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The Onset-Offset N1-P2 Auditory Evoked Response in Individuals with High-Frequency Sensorineural Hearing Loss

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The "classic" profile of central auditory processing disorder (CAPD) includes difficulty understanding speech in background noise despite normal audiometric thresholds; however, CAPD does not always occur in isolation and is likely under-diagnosed in the hearing loss population. The effects of sensorineural hearing loss on central auditory function are not well understood and diagnosing CAPD in individuals with sensorineural hearing loss remains difficult. This study examined the onset-offset N1-P2 auditory evoked response in two groups of individuals (one with normal hearing and a second with hearing loss) as a first step in evaluating whether peripheral hearing loss may be more definitively separated from central auditory dysfunction using this objective paradigm.

The response was measured in 10 normal hearing participants and 7 participants aged 40 to 67 years with moderate high-frequency sensorineural hearing loss. Four experimental noise conditions were tested, including three noise conditions presented at 50 dB SL (500 Hz-centered narrowband, 4000 Hz-centered narrowband, and broadband) and one at 70 dB SL (broadband). Waveform amplitudes and latencies were measured for N1 onset, P2 onset, N1 offset, and P2 offset.

Waveforms obtained with broadband noise did not demonstrate significant differences between groups. Four waveform component measurements (500 Hz N1 onset latency, 4000 Hz N1 onset latency, 4000 Hz N1 offset latency, and 4000 Hz N1 offset amplitude) were enhanced (i.e., shorter latency and increased amplitude) in individuals with hearing loss compared to individuals with normal hearing. Offset-to-onset N1-P2 amplitude ratio comparisons between groups were significant for the 4000 Hz-centered narrowband noise condition but were not significant for the other conditions.

Overall, amplitudes were not reduced and latencies were not delayed for the hearing loss group compared to the normal hearing group. These findings support the use of dB SL presentation levels rather than dB nHL or dB SPL presentation levels used for cortical electrophysiologic measurements of central auditory function in individuals with high-frequency sensorineural hearing loss. The significant waveform enhancements of the hearing loss group suggest that homeostatic plasticity, or "brain gain," in the central auditory nervous system may have contributed to the results of this study.

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The Onset-Offset N1-P2 Auditory Evoked Response in Individuals with High-Frequency Sensorineural Hearing Loss

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"Fall seven times and stand up eight." –Japanese Proverb

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CHAPTER 1

Introduction

Difficulty understanding speech in the presence of background noise is a common complaint expressed by individuals with and without peripheral hearing loss who seek audiological services. While such complaints are common, the underlying reasons for them vary. Among the possible reasons are physiological changes that negatively affect cochlear function as a result of outer hair cell loss, including a narrowing of the dynamic range, loss of nonlinearity, and broadening of auditory filters (Bellis & Jorgensen, 2013; Van Tasell, 1993). In addition, technological limitations of hearing aid algorithms for the processing and reduction of environmental noise as well as the adequate separation of meaningful speech from less meaningful competing stimuli can affect speech understanding for hearing aid users in the presence of background noise (Dillon, 2012; Venema, 2006). Sergei Kochkin's (2009) analysis of the MarkeTrak VIII survey on the hearing health market over the previous 25 years revealed that 66% of hearing aid users described their difficulties hearing in noise as being "quite difficult" to "extremely difficult," while 34% of non-hearing aid users described their difficulties using the same descriptors. Notably, only 6% of non-hearing aid users described hearing in noise as "not at all difficult," leaving 94% of non-hearing aid users with at least some degree of difficulty hearing in noise. While non-hearing aid users tend to have milder degrees of hearing loss compared to hearing aid users, the numbers of individuals who acknowledge having these difficulties hearing in noise whether or not they are hearing aid users suggest that there likely are both physiological and technological contributors to the

difficulties that individuals with hearing loss experience in many listening environments (Kochkin, 2009).

There are also cases of experienced hearing aid users who encounter changes in their hearing aid satisfaction and/or benefit status over time despite their audiograms, amplification devices, and fittings remaining stable (Givens, Arnold, & Hume, 1998; Stach, Loiselle, & Jerger, 1991; Stach, Loiselle, Jerger, Mintz, & Taylor, 1987). In many of these cases, a move to monaural hearing aid fitting in the right ear from a previous binaural fitting in order to exploit a right ear advantage (REA) or the addition of a personal frequency modulation (FM) system for individuals who were previously monaural hearing aid-only users resulted in improved listening performance beyond what was provided by their original amplification fittings. The fact that these types of amplification modifications resulted in improved listening performance may suggest that a central auditory system deficit can negatively affect listening performance.

Difficulty understanding speech in background noise or in reverberant environments is not only experienced by individuals with peripheral hearing loss and/or those who use hearing aids; it is also the hallmark complaint of individuals with central auditory processing disorder (CAPD) (American Academy of Audiology, 2010). It is now known through animal studies that widespread cochlear synaptic degeneration targeting low spontaneous-rate auditory nerve fibers can occur as a result of noise exposure even when thresholds return to normal; this is a condition referred to as "hidden hearing loss" by Kujawa and Liberman (2009). Despite this finding, what has traditionally distinguished instances of "classic" CAPD from peripheral hearing disorders is the presence of normal hearing sensitivity across the frequency range as determined by

the pure-tone audiogram. While the etiology underlying central auditory dysfunction can be identified in many cases and may include traumatic brain injury, stroke, seizures, or other neurologic disorders or abnormalities, in other cases the etiology remains unknown (Bellis, 2013). It is important to note that each of the etiologies of CAPD mentioned above may be experienced across the population of individuals with CAPD regardless of the status of the peripheral hearing system. Thus, there are four profiles of individuals related to peripheral hearing status and CAPD: 1) those who have normal hearing thresholds and central auditory function within normal limits, 2) those who have normal hearing thresholds and central auditory dysfunction (the "classic" profile), 3) those who have peripheral hearing loss and central auditory function within normal limits, and 4) those who have both peripheral hearing loss and central auditory dysfunction (Bellis & Jorgensen, 2013).

Audiologic and central auditory evaluations of individuals from these four profile categories include testing that is routinely performed to assess peripheral hearing sensitivity (e.g., pure-tone audiometry, speech reception threshold, and word recognition in quiet), as well as a battery of central auditory processing tests that is carefully constructed with peripheral auditory status in mind (i.e., choosing tests that may be used in cases of hearing loss with adjusted norms) in order to assess a patient's unique auditory complaints. Individuals with normal hearing and normal central auditory function present with normal audiometric results and central auditory processing test scores within the norms for their age group. Those with normal hearing and central auditory dysfunction typically present with normal audiometric results and scores that are two standard deviations or more below the mean in one ear on at least two behavioral

tests of central auditory function (American Academy of Audiology, 2010; Bellis, 2011; Chermak & Musiek, 2007). In addition, the use of electrophysiologic measures such as the auditory brainstem response (ABR), middle latency response (MLR), and auditory late response (ALR, consisting of N1-P2 and P300 responses) has been recommended in order to provide objective physiologic support for the findings of the behavioral test measures (American Academy of Audiology, 2010). The use of high-intensity ABR measurements may also aid in ruling out the possibility of "hidden hearing loss" as described by Kujawa and Liberman (2009), though it may be possible that using electrocochleography (ECochG) to evaluate the reportedly reduced amplitudes of the auditory nerve response (i.e., wave I of the ABR) in these cases may provide more detailed insight for diagnosis. Individuals who have peripheral hearing loss and normal central auditory function present with audiometric results reflecting the type, degree, and configuration of the hearing loss, and they score above hearing loss adjusted norms for both ears on tests of central auditory function. However, it should be noted that the phrase, "normal central auditory function," may be an oversimplification of central auditory status in individuals with peripheral hearing loss, as processes such as transynaptic degeneration as a result of the peripheral hearing loss may affect central auditory processing to some degree (Kujawa & Liberman, 2009). Individuals with peripheral hearing loss and CAPD demonstrate audiometric results reflecting the presence of a peripheral hearing loss as well as abnormal performance on CAPD tests. However, the identification of CAPD in individuals with peripheral hearing loss remains a challenge as performance on central auditory tests can be affected by peripheral deficits as well as by central deficits (Humes et al., 2012). Currently, there is no definitive

method of identifying the presence of CAPD in individuals with comorbid peripheral hearing loss, although in some cases the presence of a CAPD is strongly indicated (e.g., in an individual with a bilaterally symmetrical peripheral hearing loss and significant ear differences on central auditory tests; American Academy of Audiology, 2010). As a group, this population of patients demonstrates highly variable results on central auditory processing tests, with some cases demonstrating scores below normal limits but with less significant ear differences; as such, it is the current position of the American Academy of Audiology (2010) that "in such cases, a definitive diagnosis of CAPD should be withheld, even though the possibility of a CAPD may exist" (p. 12).

Through the study of brain activation patterns evoked by speech and measured by functional magnetic resonance imaging (fMRI), it has been found that individuals with mild to moderate hearing loss and who exhibit poor pure-tone averages (PTAs) for 1000, 2000, and 4000 Hz experience greater loss of grey matter density in primary auditory cortical areas including Heschl's gyrus and planum temporale (Peelle, Troiani, Grossman, & Wingfield, 2011). This loss of density is observed in individuals with PTAs in the mild to moderate range, with increased loss of density noted for those with moderate as opposed to mild hearing losses (Peelle et al., 2011). Given these findings, it is reasonable to assume that peripheral hearing loss could have deleterious effects on tests that require central auditory processing even though the loss of grey matter density is considered a normal consequence of peripheral hearing loss; however, this assumption requires that the loss of grey matter also results in functional changes in the brain that do not act to adequately compensate for the hearing loss. Multiple studies have documented that behavioral central auditory processing tests – even those that are more resistant to

hearing loss (e.g., dichotic digits, frequency patterns, and duration patterns) – must be interpreted with caution when administered to individuals with any degree of hearing loss (Divenyi & Haupt, 1997; Humes, Coughlin, & Talley, 1996; Musiek, Baran, & Pinheiro, 1990; Musiek, Gollegly, Kibbe, & Verkest-Lenz, 1991; Neijenhuis, Tschur, & Snik, 2004).

Poor performance on central auditory processing tests by individuals with peripheral hearing loss does not definitively indicate that these individuals present with CAPD, per se. In addition to the loss of grey matter density in the primary auditory cortex of individuals with peripheral hearing loss, the poor performance by these individuals may be the result of peripheral deficits already mentioned, including decreased audibility, broadened auditory filters, and distortion, as well as alterations in auditory nerve function, including changes in characteristic frequency, spontaneous discharge rate, threshold tuning curves and rate and phase level functions (Liberman, 1984; Liberman & Dodds, 1984a, 1984b; Liberman & Kiang, 1984). While behavioral tests such as the Dichotic Digit Test, Frequency Pattern Test, and Duration Pattern Test are minimally influenced by mild to moderate sensorineural hearing loss (Musiek et al., 1990; Shinn, 2013) and may be used in evaluating these individuals to determine the integrity of the central auditory nervous system (Emanuel, 2002; Emanuel, Ficca, & Korczak, 2011), conclusions regarding central auditory status can only be made if an individual scores within the criteria for normal function or when specific and dramatically abnormal patterns of test scores are found in individuals with hearing loss (American Academy of Audiology, 2010). Among those specific patterns are "poorer performance in the normal hearing ear in individuals with unilateral hearing loss,

asymmetrical performance on a central test battery in individuals with symmetrical hearing loss, [and/or] the presence of ear or electrode effects on electrophysiologic test measures in individuals with symmetrical hearing loss" (American Academy of Audiology, 2010, p.12). In the event that an individual with peripheral hearing loss does not score within the norms for the central auditory tests performed, it may be difficult to discern whether the poor performance stems from the hearing loss itself or from the existence of CAPD. Thus, it has been a continuing challenge in audiology to find central auditory test procedures that are minimally influenced by peripheral hearing loss. Objective measures of central auditory function such as the auditory brainstem response (ABR), middle latency response (MLR), and passive cortical auditory evoked potentials such as the N1-P2 complex are affected in latency and amplitude by peripheral hearing loss to varying degrees (Bertoli, Smurzynski, & Probst, 2005; Hyde, 1997; Oates, Kurtzberg, & Stapells, 2002, Picton, Woods, Baribeau-Braun, & Healey, 1977). The onset-offset N1-P2 has not yet been evaluated in individuals with sensorineural hearing loss and it is unknown if the response will be affected by hearing loss.

CHAPTER 2

Review of the Literature

As mentioned earlier, the effects of sensorineural hearing loss on central auditory function are poorly understood. As the present study recruited participants with normal audiometric thresholds and participants with sensorineural hearing loss to evaluate an electrophysiologic measure of central auditory function, a review of the literature concerning the known neuroanatomical and neurophysiological effects of sensorineural hearing loss on the peripheral and central auditory systems is provided. This review is then followed by a review of the traditional N1-P2 response and the onset offset N1-P2 auditory evoked response literature.

Sensorineural Hearing Loss: Changes in the Peripheral Auditory System

Though there are many etiologies of sensorineural hearing loss including ototoxicity, Menière's disease, and autoimmune disorders, common causes of sensorineural hearing loss include noise exposure and aging, either occurring independently or in combination (Nadol, 1993). Noise-induced hearing loss can occur either through overstimulation, resulting in elevated levels of calcium in the hair cells and supporting cells and apoptosis, or short-term exposures to intense sounds, which results in mechanical damage in the cochlea such as the breakage of stereocilia tip links. Cochlear alterations as a result of noise exposure involve reductions in the cochlear microphonic, electromotility, and the non-linear gain mechanism, as well as threshold elevations and decreases in the dynamic range for intensity, all of which involve outer hair cell function (Jacob, Johansson, & Fridberger, 2013). These same alterations also

occur in age-related hearing loss, or presbycusis, though the mechanism underlying this etiology of hearing loss is not attributed specifically to noise exposure. In presbycusis, a loss of hearing sensitivity is thought to occur as a result of peripheral tissue damage (i.e., hair cells, stria vascularis), oxidative processes, and apoptosis, or cell death, in the cochlea resulting from an accumulation of low-level damage from noise as well as vascular or metabolic disorders (Gates & Mills, 2005; Wong & Ryan, 2015). While both etiologies are characterized by outer hair cell loss, the first row of outer hair cells are especially vulnerable in hearing loss occurring as a result of noise exposure, while all three rows of outer hair cells are vulnerable in hearing loss that is related to age (Sergeyenko, Lall, Liberman, & Kujawa, 2013; Wang, Hirose, & Liberman, 2002).

While outer hair cells are particularly susceptible to the effects of age, inner hair cells are not, with greater than an 80% survival rate throughout the cochlea even at the end of the lifespan (Sergeyenko et al., 2013). Even though inner hair cells do not seem to be vulnerable to the effects of age, spiral ganglion cells are, with a steady decline occurring throughout life along the entire length of the cochlea from base to apex. Thus, age-related hearing loss seems to arise from the loss of two types of cells – cochlear outer hair cells and the spiral ganglion cells of the auditory nerve. Though only the first row of outer hair cells is susceptible to damage caused by noise exposure, this damage is often also associated with damage to inner hair cell stereocilia. Also, exposure to high levels of noise affects the ribbon synapses of auditory nerve fibers onto the inner hair cells (Kujawa & Liberman, 2009; Wang et al., 2002). Specifically, when temporary threshold shifts are present, a swelling of the ribbon synapses occurs after exposure to the noise. Shortly after the exposure, thresholds return to normal; however, responses to

suprathreshold sounds via ABR suggest that the synaptic terminals damaged from the exposure do not fully recover, eventually leading to pre-synaptic and post-synaptic neural degeneration (Kujawa & Liberman, 2009). While noise-induced hearing loss and presbycusis differ in the contributors driving their existence, they both exhibit some degree of outer hair cell and spiral ganglion cell loss as well as degeneration of the neurons that compose the auditory nerve.

In a series of papers on chronic cochlear pathology and its effects on auditory nerve fibers, Liberman (1984), Liberman and Dodds (1984a, 1984b), and Liberman and Kiang (1984) found that stereocilia damage and threshold shift alter the characteristic frequencies of auditory neurons as well as their spontaneous discharge rates, threshold tuning curves, and rate and phase level functions. For neurons with characteristic frequencies above 1000 Hz, downward shifts in characteristic frequency were observed with increases in threshold. With regard to the effect of cochlear pathology on tuning curves of the auditory nerve fibers, damage to outer hair cells alone results in elevations of the "tips" of tuning curves as well as hypersensitivity of the "tails" of the tuning curves. Damage to both outer hair cells and inner hair cells results in elevations of the tuning curve tips as well as elevations of the tails of the tuning curves. Spontaneous discharge rates of auditory nerve fibers become abnormally low in cases of chronic cochlear pathology (Liberman & Dodds, 1984a; Liberman & Kiang, 1978). In cases without cochlear pathology, "…high [spontaneous rate] fibers can be as much as 80 dB more sensitive than fibers with low [spontaneous rates]" (Liberman & Dodds, 1984a, p. 43). Thus, the loss of high spontaneous nerve fibers results in a loss of sensitivity to low intensity sound. Maximum firing rates of remaining high-spontaneous nerve fibers also

decrease, with rates less than 150 spikes per second compared to close to 250 spikes per second for normal high-spontaneous rate fibers. These alterations in auditory nerve fiber function result in reductions in the amplitude of the compound action potential of the auditory nerve; reduced input to the central auditory nervous system is a consequence of the diminished amplitude of the compound action potential (Salvi, Wang, & Ding, 2000).

Individuals with sensorineural hearing loss very often present with an abnormal growth in the perception of loudness. This is generally thought to be the result of the combination of elevated thresholds of auditory sensitivity and normal or near-normal judgments of loudness discomfort at the upper boundaries of the dynamic range for intensity (Denes & Naunton, 1950). This narrowing of the dynamic range between sensitivity threshold and loudness discomfort level results in more drastic judgments of loudness increase in individuals with hearing loss compared to normal hearing individuals, given the same incremental change in intensity level. At the peripheral level, recruitment has traditionally been thought to arise from increases in the steepness of the rate-level functions of auditory nerve fibers (Harrison, 1981) and the basilar membrane velocity-intensity relationship after outer hair cell loss (Ruggero & Rich, 1991). These findings, however, contradict those reported by Liberman (1984), Liberman and Dodds (1984a, 1984b) and Liberman and Kiang (1984) that describe compromised cochlear transduction and reduced firing rates of auditory nerve fibers. The recruitment phenomenon, then, likely arises when there is a combination of outer and inner hair cell damage from acoustic trauma and not from outer hair cell damage alone (Cai, Ma, & Young, 2009). Thus, even if cochlear changes resembling recruitment are present as a

result of hearing loss, reductions in the compound action potential of the auditory nerve may override these effects to some degree.

Sensorineural Hearing Loss: Changes in the Central Auditory Nervous System

Cellular degeneration resulting from cochlear pathology has been observed in the cochlear nucleus, the most caudal structure in the central auditory nervous system (Hall, 1976; Mair, 1973; Morest & Bohne, 1983). In cases of monkeys exposed to either dihydrostreptomycin or noise, total numbers of cells in all divisions of the cochlear nucleus were reduced (Hall, 1976). Average total cell counts in the monkeys with hearing loss were 83,400 compared to the 107,500 cells counted in the controls. Of all of the divisions of the cochlear nucleus, the dorsal division experienced the most cellular loss, with an average loss of 28% of cells. The ventral nucleus, including both the anteroventral and posteroventral divisions, lost an average of 21% of cells. Monkeys with milder degrees of hearing loss experienced less cellular loss than monkeys with more severe degrees of hearing loss. The sizes of the cochlear nuclei were also reduced in monkeys with hearing loss compared to the controls, with volumes of 5.5 mm^3 for those with hearing loss and 7 mm^3 for the controls. As would be expected, the monkeys with greater reductions in cell counts also had greater reductions in cochlear nucleus size. In their investigation of noise-induced degeneration in the central auditory nervous systems of chinchillas, Morest and Bohne (1983) found that the pattern of degeneration in the cochlear nucleus was correlated to the pattern of hair cell loss resulting from the noise exposure. Inner hair cell loss resulted in course fiber degenerations in the ventral cochlear nucleus, while outer hair cell loss resulted in degeneration of fine fibers in the

dorsal cochlear nucleus. Both types of fibers demonstrated degeneration at the root entry zone, which is the point where the auditory nerve enters the cochlear nucleus (Morest & Bohne, 1983). Functional consequences of these degenerations include reductions in the amplitudes of local field potentials and elevations of response thresholds (Salvi et al., 2000). Cochlear lesions resulting from exposure to intense sound have also been found to change the tonotopic map of the dorsal cochlear nucleus in hamsters, with expanded map areas representing characteristic frequencies at the center of the lesions (Kaltenbach, Czaja, & Kaplan, 1992). The patterns of the expanded map areas (i.e., downward shifts of characteristic frequencies, loss of neural tuning curve tips), however, suggest that the tonotopic map changes may be the result of changes in auditory nerve function rather than central auditory nervous system plasticity (Kaltenbach et al., 1992). Despite these cellular degenerations and functional changes, increases in the number of projections from the cochlear nucleus to the ipsilateral inferior colliculus have been reported in ferrets and chinchillas (Moore, 1994; Salvi et al., 2000). In addition, spontaneous activity rates of neurons in the dorsal cochlear nucleus are reported to increase, while decreases in spontaneous activity rates are observed from the ventral cochlear nucleus (Basta & Ernest, 2004; Eggermont & Roberts, 2004). Inhibition is also reported to decrease in the dorsal cochlear nucleus (Basta & Ernest, 2004; Salvi et al., 2000).

The superior olivary complex (SOC) receives afferent input from both cochlear nuclei; as such, the SOC is the first central auditory structure to receive auditory input from both right and left ears. Thus, the SOC has a functional role in using the information it receives from both ears to determine where sounds are located in space (localization). The SOC is composed of multiple nuclei, three of which are considered

"primary" – the medial superior olive (MSO), the lateral superior olive (LSO), and the medial nucleus of the trapezoid body (MNTB). The MSO mainly responds to low frequencies, and it receives excitatory input from the anterior ventral cochlear nucleus (AVCN) bilaterally, with ipsilateral AVCN inputs synapsing laterally and contralateral AVCN inputs synapsing medially. The MSO projects mainly to the ipsilateral inferior colliculus, and the majority of these projections are excitatory. The LSO responds to the full frequency range and receives direct excitatory input ipsilaterally from the AVCN. The LSO also receives input from the contralateral AVCN; however, this input is indirect, as the excitatory input from the AVCN arrives first at the MNTB, which then sends inhibitory (glycinergic) output to the LSO. While the MSO is well developed in humans, the MNTB and LSO are smaller and less developed in humans than they are in other species, including rats and cats (Malmierca & Hackett, 2010).

The main neurotransmitters in the SOC are glutamate (excitatory) and glycine (inhibitory). Alterations in the release and uptake of glutamate as well as the number of glycine puncta on the somata of principal cells have been found in the SOC of guinea pigs as a result of lesions originating in the cochlea. In cases of unilateral cochleotomy, principal nuclei in the LSO, MSO, and MNTB show decreases in glutamate release within five days of receiving the lesion (Potashner, Suneja, & Benson, 1997). Those same nuclei, however, demonstrate increases in glutamate release by 145 days post-lesion compared to normal hearing controls. Increases in glutamate uptake are also seen bilaterally in the LSO and in the MSO contralateral to the lesion at 145 days post-cochleotomy. Thus, it appears that excitation immediately after cochleotomy is reduced but is then enhanced with increased time post-lesion. In their study of deafness-related

changes in glycine in the SOC in bilaterally deafened rats, Buras and colleagues (2006) found that the cell bodies of principal cells showed significant decreases in the number of glycine immunoreactive spots for all regions they assessed, "with changes ranging from 50% in the VNTB [ventral nucleus of the trapezoid body] to 23% in the LSO" (p. 179). This suggests that in addition to the increases in excitation in the SOC, there is also a reduction in the inhibitory activity resulting from peripheral hearing loss.

Also reported in the SOC as a result of hearing impairment is the expression of growth-associated protein 43 (GAP-43). This protein is known to be involved in development, learning, and plasticity, and it is considered to be one of the key players in "all stages of reactive changes in brain organization" (Illing, Kraus, & Michler, 2000, p. 365). One week following unilateral noise exposure in rats, Michler, Illing, Häufel, Horváth, and Latzig (2000) reported GAP-43 positive nerve fibers in the ventral cochlear nucleus and GAP-43 positive cell bodies in the lateral superior olive. GAP-43 immunoreactivity increased in the ipsilateral and contralateral cochlear nuclei, and GAP-43 significantly increased in the neurons of the contralateral LSO as a result of hearing impairment. The expression of GAP-43 in the SOC and cochlear nucleus suggests that there is a reorganization process that occurs in the caudal brainstem after peripheral hearing loss. Overall, then, there appear to be increases in excitation, decreases in inhibition, and reorganization occurring at the level of the SOC as a result of cochlear lesions.

While the auditory nerve compound action potential and local field potential of the cochlear nucleus demonstrate reduced amplitudes overall as a result of acoustic trauma, the inferior colliculus demonstrates the opposite effect (Salvi, Saunders, Gratton,

Arehole, & Powers, 1990; Salvi et al., 2000). Evoked response amplitudes measured from the inferior colliculus of chinchillas increase following acoustic trauma (Salvi et al., 1990, 2000). The hearing loss resulting from the noise exposure increases the threshold of the response in the region of the hearing loss; however, once threshold is reached and then exceeded, amplitudes rise rapidly for moderate intensities before leveling off to pre-exposure amplitudes for high intensities (Salvi et al., 2000).

In their study investigating the effect of bilateral deafness on excitatory and inhibitory synaptic strength in the inferior colliculus of gerbils, Vale and Sanes (2002) reported that bilateral cochlear ablation resulted in significant increases in total excitatory post-synaptic current amplitude, with gerbils from the experimental group demonstrating amplitudes that were 70% greater than those obtained from the control gerbils. In an earlier study, Vale and Sanes (2002) found that bilateral cochlear ablation resulted in rapid losses of inhibitory synaptic strength. This finding indicates that the increases in evoked response amplitude in the inferior colliculus post-exposure or post-ablation resulted not only from increases in response strength of excitatory neurons but also from decreases in response strength of inhibitory neurons. Interestingly, these increases in response amplitude were not only seen in the region of cochlear hearing loss, but also for regions with normal hearing thresholds. Salvi and colleagues (1990) investigated the effects of acoustic trauma on evoked response amplitudes in the inferior colliculus of chinchillas. The evoked potential amplitude measurements indicated that even though permanent threshold shifts due to a 2000 Hz trauma-inducing stimulus were present from 2000 through 8000 Hz, amplitude-level functions were steeper and maximum amplitudes were larger post-trauma compared to pre-trauma measurements when responses were

evoked by a 500 Hz stimulus. This is particularly interesting considering that these enhancements were observed even though hearing loss was not present at 500 Hz.

Popelár, Grecova, Rybalko, and Syka (2008) reported similar findings to those reported by Salvi and colleagues (1990, 2000). These authors found reduced ABR amplitudes and enhanced MLR amplitudes in pigmented rats post-noise exposure compared to pre-exposure recordings. These researchers (2008) also found that the slope of the amplitude-intensity function for the ABR did not change, while the MLR amplitude-intensity function increased significantly with increased threshold shifts. This pattern demonstrated in the MLR measurements – and not in the ABR measurements – resembled that which is found in measures of loudness recruitment and suggested that the amplitude enhancements arose from structures rostral to the cochlear nucleus (Popelár et al., 2008).

