Measuring mismatch negativity responses to gaps in noise for a better understanding of tinnitus

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General abstract

Hearing in noise is facilitated by the auditory system's ability to separate sound into small auditory segments. Separation of sound is achieved using an auditory mechanism called temporal resolution that codes for small silent gaps in an acoustic stimulus. This thesis proposes a new method for measuring temporal resolution and applied it to a small pilot group of individuals with tinnitus.

Previous studies have postulated that tinnitus can "fill" in silent gaps thereby making gap detection more difficult. This was shown in studies using the gap prepulse inhibition acoustic startle where the amplitude of a startle response indicates the subject's ability to detect a small silent gap. However studies using behavioural gap detection do not show significant differences in people with reported tinnitus. Thus the behavioural evidence does not appear to support the hypothesis that tinnitus can "fill" in silent gaps.

In this thesis a new method was proposed for measuring neural gap detection: the mismatch negativity response (MMN). The mismatch negativity responses were compared to behavioural measures of gap detection in thirty-five normal hearing adults: five with reported tinnitus and thirty without tinnitus. They underwent recordings to gapped stimuli ranging from 2- to 40-ms gap durations. The stimuli were either a broadband or narrowband noise presented in the absence or presence of a filler noise.

Results of these experiments found the broadband and narrowband noises elicited MMNs to silent gaps. The amplitude of the MMN increased with larger gap durations. When filled, the amplitude of the entire waveform was proportionally reduced for all gap durations. However, for the tinnitus group the filler reduced the largest gap durations elicited MMNs amplitudes disproportionately more than for the smaller gap durations. The high and low filler noise reduced the

amplitude of the 40-ms gap MMNs. This was not reflective in the behavioural performance of gap detection as there were no significant group differences.

These studies show that neural gap detection can be measured using mismatch negativities. Reduced behavioural gap detection performance is reflected by a smaller amplitude of the MMN for suprathrehold gaps. This was shown in both normal hearing participants with elevated behavioural gap detection thresholds and participants with tinnitus. Therefore, electrophysiological recordings to gaps may provide further information on the underlying mechanisms involved in impaired gap detection that may not be captured by behavioural measures alone.

Keywords : Oddball, mismatch negativity, optimised, gap detection, temporal resolution, tinnitus, electrophysiology.

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List of abbreviations and acronoymes

GIN-ABR: Gap in noise auditory brainstem responses

GPIAS: gap prepulse inhibition acoustic startle

MMN: mismatch negativity

ABR: auditory brainstem response

RT: reaction time

ERP: event-related potential

EEG: electroencephalogram

dB: decibel

HL: hearing loss

SPL: sound pressure level

SL: sensation level

kHz: kilohertz

ms: miliseconds

N1: negative-going evoked potential occurring around 100 ms after the onset of the stimulus

P3a: positive-going evoked potential occurring around 300 ms after the onset of the stimulus

N2b: negative-going evoked potential occurring around 200 ms after the onset of the stimulus

TP9 and TP10: left and right electrodes on the surface of the temporoparietal lobe

Cz: central electrode located on the midline sagittal plane of the skull

Fz: frontal electrode located on the midline sagittal plane of the skull

ICA: Independent Component Analysis

SR: spontaneous rate

ASSR: Auditory steady state response

Acknowledgements

If you're going to try,
Go all the way.
There is no other feeling like that.
You will be alone with the gods
And the nights will flame with fire.
Do it, do it, do it,
Do it.

All the way.
All the way.

-*Charles Bukowski*

I did not know when I started this thesis 5 years ago exactly where it would lead me. The path started quite different than the end. The process has challenged me beyond what I could have ever fathomed. As I write this, I have a better understanding of what it means to have grit, integrity, and perseverance. Working on this thesis has distilled my life to the bare essentials anchored in unconditional love, which I have learned can push through the hardest challenges and the biggest emotions. With that, I would like to thank the people who have stood their loving ground with me and anchored me when I thought I would be tossed up with the waves.

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1 CHAPTER 1: Introduction

1.1 Clinical Problematic

Tinnitus is known as a phantom noise that is perceived in the absence of acoustic stimulation (Jastreboff, 1990). It is described by patients in a variety of ways that can be as simple as a single pure tone and as complex as a physical sensation accompanied by a combination of different sounds (Pan et al., 2009). It can also be perceived differently in each ear and can be variegated by movements of the jaw, dietary habits, stress level, anxiety, and level of attention (Vielsmeier et al., 2012).

Current understanding of tinnitus pathophysiology has been historically based on animal research. Animals models of tinnitus have allowed for controlled manipulations that are far too invasive to perform in humans. Animals can be subjected to noise trauma and ototoxic medications to induce tinnitus and subsequently mesure directly the areas along auditory pathways that are of interest. The problem with these animal models is that they are based on the assumption that tinnitus is present when there is cochlear damage. In reality, this is not always the case as tinnitus can also persist when input from the ear is removed by severing the auditory nerve (House and Brackman, 1981). It is thus presumptive to suggest that subjective tinnitus would be perceived in all cases of cochlear damage.

In humans, tinnitus can be reported in the presence or absence of detectable hearing loss. Tinnitus presence is confirmed through self-reported questionnaires, and psychoacoustic measurements of tinnitus loudness and intensity. Obviously, such verbal confirmations are not possible with animals. Despite this limitation, developments of neuroimaging techniques over the last two decades, have opened the possibility of developing an indicator of tinnitus common

to both humans and animals –potentially bridging the findings between both populations. Neuroimaging can thus potentially clarify the role of hearing loss in tinnitus generation and lead to the development of tinnitus biomarkers along the auditory pathway. However, before this can be accomplished, basic studies using electrophysiological techniques are necessary to establish normative data to which tinnitus samples can be compared.

Gap detection (the detection of a silent interval in an auditory stream) has been suggested as a possible indicator/biomarker of tinnitus. This method was originally introduced using mouse models measuring the amplitude of the startle reflex (Turner et al., 2006) and later an early electrophysiological response called the auditory brainstem response (Lowe & Walton, 2015). It is based on the "fill-in" hypothesis which states that tinnitus can "fill-in" silent gaps, thus making gap detection more difficult. Both the startle reflex and auditory brainstem responses showed significantly different amplitudes in the tinnitus mice compared to controls. In humans reporting tinnitus, the replication of these findings, using behavioural and objective measures of gap detection, have been contradictory (Campolo, Lobarinas, & Salvi, 2013; Fournier & Hébert, 2013).

Some of the issues with the behavioural measurements have been the effects of attention and responsiveness on gap detection (Cromwell et al. 2008). For example, if a patient is too tired or distracted they may perform worse than when they are alert and calm. Electrophysiological recordings such as the ABR or the startle reflex probe pre-attentive mechanisms (Davis et al. 1982, Lee et al. 1996) therefore they may not be sensitive to changes in alertness or attention, however they use few electrodes and can pick up unrelated potentials that are unrelated to the auditory response. The mismatch negativity has the advantage of not being affected by attention

(Campbell & Macdonald, 2011), and displaying less noise because it is based on a difference wave that subtracts all exogenous variables that are unrelated to the auditory event.

1.2 Objectives of the thesis

The main research goal of the thesis is to determine the feasibility of using the MMN as an objective clinical tool for measuring neural gap detection in human populations with tinnitus. The main hypotheses of the thesis are that MMN amplitudes can be used as a clinical measure of neural gap detection and it can be applied to a tinnitus sample to support the "fill-in" model. In order to test the first hypothesis, the MMN amplitude must change in relation to gap duration using a paradigm that is more time-efficient. To test the second hypothesis, the MMN must be measured on stimuli of a specific frequency range and intensity that are "filled" with a second stimulus. This can be summarized into three specific objectives:

Objective 1: To demonstrate that a time-efficient MMN paradigm can be applied to a range of gap durations

Objective 2: To test confounding variables of the "fill-in" model (i.e. intensity and frequency) on the MMN amplitude

Objective 3: To compare the MMN amplitude of noise-filled gaps to tinnitus-filled gaps

1.3 Overview of the thesis

The thesis begins by providing a review of the literature in chapter 2. This review discusses the previous published works on the pathophysiology of tinnitus, the clinical measurements of tinnitus, the disadvantages of current measurement tools and the advantages of objective markers. It also discusses the use of neural gap detection as a biomarker of tinnitus, the conflicting evidence of the "fill-in" hypothesis and the suspected confounds. Finally it gives

background knowledge on electrophysiological measures and how the MMN is used to resolve the confounding factors of previous studies testing the "fill-in" hypothesis.

Chapter 3 includes all the journal articles written to answer the research question. The first article entitled "A time-efficient multi-deviant optimised paradigm to determine the effects of gap duration on the Mismatch Negativity" decribes a study that replicates the use of a traditional oddball paradigm for eliciting MMNs to various gap durations and compares it to a new time-efficient optimised paradigm. This article answers the first objective of making the MMN gap detection method more time-efficient. The results from this study showed evidence that the optimised paradigm provides similar responses to gaps as the traditional method. Thus the optimised paradigm was used to evaluate objectives 2 and 3.

The second article entitled "Optimising the Mismatch Negativity for neural gap detection: determining the effects of intensity on gaps in noise" was the second study conducted based on the first article. This study changed the stimulus of the first study in two ways: it filtered the stimulus to a narrow bandwidth centered on a high frequency and it presented the filtered stimulus in two intensity conditions. This responds to the second objective of demonstrating that neural gap detection using the MMN can be applied to stimuli of various frequencies and intensities. This is an important consideration as clinical populations with tinnitus must have the tinnitus pitch matched to the gapped stimulus to test the "fill-in" hypothesis, and the intensity of the stimulus can have an effect on the perception of the gap (see literature review for more details). This study validates the use of a filtered high-frequency gapped stimulus at a high intensity for the third and fourth articles.

The third and fourth articles entitled "The Mismatch Negativity used to determine the effects of background filler noise on neural gap detection" and "The effects of tinnitus on

mismatch negativity responses to gaps in noise" describe a two-phase study that responds to the third objective. The "fill-in" model states that tinnitus "fills" the silent gaps of an acoustic stimulus. This hypothesis was tested using behavioural and MMN gap measurements in the presence of a second continuous filler stimulus in order to "fill" in the silent gaps. The purpose of the "filler" stimulus in the third article was to simulate the perception of a tinnitus percep in normal hearing non-tinnitus participants. This was replicated in the fourth article on a small pilot group of patients reporting high-frequency tinnitus. The "filler" stimulus in this fourth article acted as a "masking" stimulus that could inhibit the perception of tinnitus, a phenomenon known as residual inhibition.

2 CHAPTER 2: Literature review

2.1 Tinnitus

Tinnitus is a perception of sound that occurs in the absence of an external acoustic stimulus (Jastreboff, 1990). Its prevalence and incidence is difficult to capture as it does not have a defined population and the tinnitus sample is highly heterogeneous (Landgrebe, 2010). Tinnitus has been classified as either objective or subjective (Lockwood, Salvi & Burkard 2002). Objective tinnitus refers to a noise that can be heard using a stethoscope. This includes spontaneous sounds emitted by the outer hair cells (Penner, 1992), pulsatile sounds from the turbulent flow of blood vessels that surround the cochlea (Remely et al., 1990), or clicking from muscle contractions of the tensor tympani, stapedius or mandibular joint (Fox and Baer, 1991; Chole and Parker, 1992; Chan and Raede, 1994). Subjective tinnitus is the perception of a phantom sound in the absence of an external acoustic stimulation with possible origins linked to psychological disorders (Crönlein, Langguth, Geisler, Hajak, 2007; Langguth et al., 2007), infections (Shulman and Goldstein B, 1997) and ototoxicity (Mulheran, 1999). In addition to these possible origins, noise-induced hearing loss has been well documented as a correlate of subjective tinnitus (Emmerich et al., 2002; Attias et al., 1993; Hébert and Lupien 2009; Heffer and Koay, 2005; Kreuzer et al., 2012; Noreña and Eggermont, 2003; Rüttiger et al., 2013).

Incidence rates of tinnitus do not distinguish between objective or subjective tinnitus and they have been inconsistently reported as occurring in 30% (Heller, 2003), 15-18% (Coles, 1984) and 10% (Davis and El Rafaie, 2000) of the general population. Of those that report tinnitus, 0.5 to 1% (Erlandsson and Hallberg, 2000) or 6% (Heller, 2003) report symptoms that are debilitating and life-altering. Age is an important bias in these statistics as 30% of adults above the age of 50 report tinnitus (Davis & El Rafaie, 2000). Studies on children with tinnitus have reported an incidence of between 1.6 to 6.5% (Coelho et al. 2007; Mills et al 1986; Nodar and

Lezak 1984; Savastano 2007) however this is likely an inaccurate estimation. Children are known to rarely report the presence of tinnitus unless asked directly and questions on tinnitus are not a routine part of practice in pediatric otolaryngology offices (Møller, 2001).

There is no consensus on the origin of tinnitus due to the heterogeneity of the population, however there exist some working models on particular subpopulations. One of these models, called the Central Gain Theory, describes the potential mechanism underlying the relationship between noise-induced hearing loss and tinnitus (Noreña and Farley, 2013). This model proposes that auditory deprivation, or a diminished output from noise-induced cochlear damage, leads to compensatory hyperactivity at various levels of the central auditory nervous system. This hyperactivity has been studied in animals trained to signal the presence of tinnitus and has been related to the increased spontaneous firing rate of auditory fibers at the peripheral levels of the auditory nervous system such as the dorsal cochlear nucleus (Dehmel et al., 2012; Kaltenbach et al., 2002; Melamed et al., 2000; Middleton et al., 2011), and the central levels such as the primary auditory cortex (Salvi et al. 1990 and 2000; Noreña, Tomita and Eggermont, 2003). The central gain theory suggests that through homeostatic regulation, measured increases in spontaneous activity are biomarkers of tinnitus.

Clinical measurement of tinnitus is currently done through self-reported questionnaires such as the Tinnitus Functional Index (Meilkle et al., 2012), the Tinnitus Handicap Inventory (Newman, Jacobson and Spitzer, 1996), the Tinnitus Handicap Questionnaire (Kuk et al., 1990) and the Tinnitus Reaction Questionnaire (Wilson et al., 1991). These questionnaires all use scoring systems for the participant to rate the degree they agree with the question. Although these questionnaires are easy to administer, they exclude populations that cannot complete self-reports due to language barriers or communication limitations. Populations of particular concern

would be children or people with developmental disabilities. Another form of measurement that is performed clinically are psychoacoustic measures of tinnitus intensity and pitch. These are measures that require the participant to match the perception of their tinnitus to a presented tone. These measures provide the benefit of determining a quantitative value associated with the perception of the tinnitus, however, similar to questionnaires, they exclude populations with communication or linguistic limitations. Tinnitus measured using these subjective techniques can also be easily feigned.

Objective measures using neuroimaging for tinnitus have not gained widespread acceptance into clinical practice due to the variability of results and the time-consuming nature of the methodologies used. One of these measures is the auditory brainstem response (ABR) which is reviewed in a published article titled "Auditory brainstem responses in tinnitus: a review of Who, How and What?" found in Appendix 1. A review of the literature on auditory brainstem responses used on tinnitus sample found inconsistencies in the amplitude data reported. This may have been due to high levels of noise which are inherent of ABRs that are recorded from only 3 to 4 electrodes. The ABR can be sensitive to capturing noise unrelated to the acoustic stimulus that make the signal less distinct and change the amplitude recorded. For example a negative-going noise can reduce the amplitude of a positive-going component. The advantage of using electrophysiological recordings based on difference waves is that the noise for the conditions are subtracted, leaving only the deviations that are specific to the change in the stimulus.

Electrophysiological recordings using alternative stimuli have also been explored in the literature. The gap-in-noise ABR (or GIN-ABR) has been used in animal participants with different background noise frequencies before and after tinnitus induction by salicylate (Lowe

and Walton, 2015). Using this method, they found a significant reduction in gap detection after salicylate treatment for only the 16 kHz background noise condition. The authors concluded that since salicylate is known to produce a 16 kHz tinnitus percept that appears to fill the gap, the GIN-ABR may be effective for objectifying the presence of tinnitus in animals. Using this gap detection model may thus be a promising new method that can be applied using other techniques.

2.2 Gap detection and the "fill-in" hypothesis

Gap detection has been proposed as a potential objective measure of tinnitus. In animal research, the gap pre-pulse inhibition startle reflex (GPIAS), which uses gap detection, has been the gold standard to detect the presence of tinnitus in animals (Dehmel et al., 2012; Koehler & Shore, 2013; Kraus et al., 2010; Ralli et al., 2010). In this method, the animal reflexively responds to very loud stimuli with a primitive muscular contraction known as the acoustic startle reflex (Basavarah and Yan, 2012). In order to inhibit this reflexive response, a gap is introduced in the signal as a prepulse indicator of the incoming startling sound (Hoffman and Searle, 1965). Since animals are unable to report the presence of tinnitus verbally, the GPIAS test can be applied before and after tinnitus-inducing methods such as injections of known ototoxic agents (ex. salicylate or cisplatin), or exposure to loud sounds. In Turner et al. (2006), the first publication on GPIAS and tinnitus, the acoustic startle reflex was measured using a piezo transducer attached to the floor of the cage within which the animal is contained. To measure the detection of gaps, the animal is presented with a 60 dB SPL broadband noise or a 10 or 16 kHz bandpass filtered noise typically matched to the known frequency perception of tinnitus followed by a loud 115 dB SPL startling noise burst. The authors found when the animal heard a 50 ms silent gap, inserted within the background noise, prior to the loud noise burst, the amplitude of the startle response was reduced. However when the background noise was bandpass filtered to

match the frequency perception of the tinnitus, the startle response was less inhibited. Thus it was determined the impaired gap detection was a consequence of tinnitus perception "filling in" the gap when the background noise was qualitatively similar to the tinnitus percept. In other words, since tinnitus is believed to make the perception of gaps less noticeable, thereby reducing the inhibition of the startle reflex, the "fill-in" hypothesis suggests that gap detection can be used as an objective measure of the presence of tinnitus.

The "fill-in" hypothesis was tested in humans with a modified version of the GPIAS method using an eye-blink reflex. Fournier and Hébert (2013) tested participants with high frequency tinnitus and near-normal hearing thresholds compared to non-tinnitus normal hearing controls. They attached electrodes below the subject's eye and measured the amplitude of the ocular muscle contraction in response to loud sounds, a known startle reflex in humans (Blumenthal et al., 2005). They presented a 50 ms silent gap within a 65 dB SPL narrowband noise centered at either 500 or 4000 Hz, followed by a broadband startle noise at 105 dB SPL. Although the magnitude of the startle reflex was reduced using the 4000 Hz noise, closer to the tinnitus frequency perception, unexpectedly it was also reduced using the 500 Hz narrowband noise, a frequency much lower than the tinnitus. This finding contradicted the animal data which consistently showed the startle reflex was reduced only for frequencies matching the tinnitus percept. Behavioural pitch-matching revealed the dominant tinnitus percept was mostly in the high frequencies (11 and 16kHz), therefore it is unclear why the low-frequency stimulus also elicited a reduced startle. One possible explanation for the low frequency response is the tinnitus frequency perceptions were not precisely controlled to match the narrowband noise center frequencies, thus the patients may have had some of the tinnitus perceived at lower frequencies in addition to higher ones. Another explanation is the GPIAS method is less sensitive in the high

frequencies and produces a weaker startle response than in the low frequencies. In fact, a follow-up study demonstrated that normal hearing non-tinnitus sample showed greater startle reflex inhibition at the lower frequencies than at the higher frequencies (Fournier & Hébert, 2016). Although the human adaptation of the GPIAS method partially supported the "fill-in" theory, tinnitus participants had greater startle inhibition than controls, it did not appear to be specific to the frequency of the tinnitus percept.

The "fill-in" hypothesis was tested again on humans using psychophysical/behavioural adaptations of the GPIAS method. To evaluate whether gap detection is dependent on matching the frequency of the stimulus to tinnitus, one study asked hearing loss participants with and without tinnitus to press a button when they detected a gap in a 90 second narrowband noise (Campolo, Lobarinas, & Salvi, 2013). The narrowband noise had eighteen randomly-inserted 50-ms gaps and its centre frequency was either matched, 1 octave above, or 1 octave below the tinnitus percept. The intensity of the noise was mostly set to 15 dB above hearing thresholds. They found there was no difference between the ability for the tinnitus and non-tinnitus participants to detect the gaps even when the center frequency was altered, thus disproving the tinnitus "fill-in" hypothesis altogether and contradicting the eye-blink GPIAS data.

A more recent study evaluated the psychophysical GPIAS method on tinnitus and non-tinnitus participants matched by age, gender and hearing loss, using 3 intensity levels and 4 frequency ranges of gap-embedded noises (Boyen, Baskent, & van Dijk, 2015). The presented noises were bandpass filtered at 4-8, 4-5, 5-6.3 and 6.3-8 kHz presented at 5, 10 and 25 dB sensation level (SL). Within each noise a gap of varying durations was presented, and the gap detection threshold was determined based on the subject's ability to respond to the gap by pressing a button. The authors found the gap detection thresholds were all less than 15 ms and

did not differ significantly neither between any of the tinnitus participants (stratified into four tinnitus frequency groups) nor between the tinnitus and non-tinnitus groups. Thus, like Campolo, Lobarinas, & Salvi (2013), their findings also disprove the "fill-in" hypothesis and contradicted the eye-blink GPIAS results.

Although both psychoacoustical/behavioural adaptations of the GPIAS showed null results, a potential limitation of behavioural gap detection is the possibility of teaching tinnitus participants to discriminate their tinnitus from the task stimuli. If this is the case, the participant may learn to detect the gaps by placing greater attention on the stimulus and less attention on the tinnitus. This would potentially eliminate any behavioural differences between the tinnitus and control groups. Furthermore, a closer look at the data shows the tinnitus participants may have attended to the stimulus differently from the controls. Indeed, Boyen, Baskent, & van Dijk (2015) demonstrated that increasing stimulus loudness up to 20 dB SL improved the average gap detection threshold by 5 ms for all groups, however at 5 dB SL the tinnitus group appeared to have slightly poorer, but not significant, average gap detection thresholds. One possible explanation of the null results is the effect of an abnormal loudness growth curve, called hyperacusis, known to co-exist in tinnitus participants (Hébert, Fournier, & Noreña, 2013). It is possible the 5 dB SL stimulus was perceived louder in the tinnitus participants than the controls making the gap relatively easier to detect than if loudness was equal in both groups. Increasing stimulus loudness from 5 to 25 dB SL decreased the gap detection threshold for both groups, but at 5 dB SL the tinnitus group tended to have lower thresholds than the no tinnitus and control groups. Is it possible that hyperacusis may skew the gap detection thresholds at higher intensities? A recent study on the confounding effects of hyperacusis showed both an enhancement to the acoustic startle stimulus and an increase in the suppression of the startle

responses in noise-exposed mice (Salloum et al., 2016). Another possible explanation for the conflicting results with the startle GPIAS method is that not all the participants responded to the startle stimulus. A study evaluating the startling acoustic stimulus in patients with Parkinson's disease showed a range of responses (Carlsen, Almeida, & Franks, 2013). This suggests the startle method may not be a sensitive measure of the changes in gap detection. Another consideration for the startle method compared to the psychophysical approach are the different circuitries involved: the startle reflex uses subcortical, pre-attentive pathways (Davis et al., 1982; Lee et al. 1996) versus the psychophysical task which uses presumably the auditory and motor corticies (Zscholich and Köhling, 2013). The pre-attentive subcortical methods of gap detection (i.e. the startle reflex) possibly support the "fill-in" hypothesis but cortical compensation mechanisms involved in the psychophysical methods may not.

Another important consideration between all the studies is the level of hearing loss. The Boyen, Baskent, & van Dijk (2015) and Campolo, Lobarinas, & Salvi (2013) studies used tinnitus populations with various types and degrees of hearing loss. Since gap detection capacity can change as a function of hearing loss (Moore, 1995; Sturm et al., 2017), it is possible that even if the gap detection was "filled" in by the perception of the tinnitus, that the various degrees of hearing loss also increased gap detection. Even the normal hearing populations with and without tinnitus compared in Fournier and Hébert (2013) may have had hidden hearing loss (i.e. damage to low spontaneous rate auditory nerve fibers) affecting gap detection in addition to the tinnitus. Thus it is possible that hearing loss was not precisely controlled making the gap detection method less sensitive for detecting tinnitus alone.

2.3 Electrophysiological measures

This thesis proposes testing the "fill-in" hypothesis by measuring neural gap detection in tinnitus and non-tinnitus participants using event-related potentials (ERPs). ERPs are small changes of electrical activity, measured non-invasively from the scalp of the head using electrodes. These electrical changes measured from various places on the scalp can be related to the time of a specific event such as an external sound stimulus. The measured changes appear as a waveform with various positive and negative deflections described by polarity, latency and amplitude (Näätänen & Picton, 1987). The latency and amplitude of these waveforms are highly dependent on the integrity and maturation of the nervous system when factors related to the stimulus and subject are well controlled (Näätänen, Kujala and Winkler, 2011). There are many types of auditory evoked potentials, but the long latency potentials are particularly interesting to measure auditory processing at the cortical level. In essence, the generators of these long latency potentials are the temporal and frontal lobe (Picton et al., 1999).

In clinical and applied studies, auditory ERPs are usually recorded in a "passive" paradigm in which the individual attends to a non-auditory "task" (e.g., watching a video or reading a book) and does not actively attend to the auditory stimuli. The ERP to the auditory stimulus can usually be elicited reliably even though attention is not directed to the auditory channel. If non-sensory factors such as attention and motivation do affect the gap-elicited ERP, whatever differences are found across conditions or groups might not necessarily be a result of the perceptual ability to detect the gap.

The N1 deflection, an auditory ERP maximum over fronto-central areas of the scalp peaking at about 100 ms, elicited by either the onset or offset of the stimulus (see Näätänen and Picton, 1987 for a classic review), has been used for the study of neural gap detection. The amplitude of N1 following the presentation of a gap increases in amplitude as the duration of the

gap lengthens (Lister, Maxfield, & Pitt, 2007; Atcherson et al., 2009; Palmer & Musiek, 2014) and can still be observed for near-threshold gaps (Pratt et al., 2005; Palmer & Musiek, 2013). The gap-elicited N1 is present from children to the elderly depending on the duration of the gap and the time of occurrence of the gap (Harris et al., 2012; He et al., 2013; Ross et al., 2010). Attention may however act as a confounding factor. Harris et al. (2012) noted that attention fluctuation can predict gap ERPs in the elderly. On the other hand, the manipulation of attention appears to have minimal effect on the gap-elicited N1 in young adults (Campbell & Macdonald, 2011). Importantly, factors such as fatigue and sleepiness may result in a large decrease in the amplitude of N1 (see Campbell & Colrain, 2002 for a review). Thus the use of N1 to estimate gap duration threshold in subjects who are either very fatigued or sleepy may seriously misrepresent the actual threshold.

Another derived waveform related to changes in auditory events is the mismatch negativity response (MMN) which was first described by Näätänen et al. (1978). It is maximum over frontocentral areas of the scalp and inverts in polarity at the mastoids (Näätänen, 1990). This waveform is predominantly generated when the subject is not paying attention to the stimulus. Accordingly, while the N1 reflects a change in the auditory stimulus, the MMN is the automatic detection of changes to features of the auditory stimulus (Näätänen, 1990). The MMN is derived using the oddball paradigm where a sequence of auditory stimuli is presented with a high or low probability. The low probability stimulus may differ from the high probability stimulus by intensity, frequency, and duration (Näätänen, 1990). The evoked potential wave from the low probability stimulus has a higher negative amplitude from the high probability stimulus. The subtraction of these two waves result in a MMN wave. The MMN wave

corresponds to the activity of the cerebral cortex or sensory auditory memory (Näätänen, 1990) and occurs approximately 50-150 ms after the onset of the stimulus (Näätänen & Picton, 1987).

The classical method of acquiring the MMN is to use an oddball paradigm which tests one deviant for every separate stimulus block. An alternative, more efficient method, called the optimised paradigm, alternates the standard stimulus with all deviants thus reducing testing time significantly (Näätänen et al., 2004). One of the aims of this thesis was to explore to use of the optimised paradigm for the purpose of eliciting MMNs to various gap durations. This will be further discussed in the following section and in Milloy et al. (submitted).

Many studies on tinnitus populations have found abnormalities in the MMN wave. Tinnitus participants showed significantly different amplitudes for deviants altered by frequency such as comparing 500 and 1000 Hz (Jacobson et al., 1996), or 1000 and 1100 Hz stimuli (Holdefer, Oliveira, & Ramos, 2013). Other studies showing significant MMN changes compared deviants altered by frequencies 1, 2 and 4% higher (Weisz et al., 2004) or 10% higher and lower (Mahmoudian, al., 2013, 2015) than the standard frequency. In addition to frequency, Mahmoudian et al. (2013) also showed significantly reduced MMNs for deviants altered by a silent 7-ms gap. Indeed, based on the studies of the GPIAS, it is expected that tinnitus may reduce the perception of the gap if attentional mechanisms are controlled. Testing a tinnitus group using more than one gap duration to our knowledge has not yet been done. For this reason we propose testing a range of gap durations, including gaps smaller than 7 ms, to compare the perception of tinnitus and control populations.

2.4 Gap detection and the MMN

Gap detection using the MMN has been performed on young normal hearing participants. Bertoli, Smurzynski & Probst (2002) showed that short gaps in noise (3, 6, 9 or 15 ms) can elicit

MMN responses using an oddball paradigm. They found using a psychoacoustic method that the gap detection threshold was 6.4 ms. The MMN was detectable at 6 ms (1 subject) and 9 ms (5 participants) and not detectable at 3 ms by any of the participants. Other studies that have used MMN to study neural gap detection using tone pairs (Heinrich, Alain, & Schneider, 2004), nonsense words (Pihko et al., 1997) and short tone pips (Desjardins et al., 1999) all showed the MMN can be elicited by gaps. Significant MMNs were found for gaps as low as 5 and 1.13 ms (Desjardins et al., 1999 and Heinrich Alain, & Schneider, 2004 respectively).

A number of other oddball studies have demonstrated that rarely occurring deviant stimuli containing a supra-threshold gap will elicit a robust MMN (Bertoli et al., 2001; Todd et al., 2011; Yabe et al., 2005). The MMN will vary depending when the gap is placed in the standard stimulus (Yabe et al., 2005) or if the gap is partially filled (Tamakoshi et al., 2016). The amplitude of the MMN also varies with the duration of the gap being visible for gap durations that exceed the behavioural threshold for its detection (Alain et al., 2004; Bertoli et al., 2001). With very long gap durations, the MMN may reach a ceiling level. Larger increases in gap duration will then not be associated with a concomitant increase in the MMN (Torppa et al., 2014). The gap MMN appears to be mature within 6 months of birth (Trainor et al., 2001).

