevance are amplitude, absolute latency, latency variations, inter-peak latencies, and the overall morphology of the waveform (Rouillon et al., 2016). The amplitude of a peak is measured relative to the preceding or the following trough and reflects the activity level of a specific neurogenerator. The absolute latency of a peak (commonly known as latency) is measured as the time interval between the onset of a stimulus and the peak of a wave. The latency is thought to reflect the conduction time along the neural pathway. It is also valuable to define the inter-peak latencies which are relative time intervals measured between two different waves. For example, inter-peak latencies between I-III, I-V and III-V where they represent the axonal conduction time along neuron pathways and/or synaptic delays between the respective neuronal population/s responsible for the generation of a specific evoked component (Moore et al., 1996). Prolonged inter-peak latencies indicating increased central conduction time could suggest a central auditory lesion between the neurogenerators such as auditory neuropathy and vestibular schwannomas (Aihara et al., 2014). Normative values for such absolute and inter-wave latencies and peak amplitudes of the ABR using clicks at 80 dB normalised hearing level (nHL) are shown in **Table 1**. In addition, the morphology of the ABR which is the overall shape of the waveform should roughly coincide with reference to a standard template for the response to be considered of true response (Kelly et al., 2016). Understanding the brain structures along the auditory pathway that contribute to the features of the ABR are crucial in the interpretation of ABR abnormalities and thereby the diagnosis.

Table 1

Normative Wave Latency and Amplitude Values For Human Click-Evoked ABR at 80 dB nHL.

	I	II	III	IV	V	VI
Latency Mean (ms)	1.69	2.78	3.77	4.97	5.63	7.23
Standard Deviation (ms)	0.13	0.19	0.20	0.24	0.24	0.31
Amplitude Mean (μV)	0.3	0.17	0.34	0.06	0.61	0.25
Standard Deviation (μV)	0.13	0.11	0.16	0.02	0.22	0.23

Note. Adapted from 'Human auditory evoked potentials' by Picton, 2011, Plural Publishing, Inc. (Picton, 2011)

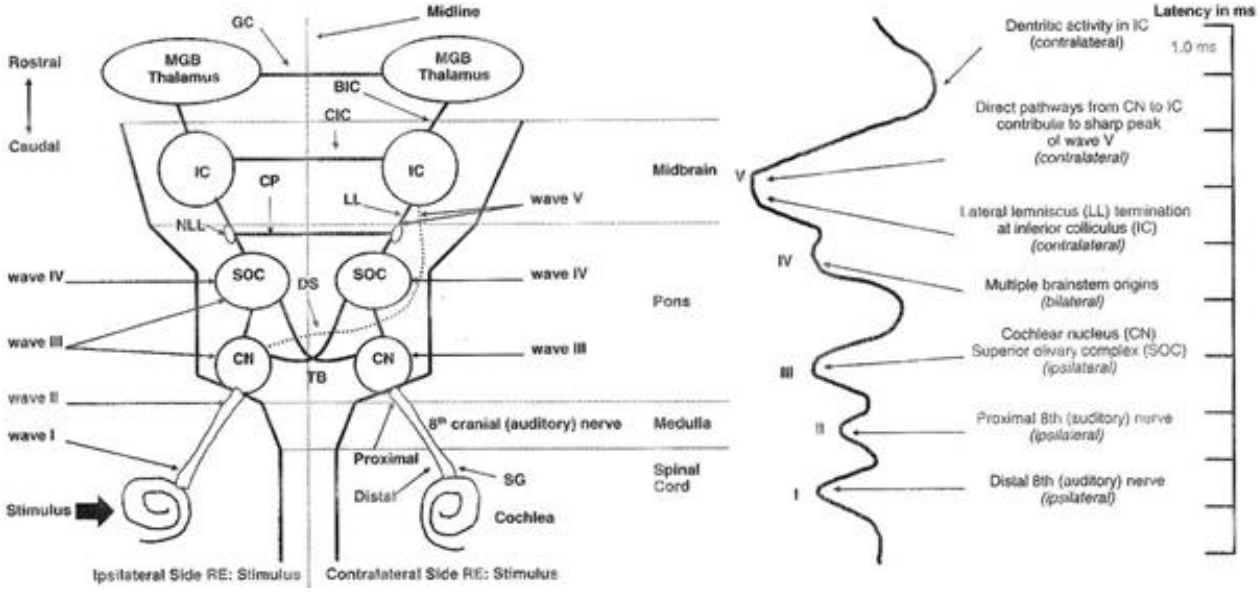
The auditory pathway can be divided into the peripheral and central auditory systems. The activation of the peripheral auditory pathway (e.g., cochlea and spiral ganglion) is essential for the activation and assessment of the subsequent central auditory pathway. The initial central structure stimulated is the auditory portion of the eighth cranial nerve (CN VIII) which terminates in the cochlear nucleus (CN) at the pontomedullary junction with topographic organization of acoustic frequency that continues throughout the auditory pathway (Figure 2). The CN can be subdivided anatomically into dorsal cochlear nucleus (DCN) and ventral cochlear nucleus (Middlebrooks, 2015). The ventral portion is further divided, on the basis of the pattern of termination of CN VIII fibres, into the anteroventral cochlear nucleus (AVCN) at which the ascending branch terminates and the posteroventral cochlear nucleus (PVCN) where the descending branch courses through before terminating in the DCN. Sequential activation involves the superior olivary complex (SOC) in the caudal to mid-pons, the lateral lemniscus in mid-pons, the inferior colliculus (IC) in caudal midbrain, up to the medial geniculate body (MGB) as part of the metathalamus, and projects to the auditory cortex in the temporal lobe (Figure 2). These subcortical nuclei conduct preliminary analyses of the auditory signal, and each seems responsible for examining a specific acoustic feature. The SOC, as the first major site of binaural convergence, is thought to be central for sound localization in the horizontal dimension by discerning the intensity differences (Hodges, 2010). The IC acts as an obligatory relay and feedback pathway to the lower

auditory system. Whereas, the tonotopically organised MGB, which receives majority of its input from IC, serves as a thalamic relay to the auditory cortex (Hain, 2007).

The exact neuronal structures that contribute to the human ABR is still a subject of controversy despite the claims by Jewett & Williston 1971 who mostly inferred from rodent studies (Hall, 2007; Jewett & Williston, 1971). The determination of the precise generators of ABR components is complicated by the likelihood of multiple decussations of auditory fibres beyond the cochlear nucleus affecting the size of the current dipole to be detected by the far-field electrodes. In addition, the activation of higher anatomical structures of the auditory pathway also depends on the summation of positive or negative dendritic inputs from other nuclei. Furthermore, as the ABR is a measure of the synchronous neural activity of the auditory system, structures with asynchronous activity may not be detected during the ABR recordings although activated by the acoustic stimulus (Biacabe et al., 2001). Figure 3 illustrates the ABR waves and their proposed corresponding anatomical sites. Wave I represents the ipsilateral distal action potential of CN VIII (analogous to compound action potential of electrocochleogram) (Hall, 2007). Based on intra-cranial recordings and clinical studies, wave II is believed to relate to the activation of either the ipsilateral proximal CN VIII or the CN (Hall et al., 1985; Møller et al., 1981; Møller et al., 1995; Møller, 1987; Wada & Starr, 1983). Wave III was initially thought to originate from the contralateral SOC based on feline brain lesion studies (Buchwald & Huang, 1975). However, later study of intra-cranial recordings in humans demonstrated an ipsilateral origin for wave III (Møller et al., 1995). Wave IV, which often appears as the leading shoulder on wave V, was proposed to be generated by the second and third order neurons (decussates at pons and up into the cortex) located in the SOC with minor contribution from lateral lemniscus (Moore, 1987; Scherg & Von Cramon, 1985). Due to often inconsistent observation of isolated wave IV in clinical practice, it is less commonly used as a diagnostic factor. Wave V appears as a result of the innervation of the contralateral inferior colliculus (Figure 3) (Land et al., 2016). It is one of the largest peaks shown in ABR waveform due to the rough alignment of the signalling pathway from CN to IC with the recording electrodes. Absence in wave IV and/or V are seen in pathologies involving the mid-upper pons. Waves VI and VII are presumed to be generated by the medial geniculate body and the thalamocortical pathways, respectively, however they are not clinically useful as they are only variably present.

Figure 3

ABR Waves and Proposed Corresponding Neurogenerators.



Note. Adapted from 'New Handbook of Auditory Evoked Responses', by J.W. Hall, 2007, Pearson. Copyright 2007 Pearson Education, Inc. (Hall, 2007)

1.3 ABR Acquisition

The ABR is an electroencephalographic response from synchronised activities of various neuronal populations along the auditory pathway measured with scalp electrodes. Every sequential step in the data acquisition process - from electrode application, filtering to averaging methods - is designed to enhance the SNR in order to optimally extract the sub-microvolt amplitude ABR (<0.5 µV). For example, in preparation for recording, the epidermis of the electrode sites is gently and carefully abraded using a suitable sterile abrasive electrode paste and a clean gauze - or disposable abrasive pad. The purpose is to reduce the electrical impedance, thus, yielding a better-quality signal. The raw analogue responses evoked by series of transient stimuli, are amplified, filtered, and converted to digital signal via the acquisition system where the signals are then digitally processed to improve the SNR using various denoising techniques including averaging, filter, and artefact rejection. Two replications are then displayed digitally on the screen, and the replicability of the waveforms are determined by visual interpretation.

1.3.1 Determination of the presence of an ABR

To date, the determination of a present response still often relies on the subjective visual interpretation of the SNR (where the signal should be at least 3 times the background noise) and replicability of the final waveforms (superimposed with $\leq$ 25nV difference between the two replicates) (Kelly et al., 2016; Lightfoot et al., 2019). The presence of wave V is used as an indicator of a present response as it is the most robust and consistent aspect of the ABR morphology. However, bias can be introduced as a result of poor SNR when interpreting the results visually. Furthermore, variations in the background noise can result in spurious replications of the ABR wave components.

There are two approaches which aim to optimise the reliability of the response determination process. Firstly, the statistical application of confidence measures (fsp/fmp) utilised in conventional ABR to augment the objectivity of response determination process. The fsp value (F-statistic for a single point) is used to determine the degree of confidence in the presence of an ABR by comparing the discrepancy of the averaged waveform to the difference of the background noise level (Elberling & Don, 1984). Fmp statistics provide a multiple point measurement of the same discrepancy, and thus are slightly superior to fsp. Both cumulative distribution of fsp and fmp have been shown to closely match to F (5,250) after appropriate multiplication. Values of 2.37 and 6.8 correspond to a 97.5% confidence in the presence of a response for fmp and fsp, respectively (Lightfoot et al., 2019; Stevens et al., 2013).

Both confidence measures offer an alternative to measuring the SNR by inspection of a pair of replicated waveforms, SNR is a more robust and reliable measure of the ABR waveform. Furthermore, low values of the response confidence measures cannot be used to disregard a response as absence. Secondly, the reliability of the measured ABR can be improved by improving the SNR. This can be achieved by identifying potential sources of noise and implement early mitigation (noise reduction approach) or signal enhancement. The following section (**Section 1.3.2**) reviews the origin of the noises and best practice to minimise the negative effects on SNR.

1.3.2 Noise and interference

Background noise, as it pertains to AEPs, is ‘electrical activity that is not part of the response and should not be included in analysis of the response’ (Hall, 2007). These

electrical activities can either arise physiologically from the patient or electrically from the surrounding and the recording device. Physiological noises can be of a number of origins within the human body. The electrical activity from the motor neurons can induce voltage fluctuations to approximately 100 μV saturating the bio-amplifier. The muscle activities generated either voluntarily or involuntarily can be picked up from around the areas of the electrode sites such as the forehead (electromyography) and the eyes (electrooculography), or from the heart (electrocardiogram). Another bioelectrical interference that can impact the quality of the recording is of encephalic origin (electroencephalography) such as variations in brain activity due to a changing state of arousal. For instance, a child is more likely to pass an ABR screening when asleep than in awake state (McCall & Ferraro, 1991). Therefore, patients are asked to be relaxed and preferably with their eyes closed with the aim to alleviate the influence of myogenic-induced noises. This may sometime be challenging especially in difficult-to-test populations such as infants as the available test time is unpredictable. Thus, sedation or anaesthesia may be required which adds another layer of complication including health risks and costs involved with sedative drug administration especially in young patients, and clinical time and labour required by the personnel (Reich & Wiatrak, 1996). Sedation has also been indicated in prolonging ABR wave latencies due to interrupted neural transmission at the neuromuscular junction and increasing hearing threshold by an average of 8 dB nHL (Hall, 2007; van Looij et al., 2004). In addition, low frequency myogenic signals ranging from 30-500 Hz overlaps with ABRs and thus is difficult to be removed with conventional analogue filter (Hall, 2007; Sokolov et al., 2006).

Signal processing strategies such as time domain averaging, artefact rejection and weighted averaging are utilized to reduce the noise. Signal averaging of sweeps takes advantage of the difference between unwanted noise and time-locked ABR. This method is particularly effective as the random and stationary noise is reduced in the final averaged waveform by the square root of the number of sweeps (Picton, 2011). Therefore, the greater the number of sweeps, the lower the noise. On the downside, the number of sweeps is proportionate to acquisition time. Artefact rejection can be employed to eliminate (and not contribute to the average) epochs of electrical activity exceeding the limit which usually is the result of transient bursts of muscle activity (Sanchez & Gans, 2006). The

determination of the rejection level, however, has been proven to be complex depending on the amplitude of the residual noise. This is because a high rejection level would permit noise and be ineffective in removing undesirable sweeps. Whereas a lower or stricter rejection level would indicate a sweep is more likely to be rejected and resulting in the increase of the number of sweeps for the final averaged waveform and acquisition time. In fact, rejected sweeps can be so numerous that a given clinical value of accepted sweeps may never be obtained. For example, a strict residual level of ± 10 μV have shown to be effective when testing quit and relaxed subjects, but the acquisition time is significantly increased when testing subjects in an active state (e.g., performing a motor activity) (Don & Elberling, 1994; Norrix et al., 2019; Sanchez & Gans, 2006). A further lowering of rejection level to ± 2.5 μV resulted in the deterioration of quality of the waveforms (Don & Elberling, 1994). The noise or artefact mentioned can often be controlled by meticulous setup and patient instruction and preparation allowing easier and clearer waveform determination.

Noise can be generated from the recording equipment due to the physics inherent to the recording process. This includes thermal noise created by the amplifier and noise created at junctions in the circuit, also known as Johnson noise. For example, between the electrical components of the recording equipment or between electrode and epidermis (Cutmore & James, 1999). 50 or 60 Hz mains power frequency and its harmonics can also alter the post-average ABRs as they can be amplified along with the AEPs (signal of interest). Devices that are connected to the mains supply alternating current can generate transient or continuous noise. These can be picked up wirelessly by the electrodes acting as antennae or via the cables connected to the same circuitry as the amplifiers (Sininger & Cone-Wesson, 2002). For example, the fluctuating electric field from nearby computers and fluorescent lights can induce undesired voltages and eddy currents which are electrical currents induced by changing magnetic field (Sininger & Cone-Wesson, 2002). Poorly connected electrodes (or unused but connected to the amplifiers) picking up the noise can permit noise that propagate through cables and connectors. Ideally, the interference from many of the aforementioned sources can be lessened by isolating the patient with a Faraday shield. However, in reality, the electromagnetic shield is not commonly in place and other means are substitutes to reducing electrical interferences. Other substitutes to remedy the interference include having adequate cooling to equipment generating thermal noise,

turning off unnecessary electrical appliances such as fluorescent lights, having appropriate grounding to avoid electrical pickup from circuitries in the room, or placing electrical equipment further away from the subject (Cutmore & James, 1999). In respect to cable management and unwanted noise reduction, all cables should be shielded to avoid field artefacts. The electrode cables should be intertwined to cancel the common mode interference from the current and should be drape over metal surfaces. Additionally, frequency filter techniques can be implemented to deal with interference from kilohertz sources such as radio wave as ABR is mostly low frequency (Cutmore & James, 1999). Frequency distortions can be introduced if the frequency range of the signal of interest overlaps with the noise source. For instance, the 50-Hz mains noise overlaps with frequency components of ABR that is mostly less than 100Hz. The use of inadequate low-pass filter set at 45Hz can attenuate both the noise from the mains and ABR. More details on filtering can be read in the review by Cutmore and James (Cutmore & James, 1999). Though the ability to reduce the noise intrinsically associated with the electronic circuitry may be limited, knowing the effects will aid in the understanding of the limits of recording resolution.

1.4 Factors Affecting the ABR Quality and Morphology

Subject factors recording parameters and stimulus parameters can all affect the quality of the ABR. The following section will discuss some of the main factors to aid the understanding of the study design and contrast the differences of certain aspects of the setup used in present study to the current New Zealand ABR recommendation. These include the subject factors (age, sex, and hearing status), electrode montage, post-collection signal processing methods, and stimulus parameters (type, intensity, polarity, and rate).

1.4.1 Subject Factors – Age, Sex, and Hearing Status

The intra- and inter-individual differences such as age, sex, state of arousal, and hearing status attribute to the variations in ABR. Since the ABR evaluates neurologic function of the auditory system, it is no surprise that maturation of the nervous system affects the amplitude and latencies of the ABR. ABR latencies, particularly of wave V, are shorter in adults compared to new-borns due to immature and developing nervous system in neonates (Lasky, 1984; Pratt & Sohmer, 1976). Though the cochlea matures prenatally and

the myelination of the central portion of the cochlear nerve begins in the third trimester of pregnancy, myelination and synaptic transmission do not reach full efficiency until close to two years of age. Similarly, due to this slower conduction velocity, ABR interpeak latencies are prolonged in neonates compared to adults (Eggermont & Salamy, 1988). Furthermore, as the peripheral auditory system matures earlier than the central portion, wave I amplitude has been shown to be more prominent than wave V in neonates compared to adults (Burkard & Sims, 2002; Stockard et al., 1983). Nevertheless, ABR wave latencies provide insights into the auditory neural conduction which could be used as an early predictive marker for developmental issues such as brainstem development (Majnemer & Rosenblatt, 1996; Pasman et al., 1997)

The differences in ABR between women and men have been well-documented. ABR latencies in young women have been shown to be shorter than young men. The discrepancy changes with increasing age resulting in postmenopausal women presenting similar latency values as men of the same age (Wharton & Church, 1990). Similar relationship between amplitude and age was also shown in the same study; when compared to men of the same age, young women have larger amplitudes and the difference in amplitude between women and men diminishes with increase in age (Wharton & Church, 1990). The role of oestrogen has been implicated in the gender difference in ABR observed based on oestrogen receptor knock-out animal studies and hormone replacement studies (Hultcrantz et al., 2006).