Kotak and colleagues (2005) investigated the effects of sensorineural hearing loss on the function of the ventral division of the medial geniculate body (MGv) and the primary auditory cortex in gerbils. After inducing sensorineural hearing loss in the animals, thalamocortical brain slices were prepared and whole-cell recordings were analyzed. Sensorineural hearing loss was found to result in multiple functional alterations in the MGv and primary auditory cortex. The neurons evaluated in the samples from gerbils with sensorineural hearing loss were found to have depolarized membrane potentials, increased input resistance, and higher rates of sustained firing. Excitatory synaptic responses were significantly larger in thalamocortical and cortical neurons of gerbils with sensorineural hearing loss. This result was thought to arise from a decrease in frequency and an increase in amplitude of excitatory post-synaptic currents

and suggests that the increase in excitatory response is a compensation for declines in presynaptic release properties. Kotak and colleagues (2005) also found that the synaptic responses of inhibitory neurons were significantly reduced in the cases of sensorineural hearing loss. Thus, sensorineural hearing loss appears to increase excitability in the MGv and primary auditory cortex while decreasing the inhibitory response in the primary auditory cortex. It appears as though these central auditory changes "reflect an attempt by A1 [the primary auditory cortex] to sustain an operative level of cortical excitability that may involve homeostatic mechanisms" (Kotak et al., 2005, p. 3908); that is, the auditory cortex may be compensating for the decline in auditory sensation by increasing the excitation strengths of neurons and decreasing the inhibition strengths of neurons in a balanced, or "scaled," way. This is referred to by some individuals who study cortical plasticity as "brain gain" (Chen et al., 2015)

Tonotopic map reorganization also occurs in the auditory cortex as a result of cochlear hearing loss, with increased spontaneous activity rates and increased neural synchrony observed in the cortical regions of the loss (Eggermont & Roberts, 2004; Harrison, Nagasawa, Smith, Stanton, & Mount, 1991; Komiya & Eggermont, 2000; Robertson & Irvine, 1989; Seki & Eggermont, 2003). In addition, minimum spike latencies of neurons in the region of the hearing loss in the auditory cortex are reported to be significantly shorter in cats that experienced tonotopic reorganization of the auditory cortex than in those that did not experience tonotopic reorganization (Seki & Eggermont, 2002). Amplitude enhancements of excitatory neurons are also observed in measurements from the auditory cortex of guinea pigs and gerbils in cases of cochlear

hearing loss when compared to cases of normal hearing (Eggermont & Roberts, 2004; Kotak et al, 2005; Popelár, Syka, & Berndt, 1987; Syka, Rybalko, & Popelár, 1994).

Along with amplitude enhancements of the response, the steepness of amplitude-intensity functions derived from auditory cortical measurements in cats with hearing loss has also been found to be greater (Popelár et al., 1987). Popelár and colleagues (1987) stated that this enhancement of amplitude and increase in amplitude-intensity function steepness in the auditory cortex closely resembled changes in cortical function often associated with recruitment, or the abnormal loudness growth phenomenon that frequently accompanies sensorineural hearing loss. Interestingly, these amplitude enhancements and steep amplitude-intensity functions from the auditory cortex only occurred when the noise-exposed animals they studied were awake, while they were significantly reduced when the animals were anesthetized (Popelár et al., 1987). This supports the possibility that recruitment may actually be, to a substantial extent, a centrally mediated phenomenon versus one that is typically thought of as predominantly peripheral. Given that hearing loss results in reductions in the compound action potential of the auditory nerve while increasing excitatory response amplitudes more rostrally in the central auditory nervous system, it is likely that the mechanisms underlying all of the central changes described above (i.e., changes in neural excitation, neural inhibition, spontaneous activity rates, neural synchrony, and tonotopic organization) may contribute to the perception of abnormal loudness growth.

The Traditional N1-P2 Auditory Evoked Response

First described by Davis (1939), the N1-P2 auditory evoked potential is a measurement of cortical activity elicited by the physical characteristics of a sound

presented to the auditory system. The potential is most clearly observed as a derivative of an electroencephalogram, or EEG, after filtering to expose the lower frequencies of cortical activity – typically with a bandpass filter with a high-pass cutoff between 0.1-1 Hz and a low-pass cutoff between 30-100 Hz. The N1 component presents as a negative shift from pre-stimulus baseline and occurs at around 100 ms after the onset of a stimulus, while the P2 component presents as a positive shift from pre-stimulus baseline occurring about 200 ms after the onset of a stimulus. The P2 component follows the N1 component, allowing for three types of voltage measurements (in microvolts, or μV) to be made: 1) absolute baseline-to-trough N1 amplitude, 2) absolute baseline-to-peak P2 amplitude, and 3) trough-to-peak N1-P2 amplitude. A typical N1-P2 evoked response is demonstrated in Figure 1.

Methods of Acquisition

In order to obtain a clear N1-P2 response, one must use a relatively brief stimulus (about 100 ms) presented at a rate of about once per second. In order for an evaluator to deem the N1-P2 response to be present and reliable, individual responses to about 100 repetitions of a stimulus must be obtained and averaged together. At least two waveforms from 100 repetitions each are then averaged together before amplitude, latency, and morphology analyses are attempted (Hall, 2007). Nearly any type of stimulus can be used to elicit the response, including pure tones, tone complexes, noise, or speech; however, using stimuli that are more complex yields more robust responses than pure tones (Evans, 1992; Whitfield & Evans, 1965).

Electrodes placed at various locations on the scalp record the cortical activity

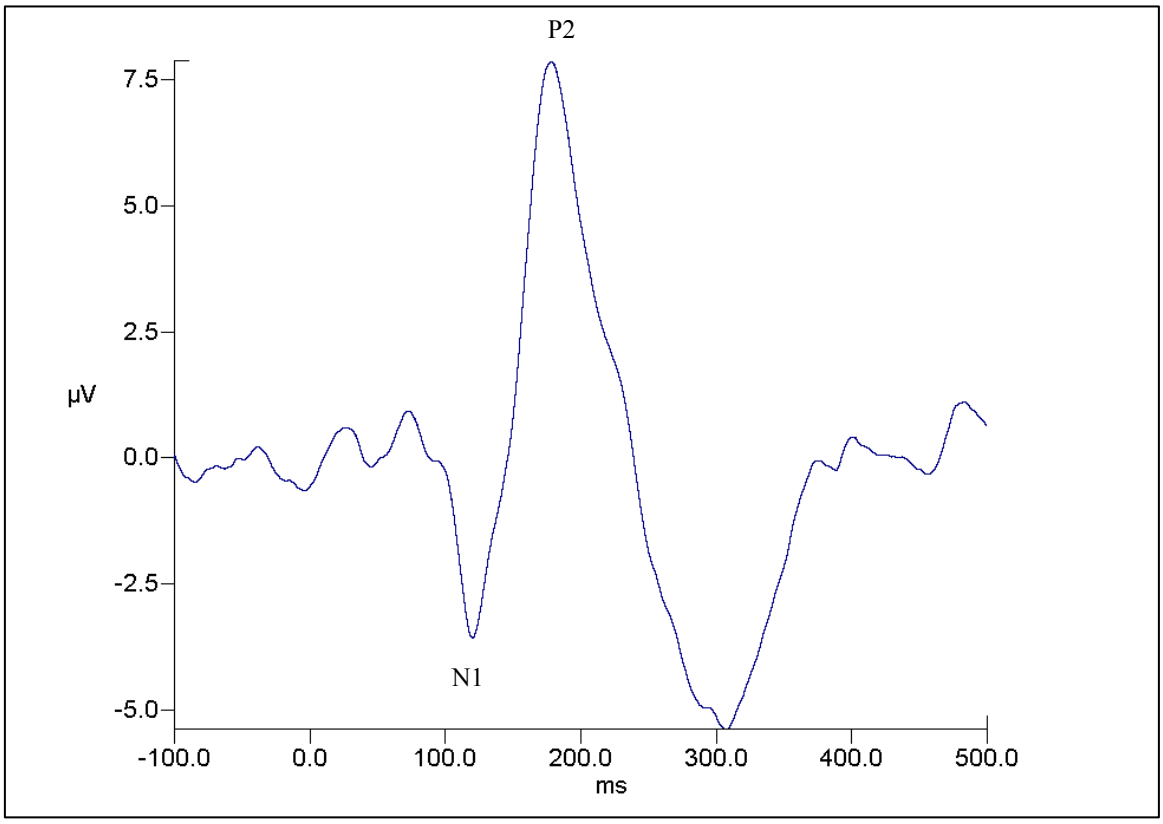

Figure 1. A typical (single) N1-P2 waveform obtained from one normal-hearing subject using a 2000 Hz pure tone presented at 70 dB nHL.

elicited by the stimulus, with active (non-inverting) electrodes typically placed along the vertex (Fz, Cz, and/or Pz), reference (inverting) electrodes typically placed on the earlobe or mastoid (A1 and/or A2), and a ground electrode that can be placed at another location on the head or on the body (scalp electrode placements re: International 10-20 System). An eyeblink rejection electrode located at the outer canthus of the eye is often included to allow for the reduction of artifacts.

As a result of changes in brain activity that occur during sleep, such as increased synchronization and strong fluctuations in low-frequency activity in the cortex (Harris & Thiele, 2011; Steriade & McCarley, 2005), participants must remain awake and passively alert during the recording of the response (Musiek & Lee, 1999; Rapin, Schimmel, & Cohen, 1972). According to Harris and Thiele (2011), cortical state (i.e., wakefulness) also seems to affect how the central nervous system processes "isolated punctuate stimuli" versus "temporally extended or rapidly repeated stimuli" (p. 516), with responses to the latter being more drastically affected by reductions in the amount of synchronized brain activity or sleeping. Stimuli used to evoke the N1-P2 response are temporally extended (i.e., longer in duration compared to stimuli used to evoke more caudal responses) and rapidly repeated; thus, individuals from whom the N1-P2 response is obtained must remain awake and alert throughout testing.

Clinical Utility

Clinically, the N1-P2 response has been used to estimate auditory threshold (Cone-Wesson & Wunderlich, 2003; Hyde, 1997; Rickards, De Vidi, & McMahon, 1996) as well as to test the integrity of the central auditory nervous system, or CANS (Jirsa &

Clontz, 1990; Knight, Hillyard, Woods, & Neville, 1980; Knight, Scabini, Woods, & Clayworth, 1989; Tonnquist-Uhlén, 1996). The N1-P2 response is an objective measure of auditory function that relies on normal function of the auditory system from pinna to auditory cortex for normal robust responses to be evoked; therefore, this response is also appealing for the evaluation of difficult-to-test or uncooperative individuals (Hyde, 1997; Rickards et al., 1996).

Threshold Estimation

When using the N1-P2 to estimate auditory thresholds, decrements in stimulus intensity lead to increases in the latency and decreases in the amplitude of the response. Much like the latency-intensity functions that are used in the interpretation of ABRs, a latency-intensity function can be obtained for the N1-P2 response. While the N1-P2 latency-intensity function in normal hearing individuals has an average slope of -0.5 ms/dB, the slope for low intensity stimuli is steep (-2.5 ms/dB) and then becomes shallow for stimuli presented around 70 to 75 dB sensation level (SL). At high intensities the latencies begin to increase again, or "roll over" (Adler & Adler, 1989; McPherson, 1996). This leads N1-P2 latency-intensity functions in normal hearing individuals to be steep for stimuli between 30 to 70 dB nHL before leveling off and/or rolling over for stimuli presented above 70 dB nHL (Adler & Adler, 1989). Threshold is defined as the lowest level at which a visually detectable N1-P2 response is obtained (McPherson, 1996).

Effects of Hearing Loss

When stimuli are presented at the same dB SPL or dB nHL to individuals with

normal hearing and to individuals with sensorineural hearing loss, the N1-P2 response in individuals with hearing loss has consistently been reported to be delayed and reduced in amplitude at low to moderate intensity levels when compared to individuals with normal hearing (Oates et al., 2002); however, at moderate to high intensity levels, individuals with sensorineural hearing loss demonstrate latency and amplitude measurements that are similar to those obtained from normal hearing individuals (Hyde, 1997). Thus, individuals with sensorineural hearing losses demonstrate a steeper N1-P2 latency-intensity function than individuals with normal hearing. N1-P2 amplitude-intensity functions of individuals with sensorineural hearing loss are similar to those of individuals with normal hearing in that the amplitudes continue to increase with increases in presentation level (McPherson, 1996).

Effects of Central Auditory Processing Disorder (CAPD)

Individuals with abnormal central auditory function as determined through central auditory processing tests who have confirmed lesions at the level of the auditory cortex (e.g., as determined through MRI) demonstrate increased latencies and/or decreased amplitudes of cortical auditory evoked potentials compared to measurements taken from individuals with normal central auditory function (Jirsa, 1992; Knight et al., 1980; Knight et al., 1989; Musiek, Baran, & Pinheiro, 1992; Warrier, Johnson, Hayes, Nicol, & Kraus, 2004). Interestingly, these differences are specific to auditory stimuli, as measurements obtained from non-auditory areas of the brain are not affected (Knight et al., 1980). Further evidence that the N1-P2 complex is adversely affected by CAPD is provided by Tremblay, Kraus, and McGee (1998) in their study examining the effects of temporal

auditory training on the N1-P2 complex. After participating in temporal auditory training, their subjects demonstrated increased N1-P2 amplitudes, suggesting that the initially reduced amplitudes were a consequence of central auditory dysfunction. While assessment of central auditory function can be enhanced by using the N1-P2 auditory evoked response, careful consideration of peripheral auditory status must be exercised, as individuals with sensorineural hearing loss present with increased latencies and reduced amplitudes that are similar to those observed in individuals with CAPD, at least for measurements obtained using the same dB SPL for normal hearing and hearing impaired listeners. These increased latencies and decreased amplitudes, however, may be the result of decreased audibility of the stimulus. If stimuli are presented at a sufficiently high level (i.e. dB SL), it is possible that these peripheral hearing loss effects could be overcome; this effect is reported to occur in ABR measurements using high intensity levels (i.e., 90 dB nHL, 60 dB SL) in individuals with sensorineural hearing loss (Hall, 2007; Rosenhamer, Lindstrom, & Lundborg, 1981).

The Onset-Offset Auditory Evoked Response

Davis (1939) first reported the "off effect," or offset response, in awake adults, though at the time it was believed that acoustic transients could have elicited the response. A later study by Davis and Zerlin (1966) confirmed the existence of the offset response with their discovery that offsets appear with fall times as long as 100 ms and, thus, are actual responses to the offsets of stimuli. While the typical N1-P2 auditory evoked response is obtained using stimuli of relatively brief durations (50-100 ms) using a repetition rate of one stimulus per second (Hall, 2007) as described earlier, a variant of

the response can be obtained using longer stimulus durations (>100 ms) and interstimulus intervals (ISIs) and by increasing the duration of the acquisition time-window beyond the 300 to 350 ms duration typically employed. This extension of the acquisition time window must be sufficient to accommodate the longer stimulus duration and the resulting N1-P2 auditory evoked response. Under such conditions, the measure is referred to as the onset-offset N1-P2 auditory evoked response and differs from the traditional N1-P2 response in that it demonstrates two N1-P2 components – one elicited by stimulus onset and the other elicited by stimulus offset. While a traditional N1-P2 response represents the auditory cortex's response to very brief stimuli, the onset-offset N1-P2 response represents a response to longer duration stimuli, the evaluation of which may be more ecologically valid and may reveal activity of greater numbers and/or types of neurons. The length of the stimulus used may also evoke auditory adaptation, which could be of value when evaluating individuals for central auditory pathology.

Methods of Acquisition

As the latencies and amplitudes of the offset N1-P2 component are dependent on stimulus duration and ISI, different recording procedures are required to elicit the onset-offset N1-P2 response than the traditional N1-P2 response. The latency of the offset N1-P2 component is dependent on the duration of the stimuli that are presented to an individual. Amplitude measurements for the offset component are usually between one-quarter and one-half those of the onset component (Hillyard & Picton, 1978; Onishi & Davis, 1968; Spychala, Rose, & Grier, 1969). Aside from the stimulus and ISI differences, recording parameters used to obtain the onset-offset N1-P2 response (e.g.,

filter characteristics, electrode montage, passive alertness of the participant, etc.) are identical to those used to obtain the traditional N1-P2 response. Specific effects related to stimulus manipulations and their effects on the onset-offset N1-P2 response will be discussed in the following section.

Consequences of Stimulus Manipulations on the Response

In general, the published literature on the onset-offset N1-P2 auditory evoked response is composed of two major themes. The earlier literature through the late 1970s consists of studies that describe the response and examine how the response is altered with changes in stimulus characteristics (Davis & Zerlin, 1966; Hillyard & Picton, 1978; Kiang & Sandel, 1961; Onishi & Davis, 1968; Pfefferbaum, Buchsbaum, & Gips, 1971; Picton, Woods, & Proulx, 1978a, 1978b; Rose & Malone, 1965; Sandel & Kiang, 1961; Spychala et al., 1969). The later literature, from the late 1970s to present, is mainly focused on describing possible physiological generators of the response (Hari et al., 1987; Hillyard & Picton, 1978; Joutsiniemi, Hari, & Vilkman, 1989; Noda et al., 1998; Pantev, Eulitz, Hampson, Ross, & Roberts, 1996; Scholl, Gao, & Wehr, 2010; Takahashi, Nakao, & Kaga, 2004; Wakai, Lutter, Chen, & Maier, 2007).

Picton, Woods, & Proulx (1978b) and Davis and Zerlin (1966) describe onset-offset amplitudes that are larger for lower frequency stimuli (250 Hz) and smaller for higher frequency stimuli (8000 Hz). While the amplitudes are affected by stimulus frequency, there appear to be no significant differences in onset and offset latencies related to the frequency of the stimuli (Davis & Zerlin, 1966). Stimulus intensity has been shown to influence the onset response, with higher intensities leading to increases in

amplitude and decreases in latency (Picton et al., 1978b; Onishi & Davis, 1968). While some investigators suggest that there is little-to-no effect of stimulus duration and ISI on the amplitudes of the response (Johannsen, Keidel, & Spreng, 1972; Keidel, 1976), the opposite has also been suggested (Hillyard & Picton, 1978). Hillyard and Picton (1978) and Pantev and colleagues (1996) report that stimuli longer than 1000 ms and separated by ISIs longer than 4000 ms optimally evoke the onset-offset N1-P2 response. Pfefferbaum and colleagues (1971) found that when shorter stimuli (<1000 ms) are used to elicit the onset-offset response, the offset component is also reduced in amplitude, and when shorter ISIs (<4000 ms) are used to evoke the response, the onset component is reduced in amplitude. This disagreement among the small number of researchers who have studied this response has led to an ongoing debate concerning the generators of the onset and offset components of the response.

Generators of the Response

An important question that arises in the onset-offset N1-P2 literature is whether the onset and offset components share the same physiological generators or if there are distinct or possibly partially overlapping neural populations that give rise to the different components.

Same Generators

Hillyard and Picton (1978) sought to determine whether varying the duration and ISI of the stimuli eliciting the onset and offset components, respectively, of the N1-P2 response could shed light on whether or not the underlying neural generators of the onset

and offset components are independent of one another. When altering stimulus duration while keeping the inter-trial interval (ITI) stable at 10.24 seconds between stimulus onsets (thus, shortening the time between offset and onset), these researchers found that the onset response progressively decreased in amplitude with increasing stimulus duration, whereas the offset amplitudes decreased with progressively decreasing stimulus durations. These results echo those previously obtained by Pfefferbaum et al. (1971). Both groups of researchers state that their results support the idea that the onset and offset components either share the same generator or arise from systems that are closely and strongly related.

Overlapping Generators

Source analyses conducted via magnetoencephalography (MEG) in attempts to pinpoint specific generator sites of the components suggest that the N1 onset and N1 offset components of the response are generated in overlapping regions in the supratemporal plane of the auditory cortex, as are the P2 onset and P2 offset components, with the onset components showing greater source strength (similar to measurements of amplitude in electrophysiology) than the offset components (Hari et al., 1987; Joutsiniemi et al., 1989; Pantev et al., 1996). The generators of the N1 onset and N1 offset components seem to be located posterior and laterally to those generating the P2 onset and P2 offset components. Pantev and colleagues (1996), however, mention that although the areas of the cortex that generate these onset and offset responses appear to overlap, the activity may not be generated by the exact same neurons; rather, the

"overlapping spatial distribution of these neurons is consistent with the conclusion that a related functional role is performed" (p. 261).

Different Generators

While the neurons generating the onset and offset responses may be very close together in location, different neurons (i.e., excitatory versus inhibitory) may be responsible for evoking the onset and offset components. It is possible that the offset represents a "rebound after the inhibition in the presence of a stimulus" (Takahashi et al., 2004, p. 1568), such that a larger offset response is elicited when greater inhibition occurs during stimulus presentation and is then released when the stimulus turns off. The findings of Hillyard and Picton (1978) and Pfefferbaum et al. (1971) cited previously showing that offset amplitudes increase in size with increases in stimulus duration may support this idea. If true, the onset component would be the result of a largely excitatory response, while the offset component would be the result of an inhibitory process being released when the stimulus is turned off. According to Takahashi and colleagues (2004), "offset responses become large when inhibition becomes strong and long or terminates synchronously" (p. 1565), and the largest offset responses are noted with stimuli of long duration utilizing brief fall times. Also supporting the idea of different physiological generators of the onset and offset responses is the tonotopicity of the responses. While the onset response demonstrates frequency specificity in the auditory cortex, the offset response shows poor tonotopicity, with the response appearing along inhibitory response areas, or "inhibitory sidebands," that border the edges of the onset response (Takahashi et al., 2004).

A study by He (2001) supports the notion of distinct onset and offset response generators as well as differences in the tonotopicity of the responses in the auditory cortex by evaluating the responses in the medial geniculate body. In this study, neural generators of the onset response were found in the core of the ventral division of the medial geniculate body (MGv), while generators of the offset response were found along the periphery of the MGv or along its boundaries with other MGB divisions (i.e., medial and dorsal nuclei). The MGv is known to have precise tonotopic organization, whereas the medial and dorsal nuclei generally demonstrate broader frequency tuning (Malmierca & Hackett, 2010). The MGv projects to the tonotopically organized primary, or core, areas of the auditory cortex, while the dorsal nucleus projects to the non-primary, or belt, areas of the auditory cortex; these areas are known to have tonotopicity that is weak or absent (Malmierca & Hackett, 2010). The medial nucleus of the MGB projects to multiple areas of the auditory cortex, including the tonotopic (core) and non-tonotopic (belt) areas. According to Doron and Ledoux (1999), the medial nucleus also projects to non-auditory areas of the brain such as the striatum and amygdala. Thus, considering the segregated loci of the generators of the onset and offset responses in the MGB along with the known projections of the MGB to the auditory cortex, it is likely that the onset and offset responses in the auditory cortex also have distinct generators.

More advanced in-vivo single-cell animal recordings have also challenged the concept of a single onset-offset generator (Hari et al., 1987; Joutsiniemi et al., 1989; Pantev et al., 1996; Qin, Chimoto, Sakai, Wang, & Sato, 2007; Scholl et al., 2010; Takahashi et al., 2004). Evidence suggests that the onset and offset components of the response are generated by distinct, non-overlapping synapses in the auditory cortex

whose cells demonstrate imbalances in their excitation and inhibition patterns to the same stimuli (Qin et al., 2007; Scholl et al., 2010). Additionally, some cells respond primarily to stimulus onset, some to stimulus offset, and some to both stimulus onset and offset. Taken together, these findings suggest that the onset-offset auditory evoked response may reveal more information about how an individual processes sound at the level of the auditory cortex than does the traditional N1-P2 response. Despite this apparent advantage of the onset-offset N1-P2 response, an extensive literature search has revealed no research on this electrophysiologic response in individuals with disorders of the auditory system.

All studies investigating the onset-offset auditory evoked response have been completed on subjects with normal hearing, and the majority of these studies have utilized a 1000 Hz tone to evoke the response. As mentioned earlier, what is known about the response in normal hearing individuals is that the offset component is smaller in amplitude than the onset component (Spychala et al., 1969), the offset is larger with longer stimulus durations (>1000 ms), and the onset amplitude is reduced when shorter interstimulus intervals (<4000 ms) are used (Hillyard & Picton, 1978; Pantev et al., 1996). In their study on the onset-offset N1-P2 in normal hearing individuals using a broadband noise stimulus, Gonzalez and Musiek (2012) found that an increase in stimulus intensity from 40 dB SL to 70 dB SL resulted in increased onset and offset amplitudes and shorter onset latencies, while offset latencies remained stable. Additionally, the offset latencies measured appeared to be related to the ramp time (40 ms) of the broadband stimulus independent of intensity, with offset N1-P2 latency measurements for both intensities occurring about 40 ms earlier than predicted based on

onset N1-P2 criteria. These results suggest that the onset N1-P2 components are affected by the intensity of the stimulus and the steepness of the ramp at stimulus onset, while the offset appears to follow only the envelope of the stimulus. In both intensity conditions the offset was time-locked to the beginning of the offset ramp, occurring about 40 ms before the expected latency at the termination of the stimulus. Davis and Zerlin (1966) found that the onset response occurred when 10% of the stimulus dB SPL was reached, while the offset response occurred when the dB SPL fell to 90%, or when the total dB SPL of the stimulus decreased by 10%. This relationship of the offset was consistent for fall times up to at least 100 ms, and amplitude and latency measurements did not demonstrate consistent changes related to steepness, per se. A review of data presented by Pantev et al. (1996) and Hillyard and Picton (1978) revealed that the offset latencies may be related to the 10 ms ramp times used, as the offset components appear to have occurred an average of 13 ms earlier than would be expected using onset latency criteria. This suggests that the offset N1-P2 component is elicited shortly after the envelope changes from its plateau to offset ramp and not at the termination of the stimulus. As a result of the resistance of the offset latency to stimulus intensity changes (i.e., changes in stimulus audibility), this is an appealing measure to evaluate in individuals with peripheral hearing loss in an attempt to shed light on methods of distinguishing the effects of sensorineural hearing loss from central auditory dysfunction.

Purpose of the Study

While the changes in the central auditory nervous system resulting from sensorineural hearing loss mentioned earlier (i.e., neural excitation, neural inhibition,

spontaneous activity rates, neural synchrony and tonotopic organization) have been well documented in the auditory neuroanatomy and neurophysiology literature, the literature on the traditional, far-field N1-P2 in humans does not reflect the existence of enhancements in the response as a result of sensorineural hearing loss, and the literature on the onset-offset N1-P2 in sensorineural hearing loss is nonexistent. It is this author's position that the lack of support in the traditional N1-P2 literature may be related to the presentation level method used in the studies; i.e., the studies used dB nHL and/or dB SPL presentation levels without considering the participants' thresholds for the specific stimulus to record the responses while presenting the stimulus to both normal hearing and hearing impaired participants. As the presentation levels were closer to threshold in individuals with hearing loss than in individuals with normal hearing, reductions in amplitude and delays in latency could be expected. This method may not be the best to use when evaluating central auditory function. A more advantageous method for evaluating central auditory function in individuals with sensorineural hearing loss may be to use presentation levels referenced to each individual's threshold for the test stimulus. This could reduce the effect of sensorineural hearing loss on the N1-P2 auditory evoked response and allow for more "pure" and accurate evaluations of central auditory function in all individuals, regardless of peripheral hearing status; thus, any reduced amplitudes and delayed latencies observed would be indicative of central auditory dysfunction. Sensation level presentations are already used in behavioral central auditory tests that are least affected by sensorineural hearing loss (Musiek et al., 1991; Weihing, Musiek, & Shinn, 2007); thus, using dB SL in electrophysiologic evaluations of individuals with sensorineural hearing loss in order to specifically target their central auditory function

may be diagnostically valuable and may provide a solution to the comorbid CAPD and sensorineural hearing loss diagnostic dilemma that has plagued CANS testing for years.

The purpose of the present study was to determine if the N1-P2 onset-offset evoked response is affected by high-frequency sensorineural hearing loss when administered at two sensation levels – a moderate level (50 dB SL) such as is commonly done during the administration of most central auditory tests (Musiek, 1983) and a 70 dB SL intensity level to evaluate the effects of intensity. This study also examined whether the onset-offset N1-P2 evoked response is affected by high-frequency sensorineural hearing loss when evoked by broadband noise and narrowbands of noise centered at either 500 Hz or 4000 Hz. Evaluating the effects of high-frequency sensorineural hearing loss on the onset-offset N1-P2 evoked response was considered to be a necessary early step toward documenting the potential utility of this electrophysiologic response in the evaluation of patients at risk for CAPD, as many individuals evaluated in audiology clinics present with this type of hearing loss.