Tinnitus groups have not yet been explored using the MMN to a various gap durations. Given the startle reflex gap detection data explained above, it may be relevant to study this population using stimuli similar to the tinnitus percept. Although the effects of tinnitus on neural gap detection have not been elucidated, GIN-ABR has been used in animal participants with different background noise frequencies before and after tinnitus induction by salicylate (Lowe & Walton, 2015). Using this method, they found a significant reduction in neural and behavioural gap detection after salicylate treatment for only the 16 kHz background noise condition. As

salicylate is known to produce a 16 kHz tinnitus percept, the authors concluded that tinnitus fills in the gap at 16 kHz which was demonstrated by a reduction in the amplitude of specific components of the ABR waveform. If this phenomenon exists using the ABR amplitude as a marker of neural gap detection, then it would be interesting to see if the same frequency-specific effect can be found in populations with tinnitus using a different electrophysiological marker, the MMN. Accordingly, this thesis focuses on the application a frequency specific gap-in-noise stimulus to elicit an MMN in a tinnitus pilot group.

2.5 Hearing loss and the MMN

As mentioned above, Mahmoudian et al. (2013) suggest that the MMN may show different pre-attentive processing of silent gaps in normal hearing than in tinnitus groups; the MMN being more reduced in amplitude in tinnitus groups than normal hearing group. However given that tinnitus typically present with hearing loss, hearing loss is a covariable that may also reduce the MMN amplitude and not the tinnitus. Indeed ERP amplitudes are reduced and larger psychoacoustic gap detection thresholds are found in patients with auditory neuropathy (Michalewski et al., 2005). Interestingly there was no difference in the gap detection threshold between the passive and active conditions: passive being the condition where the subject was presented with gaps but did not actively attend to them, and active conditions being when the patient pressed a button in response to the presented gaps. This suggests that attention does not change the gap detection threshold in either those with or without hearing loss. Therefore it does not appear that hearing loss changes gap detection thresholds whether tested using behavioural (active) or electrophysiological (passive) measures. However, this is not the case in populations with tinnitus. Recall studies on GPIAS using the startle reflex showed tinnitus impairs gap detection using the passive startle method, but not when gaps are detected with active

behavioural methods. Thus this effect cannot be explained by hearing loss. The studies presented in this thesis will compare electrophysiological and behavioural measures of gap detection in tinnitus to determine if gap detection differs between both methods.

2.6 Forward filler and residual inhibition

Residual inhibition is the temporary cessation of tinnitus perception following the presentation of a "filler" noise that matches its intensity and frequency (Roberts et al., 2008). The degree of change to the tinnitus loudness following the noise is called residual inhibition depth (Roberts et al., 2008; Roberts, 2010). There is evidence that filler noise can also alter the pattern of electrophysiological responses in tinnitus differently than controls. Roberts et al. (2015) found filler noises that were narrowband filtered at 5 kHz reduced the off-frequency probed ERP amplitude in normal hearing groups but increased the on-frequency probed ERPs for tinnitus groups. The authors believe these differences were due to the effects of the probe frequency (i.e. the frequency of the stimulus used to elicit the ERPs) and the large individual variability. Indeed, Milloy et al. (2017) showed that literature on ERP measures with contributions from the brainstem used on tinnitus groups can be sensitive to noise artifacts. This can make measured ERP amplitudes very unstable. There was comparatively less variability for the N1 measure and the authors found the filler effects for the high frequency probes were larger N1 amplitude decreases for greater residual inhibition depth. Since filler noise appears to have an effect on the N1 amplitude, there is a possibility it can also alter the MMN amplitude. Our study will thus observe the effects of filler on the behavioural and MMN responses to gaps in noise.

3 CHAPTER 3: Journal articles

This chapter contains the following four articles:

Article 1: A time-efficient multi-deviant optimised paradigm to determine the effects of gap duration on the Mismatch Negativity (resubmitted to Hearing Research, April 2018, under second review)

Article 2: Optimizing the Mismatch Negativity for neural gap detection: determining the effects of intensity on gaps in noise

Article 3: The Mismatch Negativity used to determine the effects of background filler noise on neural gap detection

Article 4: The effects of tinnitus on mismatch negativity responses to gaps in noise

Article 1: A time-efficient multi-deviant optimised paradigm to determine the effects of gap duration on the Mismatch Negativity

This section describes the first article in this thesis on the study of MMNs for neural gap detection. It describes the use of two techniques, the oddball and the optimal, used to elicit Mismatch Negativity (MMN) responses for stimuli with various gap durations. The gaps with increasing duration elicited MMNs of increasing amplitude for both techniques. This was an important step as the oddball paradigm has been used in the past to demonstrate the MMN elicited by gaps however, by testing only one deviant (i.e. a single gap width) at a time. The optimal paradigm allows for multiple deviants to be tested within the same sequence, thus making it possible to test multiple gap widths at once. Demostrating the effect of gap duration on the MMN using the optimal allows for the subsequent studies to use this more time effective technique in place of the oddball.

3.1 Article 1: A time-efficient multi-deviant optimised paradigm to determine the effects of gap duration on the Mismatch Negativity

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3.1.1 Abstract

The insertion of a silent period (or gap) in a frequently occurring standard stimulus elicits a negative-going event-related potential (ERP), called the Mismatch Negativity (MMN). This is often studied using a so-called oddball paradigm. To study the effects of gaps having a different duration, a different oddball sequence would be required for each gap. A more time-efficient multi-deviant optimised paradigm has been developed in which various gapped stimuli are included in a single sequence. In the present study, 14 young adults watched a silent video while ignoring an auditory sequence. A single run of a multi-deviant optimised sequence was presented in which 6 different rare deviants alternated with a standard stimulus. The standard was a 200-ms white noise burst. The deviant was constructed by inserting a gap in the standard. The duration of the 6 deviants ranged from 2 to 40 ms. Participants were also presented with multiple runs of single-deviant oddball sequences. Each of the 3 deviants was run in a separate sequence. The amplitude of the MMN elicited by the deviant increased as the duration became longer, although it did plateau for the longer duration gaps. Importantly, the amplitude of the MMNs did not differ between the multi-deviant optimised and single-deviant oddball paradigms. Behavioural data showed an average gap detection threshold of 5 ms with a detection rate of approximately .5. None of the participants were able to detect the 2-ms gap as the mean detection rate was only .01. Supra-threshold gaps representing a change in a frequently occurring standard stimulus elicited robust MMNs. The multi-deviant optimised paradigm provides a time-efficient and reliable alternative to the frequently-used but time-demanding oddball paradigm for the study of neural gap detection.

Key words: Mismatch Negativity, Optimised, Oddball, Temporal Processing, Gap Detection, Event-related potentials.

Highlights:

- A multi-deviant optimised paradigm was used to determine the effects of gap duration on the MMN
- MMN amplitude was similar for both multi-deviant optimised and single-deviant oddball paradigms.
- MMN amplitude increased with gap duration but plateaued for longer gaps.

3.1.2 Introduction

Temporal resolution (or acuity) is the ability to make discriminations of a changing sound, an ability thought to be critical for the perception of speech and sound localisation since most acoustic signals vary over time (Moore, 2008). Temporal resolution is often studied using gap detection. A participant might, for example, be asked to judge whether a silent period (or "gap") had occurred within a continuous or long duration auditory stimulus.

A restriction for the use of such behavioural measures of gap detection is that they require active participation and the maintenance of attention for relatively long periods of time. This may not be possible in certain populations such as infants and young children or neurological and psychiatric patients. Importantly, behavioural methods require a perceptual decision, which is affected by cognitive processes such as memory, motivation and attention. Some authors hypothesize that, for example, older adults may compensate for hearing loss by exerting additional attentional effort during behavioural testing (Bertoli et al., 2001; Alain et al., 2004; Harris et al., 2012). Normal hearing young adults can detect gaps as short as 3 to 5 ms when presented in moderate intensity white noise (Musiek et al., 2005; Samelli and Schochat, 2008). Longer duration gaps are also clinically relevant; commercially distributed tests for temporal resolution such as the Random Gap Detection Test (RGDT) (Keith, 2002) and the Gaps

in Noise test (GIN) (Musiek et al., 2005) include gap durations up to 40 and 20 ms, respectively. Nevertheless, some individuals having high gap thresholds may still readily detect the longer 20- to 40-ms duration gaps. This does not imply, however, that theses individuals perceive or process the supra-threshold gaps "normally", in the same manner as those with low gap thresholds.

Event-related potentials (ERPs) provide an exquisite means to monitor the extent of processing of a gap stimulus or intensity change occurring within a long duration stimulus. ERPs are the minute changes in the electrical activity of the brain that are elicited by an external stimulus or internal psychological event. ERPs consist of a series of negative- and positive-going components thought to reflect different aspects of information processing. The amplitudes of these different components are usually much smaller than that of the ongoing random "noise" of the EEG in which they are embedded. The background noise can be reduced through averaging procedures. With repetition of the stimulus, the average of the random background activity of the background EEG (the noise) will gradually reduce allowing the "signal" (the ERP) to emerge. Small amplitude ERPs will however require a large number of stimulus repetitions. Thus, a disadvantage to the use of ERP methods is that a long period of time may be required for the collection of the data.

In clinical and applied studies, auditory ERPs are usually recorded in a "passive" paradigm in which the individual attends to a non-auditory "task" (e.g., watching a video or reading a book) and does not actively attend to the auditory stimuli. The ERP component of interest to the auditory stimulus should therefore be elicited reliably even though attention is not directed to the auditory channel. If non-sensory factors such as attention and motivation do affect the gap-elicited ERP, whatever differences are found across conditions or groups might not necessarily be a result of the perceptual ability to detect the gap.

An auditory ERP that has been employed in the study of neural gap detection is the mismatch negativity (MMN). The MMN is often recorded using the so-called auditory oddball paradigm. The participant is presented with a frequently occurring homogenous "standard" stimulus. At rare (or odd) and unpredictable times, a feature of the standard is changed to form a "deviant". Both the standard and the deviant elicit a N1 occurring around 100 ms, and a later P2, occurring around 180-200 ms after the onset of the stimulus. The deviant, in addition, elicits the MMN. The MMN can be elicited by a change in almost any feature of the standard, such as its frequency, intensity, location or duration. It peaks from 100-200 ms following presentation of the deviant and is maximum over fronto-central areas of the scalp, inverting in polarity at the mastoids (i.e., becomes a positive potential). In the classic Näätänen model (1990; 1992), the MMN is claimed to be associated with a pre-conscious memory-based comparison system in which features of the incoming stimulus are compared against features of the preceding stimuli (the standard) stored in sensory memory. When a deviant is presented, one of its features fails to match those stored in sensory memory and a change is detected. A more recent model maintains that the MMN is elicited by a mismatch between the current auditory input and predictions formed on the basis of rule-based acoustic patterns that are automatically detected in recent auditory stimulation (Näätänen, Kujala & Winkler, 2011; Paavilainen, 2013; Winkler, 2007; Winkler, Denham, & Nelken, 2009). As such, the repeating, homogenous standard used in the oddball sequence is a special case of an acoustic pattern, the occurrence of the deviant violating this pattern. The output of the change detection system varies directly with the extent of stimulus change, the amplitude of the MMN reflecting this output. Importantly, the MMN is still robust in the absence of attention (Muller-Gass et al., 2006; Sussman, 2007). The MMN is also unaffected by factors such as drowsiness and fatigue. Four hours of sleep loss at the beginning of the night

and even total sleep deprivation have a minimal effect on the MMN (Zerouli et al., 2010; Bortoletto et al., 2011).

Gap stimuli have been presented in oddball paradigms to elicit the MMN. The frequently occurring, relatively long duration standard stimulus (100 to 300 ms in different studies) does not contain a gap. A deviant is created by inserting a silent period (or gap) in the standard. A number of oddball studies have demonstrated that rarely occurring deviant stimuli containing a supra-threshold gap elicit a large MMN (Bertoli et al., 2001; Tamakoshi et al., 2016; Todd et al., 2011; Yabe et al., 2005). The MMN varies depending on when the gap is placed in the standard stimulus (Yabe et al., 2005) or whether the gap is partially filled (Tamakoshi et al., 2016). The amplitude of the MMN also varies with the duration of the gap being measurable for gaps that exceed the behavioural detection threshold (Alain et al., 2004; Bertoli et al., 2001). With very long duration gaps, the MMN may reach a ceiling (Torppa et al., 2014). The gap MMN appears to be mature within 6 months of birth (Trainor et al., 2001).

While almost all studies label the negativity that is elicited by the rarely occurring gap as an MMN, this may not be a "true" MMN. The onset of the gap will also elicit another negativity, the N1. N1 overlaps temporally and spatially (occurring at about the same time and sharing a similar scalp distribution) with the MMN. The occurrence of the gap does signal change from the acoustic past, the frequent occurrence of the standard not containing a gap. The gap deviant will thus also elicit an MMN. The negativity that is observed following presentation of the gap is thus probably a composite N1+MMN.

In most studies, a single deviant is presented within the oddball sequence. This can be problematic when the effects of several different types of deviants are to be examined. For example, to determine the effects of different gap durations, several different gaps need to be

presented. This would require a different oddball sequence for each gap, thus requiring long testing times. The amplitude of the MMN can be very small (less than 1 μV). Because the deviant is rarely presented, about 20-30 minutes of testing may be required for the MMN to be clearly observed. If the MMN is recorded to different deviants in separate single deviant oddball sequences, total testing times may exceed 2 hours. This may not be practical in many applied and clinical settings.

An alternative time efficient multi-feature "optimised" paradigm was developed by Näätänen et al. (2004). The optimised paradigm is time efficient because it allows several deviants to be presented in a single sequence. The sequence consists of an alternating pattern of standards and deviants. Five or more different deviants are often presented within the sequence. Thus, while the overall probability of standard and deviant occurrence is 0.5, the probability of any specific type of deviant is lower. If five deviants are presented, the probability of occurrence of each is 0.1. As the multi-feature label implies, each deviant is created by changing a different feature of the standard (e.g., its frequency, intensity, duration, location or the insertion of a silent period). Thus, one deviant might represent a change in frequency, another deviant a change in duration, and so forth. Näätänen et al. (2004) compared the MMNs elicited by the different deviants in a multiple-feature optimised paradigm and those elicited by the same deviants but presented in multiple runs of a single-deviant oddball paradigm (i.e. a single different deviant being presented in each oddball sequence). The MMN was essentially identical for the different deviants in the single multi-deviant optimised paradigm and multiple runs of the single-feature oddball paradigm.

As already mentioned, the classic model of the MMN maintains that acoustic change is detected when the extracted features of the deviant fail to match to those of the well-established

sensory memory for the standard. In the multi-feature optimised paradigm, because the standard is presented on 50% of trials, the memory for its features will also be well-established, although weaker than in the oddball paradigm when the standard is presented much more frequently. In the multi-feature optimised paradigm, all deviants, however, share all features of the standard except for the single feature that changes. Thus, even though the deviants are also presented on 50% of trials, the memory for the common features shared with the standard is also strengthened. When a specific deviant is presented, one of its features fails to match that of the standard but also fails to match that of all other deviants. Thus, while a deviant is presented on 50% of trials, the occurrence of a change in one specific feature is rare.

The multi-feature optimised paradigm provides a means of testing those individuals unable or unwilling to participate for the very long testing times required by multiple runs of the traditional single-deviant oddball paradigm. The optimised paradigm was nevertheless originally designed for the use of "multi-feature" deviants. Each deviant thus represents a change of a different feature of the standard, but each deviant also represents the same change from all other deviants. In the present study, each deviant was created by inserting a gap in the standard stimulus, the different deviants having a different gap duration. Note that the same feature, the introduction of a gap, is common to all deviants. This is unlike the original multi-feature design, in which each deviant represents a different change from the standard and from all other deviants. In the present gap study, what does change among the deviants is a single feature, the duration of the gap. The concern is that in the original multi-deviant optimised paradigm, the probability of occurrence of a change to a specific feature is low, while in the present study, the probability of change of a single feature (the occurrence of a gap) is very high, occurring on 50% of stimulus presentations. Will this multi-deviant optimised paradigm be successful in eliciting

an MMN when the probability of occurrence of standards (no gap) and deviants (gap) is the same?

The amplitude of MMN elicited by multiple runs of a single deviant oddball paradigm varies directly with the duration of the gap deviant. The question the present study asks is whether the amplitude of the MMN will also vary directly with gap duration when these different gap deviants are presented in a single run of a multi-deviant optimised paradigm. Because the processing of long duration gaps is also of interest, the duration of the gap varied from sub-threshold (2 ms) to supra-threshold (40 ms). These MMNs were then compared to those elicited when multiple single feature oddball sequences were employed, one for each gap duration.

3.1.3 Methods

3.1.3.1 Participants

Fifteen adults (10 females, 5 males) between the ages of 20 and 40 years (mean=30, SD=6 years) volunteered to participate in this study. None reported a history of neurological or psychiatric disorders. Hearing thresholds were measured using an audiometer (Madsen) from 250 to 8000 Hz using TDH 50 (Telephonics) headphones. All participants had thresholds below 15 dB HL. This study was approved by the University of Ottawa Research Ethics Board in accordance with the Canadian Tri-Council (Natural, Health and Social Sciences) guidelines on ethical conduct involving human participants. These guidelines are similar to those used by the Declaration of Helsinki. In accordance with these guidelines, all participants gave written consent and the nature of the experiment was explained to them. All participants received an honorarium for their participation.

3.1.3.2 Procedure and stimuli

Auditory stimuli were presented monaurally to the right ear through EAR3A insert earphones. Ear of presentation has little effect on the MMN (Grimm et al., 2008). Participants sat

in a sound-attenuated room watching a silent, sub-titled video. They were asked to minimize movement and eye-blinking.

The multi-deviant optimised sequence consisted of the presentation of a standard alternating with deviants, as shown in Figure 1-1A. The standard was an 80 dB SPL broadband Gaussian white noise burst (created in Audacity® recording and editing software version 2.1.0), 200 ms in duration with an instantaneous rise and fall time. The stimulus was calibrated using a sound level meter and a type 2 coupler (RK0045, GRAS). The timing and presentation of all stimuli were controlled by a computer running E-Prime ® (Psychology Software Tools, version 2.0) software. Six deviants were created by including a silent interval (a "gap") in the standard. The duration of the gap was 2, 5, 10, 20, 30 or 40 ms, each having an instantaneous onset and offset. The gap was placed in the centre of the noise burst. The use of broadband noise minimized spectral splatter produced by the gap (Trainor et al. 2001). While the overall probability of occurrence of a deviant was 0.50, the probability of occurrence of any one of the six deviants was 0.083. The offset-to-onset inter-stimulus interval (ISI) was 400 ms (see Figure 1-1B). The order of occurrence of deviants was pseudorandomized, such that in a group of six deviants, the same deviant was not presented consecutively and the order of deviants within the array was never the same throughout the sequence. Each sequence began with the presentation of 10 standards in order to establish a representation of it in sensory memory. The multi-deviant optimised sequence was repeated 3 times. Each sequence lasted about 10 minutes with 472 standards (including 10 standards presented before the alternating sequence) and 77 of each deviant being presented. A brief rest period was provided between sequences in which movement was encouraged.

The single-deviant oddball sequence consisted of the same standard stimulus presented on 91.7% of the trials (see Figure 1-1A). A single deviant was presented on the remaining 8.3% of trials. In different conditions, the duration of the deviant gap was either 5, 20, or 40 ms. These gap sizes were chosen to reflect a wide range of gap durations, from near-threshold to supra-threshold and those used in commercial equipment in clinical settings (see Introduction). The order of the stimuli was pseudo-randomized such that at least 3 standards were presented between the deviants. Each single-deviant oddball sequence also began with the presentation of 10 standards. Each sequence again lasted about 10 minutes, a total of 857 standards and 77 deviants thus being presented. A single-deviant oddball condition was presented three times for each gap duration (i.e., a total of 9 oddball sequences was run). Again, a brief break was provided between sequences. The total time to complete the single-deviant oddball sequences, including breaks, was about 2 hours. The multi-deviant optimised conditions were presented in alternating order with the single-deviant oddball conditions for the first half of the presentations followed by the single-deviant oddball conditions for the remainder of the presentations. Single-deviant oddball sequences with the same gap duration were not presented consecutively.

3.1.3.3 EEG/ERP recording

The EEG was recorded from 28 active silver/silver chloride electrodes attached to an electrode cap (Brain Products GmbH, Munich, Germany). The electrodes were placed over frontal, central, parietal, temporal, and occipital areas of the scalp. Two additional electrodes were placed on the left and right mastoids (TP9 and TP10). Vertical eye movements and blink artifacts were recorded from an electrode placed on the infra-orbital ridge of the left eye. The tip of the nose served as a reference for all channels, including the electro-oculogram (EOG). Inter-electrode impedances were kept between 25 and 50 kΩ. The physiological data were digitized

continuously at a 500-Hz sampling rate and stored on hard disk for later analyses. The amplifier hardware low pass filter was set at 250 Hz and high pass filter at 0.08 Hz (a time constant of 2 s).

The data were analysed using Brain Products' Analyzer2 software. The EEG and EOG data were digitally filtered using a low-pass filter set at 20 Hz (24 dB roll-off). The EEG was visually inspected for channels containing high levels of noise. These channels were replaced by interpolating the data from the surrounding electrode sites (Perrin et al., 1989). When more than 4 channels contained high levels of noise, the data were rejected. This was the case for one participant.

Independent Component Analysis (Chaumon et al., 2015; Makeig et al., 1996) was subsequently used to identify eye movement and blink artefacts that were statistically independent of the EEG activity. To correct for eye movement and blink artefact occurring within the EEG signals, vertical and horizontal EOG activity needed to be computed. A vertical EOG channel was computed by subtracting activity recorded at FP1 from that of the EOG located on the infra-orbital ridge. A horizontal EOG channel was computed by subtracting FT9 activity from that of FT10. The ICA model is based on the assumption that the observed electrophysiological signals represent a linear mix of neural sources and artefact. The mixture and sources are however unknown but are mutually statistically independent. Thus, the algorithm relies on what is called blind source separation (BSS) to estimate the statistically independent sources. This algorithm was trained to recognize each participant's ocular artefact signature, and this component was then partitioned out of the EEG traces.

The continuous EEG data were partitioned into single-trial 700-ms segments, beginning 100 ms before stimulus onset. In many ERP studies, the average of all activity in the pre-stimulus period (-100 to 0 ms in this study) serves as a zero-voltage pre-stimulus baseline.

Because the stimulus has yet to be presented, it is assumed that this pre-stimulus interval would be the same for all stimuli. This was, in fact not the case. The pre-stimulus baseline was not stable across the various stimuli. This might reflect a psychological expectation for a stimulus (the participant could predict whether the next stimulus would be a standard or a deviant and could also predict its time of onset, because stimuli were presented at a constant ISI). It might also reflect random fluctuations. The standards and deviants were physically identical for at least the first 80 ms after stimulus onset. Processing of these stimuli in this initial period should thus also have been the same. For this reason, a para-stimulus (i.e. beside the stimulus) baseline was computed as the average of all activity from -50 to +50 ms.

Drifts in voltage from the baseline were then corrected for each single segment. The mean amplitude of all data points within the baseline period were subtracted from all subsequent data points in the post-stimulus period. Segments in which EEG activity exceeded +/- 100 μV were excluded from further analyses. The single segments were then sorted and averaged on the basis of stimulus type (standard, different types of deviants) and electrode site.

3.1.3.4 Behavioural measures

Behavioural measures of gap detection were conducted following the electrophysiological procedure. This was done to avoid the risk of the participant paying attention to the gaps during the electrophysiological task. In the behavioural task, the participant was asked to press one of two buttons when they heard a gap. The second button was to be pressed when no gap were detected. The system recorded any non-responses to the stimulus, after 600 ms, as "incorrect". The stimulus was identical to the one used for the passive condition. The gapped deviants were presented in random order with the standard stimuli. A total of 40 standard stimuli were presented with 20 stimuli of each deviant, thus a total of 120 deviants.

3.1.3.5 Quantification and statistical analyses

Both the standard and the deviant elicited ERPs such as the N1 and P2. The deviants elicited a series of additional deflections, such as the MMN and at times the P3a. These additional deflections are best observed in a difference wave computed by subtracting point-by-point the average response to the standard from that to the deviant. The subtraction process removes responses that are common to both the standard and the deviant.

For individual participants, the MMN was initially identified as the mean of all data points within +/- 25 ms of the peak amplitude identified in the grand average (average of all participants' averages). Another commonly used method to measure the MMN is to identify its minimum peak amplitude within a latency range. However, the minimum peak measure is biased by noise. The peak that is identified is a summation of the actual signal (the MMN) and noise. The minimum peak measurement technique is especially problematic when the amplitude of the signal (the MMN) is small, which would be expected when the gap is brief. The mean amplitude measure, in contrast, is not biased by overlapping noise because negative- and positive-going drifts would tend to cancel within the time interval (Luck, 2014). The disadvantage of the mean amplitude measure is that a peak latency cannot easily be determined.

It was first necessary to assess whether a significant MMN was elicited by each deviant. Confidence intervals were therefore computed around the group mean of the MMN in the difference wave for each deviant. When the upper limit of a confidence interval was significantly less than 0 μV, the interval was considered to contain a significant negativity. This procedure is equivalent to computing a t-test between the standard and deviant waveforms (Winer et al., 1971). The tests were run on the Fz data, where the MMN tends to be maximum in amplitude. Because a negative directionality was predicted, a one-tailed test of significance ($p<.05$) was used.

A series of ANOVAs were run to determine the effect of gap duration on the amplitude of the MMN. A separate one-way ANOVA was run for the multi-deviant optimised and single-deviant oddball data with repeated measures on gap duration because the number of deviants was different in condition (2-, 5-, 10-, 20-, 30, 40-ms gaps for the multi-deviant optimised condition and 5-, 20-, 40-ms gaps for the single-deviant oddball conditions). These ANOVAs were run separately for the Fz and Cz sites where the MMN is maximum. The same analyses were also run on the mastoid (TP9, TP10) data where the MMN inverts in polarity. Hemisphere differences were compared at F3 and F4 and also at C3 and C4 using a 2-way ANOVA with repeated measures on gap duration and electrode site (left, right). In all cases, when significant differences were found, a Fisher's Least Significant Difference (LSD) post-hoc test was employed as a follow-up procedure. Greenhouse-Geisser corrections were applied to all ANOVAs to correct for any possible sphericity violations.

The MMNs elicited in the multi-deviant and single-deviant oddball paradigms were compared using separate t-tests for the 2-, 20- and 40-ms duration gaps. Separate t-tests were run at Fz and Cz. The use of multiple t-tests does, of course, increase the risk of finding significance by chance alone (increases the likelihood of type I error). Such a liberal statistical procedure was used to ensure that any differences between the multi-deviant optimised and the single-deviant oddball paradigms would be identified, even if these differences might reflect chance findings. For this reason, no corrections were made for the use of multiple t-tests.

3.1.4 Results

3.1.4.1 Physiological data

3.1.4.1.1 Standard ERP

The MMN was measured in a standard-deviant difference wave. The use of the difference wave assumes that the MMN was elicited by the deviant stimulus and that differences in the

MMN between the multi-deviant optimised and single-deviant oddball conditions was a result of differential processing of the deviant. This assumption is valid only if processing of the standard did not vary between the two conditions. This may not have been the case. In the single-deviant oddball conditions, the standard was presented much more frequently than in the multi-deviant optimised condition. The ERPs evoked by the standard stimulus in the multi-deviant optimised and single-deviant oddball conditions were therefore compared (Figure 1-2). In this Figure a negative-going deflection is apparent at about 100 ms and followed by a positive-going deflection at about 180 ms. These are the N1 and P2 deflections that were elicited by the onset of the standard. The standard waveforms within the three single-deviant oddball conditions were very similar and were therefore collapsed for the purpose of comparison with the multi-deviant optimised data. A t-test at Cz revealed that neither the amplitude of the standard N1 nor that of P2 significantly differed between the multi-deviant optimised and single-deviant oddball conditions ($t < 1$ in both cases). Thus, it would appear that the processing of the standard was indeed very similar between the two conditions. The duration of the standard was 200 ms. At the offset of the stimulus, an N1-P2 was again elicited. At Cz, the small P2 response occurring at about 360 ms after the onset of the stimulus was significantly larger in the multi-deviant optimised condition, $t(13)=3.49$, $p< .01$. Because this response occurs after the MMN, it would not have contributed to its morphology.

3.1.4.2 Difference waves

3.1.4.2.1 Multi-deviant optimised paradigm

Figure 1-3 illustrates the grand-average deviant-standard difference waveforms for the 6 deviants in the multi-deviant optimised paradigm. Table 1-1 presents the mean amplitude of the MMN in the multi-deviant optimised and single-deviant oddball paradigms as a function of gap

duration. A fronto-central maximum MMN at about 100 ms following the onset of the gap was elicited, inverting in polarity at the mastoids. Confidence intervals revealed a significant MMN for all deviants with the exception of the 2- and 10-ms deviants at Fz and Cz. The ANOVA revealed that the main effect of gap duration was significant at both Fz and Cz, $F(5,65)=8.60$, $p=.0001$, $\eta_p^2=.41$ and $F(5,65)=5.52$, $p=.0001$, $\eta_p^2=.30$, respectively. The amplitude of the MMN increased varied with increasing duration of the gap. At Fz and Cz, post-hoc tests revealed no significant MMN differences among the 2-, 5- and 10- ms gaps. The MMN amplitudes significantly increased for the 20-, 30- and 40-ms gaps compared to that for the 10-ms gap. While the amplitude of the 40-ms gap did increase slightly compared to that for the 20-and 30-ms gaps, the differences were not significant. The MMN recorded at the mastoids was also significantly affected by gap duration, at both TP9, $F(5,65)=3.55$, $p=.007$, $\eta_p^2=.21$, and TP10, $F(5,65)=3.85$, $p=.004$, $\eta_p^2=.23$. Post-hoc comparisons revealed significant differences between the 2-ms and the 30- and 40-ms gaps. The amplitude of MMNs elicited by 5- and 10-ms gaps were not significantly different from that elicited by the 2-ms gap. MMN amplitude differences between the left and right hemispheres were not significant, $F<1$. The deviant x hemisphere interaction was also not significant, $F<1$.