Neurological degeneration and abnormalities such as in SNHL patients, is also reflected in the ABR waveform morphology. The observed ABR varies depending on n the location and extent of the lesion or dysfunction. The wave V and I-V interpeak latencies of cochlear HL are similar to those with NH when evoked with high intensity clicks. The cochlear SNHL however, has a characteristic steep latency-intensity curve where the latency values fall out of the normative range at lower intensity levels. Furthermore, high-frequency cochlear hearing loss is often associated with poor waveform morphology and reduced wave I amplitude, or even absent in moderate to severe loss. Therefore, depending on the severity of the loss, the normative measured ABR parameters varies, and care should be taken when interpreting the results. In contrast, abnormal I-V interpeak latency is observed in retrocochlear hearing loss patients when elicited with high intensity clicks (Rosenhamer, 1981; Thomsen et al., 1982). However, the prolongation of the wave V latency is not

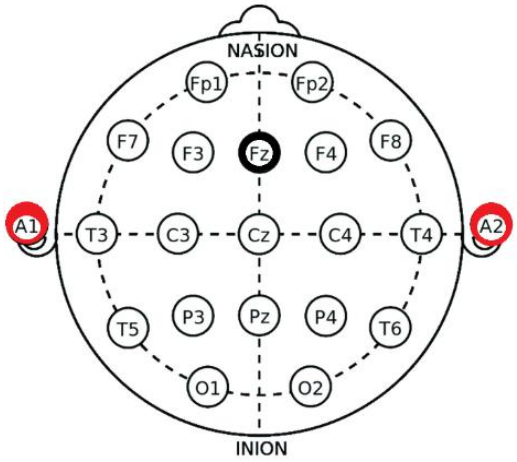
observable in patients with smaller and more localised retrocochlear lesions which have an insignificant number of the high-frequency fibres that are compromised. Thus, to assess the activities of all auditory nerve fibres, stacked derived-band ABR was developed (Don et al., 1997). The stacked ABR represents the sum of synchronised neural responses across the entire cochlea by aligning the wave V of each derived-band ABR (Don et al., 2005). Furthermore, a diagnostic index, which is calculated from the wave V latency and pure-tone hearing threshold at 2000 Hz and 4000 Hz, has also been suggested as a tool to differentiate the site of lesion (Don, 2007; Prosser & Arslan, 1987).

1.4.2 Recording Parameters – Electrode Montage

Electrode placement affects the quality of the recorded biopotentials. Moreover, different configurations such as electrode montage can emphasize different neurogenerators and enhances certain ABR wave components. The evoked potentials are the measurement of potential differences between the non-inverting and inverting electrodes. The locations of the electrode (active, reference, and ground) placement, as illustrated in Figure 4, are identified based on an internationally recognised system for known as the 10-20 system (Hall, 2007; Jasper, 1958; Jurcak et al., 2007; Klem et al., 1999). The conventional electrode placement, ipsilateral electrode montage, is where the non-inverting electrode (active) is placed at Cz (vertex) or Fz (forehead), inverting (reference/indifferent) electrodes at A1 and A2, and ground (common) electrode at Fpz (just above nasal bridge) (Figure 4). These positions are chosen due to the close proximity to the ABR generators. Other montages include vertical (Cz - Nape or C7), contralateral (Cz - contralateral mastoid or earlobe), and horizontal (ipsilateral mastoid – contralateral mastoid). Ideally, the reference should have zero potential, however, it is impossible to obtain such point anywhere on the scalp or body. Furthermore, one cannot guarantee the recorded ABR is not contaminated by brain activity which can introduce distortion effect (though scalp is still being used as the reference electrode placement, conventionally).

Figure 4

10-20 System of Electrode Placement for Electroencephalogram.



Note. Conventional ABR electrode placement locations are Fz (active; black), A1 and A2 (reference; red), and ground (not indicated). Adapted from Rojas G.M., et al, 2018 (Rojas et al., 2018)

Many studies have investigated the optimal reference electrode placement for ABR, and the most researched sites are the earlobes, mastoids, the 7th cervical vertebra (C7) and nape (Beattie et al., 1986; Dobie & Berlin, 1979; Dzulkarnain et al., 2007; Hall, 2007; Kevanishvili & Aphonchenko, 1981; King & Sininger, 1992; Pethe et al., 1998). Both ipsilateral and vertical recording montages in adults have shown similar ABR waveforms that were morphologically similar except the waveform expressions varied between the montages (Stuart et al., 1996). For example, the ipsilateral montage generates a larger wave I amplitude (Dobie & Berlin, 1979; Ebersole et al., 2014; Katbamna et al., 1996; Kavanagh & Clark, 1989; Pethe et al., 1998; Picton, 2011; Terkildsen et al., 1981). Whereas vertical montage had been shown to generate a larger amplitude of wave V with no change in wave V latency, and reduced amplitudes of wave I and III (Beattie et al., 1986; Dzulkarnain et al., 2007; Howard, 2017; Kevanishvili & Aphonchenko, 1981; King & Sininger, 1992; Stuart et al., 1996). It has been suggested that the increase in wave V amplitude with vertical electrode

montage may be due to the electrically silent characteristic at these non-cephalic locations where the encephalic and myogenic activities have less likelihood in interfering with ABR (Howard, 2017). An additional advantages of the vertical montage are that having only one electrode as reference at C7 or nape minimises the time spent on switching electrodes from one test ear to the other; and that more space is left around the ear for supra-aural headphones which can reduce the interference of stimulus presentation (Kevanishvili & Aphonchenko, 1981). Therefore, the ipsilateral recording array that displays the highest expression of wave components should be adopted for recording neonatal ABRs at high intensity levels of neurodiagnostic evaluations, whilst the vertical montage for screening applications or threshold seeking would be appropriate.

1.4.3 Recording Parameters – Signal Processing

In addition to the aforementioned steps taken prior to and during data collection to optimise the SNR, other signal processing strategies have also been evaluated. These include the evaluation of amplitude and power histograms of the incoming data and their level, and weighted averaging techniques (Pantev & Khvoles, 1984). The amplitude and power histograms have been discarded since no evident advantage has been found compared to the artefact rejection method (Lightfoot & Stevens, 2014; Pantev & Khvoles, 1984). In contrast, weighted averaging, such as Bayesian weighting is a more powerful signal processing method, especially in high residual noise conditions. All weighted averaging methods reduce residual noise in ABRs by allowing all sweeps into the average but allocate more weight to the sweeps with lower noise levels and less weighting to the sweeps with higher noise levels. Bayesian averaging - also known as block-weighted averaging - weighs blocks of sweeps inversely to the level of noise calculated for each block. It uses an estimating technique derived from Bayesian inference based on condition probability dependent on theoretical assumptions including likelihood function, *priori* knowledge, and *posteriori* information where new data is continuously added to prior data and averaged (Elberling & Wahlgreen, 1985; Lightfoot & Stevens, 2014). For full breakdown of Bayesian weighting see Elberling & Wahlgreen, (1985). In comparison to a pre-set of rejection level, Sanchez and Gans, 2006 demonstrated Bayesian weighting yielded a larger amplitude of wave V (consisting mainly of energy below 350 Hz) compared to a strict artefact rejection of 10 µV in low noise level (Sanchez & Gans, 2006). The finding suggests that a strict artefact

rejection reduces low-frequency energy. Furthermore, the pruning of low-frequency energy caused by strict artefact rejection, together with the potential phase interactions between ABR and noise, may lead to biased or altered post-averaged ABR waveform (Kodera et al., 1977; Suzuki et al., 1982). In addition, a 30% improvement on fsp has been shown using Bayesian-weighted estimation technique when compared to conventional rejection artefact averaging (Lightfoot & Stevens, 2014). Bayesian method has several advantages and is often use conjointly with artefact rejection where a relatively lax rejection level is used to weed out particularly noisy data while Bayesian averaging aims to optimise the SNR of AR-accepted input.

1.4.4 Stimulus Parameters – Stimulus Type

The following section discusses the two stimuli used (tone burst and clicks) in New Zealand ABR protocol in order to better understand why a particular stimulus is employed and the limitations of each. After a screening referral, tone burst ABR is utilized to obtain estimated thresholds at 2kHz and 500Hz (and 1kHz and 4kHz if required) (Kelly et al., 2016). Air conduction (AC) threshold estimation is performed in both ears in sequential order using insert earphones, unless where contraindicated. Tone bursts are chosen for their frequency specificity in comparison to clicks as the purpose after screening referral is to determine the degree and configuration of hearing loss. Tone bursts are brief sinusoidal pulses with relatively short rise and fall times with their spectra characterised by the energy spread around the centre frequency (Stapells et al., 1985). The narrow spectral bandwidths reduce the likelihood of contributions to the ABR from neural populations apical to the centre-frequency region (Henry et al., 2011). These have been utilised to mimic the in-clinic pure-tone audiogram and accurate correlation in predicting the magnitude and pattern of hearing loss (Durrant, 1983; Kumar et al., 2014). ABR can be elicited down to 500Hz with appropriate filter settings and sampling epochs (Chertoff et al., 2010; Dau et al., 2000; Durrant, 1983; Pantev et al., 1985; Wegner & Dau, 2002). A similar level of correlation was observed between visual detection of tone burst-evoked auditory nerve and brainstem potentials at frequencies from 500 Hz and above (Coats & Martin, 1977; Don et al., 1979; Gorga et al., 1985; Jerger & Mauldin, 1978; Møller & Blegvad, 1976). Due to the stimulus construct of the tone burst, where rise time decreases with increase in frequency for a given intensity, an increase in frequency yields a shorter latency ABR waveforms which reflect the

difference in traveling wave propagation time in the cochlea (Durrant et al., 1981; von Békésy & Peake, 1990). Therefore, a normalised data specific for tone-burst evoked ABR is required upon data interpretation. Though tone bursts yield frequency-specific responses which provide valuable diagnostic data, there is an increased risk of stimulus artefact contamination due to the relatively long rise time in low frequency tone bursts.

In cases where elevated tone burst thresholds were observed, click ABR is then conducted with alternating polarity is conducted in order to evoke clearer and more reliable ABR responses. Clicks are brief rectangular pulses, typically 100ms in duration, delivered to an acoustic transducer as a direct current pulse (Durrant et al., 1981; von Békésy & Peake, 1990). The abrupt onset and brief duration evoke a larger response due to a better neural synchrony and broader stimulation of the frequency spectrum (spectral splatter). However, as a consequence of the tonotopical organisation of the cochlea, the neural elements along the cochlear partition are not excited simultaneously. For example, there is more synchrony with high-frequency neural fibres at the cochlear based compared to the more scattered neural activity with low-frequency fibres at the cochlear apex (Bargen, 2015; Chertoff et al., 2010; Dau et al., 2000; Elberling & Don, 2008; Wegner & Dau, 2002). The temporal discrepancy at frequencies is also attributed by the intensity-dependent nonlinearity of the outer hair cell (filter build-up time of the basilar membrane) (Ruggero, 1994). Furthermore, the constant delay in the hair cell synapse contribute to the temporal delay at the summed output of the neural elements render the click-evoked responses limited in frequency specificity (Chertoff et al., 2010; Dau et al., 2000; Elberling & Don, 2008; Shore & Nuttall, 1985).

There are, limitations with both sinusoidal pulses (tones) and clicks. Firstly, the aforementioned effect of frequency on latency, the increase in effective rise time as the frequency decreases reduce synchrony in the apical end of the cochlea, increasing the recording difficulty. The amplitude of the early components also diminishes with decrease in frequency (especially below 1000 Hz) resulting in ill-defined waveforms. Similar to the broadband clicks, frequency specific stimuli can also cause broad stimulation pattern at high stimulus levels (Durrant et al., 1981; von Békésy & Peake, 1990). Lastly, the increased risk of contamination from stimulus artefact with longer stimuli compared to the clicks.

To address the issue of temporal delay (and hence asynchronous activation) inherent to the transient stimuli, chirp stimuli have been designed to compensate for the time delay in the auditory periphery. The chirp, design attempts to increase the temporal synchrony between the neural elements. The lower frequency component reaches to the apex approximately at the same time as the higher frequency component. With such a design, the chirp promotes simultaneous neural activation (synchrony) and enables reproducibility of waveforms with larger amplitudes (Bargen, 2015; Chertoff et al., 2010; Dau et al., 2000; Elberling & Don, 2008; Wegner & Dau, 2002). Duration of the chirp at various intensities has been demonstrated to affect the amplitude and latency of ABR. Furthermore, when evoked by rising-frequency chirps which is designed to compensate for traveling-wave dispersion, the amplitude of wave V is larger than it is for both clicks and falling-frequency chirps (Chertoff et al., 2010; Dau et al., 2000; Elberling & Don, 2008; Shore & Nuttall, 1985). Shorter chirps are the most efficient at higher intensity levels of stimulation whereas longer chirps are superior at lower intensities (Elberling et al., 2010). For completeness, other strategies of stimulus construct such as verbal stimuli in clinical ABR have also demonstrated potential in clinical use primarily due to recent technological advances (Sanfins et al., 2017). Verbal stimulus unravels the opportunity to understand how speech stimuli are encoded in the brainstem which actively participates in the analysis of the complex speech (Blackburn & Sachs, 1990). Since the perception of speech sounds seems to begin in the brainstem, speech ABR could predict early auditory processing impairments in young children which conventional click-evoked ABR cannot (Basu et al., 2010; Dhar et al., 2009; Hornickel et al., 2009).

It is also important to note that conventional ABR measures are only suitable for threshold estimation due to aforementioned frequency and intensity limits. For example, Talaat et al. (2020) claimed that the click- and tone burst-evoked ABR hearing thresholds significantly overestimate the behavioural threshold (Talaat et al., 2020). Mean threshold difference of 5 to 20 dB were reported when comparing ABR and pure-tone audiometric thresholds (Canale et al., 2012; Ceylan et al., 2018). On the other hand, there is a high degree of correlation between click ABR and behavioural pure-tone thresholds (Hoda et al., 2019). More research is needed to obtain reliable ABR waveform morphologies for accurate

diagnostic purposes for ABR thresholds to be used in replacement of the behavioural pure-tone audiometry.

1.4.5 Stimulus Parameters – Stimulus Rate

The effects of stimulus rate on ABR have been investigated since the notion of using rapid stimulus repetition rate as a diagnostic feature was suggested in the late 1970s (Don et al., 1977; Stockard et al., 1977). As thousands of AEPs are required for a single ABR trace and stimulus repetition rate directly influences the ABR data acquisition time, it is desirable to use rapid rate when appropriate. However, increased rate has been associated with increased latency, decreased amplitude and alterations of waveform morphology regardless of age or hearing status (Chiappa & Ropper, 1982; Dey-Sigman et al., 1984; Don et al., 1977; Parthasarathy et al., 1998; Pratt & Sohmer, 1976; Thornton & Coleman, 1975; Weber & Fujikawa, 1977). For instance, the effects of increased rate on ABR latencies and amplitudes have been demonstrated in both infants and adults with its effect on infants are more pronounced compared to adults (Despland & Galambos, 1980; Lasky, 1984; Zimmerman et al., 1987). For a given intensity level, the latency-rate functions decreases with an increase in age (Weber & Fujikawa, 1977). Specifically, an increased rate of tone-burst presentation from 11.1/s to 55.5/s prolonged the wave V latency in adults and neonates (Parthasarathy et al., 1998). Furthermore, the wave V latency-rate effect in infants as a function of stimulus intensity level have been shown to cause the greatest increase in latency at high intensities (Dey-Sigman et al., 1984). In adults, however, wave V latency-rate effect seems to be independent of stimulus intensity over a moderate range of intensity levels (30- 70 dB HL) (Don et al., 1977; Gerling & Finitzo-Hieber, 1983; Paludetti et al., 1983; Weber & Fujikawa, 1977).

Many studies have also demonstrated the differential impact of stimulus rate on the peripheral (e.g., wave I) and central components (e.g., wave V) of the ABR (Burkard & Sims, 2002; Don et al., 1977; Eggermont & Odenthal, 1974; Gerling, 1989; Picton et al., 1981; Weber & Fujikawa, 1977). The wave V latency was shown to be delayed for an additional 0.39ms when the presentation rate increased from slow rates of 10 and 20 clicks/s to a faster rate at 80clicks/s. In contrast, the wave I latency increased for a mere 0.14ms for the same rate change (Picton et al., 1981). In relation to the wave latency as a function of click repetition rate, wave I was shown to be logarithmic and wave V somewhat more linear,

suggesting the peripheral and central portions of the auditory pathway differ in responsiveness to repetitive acoustic stimulation (Don et al., 1977; Eggermont & Odenthal, 1974). However, it is difficult to identify the specific neurogenerator along the auditory pathway of which a linear response function is first encountered as wave I-III resolution deteriorates with increase in repetition rate. On the other hand, the amplitudes of waves I and V seem to be affected differently than their respective latencies (Hall, 2007; Picton, 2011; Pratt & Sohmer, 1976). An increase in stimulus presentation rate from 10 clicks/s to 80 clicks/s reduced the wave I amplitude by 50% and only a reduction of 10-30% in wave V amplitude was observed.

1.5 Proposed mechanisms for the rate effect on ABR

The rate effect on the amplitude and latency shift has been proposed as a type of neural adaptation (Don et al., 1977; Valderrama et al., 2014). Neural adaptation is a change in the responsiveness of the sensory system over time to a constant stimulus (Webster, 2012). Adaptation is thought to be an evolutionary development to ensure maximal response to a range of inputs. It occurs widely and at various levels of the brain, with each higher function involving more and more abstract properties of sensory inputs. In AEP studies, the adaptation can be quantified by comparing the responses of preceding and successive auditory stimulation, and specifically, the change in wave latencies and amplitudes.

The postulated mechanisms responsible for the latency changes include the involvement of the middle ear (ME) muscle and olivo-cochlear bundle (efferent feedback systems) and neural desynchrony. Animal studies using anaesthesia to eliminate ME muscle responses have ruled out ME muscle activity as a contributor of the adaption (Sørensen, 1959). In addition, since the ME muscles and the olivo-cochlear efferent system respond bilaterally following a monaural stimulation, evidence of latency shift restricted to inputs arising from the ipsilateral side of rapid stimulation exclude the involvement of ME muscles and efferent systems (Don et al., 1977). The latency of an ABR wave indicates the response of a neural element, or the strongest response of several elements, or the combination of these two, changes in neural firing synchrony. Therefore, a reduction in the number of responding neurons and/or a change in varying degrees of synchronisation of the neural

components giving rise to the ABR component (e.g., wave V), could explain the latency shift observed in rapid stimulation.