CHAPTER 3

Research Questions and Hypotheses

As mentioned earlier, while the auditory neuroanatomy and neurophysiology literature documents an enhancement effect of sensorineural hearing loss on the evoked responses from the rostral structures of the central auditory nervous system, these enhancements are not well documented in the traditional N1-P2 evoked response literature and are nonexistent in the onset-offset N1-P2 auditory evoked response literature. The hypotheses stated for the each of the research questions posed in this chapter reflect the results that would be expected based on the findings of the available N1-P2 auditory evoked response literature in experiments that have used common values of dB SPL to elicit waveforms (i.e., delayed latencies and reduced amplitudes for waveforms obtained from individuals with hearing loss compared to individuals with normal hearing). This was done in an effort to emphasize any differences in the results of the present study from those reported in the literature.

1. **Broadband Noise Stimuli**

   Are there significant differences in the onset-offset N1-P2 auditory evoked response between individuals with normal hearing and individuals with hearing loss for a broadband stimulus presented at 50 dB SL and 70 dB SL?

   Hypothesis 1a: For the 50 dB SL presentation level, participants with hearing loss will demonstrate longer onset latencies and smaller onset and offset amplitudes than the participants without hearing loss. Offset

latencies will not differ between groups (Gonzalez & Musiek, 2012; Hyde, 1997).

Hypothesis 1b: For the 70 dB SL presentation level, there will be no significant differences in amplitude or latency for the onset and the offset measures between the normal hearing group and the hearing loss group. Onset measurements for the hearing loss participants should approximate those obtained from the normal hearing participants at moderate to high sensation levels (Hyde, 1997).

2. **Intensity Effects**

   Across all subjects, are there differences in amplitude and latency measurements of the N1-P2 onset and offset waveform components to a broadband stimulus when presentation level increases from 50 dB SL to 70 dB SL?

   Hypothesis: For the onset response, increased amplitudes and shorter latencies will be observed when increasing the presentation level of a broadband stimulus from 50 dB SL to 70 dB SL. For the offset response, increased amplitudes will be observed with an increase in presentation level; however, there will be no significant changes in offset latency (Gonzalez & Musiek, 2012).

3. **Narrowband Noise Stimuli**

   Are there significant differences in the onset-offset N1-P2 auditory evoked

response obtained from individuals with normal hearing and individuals with hearing loss for a narrowband noise stimulus centered at 500 Hz and a narrowband noise stimulus centered at 4000 Hz when presented at 50 dB SL?

Hypothesis 3a: For the narrowband noise stimulus centered at 500 Hz, onset and offset amplitudes and latencies will not differ between groups (Lightfoot & Kennedy, 2006).

Hypothesis 3b: For the narrowband noise stimulus centered at 4000 Hz, onset and offset latencies will be longer and amplitudes will be decreased for the hearing loss group compared to the normal hearing group as there are audiometric differences between groups in this frequency region (Hyde, 1997; Lightfoot & Kennedy, 2006).

4. **Broadband versus Narrowband Noise Stimuli**

Are there significant differences in amplitude and/or latency measurements of the N1-P2 onset-offset waveform components when comparing responses to a narrowband noise centered at 500 Hz, a narrowband noise centered at 4000 Hz, and a broadband noise stimulus presented at 50 dB SL, regardless of group?

Hypothesis: The broadband noise condition will elicit the largest and earliest responses of the three noise conditions. The 4000 Hz-centered narrowband noise condition will elicit smaller amplitude responses than the 500 Hz-centered narrowband noise condition. Therefore, the progression of onset-offset N1-P2 amplitudes observed from smallest to

largest will be the following: narrowband noise centered at 4000 Hz, narrowband noise centered at 500 Hz, and broadband noise.

CHAPTER 4

Method

All procedures were approved by the Institution Review Board at the University of Connecticut prior to the recruitment of any study participants. Informed consent was obtained from each participant before the procedures were initiated.

Participants

Two groups were recruited for this study for a total enrollment of 17 participants. One group consisted of individuals with normal hearing bilaterally (n = 10; seven female, three male; mean age 52.9 years; age range 40 to 62 years) for all octave frequencies between 250 and 8000 Hz, while the other group consisted of subjects with bilateral high-frequency sensorineural hearing loss (n = seven; three female, four male; mean age 58.29 years; age range 50 to 67 years). High-frequency sensorineural hearing loss was defined as air conduction and bone conduction hearing thresholds less than or equal to 25 dB HL for octave frequencies between 250 and 1000 Hz, sloping to 40 to 55 dB HL thresholds for octave and interoctave frequencies between 2000 and 8000 Hz with air-bone gaps no greater than 10 dB. An a priori power-analysis completed in G*Power indicated that a total sample size of 14, or seven participants per group, would be appropriate to detect a medium effect-size of 0.5 with an alpha of 0.05 and a power of 0.95. Three participants in the hearing loss group were hearing aid users (two years, three years, and six years of experience), while the other four participants had no experience with hearing aids. Normal hearing participants were recruited from the University of Connecticut student body, faculty, and staff as well as through word of mouth. Participants with high-

frequency sensorineural hearing loss were recruited from the University of Connecticut Speech and Hearing Clinic, from the surrounding community, and through word of mouth. In order to participate in the study, participants in the hearing loss group were required to have had previously documented high-frequency sensorineural hearing loss, type A tympanograms (Jerger, 1970), speech reception thresholds (SRTs) that were in good agreement with pure-tone averages (i.e. within 10 dB), and a word recognition score of 72% or better in both ears using whole-word scoring. Each participant underwent preliminary qualifying procedures to ensure that he or she met the criteria for participation. Figure 2 displays the average pure-tone audiometric thresholds per group for all frequencies tested. Monetary compensation was provided to each participant. If the qualifying procedures revealed that a participant did not fit the criteria for participation, he or she was dismissed from the study and received partial compensation.

Procedures

Qualifying Phase

The preliminary auditory assessment included otoscopy, tympanometry, pure-tone audiometry, speech reception thresholds (SRT), and word recognition in quiet. Central auditory processing ability was screened using the Dichotic Digit Test (Musiek, 1983).

Otoscopy

Inspection of the ear canals and tympanic membranes of all study participants was conducted in both ears. Criteria for inclusion in the study included normal appearance of the external ear canals and tympanic membranes. Normal findings included tympanic

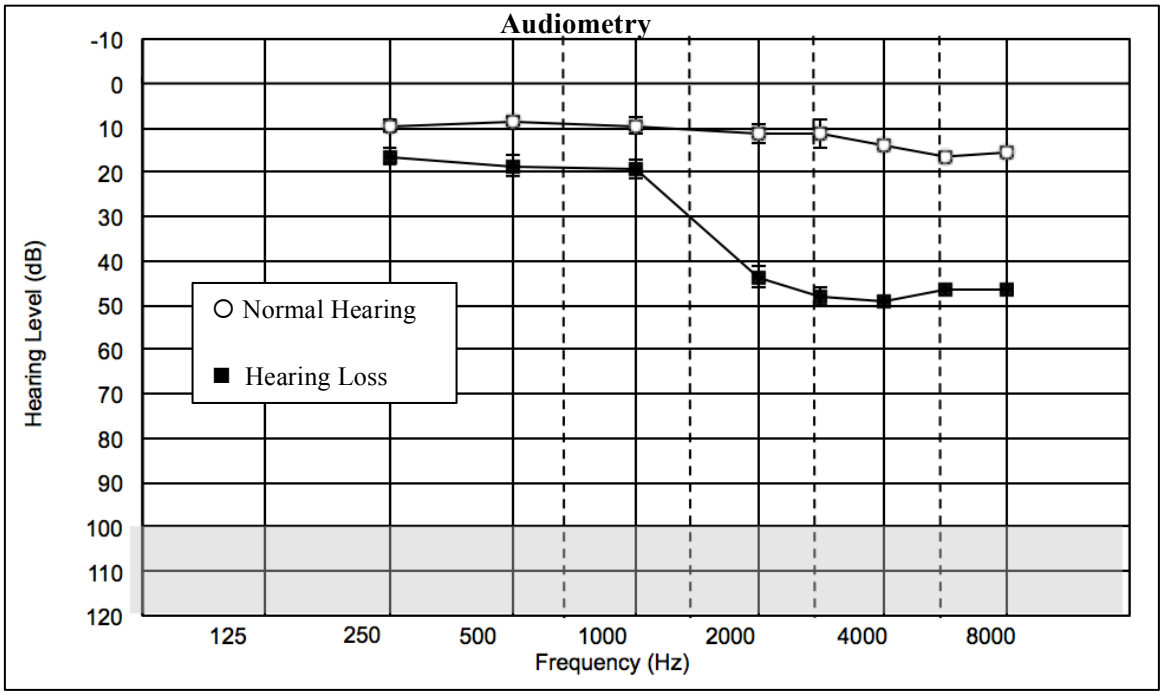

Figure 2. Mean pure tone thresholds for normal hearing (n = 10) and hearing loss (n = 7) groups. Brackets at each point indicate standard error.

membranes that were pinkish-grey in color and translucent in appearance with a cone of light visible in the anterior-inferior quadrant of the membrane. Ear canals were to be free of cerumen, which would prevent visualization of the tympanic membrane.

Tympanometry

Using a 226 Hz constant probe tone, tympanograms were obtained from both ears for each subject. Type A tympanograms (Jerger, 1970), were required for participation in the present study and are characterized as having tympanometric peak pressure between -150 and +100 daPa and static admittance/compliance between 0.3 and 1.7 mmho (Margolis & Goycoolea, 1993).

Audiometry

A pure-tone audiometric evaluation using a GSI 61 clinical two-channel audiometer (Grason-Stadler, Inc.) and utilizing the modified Hughson-Westlake procedure (Carhart & Jerger, 1959) was performed bilaterally for each subject using ER-3A insert earphones for air conduction and a B-71 bone oscillator for bone conduction. The difference between air and bone conduction thresholds was required to be no greater than 10 dB for each frequency tested.

Normal hearing was defined as hearing thresholds less than or equal to 25 dB HL for octave frequencies between 250 and 8000 Hz (American Speech-Language-Hearing Association, 1997). All subjects enrolled in the hearing loss group presented with high-frequency sensorineural hearing loss, defined as air conduction hearing thresholds in each ear less than or equal to 25 dB HL for octave frequencies between 250 and 1000 Hz,

sloping to 40 to 55 dB HL thresholds for each octave frequency between 2000 and 8000 Hz. Air bone gaps did not exceed 10 dB.

Speech Reception Threshold (SRT)

Using spondee words, speech reception thresholds were obtained for each participant for both ears. A descending and bracketing procedure with two spondee words presented at each level was utilized to obtain the SRT (Newby, 1958). Threshold was defined as the lowest level at which participants correctly repeated at least 50% of the spondee words and 5 dB below which there were no correct repetitions. Thresholds demonstrated good agreement (≤10 dB difference) with the three-frequency pure-tone average (500, 1000, and 2000 Hz) for normal hearing participants and the two-frequency pure-tone average (500 and 1000 Hz) for participants with hearing loss.

Word Recognition

Using NU-6 Ordered by Difficulty recorded word lists (Hurley & Sells, 2003; Tillman & Carhart, 1966) presented in quiet, word recognition percentages were obtained for each subject in each ear. Words were presented at 50 dB SL re: SRT for each participant. The NU-6 recorded word lists are organized such that the first 10 words are the most difficult. If a participant repeated all 10 of these first words correctly, that participant was deemed to have passed the screening for that ear. If at least one out of the 10 words was not repeated correctly, testing continued until 25 words were presented to that ear. A percentage of 72% or better (18 out of 25 words correct) on a 25-word list using whole-word scoring was required for participation in the study. A score of 72%

corresponds to a maximum pure-tone average (PTA) of 28 dB HL (aligning with the maximum two-frequency PTA allowed for 500 and 1000 Hz) using the 95% confidence limits published by Dubno, Lee, Klein, Matthews, and Lam (1995); thus, a minimum score of 72% on word recognition in quiet was required of all participants with hearing loss in order to participate in the study.

Dichotic Digit Test

This test was used to screen the integrity of the central auditory nervous system. The task involves the presentation of four different numbers (digits 1-10, excluding 7) in two pairs to the ears – one delivered to the right ear and left ear simultaneously (first pair) followed in quick succession by another delivered to the right and left ear simultaneously (second pair). The participant was required to repeat all four numbers presented in no particular order. The numbers were presented bilaterally to each participant through ER-3A insert earphones at 50 dB SL referenced to the previously obtained SRT. A score of 90% or better bilaterally for normal hearing individuals or 80% or better bilaterally for individuals with moderate high-frequency sensorineural hearing loss was required for participation in the study (Musiek, 1983; Musiek et al., 1991).

Experimental Phase

Equipment

Participants who met the inclusion criteria for the study were asked to continue through the experimental procedure. Onset-offset N1-P2 evoked responses were obtained using the Neuroscan evoked potential system with SynAmps^2 amplifier. Stimuli

were delivered to the right or the left ear (chosen randomly) of each subject via ER-2 insert earphones. Stimuli were generated using the MLSig toolbox in Matlab R2009a and stored on a desktop PC. The code used to construct the stimuli is demonstrated in Appendix B, with explanations of the coding terminology demonstrated in Appendix C. Sequences of each stimulus type were constructed in the Gentask module in the Neuroscan system. Each sequence file consisted of 400 stimuli. This ensured that 100 accepted trails to each stimulus type would be obtained in case of rejected trials due to artifact rejection, as a greater number of stimulus repetitions were contained in the file than were required to reach the 100 accepted trial and rejection rate criteria. The Neuroscan Acquire module of the Scan 4.4 software was used to record the onset-offset N1-P2 auditory evoked response waveforms. The resulting waveforms were edited using the Neuroscan Edit module.

Stimuli

The three stimulus types used in the study included broadband noise (20 to 10,000 Hz) and two narrowband noises centered at 500 and 4000 Hz respectively, each of which was one equivalent rectangular bandwidth (ERB) wide (Glasberg & Moore, 1990), where F is frequency in kHz:

$$\mathrm{ERB(Hz)} = 24.7(4.37F + 1) \qquad \text{(Eq. 1)}$$

Using Eq. 1 resulted in the 500 Hz-centered narrowband noise containing frequencies ranging from 460 through 540 Hz (80 Hz wide), and the 4000-Hz centered

narrowband noise containing frequencies ranging from 3,771 Hz through 4,229 Hz (458 Hz wide). A 20,000 Hz sampling rate was used in the construction of each stimulus. All stimuli were 2000 ms in duration, including 40 ms cosine-squared onset and offset ramps, and a 4500 ms interstimulus interval was utilized (Hillyard & Picton, 1978; Pantev et al., 1996). Ten versions of each noise were used to construct the string of 400 repetitions mentioned earlier. Each stimulus type is displayed in Figures 3a through 3c.

*P*rocedure

Behavioral thresholds for each of the three stimulus types were obtained using a bracketing procedure similar to the modified Hughson-Westlake method (Carhart & Jerger, 1959). Each stimulus condition was presented to each subject at 50 dB SL, and the broadband noise condition was presented to each subject a second time at 70 dB SL. Thus, four stimulus conditions were presented to each participant in this study.

Grass Ag/AgCl disc electrodes were placed on the participant's head at the following locations specified in the International 10-20 system: Cz (active/non-inverting), the earlobe on the side of stimulation (A1 or A2 – reference/inverting), the earlobe opposite to the side of stimulation (A2 or A1 – ground), and the outer canthus of the eye (eyeblink rejection). Electrode impedances did not exceed 5.4 kohm.

After the electrodes were placed, the participants were led into a sound-treated booth where they sat in a reclining chair. Participants were instructed to remain as still and relaxed as possible and to fixate their eyes on a designated point at eye level while relaxing their neck and jaw. If waveform acquisition with eyes open led to excessive rejections (i.e., rejection rates nearing the upper bound of acceptance for waveform

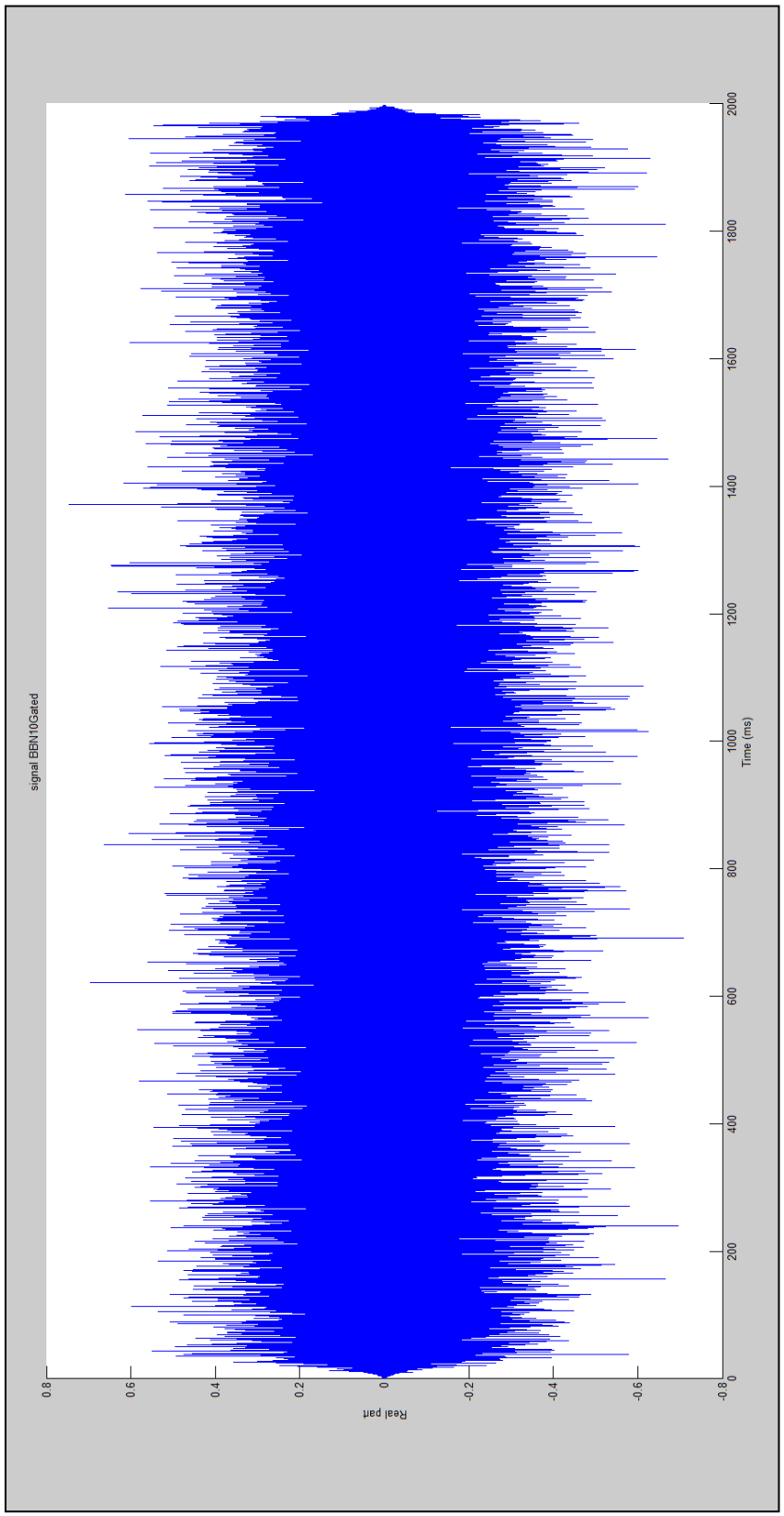

Figure 3a. One of 10 broadband noises created using the MLSig toolbox for MatLab.

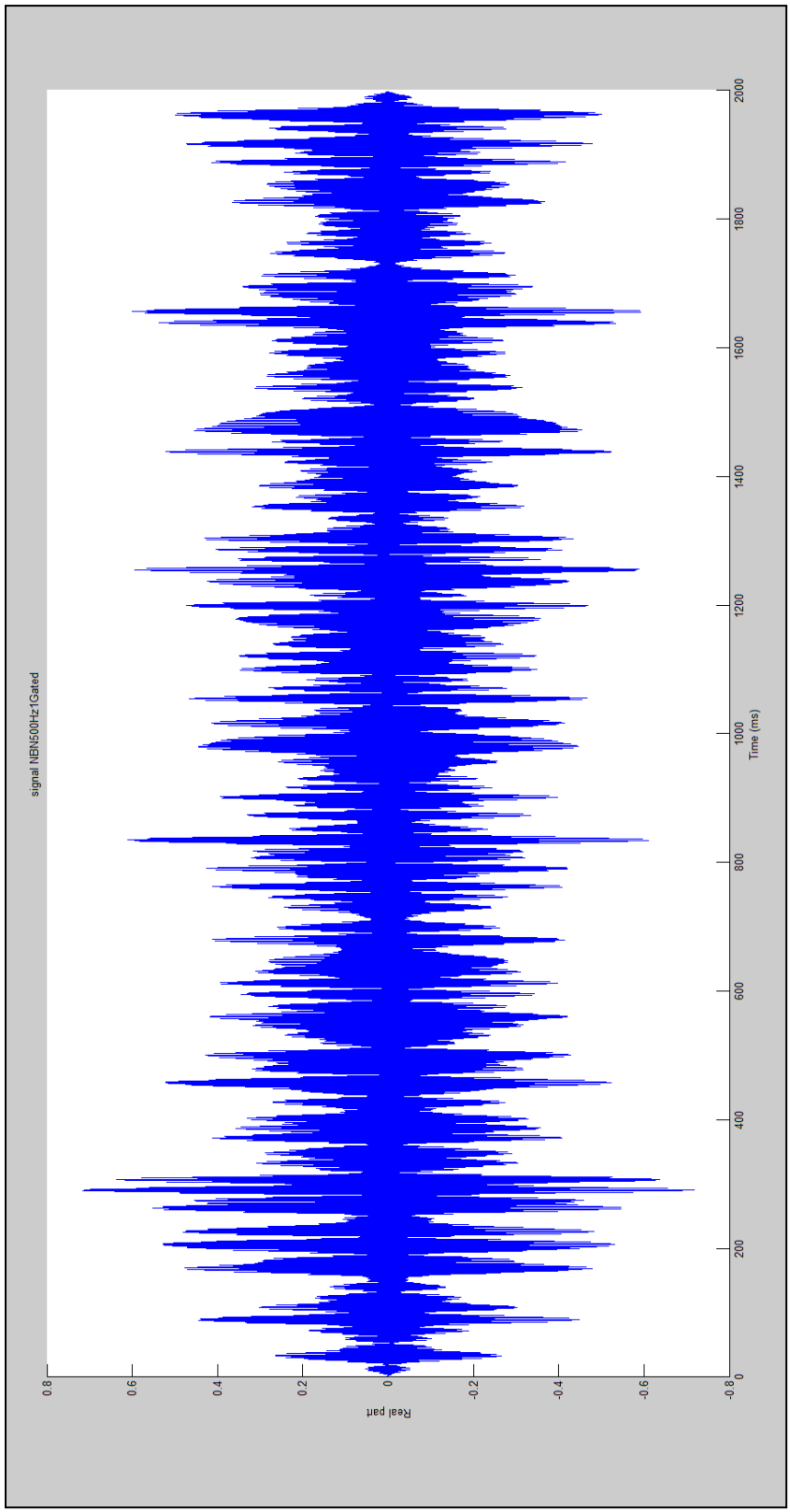

Figure 3b. One of 10 500 Hz-centered narrowband noises created using the MLSig toolbox for MatLab.

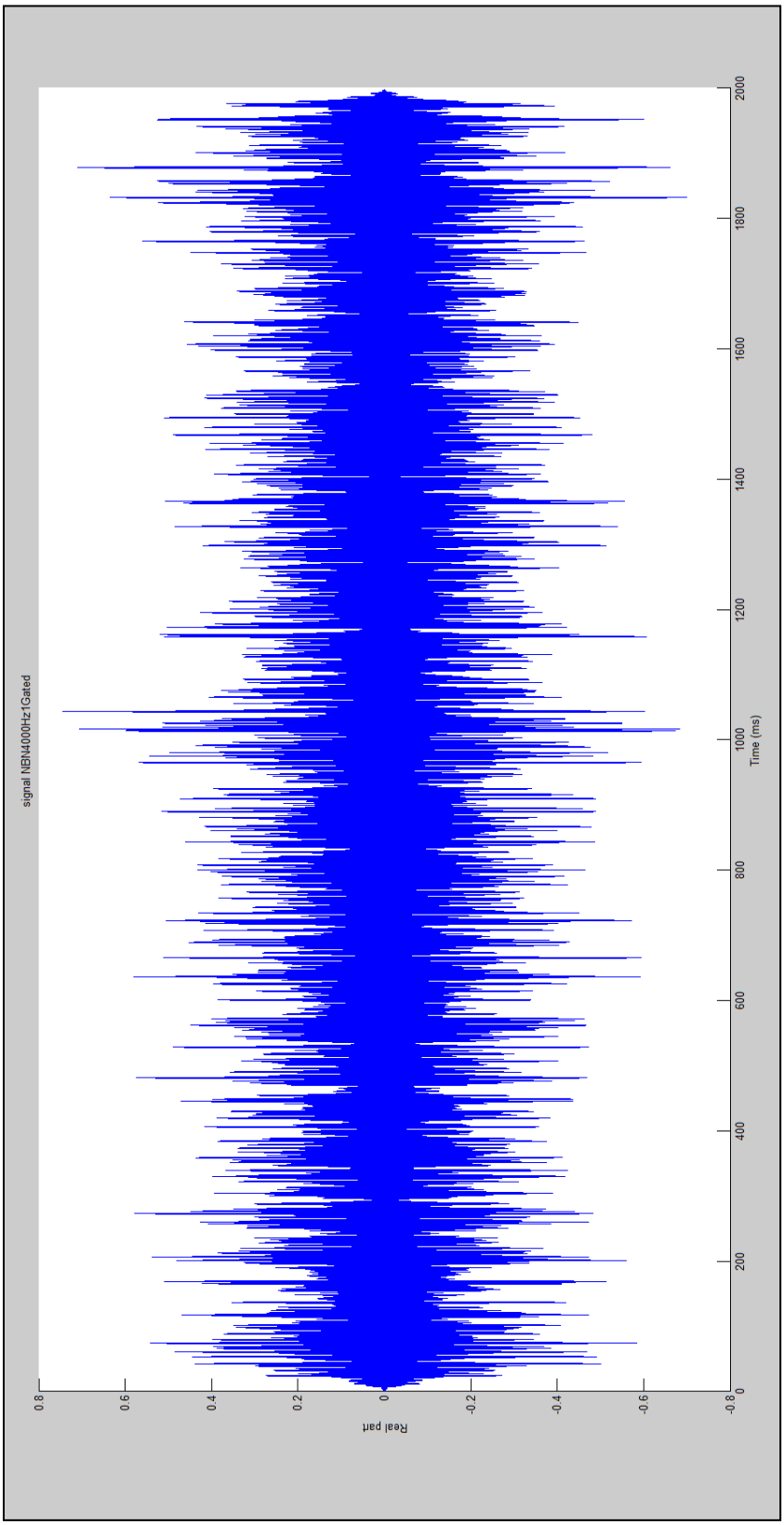

Figure 3c. One of 10 4000 Hz-centered narrowband noises created using the MLSig toolbox for MatLab.

analysis, or 20%), waveforms were acquired with the eyes closed. Ongoing EEG activity was monitored throughout the testing session to ensure that each subject remained awake during the experimental procedures.