3.1.4.2.2 Single deviant Oddball paradigm

The difference waves for the single-deviant oddball paradigm are shown in Figure 1-4. Again, the gap stimuli elicited a negativity (the MMN) occurring from 100 to 150 ms following the onset of the gap in the deviant. It also was maximum over fronto-central areas of the scalp and inverted in polarity at the mastoids.

Confidence interval testing revealed that all deviants elicited a significant ($p<.05$) MMN at the Fz and Cz electrode sites for the 5-, 20- and 40-ms deviants. The effect of gap duration

was significant at both Fz, F(2,26) = 27.53, p = .0001, η_p^2=.68. and Cz, F(2,26) = 11.56, p = .0001, η_p^2=.47. Post-hoc testing revealed that at Fz, MMN amplitude was significantly larger for the 20- and 40-ms gaps than for the 5-ms gaps. However the MMN amplitude for the 40-ms gap was not significantly larger than for the 20-ms gap. At the mastoids, the effect of gap duration was also significant at both TP9, F(2,26) = 9.15, p = .001, η_p^2= .41, and at TP10, F(2,26) = 11.11, p = .0001, η_p^2=.46. Post hoc comparisons showed significant differences between all gap durations for both mastoids (p<.05). Differences between the MMN amplitudes of the right and left hemispheres were not significant. Similarly, the hemisphere x gap interaction was not significant, F<1.

3.1.4.2.3 Multi-deviant optimised compared to single-deviant oddball paradigms

In both paradigms, the amplitude of the MMN became larger as gap duration increased. Differences between the two paradigms were compared using separate t-tests for the 5-, 20- and 40-ms duration gaps at both Fz and Cz. In spite of the use of multiple t-tests, the amplitude of the MMN did not significantly differ between the multi-deviant optimised and the single-deviant oddball paradigms, regardless of gap duration (p>.05 in all cases), at either Fz or Cz.

Some studies employ a mastoid rather than a nose reference. The MMN is recorded as a positivity at the mastoids. For this reason, the use of a mastoid reference will increase the overall amplitude of the MMN at the fronto-central sites. The data were thus re-referenced to the mastoids to increase the signal-to-noise, particularly in the case of the smaller MMNs. While the overall amplitude of the MMN did increase, the effects of gap duration were very similar to those found when the nose reference was employed. Some laboratories use peak-to-peak (MMN to following positive peak) rather than baseline-to-peak measurements. The data were thus

rescored using the peak-to-peak measurement. These results were, however, also very similar to those obtained when baseline-to-peak measurement was used.

3.1.4.2.4 Scalp distribution maps.

Spline scalp distribution maps (Perrin et al., 1989) of the MMN were computed for the three gap durations in both the multi-deviant optimised and single-deviant oddball conditions (Figure 1-5). The scalp distribution maps were very similar regardless of gap duration and condition; the MMN was maximum over fronto-central areas of the scalp, with a polarity inversion at inferior sites. There were slight differences in the distribution for the 5-ms gap but this might be because the MMN amplitude was quite small and thus more susceptible to measurement of residual background noise.

3.1.4.3 Behavioural data

Performance was measured in terms of accuracy. Accuracy is defined as the proportion of correct detections of deviants containing a gap (a "hit"), and also of standards not containing a gap (a "correct rejection"). The mean proportion of correct detections of the standard was .98 (SD= .03). The mean proportion of erroneous false positives for the standard was .02. Mean accuracy of detection was very high for the largest gaps, .87, .97, .96 and .98 (SDs = .26, .04, .07, .02) for gap durations of 10, 20 30 and 40 ms, respectively. The 5-ms gap had a mean hit rate of .53 (SD= .41) while the 2-ms had a mean hit rate of only .01 (SD=.02) . A one-way ANOVA was used to determine the effect of gap duration on the accuracy of detection of the six deviants. The main effect of gap duration was significant, $F(5,78) = 48.31$, $p<.001$. Post hoc testing revealed that accuracy was significantly different for all gap sizes at and below 10 ms, but not for gap durations 20 ms and higher.

3.1.4.3.1 ERPs Sorted on the Basis of Gap Threshold

All participants were able to detect 10-ms duration gaps. Half of the participants were able to detect the 5 ms with a hit rate above .50 while the other half did not. These were thus sorted into low (5-ms) and high (10-ms) threshold groups. ERPs were compared for the two groups. The Fz data are presented in Figure 1-6. A liberal one-tailed t-test was used to compare the mean MMN amplitudes with the expectation that the low threshold group would have had a larger MMN for the different gap duration deviants. There was a weak trend for the low threshold participants to have a slightly larger MMN amplitude than for the high threshold participants for 20-, 30- and 40-ms gaps. However, differences between the groups were not significant for any of the gap durations, $t<1$ in all cases.

3.1.5 Discussion

The purpose of this study was to examine the effects of gap duration on the MMN using a time efficient multi-deviant optimised paradigm. Previous studies have typically used a single-deviant oddball paradigm and have found that the MMN can be elicited by supra-threshold gap deviants (Bertoli et al., 2001; Bertoli, Smurzynski & Probst 2002; Alain et al., 2004).

A multi-feature optimised paradigm was originally developed for the study of several deviants in which each deviant was created by changing a different feature of the standard (Näätänen et al., 2004). In the present study the deviant was created by changing the same feature of the standard, the insertion of a silent period, or gap. Multiple deviants were created by varying the duration of the gap. In spite of the change to the multi-feature optimised paradigm, the results demonstrate that the different gaps can successfully elicit an MMN. The amplitude of the MMN generally increased as gap duration became longer. When oddball sequences have been used, a similar trend has also been reported (Bertoli et al., 2001; Bertoli, Smurzynski &

Probst 2002; Alain et al., 2004) although their maximum gap durations were 15 and 13 ms, respectively. Torppa et al (2014) presented 40- and 100-ms gaps but reported no concomitant increase in the amplitude of the MMN. In the present study, the amplitude of the MMN reached a plateau at 20 ms and did not significantly increase for the 30- or 40-ms gaps.

Single-deviant oddball sequences were also run for the 5-, 10- and 20-ms duration gaps. Importantly, the amplitudes of the MMNs for each of these gaps did not significantly differ between the single-deviant oddball and multi-deviant optimised paradigms, even when very liberal statistical procedures were applied. In brief, results were very similar whether very time-consuming multiple single-deviant oddball sequences were run or a time efficient single multi-deviant optimised sequence was run. Time permitted the inclusion of only 3 deviants in the single-deviant oddball sequences. Had the entire 6 deviants been presented in multiple runs of the single deviant oddball paradigm, testing time would have approached 4 hours, including brief breaks between sequences. By comparison, testing time was reduced to about 30 minutes with the multi-deviant optimised paradigm.

In the present study, the duration of each of the single-deviant sequences was the same. This need not be necessary. The single-deviant oddball paradigm could be made more efficient. The amplitude of the MMN was much larger for the longer duration gap deviants. As such, the number of stimulus repetitions could be reduced. There is however a trade-off. The residual noise will then be higher. Background noise in the ongoing EEG is not reduced in a linear manner with the number of stimulus presentations but rather by a factor of $1/\sqrt{N}$ (inverse of square root of the number of stimulus repetitions). Knowing how many stimulus repetitions are required to achieve a satisfactory signal-to-noise ratio will require a judicious weighing of these factors. Moreover, a reduction in the number of trials also assumes a priori knowledge of the

expected amplitude of the ERP, and this may not be possible, particularly for clinical populations. There are also other limitations to the use of the multi-deviant optimised paradigm. The MMN following presentation of the short duration gaps was small relative to the residual background noise. Improving the signal-to-noise ratio would require many more stimulus presentations. The multi-deviant optimised sequence is however unusual as the standards and deviants alternate. Each of the deviants need to be presented an equal number of times. Thus if the number of short duration deviants is increased, the number of all other deviants will also need to be increased accordingly. Testing time would therefore be long. It might be feasible to alter the multi-deviant optimal paradigm by increasing the number of short duration deviants but reducing the number of repetitions of long duration gap stimuli. This would however require a significant change to the alternating standard-deviant sequence. The multi-deviant optimised sequence is a recent development and as such, the effects of varying the typical alternating standard-deviant sequence have not been extensively studied.

There were some problems with the data. Although a clear MMN was observed in the grand average for the 10-ms gap, its amplitude was not statistically different from the zero-voltage baseline. This finding is difficult to explain, especially considering that a significant MMN was observed for the shorter 5-ms and longer 20-ms gaps. A significant MMN was also elicited by the 2-ms duration gap. Many studies have now indicated that a MMN will not be elicited if a deviant cannot be perceived as being different from the standard. Behavioural testing indicated that the 2-ms was detected on fewer than 2% of trials. In other words, participants could not perceive the difference between the standard and the 2-ms duration gap deviant. It is possible that participants might have employed a very conservative strategy, only signalling their detection of a gap when they were certain of its occurrence. Since the concern of the present

study was not the establishment of the gap threshold, an alternative forced-choice testing procedure can be used to resolve this issue. In this procedure, the participant must decide which of two stimuli contain a gap. The proportion of correct detections of very short duration gaps, such as a 2-ms gap, might then be above chance level. A more likely explanation of the MMN to the 2-ms duration gap was the use of the alternating standard-deviant pattern within the multi-deviant optimised paradigm. Current models indicate that the MMN is elicited by a violation of such rule-based patterns. (Näätänen, Kujala, & Winkler, 2011; Winkler, 2007; Winkler, Denham, & Nelken, 2009). When a simple rule-based alternating tone pattern (e.g. ABABAB) is violated by repetition of either the A or B tone (Alain et al., 1994; Sculthorpe et al., 2008; Campbell & Macdonald, 2011), a large MMN is elicited. In the present study, participants were presented with an alternating standard-deviant (SDSDSDSD) pattern. Because the 2-ms gap deviant may have been perceived as a standard, its occurrence essentially violated the alternating standard-deviant pattern and the standard was perceived to repeat (SDSDSSSD). In this explanation, the occurrence of the MMN is not a result of the perception of a very short duration 2-ms gap, but rather a result of a failure to perceive it. The MMN was elicited by the perception of a change to the alternating pattern.

Although the purpose of this study was not to examine how individual differences in gap threshold (a much larger sample size is required to do so) affect the MMN, some intriguing results did emerge. About half the subjects could detect the 5-ms gap on more than 50% of the trials. This gap would thus have been expected to elicit an MMN in this group. On the other hand, because half of the participants could not detect the 5-ms gap, an MMN would not thus have been expected to be elicited in this group. An MMN was observed following the presentation of the 5-ms gap in the high threshold group, even though they could not apparently

perceive a gap of this duration. Group differences for the 5-ms MMN were not statistically significant. It is possible that the high threshold group adopted a much more conservative criterion for responding, but again future studies might explore this issue further. The amplitude of the MMNs to the longer supra-threshold duration gaps also did not significantly differ between the two groups; however, the low threshold group showed a trend towards larger MMN amplitudes for 20-, 30- and 40-ms gaps. This may be suggestive of temporal discrimination deficits similar to those reported in other literature. For example, Todd et al. (2011) noted that normal-hearing participants having "good" temporal discrimination had larger MMN amplitudes than those with "poor" discrimination following presentation of long-duration 40-ms and 60-ms gap deviants.

A second negative peak occurring at about 300 to 350 ms, after the onset of the stimulus, was also apparent in the grand averages, especially for the longer duration gaps. This might reflect an N1-off response (Näätänen & Picton, 1987) occurring about 100 ms after the offset of the 200-ms deviant stimulus. However, a similar N1 should have occurred for the same duration standard. Such a common N1-off response should thus have been removed in the difference wave. It is also possible that this may reflect an N1 occurring to the offset of the long duration gap (or the onset of the stimulus after the silent period). The latency of this negativity, about 200 ms after the offset of the gap would however be unusually long for an N1. It is possible that this negativity might also reflect a second MMN. The MMN can peak quite late when a deviant is difficult to perceive.

3.1.6 Conclusion

The purpose of this study was to determine if a time-efficient multi-deviant optimised paradigm could be used to study the effects of varying gap durations. Six different gap durations

varying from sub- to supra-threshold served as deviants. When the 6 deviants were included in the multi-deviant optimised paradigm, the amplitude of the MMN was observed to vary as a function of gap duration. Its amplitude did tend to plateau for the longer gaps. These results were compared to those obtained when the gaps were used in multiple runs of single-deviant oddball paradigms. A different gap duration was used as a deviant within each of these oddball paradigms. The amplitude of the MMN again varied as a function of gap duration. Critically, the MMNs that were elicited in the multiple single-deviant oddball sequences did not differ significantly from those elicited in a single multi-deviant optimised sequence. The present study thus demonstrates that when multiple gap deviants are presented in a single highly time-efficient optimised paradigm, MMN results will be very similar to those obtained when time-demanding multiple runs are used in a single-deviant oddball paradigm. The multi-deviant optimised paradigm can be used in many applied and clinical settings in which short testing times are essential.

3.1.7 Tables

Table 1-1: MMN amplitude, in μV, in the single-deviant oddball and multi-deviant optimised paradigms as a function of gap duration. (SD in parentheses)

Gap duration (ms)	Electrode	Paradigm	
		Multi-deviant Optimised	Single deviant Oddball
2	Fz	-.29 (.95)	
	Cz	-.30 (1.11)	
5	Fz	-.80 (.76)	-1.03 (.83)
	Cz	-.71 (1.00)	-1.04 (.91)
10	Fz	-.66 (1.57)	
	Cz	-.54 (1.61)	

20	Fz	-1.81 (1.35)	-2.49 (1.05)
	Cz	-1.65 (1.18)	-2.06 (1.31)
30	Fz	-1.77 (1.15)	
	Cz	-1.46 (1.01)	
40	Fz	-2.25 (1.16)	-2.76 (.88)
	Cz	-1.98 (1.13)	-2.35(1.00)

Table 1-1: Mean accuracy and RT as a function of gap duration (SD in parentheses).

Gap duration (ms)	Accuracy	RT (ms)
0 (Standard)	.98 (.03)	533 (66)
2	.01 (.02)	541(61)
5	.53 (.41)	627 (103)
10	.87 (.26)	595 (101)
20	.97 (.04)	536 (54)
30	.96 (.07)	541 (62)
40	.98 (.02)	543 (64)

3.1.8 Figures

Figure 1-1: Multi-deviant optimised and single-deviant oddball sequences. A: In the multi-deviant optimised sequence, standard and deviant stimuli alternate. The probability of occurrence of the standards and deviants was thus .50. The standard stimulus was a white noise burst. The deviant was created by inserting a silent period (a "gap") in the center of the standard. Six gap durations served as deviants. In the Figure, three of these gaps durations are illustrated (note that gap duration is not to scale). The probability of occurrence of a specific deviant was .083. In the oddball sequence, a single deviant was presented. The probability of occurrence of the standard was .917 and the deviant, .083. In separate single-deviant oddball sequences, different deviants, varying in gap duration were presented. B: Timing of stimulus presentation. A zoom of the presentation of deviant and standard stimulus presentations is illustrated. In both the multi-

deviant optimised and single-deviant oddball sequences, the duration of the standard and deviant stimuli was 200 ms followed by an ISI of 400 ms. The different deviants were created by varying gap duration. In the figure, a representative gap of 40 ms is illustrated.

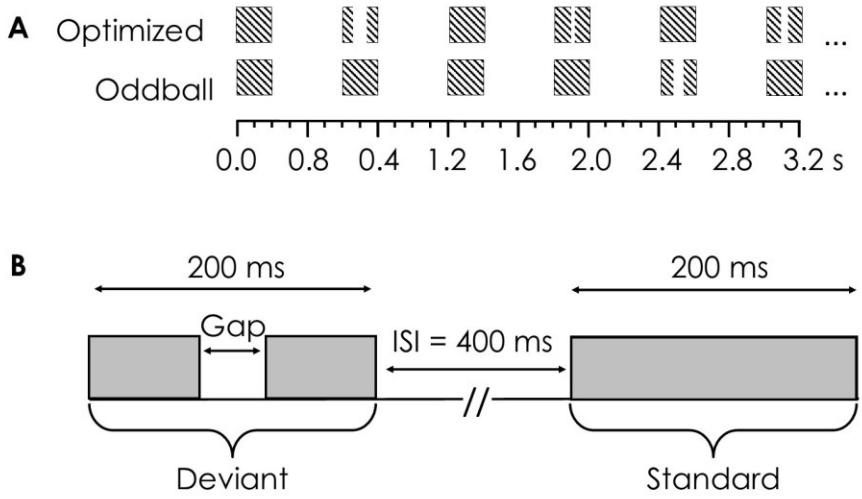


Figure 1-2: Standard ERPs. The grand averaged ERP waveforms following the standard stimulus in the multi-deviant optimised and single-deviant oddball paradigms. Positivity in this and all other figures is indicated by an upward deflection. A small negative-going deflection at about 100 ms is followed by a positivity at about 150 ms. This is the N1-P2 waveform. The N1 and P2 are also visible at the offset of the 200 ms duration standard.

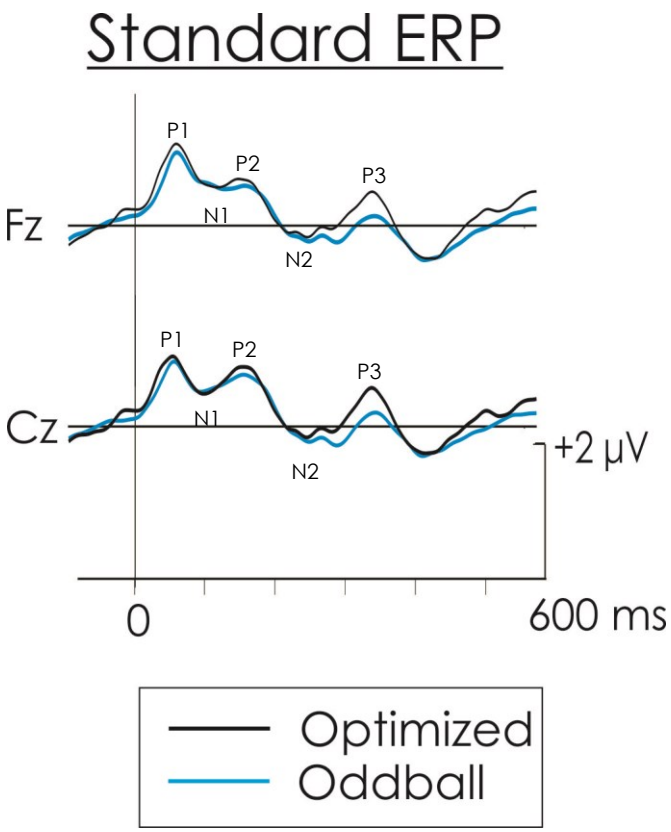


Figure 1-3: Multi-deviant optimised deviant-standard difference wave. An MMN is visible at about 100 to 150 ms following the onset of the gap. (Note that time 0 in the Figure represents the onset of the deviant stimulus with the offset occurring 80 to 99 ms later). The MMN is maximum over fronto-central areas of the scalp and inverts in polarity at the mastoids.

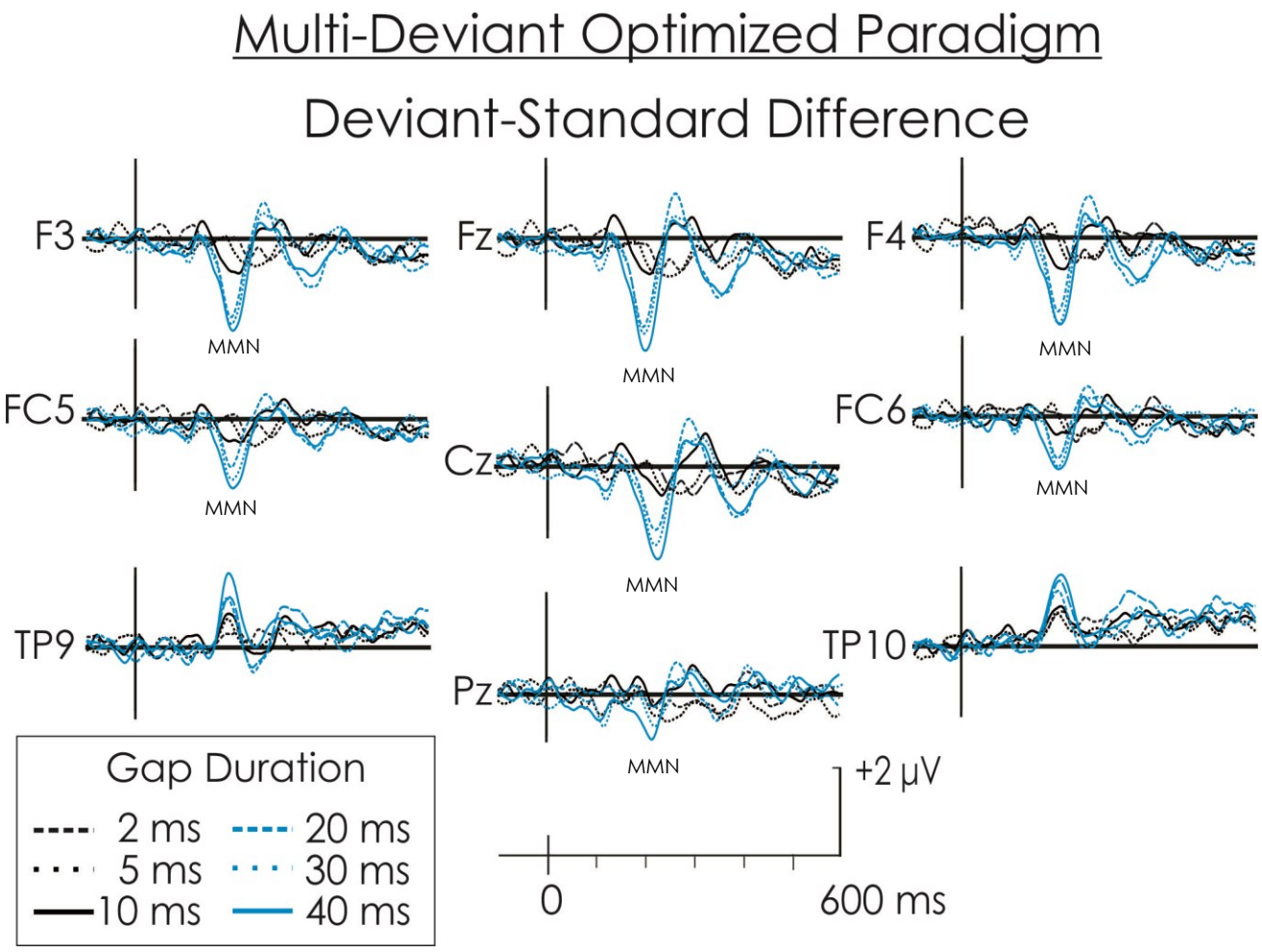


Figure 1-4: Single-deviant oddball deviant-standard difference wave. A MMN is apparent 100-150 after onset of the gap (again 200 to 250 ms after the onset of the deviant). It is also maximum in amplitude over fronto-central scalp sites and inverts in amplitude at the mastoids.

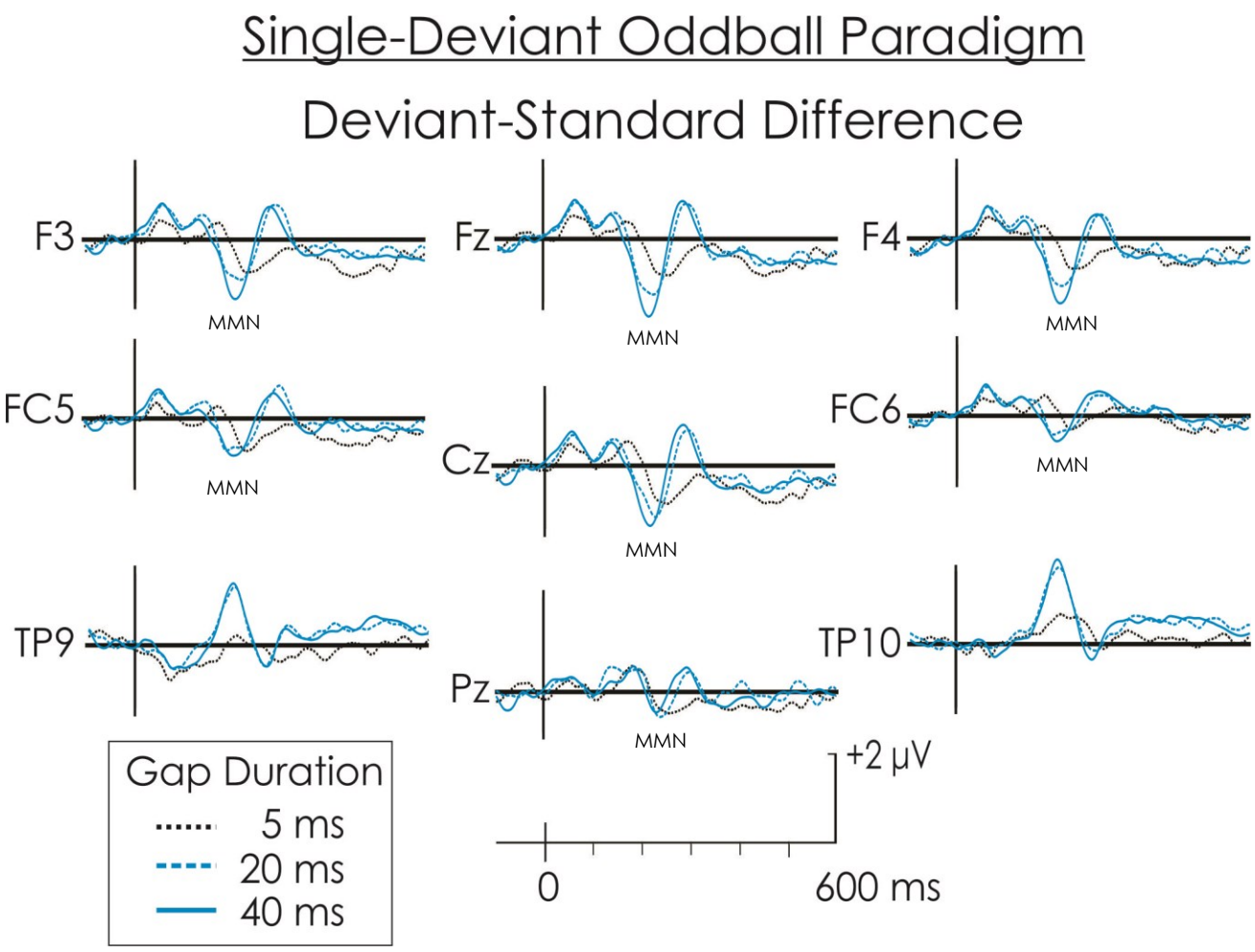


Figure 1-5: Spherical spline scalp distribution maps as a function of paradigm and gap duration. The maps were calculated by interpolating the amplitude of the surface scalp potentials of surrounding electrode sites (Perrin et al., 1989). A top linear perspective of a "flattened" head, with electrodes equally spaced, is illustrated. The view of the projection extends 20° below the Fp1-T7-Oz-T8-Fp2 circumference to show the inferior electrodes. Note that maximum and minimum amplitudes vary across conditions, because the MMN was very small for the smallest gap duration.