There are three determinants within the neural transmission pathway that could also contribute to the adaptation of a neuron, at axon hillock, synapse terminal, and at the receptors which are involved in the transmission. When a neuron reaches the threshold potential at the axon hillock, sodium ion (Na^+) voltage-gated channels are opened causing an influx of Na^+. This is followed by repolarisation which triggers the opening of potassium ion (K^+) voltage-gated channels. Over the period when the Na^+ gated channels are open, the neuron is incapable of eliciting an action potential in response to another stimulus, this is called the absolute refractory period. Relative refractory period, where action potential is only generated in response to a strong enough stimulus, occurs during the repolarisation phase when the Na^+ voltage-gated channels are closed and the K^+ voltage-gated channels remained open. This is because the efflux of K^+ which causes hyperpolarisation of the membrane and lowers the membrane potential below its resting potential resulting in a larger stimulus required to reach the threshold potential. In other words, constant stimulation and therefore uninformative stimulation is diminished allowing the neuron to be more responsive to novice input or changes in stimulation (Brenner et al., 2000). However, these refractory periods are of the order of milliseconds which is much shorter than the period between auditory stimulation (ISI), thus unlikely to account for the latency shift seen with increasing stimulation rate.

At the neural transmission site, the synaptic cleft, an action potential is passed on to the next neuron (post synaptic neuron) primarily via chemical signals, termed neurotransmitters. Once depolarisation reaches the end of the axon (i.e., the synaptic terminal), the neurotransmitters stored in vesicles are released into the cleft. Via diffusion, they bind to the postsynaptic receptors causing an influx of positive ions and generating a postsynaptic potential. In order for the new signal to be passed on again, the neurotransmitters need to be removed from the synaptic cleft via diffusion, degradation or reuptake. These synaptic transmission processes are much more time consuming and if subsequent stimuli occur before the recovery is complete, the response will be attenuated and hence shown as prolonged in latency (Thornton & Coleman, 1975). However, this synaptic transmission is also unlikely to be at the central portion of the auditory pathway

since contralateral stimulation yields the same latency as the ipsilateral ear (Don et al., 1977). Therefore, it is more likely that the cause for the latency shift induced by rapid stimulation is due to metabolic changes of receptor consequent on their activation. Possibly through a similar ionic mechanism of short acting fatigue process observed in the cochlea as described by Legouix and colleagues (Legouix et al., 1980).

The observed latency shift has been suggested to occur at the peripheral portion of the auditory system (Don et al., 1979; Eggermont & Odenthal, 1974). Don et al., 1979 demonstrated that the wave V latency shift is restricted to the stimulated ear by presenting a train of twenty clicks at moderate intensity (40 dB sensation level) and rate of 100/s. As shown in the schematic diagram in Figure 5, the first click was presented to the right ear serving as the control signal, the second to ninetieth clicks were presented to the left ear as the adapting stimuli, and the last click was presented to the right ear as a test click. A 500 ms silence follows a set of twenty clicks before the next set of twenty is presented. In other words, the right ear was stimulated at 10 clicks/s. If there was a latency shift induced by rapid click rates originating from the central portion of the auditory pathway, a similar prolonged latency trend should be found between the first and last ABRs. Interestingly, the wave V latency of the twentieth click did not show a significant difference to the control (first) click. Furthermore, the rate effects on wave V latency and amplitude were observed in the eighteen successive ABRs of the left ear.

Figure 5

Schematic Diagram of the Paradigm Used by Don, 1977.

Note. A train of twenty clicks was presented at a rate of 100/s and at 40 dB sensation level. The first click which served as the control signal was presented to the right ear (red). The second to ninetieth clicks were presented to the left ear (blue) as the adapting stimuli. The last click was presented to the right ear and served as a test click. A 500ms silence follows a set of twenty clicks before the next set of twenty is presented (Don et al., 1977).

1.6 Study Rationale

Based on the notion that the rapid rate-induced wave V latency shift occurs at the peripheral portion of the auditory system, an interleaving clicks paradigm where click stimuli alternate between the ears, was designed to elicit ABRs at a faster rate whilst preserving the relevant ABR parameters (Bencito, 2020; Don et al., 1977). A similar study was done using train of tones with each presents tested frequency and level which showed significant reduction in adaptation and improved wave I amplitude (Buran et al., 2020). Furthermore, Polonenko and Maddox, 2019, demonstrated the validity of a stimulus paradigm which comprises of simultaneous, independently randomised sequences of tonebursts, in normal hearing adults. Furthermore, their stimulus design suggests that the masking provided by the other simultaneous toneburst sequences could have improved the place specific of the responses (Polonenko & Maddox, 2019). The preliminary data from the O'Beirne group have recently demonstrated that interleaving clicks paradigm shortens the acquisition time with no significant delay in wave V latency in NH subjects (Bencito, 2020). The wave V latency and overall morphology of the ABRs evoked with the interleaving paradigm (binaural stimulation at a fast rate) were also shown to be comparable to the conventional ABR (monaural stimulation at a slow rate) in NH individuals (Bencito, 2020). The overarching hypothesis of the present study is that the same effect of interleaving paradigm would be similar in the SNHL individuals.

The study thus aims to:

- investigate whether the same stimulus paradigm (alternating clicks delivered binaurally at a fast rate) affects the wave V latency compared to the conventional slow rate paradigm (monaurally delivered at a slow rate) and fast rate paradigm (monaurally delivered at a fast rate) in both NH and SNHL individuals
- examine whether the rapid interleaving clicks affects the wave V amplitude compared to the monaural slow and fast rate paradigms in NH and SNHL individuals

Specifically, it was hypothesised that in the NH and SNHL groups, the mean wave V latency

1. of the monaural fast condition is significantly different to the monaural slow condition

2. of the interleaving R ABR is not significantly different to the monaural slow condition
3. of the interleaving R ABR is significantly different to the monaural fast condition

Furthermore, it was also hypothesised that in the NH and SNHL groups, the mean wave V amplitude

4. of the monaural fast condition is significantly different to the monaural slow condition
5. of the interleaving R ABR is not significantly different to the monaural slow condition
6. of the interleaving R ABR is significantly different to the monaural fast condition

Similarly, it was hypothesised that in the NH and SNHL groups, the mean wave III latency

7. of the monaural fast condition is significantly different to the monaural slow condition
8. of the interleaving R ABR is not significantly different to the monaural slow condition
9. of the interleaving R ABR is significantly different to the monaural fast condition

In addition, it was hypothesised that in the NH and SNHL groups, the mean wave III amplitude

10. of the monaural fast condition is significantly different to the monaural slow condition
11. of the interleaving R ABR is not significantly different to the monaural slow condition
12. of the interleaving R ABR is significantly different to the monaural fast condition

2 Methods

2.1 Participants

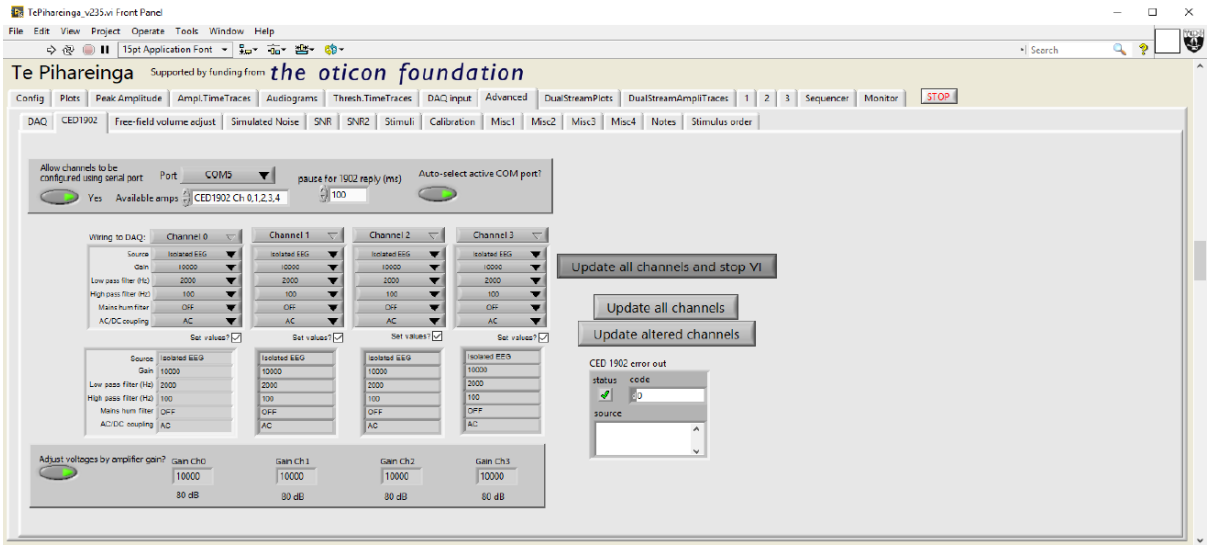
Subjects were asked to read the information sheet and sign an informed consent form prior to participation (Appendices A and B). The participants were recruited either by print material or by word-of-mouth (Appendix C). All procedures were performed in compliance with the University of Canterbury Ethics Committee (Appendix D) by myself and classmate Shatha Nofal. The ABR data were acquired from thirty-one adults. The inclusion criteria were 1) normal otoscopic examination (clear outer ear and unremarkable tympanic membrane), 2) and the presence of type A tympanometric curve at 226Hz (peak-compensated static admittance between 0.3 and 2.5mmhos), in attempt to minimise the potential contribution of ME and outer ear on the evoked responses, and 3) hearing thresholds (Appendix E) within normal or exhibiting sensorineural type with slight to moderately severe SNHL (average threshold of 500, 1000, 2000, 4000Hz less than 70dB HL). Twenty-one subjects (mean age = 30.5 yr, SD = 6.8 yr; 7 males; 14 females) had NH (pure-tone audiometric threshold ≤ 15 dB hearing level between 0.25 and 8 kHz). Ten subjects (mean age = 58.2 yr, SD = 14.3 yr; 6 males; 4 females) had SNHL based on Goodman's scale for classification of degree of hearing loss (Goodman, 1965).

2.2 Equipment set up

ABRs were evoked with clicks, measured, and processed Te Pihareinga, a software developed by the O'Beirne group (Bencito, 2020; O'Beirne & Bird, 2015). A screenshot of the Te Pihareinga configuration page is shown in Figure 6. More specifically, as depicted in Figure 7, the acoustic stimuli were digitally generated (cDAQ-9174 data acquisition system with 16-bit analogue-to-digital and digital-to-analogue converter NI-9269 module, National Instruments), amplified (MX28 Stereo Mini-mix VI, Rolls, UT, USA), and delivered via calibrated 3MTM E-A-RTONETM Insert Earphones. The peak voltage drive to the insert earphones had previously been calibrated to match of the Interacoustics Eclipse (Bencito, 2020). The voltage difference between the active (Fz) and reference (nape) electrodes was amplified (10000 x) and filter bandpass set at 100 Hz and 2000Hz. The raw traces were digitized for the subsequent analyses. Quad-channel CED 1902 Mk III (Cambridge Electronic Designed Ltd., Cambridge, UK) isolated pre-amplifier and NI-9222 module (National Instruments, TX, USA) were used to record amplified output.

Figure 6

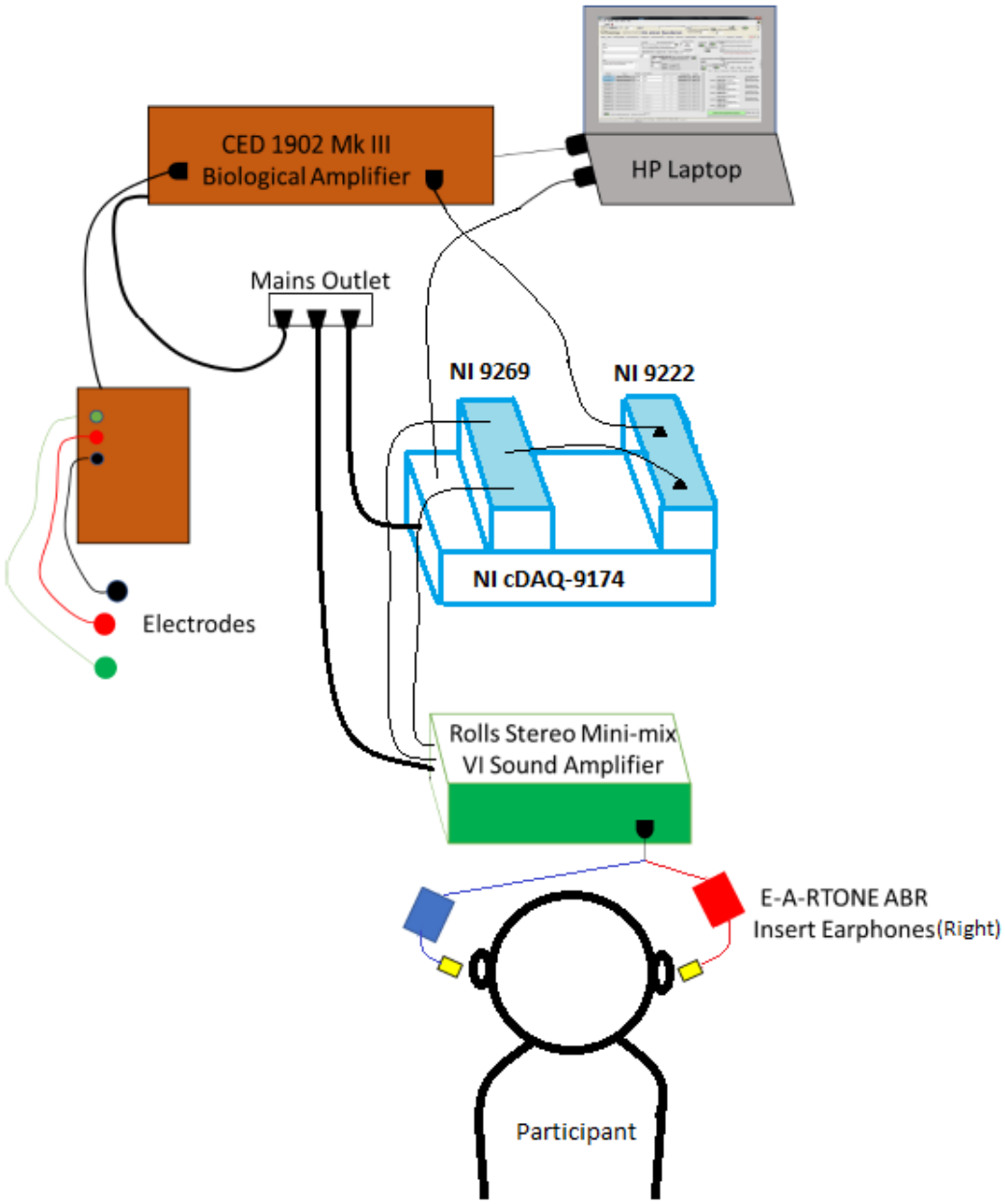
Screenshot of the CED1902 Configuration From the Te Pihareinga Software.



Note. The software was developed by the O'Beirne group (Bencito, 2020; O'Beirne & Bird, 2015). Signal gain was set at 10,000x with filter bandpass set at 100 Hz and 2000Hz.

Figure 7

Schematic Diagram of the ABR Acquisition System Used in This Study.



Note. The ABRs are measured via the electrodes, processed by software (HP Laptop). The software connecting to the data acquisition system (NI cDAQ-9174) which produces the audio stimuli (NI9269) and records the amplified audio output (amplifier, CED 1902 Mk III; recording module, NI 9222). The stimuli are delivered to the participant with the appropriate transducers (E-A-RTONE ABR insert earphones). Adapted from 'Interleaved Recording of the Auditory Brainstem Response' by S. Bencito, 2020) (Bencito, 2020)

2.3 Stimulus

In order to elicit largest possible wave V amplitude, rarefaction click stimuli generated by 100-μs-wide electrical pulses with 0.1ms length and rise-fall of 0 were presented via insert earphones. The presentation level was set at 70 or 71 dB nHL to maintain comfort in the NH groups whilst having a presentation level high enough to elicit ABRs for the SN hearing group. The purpose of the 1 dB difference in presentation level was used to allow the measurement two replicate waveforms in practice. The difference is minute to human perception and thus deemed to be clinically insignificant and irrelevant.

To examine the effect of presentation rates on ABRs on participants with NH and SNHL, each participant was presented with the three sequences in shown in Table 2, in a randomized order to avoid the order effect. The fastest rate (90.91/s) out of the three presentation rates that were used in the study conducted by Bencito, 2020 was chosen.

Furthermore, to minimise the stress on the participants and to increase experiment efficiency, the sequences were played automatically with 5 second pause in between. The specific rates were chosen based on preliminary results from the O'Beirne group (Bencito, 2020). The monaural slow sequence presented the click stimuli specified in the previous section to the right ear at a rate of 45.45/s (22ms ISI). The monaural fast paradigm delivered the click stimuli to the right ear at a rate of 90.91/s (11ms ISI). The Interleaved sequence presented the click stimuli that alternated between the left and right ears and in theory, the presentation rates to each ear were 45.45/s (22ms ISI) and to the central structures at a doubled rate, at 90.91/s (11ms ISI).

Table 2

Recording Paradigms Presented to Each Participant in Randomised Order.

Conditions	Presentation Ear	Central Rate (clicks/s)	Peripheral Rate (clicks/s)
Monaural Slow	Right ear	45.45	45.45
Monaural Fast	Right ear	90.91	90.91
Interleaved	Interleaved binaural	90.91	45.45

Note. 100-μs-wide rarefaction clicks presented at 70 and 71 dB nHL were used.

2.4 ABR acquisition

To minimise the electrical and physiological noises, the participants were seated on a recliner chair in a low ambient noise room and asked to relax. The electrode sites were prepared by wiping the sites with alcohol wipes and if required, lightly exfoliated using 3MTM Red Dot Trace Skin Prep tape (3M, New Zealand) to reduce the impedance of the electrode connection. BlueSensor ECG (Ag/AgCl) electrodes (Ambu, Denmark) were then placed using vertical montage to optimise the peak amplitude of wave V. The sites are as shown in Figure 1 in the previous Chapter, where reference electrodes were placed on the nape, the active on the forehead (Fz) and the ground on the clavicle. The corresponding electrode wires were then connected to the electrodes and electrode impedances for each site was checked to ensure that there were below 3kΩ and the interelectrode impedance below 1 kΩ. A rejection criterion at ±40 μV was used to optimise the ABR waveforms. The stopping criteria of 4000 averages was used to ensure enough traces were obtained to produce an appropriate signal-to-noise ratio (at least 3:1) and fsp values were measured throughout the recording. Two traces of an ABR were examined to determine the presence of the ABR wave components.