The order of presentation of the four stimulus conditions was pseudorandomized within each group. Each stimulus was presented once every 6.5 seconds to each participant in blocks such that the broadband, 500 Hz-centered narrowband, and 4000 Hz-centered narrowband noise stimuli were presented in separate blocks. Stimuli were repeated until 100 accepted trials were obtained for each block. A rejection rate of less than 20% was required in order for a waveform to be included in waveform analysis. Actual rejection rates were typically 10 to 15% or less. Waveforms were acquired using a 3000 ms interval. Two waveforms for each stimulus were obtained and filtered online from 0.1 to 100 Hz. The two waveforms obtained were then averaged together and post-hoc filtered from 1 to 30 Hz. Thus, there were four "final" onset-offset N1-P2 waveforms for each participant – one for each noise condition. Participants were checked for fatigue and breaks were offered, though not always taken, after each waveform was obtained.

Waveform Analysis

Waveform analysis consisted of baseline-to-trough, baseline-to-peak, and trough-to-peak amplitude (in μV) (Davis & Zerlin, 1966; Onishi & Davis, 1968) and latency measurements for the N1 and P2 components of both the onset and offset portions of each waveform. N1 onset was defined as the deflection of greatest negative amplitude occurring between 80 and 150 ms post-stimulus onset, and P2 onset was defined as the

deflection of greatest positive amplitude that occurred between 140 and 250 ms post-stimulus onset. For the offset components, N1 was specified as the deflection of greatest negative amplitude occurring between 2030 and 2150 ms post-stimulus onset, while P2 was specified as the deflection of greatest positive amplitude occurring between 2110 and 2290 ms post-stimulus onset. These latency ranges were chosen based on traditional N1-P2 evoked response literature (Hall, 2007; Picton et al., 1977) as well as onset-offset N1-P2 latency results obtained from normal hearing participants in studies previously conducted in the Neuroaudiology Lab at the University of Connecticut (Gonzalez & Musiek, 2012, 2014). A bifid peak (P2) or trough (N1) was considered present in the response if two peaks or troughs of maximum amplitude differed by 0.1 μV or less. If bifid peaks (P2) or troughs (N1) were present, latency was defined as the midpoint between peaks or troughs, and the largest peak or trough was used for measurements of amplitude. In order for waveforms to be deemed present, troughs and peaks had to be distinguishable from the ongoing baseline in amplitude and morphology and needed to occur within the specific time ranges just described. Appropriate waveform morphology and presence of waveform components for all participants in both groups was verified by at least two individuals who were experts in the analysis of cortically evoked auditory potentials. Presence of any questionable waveform components was confirmed by viewing mean global field power (MGFP) plots on the Neuroscan evoked potential system. Use of MGFP allows for the estimation of overall background noise so that waveform components may be more easily identified (Baltzell & Billings, 2014). Figure 4 shows representative onset-offset N1-P2 responses from two individuals with normal hearing when a broadband stimulus was presented at a moderate intensity level.

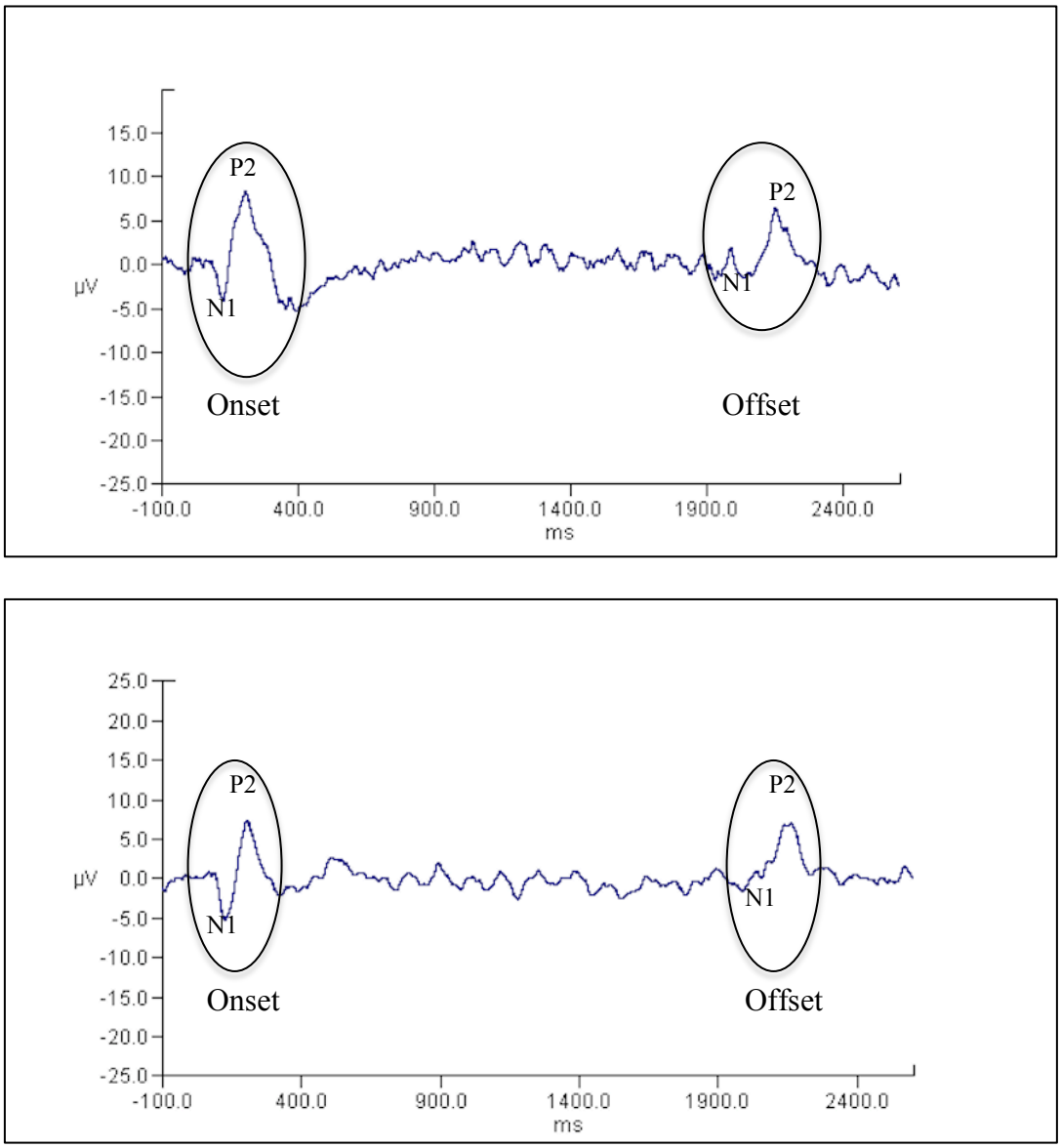

Figure 4. Onset-offset N1-P2 waveforms obtained from two different subjects using a broadband noise stimulus 2000 ms in duration and presented at a moderate intensity level. The interval between the onset and offset components is commonly referred to as the "sustained potential."

CHAPTER 5

Results

Overview

Grand average waveforms for all four stimulus conditions are presented in Figures 5 through 8. Mean presentation levels in dB SPL are presented in Appendix A. There were no significant differences between groups for any of the waveform components elicited by the two broadband noise conditions. Significant and meaningful between-group differences were found for four waveform components (N1 onset latency, P2 offset latency, and P2 offset amplitude to 4000 Hz-centered narrowband noise and N1 onset latency to 500 Hz-centered narrowband noise), with the participants with hearing loss having shorter latencies and larger amplitudes than the participants with normal hearing. Offset-to-onset N1-P2 trough-to-peak amplitude ratios for the 4000 Hz-centered narrowband noise condition were meaningfully and significantly larger for the participants with hearing loss than they were for the participants with normal hearing.

Two-tailed independent samples t-tests were performed to test for significant differences between groups for age or pure-tone thresholds at 250, 500, and 1000 Hz. The groups did not differ in age [$t(15) = -1.662$; $p = 0.117$]. Although thresholds for each of these three frequencies for each participant fell within the range of clinically normal hearing for adults ($\leq$ 25 dB HL) as was required by the inclusion criteria for the study and group averages did not differ by more than 10 dB (250 Hz, normal hearing = 9.5 dB HL, hearing loss = 15.8 dB HL; 500 Hz, normal hearing = 8.5 dB HL, hearing loss = 18.3 dB HL; 1000 Hz, normal hearing = 9.5 dB HL, hearing loss = 18.3 dB HL), statistically significant differences between groups were found for the 250 Hz [$t(15) = -2.695$; $p =$

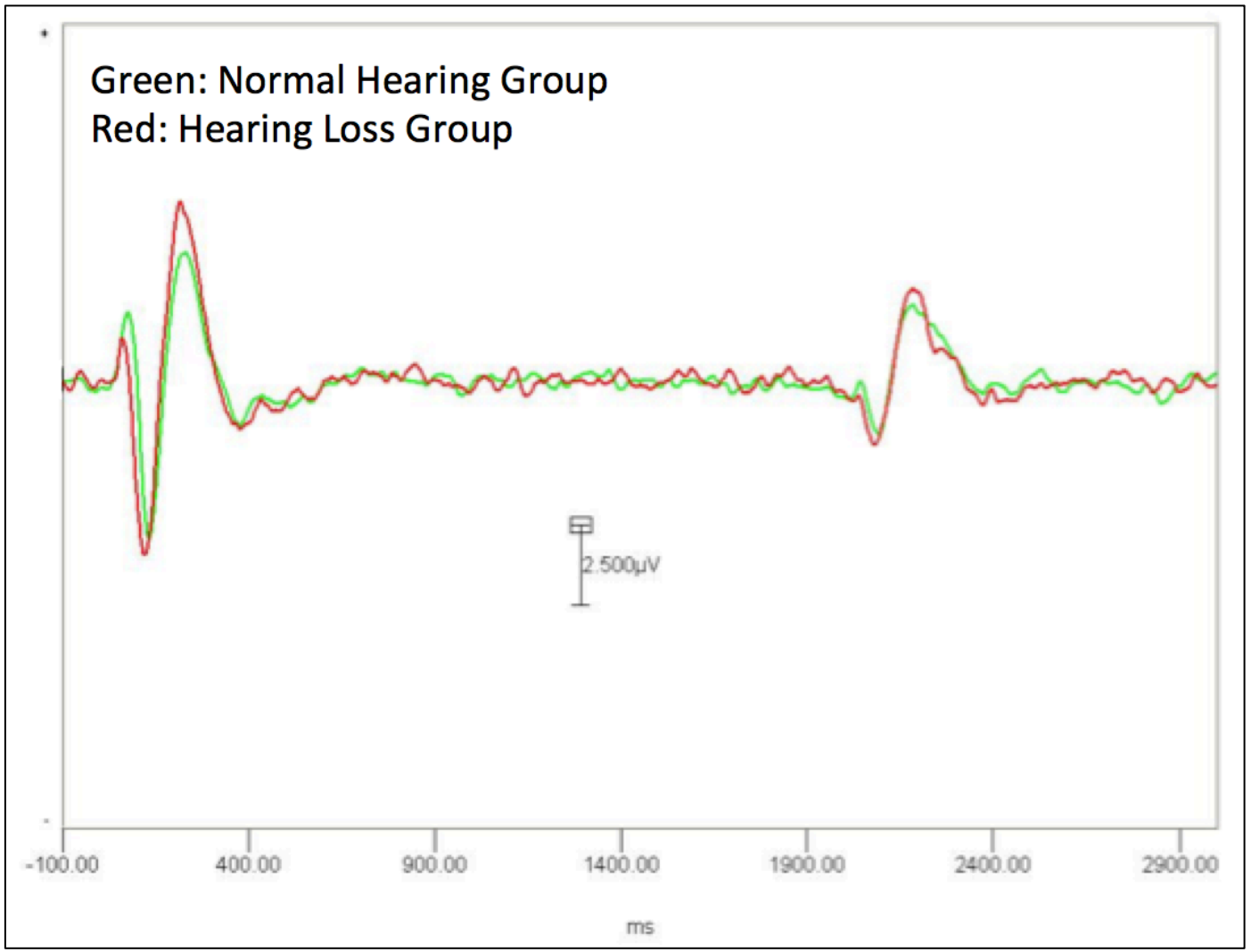

Figure 5. Grand average onset-offset N1-P2 waveforms evoked by broadband noise presented at 50 dB SL (GREEN: normal hearing group, n = 10; RED: hearing loss group, n = 7).

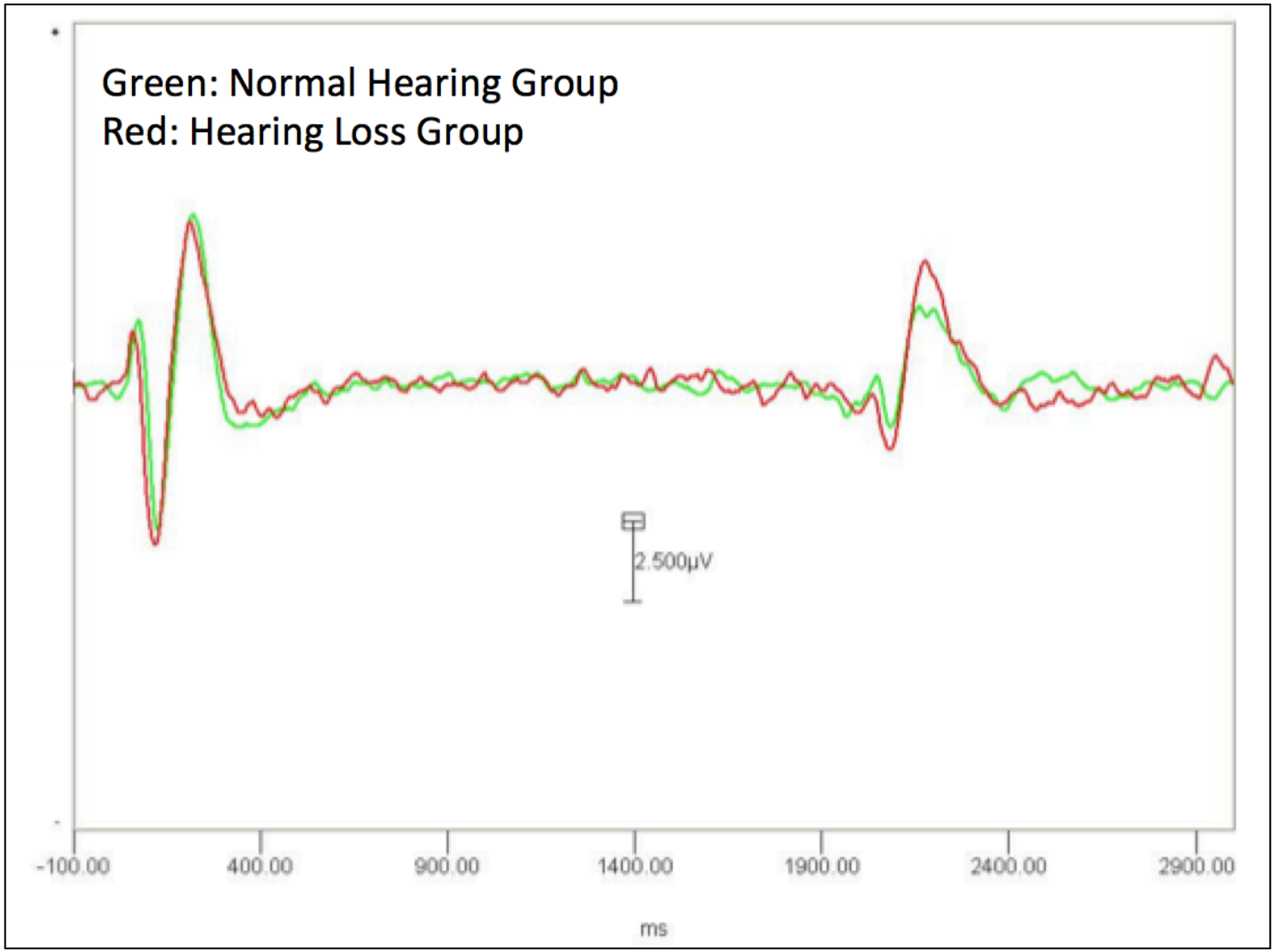

Figure 6. Grand average onset-offset N1-P2 waveforms evoked by broadband noise presented at 70 dB SL (GREEN: normal hearing group, n = 10; RED: hearing loss group, n = 7).

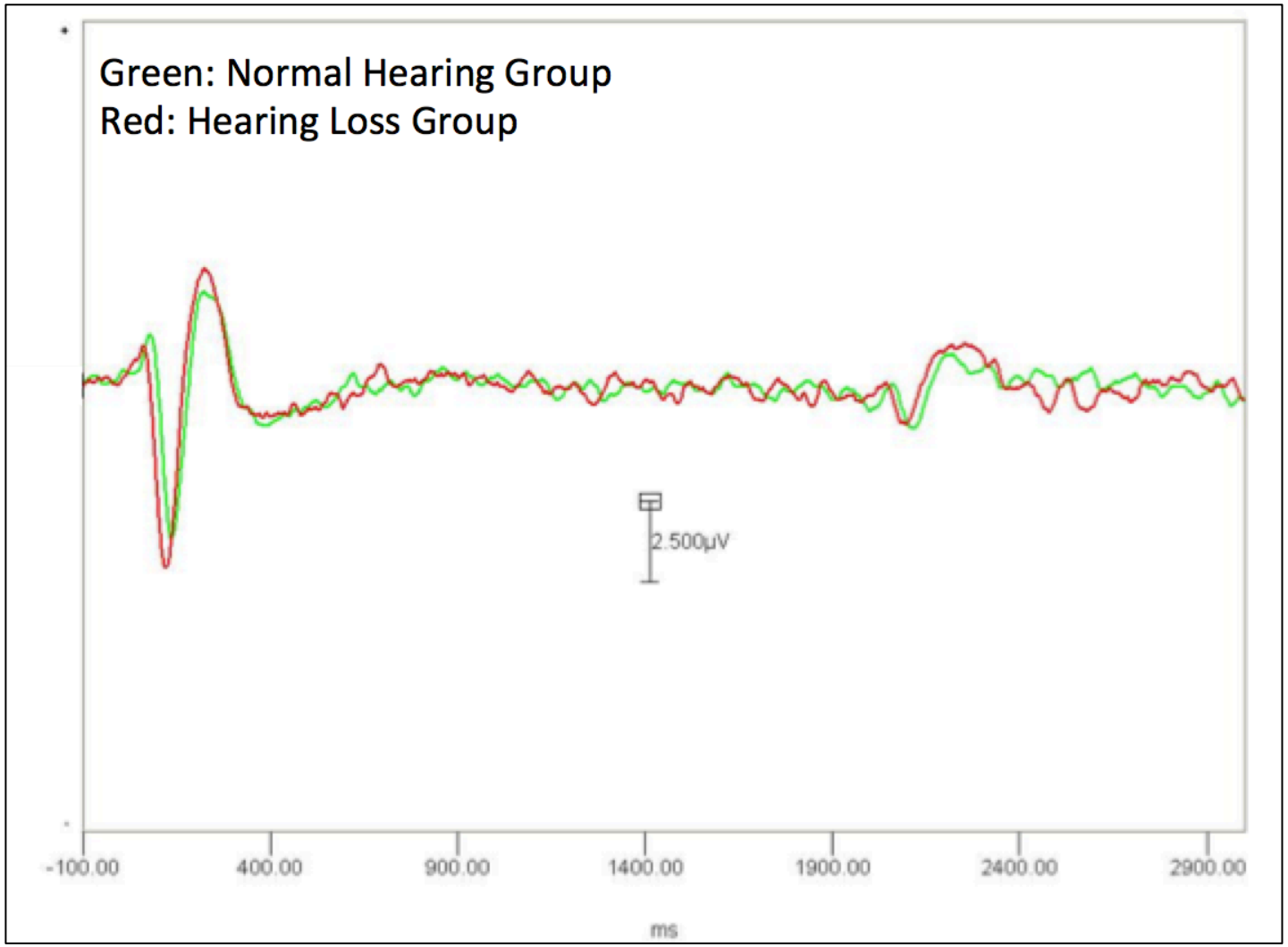

Figure 7. Grand average onset-offset N1-P2 waveforms evoked by 500 Hz-centered narrowband noise presented at 50 dB SL (GREEN: normal hearing group, n = 10; RED: hearing loss group, n = 7).

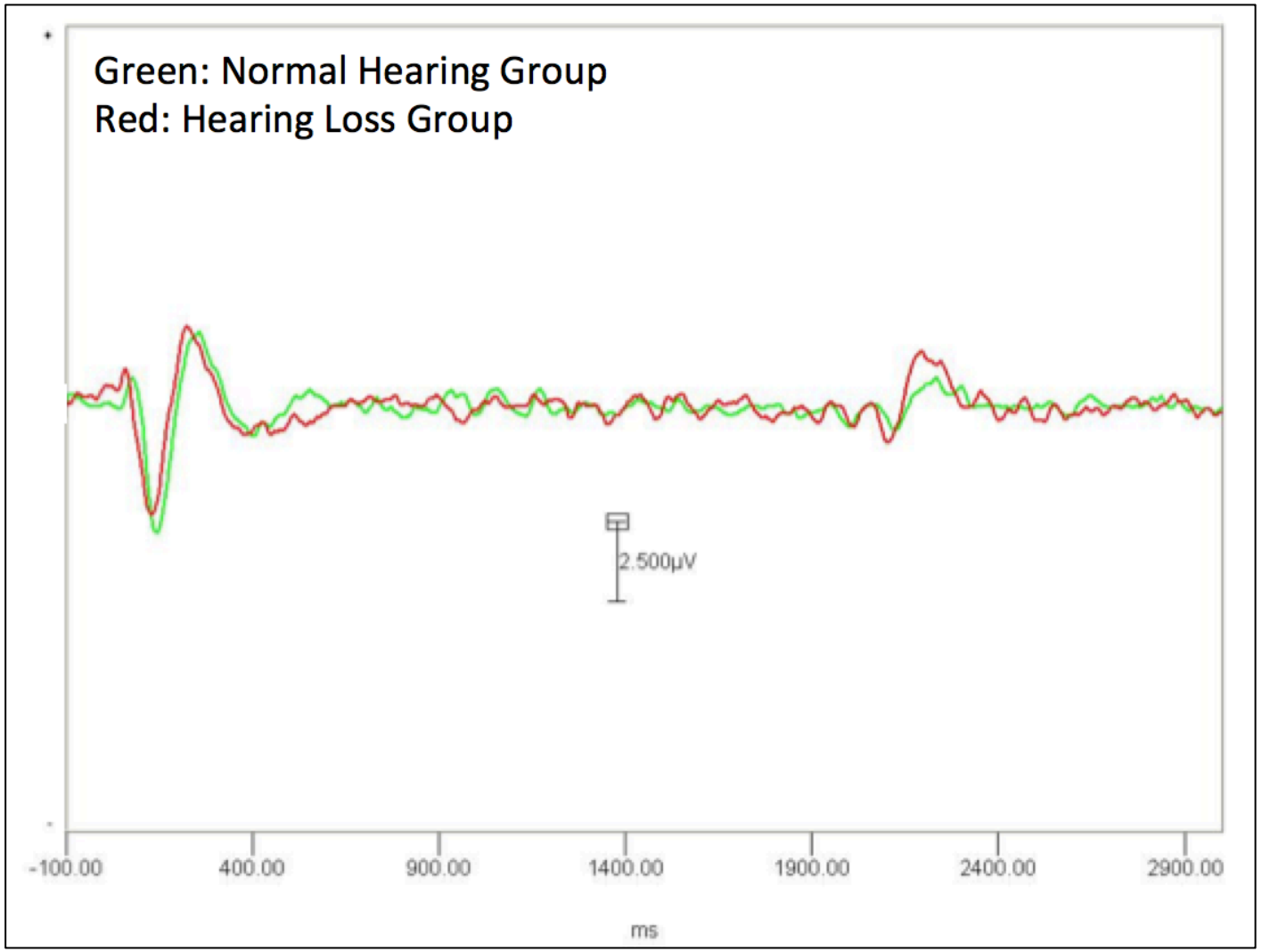

Figure 8. Grand average onset-offset N1-P2 waveforms evoked by 4000 Hz-centered narrowband noise presented at 50 dB SL (GREEN: normal hearing group, n = 10; RED: hearing loss group, n = 7).

0.017], 500 Hz [t(15) = -4.304; p = 0.001], and 1000 Hz [t(15) = -4.486; p = 0.000] pure-tone audiometric threshold data.

Waveforms were obtained from equal numbers of right and left ears in the normal hearing group, and from three right ears and four left ears in the hearing loss group. N1-P2 onset-offset responses to all four stimulus conditions were evoked in 16 of the 17 participants. One participant in the normal hearing group had onset and offset responses to the 4000 Hz-centered narrowband noise stimulus as well as to both intensities of the broadband noise stimulus; however, while this participant demonstrated a distinct N1-P2 onset response to the 500 Hz-centered narrowband noise stimulus, a clearly defined offset response could not be identified.

Morphologically, onset N1-P2 responses were robust, with amplitudes and latencies that were easily identifiable in both groups. While the hearing loss group had robust offsets to the broadband noise conditions, overall, their individual offset responses to the 500 Hz- and 4000 Hz-centered narrowband noise conditions were more clearly defined from the ongoing baseline compared to those obtained from their normal hearing counterparts. This is likely due to slightly larger response amplitudes demonstrated by the hearing loss group compared to the normal hearing group. Paired samples t-tests revealed that onset N1-P2 trough-to-peak amplitudes were significantly larger than offset N1-P2 trough-to-peak amplitudes for the normal hearing group for all stimulus conditions [500 Hz: t(8) = 7.864, p = 0.000; 4000 Hz: t(9) = 5.546, p = 0.000; broadband noise at 50 dB SL: t(9) = 4.055, p = 0.003; broadband noise at 70 dB SL: t(9) = 6.004, p = 0.000]. For the hearing loss group, onsets were significantly larger than the offsets for all stimulus conditions as well [500 Hz: t(6) = 6.040, p = 0.001; 4000 Hz: t(6) = 2.987, p =

0.024; broadband noise at 50 dB SL: $t(6) = 4.078$, $p = 0.007$; broadband noise at 70 dB SL: $t(6) = 4.331$, $p = 0.005$].

Statistical analyses of the N1-P2 onset-offset waveform components were performed via repeated-measures analyses of variance (ANOVA) of mixed design. There were two major groupings of analyses, one consisting of the responses from the 500 Hz-centered narrowband, 4000 Hz-centered narrowband, and broadband noises presented at 50 dB SL (3 stimulus types and 2 groups) and another consisting of the responses from the broadband noise conditions presented at 50 and 70 dB SL (2 stimulus types and 2 groups). Separate analyses were performed for each waveform component (N1 onset, P2 onset, N1 offset, P2 offset) for amplitude and latency. Pairwise comparisons of the stimulus types were made for the analyses that consisted of the three noises presented at 50 dB SL, with significance determined using a Bonferroni corrected alpha level of 0.017 (0.05 divided by three) to reflect the three comparisons and to reduce the chance of false positive results (i.e., type I error). As the analyses of the broadband noise conditions only consisted of two stimulus levels, pairwise comparisons were not necessary; therefore, significance between these two conditions was determined at the 0.05 alpha level. Between-group comparisons of trough-to-peak N1-P2 offset-to-onset amplitude ratios were performed using two-tailed independent samples t-tests, as were comparisons of absolute offset-to-onset latency measurements.

The statistical analyses were performed using type III sums of squares, which is the sum of the squared differences of unweighted marginal means (Shaw & Mitchell-Olds, 1993). Use of the type III sums of squares is recommended for analyses of data from unbalanced samples, as effect estimates using this method are not a function of the

frequency of observations in either group and, therefore, are not sample size dependent (Shaw & Mitchell-Olds, 1993; University of Toronto, 2009). Thus, the unbalanced group sizes in the present study did not affect the results of the statistical analyses.

Research Question 1: Broadband Noise Stimuli

Hypothesis 1a

The expectation was that participants with hearing loss would demonstrate longer onset latencies and smaller onset and offset amplitudes than the participants without hearing loss. It was also hypothesized that offset latencies would not differ between groups.