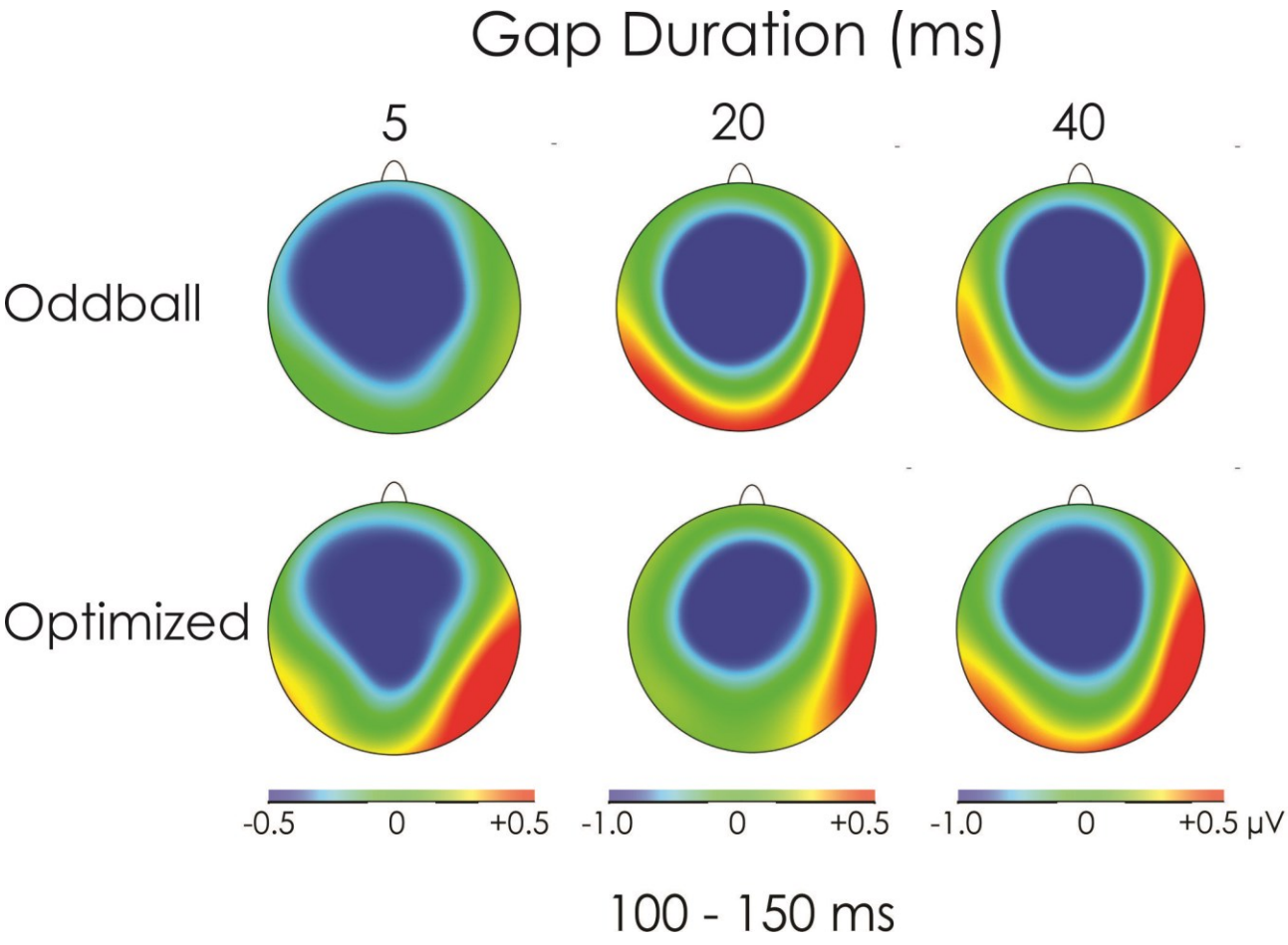
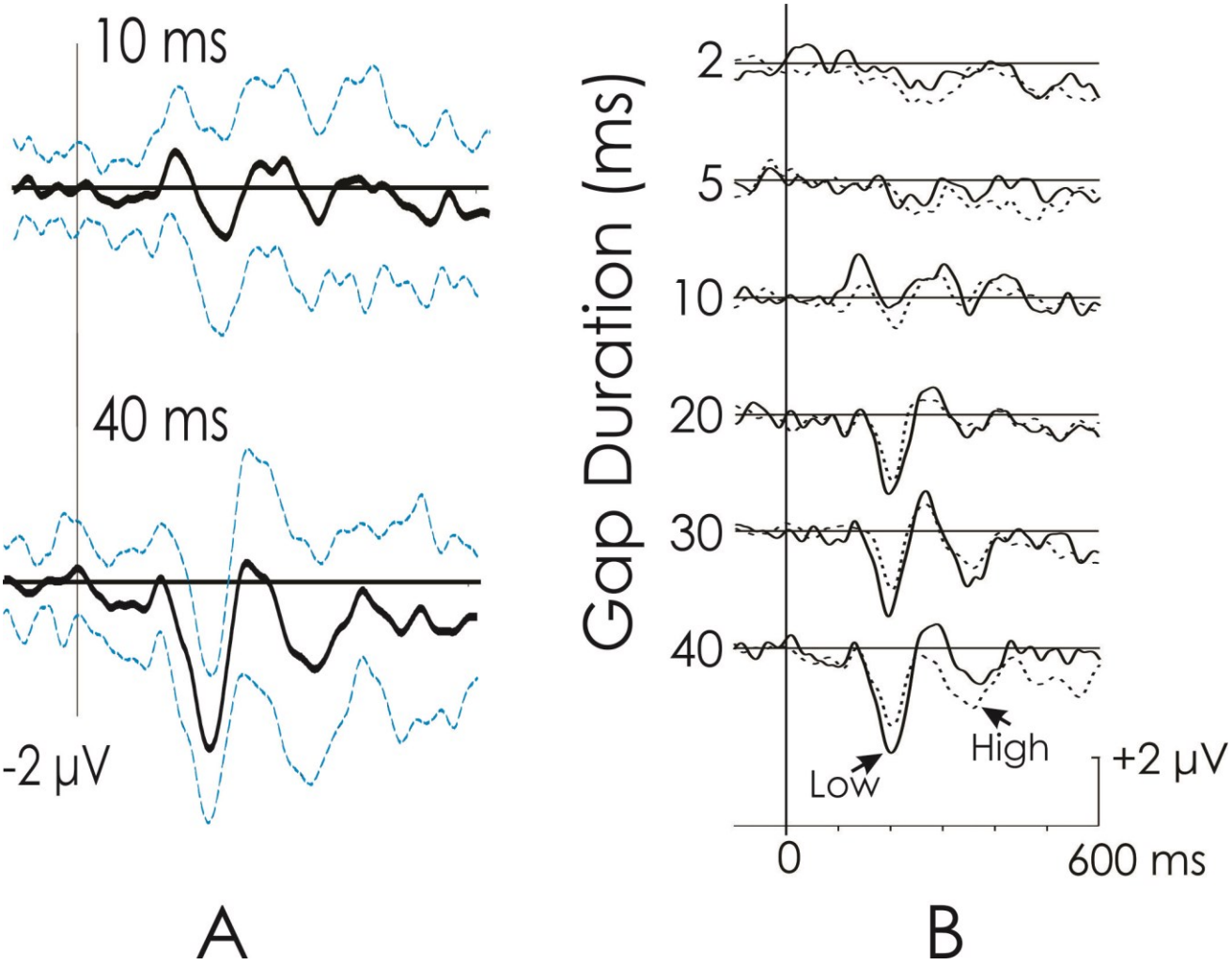


Figure 1-6: ERPs elicited for various gap durations as a function of individual differences in gap duration threshold. ERPs were recorded at the Fz electrode. Panel A illustrates the standard deviations (blue) of the group mean ERP (black) elicited by the 10- and 40-ms gaps. The low-threshold participants (solid) were able to detect the 5-ms gap with an accuracy >.50. The high-threshold participants (dotted) were only able to detect the 10-ms gap with an accuracy >.50. Panel B shows the low threshold group had a trend towards larger MMN amplitudes compared to the high threshold group for 20-, 30-, and 40-ms gaps, however this was not significant.



3.1.9 Conflicts of interest

The authors do not have any known conflicts of interest associated with the publication of this article.

3.1.10 Acknowledgements

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Article 2: Optimizing the Mismatch Negativity for neural gap detection: determining the effects of intensity on gaps in noise

This methodological paper describes the effect of a high and low intensity narrowband noise stimulus on the MMN elicited by gaps. The optimal paradigm was similar to the one described in Article 1, however it differs in the use of intensity and stimulus bandwidth. These two variables are of importance to the study of tinnitus. Tinnitus is known to have a comorbidity of hyperacusis, a sensitivity to sound intensity. This may make the use of a high intensity stimulus, such as the 80 dB SPL stimulus used in article 1, intolerable to sustain for the length of the testing. The use of a narrower bandwidth is also of interest to the study of tinnitus. Tonal tinnitus, which is typical of subjects with noise-induced hearing loss, is often perceived in a narrow frequency range. In order to match the stimulus to the perceived tinnitus, the frequency range of the stimulus was changed from the broadband noise used in Article 1, to a narrowband noise that is centered around 4 kHz. In this way, the "fill-in" hypothesis can be later tested by using this stimulus on populations with tinnitus perceived around 4 kHz.

3.2 Article 2: Optimizing the Mismatch Negativity for neural gap detection: determining the effects of intensity on gaps in noise

(Manuscript will be submitted to Brain Research Journal)

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3.2.1 Abstract

Objective: Impaired auditory temporal resolution can lead to difficulties understanding speech in noise for populations with normal hearing thresholds and those with sound sensitivity (known as hyperacusis). Electrophysiological gap detection can be used to measure temporal resolution however sound sensitivity may change the perception of stimulus intensity. This study aims to explore the effects of intensity on the gap-elicited cortical response.

Methods: Electrophysiological recordings were investigated in 10 young adult participants with normal hearing. The mismatch negativity (MMN) wave was obtained using the optimised paradigm at a high intensity of 80 dB SPL or low intensity of 60 dB SPL. Stimuli for the MMN recordings were narrowband noises centered at 4 kHz with gaps of 2, 5, 10, 15, 20, 30 and 40 ms durations.

Results: There were no significant MMN amplitude differences between the high and low intensity conditions when referencing to the tip of the nose. In contrast, when referencing to the mastoids the peak to peak MMN-P3a amplitude was significantly smaller in the low intensity condition. There was also a significant effect of deviant on the peak to peak amplitude at the Fz and Cz electrodes, where the larger gaps elicited larger amplitudes for all gap durations at both intensity levels.

Conclusions: The MMN to gaps in noise, using peak to peak measures, can be elicited at high and low intensities. Still, the largest amplitude changes to gaps appear at the higher intensity condition.

Key words: Mismatch Negativity, Optimised, Gaps-in-Noise, Temporal Processing, Gap Detection, Event-related potentials, Intensity effect

3.2.2 Introduction

Difficulties in discriminating speech in noise is a very common issue among people with and without hearing loss. In fact, in a survey of 239 hearing-impaired participants, the most commonly reported handicap was the inability to understand speech in noisy environments (Kramer et al., 1998). However, diagnosis of difficulties listening in noise is contentious as audiometric thresholds are not always elevated and even outer hair cells may provide normal responses when assessed by otoacoustic emissions (Kujawa and Liberman, 2009). In a UK study, 26% of tinnitus patients reported difficulties hearing in noise of which 10% had normal audiometric thresholds (Davis, 1989). Patients with this type of profile are often referred to as "hidden" hearing loss, King-Kopetzky syndrome or obscure auditory function (Zhao & Stephens, 2007; Schaette and McAlpine, 2011; Plack, Barker & Prendergast, 2014).

There is no evidence demonstrating a direct link between hidden hearing loss and difficulties in noise, however hidden hearing loss may explain changes to underlying central mechanisms responsible for hearing in noise. Animal studies have revealed that noise exposure can damage high-threshold auditory nerve fibers (Kujawa and Liberman, 2009) and this damage reduces the synchronization and phase-locking of low-threshold fibers responsible for central temporal coding (Kumar, Ameenudin and Sangamanatha, 2012). Problems with the central temporal coding of the fundamental frequency of a stimulus in noise has been related to perceptual difficulties of listening to speech in noise (Song et al., 2011). Thus measuring temporal coding or processing may be a valuable tool for further investigating the central changes in populations with listening difficulties in noise in the absence of a detectable hearing loss.

Many investigations on temporal processing have used behavioural measures to obtain psychometric data. This has been done by determining the threshold of detecting a gap, or a just-noticeable silent interval, within a sound (Plomp, 1964; Irwin et al., 1981; Phillips et al., 1994). These studies have used gaps placed within broadband noise and found normal hearing participants could detect gaps as small as 2 to 3 ms in length (Plomp, 1964), however its perceptibility can vary when altering stimulus parameters such as intensity (Plomp, 1964, Irwin et al., 1981) and stimulus bandwidth (Fitzgibbons, 1983; Shailer & Moore 1983; Eddins et al. 1992). In addition to this, performance is also affected by the level of attention, concentration, motivation, and the response criteria that was used (Wightman et al., 1989; Green, 1990). It is thus of interest to use alternative measures that are more objective to mitigate the potential effects of performance on the detection of gaps.

Scalp measured responses to auditory stimuli, known as auditory evoked related potentials, have the advantage of being detected in the absence of conscious effort. They are thus independent of the various cofactors that can affect behavioural responses. The mismatch negativity (MMN) in particular is derived from the evoked potential that is known to be a response to the detection of change in a rare deviant stimulus compared to the frequent standard (Näätänen et al. 1993). A memory trace is formed in the auditory cortex, in the absence of attention, to represent the repetitive features common between the standard and the deviant stimuli. When there is no detectable difference between the deviant and the standard, no MMN waveform is formed except for the obligatory P1-N1-P2 complex (Näätänen & Picton, 1987). When a difference between the stimuli is detected, new afferent neurons are activated approximately 200-250 ms after the onset of the stimulus within the bilateral supratemporal process (which generates the polarity inversed waveform at the mastoids), and the right frontal

process (which is responsible for the positive waveform maximal around the Fz and Cz electrodes) (Näätäten, Gaillar & Mäntysalo, 1978). Since the latency of the MMN occurs at the same time as the N1, which is evoked by variables that do not have to do with the difference between the standard and the deviant, a difference wave is calculated (Näätänen et al., 1988). Hence, the MMN is derived from the difference between the waveform of the standard stimulus and the deviant thus representing only the changes detected in the deviant.

In addition to the MMN, one can also find the a positivity at 300 ms after the onset of the stimulus within the difference wave known as the P3a (Escera et al., 1998) and it represents the process of attention-switching in response to a large enough change that would elicit a behavioural response (Schröger and Wolff, 1998). The P3a is related to the conscious but involuntary detection of change in the auditory sequence, unlike the MMN response which is elicited pre-consciously. Both the P3a and MMN are elicited using the same testing procedure. Grimm et al. (2008) showed that the P3a is significantly reduced when the auditory sequence is ignored as opposed to when it is actively listened to (which is referred to as the P3b). The P3a is initially generated by the same sources as the MMN however when the change is large enough, it elicits the activation of the central executive processes which update the cognitive activities to include the interrupting event (Donchin and Coles, 1988). However, while the MMN is produced from the summation of the N1, the P3a arises from a later second negativity that occurs around 200 ms after the onset of the stimulus, the N2b. The N2b may overlap with the N1 –making it difficult to distinguish from the MMN (Sams et al., 1985). Thus various studies have contested whether the MMN is in fact "pure" or if other overlapping components, like the P3a or N2b, can elevate or reduce its amplitude (Deacon et al., 2000).

A multi-feature "optimised" paradigm was developed by Näätänen et al. (2004) as an efficient method for recording the MMN and P3a. In this method, several deviant stimuli are presented in alternation with the standard by a probability of .1 and .5, respectively. As opposed to the traditional oddball paradigm, where a single deviant can be tested within a trial block, the optimised allows for up to seven deviants be tested at once. While it has been shown with the optimised that increasing differences between the standard and the deviant produce proportional MMN amplitudes (Pakarinen et al. 2007), only the largest stimulus changes elicited a P3a (Sorokin et al., 2010).

Previous works have used the MMN to measure the evoked responses to gaps embedded in noise. In Bertoli, Smurzynski & Probst (2002), elderly and young participants were presented with a 1 kHz pure tone with embedded gaps of 6, 9, 12, 15, 18, 21 and 24 ms in duration and measured both the MMN and behavioural thresholds. They found the mean gap detection threshold for the elderly participants was 7.8 ms. There was a clear MMN at 240 and 280 ms for the 15-, 18-, 21- and 24-ms gaps but not the smaller ones. The amplitude of the MMN was also smaller in response to the 15-ms gap than for the larger ones. Using the same procedure, for the young participants Bertoli et al. (2001) showed a significant response to the 9- and 15-ms gaps. The smallest gap that elicited an MMN was higher than the smallest gap detected behaviourally (i.e. the behavioural threshold). In addition to this, the testing took a total of 6 hours to collect all the data. This is a common problem with oddball paradigms as the very long protocol limits the number of gaps that can be tested. Each deviant takes typically 10 minutes to record and if it is replicated three times, this would mean about 30 minutes per deviant. However when the optimised paradigm is used it can reduce this time significantly by testing up to seven deviants in the same amount of time as the oddball would for one deviant (30 mins) (see Duda et al.,

submitted). Additionally, the optimised is just as effective as the oddball at eliciting MMN waveforms for the detection of gaps (Duda et al., submitted). This study showed both methods recorded significant MMNs for gaps in broadband noise of 5, 20 and 40 ms in duration in young participants. In addition to these gaps, the optimised paradigm was able to also test 2, 10, and 30 ms all of which were also significant.

The MMN can be captured using a variety of stimulus parameters. It is known that the MMN amplitudes can change with various gap durations using a filtered and unfiltered noise stimulus. The previous MMN gap studies have used 1 kHz filtered tones (Bertoli et al., 2001; Bertoli, Smurzynski & Probst 2002) and broadband noise (Milloy et al., submitted) as the standard and deviant stimuli. It is however unclear if changing other parameters, like intensity, would maintain the relationship of MMN amplitude to gap duration. Previous studies using pure tones showed the intensity of the stimulus can have different effects on the MMN depending on the features changed between the standard and deviant. The MMN amplitude did not change significantly between the high and low intensity conditions when presenting a different frequencies between the standard and the deviant in an oddball sequence (Schröger 1996; Paavilainen et al., 1993). However there was an effect of intensity when the standard and deviant stimuli differed in length (Paavilainen et al. 1993).

The current study aims to determine the effect of intensity on the gapped filtered stimuli on the MMN amplitude. The MMN amplitude elicited by filtered noise at 4 kHz will be compared at two intensity levels. It is hypothesized that changing the intensity of the standard and deviants that differ by gap duration will show significant changes to the MMN amplitude similar to Paavilainen et al. (1993). It is also expected the higher intensity stimulus will provide larger MMN amplitudes than the lower intensity. This study aims to determine if the relationship

between the MMN amplitude and gap duration is maintained when modifications are made to standard and deviant stimuli. This is an important step towards developing the optimal methodology for the clinical use of MMN supra-threshold gap detection. This information would be useful for understanding how listeners operate in everyday environments.

3.2.3 Methods

3.2.3.1 Participants

Ten participants (2 male and 8 female) between the ages of 20 to 35 years (mean=24, SD=3.3) were recruited for this study. All participants had normal hearing thresholds under 25 dB HL from 250 Hz to 8000 Hz and did not report any known pathologies of the external, middle, or inner ear. They gave informed and written consent and all procedures and protocols were approved by the University of Ottawa Research Ethics Board.

3.2.3.2 Procedure and stimuli

The auditory stimuli were created using Audacity® recording and editing software (version 2.1.0, Audacity team, Carnegie Melon University), and presented through a desktop computer (Dell) only to the right ear through insert earphones (ER2A, Etymotic Research Inc, Elk Grove Village)while the subject sat in a sound and electrically isolated booth. The participants were asked to watch a sub-titled film of their choice while ignoring the auditory stimuli. The auditory stimulus was a 200-ms, passband filtered, Gaussian noise centred around 4 kHz. A silent interval of 2, 5, 10, 15, 20, 30 or 40 ms was inserted equidistant from the onset and the offset of the stimulus. All stimuli were calibrated using a sound level meter (type 2235, Bruel and Kjaer, Denmark) and a type 2 artificial ear (RK0045, GRAS Sound and Vibration, Denmark). The stimuli were presented at a low intensity of 60 dB SPL and a high intensity of 80 dB SPL. The multi-feature optimised protocol was followed for the order and sequencing of the stimuli. The optimised protocol uses an alternating pattern between a standard stimulus and a

deviant. The standard was defined as the no gap (0 ms) noise which was presented on 50% of the total number of conditions within the trials and the deviants were each presented on 7.08% of the trials. The stimulus presentations alternated between the standard stimulus and one of the deviants, which were presented in a pseudo-randomized order (deviants were presented once within a block of seven standard-deviant pairs). The first 10 presentations in each sequence were all standard stimuli in order to strengthen the memory trace. The interstimulus interval was 300 ms. All stimuli were presented using Presentation® software (version 20.1, Neurobehavioural Systems, San Franscisco). The sequences were presented three times for each intensity condition, thus a total of six sequences were played lasting about 1 hour. The standard stimulus was presented 548 times (which includes the 10 standards for the memory trace) and the deviants were presented 539 times within the sequence (77 presentations of each gap duration deviant).

A non-adaptive, two-alternative, forced-choice procedure was used to determine the gap detection thresholds. The same stimuli were used as for the electrophysiological testing and presented through the Presentation® software (version 20.1, Neurobehavioural Systems, San Franscisco) at 80 dB SPL. The participants were asked to press a button (wireless mouse M325, Logitech, Switzerland) when they heard a gap or a different button when there was no gap. Each participant underwent a practice session prior to commencing the testing. The test consisted of a total of 180 standards and deviants presented in random order. Total testing time was 10 mins. The standard was presented twice as many times as the deviant. The behavioural threshold was determined as the gap duration that corresponded to 50% accuracy of correct identification of the average responses. The behavioural testing was conducted following the electrophysiological recordings to ensure attention was not placed on the stimuli during the passive conditions.

3.2.3.3 Electrophysiological recordings

Event related potentials were recorded at the onset of each standard and deviant stimulus from 32 active silver/silver chloride electrodes (ActiCap, Brain Products, Germany) placed across the frontal, central, parietal, and occipital areas of the scalp. The vertical ocular movements were recorded using an electrode placed at the upper right cheekbone. A reference electrode (ActiCap) was placed at the ball of nose to which all channels were compared. All impedences were kept below 20 kohms. Recordings were averaged and collected using the BrainVision Recorder v1.21.0102 (Brain Products) software.

BrainVision Analyzer v2.1.2 (Brain Products) software was used offline to analyse the EEG. The MMN polarity is known to reverse at the temporal channels when using the nose as a reference (Näätäten et al., 1978; Giard et al., 1990; Baldeweg et al., 1999; Rinne et al., 2000). This was also shown in our previous study (Milloy et al., submitted) that used a nose-reference and a protocol almost identical to this study. It was decided to re-reference all the electrode traces to the average of the electrodes closest to the mastoid region (electrodes TP9 and TP10 on the left and right temporoparietal lobe, respectively) to enhance the MMN. This was necessary as the lower intensity condition made the recording more susceptible to noise contamination from other sources. The electroencephalogram (EEG) was filtered digitally using a low-pass filter set to 20 Hz and all channels were visually examined for noise. Any segments that contained high levels of noise were replaced by the interpolated data of the surrounding electrodes (Perrin et al. 1989). Ocular movements were removed from the EEG using the Independent Component Analysis (ICA) (Chaumon et al., 2015; Makeig et al., 1996). The vertical ocular movements were computed by subtracting the activity of the ocular electrode from the FP1 electrode that was directly above it. Horizontal eye movements were computed using the difference between

the FT9 and FT10 channels. The continuous EEG was divided into 600 ms epochs. Epochs were subsequently organized and averaged based on the stimulus type, electrode site, and condition.

An evoked potential wave is recorded as the response to the deviant and the standard stimulus. It is the difference between the evoked potential waves to the deviant and standard that allows the visualization of the mismatch negativity and P3a waveforms. It is assumed that the deflections of the standard evoked potential before the onset of the gap, at approximately 100 ms following the onset of the stimulus, do not change significantly irrespective of the deviant presented. Thus any differences between the standard and the average deviant wave is assumed to represent responses related to the features unique to the deviant – thus the length of the gap. The standard waveforms of the two intensity optimised conditions were compared: one where the stimulus was presented at 60 dB SPL and the other at 80 dB SPL.

3.2.3.4 Statistical analyses

Deviant-standard difference waves were used to calculate the MMN and the P3a. Since the deviants elicited a waveform with various deflections that are different from the waveform produced by the standard, subtraction of these waves removed any elements that were common between the two stimuli. The time range of the MMN and P3a was determined from the grand average difference waveform calculated from the EEG of all participants. The mean voltage activity for each separate subject was calculated 25 ms +/- from the grand average latency for each waveform.

The baseline-to-peak measurements are typically used to measure the MMN, however doing so may not be a true measure of the MMN as it might temporally overlap with the P3a or N2b. This would risk the MMN being pulled in a positive direction, thereby reducing its

amplitude. To minimize an MMN/N2b overlap, the MMN and P3a average voltage activities were subtracted to determine the absolute peak to peak value (Picton et al., 2000).

A repeated-measures ANOVA (with Greenhouse-Geisser corrections) was performed on the mean voltage MMN and peak to peak averages for condition (high and low intensity) and deviant (gaps 2-40 ms) in order to determine any changes to amplitude. Standards were compared using paired one-tail t-tests for the N1 and the P2 at the Cz and Fz electrodes for the high and low intensity conditions. One-tailed statistics were used because it was expected that the N1 and P2 would occur above zero. The latencies were determined based on the peaks found in the grand average (average of all individual waveform averages). This was done to ensure the difference wave did not include any alteration between the standard waveforms. The N1 and P2 were used to analyze the response for the deviant conditions as they risk being affected by fatigue and attention (Campbell & Macdonald, 2011; Harris et al., 2012; for further explanation see Milloy et al. submitted).

For the behavioural task, the accuracy of the button pressing was compared to the amplitude of the MMN for the corresponding gap durations in the high intensity condition only. A one-way ANOVA with accuracy and gap duration were used as within-factors and the amplitude of the MMN was the dependant variable. Correlations between the accuracy and the amplitude of the MMN at the Cz electrode were also done to determine whether the behavioural results concord with the increases in MMN amplitude.

3.2.4 Results

3.2.4.1 Standard ERP between the two intensity conditions (60 and 80 dB SPL)

Visible peaks at N1 and P2 occurr around 100 and 140 ms, respectively, at an amplitude between approximately 1 to 2 μV (Figure 2-1). These are known obligatory responses for

transient sounds (Näätänen and Picton, 1987). A t-test found the P2 was significantly larger for the 80 dB condition relative to 60 dB for both the Cz ($t(9)=3.16$, $p=0.01$) and Fz electrodes ($t(9)=2.39$, $p=0.04$). However the N1 did not differ significantly at either electrodes for the intensity conditions (Fz: $t(9)=-2.01$, $p=.08$; Cz: $t(9)=-1.59$, $p=.15$).

3.2.4.2 The MMN amplitude for the high and low intensity conditions using the nose-reference

The difference wave between the standard and the deviant evoked potentials was derived and comparisons were made between the low and high intensity conditions. A one-way ANOVA found that the effect of gap on the MMN amplitude was not significant at either the Fz, Cz or TP9 electrodes in the 60 or 80 dB conditions (all $F<1$). The left and right hemispheres were also non-significant for both intensity conditions ($F<1$).

3.2.4.3 The MMN amplitude for the high and low intensity condition using the mastoid reference and peak-to-peak measures

Since the ANOVA for the nose-reference was not significant, an alternative type of processing was done whereby the amplitude between the peak of the MMN and the subsequent positivity (P3a) was measured and referenced to the mastoid. This was done in order to ensure that any exogenous noise did not mask the signal from the auditory pathways. The mastoid is known to be a positivity at the latency range of the MMN and thus when referenced to the mastoid, the amplitude of the MMN is increased. Measuring to the subsequent positivity peak is a method that was described in Picton et al. (2000) to correct for baseline drifts due to the overlapping segments.

A one-way ANOVA was performed at the Fz, Cz, and TP9 electrodes to measure the effects of the two intensity conditions and the gap durations on this peak to peak amplitude. It showed that at a the high intensity condition, there was a significant effect of gap duration at the Fz electrode ($F(6,54)=10.36$, $p=0.001$, $\eta_p^2= .53$) as well as the Cz electrode ($F(6,54)=8.13$,

p=0.001, η_p^2= .48). However at the low intensity condition a significant effect of gap was only at the Cz electrode, (F(6,54)=4.50, p=0.001, η_p^2= .45), and not at Fz (F<1). At both electrodes, the peak-to-peak amplitude increased with increasing gap duration. However, as expected, there was no effect of deviant at the TP9 electrode as the electrodes were all re-referenced to the mastoids (F<1). At the TP9 electrode, neither condition had a significant effect on gap (F<1 for all).

3.2.4.4 Comparing the two intensity conditions at each gap duration

A two-way ANOVA was conducted for condition and gap at the Fz and Cz electrodes. The Fz electrode showed a significant interaction between condition and deviant (F(6,54)=5.30, p=0.0001, η_p^2=0.37) but no effect of condition alone (F<1). This interaction was due to the 80 dB condition showing an increasing trend for gap duration but not for the 60 dB condition. In contrast, at Cz there was no interaction since both the 60 and 80 dB conditions showed the same increase in amplitude with increasing gap duration (effect of the deviant). Still, when all gaps were collapsed, the 80 dB condition was significantly higher in amplitude than the 60 dB condition (F(1,9)=6.99, p=0.03, η_p^2=0.43). Post-hoc Fisher's least significant differences were calculated for each gap duration. At the Fz electrode, the 5-, 20- and 30-ms gap durations varied significantly between the two conditions (P<.05). At the Cz electrode there were no significant differences for any of the gap durations between conditions (P>.05).

3.2.5 Discussion

The purpose of the present study was to determine if a MMN could be captured from gaps in noise presented at different intensities. All gap durations elicited deflections within the latency of the MMN at both 60 dB and 80 dB stimulus intensities, however the effect of gap was only significant when the MMN was measured to the peak of the P3a and referenced to the mastoids. This is likely due to the lower signal to noise ratio in the low intensity condition. The

effect of gap was maintained in both conditions at the Cz electrode but not at Fz. In order to have an effect of gap at Fz, the stimulus needed to be a higher intensity.

3.2.5.1 Intensity effects on the MMN and P3a

The lower amplitude of the waveform in the low intensity condition supports the memory trace hypothesis. The memory trace hypothesis states that in order to elicit a MMN, the auditory cortex requires short-term memorization of repeating elements prior to the presentation of the deviant (Näätänen et al., 2007). For this reason, the recording begins with 10 standard stimuli in order to establish a strong memory trace of the no-gap stimulus. This means the MMN represents the auditory system's identification of the incongruence between the gapped deviant and the memory trace of the no-gap stimulus. These results support this hypothesis as they indicate the MMN is elicited by gapped deviants. This is similar to previous studies using broadband gapped noises (Milloy et al., submitted) and pure tone gapped noises (Bertoli et al., 2001), both showing significant MMNs to gapped stimuli using the optimised (Milloy et al., submitted) and oddball paradigms (Milloy et al., submitted; Bertoli et al., 2001). Paul, Schoenwiesner and Hébert (2018) measured the N1 to 20-ms gapped narrowband noises at 5 and 10 kHz at a level of 5, 15 and 30 dB SL. The N1 was present at all three levels and increased with stimulus intensity. These results of this study compliment previous results further showing that when stimulus intensity is reduced, the auditory system cannot as easily encode the neural representation of the gaps thus reducing the amplitude of the MMN-P3a peaks. This is supported by theories on the mechanism of the cochlear nerve. Auditory fibers that innervate the cochlear inner hair cells are grouped into (at least) two populations of high and low spontaneous rate fibers that are responsible for coding low and high level intensities, respectively (Florentine et al., 1987; Viemeister, 1988). The temporal information coded by the auditory nerve fibers is either fine temporal structures of the

carrier frequency or the temporal envelope changes that are limited by the cochlear filters (Bharadwaj et al., 2014). Since this study used high frequency stimuli with embedded gaps, the temporal information available for the auditory nerve fibers to encode would be limited to the envelope changes. This is due to the fact the auditory nerve fibers are unable to phase lock to the temporal fine-structures. In addition to this, the high-SR fibers that would be responsible for encoding the lower intensity stimuli are comparatively less synchronized to envelope changes than the low SR. This would mean that the poorer encoding of temporal information could be the rationale behind the smaller amplitude of the MMN in the lower intensity condition. This was also seen in other studies showing a reduced MMN amplitude for intensity-differences between the standard-deviant (Näätänen et al., 1992; Paavilainen et al., 1991).

These findings are reminiscent of previous oddball studies that measured changes to the intensity of pure tone stimuli. Schröger (1996) showed no significant difference in the MMN or N2b (the summate of the P3a) amplitude between the higher and lower intensity conditions for pure tone standards and deviants that differed by intensity. Similarly, our mean voltage amplitude of the MMN did not show a significant difference between the high and low intensity conditions when measured using the nose as the reference. This may be due to the overlap of the N2b with the MMN (Picton et al., 2000). Recall, auditory attention shifts due to notable changes to the stimulus can elicit the N2b (or P3a). Thus it is possible some changes between the standard and the deviants were sufficiently large to elicit the P3a, which may have lifted the negativity of the MMN making it less significant. Indeed other studies have shown the P3a can be elicited by large 9-10 dB increments and 20 dB decrements (Macdonald et al., 2008; Muller-Gass et al., 2007). Still, this would have had no bearing on the overall difference between the high and low conditions of this experiment as the relative intensity between the standard and deviant remained

constant. Thus in order to determine the effects of the condition intensity without the contamination by the overlapping N2b, the MMN and the P3a were calculated together as a peak to peak measurement – any overlapping deviations are assumed to be included in the amplitude. The MMN can also be enhanced by referencing all channels to the mastoids, where its polarity is reversed. By doing both these adjustments, the peak to peak difference was significantly reduced in the lower intensity condition showing that overall intensity does indeed have an effect on the amplitude of the waveform.