2.5 Determining a present ABR and data analysis

Two examiners independently determined the peaks and troughs of wave III and wave V for each ABR. The supervisor was consulted to interpret the recording for instances when there were disagreements in the determination or the labelling of ABR component. A wave peak was defined at the highest point within the expected time period. Wave latency was calculated as the delay between a wave peak and stimulus onset. Absolute wave amplitude was calculated by subtracting the wave peak to the immediate lowest point. The latency and amplitude of each ABR were calculated after averaging the two repetitions so as to increase the reliability of the estimates. As the interleaved condition evokes ABR binaurally, both right ear (interleaved R) and left ear (interleaved L) data are shown for completeness. However, because the ABR for the two monaural conditions (monaural slow and monaural fast) were recorded from the right ear, the analysis below focusses somewhat on the right ear interleave trace, particularly where the audiometric thresholds and sensorineural lesions are likely to differ between the ears. All data was presented as mean ± SEM unless specified. Differences between the sequences were assessed by a repeated measure

analysis of variance (ANOVA) with post hoc tests to detect significant difference. A p value < 0.05 was considered as statistically significant. Prior to the analysis, a descriptive statistics test was run to ensure there were no significant skewness, kurtosis or outliers, and the assumptions of parametric testing were met. Skewness and kurtosis were calculated by dividing the value over standard error. An absolute skewness or kurtosis value larger than 1.96 was considered as statistically significant in the data. Mauchly's test of sphericity with p < 0.05 was used to indicate the assumptions of sphericity was met.

3 Results

3.1 Effect of Click Stimulus Paradigms on the Mean Wave V Latency

We compared the wave V latencies (ms) of both NH and SNHL groups as shown in Tables 3 and 4 under the three stimulus conditions outlined in Table 2. A representative set of ABRs from a NH participant under all stimulus conditions is shown in Figure 8. The descriptive statistics test showed no significant skewness and kurtosis and the Mauchly's test of sphericity indicates that the assumption of sphericity was met as shown in Table 5. $W(3) = 0.86$, $p = 0.60$. The values of minimum, lower quartile, median, upper quartile, and maximum of the data sets in Figure 9 are shown in Table 6.

Table 3

Wave V Latency (ms) Data – NH.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	6.30	5.73	6.73	6.32
Participant 2	6.57	6.80	7.14	6.71
Participant 3	6.68	6.48	6.48	6.57
Participant 4	6.19	6.57	7.02	6.00
Participant 5	6.0	5.51	6.16	-
Participant 6	6.32	5.91	6.64	6.48
Participant 7	6.16	5.82	6.37	6.16
Participant 8	6.48	6.64	7.18	6.41
Participant 9	6.30	6.37	6.39	6.19
Participant 10	6.48	6.25	6.68	6.34
Participant 11	6.68	6.71	6.62	6.28
Participant 12	6.34	6.55	6.80	6.50
Participant 13	6.57	6.16	6.87	6.50
Participant 14	6.46	6.44	6.75	6.44
Participant 15	6.32	6.21	6.66	6.37
Participant 16	6.00	6.16	6.16	6.28

Participant 17	6.34	6.59	6.80	6.46
Participant 18	6.93	6.73	7.25	6.44
Participant 19	6.5	6.64	6.19	6.21
Participant 20	6.82	7.05	7.00	-
Participant 21	6.00	5.6	6.96	6.66

Note. –, indicates excluded outliers.

Table 4

Wave V Latency (ms) Data – SNHL.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	6.91	6.73	7.09	6.75
***Participant 2**	*	*	*	*
Participant 3	6.23	6.48	6.55	6.48
Participant 4	6.00	-	6.11	6.21
Participant 5	6.00	6.62	6.66	6.41
Participant 6	6.91	7.12	7.41	7.00
Participant 7	6.00	6.87	6.68	6.84
Participant 8	6.89	7.05	7.09	6.98
Participant 9	6.91	6.89	7.07	6.89
Participant 10	6.64	6.48	6.71	6.21

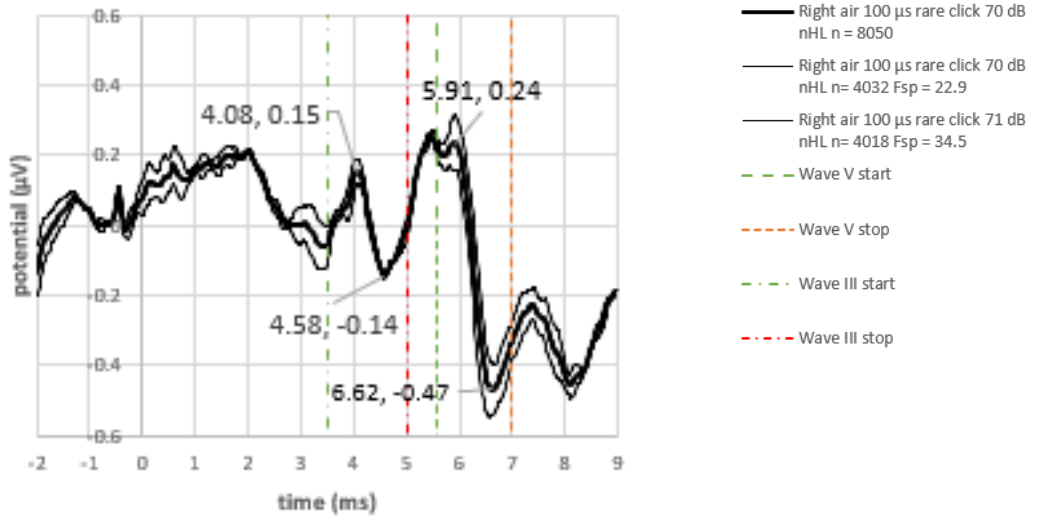
Note. *, indicates omitted data due to incomplete data points. –, indicates excluded outliers.

Figure 8

Representative ABRs of a Normal Hearing Participant.

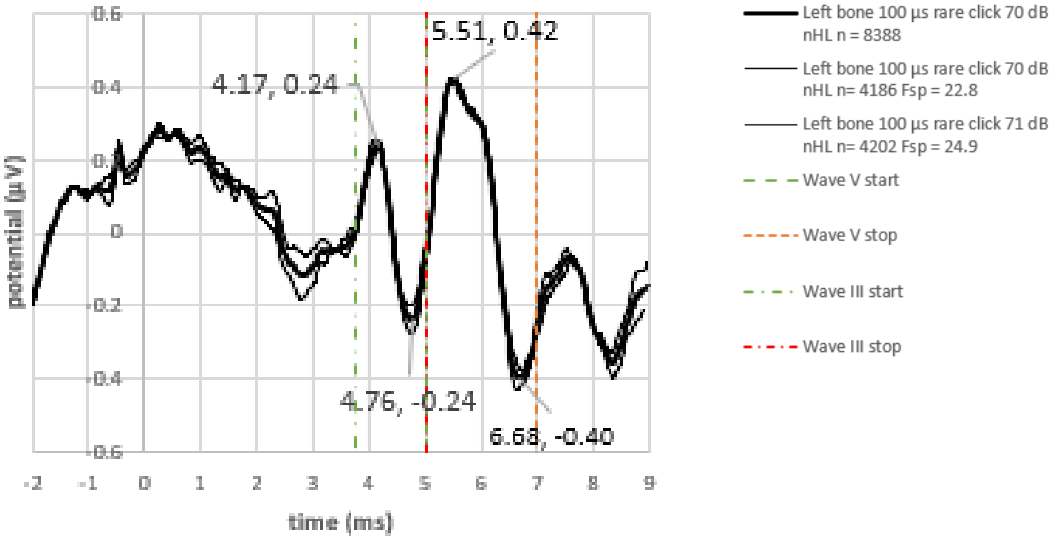
Interleaved

R



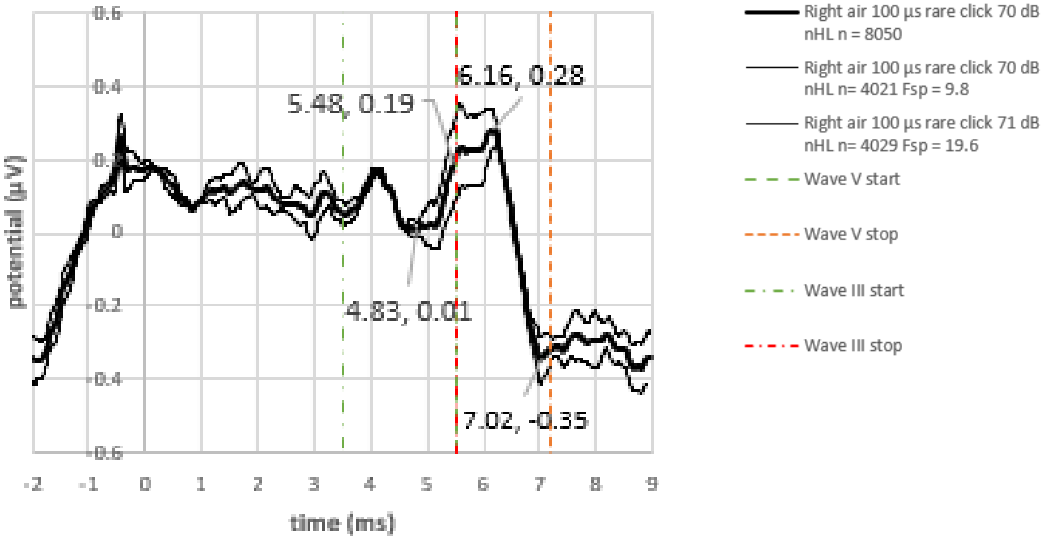
Interleaved

L

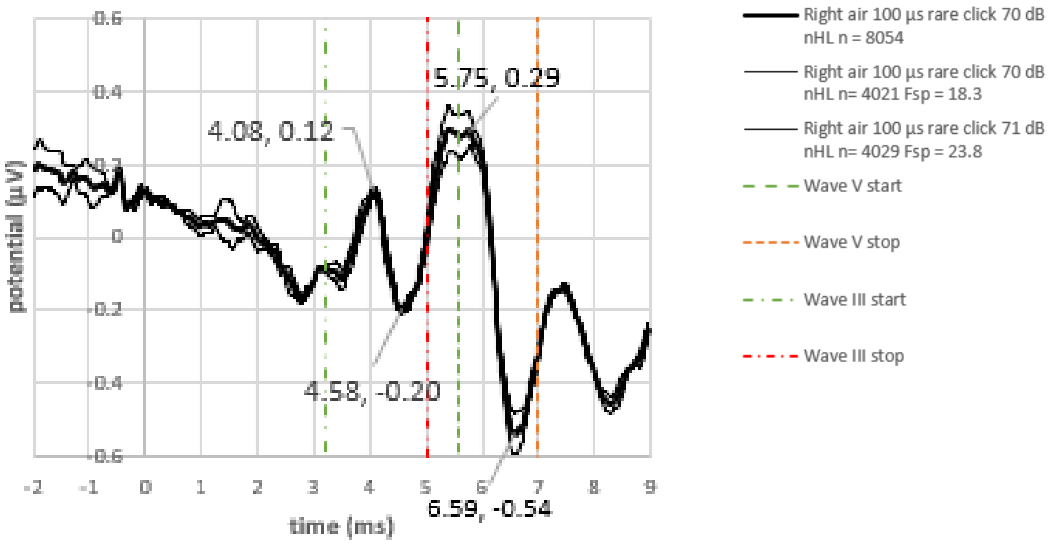


Monaural

Fast



Monaural Slow



Note. Peaks of wave III and wave V are labeled as III and V. The green and red lines indicate the start and end of the measurement bracket, respectively. The highest and immediate lowest points within each bracket were identified.

Table 5

Descriptive Statistics for Wave V Latency (ms).

		Skewness (S)			Kurtosis (K)		
	Conditions	S	SE	|S/SE|	K	SE	|K/SE|
NH (n = 20)	Interleaved R	0.17	0.50	0.34	-0.32	0.97	0.33
	Interleaved L	-0.50	0.50	1.00	-0.56	0.97	0.58
	Monaural Fast	-0.20	0.50	0.39	-0.75	0.97	0.77
	Monaural Slow	-0.22	0.52	0.41	0.10	0.97	0.10
SNHL (n = 9)	Interleaved R	-0.24	0.72	0.33	-2.28	1.40	1.63
	Interleaved L	0.04	0.75	0.05	-1.44	1.48	0.98
	Monaural Fast	-0.31	0.72	0.44	0.16	1.40	0.12
	Monaural Slow	-0.34	0.72	0.47	-1.74	1.40	1.24

Table 6

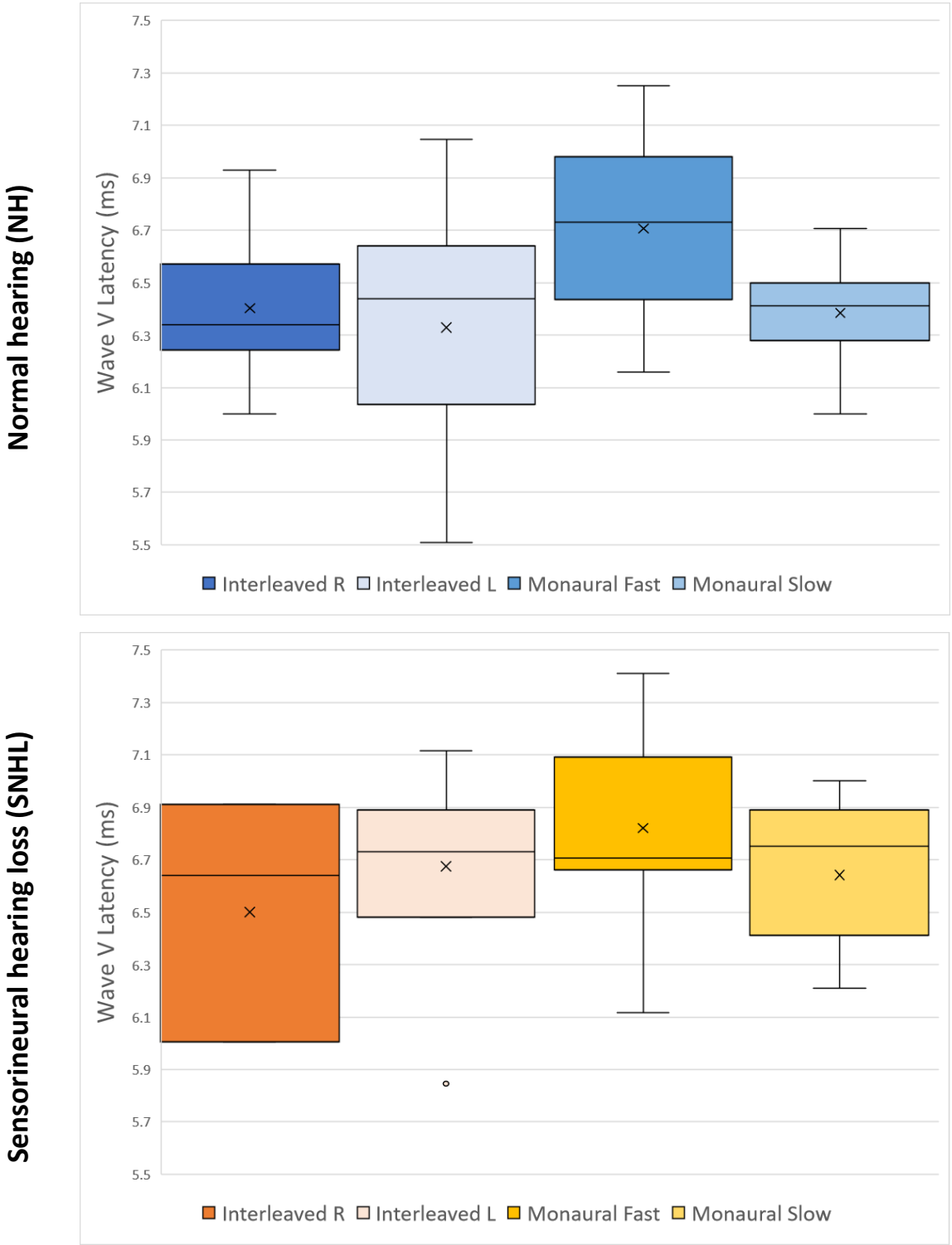
Descriptive of Wave V Latencies (ms) Under the Different Click Stimulus Paradigms.

	Conditions	Mean	SE	Med.	SD	Min.	Max.
NH (n = 20)	Interleaved R	6.40	0.06	6.34	0.26	6.00	6.93
	Interleaved L	6.33	0.09	6.44	0.42	5.51	7.05
	Monaural Fast	6.71	0.07	6.73	0.33	6.16	7.25
	Monaural Slow	6.37	0.07	6.41	0.31	5.41	7.05
SNHL (n = 9)	Interleaved R	6.50	0.14	6.64	0.43	6.00	6.91
	Interleaved L	6.78	0.09	6.80	0.24	6.48	7.12
	Monaural Fast	6.82	0.13	6.71	0.38	6.12	7.41
	Monaural Slow	6.64	0.11	6.75	0.32	6.21	7.00

Note. SE, standard error of mean; Med., median; SD, standard deviation; Min., minimum; Max., maximum.

Figure 9

Effect of 70 dB nHL Click Stimulus Paradigms on Wave V Latencies (ms).