Amplitude and latency measurements for all N1-P2 onset-offset components measured were not significant at the 0.05 alpha level. Thus, there were no significant differences between groups for the onset-offset N1-P2 auditory evoked response when elicited by the broadband noise condition presented at 50 dB SL (normal hearing: 62 dB SPL presentation level; hearing loss: 76 dB SPL) . Mean amplitude and latency measurements to the broadband noise stimulus presented at 50 dB SL for the normal hearing and hearing loss groups are presented in Figures 9 to 11.

Comparisons of N1 offset latency to N1 onset latency and P2 offset latency to P2 onset latency were made using Eq. 2 and Eq. 3, where "N1 onset," "N1 offset," "P2 onset," and "P2 offset" represent the absolute latencies of those components and "2000" represents the entire duration of the stimulus (in ms). These comparisons were made to determine the relative differences in latency of the offset components compared to the onset components.

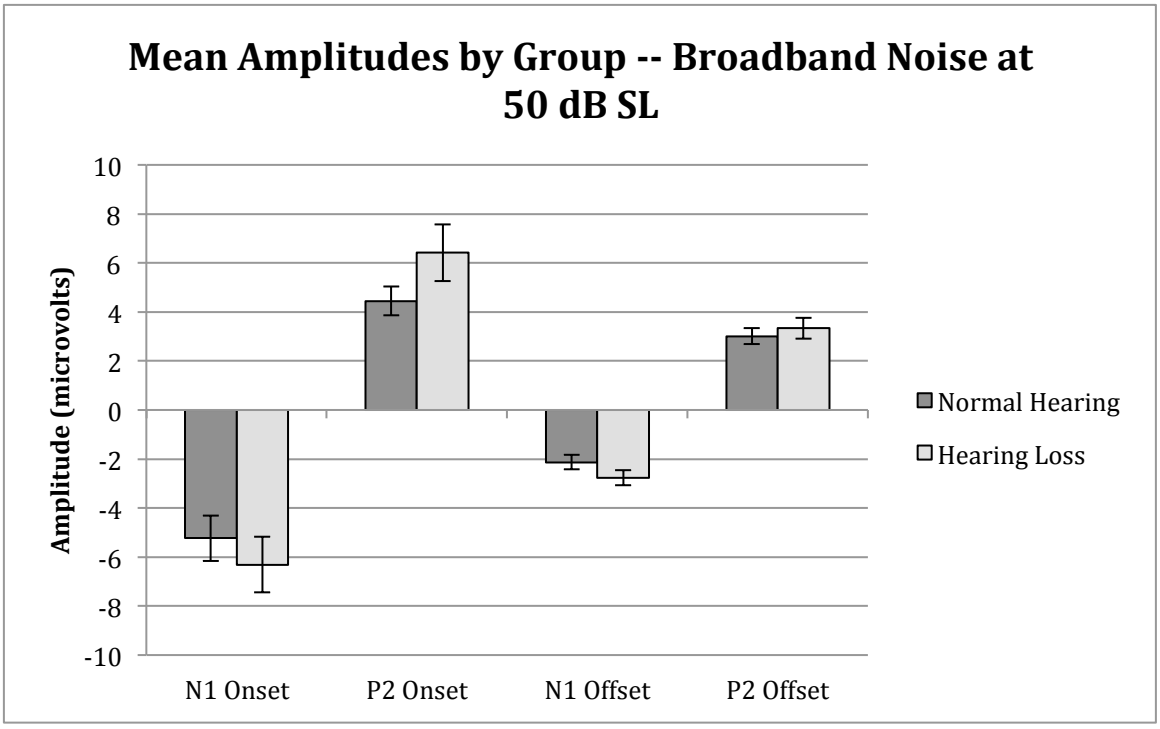

Figure 9. Mean amplitudes by group for the broadband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

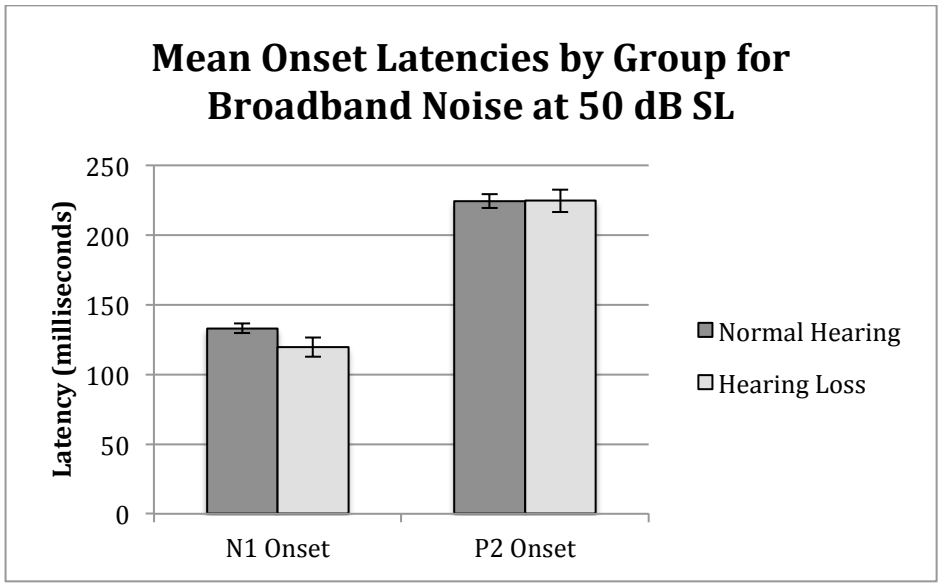

Figure 10. Mean onset latencies by group for the broadband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

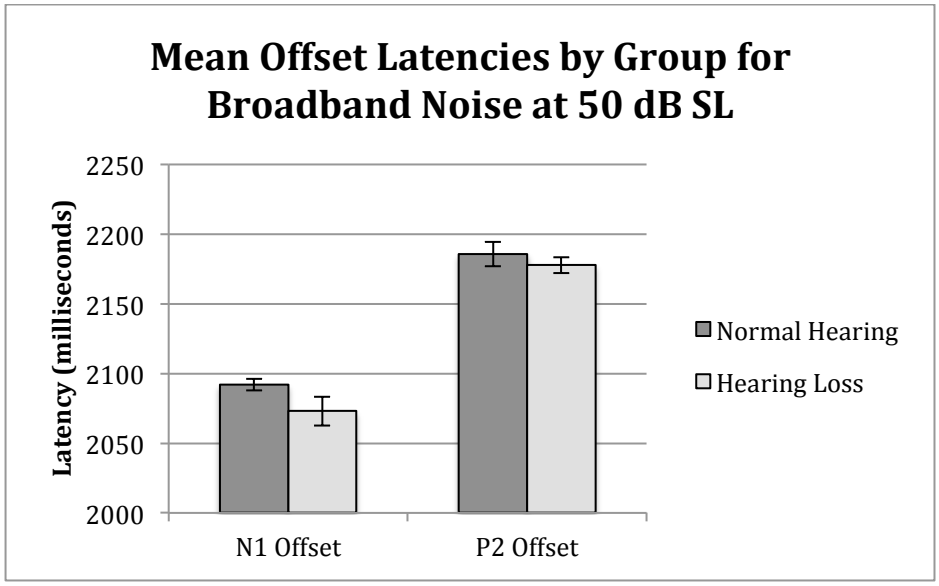

Figure 11. Mean offset latencies by group for the broadband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

$$\text{N1 Difference (ms)} = \text{N1 onset} - (\text{N1 offset} - 2000) \quad \text{(Eq. 2)}$$

$$\text{P2 Difference (ms)} = \text{P2 onset} - (\text{P2 offset} - 2000) \quad \text{(Eq. 3)}$$

Calculations using Eq. 2 resulted in mean N1 differences of 43.60 ms for the normal hearing group and 46.57 ms for the hearing loss group. A two-tailed independent samples t-test was not significant [$t(15) = -0.372$; $p = 0.715$], so the data obtained from both groups were collapsed. After collapsing the normal hearing group's data with the hearing loss group's data, the mean latency difference for N1 was 44.82 ms, with the offset having a shorter relative latency than the onset.

Using Eq. 3 it was found that the normal hearing group demonstrated a mean P2 difference of 42.80 ms, while the hearing loss group demonstrated a mean difference of 46.79 ms. A two-tailed independent samples t-test of these differences was not significant [$t(15) = -0.314$; $p = 0.758$], so the data for both groups were collapsed. The mean P2 onset-offset latency difference after collapsing the normal hearing group's data with the hearing loss group's data was 44.44 ms, with the offset response having a shorter relative latency than the onset response.

An offset-to-onset amplitude ratio was calculated for each participant by dividing the offset N1-P2 trough-to-peak amplitude by the onset N1-P2 trough-to-peak amplitude. The mean ratio for the normal hearing group was 0.62 (range 0.34-1.62), while the mean ratio for the hearing loss group was 0.51 (range 0.40-0.64). A two-tailed independent samples t-test performed on these ratios by group did not reveal a statistically significant

difference [t(15) = 0.755; p = 0.462]. The offset-to-onset amplitude ratio after combining the normal hearing group with the hearing loss group was 0.58.

Hypothesis 1b

No significant differences in amplitude or latency measurements for the onset and the offset responses between the normal hearing group and the hearing loss group were expected. It was also hypothesized that onset measurements for the hearing loss participants should approximate those obtained from the normal hearing participants at moderate to high sensation levels (Hyde, 1997). Therefore, no differences in either amplitude or latency measures were expected between groups for this broadband stimulus condition (i.e., 70 dB SL re: behavioral threshold). Results support that this was the case for all onset-offset N1-P2 measurements.

No significant differences between groups were found for amplitude or latency for the N1-P2 onset-offset waveform components when evoked by the broadband noise presented at 70 dB SL (average normal hearing presentation level: 82 dB SPL; average hearing loss presentation level: 96 dB SPL). Mean amplitude and latency measurements to the broadband noise stimulus presented at 70 dB SL for the normal hearing and hearing loss groups are presented in Figures 12 to 14.

Comparisons of N1 offset latency to N1 onset latency as well as P2 offset latency to P2 onset latency were made using Eq. 2 and Eq. 3. These calculations resulted in mean N1 differences of 50.50 ms for the normal hearing group and 37.93 ms for the hearing loss group. A two-tailed independent samples t-test was not significant [t(15) = 0.157; p = 0.157], so the data for both groups were collapsed. After combining the normal hearing

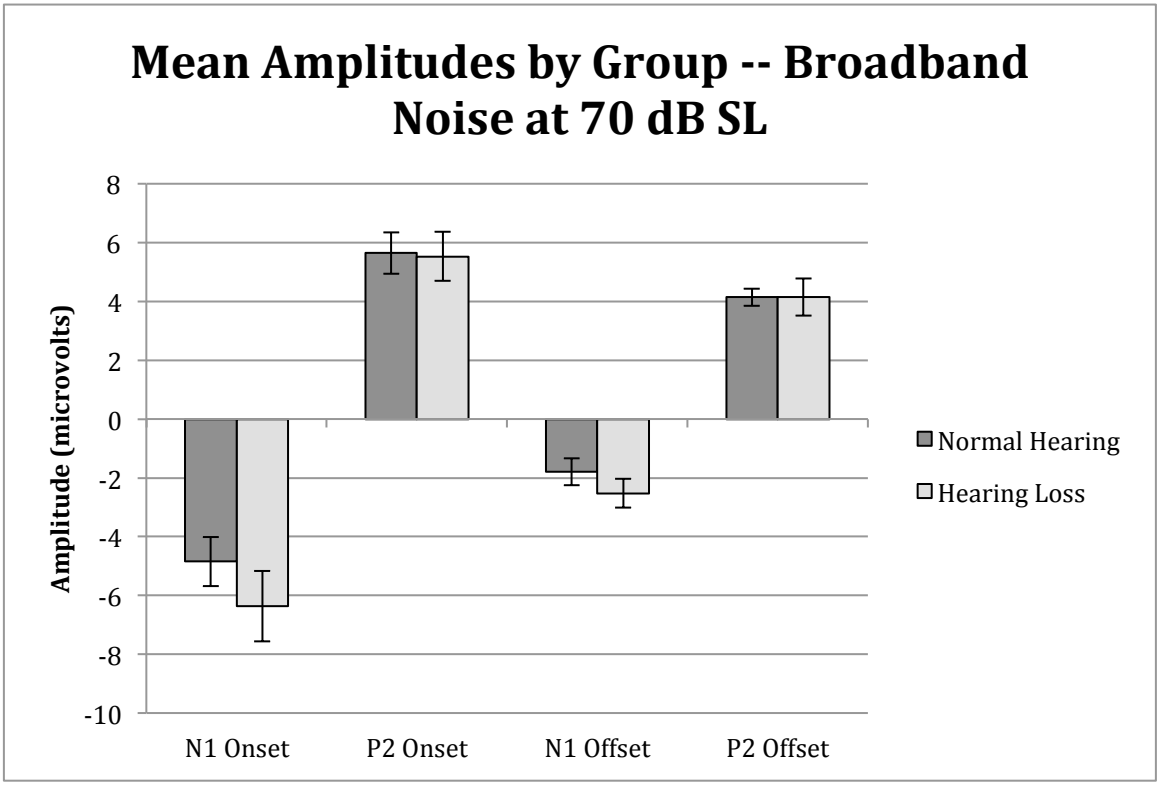

Figure 12. Mean amplitudes by group for the broadband noise stimulus presented at 70 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

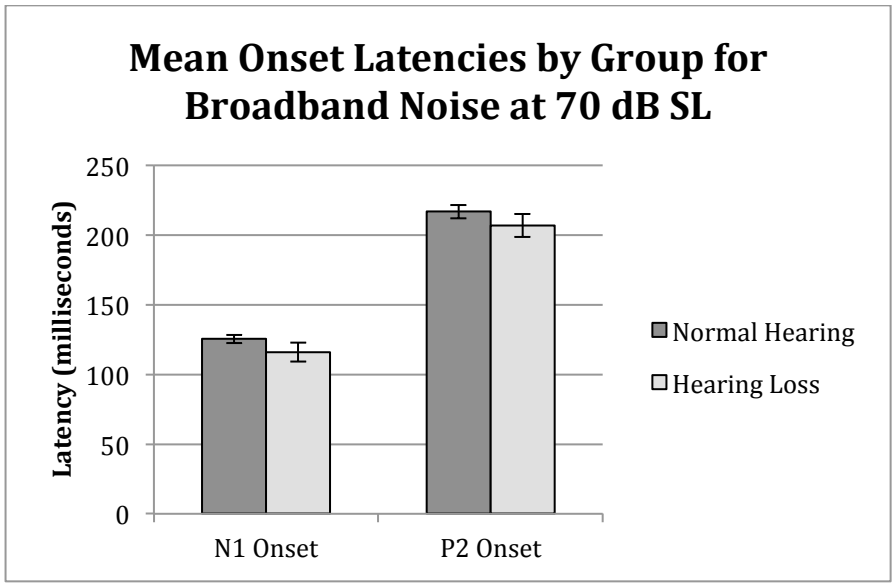

Figure 13. Mean onset latencies by group for the broadband noise stimulus presented at 70 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

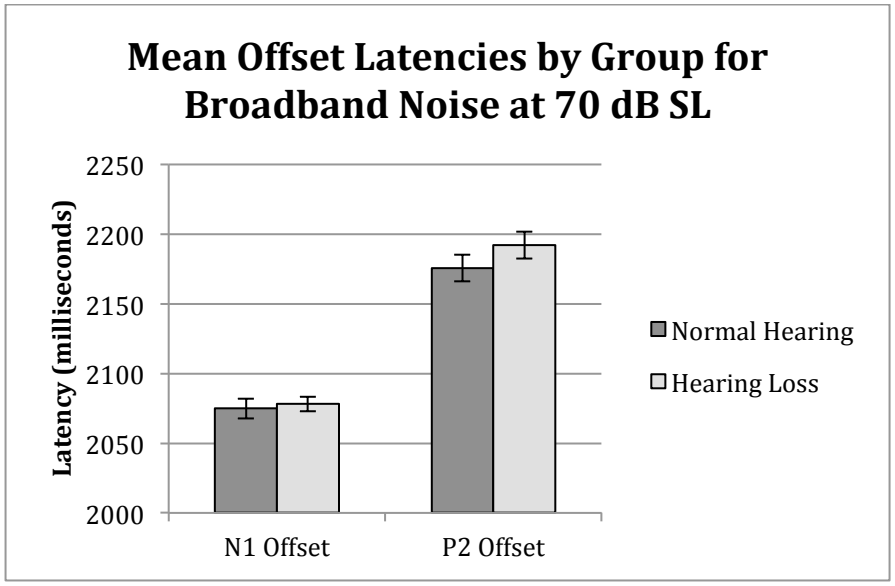

Figure 14. Mean offset latencies by group for the broadband noise stimulus presented at 70 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

group's data with the hearing loss group's data, the mean latency difference for N1 was 45.32 ms, with the offset response having a shorter relative latency than the onset response. Using Eq. 3 to calculate P2 timing differences resulted in mean P2 differences of 41 ms for the normal hearing group and 14.93 ms for the hearing loss group. A two-tailed independent samples t-test was significant [$t(15) = 2.359$; $p = 0.032$], thus the data in this case were not collapsed.

The mean offset-to-onset amplitude ratio for the normal hearing group was 0.52 (range 0.34-0.87), while the mean ratio for the hearing loss group was 0.59 (range 0.42-0.79). A two-tailed independent samples t-test performed on these ratios by group did not reveal a statistically significant difference [$t(15) = -1.105$; $p = 0.286$]. The offset-to-onset amplitude ratio after combining the normal hearing group with the hearing loss group was 0.55.

Research Question 2: Intensity Effects

It was hypothesized that for the onset response, increased amplitudes and shorter latencies would be observed when increasing the presentation level of a broadband stimulus from 50 dB SL to 70 dB SL. For the offset response, it was expected that increased amplitudes would be observed with an increase in presentation level. No significant changes in offset latency were expected in response to the increase in stimulus intensity. Grand average waveforms for the 50 dB SL and 70 dB SL broadband noise stimuli for the normal hearing and hearing loss groups are presented in Figure 15.

N1 onset amplitude did not change significantly as a result of the increase in presentation level, and there were no significant stimulus type by group interactions for

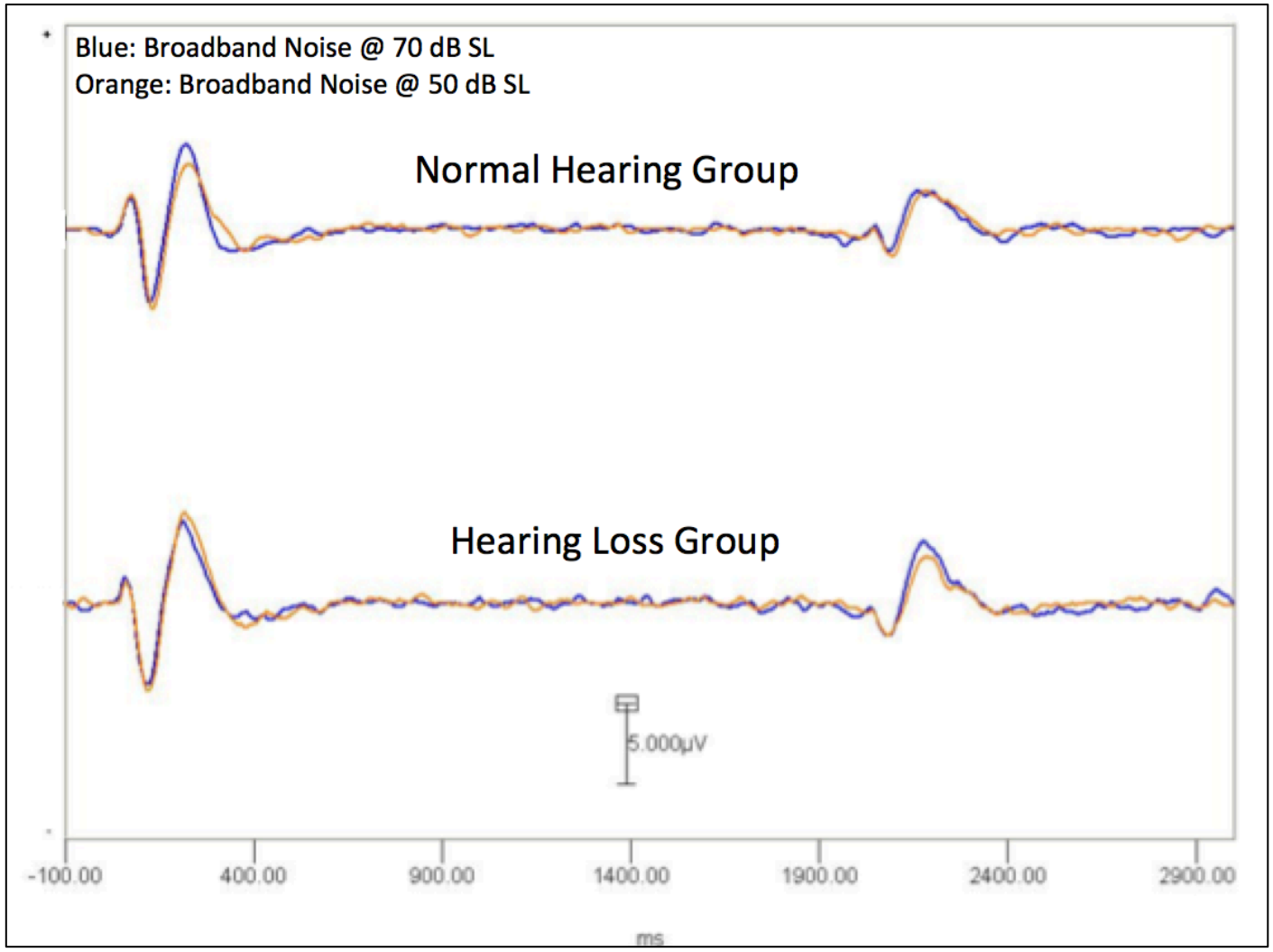

Figure 15. Grand average onset-offset N1-P2 waveforms for the normal hearing group (top, n = 10) and the hearing loss group (bottom, n = 7) evoked by broadband noise presented at 70 dB SL (blue tracings) and 50 dB SL (orange tracings)

this waveform component. P2 onset amplitude demonstrated a significant stimulus type by group interaction [$F(1,15) = 9.696$; $p = 0.007$]. Amplitudes for the normal hearing group increased by an average of 1.19 μV as a result of the increase in presentation level, with the 70 dB SL (82 dB SPL) stimulus producing larger responses on average than the 50 dB SL (62 dB SPL) stimulus. The hearing loss group demonstrated amplitudes that decreased by an average of 0.89 μV with the increase in stimulus intensity from 50 dB SL (76 dB SPL) to 70 dB SL (96 dB SPL). A within-subject comparison of the responses obtained at 50 dB SL and 70 dB SL did not produce significant results [$F(1,15) = 0.195$; $p = 0.687$], nor did a test of between-subjects effects [$F(1,15) = 0.728$; $p = 0.407$).

N1 offset amplitude did not change as a result of increasing the presentation level of the broadband noise stimulus [$F(1,15) = 1.490$; $p = 0.241$], but the P2 offset amplitude did increase with the increase in presentation level [$F(1,15) = 5.271$; $p = 0.037$]. The stimulus type by group interaction did not reach significance in either case, indicating that both groups responded to the increase in intensity level similarly.

N1 onset latency [$F(1,15) = 18.52$; $p = 0.001$] and P2 onset latency [$F(1,15) = 7.76$; $p = 0.014$] each shifted with an increase in the stimulus presentation level of the broadband noise stimulus, with the 70 dB SL stimulus producing shorter latencies for each component. For these two onset components, the stimulus type by group interactions were not significant, indicating that both groups responded to the increase in intensity level in similar ways.

The N1 offset latency stimulus type by group interaction was significant [$F(1,15) = 4.531$; $p = 0.05$], though this finding was not considered meaningful. The normal hearing group's latencies to the 70 dB SL stimulus were 15 ms shorter than those evoked

by the 50 dB SL stimulus, whereas the hearing loss group's latencies were 5 ms longer for the 70 dB SL stimulus compared to those evoked by the 50 dB SL stimulus. There were no significant findings for within- or between-subjects comparisons for this waveform component.

The P2 offset latency component did not change in latency with the increase in stimulus intensity level. Offset P2 latency measurements did not differ between groups. The stimulus type by group interaction or the P2 offset latency component also failed to reach significance at the 0.05 alpha level, indicating that the study participants did not demonstrate shifts in P2 offset latency with an increase in stimulus intensity, regardless of group.

Research Question 3: Narrowband Noise Stimuli

Hypothesis 3a

It was hypothesized that onset and offset amplitudes and latencies elicited by the 500 Hz-centered narrowband noise stimulus would not differ between groups. N1 onset latencies for the hearing loss group were meaningfully and significantly shorter than those obtained for the normal hearing group [hearing loss group mean = 121.14, normal hearing group mean = 135.50 ms; $t(15) = 2.523$; $p = 0.023$]. All other latency measurements (P2 onset, N1 offset, and P2 offset) as well as all amplitude measurements (N1 onset, P2 onset, N1 offset, and P2 offset) failed to reach significance at the 0.05 alpha level. Mean amplitude and latency measurements to the 500 Hz-centered narrowband noise stimulus presented at 50 dB SL for the normal hearing and hearing loss groups are presented in Figures 16 to 18.

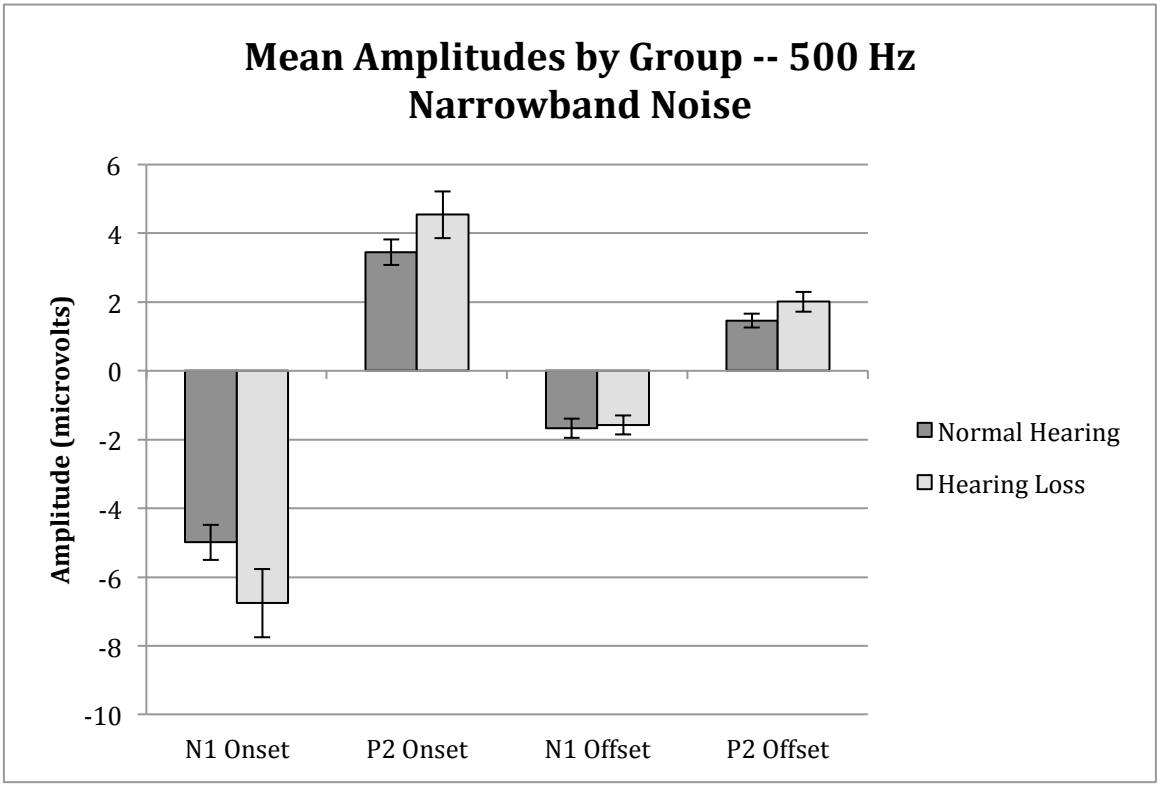

Figure 16. Mean amplitudes by group for the 500 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

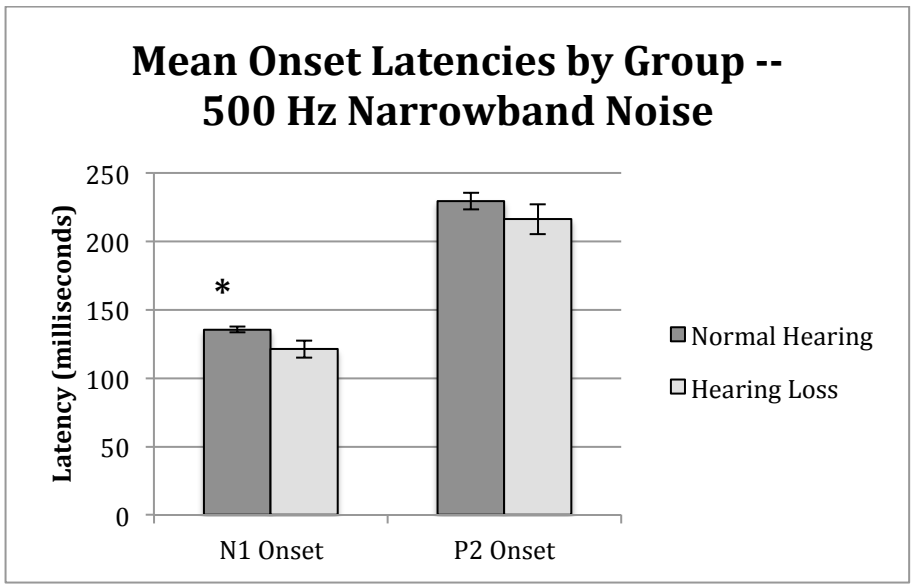

Figure 17. Mean onset latencies by group for the 500 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured. Single asterisk indicates $p < 0.05$.