3.2.5.2 Intensity effects on the relationship between gaps and the MMN amplitude

The results show the higher intensity condition gave a more accurate representation of the duration of the gaps than the lower intensity condition. Although no previous study has looked at the effects of intensity on gaps inserted within a stimulus, some studies have explored the effects of intensity on changes to stimulus duration and interstimulus interval (ISI) duration. Larger ISIs have been shown to be more dependent on intensity changes than smaller ISIs (Schröger, 1996). Similarly, MMNs elicited by differences in intensity between the standard and deviant have larger amplitudes when the stimuli have longer durations up to 10 ms (Paavilainen et al., 1993). Thus both studies suggest intensity effects on the MMN are sensitive to the duration of the stimulus and the interval between stimuli.

In gapped stimuli, the duration of the stimulus is lengthened or shortened by the duration of the gap and thus may show similar effects to those shown in Schröger (1996) and Paavilainen et al., (1993) due to similar effects on the refractory period of the auditory cortex. When the duration of the stimulus is not long enough or the interval is too small, these studies suggest there is insufficient information to elicit a memory trace. This is in line with the fresh afferent hypothesis which states that new afferent neurons encode features that are not detected in the established memory trace (i.e. the standard) (Näätänen et al., 1999). When the deviant is too

similar to the standard, fewer afferent neurons are activated and thus a smaller response ensues. Reducing the overall intensity of the signal will likely further reduce the acoustic energy and sensory information provided to the auditory system resulting in further reductions of the memory trace and activation of neuronal populations. There are thus two possibilities for the relationship between the intensity and the encoding of the gap duration: 1) temporality changes (i.e. duration of the gap) effecting the neuronal refractory period, 2) reduced acoustic energy lowering the summation of the afferent neurons' response to the change. The first suggestion is supported by Schröger (1996) who concluded the encoding of the intensity onto the sensory memory trace is not fully completed before 350 ms which is in line with other behavioural studies showing the dependence of stimulus duration on the perception of loudness (Scharf and Houtsma, 1986; Cowan, 1988). This may mean that for the gapped stimuli, since the smaller gaps reduced the total length of the stimulus, this may have impacted the system's ability to fully encode the stimuli at the lower intensities thus lowering the amplitude of the MMN. The second suggestion is based on the temporal integration model where the ability to detect a gap in a sound depends on a bandpass filter, compressive nonlinearity, a sliding temporal integrator and a cortical decision device (see Moore, 1995 for a review). This model suggests that lowering the intensity does not allow the full activation of the temporal window of integration (Moore et al., 1988; Plack and Moore, 1990). It requires time to build when an acoustic stimulus is abruptly turned on and off. This suggests that for very brief sounds, there is not enough time to allow for its full activation and thus cannot activate subsequent processes in the auditory cortex. This means that for small gaps at a low intensity, the under stimulated integrator may fail to activate higher-order afferent neurons and thus elicit a smaller MMN-P3a response.

3.2.6 Conclusion

This study showed it is possible to capture the MMN at the Cz electrode at high and low intensities when referencing to the mastoids and measuring to the following positive peak (i.e. the P3a). This will be useful information for future studies looking to use the gapped stimulus on clinical populations particularly those that are sensitive to loud stimuli. The growing interest in the relationship between difficulties in speech perception in noise and impaired temporal processing in people with normal audiometric thresholds have made electrophysiological recordings of gap detection a useful tool. Yet due to the high intensities of 80 or 90 dB SPL typically used for such tests, it may be unsuitable for such individuals who are often intolerant to loud acoustic stimulation. This current study provides evidence that gaps in noise can elicit an MMN and possibly the P3a at both high and low intensities although given the risk of high levels of noise, responses are larger and significant at higher intensities.

3.2.7 Tables

Table 2-2: Peak to peak amplitude at various gap durations for the high and low conditions at Cz, with standard deviation between parenthesis. Note that only the 20-, 30- and 40-ms gap durations showed a significant difference between the high and low conditions.

Gap duration (ms)	Condition	Mean Amplitude (μV)
2.5	Hi	0.66 (0.44)
	Lo	0.75 (0.48)
5	Hi	1.01 (0.71)
	Lo	0.70 (0.48)
10	Hi	2.02 (1.42)
	Lo	1.75 (1.15)
15	Hi	2.47 (1.75)
	Lo	1.97 (1.39)

20	Hi	2.81 (2.18)
	Lo	2.12 (1.66)
30	Hi	2.97 (1.68)
	Lo	2.17 (1.28)
40	Hi	3.07 (1.75)
	Lo	2.25 (1.25)

Table 2-3: Peak to peak amplitude at various gap durations for the high and low conditions at Fz, with standard deviation between parentheses. Note that only the 2-, 5-, 20- and 30-ms gap durations showed a significant difference between the high and low conditions.

Gap duration (ms)	Condition	Mean Amplitude (μV)
2.5	Hi	0.44 (0.26)
	Lo	1.38 (1.45)
5	Hi	0.94 (0.65)
	Lo	1.95 (1.28)
10	Hi	1.77 (1.06)
	Lo	1.62 (1.11)
15	Hi	2.53 (1.60)
	Lo	1.62 (1.13)
20	Hi	2.69 (1.53)
	Lo	1.39 (1.12)
30	Hi	2.57 (1.23)
	Lo	1.24 (0.85)
40	Hi	2.95 (1.49)
	Lo	1.85 (1.66)

3.2.8 Figures

Figure 2-1: The waveforms for the standard stimulus are shown at the Cz and Fz electrodes for the 60 and 80 dB SPL conditions. The N1-P2 complex is apparent in both conditions. The P2 is

significantly larger for the 80 dB condition (Fz: t=2.34, p=0.04; Cz: t=3.16, p=0.01) however N1 was not significantly different (p>0.05).

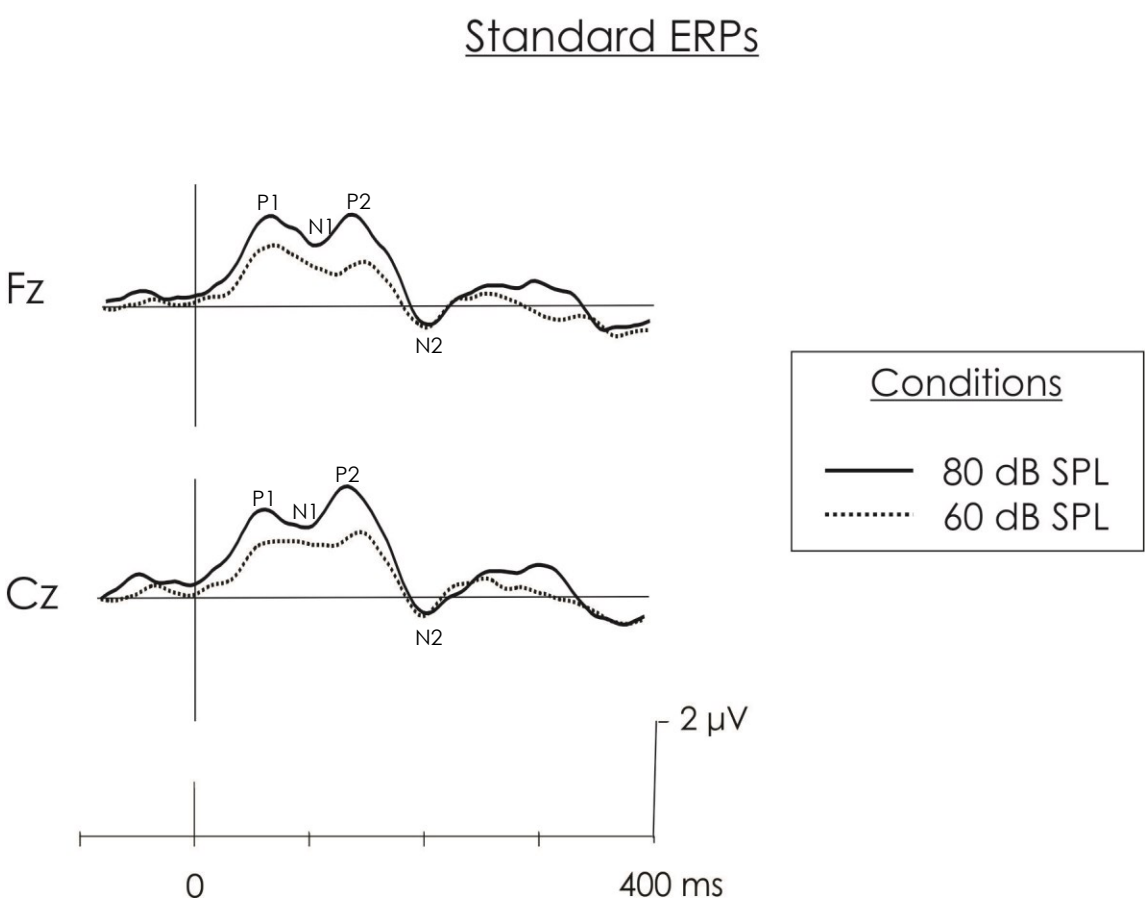


Figure 2-2: The deviant-standard difference wave obtained from gapped stimuli presented in an optimised sequence at 60 dB SPL. A large MMN deviation is found at 100 ms following the gap with a negative deflection over the fronto-central areas of the scalp and a reversal of polarity at the mastoids.

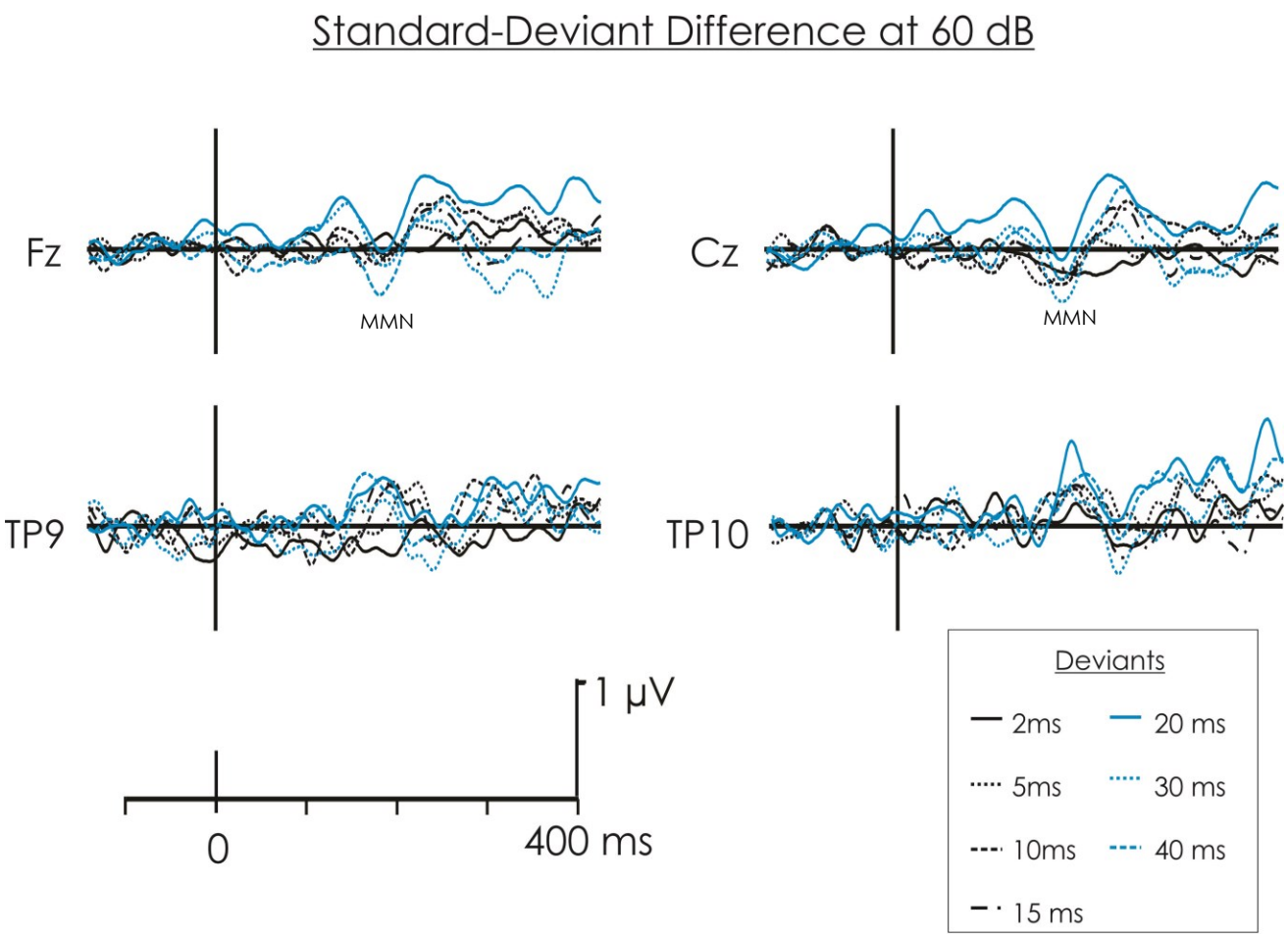


Figure 2-3: The deviant-standard difference wave obtained from gapped stimuli presented in an optimised sequence at 80 dB SPL. A large MMN deviation is found at 100 ms following the gap with a negative deflection over the fronto-central areas of the scalp and a reversal of polarity at the mastoids. Note the amplitude of the MMN is visibly more robust in the higher intensity condition.

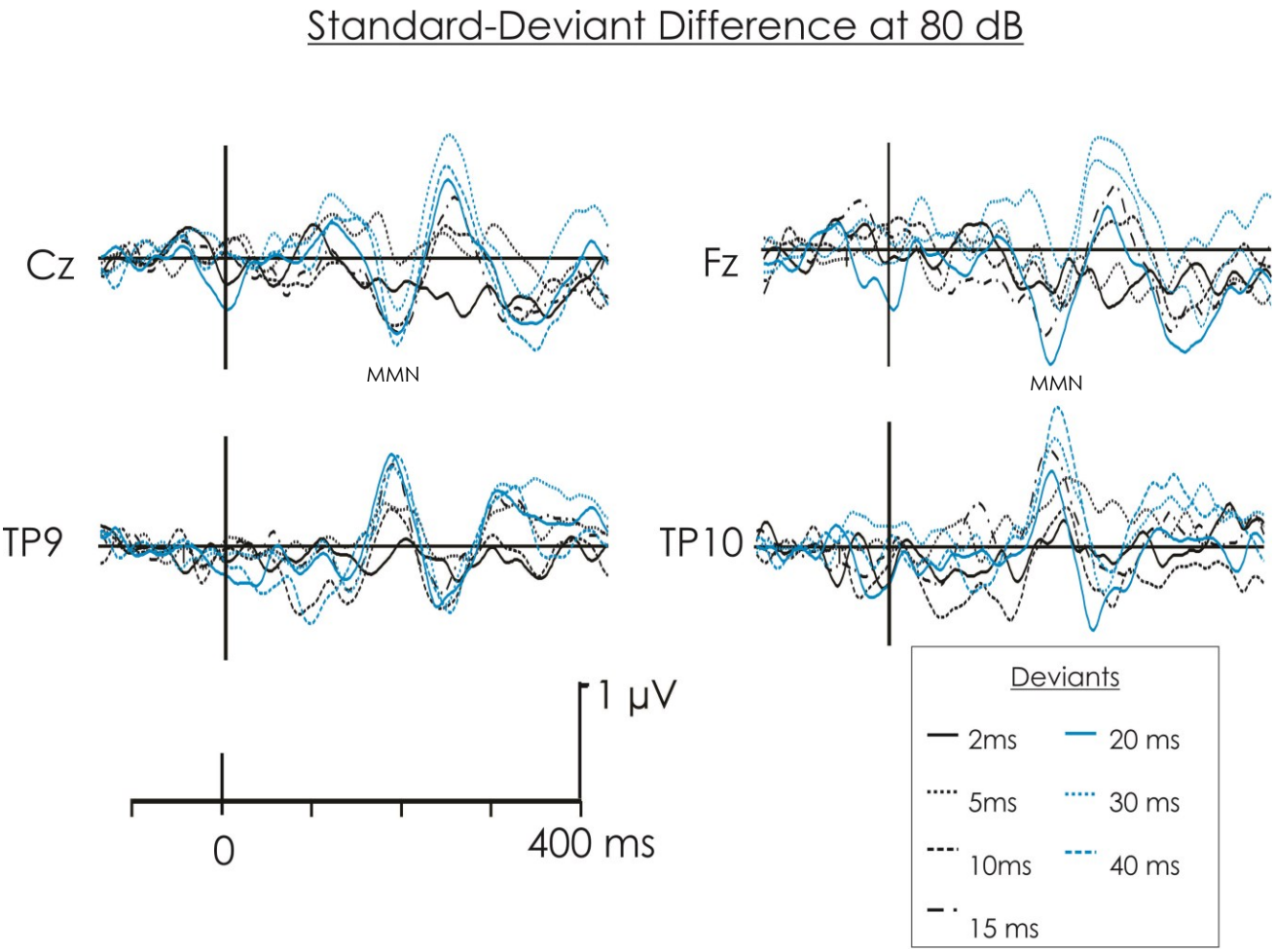
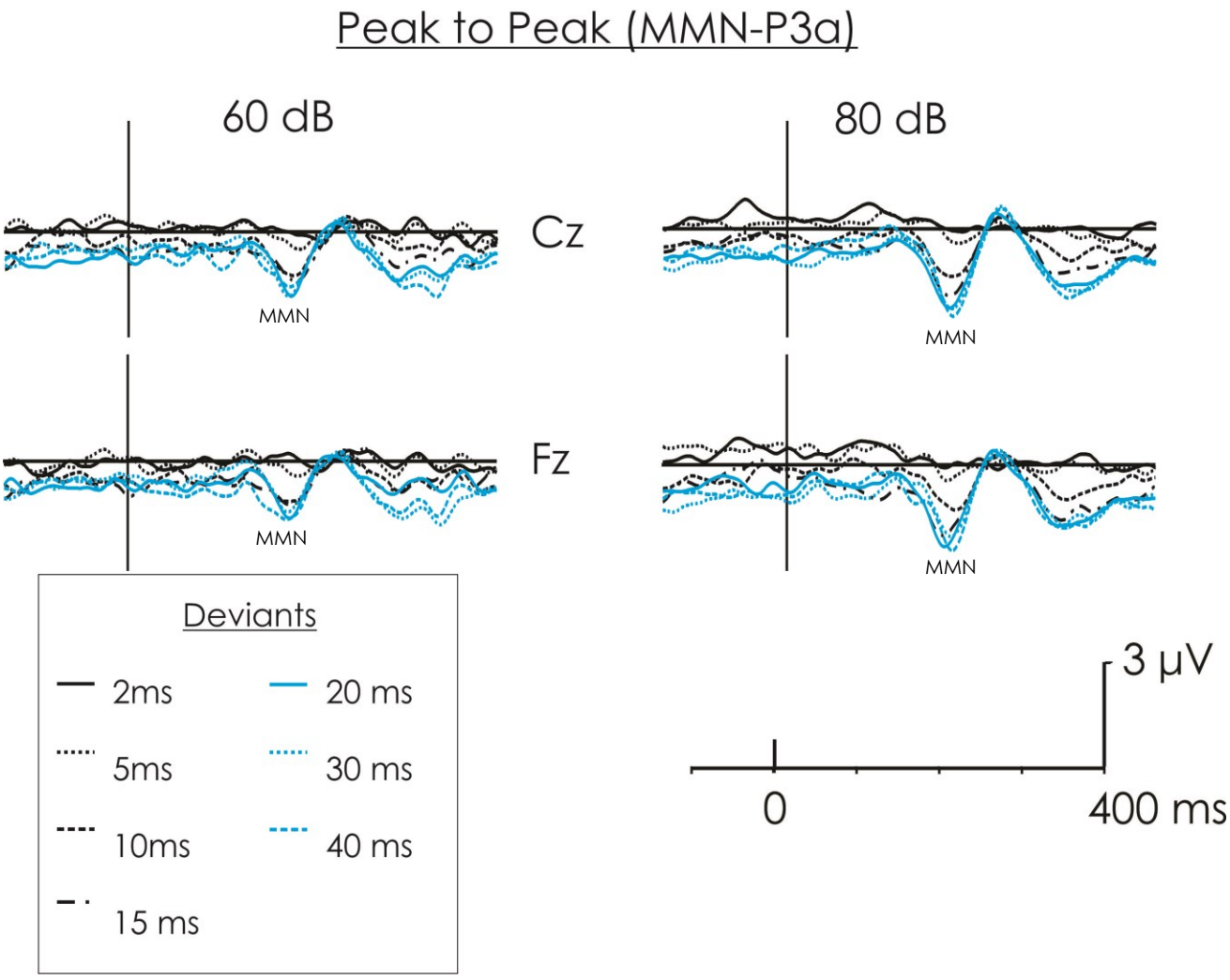


Figure 2-4: An alternative peak to peak measurement was used to enhance the visibility of the MMN. Waveforms were set to a baseline at the latency of 300 ms, approximately the location of the P3a waveform. This ensured the negativities were not offset by the contamination of a N1 which could make the MMN appear less clearly. Peak to peak amplitudes were larger in the 80 dB SPL condition compared to 60 dB SPL.



3.2.9 Conflicts of interest

The authors do not have any known conflict of interest associated with the publication of this article.

3.2.10 Acknowledgements

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Article 3: The Mismatch Negativity used to determine the effects of background filler noise on neural gap detection.

This article tested the use of a simulated tinnitus, or filler noise, on the gap-elicited MMN. This study tested a sample of normal-hearing participants presented with a narrowband noise centered around 4 kHz that simulated the perception of a 4 kHz tinnitus. This filler noise was hypothesized to "fill" the gap within the stimulus thus have a diminishing effect on the amplitude of the MMN if it were to support the "fill-in" hypothesis. In this study, two intensity levels of the filler noise were used to see if a filler intensity has an effect on the MMN amplitude. This filler study is a precursor to the final pilot study of this thesis that tests the "fill-in" hypothesis with real tinnitus. Thus the results from this study were later used for comparison with the tinnitus data.

3.3 Article 3: The Mismatch Negativity used to determine the effects of background filler noise on neural gap detection

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3.3.1 Abstract

Objective: Difficulties in noise may be a problem related to temporal resolution. Temporal resolution is often studied using gap detection. This study aims to determine if the measurements of the Mismatch Negativity (MMN) in various noise conditions can show changes to the central temporal coding of sound.

Methods: The amplitude of the MMN and psychoacoustic thresholds were measured in 15 normal hearing adult participants. A time-efficient multi-deviant optimised paradigm was used to present a continuous standard stimulus and a series of gapped deviants ranging from 2 to 40 ms at an intensity of 80 dB SPL. The stimuli were presented in three noise conditions where the background noise (i.e. the filler) was either absent, presented at a low intensity (60 dB SPL) or a high intensity (80 dB SPL). Mismatch negativity peak to peak amplitudes were measured and compared to behavioural accuracy rates.

Results: Significant MMN amplitudes were obtained for all supra-threshold gaps in the no and low noise conditions, but only at the largest gap duration for the high noise condition. In particular, the pattern of MMN amplitude increasing proportionally with the gap duration was maintained in the low and no noise conditions but not the high noise condition. The gap detection threshold in the low and no filler noise conditions were 5 ms but increased to 10 ms for the high filler noise. Behavioural gap detection accuracy correlated with the MMN amplitude for all noise conditions.

Conclusions: The processing of gaps, as shown with the MMN, are reduced when the intensity of the background filler noise is high. When attention is directed to the task, as seen through behavioural measures, high levels of noise are tolerated without having an effect on the behavioural threshold.

Key words: Mismatch Negativity, Optimised, Filler, Gaps-in-Noise, Temporal Processing, Gap Detection, Event-related potentials

3.3.2 Introduction

The perception of speech in noise is critical in everyday listening. One of the most important capacities for speech in noise discrimination is the ability to detect gaps (Bharadwaj et al., 2014; Moore, 2008). Gap detection or temporal resolution has been studied using silent periods inserted in a continuous stimulus.

Temporal resolution is clinically measured using behavioural techniques that require active participation and attention for long periods of time (Musiek et al., 2005; Keith, 2000; Samelli et al., 2008; Dias et al., 2012). Such active participation and attention is often subject to perceptual and cognitive biases (Andersson and McKenna, 2006). It may also not always be possible to reliably elicit feedback using such behavioural measures, namely for pediatric populations and populations with low-functioning cognitive abilities. Objective measures such as auditory event-related potentials have been demonstrated as an alternative method of measuring neural gap detection (Atcherson et al. 2009; Harris et al. 2012; Lister, Maxfield, & Pitt, 2007; Lister et al. 2011; Michalewski et al. 2005; Palmer and Musiek 2013, 2014; Pratt, Bleich, and Mittelman 2005).

Event-related potentials (ERP) are changes in electrical activity that reflect various aspects of information processing (Näätänen, 1992). They are subject to random "noise" of the electroencephalogram which is typically larger than the ERP components, however through various averaging techniques the background noise can be reduced allowing the ERP to emerge (Don and Elberling, 1994).

The ERP is evoked passively, thus attention to the stimulus is not required. Typically in previous studies where an auditory stimulus is used, the participant performs a non-auditory task such as watching a video or reading a book to direct attention away from the stimulation (Atcherson et al., 2009; Harris et al., 2012; etc.). In this way, the participant does not actively manipulate their attention on the auditory task, but rather the ERPs are recorded with passive awareness. If however, there are any changes to the ERP due to any extrinsic factors like attention, it is assumed these factors would equally affect all conditions and thus be removed when differences between conditions were analyzed.

One component of the ERP that has been used to measure the response to the gapped auditory stimuli is the N1: a negative-going deflection maximum at about 100 ms following the onset or offset of a stimulus (see Näätänen and Picton, 1987 for a review). Studies have found this component increases in amplitude as the gap duration lengthens (Lister, Maxfield, & Pitt, 2007; Atcherson et al., 2009; Palmer and Musiek, 2013). However, attention has been known to affect the amplitude of the N1 for gapped stimuli (Harris et al., 2012) as well as fatigue or sleepiness (Campbell and Colrain, 2002).

Another ERP component used has been the MMN which is maximum at about 100-200 ms and inverts in polarity at the mastoids (Näätänen, 1990). Both the N1 and the MMN are ERP components that reflect different types of processing. The N1 is believed to process the transient change of a stimulus while the MMN reflects the processing of specific features within the stimulus such as frequency changes, duration and intensity. The MMN also differs from the N1 because it is derived from the difference between the ERP to a standard and the ERP to a deviant stimulus.

The standard and deviant stimuli are both presented typically in an oddball or optimised sequence. The oddball sequence presents one deviant stimulus among a series of standards. The optimised sequence presents multiple deviants in an alternating pattern with the standard. Both the standard as well as the deviant elicit N1 and later P2 deflections, however it is in subtracting the ERP of the standard from the deviant that allow the MMN to be visualized. Thus the MMN is elicited by features only found in the deviant stimulus.

There are two models that associate the MMN with detection of the acoustic stimulus. The classic model (Näätänen, 1990 and 1992) associates the MMN with a memory system that preconsciously compares the features of the incoming stimulus with sensory memory of the previous stimulus (the standard). When the incoming stimulus is the deviant, the features that differ from the standard (i.e. the memory trace) are thus detected and elicit the MMN. A second model associates the MMN with a prediction based system that is formed according to rules and trends of the recent auditory stimulus (Näätänen et al., 2001; Paavilainen, 2013; Winkler, 2007; Winkler et al., 2009) of the standard. Thus the greater the change between the expectation of the system and the incoming stimulus, the larger the amplitude of the MMN. Unlike the N1, the MMN is not altered by attention (Muller-Gass et al., 2006) or fatigue (Gosselin et al., 2006; Zerouali, Jemel, & Godbout, 2010).

For very large changes to the stimulus, a difference component called the P3a can be elicited (Escera et al., 1998). This component is associated with an interrupt sent to the central executive controlling attention and additional processing evaluating the stimulus. When activated, it produces a deflection at about 300 ms after the onset of the stimulus (Squires, Squires and Hillyard, 1975). It is visulalized together with the MMN in the difference wave and can be obtained using the same recording procedures as the MMN.

A number of oddball and optimised studies have used gapped stimuli to successfully elicit an MMN. In these studies a 100-300 ms duration standard stimulus without a gap is presented in a sequence with a deviant that includes an embedded silent interval (i.e. the gap). Supra-threshold gaps have been shown to elicit an MMN (Bertoli et al., 2001; Todd, Finch, Smith, Budd and Schall, 2011; Yabe et al., 2005; Milloy et al., submitted and Article 2) such that the amplitude will vary with the duration of the gap up to a ceiling level (Alain, Mcdonald, Ostroff and Schneider, 2004). The oddball and the optimised paradigms have both shown to elicit significant MMNs to gapped stimuli. For example, various factors of the gapped stimulus can alter the MMN amplitude such as placement of the gap within the stimulus (Yabe et al., 2005), intensity (Article 2), and filling in the gap (Tamakoshi, Minoura, Katayama & Yagi, 2016).

One factor of interest is the effect of filling in the gap with another stimulus or a background noise. Tamakoshi et al. (2016) measured the MMN of normal hearing adult participants with a 1000 Hz tone standard presented at 70 dB sensation level with 30-ms gapped deviants either unfilled or filled with a 1000 Hz tone of 25% of the intensity of the stimulus. Filling in the gap elicited MMNs with smaller amplitudes than the unfilled gaps however this change was not significant. Additionally, there was a significant decrease in the correct response rate for the filled gapped stimuli but not the unfilled gaps.

Based on the notion that filling in the gap can reduce the amplitude of the MMN, our study uses the optimised paradigm to present multiple gap durations in three intensity filler conditions: high (80 dB SPL), low (60 dB SPL) and no filler. If these results are similar to previous findings (i.e. Tamakoshi et al., 2016), the low filler condition should then show a smaller MMN amplitude than in the other conditions and correlate with a reduced behavioural

accuracy rate compared to the unfilled condition. It is thus hypothesised that a proportionally larger decrease in the amplitude of the MMN is found for the the high intensity filler condition which should also be reflected in a further reduction of behavioural accuracy to gaps.