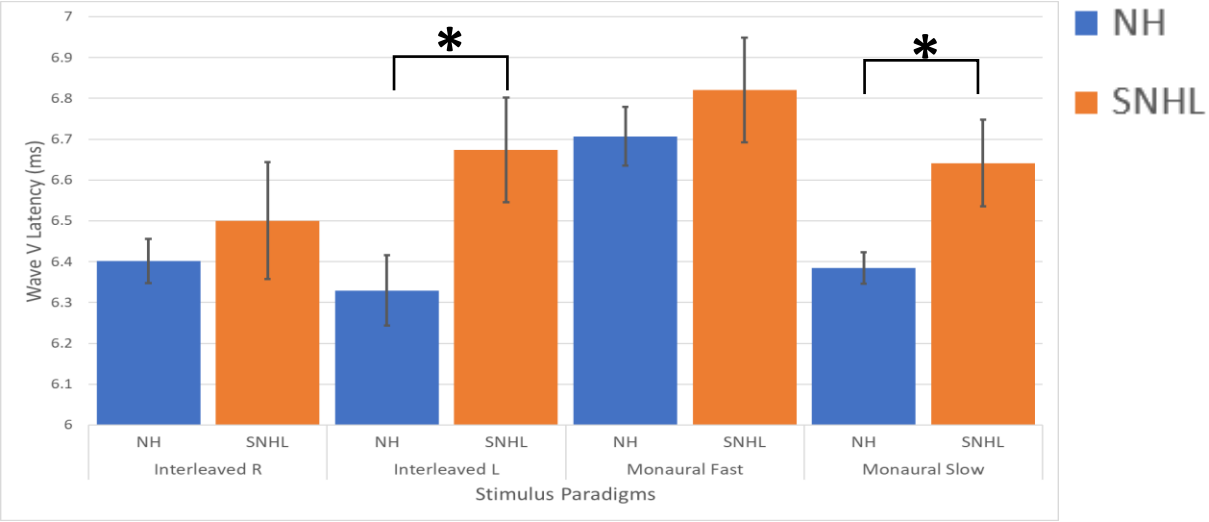


Note. Wave V latency of NH and SNHL participants measured under the interleaved, monaural fast and monaural slow conditions. The box plot depicts the minimum, lower quartile, median, upper quartile, and maximum of the data sets. Outliers are shown as the same colour dot as the group data. Cross indicates the mean.

The main effect of stimulus was identified, $F(1, 25) = 8.32$, $p = 0.008$, $\eta^2_p = .250$. The post hoc findings are described in the following. The mean wave V latencies of the interleaved R condition were 6.40 ± 0.06 (NH) and 6.50 ± 0.19 (SNHL) (Figure 10). There was no significant difference in the mean V latencies found in either the interleaved R nor monaural fast (NH: 6.75 ± 0.07; SNHL: 6.37 ± 0.07) conditions, in both the NH and SNHL groups. On the other hand, the mean wave V latencies were significantly delayed in the SNHL compared to the NH group under monaural slow condition (NH: 6.50 ± 0.14; SNHL: 6.78 ± 0.09; $p = .002$) and the interleaved L (NH: 6.35 ± 0.06; SNHL: 6.72 ± 0.10; $p = 0.004$; Figure 10).

Figure 10

Effect of 70 dB nHL Click Stimulus Paradigms on the Mean Wave V Latencies (ms) of the NH Versus the SNHL Group.

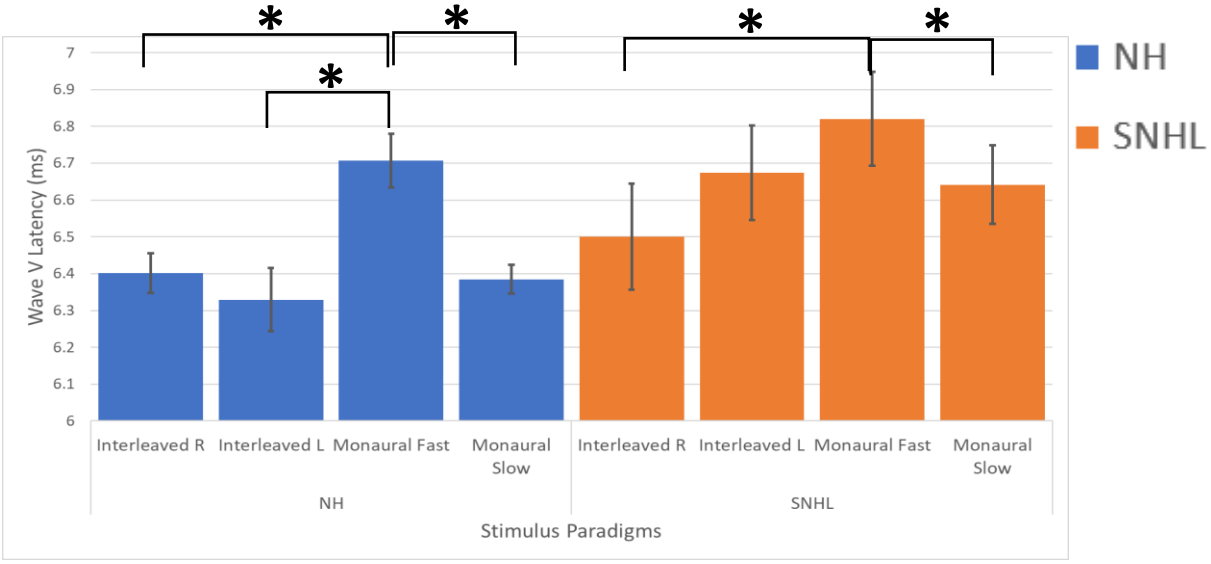


Note. No significant differences in the mean V latencies were found in either the interleaved R nor monaural fast conditions, in the NH and SNHL groups. On the other hand, the mean wave V latencies were significantly delayed in the SNHL compared to the NH group under monaural slow condition. Histograms depict group means (± SEM). *, $p < 0.005$.

A significant effect was found, $F(3, 75) = 8.93$, $p < .001$, $\eta^2_p = .263$; post hoc results showed in the NH and SNHL groups, the interleaved condition in the right ear and left ear were not significantly different to each other. Expectedly, the monaural fast condition significantly prolongs the wave V latencies compared to the monaural slow condition in both hearing groups (NH: $p = 0.002$; SNHL: $p = 0.034$). Furthermore, the mean wave V latencies of monaural fast was significantly longer compared to interleaved R (NH: $p < 0.001$; SNHL: $p = 0.003$). In the NH group, the interleaved L showed significant difference to the monaural fast ($p < 0.001$; Figure 11).

Figure 11

Effect of 70 dB nHL click Stimulus Paradigms on the Mean Wave V Latencies (ms) Within the Same Hearing Groups (NH and SNHL).



Note. In both NH and SNHL groups, the interleaved conditions in the right ear and left ear were not significantly different to each other. The monaural fast condition significantly prolongs the wave V latencies compared to the monaural slow condition and to interleaved R, in both hearing groups. In the NH group, the interleaved L showed a significant difference to the monaural fast. Histograms depict group means (± SEM). *, $p < 0.05$.

3.2 Effect of Click Stimulus Paradigms on the Mean Wave V Amplitude

Wave V amplitudes (µV pp) were recorded under the three stimulus conditions outlined in Table 2 and the data of both NH and SNHL groups are shown in Table 7 and 8. The descriptive statistics test showed no significant skewness and kurtosis and the Mauchly's test of sphericity indicates that the assumption of sphericity was met, as shown in Table 9. W (3) = 0.813, p = 0.479. The values of minimum, lower quartile, median, upper quartile, and maximum of the data sets in Figure 12 are shown in Table 10.

Table 7

Wave V Amplitude (µV pp) Data – NH.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	0.61	0.50	0.44	0.52
Participant 2	0.41	0.25	0.46	0.33
Participant 3	0.31	0.43	0.42	0.50
Participant 4	0.43	0.34	0.50	0.53
Participant 5	0.72	-	0.63	-
Participant 6	0.46	0.48	0.33	0.52
Participant 7	0.6	0.53	0.53	0.37
Participant 8	0.36	0.48	0.34	0.39
Participant 9	0.48	0.38	0.5	0.58
Participant 10	0.30	0.27	0.38	0.43
Participant 11	0.25	0.27	0.14	0.32
Participant 12	0.23	0.22	0.18	0.31
Participant 13	0.23	0.40	0.45	0.45
Participant 14	0.55	0.40	0.36	0.64
Participant 15	0.55	0.31	0.44	0.49
Participant 16	0.54	0.43	0.47	0.38
Participant 17	0.46	0.59	0.48	0.5
Participant 18	0.33	0.55	0.16	0.39
Participant 19	0.42	0.28	0.41	0.41

Participant 20	0.25	0.29	0.19	0.23
Participant 21	0.40	0.20	0.49	0.58

Note. –, indicates excluded outliers.

Table 8

Wave V Amplitude (µV pp) Data – SNHL.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	0.21	0.35	0.24	-
***Participant 2**	*	*	*	*
Participant 3	0.27	0.26	0.19	0.21
Participant 4	0.34	0.34	0.35	0.32
Participant 5	-	-	0.11	-
Participant 6	0.19	-	0.07	0.25
Participant 7	0.38	-	0.29	0.30
Participant 8	0.24	0.34	0.34	0.25
Participant 9	0.22	0.36	0.27	0.24
Participant 10	0.23	0.28	0.27	0.30

Note. *, Indicates data exclusion due to incomplete data points. –, indicates excluded outliers.

Table 9

Descriptive Statistics for Wave V Amplitude (µV pp).

		Skewness (S)			Kurtosis (K)		
	Conditions	S	SE	|S/SE|	K	SE	|K/SE|
NH (n = 20)	Interleaved R	0.30	0.50	0.60	-0.60	0.97	0.62
	Interleaved L	0.17	0.51	0.34	-1.15	0.99	1.16
	Monaural Fast	-0.69	0.50	1.37	-0.12	0.97	0.12
	Monaural Slow	-0.10	0.51	0.20	-0.50	0.99	0.51

Table 9 cont.

Descriptive Statistics for Wave V Amplitude (µV pp).

SNHL (n = 9)	Interleaved R	1.07	0.75	1.42	-0.03	1.48	0.02
	Interleaved L	-0.92	0.85	1.09	-1.26	1.74	0.73
	Monaural Fast	-0.71	0.72	0.99	-0.50	1.40	0.35
	Monaural Slow	0.01	0.79	0.01	-1.43	1.59	0.90

Table 10

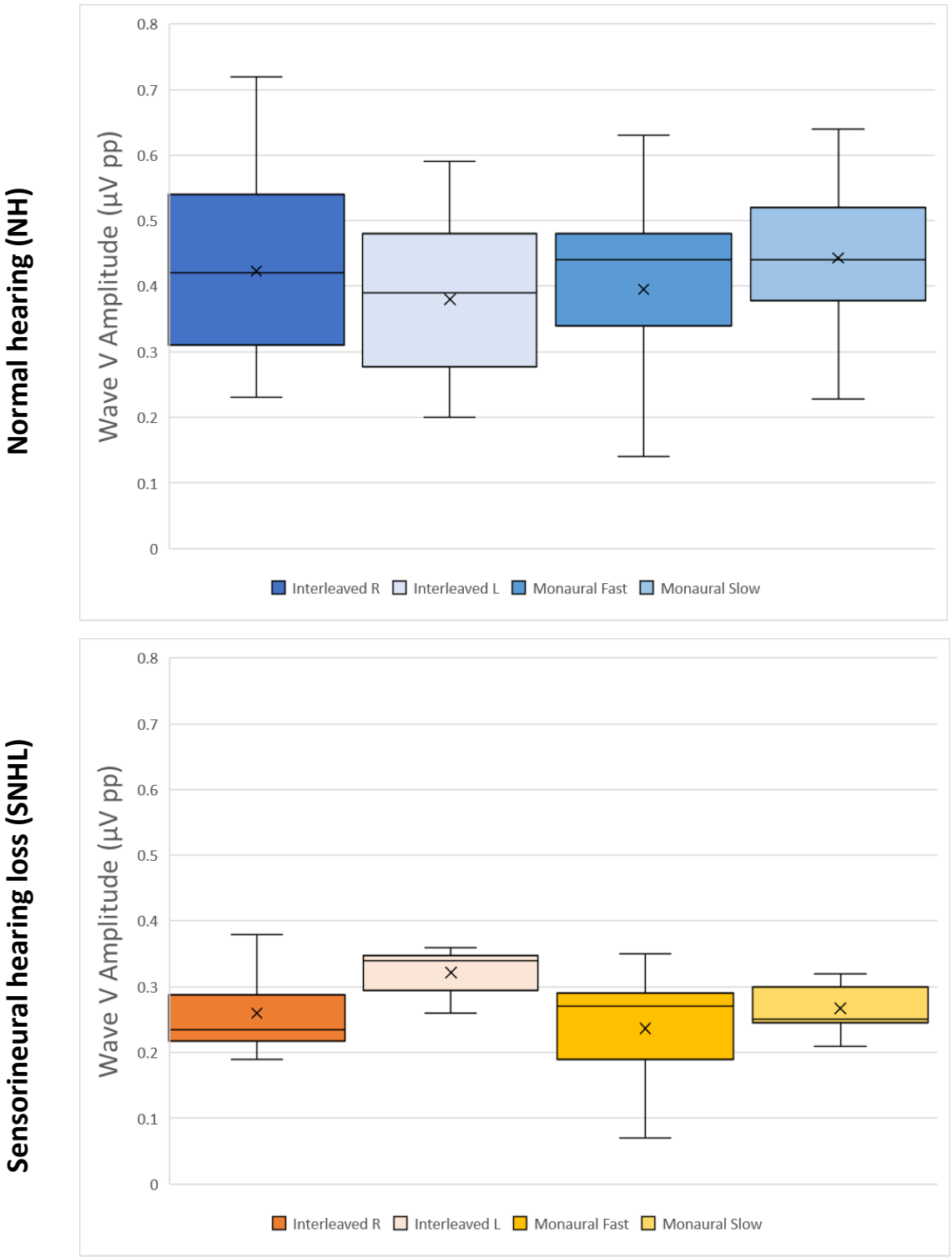
Descriptive of Wave V Amplitude (µV pp) Under the Different Click Stimulus Paradigms.

	Conditions	Mean	SE	Med.	SD	Min.	Max.
NH (n = 20)	Interleaved R	0.42	0.03	0.42	0.14	0.23	0.72
	Interleaved L	0.38	0.03	0.39	0.12	0.20	0.59
	Monaural Fast	0.40	0.03	0.44	0.13	0.14	0.63
	Monaural Slow	0.44	0.02	0.44	0.11	0.23	0.64
SNHL (n = 9)	Interleaved R	0.26	0.02	0.24	0.07	0.19	0.38
	Interleaved L	0.32	0.02	0.34	0.04	0.26	0.36
	Monaural Fast	0.24	0.03	0.27	0.10	0.07	0.35
	Monaural Slow	0.27	0.02	0.25	0.04	0.21	0.32

Note. SE, standard error of mean; Med., median; SD, standard deviation; Min., minimum; Max., maximum.

Figure 12

Effect of Click Stimulus Paradigms on Wave V Amplitudes (µV pp).

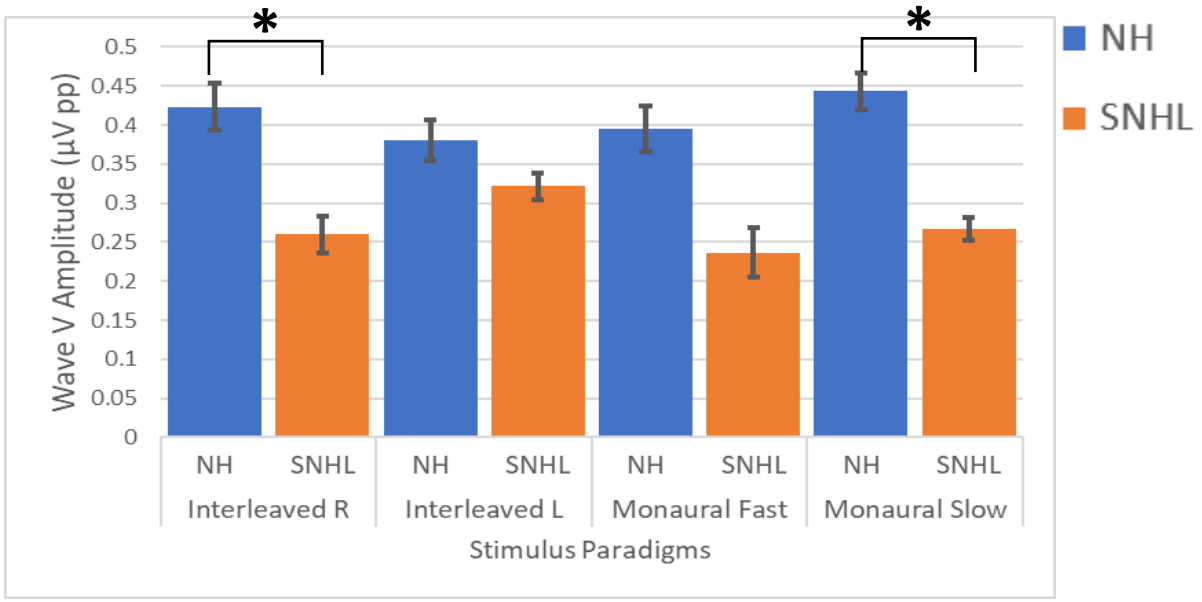


Note. Wave V amplitude of NH and SNHL participants measured under the interleaved, monaural fast and monaural slow conditions. The box plot depicts the minimum, lower quartile, median, upper quartile, and maximum of the data sets. Cross indicates the mean.

Main effect of stimulus was identified, $F(1, 23) = 9.08$, $p = .006$, $\eta^2_p = .283$. Post hoc comparisons showed that the mean wave V amplitudes in the interleaved R and monaural slow conditions are significantly larger in the NH compared to the SNHL group as shown in Figure 13 (interleaved R: $p = 0.016$; slow: $p = 0.001$) (the mean ± SEM of the conditions are shown in Table 10). No significant difference was identified in the interleaved L and monaural fast conditions. An ANOVA revealed that there was no significant main effect of stimulus within the same hearing status group. ($F(3, 69) = 0.228$, $p = 0.877$, $\eta^2_p = 0.010$). The post hoc showed significant difference in wave V amplitude between monaural slow and fast ($p = 0.016$) and between monaural slow and interleaved L as shown in Figure 14 ($p = 0.039$).