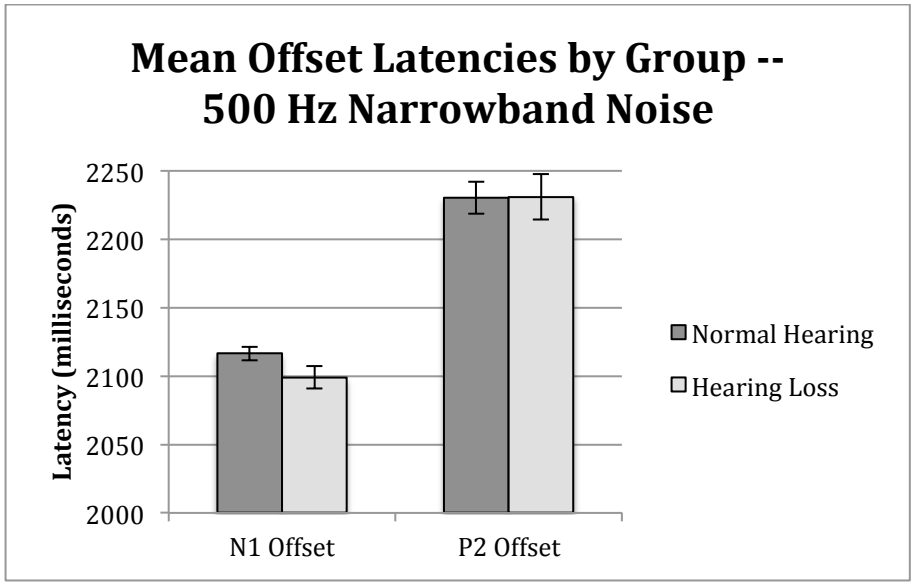

Figure 18. Mean offset latencies by group for the 500 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured.

The mean offset-to-onset N1-P2 amplitude ratio for the normal hearing group was 0.38 (range 0.20-0.55), while the mean ratio for the hearing loss group was 0.32 (range 0.26-0.46). A two-tailed independent samples t-test performed on these ratios by group did not reveal a statistically significant difference [$t(14) = 1.170$; $p = 0.261$]. The offset-to-onset amplitude ratio after collapsing the normal hearing group with the hearing loss group was 0.35.

Hypothesis 3b

Because there were audiometric differences between groups in the 4000 Hz frequency region, it was hypothesized that onset and offset latencies elicited by the 4000 Hz-centered narrowband noise stimulus would be longer and amplitudes would be smaller for the hearing loss group compared to the normal hearing group. Mean amplitude and latency measurements to the 4000 Hz-centered narrowband noise stimulus presented at 50 dB SL for the normal hearing and hearing loss groups are displayed in Figures 19 to 21. Tables 1, 2, and 3 summarize the between-subjects findings for amplitude and latency and the offset-to-onset N1-P2 amplitude ratios for all stimuli presented.

Onset N1 and P2 amplitudes and P2 onset latency did not differ between groups, nor did N1 offset amplitude and latency. However, differences across the groups in measures of onset N1 latency, offset P2 amplitude and offset P2 latency were significant and meaningful, with the hearing loss group demonstrating larger amplitudes (P2 offset: $p = 0.009$) as well as earlier latencies [N1 onset: $t(15) = 2.324$, $p = 0.035$; P2 offset: $t(14) = 2.863$, $p = 0.01$]. On average, the P2 offset component occurred 63.56 ms earlier and

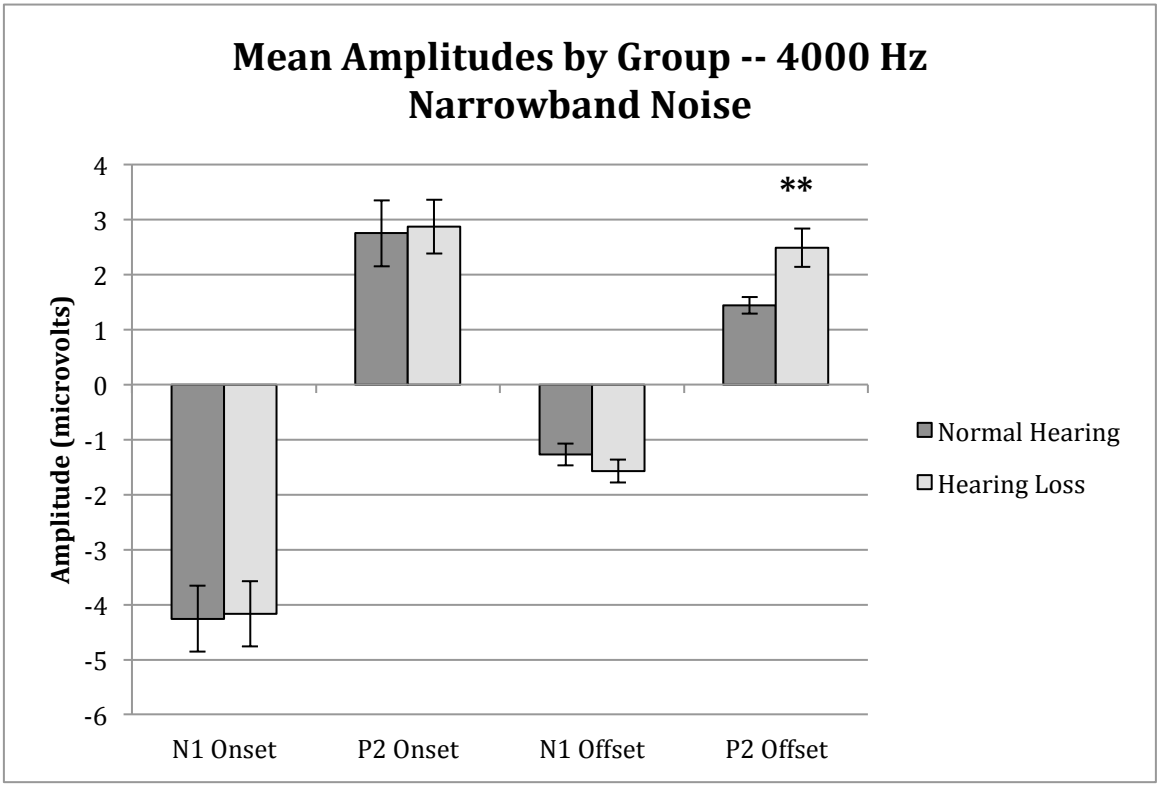

Figure 19. Mean amplitudes by group for the 4000 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured. Double asterisk (**) indicates $p < 0.01$.

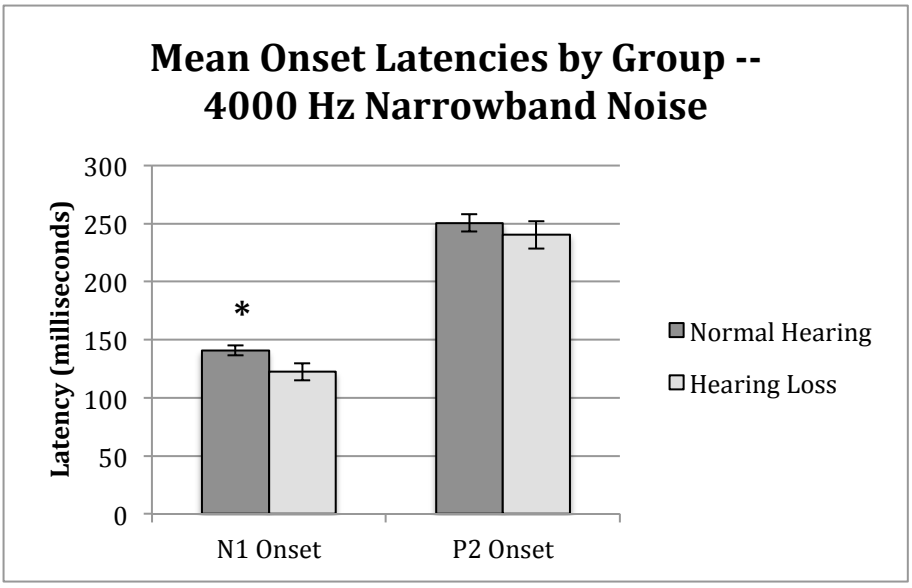

Figure 20. Mean onset latencies by group for the 4000 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured. Single asterisk (*) indicates < 0.05.

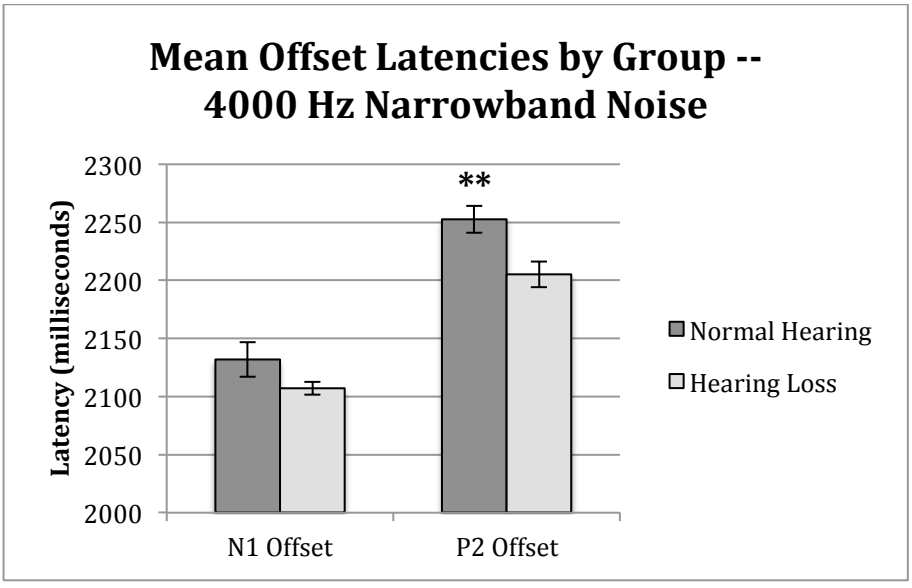

Figure 21. Mean offset latencies by group for the 4000 Hz-centered narrowband noise stimulus presented at 50 dB SL (dark grey: normal hearing participants, light grey: hearing loss participants). Bars indicate standard error for the waveform components measured. Double asterisk (**) indicates < 0.01.

Table 1. Statistically significant between-subjects amplitude measurements

		Stimulus Condition			
		500 Hz	**4000 Hz**	**BBN 50**	**BBN 70**
Waveform Component	**N1 Onset**				
	P2 Onset				
	N1 Offset				
	P2 Offset		★ ★		

Double stars indicate $p < 0.01$.

Table 2. Statistically significant between-subjects latency measurements.

		Stimulus Condition			
		500 Hz	**4000 Hz**	**BBN 50**	**BBN 70**
Waveform Component	**N1 Onset**	★	★		
	P2 Onset				
	N1 Offset				
	P2 Offset		★ ★		

Single stars indicate $p < 0.05$; double stars indicate $p < 0.01$.

Table 3. Offset-to-onset amplitude ratios per group across all stimulus conditions

	Group	
Noise Condition	**Normal Hearing**	**Hearing Loss**
500 Hz Narrowband	0.38	0.32
4000 Hz Narrowband	0.39	**0.62***
Broadband @ 50 dB SL	0.62	0.51
Broadband @ 70 dB SL	0.51	0.59

Single asterisk (*) indicates $p < 0.05$.

was 1.16 μV larger in amplitude for the hearing loss participants compared to the participants with normal hearing.

The mean offset-to-onset N1-P2 amplitude ratio for the normal hearing group was 0.39 (range 0.25-0.49), while the mean ratio for the hearing loss group was 0.62 (range 0.37-1.04). A two-tailed independent samples t-test performed on these ratios by group revealed a meaningful and statistically significant difference [$t(15) = -2.807$, $p = 0.013$].

Research Question 4: Broadband versus Narrowband Noise Stimuli

It was hypothesized that the broadband noise condition would elicit the largest and earliest responses of the three noise types for both groups. The 4000 Hz-centered narrowband noise condition was expected to elicit smaller amplitude responses than the 500 Hz-centered narrowband noise condition. It was hypothesized that the progression of onset-offset N1-P2 amplitudes observed from smallest to largest would be the following: 4000 Hz-centered narrowband noise, 500 Hz-centered narrowband noise, broadband noise. Figure 22 displays the waveforms for the three noise conditions for the normal hearing and hearing loss groups. Results of the comparisons for each of the waveform components are discussed below.

N1 Onset Amplitude

The broadband noise stimulus produced larger amplitude responses than the 4000 Hz-centered narrowband noise stimulus [$F(1,15) = 12.474$; $p = 0.003$], and the 500 Hz-centered narrowband noise stimulus produced larger amplitude responses than the 4000 Hz-centered narrowband noise stimulus [$F(1,15) = 15.27$; $p = 0.001$]. The comparison

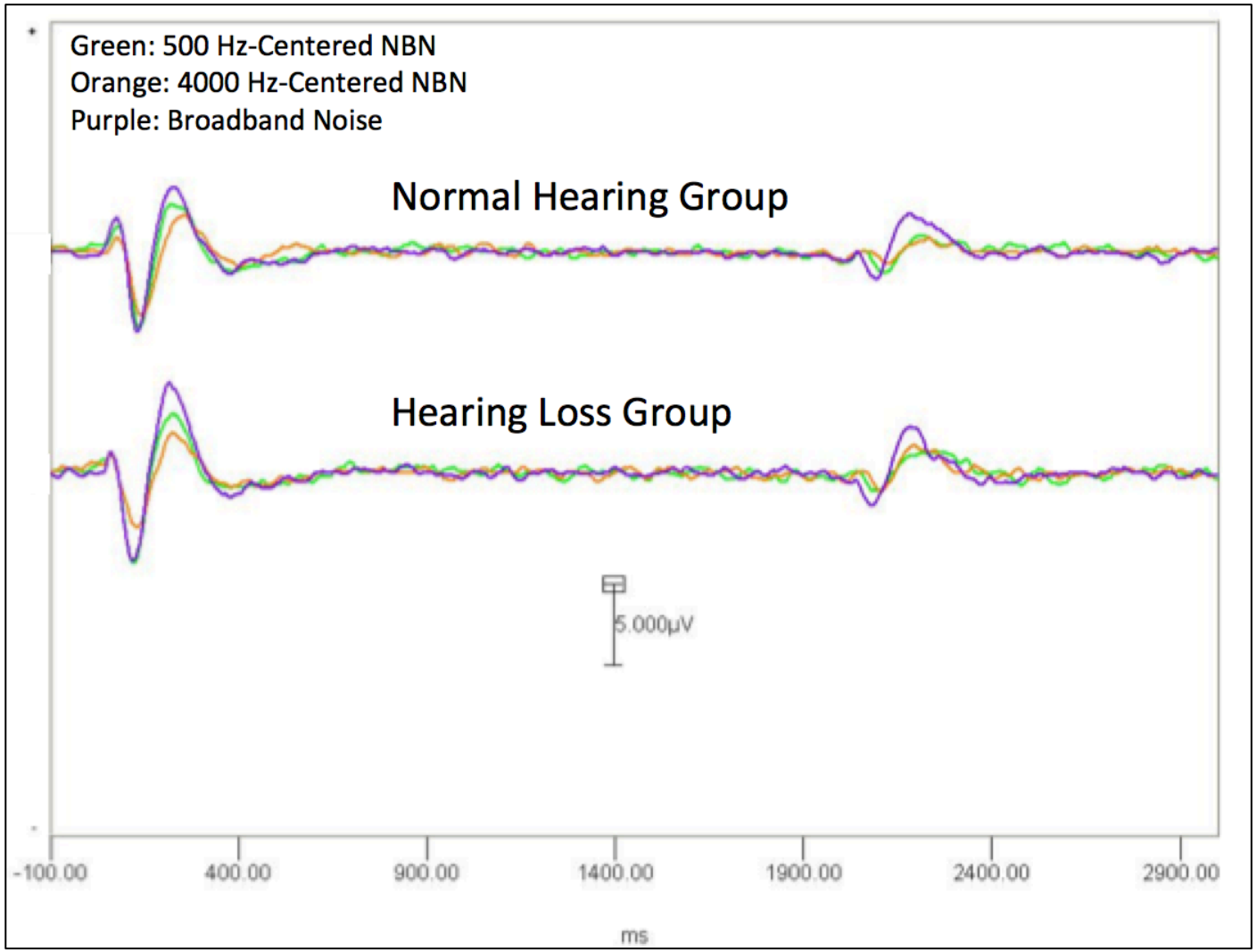

Figure 22. Grand average onset-offset N1-P2 waveforms evoked by 500 Hz-centered narrowband noise (green tracings), 4000 Hz-centered narrowband noise (orange tracings), and broadband noise (purple tracings) presented at 50 dB SL for the normal hearing (top, n = 10) and hearing loss (bottom, n = 7) groups.

between the data obtained from the 500 Hz-centered narrowband noise condition versus that obtained from the 4000 Hz-centered narrowband noise condition should be interpreted with caution as a significant stimulus type by group interaction was found [$F(1,15) = 4.783$; $p = 0.045$]. A review of the mean data shows that the 4000 Hz-centered narrowband noise stimulus evoked a 0.73 μV smaller response than did the 500 Hz-centered narrowband noise stimulus in the normal hearing group, while the 4000 Hz-centered narrowband noise stimulus evoked a response that was 2.59 μV smaller than the 500 Hz-centered narrowband noise stimulus-evoked response in the hearing loss group. This result appears to have been driven by slightly larger amplitude measurements for the 500 Hz-centered narrowband noise condition for the hearing loss group compared to the normal hearing group. The comparison of N1 onset amplitude responses obtained from the 500 Hz-centered narrowband noise and broadband noise stimuli did not reach significance [$F(1,15) = 0.715$; $p = 0.805$).

P2 Onset Amplitude

The 500 Hz-centered narrowband noise stimulus elicited larger amplitude P2 onset responses than did the 4000 Hz-centered narrowband noise stimulus [$F(1,15) = 9.316$; $p = 0.008$]. Comparisons of the responses to the broadband noise stimulus and the responses to the 500 Hz-centered narrowband noise stimulus reached significance [$F(1,15) = 18.127$; $p = 0.001$], with the broadband stimulus producing larger amplitude responses. A comparison of the responses elicited by the 4000 Hz-centered narrowband stimulus and broadband noise stimulus also reached significance [$F(1,15) = 22.357$; $p = 0.000$]. Stimulus type by group interactions were not significant.

N1 Offset Amplitude

The broadband noise stimulus evoked larger amplitude responses than the 500 Hz-centered narrowband stimulus [$F(1,14) = 11.937$; $p = 0.004$] and the 4000 Hz-centered narrowband noise stimulus [$F(1,14) = 38.591$; $p = 0.000$]. Comparisons of the responses elicited by the 500 Hz-centered narrowband noise stimulus and the 4000 Hz-centered narrowband noise stimulus did not reach significance at the 0.017 alpha level. Stimulus type by group interactions were not significant.

P2 Offset Amplitude

A comparison of the responses elicited by the 500 Hz-centered narrowband and broadband noise stimuli revealed that the broadband noise stimulus evoked larger amplitude responses [$F(1,14) = 32.692$; $p = 0.000$]. A comparison of the responses evoked by the 4000 Hz-centered narrowband noise stimulus and the broadband noise stimulus was also significant [$F(1,14) = 24.561$; $p = 0.000$], with the broadband noise stimulus again evoking larger amplitude responses. P2 offset amplitude comparisons for the 500 Hz- and 4000 Hz-centered narrowband noise stimuli did not reach significance [$F(1,14) = 1.641$; $p = 0.221$]. There were no significant stimulus type by group interactions for this waveform component.

N1 Onset Latency

The tests of within-subjects contrasts for the responses evoked by the three stimuli for this waveform component did not produce significant results at the 0.017 alpha level. Stimulus type by group interactions also did not reach significance.

P2 Onset Latency

The broadband noise stimulus evoked shorter P2 onset latencies than did the 4000 Hz-centered narrowband noise stimulus [$F(1,15) = 14.670$; $p = 0.002$]. The 500 Hz-centered narrowband noise stimulus evoked responses that were significantly shorter than those evoked by the 4000 Hz-centered narrowband noise stimulus [$F(1,15) = 8.536$; $p = 0.011$]. Comparisons of the responses elicited by the 500 Hz-centered narrowband noise stimulus and the broadband noise stimulus did not reach significance. Stimulus type by group interactions also did not reach significance.

N1 Offset Latency

A comparison of the components elicited by the broadband noise stimulus and the 500 Hz-centered narrowband noise stimulus revealed that the broadband noise stimulus evoked shorter latency responses [$F(1,14) = 23.943$; $p = 0.000$]. The broadband noise stimulus also produced shorter latency responses for N1 offset than did the 4000 Hz-centered narrowband noise stimulus [$F(1,14) = 12.622$; $p = 0.003$]. A comparison of the components elicited by the 500 Hz- and 4000 Hz-centered narrowband noise stimuli did not reach significance [$F(1,14) = 1.058$; $p = 0.321$]. There were no significant stimulus type by group interactions found for this waveform component.

P2 Offset Latency

The broadband noise stimulus evoked shorter P2 offset latencies than did the 500 Hz-centered narrowband noise stimulus [$F(1,14) = 31.591$; $p = 0.000$]. P2 offset latencies to the broadband noise stimulus were also shorter than those evoked by the 4000

Hz-centered stimulus [$F(1,14) = 14.737$; $p = 0.002$]. The comparison of the responses evoked by the 500 Hz- and 4000 Hz-centered narrowband noise stimuli did not reach significance [$F(1,14) = 0.015$; $p = 0.904$]. There were no significant stimulus type by group interactions for this waveform component.

Taken together, these results indicate that when there were significant differences in the responses evoked by the stimuli, the broadband noise stimulus evoked the largest and earliest responses for the onset components, followed by the 500 Hz-centered narrowband noise stimulus and then the 4000 Hz-centered narrowband stimulus. For the offset components, the broadband noise stimulus evoked the largest amplitude and shortest latency responses, while the responses evoked by the 500 Hz- and 4000 Hz-centered narrowband noise stimuli did not differ significantly in amplitude or latency. A summary of the amplitude and latency results is presented in Tables 4 and 5.

Table 4. Statistically significant within-subject amplitude comparisons across 500 Hz-centered narrowband noise, 4000 Hz-centered narrowband noise, and broadband noise presented at 50 dB SL

N1 Onset Amplitude				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz	** (500 Hz)		
	BBN 50		** (BBN 50)	
P2 Onset Amplitude				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz		** (500 Hz)	
	4000 Hz			
	BBN 50	** (BBN 50)	** (BBN 50)	
N1 Offset Amplitude				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz			
	BBN 50	** (BBN 50)	** (BBN 50)	
P2 Offset Amplitude				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz			
	BBN 50	** (BBN 50)	** (BBN 50)	

Double asterisk (**) indicates $p < 0.01$. Condition in parenthesis is the condition that produced larger amplitudes.

Table 5. Statistically significant within-subject latency comparisons across 500 Hz-centered narrowband noise, 4000 Hz-centered narrowband noise, and broadband noise presented at 50 dB SL

N1 Onset Latency				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz			
	BBN 50			
P2 Onset Latency				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz		* (500 Hz)	
	4000 Hz			
	BBN 50		** (BBN 50)	
N1 Offset Latency				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz			
	BBN 50	** (BBN 50)	** (BBN 50)	
P2 Offset Latency				
		Stimulus Condition		
Stimulus Condition		500 Hz	4000 Hz	BBN 50
	500 Hz			
	4000 Hz			
	BBN 50	** (BBN 50)	** (BBN 50)	

Single asterisk (*) indicates $p < 0.017$; double asterisk (**) indicates $p < 0.01$. Condition in parenthesis is the condition that produced larger amplitudes.

CHAPTER 6

Discussion

The diagnosis of central auditory processing disorder (CAPD) in individuals with peripheral hearing loss is a continuing challenge in audiology. A primary reason for this is a lack of central auditory tests that are sensitive and specific to CAPD which increases the likelihood of false positive findings in patients with peripheral hearing losses. The main purpose of this study was to evaluate the use of an objective electrophysiologic potential, the onset-offset N1-P2 auditory evoked response, in individuals with normal hearing and individuals with high-frequency sensorineural hearing loss in an effort to identify conditions that would reduce the effects of hearing loss on a measure of central auditory function.

Overall, it appears that using the N1-P2 onset-offset response evoked by broadband noise as constructed for this study shows promise in differentiating sensorineural hearing loss from CAPD, as there were no significant differences in amplitude or latency between groups for either of the presentation levels of the broadband noise stimulus. The hypothesis that the participants with sensorineural hearing loss would demonstrate reduced amplitudes and delayed latencies was not supported. Rather, participants with hearing loss showed a trend of increased amplitudes and shorter latencies overall, which is in contrast to what is typically seen in individuals who present with "classic" CAPD. Electrophysiologic responses of individuals with CAPD often demonstrate increases in latency and decreases in amplitude compared to individuals with normal central auditory function, and in some cases, the waveform components may be absent (Jirsa, 1992; Knight et al., 1980; Knight et al., 1989; Musiek

et al., 1992; Warrier et al., 2004). The differences between the results documented here and the responses of individuals with CAPD make this paradigm particularly appealing for future research and potential clinical use in individuals with hearing loss who may have central auditory dysfunction. Using a presentation level determined by dB SL re: behavioral threshold for the broadband test stimulus appears to reduce the effect of hearing loss, at least for hearing losses of the type, degree, and configuration defined in this study. Thus, deviations of an individual's results from those of the present study could be attributed to central auditory factors. When using dB SL presentation levels, delays in latency and reductions in amplitude of the onset-offset N1-P2 response in individuals with moderate high-frequency sensorineural hearing loss would be indicative of central auditory dysfunction.