3.3.3 Methods

3.3.3.1 Participants

A total of fifteen participants (13 females and 2 males) with normal hearing and no history of neurological or otological pathologies participated in this study. The ages ranged from 20 to 35 years old (mean = 24 years, SD= 3.3). All participants had normal hearing thresholds under 25 dB HL from 250 Hz to 8000 Hz. Procedures were approved by the University of Ottawa Research Ethics Board which follows the Canadian Tri-Council (Natural Health and Social Sciences) guidelines on ethical conduct with human participants. Based on these guidelines, all participants were explained the nature of the study, gave written consent, and were given an honorarium for their participation.

3.3.3.2 Procedure and stimuli

For the electrophysiological and psychometric tests, two types of stimuli were used: a stimulus and a filler noise. The stimulus consisted of a bandpass filtered broadband noise with a 4 kHz centre frequency presented monaurally to the right ear. The parameters of this stimulus noise were applied using Audacity® recording and editing software (version 2.1.0, Dominic Mazzoni, Carnegie Melon University), and its presentation and timing were controlled with Presentation® software (version 20.1, Neurobehavioural Systems, San Franscisco). All stimuli were calibrated in the same manner as our previous work (see Milloy et al., submitted and Article 2). In order to replicate a previous study on gap detection thresholds, the duration of the stimulus was 200 ms (Milloy et al., submitted and Article 2). The stimulus was either a continuous standard or a deviant with an inserted silent interval. The silent intervals were 2, 5,

10, 15, 20, 30 and 40 ms durations placed at equal distance from the onset and offset of the stimulus. The intensity of both the standard and the deviant was 80 dB SPL. This intensity was chosen over 60 dB SPL because previous work showed higher intensities elicited a comparatively larger MMN amplitude and had a significant effect on gap (Article 2).

The stimulus was presented simultaneously with a continuous filler (i.e. background) noise. The filler was a bandpass filtered Gaussian noise with peak energy at 4 (see Figure 3-1). The peak intensity of the filler was either 80 dB SPL ("high filler"), 60 dB SPL ("low filler") or 0 dB SPL ("no filler"). The filler noise was generated by a separate laptop using Audacity® recording and editing software (version 2.1.0, Dominic Mazzoni, Carnegie Melon University) and outputted to an external USB audio mixer interface, Tascam US-366 (TEAC Corporation), which combined the presentation of the filler simultaneously with the stimulus. The participant received both the filler noise and the stimulus monaurally to the right insert earphone (ER2A, Etymotic Research Inc, Elk Grove Village).

In accordance with the optimised paradigm, a series of deviant stimuli were presented with various gap durations in alternation with the no-gap standard stimulus. Within each block of seven deviants, each gap duration was presented once and no two deviants of the same gap were presented consecutively. Thus one sequence contained 548 standard stimuli without a gap (50% probability) and 77 deviants of each gap duration (7% probability). The interstimulus interval was 400 ms. Each sequence began with 10 standard stimuli in order to establish a memory trace. The sequence was repeated three times for each filler condition of high, low or no intensity. Between the sequences, the participant was given a brief moment to rest. The total time required to test each condition was 30 minutes (10 minutes per sequence).

All recordings took place in a sound attenuated and electrically shielded room. Patients were asked to lie in a supine position and to ignore the stimuli while watching a subtitled film with no sound. The supine position allowed for relaxation of the muscles around neck to avoid myogenic noise artifacts in the recording.

The electrophysiological recordings were followed by active behavioural tests of gap detection. A non-adaptive 2-alternative forced-choice procedure was used to determine the gap detection threshold. Participants were given a practice period with no filler noise where a 20-ms gap was presented in random order with the standard stimulus. Feedback for the practice period was given through sound cues. The test trials consisted of 40 standard stimuli and 20 of each type of deviant stimulus presented in random order. Each test trial was run consecutively for each filler intensity condition. The patient had the choice of pressing one of two buttons to indicate the presence or absence of a gap. The accuracy was determined as the percentage of correct identifications of a gap or no gap out of the total number of presentations. The final gap detection threshold was determined as the gap with the average detection accuracy closest to 50%. The total duration for this portion of the testing was 20 minutes.

3.3.3.3 Electrophysiological recording

The electroencephalographic (EEG) potentials were recorded using 32 active silver/silver chloride electrodes positioned at the frontal central, parietal, temporal and occipital areas of the scalp (ActiCap, Brain Products, Germany). An additional electrode was placed below the eye on the right upper cheek to measure blink artefacts and the vertical electrooculogram (EOG). The ball of the nose served as a reference to all channels including the EOG. All inter-electrode impedances were kept below 25 kohms and controlled throughout the recording. The EEG was filtered using a high-pass filter set to 250 Hz with a time constant of 2 seconds. Data was

digitized continuously using a sampling rate of 500 Hz and stored on a hard disc for offline analysis.

Offline analysis of the EEG was conducted using BrainVision Analyzer v2.1.2 (Brain Products) software. The same digital filters were used as in Milloy et al. (submitted) and Article 2. The vertical eye movements were also calculated in the same way using Independent Component Analysis (ICA) (Chaumon et al., 2015; Makeig et al., 1996) to remove ocular artifacts. EEGs were then segmented and averaged into epochs of 600 ms for the standard and deviant stimuli at each of the electrode sites. Each epoch included 100 ms prior to the onset of the stimulus which served as the zero-voltage baseline (-100 to 0 ms).

3.3.3.4 Electrophysiological statistical analyses

Previous studies (Milloy et al., submitted, Article 2) showed the maximum MMN to gapped stimuli occurred at the Fz and Cz electrodes. Therefore these electrodes were targeted for the statistical analysis. For each filler condition, individual difference waves were calculated by subtracting the standard stimulus response from the deviant stimulus response. This was done to remove any obligatory deflections common to both the standard and deviant waveforms such as the N1 and the P2. The remaining deflection found in the difference waves was the MMN which was visually determined within the expected time window. The time window was measured from the grand average of all individual difference waves. The amplitude of the MMN was subsequently calculated for each individual difference wave by averaging all data points within +/- 25 ms of the MMN found in the grand average.

A series of analysis of variance (ANOVA) calculations was used to compare the mean individual MMN amplitude data for each of the deviants and conditions. Greenhouse-Geisser corrections were applied to correct for any possible sphericity violations. A two-way repeated

measures ANOVA with measures of deviant (2-, 5-, 10-, 15-, 20-, 30- and 40-ms gap durations) and condition (high, low and no filler) were calculated based on the MMN amplitude averages from the Fz and Cz electrodes as well as the right mastoid TP10, separately. These electrodes were chosen because the MMN is known to be largest at these locations (Näätänen and Picton, 1987). A three-way repeated measures ANOVA was calculated with the deviant and condition measures as well as an additional hemisphere measure (left and right) at both the F4 and F5 electrodes to calculate laterality of the MMN amplitude.

A significant difference may be found among the MMN amplitudes of the deviants even if certain deviants do not elicit an MMN. For example, the largest gaps can elicit large negativities and the smallest gaps that are below the perceptual threshold are not expected to elicit an MMN at all. However when comparing the largest gaps with the smallest, a significant difference may suggest a small MMN was found below the threshold. In order to avoid this ambiguity, confidence intervals were applied. Confidence intervals were thus calculated to determine whether the amplitude of the MMN for a particular deviant is large enough to be considered significant. This is achieved by determining the probability that an amplitude falls within an upper and lower range relative to the pre-stimulus baseline. Similar to a t-test calculated between the standard and deviant waveforms (Winer et al., 1971), the upper limit of a confidence interval appearing less than 0 uV would have a probability of less than 0.05 and thus be considered a significant MMN. In an additional measurement to minimize the overlap of the N2b component, the MMN and P3a average voltage activities were subtracted to determine the peak to peak value. Based on these peak to peak values, a repeated measures ANOVA was calculated for conditions and deviants.

To compare the MMN amplitudes to the behavioural gap detection task, a Pearson correlation analysis was calculated between the behavioural accuracy and the MMN amplitude at the Fz electrode for each deviant in each condition.

3.3.4 Results

In general, the results show there is a significantly larger MMN in the no and low filler conditions compared to the high filler condition. In addition to this, there is an effect of deviant in each of the conditions. The following section will describe in detail the calculations made on the amplitude of the standard ERP between the three conditions, and comparisons calculated on the MMN amplitude for the various deviant gaps and each of the conditions.

3.3.4.1 Physiological data

3.3.4.1.1 Standard ERP and the filler conditions

The ERP elicited by the 200 ms (i.e. 0-200 ms) standard stimulus were compared in the three filler conditions (Figure 3-2). A positive-going deflection can be seen at about 40 ms after the onset of the stimulus in all three conditions. In the no and low filler conditions, the amplitude is not significantly different, however for the high filler conditions it is significantly reduced at both the Fz and Cz electrodes ($p<0.05$). There is also a clear negative-going deflection at about 90 ms (N1) followed by a positive deflection at 165 ms (P2) that is not significantly different between the low and no filler conditions ($T<1$) however it does not appear to be visible in the high filler condition. A one-way repeated measure ANOVA on the effect of condition was significant ($F(2,28)=17.73$, $p=0.0001$, $\eta_p^2=0.56$) for the N1-P2 complex. A Fisher's Least Significant Difference (LSD) was computed to show the high filler condition was significantly lower in N1-P2 amplitude than the no and low conditions ($p<0.05$). Conversely, there is a second negative-going deflection which was elicited at about 135 ms following the offset of the stimulus (N2). A one-way repeated measures ANOVA on the effect of condition was significant

(F(2,28)=3.94, p=0.03, η_p^2=0.22) for the N2. Pairwise comparisons corrected using the Fisher's LSD shows the no filler condition has a significantly larger N2 amplitude than the high and low filler conditions (p<0.05).

3.3.4.2 Difference waves

In all the filler conditions, the deviants represent 2-, 5-, 10-, 15-, 20-, 30- and 40-ms gap durations presented in an optimised sequence in the presence of a high, low, or no intensity level of filler noise. The peak to peak (MMN-P3a) difference waves for each of the filler conditions can be found in figure 3-3. Table 3-1 presents the mean MMN amplitude in all three filler conditions as a function of gap duration.

3.3.4.2.1 Effect of gap on the MMN amplitude on filler condition using the nose-reference

The grand average difference waveforms were obtained for 6 gapped deviants in the high, low and no filler conditions. Occurring at about 100 ms after the onset of the gap is the MMN which is maximal at the fronto-central electrodes and inverted at the mastoids. A one-way ANOVA with repeated measures on deviant type (2, 5, 10, 15, 20, 30 and 40 ms) was calculated at the Fz and Cz electrodes for each of the intensity filler conditions. It showed the main effect of gap duration on the MMN was not significant at the Fz and Cz electrodes for any of the conditions (F <1). A one-way ANOVA was also calculated at the mastoids (T7 and T8) and it also revealed no significant main effects of gap duration for any of the filler conditions (F<1).

3.3.4.2.2 Effect of peak to peak measures on filler condition

The ANOVA was not significant when using MMN amplitudes referenced to the nose and with a baseline set to the onset of the stimulus. This is likely due to a poor signal to noise ratio. An alternative method was used where the peak of the MMN to the peak of the P3a was measured. Peak to peak measurements were also used in our previous work (Article 2) as an alternative way to measure the MMN and P3a to enhance the endogenous signal and reduce

exogenous noise. Peak to peak measures of the high, low, and no filler conditions are found in figure 3-3.

3.3.4.2.3 Peak to peak measures for high filler condition

Figure 3-3 shows the grand average of the peak to peak difference wave elicited by the 7 gapped deviants in the high filler condition. A negative-going deflection at about 150 ms following the gap in the deviant is proceeded by a positive-going deflections at about 200 ms post-gap, at the Fz and Cz electrodes. These are known to be the MMN and the P3a waves. The peak to peak measurements of the MMN to P3a for the high filler condition can be found in table 3-1. Confidence interval testing showed that the peak to peak values are only significant at 40-ms gaps but not for any narrower gapped deviants. A one-way ANOVA revealed no significant effect on deviant type for either the Cz or the Fz electrodes (Cz: $F(6,98)= .989$, $p=.437$; Fz: $F(6,98)=.711$, $p=.641$). Similarly, a one-way ANOVA at the mastoid electrodes also did not show an effect on deviant type (T8: $F(6,98)=.250$, $p=.958$; T7: $F(6,98)=.292$, $p=.939$).

3.3.4.2.4 Peak to peak measures for the low filler condition

Similar to the high filler condition, a negative followed by a positive-going deflection can be seen at about 150 to 200 ms following the gap. A one-way ANOVA on the effect of deviant type reveal a significant effect on the peak to peak amplitude at the Cz, ($F(6,84)=3.04$, $p=.01$, $\eta_p^2 = .89$) but not at the Fz electrode ($F(6,84)=2.16$, $p=.06$). Confidence interval testing at the Cz electrode show significant confidence intervals from 10 ms and higher. Pairwise comparisons for the MMN amplitudes at Cz corrected using Fisher's LSD showed the 2-ms gaps are significantly smaller than the gaps greater than or equal to 10-ms, and 5-ms gaps are significantly smaller than gaps 30 ms or larger.

3.3.4.2.5 Peak to peak measures for the no filler condition

Figure 3-3 shows the grand average peak to peak difference wave elicited by gapped deviants in the no filler condition. A one-way ANOVA showed the effect on deviant type on the peak to peak amplitude was significant at the Cz electrode ($F(6,98)=2.62$, $p=.21$), but not at Fz ($F(6,98)=1.72$, $p=.12$). Confidence interval testing showed the same significant confidence intervals, from 10 ms and higher, as the low filler condition. Post-hoc LSD comparisons revealed 2-ms gaps elicited significantly smaller peak to peak amplitudes than 20-ms gaps and higher, and 5-ms gaps elicited significantly smaller amplitudes than 30- and 40-ms gaps.

3.3.4.2.6 Comparing all conditions to the peak to peak amplitude difference wave

A two-way repeated measures ANOVA was conducted on the deviant type and condition. This showed a significant effect on condition, $F(2, 294)=5.96$, $p=.001$, $\eta_p^2=.04$, and deviant type, $F(6, 294)=5.65$, $p=0.001$, $\eta_p^2=.11$, at the Cz electrode. Similarly at the Fz electrode there was also a significant effect of condition, $F(2,294)=4.32$, $p=0.01$, $\eta_p^2=.03$, and deviant type, $F(6,294)=3.99$, $p=.001$, $\eta_p^2=.08$. There was no significant interaction for gap x condition ($F<1$) at either the Fz or Cz electrodes. A post-hoc LSD tests comparing the mean amplitude of all three conditions showed the high filler condition had significantly smaller peak to peak amplitudes than the low and no filler conditions ($p=.01$ and $.001$ at Cz, and $p=.03$ and $.01$ at Fz respectively). Additionally the no and low filler conditions did not have significantly different peak to peak amplitudes from each other ($p=.84$ at Cz and $p=.51$ at Fz).

3.3.4.3 Behavioural data

3.3.4.3.1 Behavioural accuracy based on the filler condition

The behavioural performance to the standard and the various deviant stimuli can be found in table 3-2. Behavioural performance was measured using the accuracy of detection of a gap. The detection of no gap for the standard stimulus was very high and there were few false positives for all three conditions. All three conditions showed very high accuracy for the 20-, 30-

and 40-ms gaps. Conversely, gap detection accuracy was very low for the 2-ms gaps in all three conditions. The conditions however varied in the mean threshold gap detection accuracy. For the no and low filler conditions the gap detection threshold was 5 ms as the mean detection rate was .66 and .69, respectively. For the high filler condition, the mean detection rate at 5 ms was .18, thus below 50% threshold accuracy. The next wider gap had a mean detection rate of .89 thus would be considered the behavioural gap detection threshold. A two-way ANOVA was run for the detection accuracy of the six deviants in the three conditions. The main effect of gap duration was significant, F(7,336)=308.01, p=.001, η_p^2=.87, as well as the main effect of conditions, F(2,336)=15.26, p=.001, η_p^2=.08. There was also an interaction between condition x gap, F(14,336)=7.83, p=.001, η_p^2=.25. Post-hoc testing using least significant differences showed the accuracy was significantly lower for the high filler condition at 5 ms compared to the low and no filler conditions (p=.001).

3.3.4.3.2 Behavioural accuracy with the peak to peak difference amplitude

Behavioural accuracy was compared to the peak to peak difference wave at the Cz electrode for each gap duration. A Pearson correlation was calculated on the accuracy rate and the peak to peak amplitude at Cz using one-tailed significance. It was expected that an increase in amplitude would be related to an increase in accuracy as seen in our previous work (Milloy et al., submitted). The Pearson correlation was very strong for the no filler, r(103)=.292, p=.001, and the low filler, r(103)=.346, p=.0001. It was also significantly correlated for the high filler, r(103)=.169, p=.042, however less strongly than the other two conditions.

3.3.5 Discussion

In this study we demonstrated that 1) the MMN amplitude increases proportionally with the length of the embedded gap in noise similar to Milloy et al. (submitted) and Article 2, 2)

increasing background noise reduces the amplitude of the MMN, and 3) the MMN amplitude to gaps in noise is correlated to behavioural gap detection for all noise conditions.

Previous work by Tamakoshi et al. (2016) showed the MMN is reduced in amplitude when a 1000 Hz gapped stimulus, presented at 70 dB SL, is filled with a second stimulus at a quarter of the intensity. This is consistent with the results from this study which used an 80 dB SPL stimulus to show the MMN amplitude is reduced when gaps are filled with various intensities of background noise. Increasing filler background noise reduced the MMN amplitudes. It is possible that this is an indicator of reduced temporal resolution due to higher background noise. It has been argued that the bandwidth of the auditory filters are a limiting factor in coding for changes in temporality (Moore and Glasberg, 1986). This is especially true for low frequency stimuli that can have longer responses and are known to produce a "ringing" on the basilar membrane, making gap detection more difficult (Carlyon, 1988). However in this experiment, we used a high center frequency stimulus which has been known to have fast responses to temporal changes (Ronken, 1970). This is thus an unlikely explanation for the reduced amplitudes found in the higher background level conditions.

Another argument has been the rate of recovery from the auditory nerve fibers during the gap which would likely change the amplitude of the response following the gap (Glasberg, Moore and Bacon, 1987). Our results showed compared to the high intensity filler noise, the amplitude of the N1-P2 to the non-gapped standard was higher when the filler noise was either absent or low. Recall the N1-P2 complex is believed to indicate transient changes to the stimulus. In this case the transient change of the standard stimulus would be its onset (at approximately 0 ms). Previous literature has shown that a reduction in the N1-P2 could be related to the auditory system showing impaired encoding in populations with peripheral hearing

loss (Koravand, Jutras, & Lassonde, 2013) or with central auditory processing (Koravand et al, 2017). The participants in this study had normal auditory function, therefore reductions in the N1-P2 may indicate the system's inability to code for the onset of the stimulus due to background noise occupying the auditory nerve fibers. In our previous work on the effects of intensity on the MMN (Article 2), we demonstrated that a decreased stimulus intensity reduced the amplitude of the MMN. We related this to a theory presented in Bharadwaj et al. (2014) that described the functioning of the lower spontaneous rate auditory nerve fibers that may be responsible for extending the auditory system's dynamic range of hearing. In noisy environements the high spontaneous rate (low threshold) fibers may be saturated by the continuous background noise leaving only the low spontaneous rate (high threshold) fibers to respond (Costalupes et al., 1984). Unforunately, with a portion of the auditory fibers occupied, the low spontaneous rate fibers are less able to phase-lock to the onset of the stimulus and cannot code for the fine temporal structures of the frequency carrier. Instead they fire for the envelope temporal changes of the basilar membrane. This could be a possible explanation for the reduced N1-P2 to the onset of the stimulus in the high background noise condition however it does not fully explain the amplitude changes of the MMN.

In a study by Koravand, Jutras and Lassonde (2013) early components were found to behave differently than the later N2 and MMN responses. These differences were interpreted as the result of sensory coding occurring at multiple levels of the auditory system. This may mean that the changes found in the amplitude of the MMN may not be due to the same mechanisms as the amplitude changes of the N1-P2. One mechanism that is included in the temporal resolution theory is the sliding temporal integrator which is believed to occur after the auditory nerve (Plack and Moore, 1990). This integrator takes the output from the auditory nerve and it

determines a weighted average over a time interval which is known as the temporal "window" (Moore, 1995). This temporal window is believed to be effected by masking since it is limited by a build up and decay time delay. Masking may trigger the integrator to build up leaving it overloaded and unable to fully respond to the stimulus. This may be an explanation for the reduction in MMN (and thus N2) amplitude in the high background filler that does not allow the integrator to decay and produce an accurate response to the envelope of the acoustic stimulus.

3.3.5.1 Narrower gaps reduce the MMN amplitude in all conditions

Reduction of the gap duration lead to a reduction of the amplitude of the MMN. This corroborates with previous gap detection studies showing the same trend (Bertoli et al. 2001; Milloy et al., submitted, and Article 2). This reduction of the MMN amplitudes to gap duration was observed in the low and no filler conditions but not for the high filler condition. This means that the change in amplitude was not large enough in the high filler condition to make an important enough effect. This may again be explained by the limitations of the cochlear auditory filters, the adaptation of the auditory nerve and the temporal integrator. The MMN amplitude had a significant effect on gap duration at the Cz electrode for all background filler noise conditions. This was not the case at the Fz electrode which showed weaker effects on gaps for the low and no filler conditions. The effect on gap at Cz and not Fz may be due to the amplitude being larger at the Cz electrode than the Fz. This was also reported in previous studies that measured MMN to gapped stimuli showed amplitudes are almost always larger at Cz than Fz (Bertoli et al., 2001; Milloy et al., submitted and Article 2; Tamakoshi et al. 2016).

3.3.5.2 Accuracy of the behavioural gap detection reduced significantly with higher filler intensity

Behavioural accuracy was measured to see if the use of the same stimuli and fillers as the ERP experiment would produce similar or different results. Previous studies on gap detection have indicated that the gap detection threshold for young normal hearing participants is typically around 5 ms (Michalewski et al. 2005). Indeed this study showed that in the no and low filler conditions, the gap detection threshold was 5 ms with accuracy rates of .66 and .69, respectively. One of the objectives of the study was to evaluate the effect of the high filler on both the behavioural gap detection threshold. High filler appeared to reduce the accuracy rate significantly at 5 ms by lowering the rate to .18. Therefore the behavioural gap threshold was increased to 10 ms for this condition where the accuracy was well above threshold at .89. These behavioural results in the filler conditions corroborate with previous work showing that filling the gap reduces the accuracy of the behavioural accuracy but not the threshold (Tamakoshi et al, 2016). It is interesting that although the system is receiving noise, it is still able to make rather good discriminations that allow the behavioural thresholds to remain unchanged. This however was only the case when the filler noise was kept at a low level. This may be explained by the cognitive interpretation of the output of the temporal integrator. A number of previous papers have described a discrimination device that interprets the output of the temporal integrator to make the smallest detectable change (Glasberg, Moore and Bacon, 1987; Heil and Neubauer, 2003; Gerken, Bhat, and Hutchison-Clutter, 1990). This may mean that at lower levels of background noise, the discrimination device can still interpret small temporal changes to the signal but when the temporal integrator is saturated these interpretations become erroneous.

3.3.5.3 The relationship between behavioural accuracy and the MMN amplitude

The MMN amplitude correlated with the behavioural accuracy in all noise filler conditions. Significant MMN amplitudes were elicited only for gap durations the subjects were

able to detect behaviourally. In contrast, particularly for the high intensity filler noise, the participants could behaviourally detect many more gaps than the electrophysiological recordings could show. This may be explained by P3a component which is elicited only when there is a significant enough change to elicit the activation of central executive processes (Donchin and Coles, 1988). Since the MMN amplitude was measured in relation to the P3a, it is possible that the P3a was in fact contributing to the changes in the MMN amplitude. This peak to peak measure may be evidence of the discrimination device described in other studies looking at just-noticeable differences (Glasberg, Moore and Bacon, 1987; Heil and Neubauer, 2003; Gerken, Bhat, and Hutchison-Clutter, 1990). This is also evidence that the auditory system can withstand a certain level of noise and imperfection in the coding of temporal cues of the auditory stimulus in order to make cognitive decisions. This may be the reason there is a difference between the behavioural gap detection threshold and the smallest gap for which a significant MMN is produced. Previous work by Bertoli et al. (2001) showed no correlation between the psychoacoustic gap detection threshold, and the MMN peak amplitudes. They concluded that attention was the reason behind the neurophysiological thresholds always being larger than the behavioural threshold. The electrophysiological task is carried out passively without the attention of the participant whereas the behavioural task requires active detection and response to the gaps in the stimulus. In contrast, our previous work using gapped broadband stimuli showed significant MMNs can be elicited sub-threshold gaps (Milloy et al., submitted). This may have been due to factors related to the difference in stimulus parameters (i.e. a broadband signal compared to a filtered signal). We also suggested that the larger patterns of stimulus presentation may have elicited the MMN.

3.3.6 Conclusion

The results from this study show that gaps can elicit amplitude changes between the MMN to P3a peaks in the presence of noise. When comparing to unfilled gaps, low intensity filling of the gap does not appear to significantly change the behavioural thresholds or the MMN amplitudes. However, with high intensity filling, the gap detection accuracy was reduced and the MMN amplitude was no longer able to reliably code the temporal aspects of the signal. The amplitude was also significantly reduced compared to the other two conditions. It is unclear whether the changes in amplitude are a sign of reduced capacity of the central auditory system to encode the temporal resolution of the signal. Further studies using this technique on patients with known difficulties in temporal processing will further elucidate this question.

3.3.7 Tables

Table 3-4: Peak to peak measures at the Cz electrode. The Cz electrode showed a significant effect on gap. Confidence interval testing shows significant confidence intervals for the no and low filler conditions for gap durations of 10 ms and higher. The high filler condition had a significant confidence interval only at 40-ms gap durations.

Deviant	Condition	Amplitude (μV)
2 ms	No	.05 (1.43)
	Low	-.11 (0.91)
	High	-.15 (1.55)
5 ms	No	.31 (1.17)
	Low	.40 (1.97)
	High	.02 (1.29)
10 ms	No	1.09 (1.85)
	Low	.99 (1.64)
	High	.19 (1.25)
15 ms	No	1.18 (1.56)
	Low	1.13 (1.49)
	High	.47 (1.96)
20 ms	No	1.38 (1.74)
	Low	1.33 (1.39)
	High	.77 (1.81)

30 ms	No	1.63 (1.96)
	Low	1.69 (1.79)
	High	.85 (1.85)
40 ms	No	1.93 (1.55)
	Low	1.82 (1.91)
	High	.76 (0.91)

Table 3-5: Accuracy of behavioural gap detection in three conditions: no, low, and high filler. Highest detection rates were found for the standard and deviants with gap sizes 20 ms and higher. Gap detection threshold was 5 ms for the no and low filler conditions, and 10 ms for the high filler condition.

Stimulus	Accuracy		
	No	Low	High
Stan	.98	.98	.94
2 ms	.02	.01	.04
5 ms	.66	.69	.18
10 ms	.94	.94	.89
15 ms	.99	.97	.95
20 ms	.99	.99	.98
30 ms	.99	1	.96
40 ms	.99	1	.97

3.3.8 Figures

Figure 3-5: The frequency spectrum of the filler noise. A broadband noise was bandpass filtered with a centre frequency of 4 kHz. This noise was presented continuously to the same ear as the stimulus.

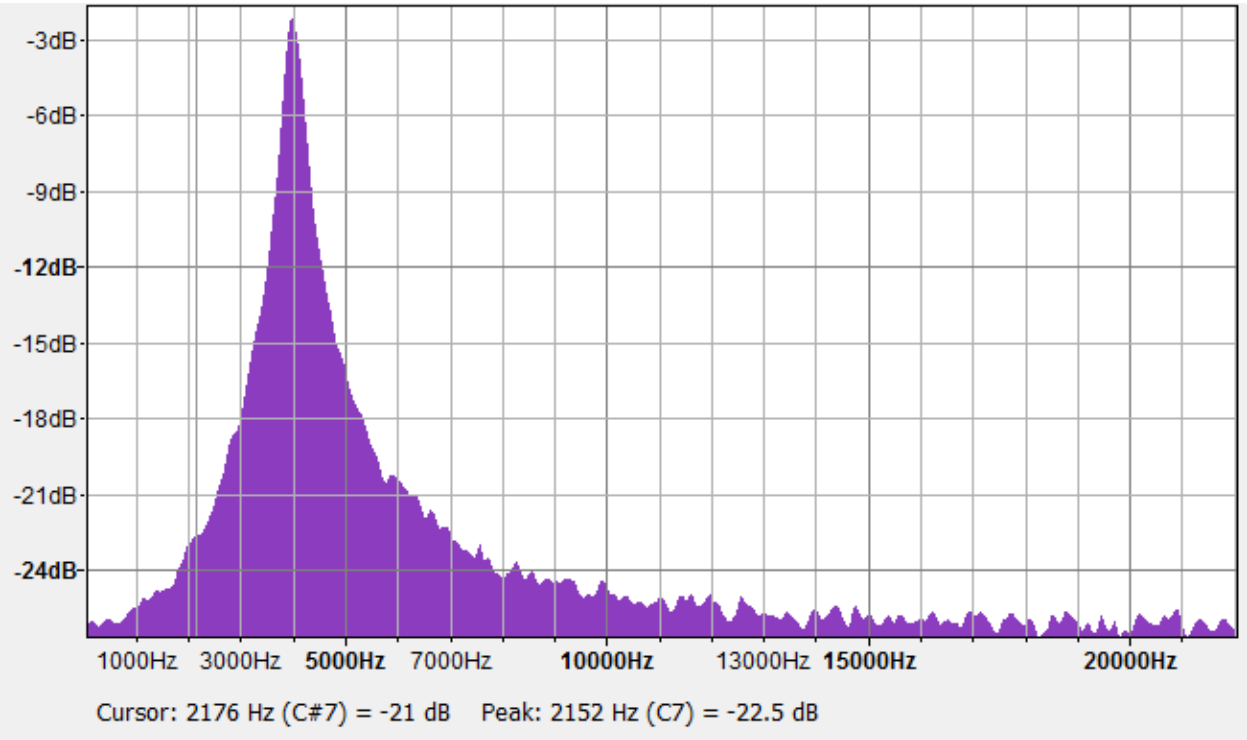


Figure 3-6: Standard ERPs to the three filler noise conditions. An N1-P2 waveform is seen as a small negative-going deflection at about 100 ms is followed by a positivity at about 150 ms. The amplitude of the N1 and P2 were significantly different for the high filler condition compared to the low and no filler conditions ($F(2,28)=17.73$, $p=.00$). A second negativity can be seen at about 135 ms following the offset of the stimulus where it was significantly larger in the no filler condition than the other conditions ($F(2,28)=3.94$, $p=.03$).