Figure 13

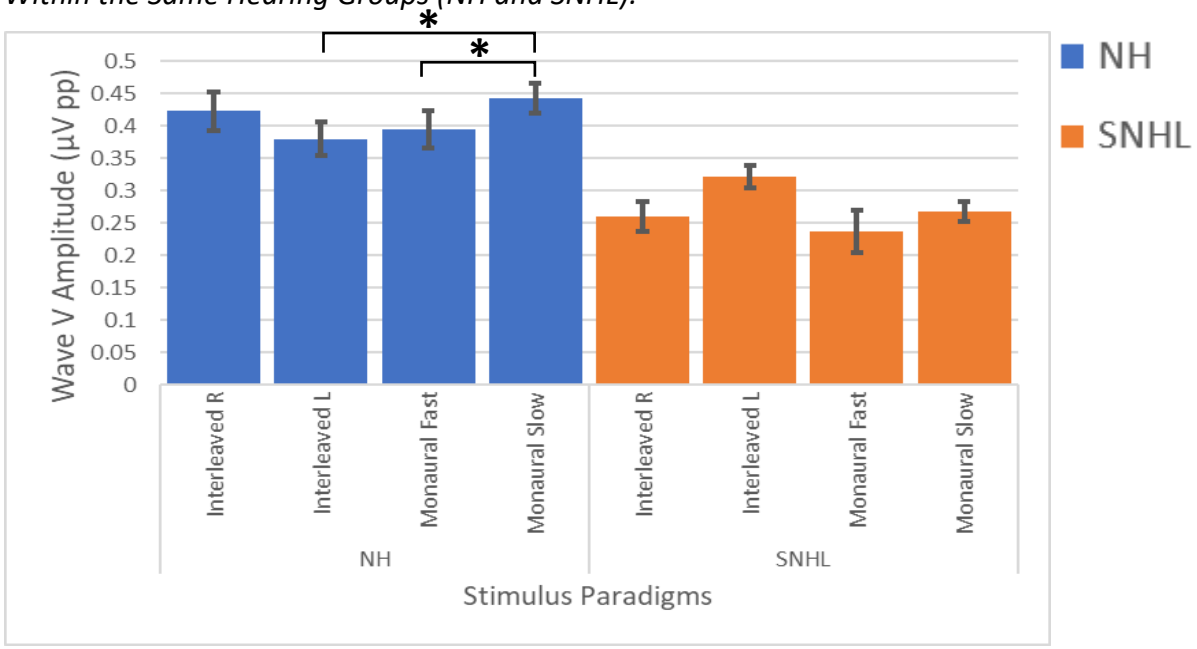
Effect of 70 dB nHL Click Stimulus Paradigms on the Mean Wave V Amplitudes (µV pp) of the NH Versus the SNHL group.



Note. The mean wave V amplitudes in the interleaved R and monaural slow conditions are significantly larger in the NH compared to the SNHL group. Histograms depict group means (± SEM). *, $p < 0.02$.

Figure 14

Effect of 70 dB nHL Click Stimulus Paradigms on the Mean Wave V Amplitudes (µV pp) Within the Same Hearing Groups (NH and SNHL).



Note. Only significant differences in the wave V amplitude between the monaural slow and fast ($p = 0.016$) and between the monaural slow and interleaved L ($p = 0.039$) were identified after ANOVA revealed no significant main effect of stimulus within the same hearing status group. Histograms depict group means (± SEM).

3.3 Effect of Click Stimulus Paradigms on the Mean Wave V Amplitude

Wave III latencies (ms) were recorded under the three stimulus conditions listed in Table 2 from the NH and SNHL groups are displayed in Table 11 and 12, respectively. The descriptive statistics test showed no significant skewness and kurtosis and the Mauchly's test of sphericity indicates that the assumption of sphericity was met. W (3) = 0.772, p = 0.434 as shown in Table 13. The values of minimum, lower quartile, median, upper quartile, and maximum of the data sets in Figure 15 are shown in Table 14.

Table 11

Wave III Latency (ms) Data – NH.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	4.42	4.98	5.46	4.26
Participant 2	5.19	4.62	5.10	4.64
Participant 3	4.01	4.55	5.12	4.30
Participant 4	4.55	4.42	-	4.53
Participant 5	4.08	4.17	5.48	4.08
Participant 6	4.35	-	4.46	4.46
Participant 7	4.03	-	4.05	3.94
Participant 8	4.69	4.37	5.10	4.89
Participant 9	4.12	4.44	4.53	4.08
Participant 10	4.96	4.28	4.83	4.92
Participant 11	4.03	4.64	3.96	4.8
Participant 12	3.62	4.53	4.42	4.58
Participant 13	4.76	4.37	4.8	4.69
Participant 14	4.46	4.55	4.92	4.37
Participant 15	4.37	4.98	4.73	4.62
Participant 16	4.05	4.39	4.26	4.17
Participant 17	4.89	-	5.32	-
Participant 18	4.39	4.49	4.98	4.67
Participant 19	4.19	4.8	4.89	4.58

Participant 20	4.64	4.83	-	4.58
Participant 21	4.51	4.49	4.98	4.46

Note. – indicates excluded outliers.

Table 12

Wave III Latency (ms) Data – SNHL.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	4.46	4.55	-	5.23
***Participant 2**	*	*	*	*
Participant 3	4.01	3.92	4.42	4.53
Participant 4	4.03	4.01	-	5.69
Participant 5	4.24	4.44	4.58	4.92
Participant 6	-	4.87	4.51	5.14
Participant 7	4.28	4.08	4.83	4.51
Participant 8	3.99	3.74	4.44	4.76
Participant 9	4.71	4.51	4.69	4.58
Participant 10	4.46	4.26	4.51	4.58

Note. *, indicates omitted data due to incomplete data points. –, indicates excluded outliers.

Table 13

Descriptive Statistics for Wave III Latencies (ms).

		Skewness (S)			Kurtosis (K)		
	Conditions	S	SE	|S/SE|	K	SE	|K/SE|
NH (n = 20)	Interleaved R	0.17	0.50	0.34	-0.11	0.97	0.12
	Interleaved L	0.59	0.54	1.10	-0.13	1.04	0.13
	Monaural Fast	-0.41	0.52	0.77	-0.45	1.01	0.44
	Monaural Slow	-0.35	0.51	0.69	-0.58	0.99	0.58

Table 13 cont.

Descriptive Statistics for Wave III Latencies (ms).

SNHL (n = 9)	Interleaved R	0.46	0.75	0.61	-0.82	1.48	-0.56
	Interleaved L	0.20	0.72	0.28	-0.70	1.40	-0.50
	Monaural Fast	1.03	0.79	1.30	0.36	1.59	0.22
	Monaural Slow	1.06	0.72	1.48	0.45	1.40	0.32

Table 14

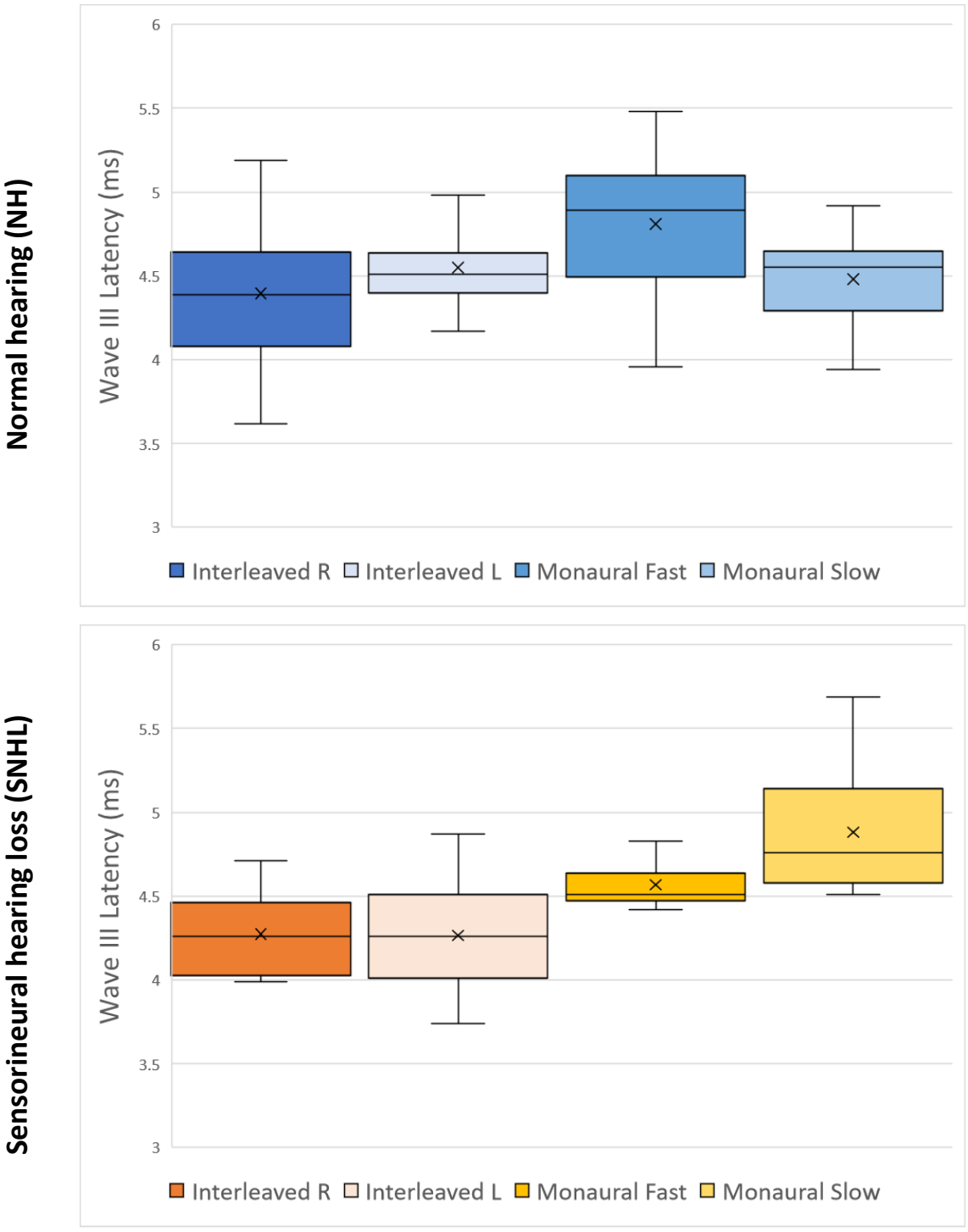
Descriptive of Wave III Latencies (ms) Under the Different Click Stimulus Paradigms.

	Conditions	Mean	SE	Med.	SD	Min.	Max.
NH (n = 20)	Interleaved R	4.40	0.08	4.39	0.38	3.62	5.19
	Interleaved L	4.55	0.05	4.51	0.23	4.17	4.98
	Monaural Fast	4.81	0.10	4.89	0.44	3.96	5.48
	Monaural Slow	4.48	0.06	4.55	0.27	3.94	4.92
SNHL (n = 9)	Interleaved R	4.27	0.09	4.26	0.26	3.99	4.71
	Interleaved L	4.26	0.12	4.26	0.36	3.74	4.87
	Monaural Fast	4.57	0.06	4.51	0.15	4.42	4.83
	Monaural Slow	4.88	0.13	4.76	0.40	4.51	5.69

Note. SE, standard error of mean; Med., median; SD, standard deviation; Min., minimum; Max., maximum.

Figure 15

Effect of Click Stimulus Paradigms on Wave III Latencies (ms).

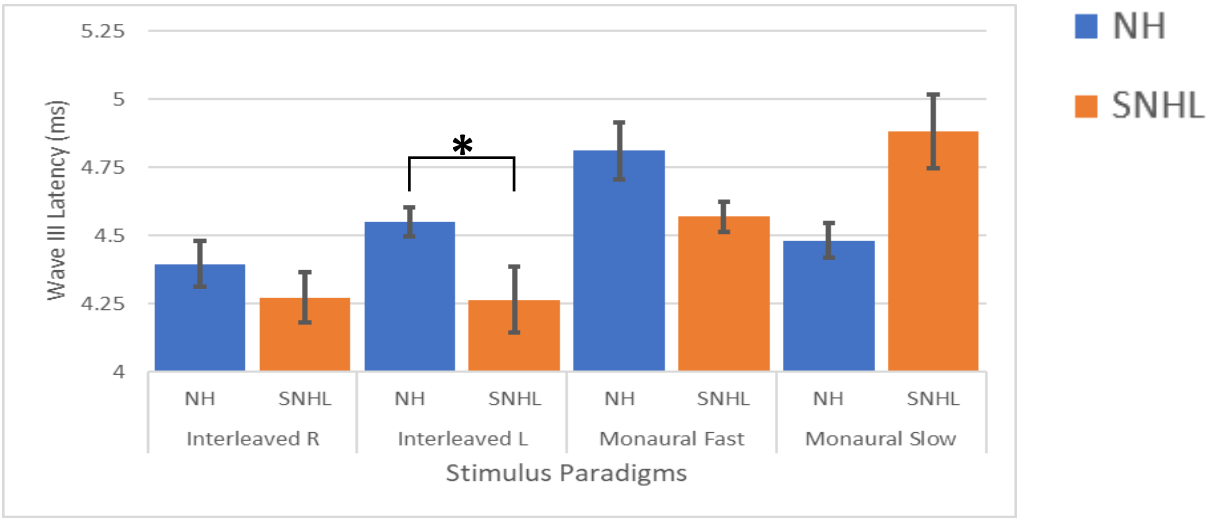


Note. Wave III latency of NH and SNHL participants measured under the interleaved, monaural fast and monaural slow conditions. The box plot depicts the minimum, lower quartile, median, upper quartile, and maximum of the data sets. Cross indicates the mean.

The ANOVA indicated no significant main effect of stimulus, $F(1, 20) = 2.70$, $p = 0.116$, $\eta^2_p = 0.119$. As shown in Figure 16, no significant delays in wave III latencies were found when comparing between hearing groups, except in the interleaved L where NH group had significantly longer latency than the SNHL group ($p = 0.004$; the mean ± SEM of each condition can be found in Table 14).

Figure 16

Effect of 70 dB nHL Click Stimulus Paradigms on the Mean Wave III Latencies (ms) of the NH Versus the SNHL group.

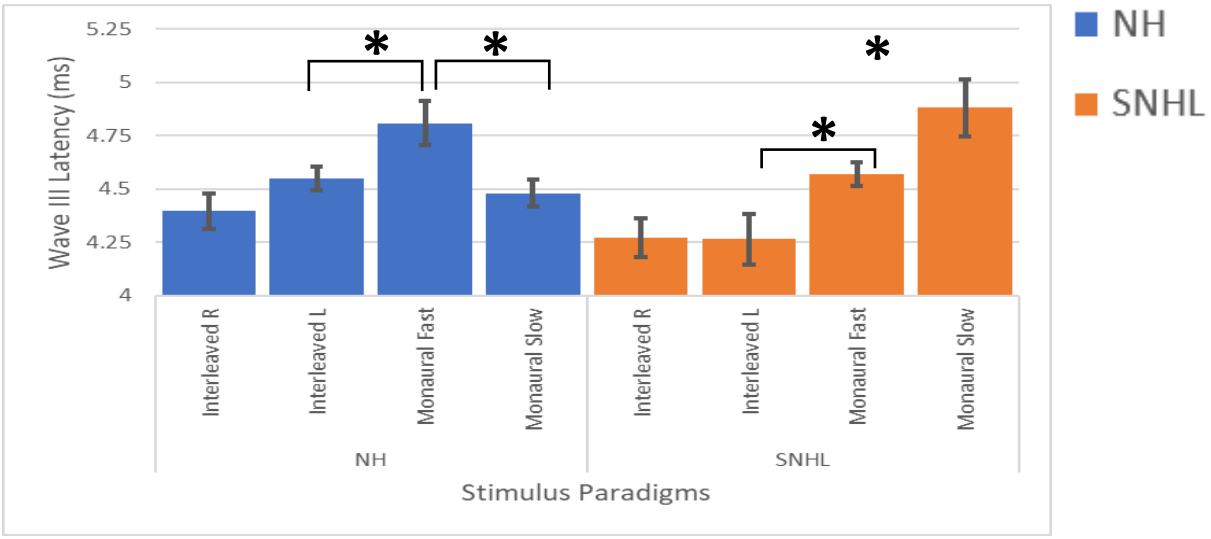


Note. No significant delays in wave III latencies were found when comparing between the hearing groups, except in the interleaved L. Histograms depict group means (± SEM). *, $p = 0.004$.

A significant main effect of stimulus was identified and post hoc findings are described in the following, $F(3, 60) = 7.41$, $p < .001$, $\eta^2_p = 0.270$. The latency of NH monaural fast was significantly longer than the other stimulus conditions of the same hearing status (NH) group as indicated in Figure 17 (interleaved R: $p < 0.001$; interleaved L: $p = 0.009$; slow: $p = 0.01$). In the SNHL group, interleaved R was significantly shorter than the monaural slow condition ($p = 0.022$) whereas the interleaved L had a significantly shorter mean wave III latencies compared to the monaural conditions (fast: $p = 0.024$; slow: $p = 0.002$).

Figure 17

Effect of 70 dB nHL Click Stimulus Paradigms on the Mean Wave III Latencies (ms) Within the Same Hearing Groups (NH and SNHL).



Note. The latency of NH monaural fast was significantly longer than the other stimulus conditions in the same hearing status group. In the SNHL group, interleaved R was significantly shorter than the monaural slow condition whereas the interleaved L had a significantly shorter mean wave III latencies compared to the monaural conditions (fast and slow). Histograms depict group means (± SEM). *, $p < 0.03$.

3.4 Effect of Click Stimulus Paradigms on the Mean Wave III Amplitude

Wave III amplitudes (µV pp) were recorded under the three stimulus conditions listed in Table 2 from the NH and SNHL groups are displayed in Table 15 and 16, respectively. The descriptive statistics test as displayed in Table 17 showed no significant skewness and kurtosis and the Mauchly's test of sphericity indicates that the assumption of sphericity was met. W (3) = 0.762, p = 0.265. The values of minimum, lower quartile, median, upper quartile, and maximum of the data sets in Figure 18 are shown in Table 18.

Table 15

Wave III Amplitude (µV pp) Data – NH.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	0.17	0.23	0.13	0.19
Participant 2	0.09	0.08	0.05	0.16
Participant 3	0.11	0.03	0.18	0.06
Participant 4	0.16	0.18	0.11	0.14
Participant 5	-	-	0.18	0.32
Participant 6	0.06	0.16	0.11	0.07
Participant 7	-	-	-	-
Participant 8	0.11	0.09	0.16	0.10
Participant 9	0.15	0.11	0.05	0.20
Participant 10	0.13	0.11	0.15	0.15
Participant 11	0.01	0.1	0.03	0.07
Participant 12	0.07	0.03	0.07	0.07
Participant 13	0.10	0.12	0.10	0.12
Participant 14	0.13	0.19	0.10	0.18
Participant 15	0.04	0.10	0.14	0.02
Participant 16	-	0.18	0.10	0.35
Participant 17	0.10	0.25	0.08	0.07
Participant 18	0.14	0.19	0.09	0.24
Participant 19	0.07	0.09	0.08	0.03

Participant 20	0.18	0.05	0.148	0.14
Participant 21	0.06	0.09	0.08	0.23

Note. –, indicates excluded outliers.

Table 16

Wave III Amplitude (µV pp) Data – SNHL.