Homeostatic Plasticity

While the measures of onset and offset amplitude and latency evoked by broadband noise presented at 50 and 70 dB SL were not found to be significantly different across groups, the N1-P2 onset-offset waveform components elicited by 500 Hz-centered narrowband and 4000 Hz-centered narrowband noise did demonstrate significant differences. N1 onset latency was significantly shorter for the hearing loss group compared to the normal hearing group for the 500 Hz-centered and the 4000 Hz-centered narrowband noise conditions, as was the offset latency for P2. P2 offset amplitude was also significantly larger for the hearing loss group compared to the normal hearing group when elicited by the 4000 Hz-centered narrowband noise. As these conditions are more frequency-specific and the groups differed audiometrically, the

effects of hearing loss from 2000 to 8000 Hz on central auditory function (i.e., increased excitatory strength, decreased inhibitory strength, increased spontaneous firing rates, increased neural synchrony, changes in tonotopic organization) are thought to have influenced these differences, especially because the use of dB SL presentation levels reduced the effect of hearing loss in the broadband noise conditions. The significant N1 onset latency difference between groups for the 500 Hz-centered narrowband noise condition is also thought to have arisen from the central auditory changes resulting from high-frequency sensorineural hearing loss. As mentioned earlier, enhancements in rostral brainstem and cortical evoked responses have been reported in animals with noise-induced trauma, even when stimulating cochlear regions with normal hearing (Salvi et al., 1990, 2000).

In the evaluation of the between-subjects results of this study, it must be restated that the groups differed in whether normal hearing or a moderate high-frequency sensorineural hearing loss was present. Thus, one assumption could be made that the differences demonstrated between groups result from peripheral hearing losses likely involving the loss and damage of a combination of both outer and inner hair cells as well as alterations in auditory nerve function. It is known that sensorineural hearing loss has roots in hair cell loss and dysfunction, which results in changes in cochlear mechanics, hair cell motility, cochlear amplification, and auditory nerve structure and function (Jacob et al., 2013; Kujawa & Liberman, 2009; Liberman, 1984; Liberman & Dodds, 1984a, 1984b; Liberman & Kiang, 1984; Sergeyenko et al., 2013). Such changes, however, do not occur in isolation. Sensorineural hearing loss can be thought of as the first domino that sets off a cascade of changes in the central auditory nervous system,

resulting in changes in the cochlear nucleus, superior olivary complex, inferior colliculus, ventral nucleus of the medial geniculate body, and the auditory cortex (Basta & Ernest, 2004; Buras et al., 2006; Eggermont & Roberts, 2004; Illing et al., 2000; Kaltenbach et al., 1992; Komiya & Eggermont, 2000; Kotak et al., 2005; Morest & Bohne, 1983; Salvi et al., 1990, 2000; Seki & Eggermont, 2002, 2003; Syka et al., 1994; Vale & Sanes, 2002). If there were no changes in these central structures as a result of the hearing loss (i.e., central physiology and morphology remained the same as it was before the loss), the reduction in compound action potential amplitude would lead to decreased input to the central auditory structures. This decreased input would in turn lead to reduced amplitudes and delayed latencies of electrophysiologic responses. This, however, does not occur. As reported by Salvi et al. (1990), noise-induced hearing loss results in shallower amplitude-intensity functions of the compound action potential and cochlear nucleus; however, amplitude-intensity functions from the inferior colliculus demonstrate the opposite effect, with steeper slopes containing amplitudes that exceed pre-exposure measurements. Moreover, these amplitude-intensity enhancements were not limited to the frequency region of the hearing loss (Salvi et al., 1990, 2000). Along with these findings, animal studies of neurons in the superior olivary complex and the more rostral portions of the central auditory system demonstrate a common theme of increased excitatory and decreased inhibitory response strengths. In the case of hearing loss, increases in excitation and decreases in inhibition could be one way that the central auditory nervous system attempts to compensate for the hearing loss. If increases in excitation or decreases in inhibition were to occur independently, however, there would be a risk of "runaway strengthening or weakening of synapses, which [would lead] to a

saturation of synaptic strength" (Burrone & Murthy, 2003, p. 560). Instead, changes in the synaptic strength due to sensory alterations such as hearing loss are thought to occur in a more balanced way in which normal strengths of the synapses are re-established, while the relative strengths of all synapses are maintained (Burrone & Murthy, 2003). This is also known as "homeostatic plasticity," and it involves processes such as synaptic scaling and synapse formation to provide a gain control mechanism to the central auditory nervous system.

The term "homeostatic plasticity" refers to the plastic changes that take place in the central nervous system in an effort to maintain the regulation of variables so that internal conditions remain stable and constant. According to Turrigiano (1999), there are two forces at work in homeostatic plasticity – one that creates differences between individual elements (i.e., effects of sensorineural hearing loss on spontaneous firing rates) and one that works to stabilize a network's overall activity (i.e., compensatory effects to bring the deviation of spontaneous firing rate back to normal). Thus, if a decrease in spontaneous activity rate occurs in the central auditory nervous system as a result of the hearing loss, the system will compensate by increasing the spontaneous activity rate to its pre-hearing loss rate. In general, this is done in several different ways. First, the system can increase its strength of excitatory inputs to increase the spontaneous activity rate. Second, the system can decrease its strength of inhibitory inputs to increase the spontaneous activity rate. Both of these would act to increase the ratio of excitation strength to inhibition strength to reach homeostasis. Lastly, increasing the excitability of the post-synaptic neuron can also contribute to achieving homeostasis, and this is generally the result of changes in passive membrane properties (i.e., membranes become

more or less resistant to depolarization) or changes in voltage activated currents (Walmsley, Berntson, Leao, & Fyffe, 2006). The changes in response amplitude, excitability of neurons, spontaneous rates, and neural synchrony that have been discussed as central consequences of peripheral loss can all be explained by an underlying mechanism of homeostatic plasticity.

It is this author's position that the differences demonstrated between groups in this study may be the manifestation of the central auditory changes that occur due to sensorineural hearing loss as discussed above. Thus, the process of homeostatic plasticity is thought to have contributed in large part to the findings of enhanced waveform components in the hearing loss group compared to the normal hearing group (i.e., significantly shorter N1 onset latencies to 500 Hz- and 4000 Hz-centered narrowband noise and increased amplitudes and shorter latencies for the P2 offset component to 4000 Hz-centered narrowband noise). Homeostatic plasticity may have also contributed to the overall trend of larger amplitudes and shorter latencies of the onset-offset N1-P2 waveform components obtained from individuals with high-frequency sensorineural hearing loss compared to their normal hearing counterparts, regardless of stimulus condition. Replications of the present study should be undertaken in order to provide further support for these claims.

Recruitment

Historically, tests of recruitment such as the Alternate Binaural Loudness Balance (ABLB), Békésy, and short-increment sensitivity index (SISI) tests have been used to differentiate "nerve deafness from middle ear deafness" (Denes & Naunton, 1950, p. 375)

and require behavioral responses of patients in order to complete. Considering that the auditory stimuli for these tests must be processed via the entire auditory system from outer ear to auditory cortex, whether the recruitment phenomenon arises from the cochlea and/or auditory nerve or the central auditory nervous system remains unclear. Use of these tests requires that individuals either experience distortions (cochlear or auditory nerve pathology) or do not experience distortions (middle ear pathology) as a result of their hearing loss, and both sensorineural and central auditory functions could contribute to the distortions. Also, the fact that these tests require behavioral responses means that a person must perceive the sounds in the test before he or she can respond. Thus, the auditory stimulus must go through the entire auditory periphery and central auditory pathway (brainstem pathway, thalamocortical pathway, and auditory cortex) before a response is given, and this does not allow for distinctions of sensorineural and central auditory effects to be made. Recruitment, then, may not be a peripheral phenomenon as traditionally thought. Rather, it may have contributions from the central auditory nervous system. It is possible that the results of the present study are representative of a central recruitment phenomenon that is mediated by homeostatic mechanisms.

Using dB SL versus dB SPL Presentation Levels

Comparisons of the present study's results to those of previously conducted studies investigating the effects of sensorineural hearing loss on cortically evoked auditory potentials such as the traditional N1-P2 response are mixed. Harkrider, Plyler, and Hedrick (2006) evaluated the effects of age and mild-to-moderate hearing impairment on the N1-P2 auditory evoked response to /ba/-/da/-/ga/ stimuli presented at

82 dB SPL. Results indicated larger N1 amplitudes for an older group with hearing loss compared to an older group with normal hearing, a result that was also reported by Tremblay, Piskosz, and Souza (2003). In addition, no statistically significant latency differences were found between the older listeners with normal hearing and the older listeners with hearing loss for N1 or P2. While the present study did not find group differences with regard to N1 onset amplitude, the lack of significant P2 onset latency differences between groups is in line with the findings of Harkrider and colleagues (2006). In a study on the effects of mild-to-moderate high-frequency (2000 to 8000 Hz) sensorineural hearing loss on the N1-P2 auditory evoked response to the consonant-vowel stimulus /ba/ presented at 65 dB HL, Campbell and Sharma (2013) found that latencies and amplitudes increased as a result of the hearing loss. Oates and colleagues (2002), in their investigation into the effects of sensorineural hearing loss on cortical event-related potentials (ERPs), found that individuals with even mild degrees of hearing loss demonstrated increased latencies elicited by CV stimuli /ba/ and /da/. Oates and colleagues (2002) also found that amplitude measurements decreased significantly as a result of increases in hearing loss. While these results seem to oppose the results found in the present study, it should be noted that the stimuli in the Oates et al. (2002) study were presented at a constant dB SPL for all participants regardless of hearing status. Moreover, if the presentation levels of the speech stimuli employed in the Oates et al. (2002) study (i.e., 65 and 80 dB SPL) were converted to dB HL levels, the dB HL presentation levels approximated 45 and 60 dB HL, respectively. Participants recruited for Oates and colleagues' study had mild (25 to 49 dB HL), moderate (50-74 dB HL), and severe/profound (75 to 120 dB HL) degrees of hearing loss as defined by pure-tone

averages computed from 1000 and 2000 Hz. When compared to the degrees of hearing loss included in their study, the stimulus presentation levels were very close to or only slightly above the pure-tone averages for many of the participants, and for some participants, the presentation levels were below their pure-tone averages. Spectral energy for the CV /ba/ occurs mainly in the 500-2000 Hz region (Sharma, Dorman, & Spahr, 2002), the region in which the hearing loss degrees were defined. Because amplitudes are reduced and latencies are delayed when measurements are made near to or slightly above threshold (Adler & Adler, 1989; McPherson, 1996), it is reasonable to conclude that the differences found between groups in this study and the study by Oates and colleagues (2002) may be the result of Oates et al. using a dB SPL that was held constant for both the normal hearing and hearing loss groups. Waveforms obtained in the present study were obtained at dB SL re: behavioral threshold for the test stimuli, not at a constant dB SPL. Thus, the presentation levels used in this study are likely more reflective of the intensity levels where individuals with hearing loss begin to demonstrate amplitude and latency measurements that are similar to those taken from individuals with normal hearing (Hyde, 1997). When comparing McPherson's (1996) amplitude-intensity functions of individuals with hearing loss to those of individuals with moderate sensorineural hearing loss in terms of dB SL rather than dB HL (i.e., with the functions shifted to begin at threshold, or 0 dB SL), amplitude measurements are similar, and it appears that the amplitudes in individuals with hearing loss may be enhanced at higher presentation levels. This is in line with the present study's findings of similar (broadband noise conditions) as well as enhanced (500 Hz- and 4000 Hz-centered narrowband noise

conditions) waveform components for individuals with hearing loss compared to individuals with normal audiometric thresholds.

Effects of Center Frequency and Bandwidth of the Noise

The observation that the 500 Hz-centered narrowband noise stimulus evoked larger onset components than did the 4000 Hz-centered narrowband noise stimulus is not surprising. This result was expected based on results of previous studies on the traditional N1-P2 auditory evoked response (Picton et al.,1978b), which demonstrated that stimuli of higher frequency evoked responses of reduced amplitude compared to responses evoked by lower frequency stimuli. Similarly, the finding that the broadband noise stimulus tended to evoke larger responses than did the two narrowband noise stimuli was also expected, as a larger area of the basilar membrane was stimulated, leading to a greater amount of neural synchrony and volume conduction along the auditory nerve and the central auditory nervous system (Durrant & Ferraro, 1999). Also, the broadband noise stimulus contained the highest frequencies of the three noises used in this study, ranging from 20-10,000 Hz. Stimuli that are of higher frequency evoke onset responses that are shorter in latency than those evoked by stimuli of lower frequency (Jacobson, Newman, Privitera, & Grayson, 1991).

Offset amplitudes and latencies did not differ significantly for the 500 Hz-centered and 4000 Hz-centered narrowband noise stimuli; however, the broadband noise stimulus presented at 50 dB SL produced waveform components that were significantly larger in amplitude and shorter in latency than both the narrowband noise conditions. Thus, the frequency composition of the stimulus does not appear to contribute to the

amplitude and latency measures of the offset response as much as does the bandwidth of the test stimulus. This interpretation is supported by findings that offset responses show poor tonotopicity (He, 2001; Takahashi et al., 2004) and suggests that the onsets and offsets are evoked by distinct neural generators. The lack of a frequency-specific effect on the offset N1-P2 evoked response could also be due to this study's use of a 40 ms rise/fall time for all stimuli, regardless of the frequencies contained in the noise. Because the rise/fall time was held constant at a duration long enough to accommodate multiple cycles of the lowest frequency present in both narrowband noise conditions, the possibility of acoustic ringing contributing to the generation of the response was eliminated. Using a long rise/fall time for both frequency-specific narrowband noises seemed to eliminate the effect of frequency on the offset response and sheds light on the effect of bandwidth (i.e., narrowband versus broadband) on the response. Also, the presence of an offset response when evoked by stimuli containing longer rise/fall times indicates that the offset response is a true response of the central auditory nervous system (Van Campen, Hall, & Grantham, 1997) and not an artifact caused by acoustic ringing as had been suggested in previous studies (Brinkman & Scherg, 1979; Laukli & Mair, 1985).

Comparisons of the offset-to-onset latencies for the N1 and P2 components evoked by the broadband noise stimuli suggest that the onset occurs as a result of the auditory system registering a change in the auditory environment from silence to the presence of sound, whereas the offset occurs in response to the 40 ms gating ramp used in this study (when stimulus plateau turns to stimulus fall). Displays of the stimuli themselves as related to the 40 ms offset ramp gating are shown in Figures 23a, 23b, and

23c. The 500 Hz- and 4000 Hz-centered narrowband noise stimuli were constructed using the ERB equation (Glasberg & Moore, 1990) which approximates the bandwidths of human cochlear auditory filters; thus, these stimuli each stimulated one auditory filter in the cochlea when they were presented. As the broadband noise stimuli contained the widest spectrum of the three types of noise, a higher number of auditory filters in the cochlea were stimulated in the broadband noise conditions compared to those stimulated in the 500 Hz- and 4000 Hz-centered narrowband noise conditions. When higher numbers of auditory filters in the cochlea are excited, the auditory system has an increased number of areas along the length of the cochlea combining to contribute to the accurate coding of the stimulus offset when it occurs. This more accurate coding leads to less statistical noise in the auditory system's estimation of stimulus offset occurrence; thus, the offset of stimulation with broadband noise would be expected to produce larger and earlier evoked responses overall compared to those elicited by the more frequency-specific noise conditions.

While the onset components followed the conventional pattern of lower frequency stimuli evoking larger responses than higher frequency stimuli, this pattern was not observed for the offset components. All offset amplitude and latency components to the 500 Hz-centered narrowband noise stimulus were not significantly different from those obtained using the 4000 Hz-centered narrowband noise stimulus. Therefore, it is reasonable to suggest that the offset gating is the physical characteristic of the stimulus that actually evokes the offset N1-P2 response, while the number of auditory filters stimulated in the cochlea influences the amplitude and latency of the response.

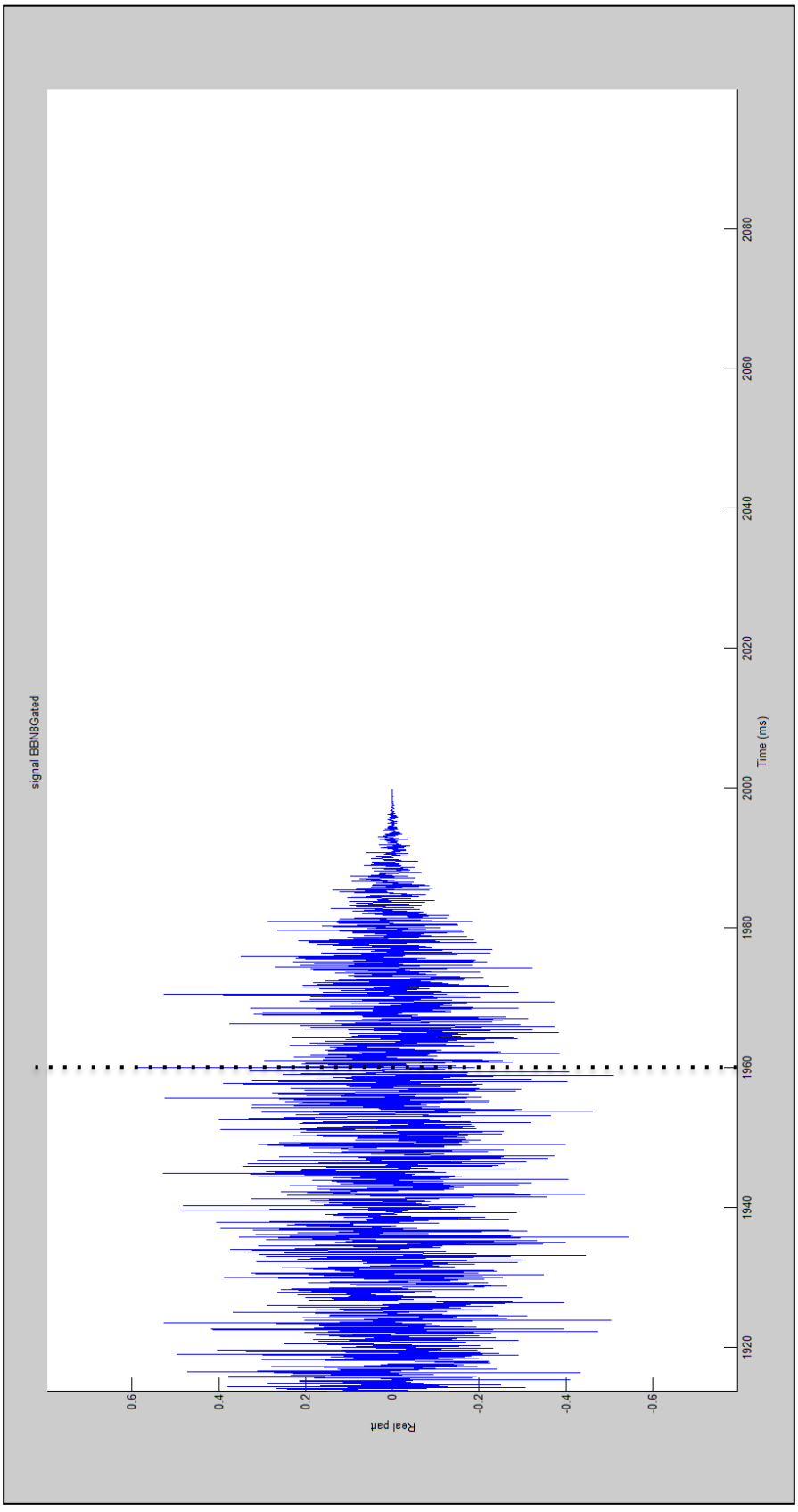

Figure 23a: Final portion of the broadband noise stimulus. Beginning of offset ramp delineated by dashed line at 1960 ms.

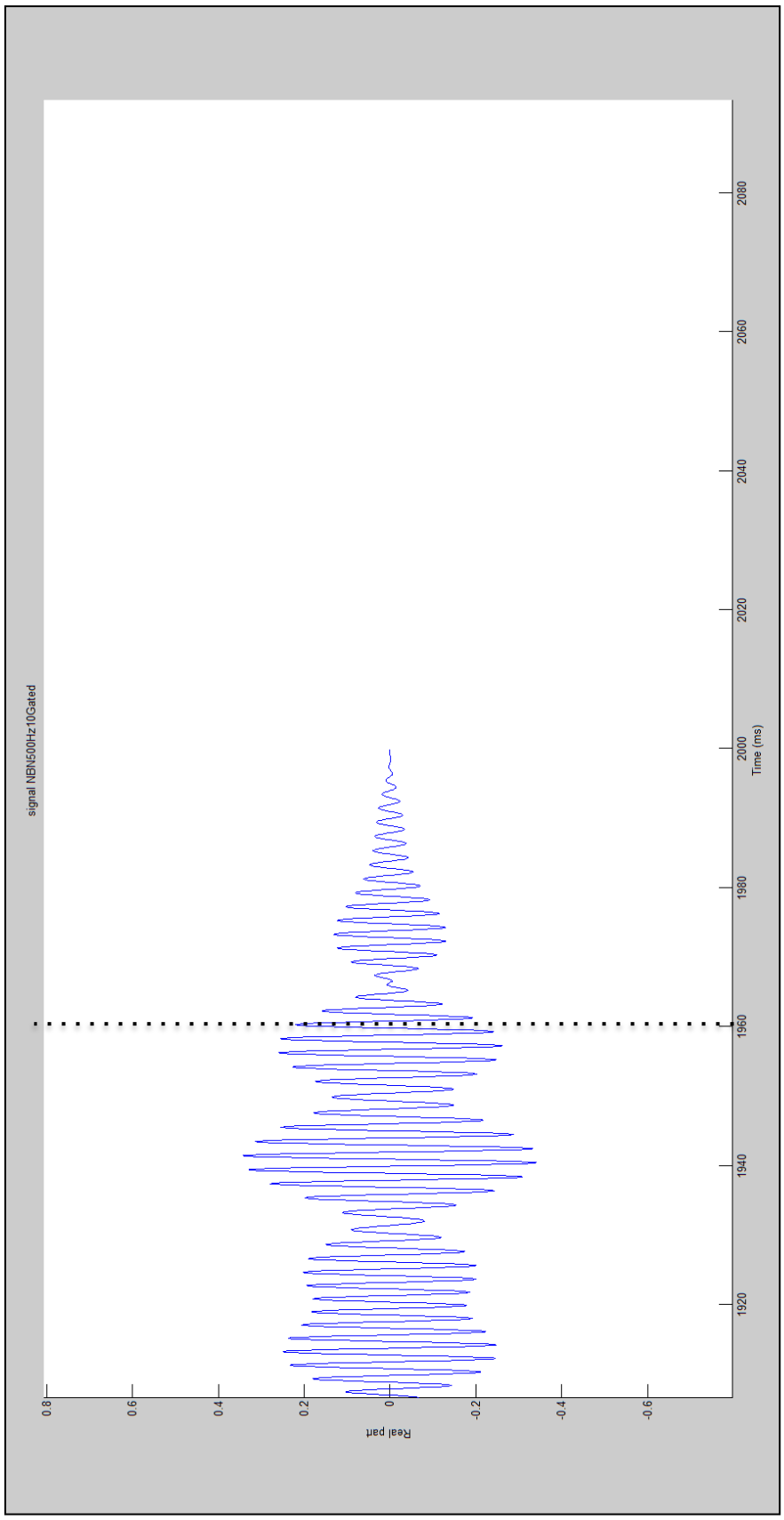

Figure 23b: Final portion of the 500 Hz-centered narrowband noise stimulus. Beginning of offset ramp delineated by dashed line at 1960 ms.

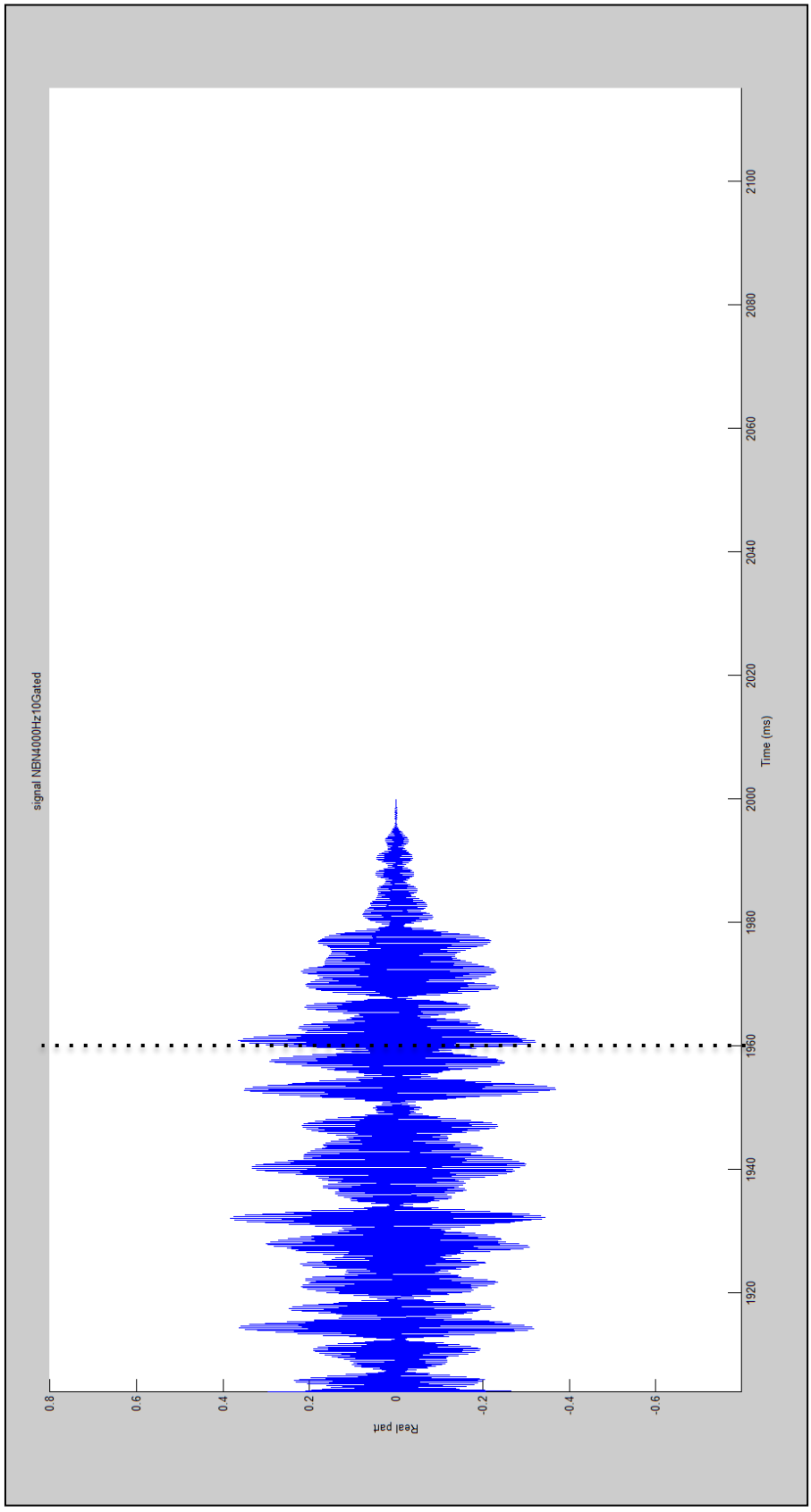

Figure 23c: Final portion of the 4000 Hz-centered narrowband noise stimulus. Beginning of offset ramp delineated by dashed line at 1960 ms.