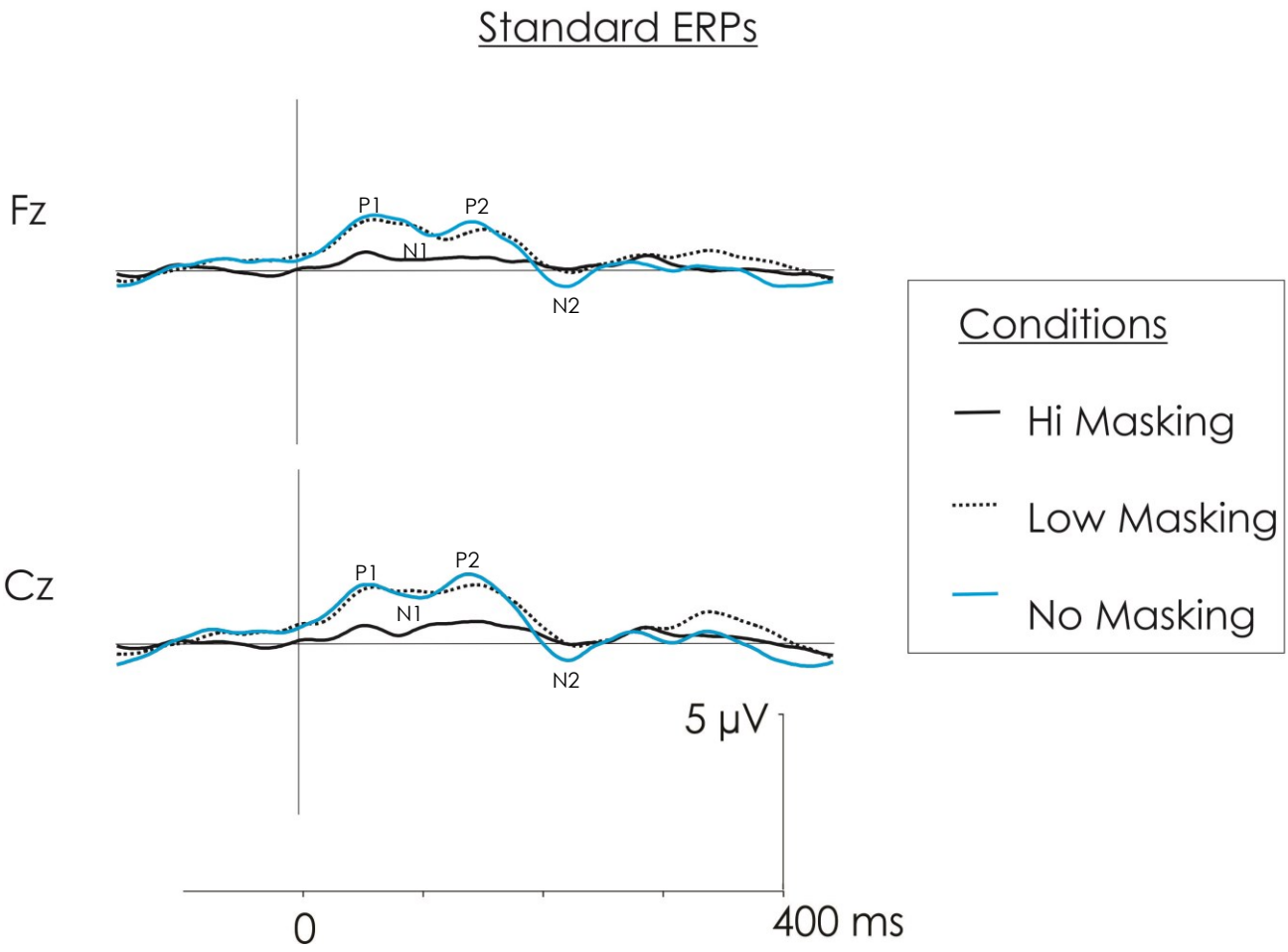
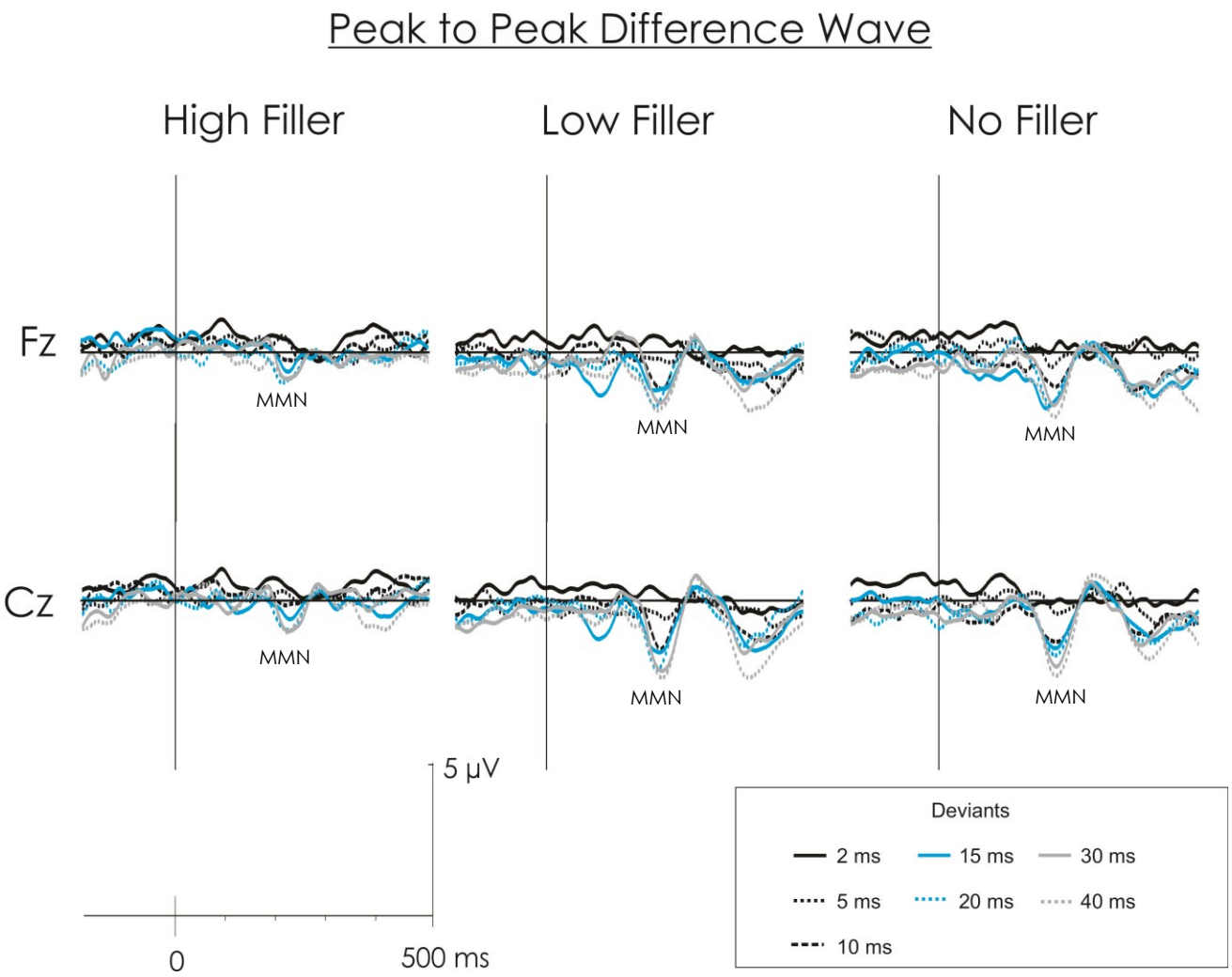


Figure 3-3: Peak to peak (MMN to P3a) waveforms in the high filler noise condition at the Fz and Cz electrodes. The deflection expect at around 200 ms is not visible. Amplitude deflection of

the MMN increases with longer gap durations in a monotonic pattern. The filler noise reduces the amplitude of the MMN.



3.3.9 Conflicts of interest

The authors do not have any known conflict of interest associated with the publication of this article.

3.3.10 Acknowledgements

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Article 4: The effects of tinnitus on mismatch negativity responses to gaps in noise

This final study piloted the effect of tinnitus perceived by a normal-hearing group on the amplitude of the MMN elicited by gaps. The methodology used in this study was identical to Article 3 which tested the effects of a filler noise on gaps. In this study, the tinnitus was perceived around 3-4 kHz and was presented in the presence and absence of the filler noise. In the absence of the filler noise, the effect of tinnitus was tested and the amplitude of the MMN was compared to the normal-hearing non-tinnitus group from Article 3. In the presence of the filler noise, the effect of masking was a secondary effect that was tested and compared with the non-filler condition. Given that this was a pilot study conducted on a small sample, conclusions were cursory. Nonetheless, the effects of tinnitus and masking shown are indicative of the potential use of the MMN as a biomarker of auditory capacities in populations with hearing impairment.

3.4 Article 4: The effects of tinnitus on mismatch negativity responses to gaps in noise

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3.4.1 Abstract

Objective: Gap detection has been a standard approach for measuring tinnitus in animal models as subjective tinnitus is believed to “fill in” silent gaps in noise. Yet human behavioural data has shown tinnitus does not alter gap detection. To better understand the inconsistent evidence, auditory event related potentials (ERPs) and behavioural measures were obtained for gapped stimuli in healthy normal hearing participants (simulated tinnitus) and in participants with subjective tinnitus.

Methods: Mismatch negativity (MMN) responses and behavioural accuracy rates were measured in five tinnitus and five healthy control participants using stimuli with silent gaps ranging from 2 to 40 ms. The optimised MMN paradigm was recorded from 32 scalp electrodes in three conditions of high, low and no intensity filler noise. Grand average MMN amplitudes were obtained at each gap duration and compared to behavioural accuracy rates for the control and tinnitus groups.

Results: The grand average MMN amplitudes obtained in the tinnitus participants were significantly lower than the normal hearing participants for all supra-threshold gap durations in all filler conditions. The amplitude of the MMN increased with wider gap durations in participants with normal hearing but not tinnitus. Thus the pattern of MMN responses appeared to have a "disorganized" representation of the gap for the tinnitus group. These changes were not reflected in the behavioural data as the accuracy of gap detection was not significantly different between the two groups in the three filler conditions.

Conclusions: The MMN responses to gaps in noise may be a more sensitive for measuring gap detection impairments than behavioural measures. Future studies on gap detection in tinnitus populations or other populations with functional difficulties related to temporal resolution, such

as hearing in noise difficulties, may benefit from using the MMN to further understand its related underlying mechanisms.

Keywords: Tinnitus, gap detection, temporal resolution, mismatch negativity, event related potentials, electrophysiology.

3.4.2 Introduction

Tinnitus is a sound experienced in the absence of external acoustic stimulation. It is often associated with exposure to noise and hearing loss (Kreuzer et al., 2012). There is no objective measurement of tinnitus which makes it difficult to diagnose especially in special populations like children or those with psychological or psychiatric disorders. Previous studies have used gap detection on tinnitus animal models as a standard practice (Dehmel et al., 2012; Koehler and Shore, 2013; Kraus et al., 2010; Ralli and Lobarinas, 2010). This was based on a pioneering paper by Turner et al. (2006) demonstrating that gap detection was impaired in mice exposed to noise who subsequently developed a notched hearing loss at 16 kHz. This finding led to the hypothesis that tinnitus "filled in" silent gaps in noise thus elevating the individual's gap detection threshold.

Following this discovery, a number of human studies attempted to replicate these findings with various degrees of success. In Fournier and Hébert (2013), gap detection was measured using myogenic recordings of the startle reflex. Participants with tinnitus were exposed to a background noise with a loud startling sound following an inserted silent gap. The loud sound was expected to elicit a maximal startle response when there was no gap heard to caution its onset. As such, the gap acted as a warning to the subject of the startling noise and inhibited the startle response. The authors concluded the tinnitus "filled in" the gap since the startle response was less inhibited compared to the non-tinnitus participants –similar to the Turner et al. (2006) findings. In other words, the amplitude of the startle response was larger in the tinnitus participants. The tinnitus participants were likely unable to detect the gap as well as the non-tinnitus participants which was likely the reason for the inability to inhibit the startle response. Behavioural gap detection was studied in people with tinnitus where gaps were inserted in a

background noise and participants were asked to press a button when a gap was heard (Campolo, Lobarinas, & Salvi, 2013; Boyen, Baskent, & van Dijk, 2015). Contrary to the startle reflex, the behavioural studies, they did not find significant differences between the gap detection of those with tinnitus compared to those without tinnitus.

This pilot study expands on the previous investigations of gap detection on populations with tinnitus by using event-related potentials (ERPs). ERPs are small electric voltages that are measured from the scalp of the head using surface electrodes. These voltages are elicited by an acoustic stimulation. Multiple components of the ERP have been studied for neural gap detection such as the N1 (Lister, Maxfield, & Pitt, 2007; Atcherson et al., 2009; Palmer and Musiek, 2013, 2014; Pratt et al., 2005; Harris et al., 2012; He et al., 2013; Ross et al., 2010), and the MMN (Heinrich et al., 2004; Pihko et al., 1997; Desjardins et al., 1999). Both of these measures are believed to be indicators of change in the acoustic signal, the N1 is believed to be indicative of the transient response to a sound and the MMN is believed to be the response to a feature of a sound (Näätänen, 1990). The N1 has been found to be affected by attention factors but the MMN has been found to be independent of fatigue or sleepiness (see Campbell & Colrain, 2002 for a review).

Studies on neural gap detection using the MMN have demonstrated that using the oddball paradigm, a supra-threshold gap can elicited an MMN (Bertoli et al., 2001; Todd et al., 2011; Yabe et al., 2005). Bertoli, Smurzynski & Probst (2002) introduced short gaps in noise of various lengths (3, 6, 9 and 15 ms) in an oddball sequence to elicit an MMN. The authors found that the larger the gap duration corresponded to a larger amplitude of the MMN up to a ceiling level. The MMN has also been shown to vary in amplitude depending on where it is placed within the

stimulus (Yabe et al., 2005), the intensity of the stimulus (Article 2) and/or whether the gap is partially filled with another stimulus (Tamakoshi et al., 2016; Article 3).

Neural gap detection to various gap sizes has not been measured using the MMN in populations with tinnitus. A couple of studies using the multi-feature optimised paradigm showed an MMN can be elicited by a 7-ms gap (Mahmoudian et al., 2013a, 2015). Mahmoudian et al. (2015) demonstrated that tinnitus participants with positive residual inhibition, a phenomenon where the tinnitus intensity decreases after exposure to auditory stimulation, had reduced MMN amplitudes to the 7-ms gapped deviants. Since literature shows gapped stimuli with filler noise (Tamakoshi et al., 2016) and positive residual inhibition in tinnitus (Mahmoudian et al., 2015) can reduce the amplitude of the MMN, this study compares both effects on multiple gap durations. It is expected based on the "fill in" hypothesis that, in the absence of background filler noise, the tinnitus group would have reduced perception of the gap compared to controls. This would be reflected in a smaller MMN amplitude for supra-threshold gaps. For the low and high filler noise conditions, it is expected that the subjects would experience residual inhibition which would reduce the perception of the tinnitus and make the gaps more noticeable. This would be seen as recovered MMN amplitudes that would be larger in the tinnitus group than in controls.

3.4.3 Methods

3.4.3.1 Participants

Five participants (4 males and 1 female) between the ages of 20 and 40 were studied (mean = 30, SD = 8.4). Hearing thresholds were in the normal range bilaterally (all measured at or below 25 dB HL). All participants had reported tinnitus and a history of noise exposure. Participants had no history of ontological or neurological problems. Tinnitus perception was

measured using pitch-matching and intensity matching procedures to determine the predominant level and frequency of the percept. Table 4-1 shows the pitch and intensity levels measured for each participant as well as the reported side of the tinnitus perception. The five normal hearing non-tinnitus participants were taken (at random) from our previous study (Article 3) for comparisons with the tinnitus data.

3.4.3.2 Electrophysiological recordings

The same electrophysiological techniques were used as in our previous work (Article 3). All participants were presented with a continuous standard at 80 dB SPL with a duration of 200 ms. The deviants differed from the standard only with an inserted gap placed in the middle of the stimulus using one of seven gap durations: 2, 5, 10, 15, 20, 30 and 40 ms. The sequence of the standard and the deviants were presented to the right ear using an optimised paradigm (Näätänen et al., 2004). A total of three noise conditions (high, low and no filler noise) were presented ipsilateral to the gapped stimulus. The sequence was presented three times within each condition. All filler noise conditions used a narrowband noise centered at 4 kHz and played continuously throughout the sequence of standards and deviants (see Article 3). The high filler noise condition presented the noise at 80 dB SPL, the low condition was set to 60 dB SPL and the no filler condition was in the absence of noise.

3.4.3.3 Behavioural testing

The same behavioural testing was used as Article-3. The participants were asked to press a button when they heard a gap in the stimulus. A practice sequence was used to familiarize the participants to the task. All conditions were presented to the subject once for each behavioural testing. Accuracy rates were recorded for each condition as a function of gap duration.

3.4.3.4 Quantification and statistical analysis

Quantification for the MMN were conducted in the same way as our previous work (Milloy et al., submitted; Article 2; Article 3). All EEG data was recorded from 32 silver/silver chloride active electrodes (ActiCap, BrainProducts, Germany) placed on the frontal (Fz), central (Cz), parietal, temporal and occipital portions of the scalp. All statistical analyses were employed on the peak to peak amplitude measurement of the MMN at the frontocentral electrodes with known maximal amplitudes of the MMN: the Cz and Fz electrodes. This was chosen because previous work (Article 2; Article 3) showed the MMNs were maximum at this channel. A three-way repeated measures ANOVA was used to calculate the effect of group (tinnitus and non-tinnitus), condition (high, low and no filler) and gap (2, 5, 10, 15, 20, 30 and 40 ms) on the MMN amplitude. To compare the MMN amplitudes within the tinnitus group, a two-way ANOVA with measures on conditions (high, low and no) and gap duration (2, 5, 10, 15, 20, 30 and 40 ms) were calculated. All ANOVAs were adjusted for possible sphericity violations using the Greenhouse-Geisser correction. When any significant differences were found, a post-hoc Fisher's Least Significant Difference (LSD) test was computed. One-tailed t-tests were calculated for each condition between the behavioural accuracy rates and the MMN amplitude of the tinnitus group. One tailed t-tests were chosen as it was expected the MMN amplitude would increase with higher accuracy rates.

3.4.4 Results

3.4.4.1 Peak to peak measures in the high, low and no filler conditions for the tinnitus participants

The peak to peak measures in the high, low and no filler conditions for tinnitus participants were evaluated using a two-way repeated measures ANOVA at the Cz electrode. A significant effect of gap was found, $F(6,24)=2.95$, $p=.03$, $\eta_p^2=.42$. Post-hoc testing showed the MMN amplitude significantly increased with the duration of the gap for all suprathreshold gaps

except for 40 ms. This can be seen in figure 4-1. However, there was no significant effect for condition, F(2,8)=2.21, p=.17, nor was there a significant interaction between condition and deviant, F(12,48)=.37, p=.97.

3.4.4.2 Comparisons between the MMN amplitudes and the behavioural accuracy rates for the tinnitus and normal hearing participants

A three-way repeated measures ANOVA was conducted on the tinnitus participants and the five normal hearing participants from our previous study (Article 3). There was a main effect of group (F(1,8)=51.1, p=.0001, η_p^2=.28) as the tinnitus group had significantly smaller MMN amplitudes than the controls. A significant interaction was found for gap and group (F(6,48)=4.23, p=.002, η_p^2=.35). This interaction means that the MMN amplitude changed as a function of gap differently for the tinnitus group compared to controls. This may be indicative of the low filler noise reducing the 40-ms MMN amplitude more in the tinnitus group than the controls. There were no main effects found for the condition, F(2,16)=.27, p=.77, or deviant, F(6, 48)=.84, p=.54. There were no significant three-way interactions, F(12, 96)=1.24, p=.27, or two-way interactions between group and condition, F(2,16)=1.33, p=.29, or conditions and gaps, F(12,96)=.81, p=.64.

3.4.4.3 Behavioural accuracy rates of the filler conditions for the tinnitus participants

The accuracy rates of the tinnitus participants are shown in table 4-2. The accuracy of correctly detecting 2-ms gaps was very low for all three conditions. Gap durations of 5 ms were detectable in the no- and low-filler noise conditions but not high. The accuracy reached a ceiling level for all supra-threshold gaps above .8, in all three conditions. Detection accuracy to the standard stimulus had a rate of approximately 20% false positives.

3.4.4.4 Comparisons between groups for the behavioural accuracy and the MMN amplitude

Independent samples, one-tailed t-tests were conducted for each gap duration between the tinnitus and control groups. It revealed significantly smaller MMN amplitude for the tinnitus

group for all supra-threshold gaps at 15 ms (high: t(8)=3.03, p=.02, no: t(8)=2.47, p=.04) and above for the high- and no-filler noise conditions with the exception of 40-ms gaps in the high condtion (t(8)=1.25, p=.25). For the low-filler noise, the significant amplitude differences were found for 10-ms gaps (t(8)=2.59, p=.03) and above.

3.4.5 Discussion

These preliminary results show that tinnitus has an effect on the MMN amplitude elicited by gaps in noise both in filled and unfilled background noise conditions. The differences in the tinnitus group were demonstrated by 1) smaller MMN amplitudes for all supra-threshold gaps in the tinnitus group, and 2) a change in the relationship between the MMN amplitude and gap duration for the noise conditions.

The tinnitus group had smaller MMN amplitudes for the supra-threshold gaps in all the noise conditions. This was expected as Mahmoudian et al. (2013b) found that tinnitus participants with positive residual inhibition had significantly smaller MMN amplitudes for 7-ms gaps. The results of this study compliment the tinnitus results as the MMN amplitude was reduced for all supra-threshold gaps but not for narrow gaps of 5 or 2 ms durations. In the Näätänen model (1990; 1992), the MMN is believed to assocated with a memory system that compares incoming stimuli with a memory trace of preceeding stimuluations. It is expected that the auditory system would have detected a change from the memory trace thus eliciting an MMN. In the case of the tinnitus subjects, there may be a reduced ability to detect this change (i.e. the gap) which would reduce the amplitude of the MMN.

The gap “fill-in” hypothesis (Turner et al., 2006), which states that tinnitus can “fill-in” the gaps in a stimulus making it more difficult to detect, could explain the change in MMN amplitude. It would be implied that the behavioural gap detection thresholds in the tinnitus group

would be elevated compared to the controls. However, our behavioural threshold for the tinnitus group was equal to the threshold of the control group (5 ms). This was consistent with previous studies showing the psychoacoustic gap detection in tinnitus patients are similar to controls. In one study, the gap detection thresholds was measured at less than 15 ms and did not differ between the tinnitus and non-tinnitus partcipants, even when they were separated into various intensity and frequency groups (Boyen, Baskent, & van Dijk, 2015). Another study showed the detection of a 50-ms gap at frequencies matched and unmatched from the tinnitus pitch were also not significantly different from the controls (Campolo, Lobarinas, & Salvi, 2013).

If tinnitus were to "fill-in" the gap then it would be expected that the narrowband noise in our previous work (Article 3) would have a similar effect on controls as the tinnitus group in this study. This was not the case. The MMNs were smaller in amplitude for the both noise filler conditions for the tinnitus group. The MMN amplitude may be altered by hidden to peripheral changes in the auditory nerve that are feeding to the cortical representations of the gap. Although all the subjects had audiometrically normal hearing thresholds, deafferentation of the auditory nerve known as hidden hearing loss (Schaette and McAlpine, 2012) may feed inaccurate temporal information to the higher-order structures of the auditory system. This may affect the change-detection system modelled by Näätänen et al. (1990, 1992). Auditory fibers that are particularly susceptible to damage in cases of noise-exposure are the low spontaneous rate fibers that are particularly important for coding information in noisy environments (Bharadwaj et al., 2014). Damage to the low spontaneous-rate fibers can be particularly noticeable in conditions with continuous noise since the high spontaneous rate fibers are occupied and cannot synchronize to temporal envelope changes (Costalupes et al,. 1984; Joris and Yin, 1992). This may explain the reduction of the amplitude of the 40-ms duration gap for the noise conditions.

Animal data have shown monotonic (linear) patterns of amplitude to duration of the gap at the level of the auditory nerve and a non-monotonic (non-linear) pattern at the dorsal and ventral cochlear nucleus (Kaltenbach et al., 1993; Shore, 1995). Shore (1995) related the change in pattern to the response rate of the high spontaneous rate fibers compared to the low spontaneous rate fibers. Indeed damage to the low spontaneous rate fibers has been related to noise exposure as well as cochlear synaptopathy (Kujawa and Liberman, 2006, 2009) thus it is possible that the non-linear amplitude response to the wide gaps is an indicator of hidden peripheral damage.

Given that the behavioural gap thresholds were not different between groups, it appears the reorganization of the gap durations related to MMN amplitudes does not have perceptual implications. The behavioural gap detection may be insensitive to peripheral cochlear damage. Jesteadt et al. (1976) found that hearing impaired ears could have better gap detection than normal subjects when the stimuli were presented at sufficiently loud levels. This suggests that the MMN amplitudes compared between the tinnitus and normal hearing groups are more sensitive to differences than the behavioural measures alone.

3.4.6 Conclusion

This pilot data demonstrates that MMN amplitudes measured to gapped stimuli may be an effective tool for studying populations with tinnitus. These results show that participants with tinnitus have reduced MMN amplitudes for supra-threshold gaps compared to normal hearing participants even though the behavioural accuracy rates do not significantly differ. Based on these findings, further exploration into the MMN measures of other populations with known difficulties in temporal processing or hearing in noise would further provide information on the mechanisms involved hearing difficulties.

3.4.7 Tables

Table 4-1: Psychometric characteristics of the tinnitus perception. The pitch and intensity of the tinnitus perception was measured using pitch and intensity matching techniques. The pitches of the tinnitus ranged from 750 to 4000 Hz with an intensity from 15 to 55 dB. Tinnitus was perceived either at the right ear only or in both ears.

Participant	Pitch (Hz)	Intensity (dB HL)	Tinnitus ear
1	750	15	right
2	3000	45	both
3	4000	55	both
4	2000	45	right
5	3000-4000	35	right

Table 4-2: Behavioural accuracy rates for the tinnitus group in the high, low and no filler noise conditions. The standard accuracy rate shows a false positive rate of 19 to 15%. The accuracy for detection 2-ms gaps was very low. Participants were able to hear gaps above 5 ms in all three conditions.

	Accuracy		
	No	Low	High
Stan	0.83	0.85	0.81
2 ms	0.12	0.12	0.13
5 ms	0.84	0.83	0.25
10 ms	0.94	0.87	0.8
15 ms	0.89	0.85	0.84
20 ms	0.95	0.84	0.87
30 ms	0.91	0.83	0.86
40 ms	0.91	0.82	0.81

Table 4-3: Mean peak to peak amplitudes of tinnitus participants (n=5) in the three filler noise conditions at the Cz electrode. Standard deviations are in parentheses.

Deviant	Condition	Amplitude (μV)
2 ms	No	-.17 (.83)
	Low	.11 (.86)
	High	-.06 (51)

5 ms	No	-.17 (.63)
	Low	.01 (.40)
	High	-.17 (.46)
10 ms	No	.59 (.69)
	Low	.41 (.43)
	High	.25 (.81)
15 ms	No	.36 (1.15)
	Low	.65 (.57)
	High	-.04 (.28)
20 ms	No	.30 (.59)
	Low	.60 (.57)
	High	.50 (.44)
30 ms	No	.73 (1.22)
	Low	.72 (.66)
	High	.29 (.36)
40 ms	No	.59 (.94)
	Low	.68 (.78)
	High	-.01 (.90)

3.4.8 Figures

Figure 4-7: The MMN amplitudes of tinnitus (n=5) and normal hearing non-tinnitus subjects (n=5) for three filler noise conditions were measured at the Cz electrode. Seven gap durations were presented within the stimulus and a grand average waveform was obtained for each gap

duration. The tinnitus MMN amplitude was significantly lower for all conditions at all gap durations compared to controls.