	Interleaved R	Interleaved L	Monaural Fast	Monaural Slow
Participant 1	0.05	0.17	0.03	0.07
***Participant 2**	*	*	*	*
Participant 3	0.17	0.17	0.05	0.13
Participant 4	0.22	0.2	0.23	0.19
Participant 5	0.07	0.11	0.01	0.02
Participant 6	0.09	0.14	0.13	0.02
Participant 7	0.02	0.14	0.02	0.04
Participant 8	0.03	0.05	0.07	0.10
Participant 9	0.06	0.07	0.14	0.18
Participant 10	0.15	0.12	0.05	0.03

Note. *, indicates omitted data due to incomplete data points. –, indicates excluded outliers.

Table 17

Descriptive Statistics for Wave III Amplitude (µV pp).

		Skewness (S)			Kurtosis (K)		
	Conditions	S	SE	|S/SE|	K	SE	|K/SE|
NH (n = 20)	Interleaved R	-0.23	0.54	0.43	-0.63	1.04	0.61
	Interleaved L	0.37	0.52	0.70	-0.68	1.01	0.67
	Monaural Fast	0.14	0.51	0.28	-0.73	0.99	0.74
	Monaural Slow	0.75	0.51	1.46	0.10	0.99	0.10

Table 17 cont.

Descriptive Statistics for Wave III Amplitude (µV pp).

SNHL (n = 9)	Interleaved R	0.80	0.72	1.12	-0.58	1.40	0.41
	Interleaved L	-0.37	0.72	0.52	-0.53	1.40	0.38
	Monaural Fast	1.22	0.72	1.70	0.98	1.40	0.70
	Monaural Slow	0.60	0.72	0.83	-1.29	1.40	0.92

Table 18

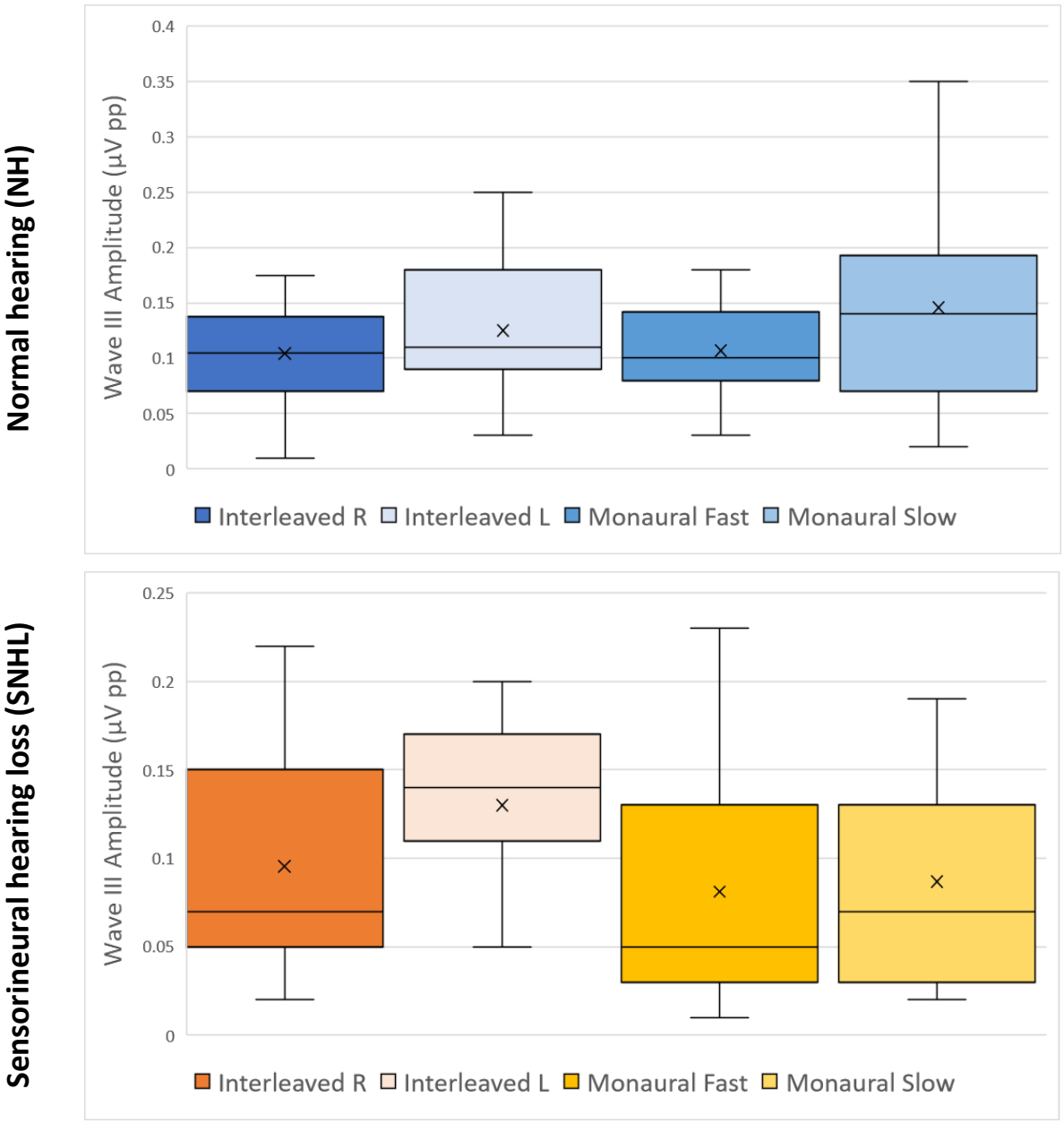
Descriptive of Wave III Amplitude (µV pp) Under the Different Click Stimulus Paradigms.

	Conditions	Mean	SE	Med.	SD	Min.	Max.
NH (n = 20)	Interleaved R	0.10	0.01	0.11	0.05	0.01	0.18
	Interleaved L	0.13	0.01	0.11	0.06	0.03	0.25
	Monaural Fast	0.11	0.01	0.10	0.04	0.03	0.18
	Monaural Slow	0.15	0.02	0.14	0.09	0.02	0.35
SNHL (n = 9)	Interleaved R	0.10	0.02	0.07	0.07	0.02	0.22
	Interleaved L	0.13	0.02	0.14	0.05	0.05	0.20
	Monaural Fast	0.08	0.02	0.05	0.07	0.01	0.23
	Monaural Slow	0.09	0.02	0.07	0.07	0.02	0.19

Note. SE, standard error of mean; Med., median; SD, standard deviation; Min., minimum; Max., maximum.

Figure 18

Effect of Click Stimulus Paradigms on Wave III Amplitudes (µV pp).

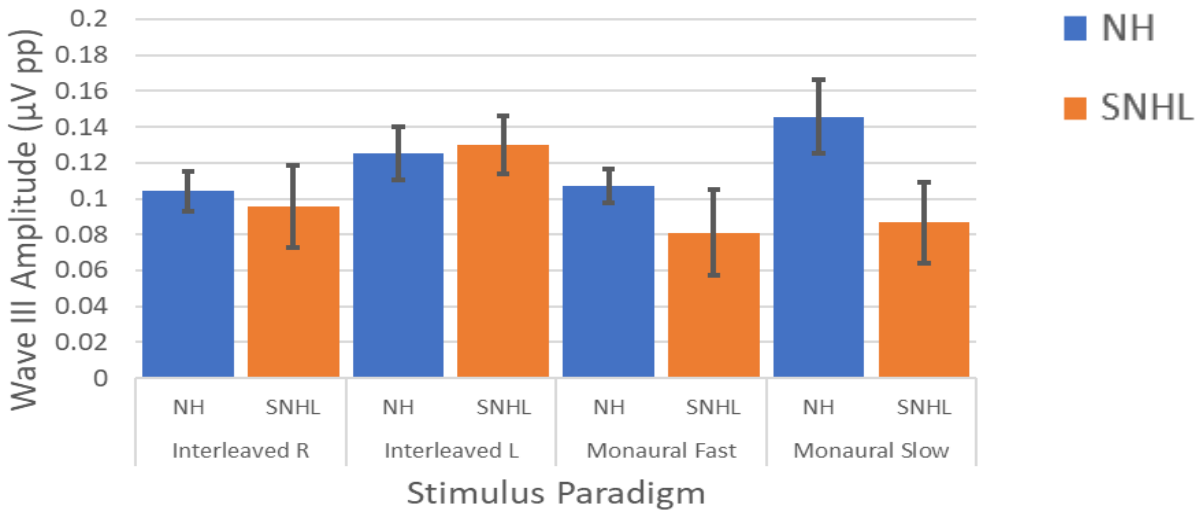


Note. Wave III amplitude of NH and SNHL participants measured under the interleaved, monaural fast and monaural slow conditions. The box plot depicts the minimum, lower quartile, median, upper quartile, and maximum of the data sets. Cross indicates the mean.

The ANOVA showed no significant main effect of stimulus between NH and SNHL under the same stimulus condition, as shown in Figure 19, $F(1, 25) = 0.841$, $p = 0.368$, $\eta^2_p = 0.033$. Within the same hearing status group, no main effect of stimulus was identified, as shown in Figure 20, $F(3, 75) = 2.049$ $p = 0.114$, $\eta^2_p = 0.076$.

Figure 19

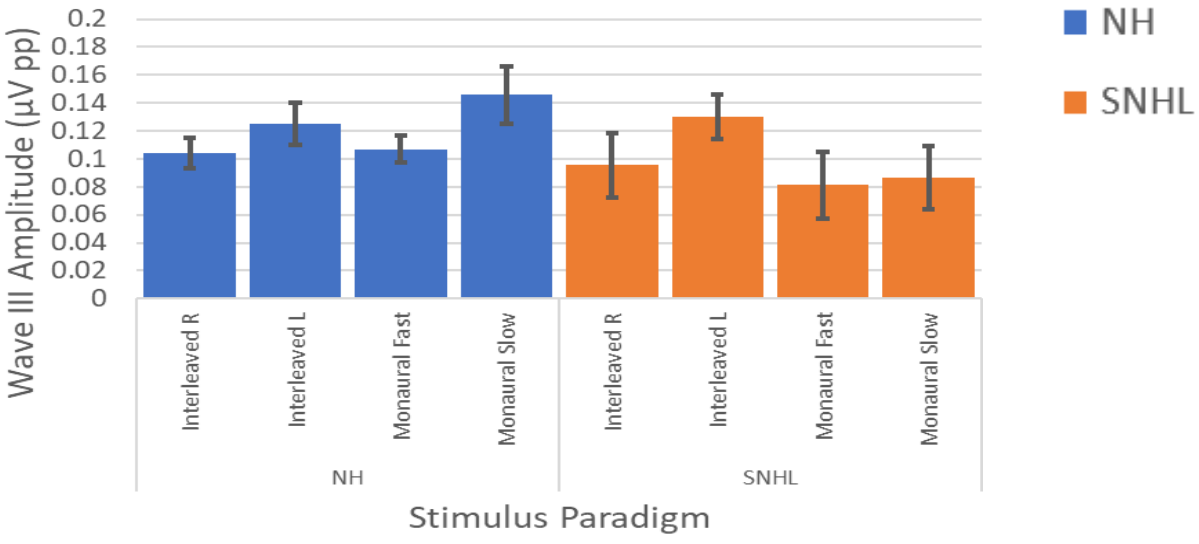
Effect of Click Stimulus Paradigms on the Mean Wave III Amplitudes (µV pp) of the NH Versus the SNHL group.



Note. No significant difference was identified across all groups.

Figure 20

Effect of Click Stimulus Paradigms on the Mean Wave III Amplitudes (µV pp) Within the Same Hearing Groups (NH and SNHL).



Note. All groups had no significant difference in the mean wave III amplitudes.

4 Discussion

Wave V Latency

The results demonstrated the interleaving clicks presented at a rate of 45.5/s peripherally (90.1/s centrally) does not prolong the ABR wave V latency when compared to the same stimulated ear presented with the conventional slow rate (clicks delivered monaurally at a rate of 45.5/s). Furthermore, the monaural fast (clicks delivered monaurally at a rate of 90.91/s) condition evoked ABRs which had significantly delayed wave V latency compared to the monaural slow and interleaved conditions of the same ear. It was expected that the monaural fast condition would result in the delay in wave V latency in both the NH and SNHL individuals (Don et al., 1977; Fowler & Noffsinger, 1983; Stevens et al., 2013). If the adaptation were to occur centrally, the interleaving clicks would evoke ABRs with delayed wave V latency similar to that of the monaural fast condition. This is because the rate presented to the central auditory pathway would be the same between the interleaved and monaural fast conditions. Our findings showed a significant difference in wave V latency between the interleaved R and monaural fast conditions in both the NH and SNHL groups. Thus, the results support the notion that neural adaptation and fatigue occurs peripherally of the ascending auditory pathway where no delay in wave V latency was found when interleaved clicks are presented at a slow rate peripherally, regardless of the presence of sensorineural lesion (Bencito, 2020; Don et al., 1977; Eggermont & Odenthal, 1974).

Wave V Amplitude

The wave V amplitude of the NH group was expected to be significantly larger than the SNHL group. This was, however, only observed in the interleaved R and monaural slow conditions. Compared to many of the studies examining the rate effect on wave V amplitude, the significant reduction observed in the study may be attributed to the vertical montage where wave V amplitude is the most prominent of all the other montages (Beattie et al., 1986; Dzulkarnain et al., 2007; Howard, 2017; King & Sininger, 1992; Stuart et al., 1996). However, it is important to note, the differences in wave V amplitude between NH and SNHL groups were not observed in the interleaved L and monaural fast conditions. There were several outliers in the interleaved L data which may have attributed to said observation. In regard to the monaural fast condition, the effect of fast rates on wave amplitudes reduction may have resulted in less noticeable significant difference from the

sample of this study (Hall, 2007; Picton, 2011; Pratt & Sohmer, 1976). Although not significant, but the monaural fast conditions had the smallest wave V amplitude compared to other stimulus conditions. In addition, the variation in sensorineural lesion of the SNHL group could have resulted in the large standard deviation in the sample, hence affecting the subsequent analyses. On the other hand, the wave V amplitude of the interleaved R and monaural slow conditions showed no significant difference in both NH and SNHL groups. This is consistent with Bencito, 2020. However, there was a significant reduction in wave V amplitude of the monaural fast condition compared to the slow rate which was not reported in Bencito's study (Bencito, 2020). This may be due to small sample size, or the bias introduced during the visual inspection of the ABR data in early analysis stage. In the SNHL group of this study, no significant in wave V amplitude was observed across all conditions. This may be due to the nature of the cochlear sensorineural lesion (peripheral) since the sensation level would be comparatively lower to the sensation level of the NH individuals when the same 70dB nHL clicks were presented to all subjects. This means a lower intensity level would have been presented to the SNHL individuals and the intensity effect on wave V amplitude would not be the same.

Wave III Latency and Amplitude

Interestingly, the wave III latency comparison between the NH and SNHL groups under the same stimulus paradigm showed no significant difference except in the interleaved L condition. Furthermore, the pattern of the results in all stimulus conditions except monaural slow indicated a shorter latency in the SNHL group. The wave component labelling may have contributed to the obscured finding as the presence of wave III is unreliable in vertical montage. The SNHL group was expected to have a reduced wave amplitude which can further complicate the data point marking process and introduce biased results. Nevertheless, in the NH group, the interleaving clicks did not prolong the wave III latency when compared to the same stimulated ear presented with the conventional slow rate (monaural slow). Moreover, the monaural fast condition showed a significant delayed in the wave III latency when compared to both the monaural slow and the interleaved conditions. Our findings demonstrated the potential use of interleaving paradigm to quicken the acquisition process. However, in cases where wave III latency is of interest, such as the use of diagnostic indicators of I-III and III-V interpeak latencies in neuropathology studies,

ipsilateral electrode montage should be used instead of the vertical montage used in this study. As expected, in the SNHL group, the monaural fast condition significantly delayed the wave III latency compared to the monaural slow. However, the significant delay was not observed when compared to the interleaved R condition. In addition, the monaural fast condition of the SNHL group showed significantly prolonged wave III latency compared to the interleaved L, despite no significant difference in the latency were found between the interleaved ears. The interpretation of the wave III amplitude data, and from which to substantiate the literature were expected to be difficult for a number of reasons pointed out previously. Firstly, the small neural activity measured using the vertical electrode montage, and secondly, wave III is not the most easily identified component of an ABR waveform. Altogether, making extracting accurate information using the current subjective method for the subsequent statistical analyses difficult and highly susceptible to bias. Clearly, a more robust and objective process of ABR waveform component labelling would improve the validity of data analysis (further discussion in subsequent section). Furthermore, a better understanding of the origin of the wave III neuroactivities would allow a more appropriate electrode montage implementation.

Study Limitations and Future Research Implications

The current study only used the wave latency and amplitude to examine the effect of interleaved clicks. Both parameters are somewhat biased as they rely on the subjective visual interpretation of the ABR waveforms. An inclusion of an objective parameter such as the fsp value would increase the validity of the results. The fsp was recorded concurrently during ABR acquisition, however, was not reported as many of the SNHL individuals did not reach 3.1 and resulted in insufficient sample size for meaningful analysis. Fsp is determined by the difference of the averaged waveform to the difference of the background noise level (Elberling & Don, 1984), though the background noise was not expected to change, the difference in response quality and the amplitude difference observed in some of the groups could have an impact on the fsp. Future study should include an objective measure of the ABR (e.g., fsp, fmp, Hotelling's T^2) to yield additional SNR data in the study (Lightfoot et al., 2019; Stevens et al., 2013).

Systematic error in wave identification was occasionally noted despite wave V peaks and troughs being more easily identifiable with the vertical electrode montage. The merge

with the succeeding wave VI can make the identification less precise. This was minimised by having consistency across multiple independent assessors who were marking the wave components. Although the number of males and females in each group (NH and SNHL) were relatively equal, in order to investigate whether biological sex has an impact in combination with the rate effect, a larger sample size would be required to maintain the statistical power of the study of the same effect size. This was not explored in this study due to the timeframe. We also noted the disparity between the average age of the NH and SNHL groups. However, age-related changes in ABR have been shown to be independent to hearing loss (Grose et al., 2019; Konrad-Martin et al., 2012). Thus, the difference in mean age between the NH and SNHL groups should not have a significant effect on the measured ABRs.