Stimulus Presentation Level Differences Between Groups

Another possible explanation of the significant results found for the narrowband noise conditions could be the differences in stimulus presentation levels (in dB SPL) between groups. Changes in the intensity level of a stimulus induce changes in the latency and/or amplitude of the response, and this occurs for both N1 and P2 components (Dimitrijevic et al., 2009; Hyde, 1997; Picton et al., 1977). In the present study, a 20 dB increase in intensity level in the broadband noise conditions produced significant decreases in latency for both the N1 and P2 onset components and significant increases in the P2 offset amplitude. However, differences in the onsets evoked by the 500 Hz- and 4000 Hz-centered narrowband noise conditions were only seen for the N1 latency components, leaving the N1 amplitude, P2 amplitude, and P2 latency unaffected. Additionally, differences in the offsets were only seen for the P2 component for the 4000 Hz-centered narrowband noise condition, while N1 amplitude and latency remained unaffected. Also, the stimulus presentation levels for the hearing loss group were 71 dB SPL for the 500 Hz-centered narrowband noise and 96 dB SPL for the 4000 Hz-centered narrowband noise (a difference of 25 dB), while for the normal hearing group they were 60 dB SPL for the 500 Hz-centered narrowband noise and 65 dB SPL for the 4000 Hz-centered narrowband noise (a difference of 5 dB). If presentation level was a factor in the N1 onset latency differences seen between groups, the 20 dB difference between groups would be expected to produce significant stimulus type by group interactions for the N1 onset latency, P2 offset latency, and P2 offset amplitude comparisons. Stimulus type (500 Hz-centered vs. 4000 Hz-centered noise) by group interactions for these

components were not significant. Thus, dB SPL presentation level differences between groups are not believed to have produced the significant between-subject results.

For the 50 dB SL versus 70 dB SL broadband noise comparisons, a significant stimulus type by group interaction was found for P2 onset amplitude, with the normal hearing group demonstrating an average 1.19 μV growth in amplitudes and the hearing loss group showing an average 0.89 μV reduction in amplitudes with the 20 dB increase in presentation level. This difference in the direction of the effect may be due to where the 50-70 dB SL presentation levels occurred in relation to the participants' dynamic ranges for intensity. While some studies have reported amplitudes that continued to increase with increases in intensity above 70 dB nHL (Picton et al., 1977; Spoor, Timmer, & Odenthal, 1969), Adler and Adler (1989) found that increases in stimulus intensity from 30 to 70 dB nHL resulted in steeply rising N1-P2 amplitudes but that further increases in intensity above 70 dB nHL resulted in slight reductions in amplitude (i.e., response saturation). Because the normal hearing group had presentation levels that both fell within the steeply rising amplitude range, and the hearing loss group had one presentation level within the steeply rising range and one that fell within the slight reduction range, this significant interaction is not surprising when viewed in the context of Adler and Alder's (1989) findings. It should be noted, however, that the reductions in amplitude with increases in intensity level beyond 70 dB nHL have been cited as "tendencies" and are not consistently reported in the literature (Picton et al., 1977).

An explanation based on response saturation could be applied to the significant stimulus type (broadband noise presented at 50 and 70 dB SL) by group interaction found for N1 offset latency. In this comparison, the groups showed a different trend in latency

change as a result of the intensity increase, with the normal hearing group's latencies occurring 15 ms earlier and the hearing loss group's latencies occurring 5 ms later with the 20 dB increase in presentation level. The between-group comparison was not significant, but the direction of the latency change demonstrated a significant effect. Adler and Adler (1989) found that for individuals with normal hearing, increases in stimulus intensity from 30 to 70 dB nHL produced decreases in latency on the order of about -4 ms for every 10 dB increase in intensity; however, increases of stimulus intensity from 70 to 90 dB nHL produced latency increases of about 3 ms per 10 dB increase in intensity. Since the normal hearing group had dB SPL presentation levels for both stimulus conditions that were within the range of latency decreases and the hearing loss group had dB SPL presentation levels that were within the range of latency increases, the significant interaction found for N1 offset latency was not surprising in the context of Adler and Adler's (1989) findings. It should be noted that for the N1 offset latency interaction, the p-value and observed power were relatively weak [$F(1,15) = 4.531$; $p = 0.05$; observed power = 0.513]. This result, though significant, may not be diagnostically meaningful, especially when considering that there were no between-group differences for either broadband noise condition. Thus, the lack of significant main effects for latency measurements of this waveform component should not be disregarded.

CHAPTER 7

Conclusion, Limitations, and Future Directions

Conclusion

It was hypothesized that when differences between groups would be found that latencies would be delayed and amplitudes would be reduced for the hearing loss group when compared to those measured from the normal hearing group. This was not the case for any of the stimulus conditions. When there were significant differences between groups, as was the case in the frequency-specific noise conditions, hearing loss participants presented with earlier mean latencies and increased mean amplitudes compared to their normal hearing counterparts. Though not originally anticipated, these findings are logical once the effects of sensorineural hearing loss on the central auditory nervous system (such as changes in excitability, inhibition, spontaneous activity rates, neural synchrony, and tonotopic map reorganization) are considered. Based on the patterns observed, the waveforms evoked by the 500 Hz-centered narrowband noise stimulus and, especially, the 4000 Hz-centered narrowband noise stimulus may provide far-field electrophysiologic support for homeostatic plasticity in the central auditory nervous system that occurs as a result of sensorineural hearing loss. This homeostatic plasticity could be the physiologic basis of the abnormal loudness growth, or recruitment, phenomenon that is often reported in cases of sensorineural hearing loss. Or, it could also be that homeostatic plasticity and recruitment are one in the same.

There were no statistically significant differences between groups in amplitude or latency for either of the broadband noise conditions. For the broadband noise conditions, it appears that using a moderate to high sensation level (dB SL re: behavioral threshold

for the stimulus used for testing) rather than a dB SPL presentation level that is held constant for both normal hearing and hearing loss groups eliminated the effects that sensorineural hearing loss was expected to have on the waveforms (i.e., delayed latencies and reduced amplitudes). Moreover, through N1 offset-to-onset and P2 offset-to-onset latency difference calculations, it appears that the offset in both groups could have been evoked by the stimulus gating envelope when the plateau of the envelope begins to fall (1960 ms post stimulus onset, or 40 ms before complete stimulus termination), a time point which was held constant in the constructions of all stimuli used in this study. The existence of a gating envelope-to-offset latency relationship is further supported by the findings that the offsets to broadband noise do not exhibit a significant latency shift with an increase in intensity.

These findings are particularly appealing when considering the use of the onset-offset N1-P2 auditory evoked response in attempts to differentiate cases of sensorineural hearing loss with normal central auditory function from cases of comorbid sensorineural hearing loss and central auditory dysfunction For this purpose, the broadband noise stimulus as constructed for this study shows promise, especially when presented at 50 dB SL as is common procedure for most behavioral central auditory processing tests. As dB SL presentation levels reduced the effects of sensorineural hearing loss on the onset-offset N1-P2 waveforms for the broadband noise conditions, reductions in latency and increases in amplitude could be attributed to central auditory factors. Homeostatic changes occurring as a natural result of the sensorineural hearing loss likely underlie instances when latencies are shorter and amplitudes are increased in individuals with hearing loss compared to individuals with normal hearing. Delayed latencies and

reduced amplitudes, as documented in the cortical auditory evoked response literature, are indicative of central auditory dysfunction (Jirsa, 1992; Knight et al., 1980; Knight et al., 1989; Musiek et al., 1992; Warrier et al., 2004).

Limitations and Future Directions

This study was designed to compare auditory cortical responses obtained from individuals with normal hearing and individuals with moderate symmetrical high-frequency sensorineural hearing loss using noise stimuli that are longer in duration than those used to elicit the traditional N1-P2 response. The high-frequency sensorineural hearing loss criteria used for this study was chosen based on the results of previous research using the Dichotic Digit Test as a central auditory screening measure for individuals with this type and degree of hearing loss (Musiek et al., 1991). As such, the individuals who participated in the study were those who would likely demonstrate the greatest effects while also allowing for appropriate central auditory screening. However, given the qualification criteria of the study it is unknown whether "hidden hearing loss," as described by Kujawa and Liberman (2009), was present in any of the participants in the normal hearing group. Future studies incorporating measures such as high-intensity ABR and electrocochleography (ECochG) in order to evaluate the amplitude of the auditory nerve action potential should be explored. Using such measures in concert with the procedures documented in this study could help determine whether the waveforms obtained from the normal hearing participants were influenced by spiral ganglion cell degeneration in the face of normal audiometric thresholds.

Moving forward with future onset-offset N1-P2 auditory evoked response studies, additional groups of participants should be recruited in order to evaluate the effects of hearing loss and central auditory dysfunction on the response. First, individuals with CAPD and normal hearing should be included in future research studies so that the effects of central auditory dysfunction alone can be evaluated. This is a necessary next step in order to determine whether the use this paradigm in central auditory assessments would be of clinical value. Second, individuals with both moderate symmetrical high-frequency sensorineural hearing loss and CAPD should be recruited for participation in future studies so that the effects of the central auditory dysfunction can be evaluated in individuals with hearing loss. Using data obtained from such a sample in comparisons with the data presented here could provide a clearer picture of the effects of CAPD on the onset-offset N1-P2 auditory evoked response in individuals with both hearing loss and CAPD. Third, additional types, degrees, and configurations of hearing loss should be evaluated using this electrophysiologic paradigm to investigate whether this procedure can be utilized in the assessment of individuals with a broader range of hearing losses. This would include recruitment of individuals with milder as well as more severe degrees of hearing loss, individuals with hearing loss affecting the lower frequencies, individuals with "flat" hearing loss configurations, and individuals with conductive as well as mixed types of hearing loss. Additionally, evaluating individuals with conductive hearing loss could provide information related to whether the results of the present study were due to decreased auditory input alone or if there was an effect of distortion. Fourth, any potential effects of hearing aid use on the onset-offset N1-P2 auditory evoked response should be examined, including duration of hearing aid use, duration of hearing loss prior

to amplification, and unilateral versus bilateral hearing aid use. This is of importance, as a great number of individuals with hearing loss wear hearing aids. Fifth, as cortical auditory evoked potentials such as the N1-P2 are known to demonstrate changes due to age, the effects of age on the onset-offset N1-P2 auditory evoked response should be evaluated. Sixth, studies should also be undertaken that utilize various dB SPL and dB SL presentation levels that are held constant for both normal hearing and groups with high-frequency sensorineural hearing loss so that the effects of spread of excitation on responses and offset-to-onset amplitude ratio patterns obtained in the regions of hearing loss can be evaluated. Seventh, as the mechanisms underlying homeostatic plasticity have also been posed as influences on tinnitus, the onset-offset N1-P2 auditory evoked response should be evaluated in individuals with tinnitus, regardless of peripheral hearing status. Lastly, it would be wise to evaluate this paradigm using different equipment than that which was used in the study documented here. The Compumedics Neuroscan, though elegant in its capabilities, is primarily a research instrument and is also quite expensive. In order to provide clinically relevant research regarding the use of this paradigm on individuals with hearing loss and CAPD, at least some of the research should be performed using evoked potential equipment that is commonly available or easily attainable for clinicians. It is this author's position that should this paradigm prove useful in aiding in the diagnoses of CAPD in individuals with peripheral hearing loss, the implementation of the paradigm, including the equipment used, needs to be deemed realistic by clinicians considering its use. Thus, in addition to research using other pieces of equipment, ways to shorten the testing time should be considered. This could be done either by investigating ways of reducing the time it takes to obtain each waveform or by

selecting one or two specific stimulus conditions that are the most sensitive and specific in the diagnosis of CAPD in individuals with hearing loss.

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Appendices

Appendix A.

Table 6. Mean Presentation Levels in dB SPL

	Normal Hearing	Hearing Loss
Broadband Noise @ 50 dB SL	62 dB SPL	76 dB SPL
Broadband Noise @ 70 dB SL	82 dB SPL	96 dB SPL
500 Hz-Centered Narrowband Noise	60 dB SPL	71 dB SPL
4000 Hz-Centered Narrowband Noise	65 dB SPL	96 dB SPL

Appendix B. Code for Stimulus Creation in MLSig Toolbox for MATLAB

***BBN refers to broadband noise**
***500HzNBN refers to 500 Hz-centered narrowband noise**
***4000HzNBN refers to 4000 Hz-centered narrowband noise**

```
BBN1=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN1Gated=GATE(BBN1,40);
BBN2=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN2Gated=GATE(BBN2,40);
BBN3=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN3Gated=GATE(BBN3,40);
BBN4=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN4Gated=GATE(BBN4,40);
BBN5=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN5Gated=GATE(BBN5,40);
BBN6=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN6Gated=GATE(BBN6,40);
BBN7=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN7Gated=GATE(BBN7,40);
BBN8=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN8Gated=GATE(BBN8,40);
BBN9=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN9Gated=GATE(BBN9,40);
BBN10=gnoise(20,10000,-15,2000,0,[],0,20000);
BBN10Gated=GATE(BBN10,40);
soundsc(BBN1Gated.data,20000);
wavwrite(BBN1Gated.data,20000,'BBN1Gated');
soundsc(BBN2Gated.data,20000);
wavwrite(BBN2Gated.data,20000,'BBN2Gated');
soundsc(BBN3Gated.data,20000);
wavwrite(BBN3Gated.data,20000,'BBN3Gated');
soundsc(BBN4Gated.data,20000);
wavwrite(BBN4Gated.data,20000,'BBN4Gated');
soundsc(BBN5Gated.data,20000);
wavwrite(BBN5Gated.data,20000,'BBN5Gated');
soundsc(BBN6Gated.data,20000);
wavwrite(BBN6Gated.data,20000,'BBN6Gated');
soundsc(BBN7Gated.data,20000);
wavwrite(BBN7Gated.data,20000,'BBN7Gated');
soundsc(BBN8Gated.data,20000);
wavwrite(BBN8Gated.data,20000,'BBN8Gated');
soundsc(BBN9Gated.data,20000);
wavwrite(BBN9Gated.data,20000,'BBN9Gated');
soundsc(BBN10Gated.data,20000);
wavwrite(BBN10Gated.data,20000,'BBN10Gated');
Plot(BBN1Gated);
Plot(BBN2Gated);
Plot(BBN3Gated);
Plot(BBN4Gated);
Plot(BBN5Gated);
Plot(BBN6Gated);
Plot(BBN7Gated);
```

```
Plot(BBN8Gated);
Plot(BBN9Gated);
Plot(BBN10Gated);

NBN500Hz1=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz1Gated=GATE(NBN500Hz1,40);
NBN500Hz2=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz2Gated=GATE(NBN500Hz2,40);
NBN500Hz3=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz3Gated=GATE(NBN500Hz3,40);
NBN500Hz4=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz4Gated=GATE(NBN500Hz4,40);
NBN500Hz5=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz5Gated=GATE(NBN500Hz5,40);
NBN500Hz6=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz6Gated=GATE(NBN500Hz6,40);
NBN500Hz7=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz7Gated=GATE(NBN500Hz7,40);
NBN500Hz8=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz8Gated=GATE(NBN500Hz8,40);
NBN500Hz9=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz9Gated=GATE(NBN500Hz9,40);
NBN500Hz10=gnoise(460,540,-15,2000,0,[],0,20000);
NBN500Hz10Gated=GATE(NBN500Hz10,40);
soundsc(NBN500Hz1Gated.data,20000);
wavwrite(NBN500Hz1Gated.data,20000,'NBN500Hz1');
soundsc(NBN500Hz2Gated.data,20000);
wavwrite(NBN500Hz2Gated.data,20000,'NBN500Hz2');
soundsc(NBN500Hz3Gated.data,20000);
wavwrite(NBN500Hz3Gated.data,20000,'NBN500Hz3');
soundsc(NBN500Hz4Gated.data,20000);
wavwrite(NBN500Hz4Gated.data,20000,'NBN500Hz4');
soundsc(NBN500Hz5Gated.data,20000);
wavwrite(NBN500Hz5Gated.data,20000,'NBN500Hz5');
soundsc(NBN500Hz6Gated.data,20000);
wavwrite(NBN500Hz6Gated.data,20000,'NBN500Hz6');
soundsc(NBN500Hz7Gated.data,20000);
wavwrite(NBN500Hz7Gated.data,20000,'NBN500Hz7');
soundsc(NBN500Hz8Gated.data,20000);
wavwrite(NBN500Hz8Gated.data,20000,'NBN500Hz8');
soundsc(NBN500Hz9Gated.data,20000);
wavwrite(NBN500Hz9Gated.data,20000,'NBN500Hz9');
soundsc(NBN500Hz10Gated.data,20000);
wavwrite(NBN500Hz10Gated.data,20000,'NBN500Hz10');
Plot(NBN500Hz1Gated);
Plot(NBN500Hz2Gated);
Plot(NBN500Hz3Gated);
Plot(NBN500Hz4Gated);
Plot(NBN500Hz5Gated);
Plot(NBN500Hz6Gated);
Plot(NBN500Hz7Gated);
Plot(NBN500Hz8Gated);
Plot(NBN500Hz9Gated);
Plot(NBN500Hz10Gated);

NBN4000Hz1=gnoise(3771,4229,-15,2000,0,[],0,20000);
```

```
NBN4000Hz1Gated=GATE(NBN4000Hz1,40);
NBN4000Hz2=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz2Gated=GATE(NBN4000Hz2,40);
NBN4000Hz3=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz3Gated=GATE(NBN4000Hz3,40);
NBN4000Hz4=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz4Gated=GATE(NBN4000Hz4,40);
NBN4000Hz5=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz5Gated=GATE(NBN4000Hz5,40);
NBN4000Hz6=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz6Gated=GATE(NBN4000Hz6,40);
NBN4000Hz7=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz7Gated=GATE(NBN4000Hz7,40);
NBN4000Hz8=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz8Gated=GATE(NBN4000Hz8,40);
NBN4000Hz9=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz9Gated=GATE(NBN4000Hz9,40);
NBN4000Hz10=gnoise(3771,4229,-15,2000,0,[],0,20000);
NBN4000Hz10Gated=GATE(NBN4000Hz10,40);
soundsc(NBN4000Hz1Gated.data,20000);
wavwrite(NBN4000Hz1Gated.data,20000,'NBN4000Hz1');
soundsc(NBN4000Hz2Gated.data,20000);
wavwrite(NBN4000Hz2Gated.data,20000,'NBN4000Hz2');
soundsc(NBN4000Hz3Gated.data,20000);
wavwrite(NBN4000Hz3Gated.data,20000,'NBN4000Hz3');
soundsc(NBN4000Hz4Gated.data,20000);
wavwrite(NBN4000Hz4Gated.data,20000,'NBN4000Hz4');
soundsc(NBN4000Hz5Gated.data,20000);
wavwrite(NBN4000Hz5Gated.data,20000,'NBN4000Hz5');
soundsc(NBN4000Hz6Gated.data,20000);
wavwrite(NBN4000Hz6Gated.data,20000,'NBN4000Hz6');
soundsc(NBN4000Hz7Gated.data,20000);
wavwrite(NBN4000Hz7Gated.data,20000,'NBN4000Hz7');
soundsc(NBN4000Hz8Gated.data,20000);
wavwrite(NBN4000Hz8Gated.data,20000,'NBN4000Hz8');
soundsc(NBN4000Hz9Gated.data,20000);
wavwrite(NBN4000Hz9Gated.data,20000,'NBN4000Hz9');
soundsc(NBN4000Hz10Gated.data,20000);
wavwrite(NBN4000Hz10Gated.data,20000,'NBN4000Hz10');
Plot(NBN4000Hz1Gated);
Plot(NBN4000Hz2Gated);
Plot(NBN4000Hz3Gated);
Plot(NBN4000Hz4Gated);
Plot(NBN4000Hz5Gated);
Plot(NBN4000Hz6Gated);
Plot(NBN4000Hz7Gated);
Plot(NBN4000Hz8Gated);
Plot(NBN4000Hz9Gated);
Plot(NBN4000Hz10Gated);
```

Appendix C. Help Commands in MLSig Toolbox for MATLAB

Explanations of "gnoise," "gate," "soundsc," "wavwrite," and "plot" commands

Creating Gaussian Noise

>> **help gnoise**

```
 GNOISE - Gaussian band pass noise MLsig object
   SYNTAX:
   [Sig, RS]= Gnoise(Flow, Fhigh, SPL, Dur, Cyclic, RandSeed, Analytic, Fs);
   where
  Flow, Fhigh: cutoff frequencies in Hz.
      SPL:    expected level in dB SPL (=RMS re 1); real part only.
            Note: true RMS may be different because of statistics.
      Dur:    duration in ms
   Optional arguments:
    Cyclic:  If true, a periodic noise buffer will be generated.
            If false (default), the noise is not cyclic (faster
            computation for non-radix2 # samples).
   RandSeed:  seed for Random  generator. If omitted, a fresh
            seed is obtained using the clock. RandSeed must
            be an unsigned integer as returned by SetRandState.
   Analytic:  if true, a complex, analytic noise signal is generated.
            If false (default), the noise is real-valued.
      Fs:     sample rate in Hz (default: defaultFsam)

   Sig is a Mlsig time signal with the specified parameters.
   The optional RS output arg is the random seed.

   The noise is generated by the inverse-fft technique. If not
   Cyclic, a 2^N-point spectrum is used.

   All input args except Fs may be vectors, resulting in
   a multi-channel MLsig object.

   See also gnoiseSpec, SetRandState MLsig/ifft
```

Adding Gating to Stimuli

>> **help gate**

```
 GATE - gating of MLsig objects
   S = GATE(S,D) applies a cos^2 window to a time MLsig object S.
   D is the duration of the ramps in ms. D==0 leaves the signal
   unaffected.
```

GATE(S) is equivalent to GATE(S,S.dur/2), i.e., the maximum total
duration of the ramps, S.dur, is evenly distributed between the
onset and offset ramps. It is an error to exceed this maximum duration.

GATE(S,RISE,FALL) applies different durations of onset and offset ramps.
By default, onset and offset ramp durations are identical.
Note that GATE(S,4,0) will apply gating only to the onset portion of S.

GATE(S,D,Wtype) or GATE(S,RISE,FALL,Wtype) where Wtype is one of the string
flags listed below, applies a specific window type rather than the
default cos^2 window. Available window types are:

```
'cos2'    cos^2 window (default)
'lin'     linear
'gauss'   gaussian    (for details see source text of GATE)
'exp'     exponential (for details see source text of GATE)
```

Some of these windows take optional arguments, e.g., GATE(S,4,'exp',12).
See source text of this function for details.

Note that you can apply different window types to the rising
and falling portions of a signal by calling GATE twice, e.g.:

```
LS  = GATE(S, 4, 0, 'lin'); % linear, 4-ms, onset ramp
LSE = GATE(LS,0, 10,'exp'); % 10-ms exponential decay.
```

The Rise and Fall arguments may be row vectors, in which case their
elements are applied to the corresponding channels of the MLsig object.

See also implant, RandCut, windowing.

Playing/Listening to Stimuli in MLSig

>> help soundsc

SOUNDSC Autoscale and play vector as sound.
SOUNDSC(Y,...) is the same as SOUND(Y,...) except the data is
scaled so that the sound is played as loud as possible without
clipping. The mean of the dynamic range of the data is set to
zero after the normalization.

SOUNDSC(Y,...,SLIM) where SLIM = [SLOW SHIGH] linearly scales
values in Y in the range [SLOW, SHIGH] to [-1, 1]. Values
outside this range are not clipped. By default, SLIM is

[MIN(Y) MAX(Y)].

See also sound, wavplay, wavrecord.

Reference page in Help browser
doc soundsc

Writing Stimuli to Microsoft Wave (.wav) Sound Files

>> help wavwrite

WAVWRITE Write Microsoft WAVE (".wav") sound file.
WAVWRITE(Y,FS,NBITS,WAVEFILE) writes data Y to a Windows WAVE file specified by the file name WAVEFILE, with a sample rate of FS Hz and with NBITS number of bits. NBITS must be 8, 16, 24, or 32. Stereo data should be specified as a matrix with two columns.

WAVWRITE(Y,FS,WAVEFILE) assumes NBITS=16 bits.
WAVWRITE(Y,WAVEFILE) assumes NBITS=16 bits and FS=8000 Hz.

Input Data Ranges
The range of values in Y depends on the number of bits specified by NBITS and the data type of Y. Some examples of valid input ranges based on the value of NBITS and Y's data type are listed in the tables below.

If Y contains integer data:

NBITS	Y's data type	Y's Data range	Output Format
8	uint8	0 <= Y <= 255	uint8
16	int16	-32768 <= Y <= +32767	int16
24	int32	-2^23 <= Y <= 2^23-1	int32

If Y contains floating point data:

NBITS	Y's data type	Y's Data range	Output Format
8	single or double	-1.0 <= Y < +1.0	uint8
16	single or double	-1.0 <= Y < +1.0	int16
24	single or double	-1.0 <= Y < +1.0	int32
32	single or double	-1.0 <= Y <= +1.0	single

Note that for floating point data where NBITS < 32, amplitude values are clipped to the range -1.0 <= Y < +1.0.

8-, 16-, and 24-bit files are type 1 integer PCM.
32-bit files are written as type 3 normalized floating point.

See also wavread, auwrite.

Reference page in Help browser
doc wavwrite

Plotting Sounds Created in MLSig

>> help plot

PLOT Linear plot.

PLOT(X,Y) plots vector Y versus vector X. If X or Y is a matrix, then the vector is plotted versus the rows or columns of the matrix, whichever line up. If X is a scalar and Y is a vector, disconnected line objects are created and plotted as discrete points vertically at X.

PLOT(Y) plots the columns of Y versus their index.
If Y is complex, PLOT(Y) is equivalent to PLOT(real(Y),imag(Y)).
In all other uses of PLOT, the imaginary part is ignored.

Various line types, plot symbols and colors may be obtained with PLOT(X,Y,S) where S is a character string made from one element from any or all the following 3 columns:

b	blue	.	point	-	solid
g	green	o	circle	:	dotted
r	red	x	x-mark	-.	dashdot
c	cyan	+	plus	--	dashed
m	magenta	*	star	(none)	no line
y	yellow	s	square		
k	black	d	diamond		
w	white	v	triangle (down)		
		^	triangle (up)		
		<	triangle (left)		
		>	triangle (right)		
		p	pentagram		
		h	hexagram		

For example, PLOT(X,Y,'c+:') plots a cyan dotted line with a plus at each data point; PLOT(X,Y,'bd') plots blue diamond at each data point but does not draw any line.

PLOT(X1,Y1,S1,X2,Y2,S2,X3,Y3,S3,...) combines the plots defined by the (X,Y,S) triples, where the X's and Y's are vectors or matrices and the S's are strings.

For example, PLOT(X,Y,'y-',X,Y,'go') plots the data twice, with a solid yellow line interpolating green circles at the data points.

The PLOT command, if no color is specified, makes automatic use of the colors specified by the axes ColorOrder property. The default ColorOrder is listed in the table above for color systems where the default is blue for one line, and for multiple lines, to cycle through the first six colors in the table. For monochrome systems, PLOT cycles over the axes LineStyleOrder property.

If you do not specify a marker type, PLOT uses no marker.
If you do not specify a line style, PLOT uses a solid line.

PLOT(AX,...) plots into the axes with handle AX.

PLOT returns a column vector of handles to lineseries objects, one handle per plotted line.

The X,Y pairs, or X,Y,S triples, can be followed by parameter/value pairs to specify additional properties of the lines. For example, PLOT(X,Y,'LineWidth',2,'Color',[.6 0 0]) will create a plot with a dark red line width of 2 points.

Example

```
x = -pi:pi/10:pi;
y = tan(sin(x)) - sin(tan(x));
plot(x,y,'--rs','LineWidth',2,...
             'MarkerEdgeColor','k',...
             'MarkerFaceColor','g',...
             'MarkerSize',10)
```

See also plottools, semilogx, semilogy, loglog, plotyy, plot3, grid, title, xlabel, ylabel, axis, axes, hold, legend, subplot, scatter.

Overloaded methods:

```
MLsig/plot
timeseries/plot
phytree/plot
clustergram/plot
channel.plot
sfit/plot
```

cfit/plot
fints/plot
idmodel/plot
idfrd/plot
iddata/plot
idnlhw/plot
idnlarx/plot
mpc/plot
dspdata.plot
wdectree/plot
ntree/plot
dtree/plot
wvtree/plot
rwvtree/plot
edwttree/plot

Reference page in Help browser
doc plot