Limitations of the custom written ABR recording software meant that the acquisition time required from the start to the end of interleaved condition did not appear to be consistent with the theorised acquisition time. The interleaved paradigm took considerably longer time than theoretical calculations would predict, and this is likely to be due to processing ability of the recording device. Therefore, hardware of the acquisition system which supports the processing speed required for the ABR acquisition should be used in order to see the benefit of the interleaved clicks in real time. On the whole, the aims of the study were to demonstrate the interleaved paradigm is similar to monaural slow and significantly shorter than the monaural fast condition, using wave V latency as a precursory parameter to establish whether the SN (peripheral) lesions would affect the use of interleaved paradigm. Therefore, the findings of this study still provide valuable insight to the site of fatigue and the practicality of interleaved paradigm in clinical setting.

A parallel project which used the same stimulus design as this study examined the use of interleaved clicks in cortical auditory evoked potentials in NH adults. Based on the unpublished data where no significant difference was found in the N1-P1-N2 complex latencies between conventional monaural slow rate and the interleaved condition. Furthermore, the monaural fast rate evoked significantly longer interleaved N1-P1-N2 complex latency compared to the interleaved condition (Nofal, 2022). These findings suggest the time saving benefit of interleaved clicks stimulus is also applicable in the AEPs higher up in the auditory system. Other studies which reduced the peripheral adaptation by

using different interleaved stimulus designs showed the possibilities of optimising the current ABR procedure. For example, Burna et al. (2020) who took advantage of the tonotopic tuning of the auditory nerve designed a train of tones ordered by frequencies. The study showed not only the interleaved ramp shortens the wave I latency, but the stimulus frequency ramp design also improved the wave I amplitude. The rapid acquisition of ABR (high rates) with the interleaved design of this study and others can be beneficial in the detection of neuropathologies (Burkard et al., 2007; Hood, 1998).

Stimulus intensity, auditory maturation state and types of hearing loss are known factors that can affect the ABR. Future studies on the use of the interleaved clicks paradigm at various intensities and in other groups of the population such as children and in adults with conductive HL or retrocochlear SNHL could provide further insights into its applicability clinically. In addition, the ability of the custom multi-channel Te Pihareinga software used in this study has the capacity of delivering multiple different stimuli at various types (e.g., tone-bursts and chirps), rates, and intensity. For example, the advantage of chirp stimulus in evoking synchronous neural activity, thus, augmenting the wave amplitudes, could be used to circumvent the inability to clearly identify the wave components in this study. The optimisation of the current stimulus paradigm is feasible with the custom software and further investigation could provide insights into the functional pathological changes in the auditory periphery.

5 Conclusion

In conclusion, the effect of interleaved clicks stimulus paradigm on wave V latency was demonstrated in the NH group by Bencito, 2020 and the SNHL subjects in this study. Our findings support the underlying notion that the adaptation mechanisms occur in the auditory periphery. Furthermore, the interleaved paradigm demonstrated the potential in allowing a more efficient acquisition time compared to the current protocol which uses the sequential method and elicits ABRs at a slower rate. This ability to evoke ABR data from both ears concurrently at a fast rate would be valuable clinically in terms of the overall ABR acquisition time savings. Another advantage offered by this stimulus paradigm is its potential increase in the likelihood of obtaining sufficient diagnostic information in difficult to test patients where the timeframe of optimal recording condition is limited.

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Appendices

Appendix A – Study Information Sheet (NH and SNHL)

NH

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2 March 2021
HEC Ref: 2021/34

Interleaved Recording of the Auditory Brainstem Response
Information Sheet for Persons Participating in Research Studies

Our names are Regina Lien and Shatha Nofal, and we are 2nd year Master of Audiology students conducting research on the auditory brainstem response (ABR). The goal is to determine if using an interleaved (also known as alternating) method of presenting sounds in ABR recordings will offer advantages the quality of the response and reduce the time it takes to complete the test.

You have been approached to take part in this study because you are over 18 years old, have normal hearing, and are able to have the auditory brainstem response recorded. If you choose to take part in this study, we will ask about a history of your ear health and hearing and have a look at your ears. You will then have a hearing test. In-ear headphones will be used to play tones at different pitches to determine your hearing threshold. You will be asked to press a button when you hear the tones. This will take about 20 minutes.

After the hearing test, we will begin the ABR test. You will be asked to sit in a comfortable armchair in a relaxed position. While you are sitting comfortably, we will measure tiny electrical signals from your scalp that are produced by the brain in response to sound (the "auditory brain-stem response"). Using a tissue and some cleaning alcohol, we will first lightly exfoliate the skin by rubbing firmly with an alcohol wipe in places where the adhesive sensors will be placed to make sure they can pick up the tiny signals. Sounds will be played through earphones placed on both ears while we record the signals. During tests, you don't have to do anything except sit and relax. After testing, the sensors will be carefully removed, and the session will be finished.

The procedures in this study are the same procedures a client would normally encounter in a hearing evaluation. When cleaning and preparing electrode sites the skin is lightly exfoliated (rubbed firmly with an alcohol wipe), which can occasionally cause these areas to be reddened. Alcohol hand cleaner will also be used, which can sometimes cause skin irritation, but if this occurs, a soothing cream will be provided. There is always a risk of emotional distress when undertaking hearing-related research. For most participants, this risk is no greater than the risk any adult would normally experience when consulting for hearing services, as most of the procedures in this study are the same procedures a client would normally encounter in a hearing evaluation (i.e., there is no deviation from the normal clinic protocol used by the University of Canterbury). There is the possibility that the placement of electrodes during ABR testing could trigger some sort of anxiety, but

this would be an extremely rare occurrence - the procedure is generally low stress, and we encourage the clients to be relaxed or even asleep so the waveforms can be more robust and therefore easier to interpret.

Participation is voluntary and you have the right to withdraw at any stage without penalty. You may ask for your raw data to be returned to you or destroyed at any point. If you withdraw, I will remove information relating to you. However, once analysis of the raw data starts on 1 August, it will no longer be possible to remove your data as it will be integrated with other data. Participants will receive $20 petrol vouchers as a token of appreciation.

The results of the project may be published as part of a Master's thesis or in a journal article. But you may be assured of the complete confidentiality of data gathered in this investigation: your identity will not be made public. To ensure confidentiality, participants will be assigned an ID number. Data (hearing history sheet, hearing test results, speech perception test results) will contain only the participant ID. The data will be stored securely and may only be accessed by the primary researcher and thesis supervisors. Identifying information (consent forms, release of information forms, and requests for study results) will be stored securely and separately from the data. The stored data will be destroyed after 5 years. A thesis is a public document and will be available through the UC Library.

Please indicate to the researcher on the consent form if you would like to receive a copy of the summary of results of the project.

The project is being carried out as a requirement for a Master of Audiology thesis by Shatha Nofal and Regina Lien under the supervision of Greg O'Beirne, who can be contacted at gregory.obeirne@canterbury.ac.nz. He will be pleased to discuss any concerns you may have about participation in the project.

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee, and participants should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

If you agree to participate in the study, you are asked to complete the consent form and return to Shatha Nofal and Regina Lien, contacted through email at shatha.nofal@pg.canterbury.ac.nz and regina.lien@pg.canterbury.ac.nz.

SNHL

School of Psychology, Speech and Hearing
Telephone: +64 33694313
Email: regina.lien@pg.canterbury.ac.nz and
shatha.nofal@pg.canterbury.ac.nz
2 March 2021
HEC Ref: 2021/34

Interleaved Recording of the Auditory Brainstem Response
Information Sheet for Persons Participating in Research Studies

Our names are Regina Lien and Shatha Nofal, and we are 2nd year Master of Audiology students conducting research on the auditory brainstem response (ABR). The goal is to determine if using an interleaved (also known as alternating) method of presenting sounds in ABR recordings will offer advantages the quality of the response and reduce the time it takes to complete the test.

You have been approached to take part in this study because you are over 18 years old, have a hearing loss, and are able to have the auditory brainstem response recorded. If you choose to take part in this study, we will ask about a history of your ear health and hearing and have a look at your ears. You will then have a hearing test. In-ear headphones will be used to play tones at different pitches to determine your hearing threshold. You will be asked to press a button when you hear the tones. This will take about 20 minutes.

After the hearing test, we will begin the ABR test. You will be asked to sit in a comfortable armchair in a relaxed position. While you are sitting comfortably, we will measure tiny electrical signals from your scalp that are produced by the brain in response to sound (the "auditory brain-stem response"). Using a tissue and some cleaning alcohol, we will first lightly exfoliate the skin by rubbing firmly with an alcohol wipe in places where the adhesive sensors will be placed to make sure they can pick up the tiny signals. Sounds will be played through earphones placed on both ears while we record the signals. During tests, you don't have to do anything except sit and relax. After testing, the sensors will be carefully removed, and the session will be finished.

The procedures in this study are the same procedures a client would normally encounter in a hearing evaluation. When cleaning and preparing electrode sites the skin is lightly exfoliated (rubbed firmly with an alcohol wipe), which can occasionally cause these areas to be reddened. Alcohol hand cleaner will also be used, which can sometimes cause skin irritation, but if this occurs, a soothing cream will be provided. There is always a risk of emotional distress when undertaking hearing-related research. For most participants, this risk is no greater than the risk any adult would normally experience when consulting for hearing services, as most of the procedures in this study are the same procedures a client would normally encounter in a hearing evaluation (i.e., there is no deviation from the normal clinic protocol used by the University of Canterbury). There is the possibility that

the placement of electrodes during ABR testing could trigger some sort of anxiety, but this would be an extremely rare occurrence - the procedure is generally low stress, and we encourage the clients to be relaxed or even asleep so the waveforms can be more robust and therefore easier to interpret.

Participation is voluntary and you have the right to withdraw at any stage without penalty. You may ask for your raw data to be returned to you or destroyed at any point. If you withdraw, I will remove information relating to you. However, once analysis of the raw data starts on 1 August, it will no longer be possible to remove your data as it will be integrated with other data. Participants will receive $20 petrol vouchers as a token of appreciation.

The results of the project may be published as part of a Master's thesis or in a journal article. But you may be assured of the complete confidentiality of data gathered in this investigation: your identity will not be made public. To ensure confidentiality, participants will be assigned an ID number. Data (hearing history sheet, hearing test results, speech perception test results) will contain only the participant ID. The data will be stored securely and may only be accessed by the primary researcher and thesis supervisors. Identifying information (consent forms, release of information forms, and requests for study results) will be stored securely and separately from the data. The stored data will be destroyed after 5 years. A thesis is a public document and will be available through the UC Library.

Please indicate to the researcher on the consent form if you would like to receive a copy of the summary of results of the project.

The project is being carried out as a requirement for a Master of Audiology thesis by Shatha Nofal and Regina Lien under the supervision of Greg O'Beirne, who can be contacted at gregory.obeirne@canterbury.ac.nz. He will be pleased to discuss any concerns you may have about participation in the project.

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee, and participants should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

If you agree to participate in the study, you are asked to complete the consent form and return to Shatha Nofal and Regina Lien, contacted through email at shatha.nofal@pg.canterbury.ac.nz and regina.lien@pg.canterbury.ac.nz.

Appendix B – Study Consent Form

School of Psychology, Speech and Hearing
Telephone: +64 33694313
Email: regina.lien@pg.canterbury.ac.nz and
shatha.nofal@pg.canterbury.ac.nz
2 March 2021

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Interleaved recording of the Auditory Brainstem Response
Consent Form for Persons Participating in Research Studies

- ☐ I have been given a full explanation of this project and have had the opportunity to ask questions.
- ☐ I understand what is required of me if I agree to take part in the research.
- ☐ I understand that participation is voluntary and I may withdraw at any time without penalty. Withdrawal of participation before 1 August will also include the withdrawal of any information I have provided. It will not possible to remove the influence of your data on the results after 1 August.
- ☐ I understand that any information or opinions I provide will be kept confidential to the researcher and their primary supervisor and that any published or reported results will not identify the participants. I understand that a thesis is a public document and will be available through the UC Library.
- ☐ I understand that all data collected for the study will be kept in locked and secure facilities and/or in password protected electronic form and will be destroyed after five years.
- ☐ I understand the risks associated with taking part and how they will be managed.
- ☐ I understand that I can contact the researchers Shatha Nofal (shatha.nofal@pg.canterbury.ac.nz) and Regina Lien (regina.lien@pg.canterbury.ac.nz) or supervisor Greg O'Beirne (gregory.obeirne@canterbury.ac.nz) for further information. If I have any complaints, I can contact the Chair of the University of Canterbury Human Ethics Committee, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz)
- ☐ I would like a summary of the results of the project.
- ☐ By signing below, I agree to participate in this research project.

Name:_____ Signed:_____ Date:_____

Email address *(for report of findings, if applicable)*:

_____

Please return form to Shatha Nofal (shatha.nofal@pg.canterbury.ac.nz) or Regina Lien (regina.lien@pg.canterbury.ac.nz)

Appendix C – Study Recruitment Advertisement Material

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Email Invitation

Hi everyone,

VOLUNTEERS NEEDED!

We are developing a new way to monitor hearing. This test will use two earphones in either ear. We will play sounds through these two speakers and measure tiny electrical signals from your skin. We will measure responses from two different types of signals: one ear at a time and both ears at the same time.

If you are:

- 18 years of age or older
- have a hearing loss

Then we would like to hear from you!

This study will take place at the University of Canterbury Speech and Hearing Clinic throughout 2021.

You would be needed for one 2 hour session, during this time you will:

- receive a free hearing test
- help to develop a new hearing monitoring technique
- receive a $20 fuel voucher as a token of our appreciation.

For more information, or to be involved in this project, please contact **Shatha Nofal (shatha.nofal@pg.canterbury.ac.nz) or Regina Lien (regina.lien@pg.canterbury.ac.nz)**
Thank you for reading ☺

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee

Appendix D – Human Ethics Committee Research Approval

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

HUMAN ETHICS COMMITTEE

Secretary, Rebecca Robinson
Telephone: +64 03 369 4588, Extn 94588
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2021/34

2 June 2021

Hsin-Jui (Regina) Lien and Shatha Nofal
School of Psychology, Speech and Hearing
UNIVERSITY OF CANTERBURY

Dear Hsin-Jui (Regina) and Shatha

The Human Ethics Committee advises that your research proposal "Interleaved Recording of the Auditory Brainstem Response" has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your email of 28th May 2021.

Best wishes for your project.

Yours sincerely

Dr Dean Sutherland
Chair
University of Canterbury Human Ethics Committee

Appendix E – Air Conduction Audiometric Thresholds for All Participants

NH

Participant				Frequency (kHz)								
#	Age	Sex	Ear	0.25	0.5	1	2	3	4	6	8	Average
1	29	F	R	10	5	5	10	5	5	5	0	6.3
			L	10	5	5	5	5	5	0	5	5.0
2	26	F	R	5	5	5	10	0	10	10	5	7.5
			L	10	10	10	10	5	0	0	5	7.5
3	38	M	R	10	10	5	0	-5	0	0	5	3.8
			L	10	10	5	10	5	10	0	5	8.8
4	43	F	R	10	15	10	15	10	10	10	15	12.5
			L	10	15	10	10	10	10	5	0	11.3
5	29	F	R	0	0	0	5	10	15	10	0	5.0
			L	5	0	0	5	15	10	10	0	6.3
6	38	M	R	5	10	10	10	15	15	10	-5	11.3
			L	15	10	10	15	15	15	15	5	12.5
7	32	F	R	5	10	15	10	10	5	10	0	10.0
			L	15	10	10	5	15	15	20	15	10.0
8	21	F	R	5	10	10	5	15	5	0	0	7.5
			L	5	10	5	10	5	5	0	-5	7.5
9	25	F	R	10	5	0	0	5	5	5	-10	2.5
			L	10	10	15	15	15	15	10	-5	13.8
10	35	F	R	0	5	5	5	5	0	0	-5	3.8
			L	0	0	10	5	5	0	0	0	3.8
11	37	M	R	5	5	5	0	10	10	10	15	5.0
			L	5	10	5	5	0	5	15	15	6.3
12	31	M	R	5	10	5	5	0	10	10	0	7.5
			L	0	0	5	10	5	5	5	-5	5.0
13	36	F	R	5	5	5	10	10	10	20	10	7.5
			L	0	0	5	10	10	5	15	15	5.0
14	26	M	R	0	0	5	5	5	0	0	-5	2.5
			L	0	5	5	0	5	0	0	-10	2.5
15	19	F	R	10	10	10	20	15	15	10	5	13.8
			L	5	5	10	20	10	15	15	-5	12.5
16	30	F	R	10	5	10	10	10	0	0	5	6.3
			L	0	-5	5	0	10	0	0	-5	0.0
17	37	F	R	15	15	10	0	5	5	15	15	7.5
			L	10	10	5	5	0	15	15	25	8.8

Participant				Frequency (kHz)								
#	Age	Sex	Ear	0.25	0.5	1	2	3	4	6	8	Average
18	19	F	R	10	0	5	10	15	15	15	0	7.5
			L	5	0	0	5	5	0	0	0	1.3
19	37	F	R	0	5	10	10	10	5	5	5	7.5
			L	0	0	5	0	5	5	5	5	2.5
20	23	M	R	-5	0	5	10	15	5	5	0	5.0
			L	0	0	5	5	5	5	5	0	3.8
21	30	M	R	5	5	5	5	5	5	15	15	5.0
			L	5	5	5	10	5	10	10	10	7.5

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Participant				Frequency (kHz)										
#	Age	Sex	Ear	0.25	0.5	0.75	1	1.5	2	3	4	6	8	Average
1	64	M	R	25	35		35		25	30	30	25	25	31.3
			L	20	25		30		30	20	20	25	30	26.3
2	60	F	R	15	15		20		20	25	40	45	45	23.8
			L	10	15		20		25	25	25	45	65	21.3
3	57	M	R	15	20		30	40	50	60	60	50	50	40.0
			L	10	20		30	45	55	50	50	50	45	38.8
4	20	F	R	40	35	45	55	65	65	55	45	45	45	50.0
			L	35	35	40	60	70	65	60	55	50	60	53.8
5	58	M	R	0	15		20		30	35	40	40	55	26.3
			L	0	25		20		25	35	50	50	65	30.0
6	63	F	R	40	45		55		55	55	70	60	65	56.3
			L	35	40		50		60	65	60	70	80	52.5
7	66	M	R	10	15		20		20	50	65	70	70	30.0
			L	10	15		20		10	35	60	60	65	26.3
8	67	M	R	20	25		35	40	55	55	65	60	70	45.0
			L	15	25		35	40	50	65	75	60	60	46.3
9	56	M	R	20	20		25		30	35	50	55	60	31.3
			L	20	20		30		40	55	55	60	65	36.3
10	71	F	R	35	40		50		50	55	55	60	60	48.8
			L	45	45		55		50	50	50	60	65	50.0