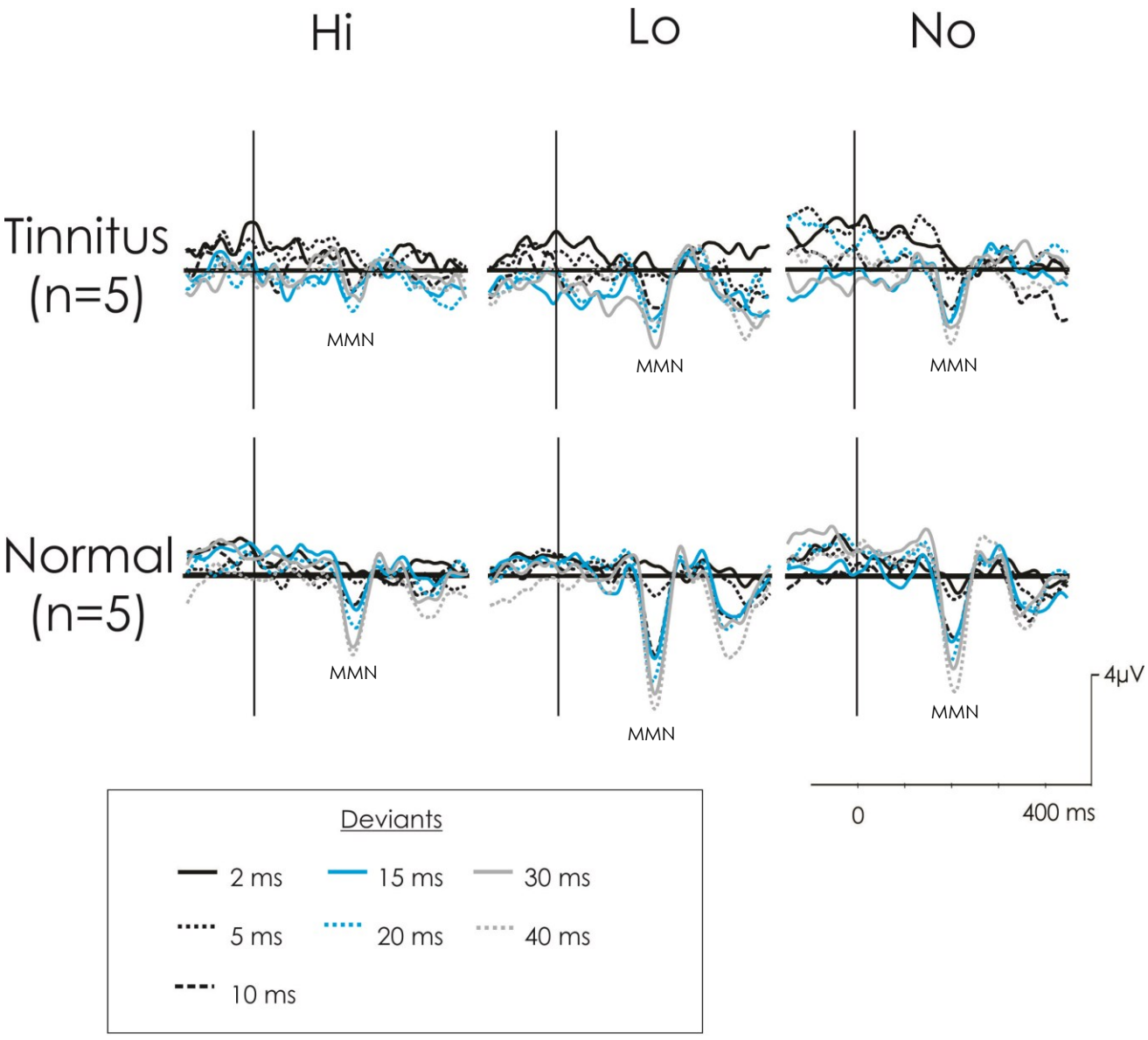
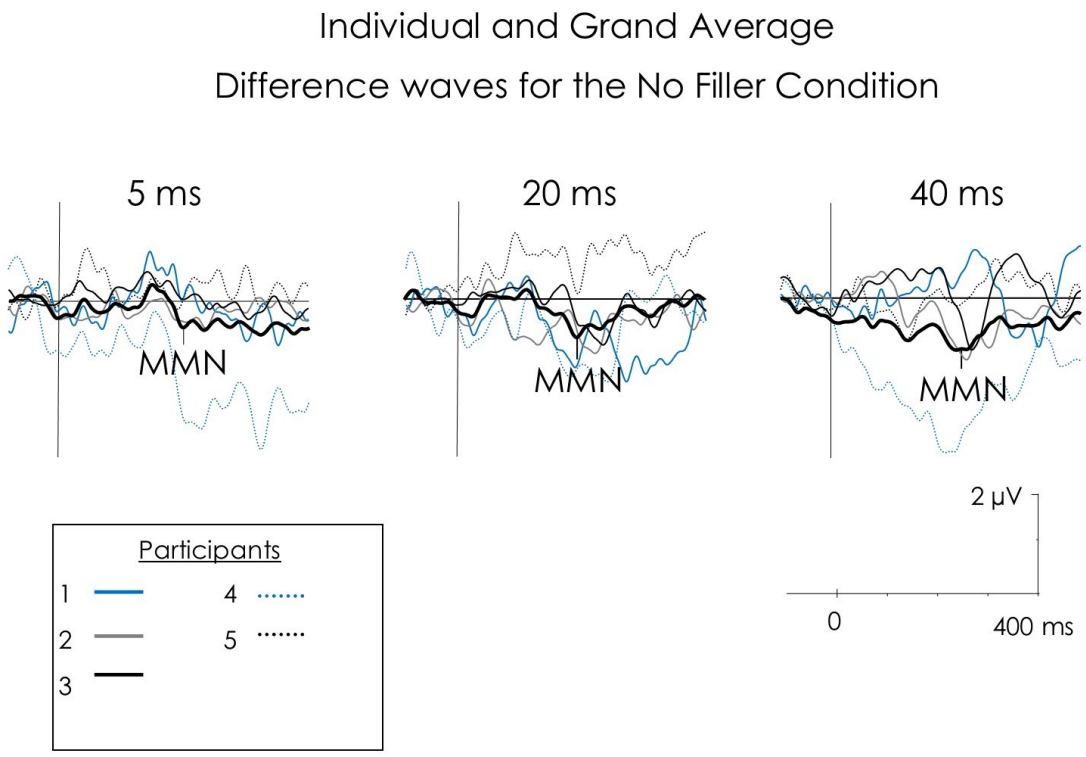


Figure 4-8: The individual and grand average difference waves of tinnitus (n=5) for the no filler noise condition at the Cz electrode. The 5, 20 and 40 ms gap durations are presented as an example of the individual variation around the average. The grand average difference wave is

shown with a thick solid line



3.4.9 Conflicts of interest

The authors do not have any known conflict of interest associated with the publication of this article.

3.4.10 Acknowledgements

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4 CHAPTER 4: General discussion

4.1 The detection of gaps in adults with noise-induced tinnitus

The main goal of this thesis was to determine the feasibility of using the MMN as a measure for detecting neural gap detection in a sample with reported tinnitus. This was generally achieved by demonstrating that neural gap detection can be measured using the MMN amplitude on a tinnitus sample. This thesis demonstrated that the traditional MMN paradigm can be made more time-efficient by applying a multi-deviant protocol to present various gap durations. In using this multiple-deviant method, six different gap durations could be presented within a single sequence. This was an improvement on the traditional method which allowed for a single gap duration to be presented at a time. The thesis also demonstrated that reducing the bandwidth and the intensity of the stimulus reduced the amplitude of the MMN, however with adjustments to the analysis of the MMN waveform by using a mastoid reference and a peak-to-peak measure, that the gap duration and amplitude relationship is maintained. Finally, the thesis demonstrated that the MMN elicited by gaps can be used on populations with simulated and real tinnitus of varying intensities. This allowed for an electrophysiological exploration of the "fill-in" hypothesis by determining whether tinnitus "fills in" the silent intervals in a stimulus. It was expected that if the gap would be filled and no silent interval could be detected, that the MMN amplitude would be reduced. This was indeed the case for both the noise-filled and the tinnitus-filled conditions.

Attention can have the effect of focusing the auditory system to one stimulus more than another due to cognitive biases (Andersson and McKenna, 2006) and this has been shown to effect gap detection (Salloum et al., 2016). Another variable is the effect of noise-induced hearing loss which can give rise to impairments of temporal resolution mechanisms at the

cellular level (Sturm et al., 2017) but not necessarily at the functional level (Jesteadt et al., 1976). Hearing loss in the form of cochlear deafferentation has also been shown to effect the temporal coding of sound in the absence of audiometric threshold shifts (Bharadwaj et al., 2015). This means that even tinnitus and non-tinnitus groups with audiometrically "normal" hearing may show differences in objective gap detection (ex. electrophysiological or startle reflex recordsings) that behavioural recordings are unsensitive to.

Studies showed the startle reflex is reduced in subjects with tinnitus matched to a gapped stimulus (Fournier and Hébert, 2013; Turner et al., 2006) however hearing loss and attention may confound these findings. The MMN measure can be used as an alternative gap elicited measure since it is elicited passively similar to the startle reflex. The N1 and Auditory Steady State Responses (ASSR, a brainstem response) has previously shown amplitude changes in tinnitus participants with positive residual inhibition (Roberts et al., 2015). However unlike the N1 or ASSR, the MMN is elicited independent of attention and sleep deprivation (Muller-Gass et al., 2006; Zerouali, Jemel & Godbout, 2010; Bortoletto et al., 2011). This is likely because the MMN is calculated from a difference wave which eliminates any factors that would be equivocally applied to both the standard and deviant stimuli.

The series of studies presented in this thesis showed that by optimising the mismatch negativity test for neural gap detection in terms time efficiency and stimulus intensity and bandwidth, this method could be used to test the "fill-in" hypothesis. The following sections discuss the behavioural and electrophysiological results and their relationship based on the four studies presented in this thesis.

4.2 Behavioural measures

In order to replicate previous behavioural studies, gap detection was measured behaviourally using either a broadband or a narrowband noise. The broadband noise stimulus was identical to the stimulus used for eliciting the MMN in Article 1. This allowed for a direct comparison between the behavioural detection of a gap and the amplitude of the MMN. Indeed, the MMN amplitude appeared to be largest for the gap widths that the subject was able to detect (i.e. suprathreshold gaps). In a similar fashion, the behavioural measures of gap detection using a narrowband stimulus were identical to the stimulus used for the MMN measures in Articles 3 and 4. Again, this showed that the MMN amplitude was largest for the gaps that were perceived by the subjects. Generally, when the gaps were sufficiently large, they were behaviourally detectable by the participants for both the narrowband and broadband stimuli.

4.2.1 Behavioural gap detection using a broadband noise

Behavioural gap detection was measured in normal hearing adults using a gapped broadband (white) noise. The gap detection accuracy was very high for the largest gaps (20, 30 and 40 ms) and the threshold (at an accuracy of 0.5) was 5 ms. Very few 2-ms gaps were detected. Young adults can detect gaps as narrow as 3 to 5 ms when presented in moderate intensity white noise (Moore, 1997; Samelli and Schochat, 2008). However this requires that the participants maintain active participation and attention for long periods of time. This may be a problem since fatigue can set in and cause various cognitive and perceptual biases (Andersson and McKenna, 2006). The gap detection threshold found in Milloy et al. (submitted) is supported by the literature in that the participants appeared to have an average threshold of 5 ms. However, some participants had a slightly higher threshold of 10 ms. This may mean that there is some variability that may be subject to various other factors that are not controlled such as attention,

cognitive biases and undetectable hearing loss (i.e. “hidden” hearing loss). These issues that may be what make the behavioural measure of gap detection less sensitive to the effects of tinnitus.

4.2.2 Behavioural gap detection using a narrowband noise in the presence of a filler

Behavioural gap detection was also measured in normal hearing participants using a narrowband noise centered at 4 kHz in the presence of a high and low intensity noise filler. The gap detection threshold was 5 ms for the no and low filler conditions at an accuracy rate of .66 and .69 but in the high filler condition, this decreased to .18. The high filler condition increased the behavioural gap duration threshold to 10 ms. The literature supports this finding showing that filling the gap reduces the behavioural accuracy (Tamakoshi et al., 2016; Badri, Siegel & Wright, 2011). However neither study manipulated the levels of filler beyond 60 dB SPL. In Article 3, only the high-filler condition of 80 dB SPL reduced the accuracy of gap detection but not the low. This may mean that the central auditory system maintains gap detection accuracy with low filler noise up to a maximum filler level. Above this maximum level (i.e. 80 dB SPL) the gap detection threshold increases which may be an indication of a loss of temporal coding. This change in temporal coding can be captured and measured using the amplitude of the MMN (see section 4.3).

4.2.3 Behavioural gap detection in the presence of tinnitus

In Article 4, behavioural gap detection was measured in 5 participants with normal hearing and known subjective tinnitus. These participants were selected and tested only in the fourth study and were not a part of the population tested in any of the previous articles in this thesis. The gap detection threshold for this tinnitus group was 5 ms for the no- and low-filler conditions and 10 ms for the high-filler condition. These thresholds were the same as the non-tinnitus group in Article 3. This is supported by previous literature showing that behaviourally

there is no difference between the gap detection abilities of the tinnitus groups compared to the normal hearing individuals (Boyen, Baskent, & van Dijk, 2015, and Campolo, Lobarinas, & Salvi, 2013). In the Campolo study, they used a 50-ms gap inserted into frequency matched stimuli at 15 dB above the threshold of the tinnitus. Boyen, Baskent, & van Dijk (2015) also did a behavioural gap detection method and showed that at three intensity levels the gaps did not appear to be different from the normal hearing participants. The null results of the two gap detection tinnitus studies provide evidence that there is indeed no difference between the tinnitus and normal participants. This means that tinnitus does not appear to effect the behavioural detection of gaps. Higher-order cognitive compensatory mechanisms such as the reorganization of the auditory pathways that make the system more sensitive to changes in temporal cues. Tonotopic maps reorganize at the level of the primary cortex in cats with hearing loss (Eggermont and Komiya, 2000). Article-4 shows that filler does not appear to improve the gap detection abilities of the tinnitus participants on a behavioural level contrary to what the "residual inhibition" hypothesis would suggest. Recall that the residual inhibition hypothesis states that noise filler reduces the perception of tinnitus; therefore, if tinnitus "fills" in the gap then it would be presumed that the gap detection threshold would improve in the presence of filler. However, the filler appeared to have a similar effect on the gap detection abilities as in the normal hearing group (i.e. the high filler condition appeared to impair gap detection in both groups).

4.3 Electrophysiological measures

4.3.1 Electrophysiological gap detection using the optimised paradigm

In our first study (Milloy et al., submitted), the optimised paradigm was found to be more time efficient than the oddball and both were successful in revealing MMNs that change in

amplitude as a function of the duration of the gap. Previous oddball studies showed that larger gaps elicited larger MMNs (Bertoli, Smurzynski, & Probst, 2002). However, the oddball paradigm is very time-consuming and limits the number of gaps that can be measured in a single testing session, making it less ideal for clinical applications where time efficiency is valued. Still, there was a concern that the optimised paradigm was originally designed to be used with deviants of different features. For example in Mahmoudian et al. (2013), the deviant stimuli differed from the standard by changing various features: a silent gap, a shorter duration, a lower intensity, a higher or lower bandwidth and a change in latency. In this thesis, the deviants were different from the standard by only a single feature: gap duration. Despite this change, the optimised methodology produced similar scalp topographies to the oddball with a negativity at the fronto-central region and inversed polarity at the mastoids. The changes of the MMN amplitude as a function of the gap duration were also similar, however the time was reduced from 90 minutes for three gap durations with the oddball to 30 minutes for six gap durations with the optimised sequences. This provided evidence that the time-efficient optimised paradigm could be used with gapped stimuli without compromising the integrity of the MMN.

4.3.2 Electrophysiological gap detection and the effect of intensity changes

In the second study (Article 2), the optimised paradigm was tested again with two important changes to the stimulus: a narrower bandwidth and lower intensity. This was done in order to later apply the optimised technique to the tinnitus "fill-in" hypothesis which requires that the signal be presented at the same frequency as the tinnitus percept and at a level that is comfortable for the patient. Since patients with tinnitus often present with hyperacusis (Hébert, Fournier, & Noreña, 2013), they may find the high stimulus presentation level intolerable. Our results showed that gaps inserted in a narrower bandwidth (Article 2) still elicit strong MMN

amplitudes that follow the same effect of gap duration as with the broadband stimulus (Milloy et al., submitted). Still, lowering the intensity of the stimulus (Article 2) made the MMN less visible even for channels where its amplitude is typically maximum (the Fz and Cz). This was similar to recent work showing the reduction of the N1 to decreasing intensity levels of a narrowband gapped stimulus centered at either 5 or 10 kHz (Paul, Schoenwiesner and Hébert, 2018). Another study showed that signal level changes the amplitude of the MMN when the standard and deviants differed by stimulus length (Paavilainen et al., 1993). Complementing these previous works, Article 2 showed the effect of intensity on the MMN amplitude also applies to gapped stimuli. The higher intensity gapped stimuli elicited significantly larger MMN amplitudes compared to lower intensity stimuli. Additionally previous studies do not show whether the lower intensity retains the positive effect of amplitude to gap duration. The results of Article 2 showed higher and lower intensity stimuli both elicited MMN amplitude changes as a function of gap duration.

The second study was also important for the point we raised in the introduction about separating the possible effects of hyperacusis on the detection of gaps. Recall that a recent study showed hyperacusis may enhance the acoustic startle stimulus and increase the suppression of the startle response (Salloum et al., 2016). This may mean that using the GPIAS in mice or humans may be elicited by an abnormal perception of loudness instead of tinnitus. However in the case of the MMN, Article 2 shows that intensity has an overall positive effect on the MMN amplitude to the duration of all the gaps (i.e. increasing the intensity would increase the MMN amplitude). We hypothesized that tinnitus would impair neural gap detection by filling in the gap and decreasing MMN amplitude, therefore hyperacusis could not explain the decrease in MMN amplitude shown in the tinnitus group in Article 4.

4.3.3 Electrophysiological gap detection and the effect of filler noise

In the third study (Article 3), the amplitude of the MMN was measured in three conditions where the filler noise was either high, low or absent. This study was important for determining if the tinnitus "fill-in" hypothesis held for the electrophysiological measurement of gap detection. If the "fill-in" hypothesis was supported, then the noise filler would 1) decrease the amplitude of the MMN and 2) present the same response to gaps as a small pilot group of tinnitus subjects. The results support the first claim. The filler noise presented with the stimulus significantly decreased the amplitude of the gap-elicited MMN. This was similar to Tamakoshi et al. (2016) where filled gapped stimuli presented in an oddball sequence elicited MMNs with smaller amplitudes than unfilled gaps. This change was not reported to be significant however it may be due to measuring the MMN at a filler intensity based on a sensation level which could vary with according to the thresholds of the participants. As seen in Article 2, presentation level can change the amplitude of the MMN. It was also presented at a lower frequency which can impair the detection of gaps due to "ringing" of the basilar membrane for the lower frequency cochlear filters (Carlyon, 1988).

Article 3 expands on this literature by presenting evidence that high intensity filler noise reduced the amplitude of the MMN as well as the N1 to a greater extent than the low and no filler conditions. Recall the N1 deflection is elicited by either the onset or offset of the stimulus (see Näätänen and Picton, 1987 for a classic review). This contrasts with the MMN which is elicited by a change detection in the stimulus (Näätänen, 1990). The amplitude of N1 following the presentation of a gap is known to increase with the duration of the gap (Lister, Maxfield, & Pitt, 2007; Atcherson et al., 2009; Palmer & Musiek, 2014) however Article 3 shows that this effect can be reversed with the presentation of a filler noise. This may due to the difficulty for

the auditory nerve fibers to phase lock to the fine temporal structures and temporal envelope of the stimulus (Bharadwaj et al., 2014). Since the N1 occurs at 100 ms, which is the offset of the stimulus before the silent gap period, it is likely an indicator of the system's detection of the stimulus, which is more an indicator of the functioning of the cochlear filters and the auditory nerve fibers. It has been suggested that a reduction in the early components of the ERP may be related to peripheral hearing loss (Koravand, Jutras & Lassonde, 2013). The MMN may therefore be elicited by higher order processes. This is an important distinction for tinnitus groups as the central gain theory states that tinnitus arises from a loss of peripheral input (i.e. hearing loss). This means that hearing loss is a potential confound for any objective measure, including any study that would use the N1 as a measure of neural gap detection. This provides further justification for the use of the MMN since the deflections of the N1 would be eliminated through the subtraction of the response to the standard and the deviant.

4.3.4 Electrophysiological gap detection and the effect of tinnitus

Article 4 shows the amplitude of the MMN elicited by filled and unfilled gaps is smaller in tinnitus participants than in non-tinnitus controls. The "filling in" the gap theory suggests that tinnitus fills in the gaps and reduces the detection of gaps (Turner et al., 2006). As noted above, although the behavioural results do not support this hypothesis since there was no difference between the tinnitus and controls, the MMN amplitude shows that there is a different pattern of encoding of the gaps in the tinnitus participants when masked with filler noise. At first glance, the amplitude of the MMN was reduced in the tinnitus group in the absence of the noise filler, which is similar to the reduced startle amplitude demonstrated in the in Fournier and Hébert (2013) study. However, there was also a secondary finding where the amplitude of the MMN showed a non-monotonic relationship to the duration of the gap in the tinnitus group and a

monotonic relationship in the normal hearing group. In other words, the amplitude of the MMN increased with the duration of the gap (monotonic) for the normal hearing group in all filler conditions, however for the tinnitus group the higher levels of filler appeared to decrease the amplitude of the MMN to the highest gap duration (at 40 ms). This unexpected finding has not been previously reported in human neural gap detection studies, however animal data has shown that a monotonic pattern is related to the healthy response of auditory nerve to the duration of the gap and the non-monotonic pattern has been seen at the level of the ventral and dorsal cochlear nucleus and higher level cortical pathways (Kaltenbach et al., 1993; Shore 1995). It has been postulated that this non-monotonic response is the reshaping of temporal cues beyond the auditory nerve (Kaltenbach et al., 1993). If this is the case, then the MMN may be an indicator of response of the cortical auditory system to the output of the auditory nerve. This may mean that it could demonstrate the tonotopic organization of the auditory pathways as they respond to temporal cues. This organization to gaps has been previous reported in mice (Sturm et al., 2017) but not in humans. Our results may therefore be human electrophysiological evidence of the reorganization of pyramidal cells suggested by Eggermont and Roberts (2004).

4.4 Comparing electrophysiological with behavioural measures

In Milloy et al. (submitted), participants underwent MMN testing using gapped stimuli presented in oddball and optimised sequences which were subsequently compared to behavioural measures of the same gap stimuli. The MMN amplitude and scalp distribution using the oddball and optimised sequences did not significantly differ, which justified the validity of the optimised method. The optimised sequences were thus used for capturing the MMN in Article 2, Article 3, and Article 4. Since the optimised method made it possible to capture MMNs for multiple gap durations in a single sequence, the number of gap durations tested were similar to the

behavioural method. This made it also comparable to clinical behavioural methods (Keith, 2002; Musiek et al., 2005). When the participants were sorted based on gap threshold, a smaller MMN amplitude was found for the high (=10ms) group for the suprathreshold gaps of 20, 30 and 40 ms compared to the low (=5ms) group; however these differences were not significant. When this study was repeated in Article 4 using only a narrowband noise centered at a high frequency, significant differences were found with an even smaller subject pool. There are two explanations for this. One explanation is that the use of a more frequency-specific stimulus may have eliminated the possible masking effects of the basilar membrane that are known to be produced by low frequency gapped stimuli. This would have made the gaps less noticeable. However given that the behavioural thresholds were the same between the broadband and the narrowband study, this is not likely. Another explanation is that the tinnitus groups had impairments in temporal resolution that were larger than those with no reported tinnitus. Indeed all suprathreshold gaps elicited significantly smaller MMNs in the tinnitus group than the controls. Given the small sample size of Article 4, however, our conclusions are cursory. Article 2 showed that amplitude of the MMN could be reduced due to a lower presentation level of the stimulus. This would mean that the amplitude for all the gap durations would be reduced. Indeed this was the case for the other MMN amplitudes to all the other gap durations. However, intensity could not explain the unexpected decrease in the MMN amplitude to the 40-ms gap. Given that this occurred for both the low and the high noise conditions, it may mean that his was an effect of noise that occurred only in the tinnitus group.

Residual inhibition may be one explanation for the reduction of the MMN amplitude for the 40-ms gap. Mahmoudian et al. (2015) showed that the MMN to a 7 ms silent gap showed a significantly smaller amplitude for the tinnitus participants that had residual inhibition compared

to controls. Only one gap duration was tested in this study therefore it is not known if residual inhibition would have the same effect at other durations as well. Again, the reduction in MMN amplitude was found for all gap durations in all conditions for the tinnitus group compared to controls. The question still remains why it was only the 40-ms gap that was reduced. Stimulus interference between the stimulus and the noise cannot explain these effects as the pattern was not observed in the normal hearing group. Interestingly, the GPIAS protocol (Turner et al., 2006) originally used a 50-ms gap to show effects of tinnitus in mice. This was also the gap duration used in the eyeblink startle reflex method in humans that showed significant tinnitus effects (Fournier and Hébert, 2013). Since the 40-ms duration is close to the gap duration used in these two studies, could similar mechanisms be underlying these effects? Perhaps the 40-ms gap is an indicator of cortical map reorganization which is a response to the previous noise damage that occurred at the level of the cochlea. Overall, the behavioural gap detection thresholds show non-significant changes similar to previous behavioural studies (Campolo, Lobarinas, & Salvi, 2013; Boyen, Baskent, & van Dijk, 2015) however different patterns worthy of further exploration are revealed through the ERP data.

4.5 Clinical implications

The data collected from the four studies presented in this thesis suggest that the MMN can be used as a measure of the neural correlates of supra-threshold gap detection. A more time-efficient optimised paradigm is similarly effective as the oddball for eliciting MMN amplitudes for a range of gap durations. This electrophysiological methodology also appears to have the advantage of revealing differences in noisy conditions that is not shown using a behavioural methodology –even when presenting the same stimulus. These electrophysiological measures can thus be further explored to study gap detection in noise in clinical populations with the

intention of revealing mechanisms currently undetected by behavioural measures alone. One population of interest are patients with noise-induced tinnitus. We hypothesized that this group would have gap detection impairments both behaviourally and with the MMN. Indeed the MMN was significantly reduced in the tinnitus group for all filler noise conditions. This however was not the case for the behavioural data as tinnitus did not have an effect on the gap detection accuracy in any of the noise conditions. Our data suggests that it is worthwhile to continue exploring the differences between the behavioural and electrophysiological differences of clinical and non-clinical groups to see if impairments can be revealed. This may lead to a further understanding of the mechanism of temporal resolution that perhaps has more peripheral implications that are not fully elucidated in the literature. Other clinical populations of interest could be children with diagnosed central auditory processing disorder, patients with noise-induced hearing loss, and patients with audiometrically normal hearing presenting with difficulties understanding speech in noise.

Given that this thesis is a part of the requirements for a Ph.D. in rehabilitation sciences, it is also important to note the ways this work contributes to rehabilitating patients with tinnitus. Rehabilitation of patients with reported tinnitus is not standardized and many treatment options exist. One of these treatments is sound therapy where a patient wears on-ear devices that produce noise in addition to amplification if a hearing loss is also present. Outcome measurements for these treatments are typically conducted using psychoacoustic measures of tinnitus pitch and intensity in addition to self-reported questionnaires. This thesis describes the potential of considering ERP measures, like the MMN, as an additional tool that could be used for patients that are unable to be realiably tested using questionnaires and psychoacoustic measures. This would be of particular importance to populations that are unable to report the presence of tinnitus

such as children or people with severe cognitive impairments. In these cases, measuring, for example, the MMN before and after a sound therapy could be an indicator of the changes occurring in the auditory system as a result of the therapy.

4.6 Limitations of this research

Hidden hearing loss, which can not be detected by audiogram, continues to be a possible confound that was uncontrolled. Efforts were attempted to control for the effects of hearing loss by testing an audiometrically normal hearing control group, however, there is the possibility that hidden hearing loss (cochlear deafferentation) may have an effect on temporal resolution. If this was the case, the differences within each group for the three filler conditions should have been the same (i.e. there should have been a similar effect of filler for both the normal hearing and tinnitus groups). Given that this was different, it appears there was an effect that is related to tinnitus that did not appear to occur in the control groups and we postulated that this was the residual inhibition and central tonotopic reorganizatoin as discussed in the literature.

Artefactual electrical noise was also an issue because it could mask the biological signal of the MMN. Attempts were made to avoid any issues with this by changing the way the MMN was averaged: the mastoid was used as a reference and peak to peak amplitude measures in place of using the absolute MMN amplitude value. As decribed earlier, these mesures were done according to Picton et al. (2000) to enhance the MMN amplitude and reduce electrical noise. According to Picton et al. (2000) the absolute amplitude of the MMN and the P3a is a more truthful measure as it incorporates the overlapping segments of N2 with the subsequent positivity. This was also described in the introduction of Article 1. These overlapping segments may have lifted the MMN making it less negative. Thus the peak to peak measure is a combination of both the positivity from the P3a component and the negativity from the MMN.

Indeed without using this referencing method and peak-to-peak difference, the changes would have not been significant. This was particularly the case for the data acquired for the intensity difference MMN study (Article 2) where the bandwidth of the stimulus was narrower compared to the broadband signal of Milloy et al. (submitted). This method was applied for the third and fourth studies (i.e. Articles 3 and 4) that used additional filler noise stimuli that would have had an even greater impact on reducing the signal to noise ratio than Milloy et al. (submitted).

Finally, the sample size of the tinnitus study (Article 4) was too small to draw any strong conclusions on the effects of tinnitus to the gap-elicited MMNs. It would be best to repeat the study on a larger sample of participants to determine if the differences between those with tinnitus and residual inhibition and those with tinnitus and a lower level of residual inhibition. At this point, the pilot study suggests the tinnitus sample shows some effects for the filler conditions that may be explained by residual inhibition, however in order to elucidate this relationship, a larger sample of tinnitus participants with various measured depths of residual inhibition would have to studied.

4.7 Future plans

In addition to the studies suggested to improve control of the possible effects of hearing loss, one of the areas of future interest could be studying sub-threshold gap detection using MMN markers. There may be a confounding effect inherent of the design of the optimised sequence since there is a pattern of occurrence that certain models of the MMN state may elicit an MMN (Näätänen, Kujala and Winkler, 2011; Winkler, 2007; Winkler, Denham and Nelken, 2009). Thus the MMN may be elicited by both simple and complex patterns of the simple alternating standard-deviant pattern (Alain et al., 2004; Sculthorpe, Collin, & Campbell, 2008; Campbell and MacDonald, 2011). This may be the 2-ms gap deviant being elicited even when

the gap was not perceived. It would be perceived as a standard which would violate the alternating pattern. Thus a future study could compare the subthreshold 2-ms gap duration between the oddball and the optimised paradigm to see if indeed the alternating pattern hypothesis is supported.

Another possible study could look at the effects of frequency on neural gap detection: one could investigate the changes the frequency specificity of neural gap detection in populations with tinnitus. Roberts et al. (2015) showed that residual inhibition recovery appear to occur only at high frequencies of 5 kHz for the ASSR but this has not been confirmed using the MMN. Mahmoudian et al. (2015) tested residual inhibition to gapped stimuli at three mid-frequency ranges (500, 1000 and 1500 Hz) and which did not show any frequency-specific differences. It could therefore be interesting to see if the MMN shows changes to gapped stimuli at a high frequency and compare it to a lower frequency. Finally neural gap detection using the MMN can be applied to children to gain a better understanding of the utility of this tool on other age groups.

5 CHAPTER 5: Statement of Contributions

The articles presented within this thesis were all collaborative works made possible by the efforts of multiple individuals. The conception of the idea was born out of discussions between Victoria Milloy and Drs. Kenneth Campbell and Amineh Koravand. The first draft of all articles were written by Victoria Milloy. The revisions to the first draft were made by Dr. Campbell, Dr. Paniz Tavakoli, and Dr. Koravand. Subsequent articles 2, 3 and 4 were written by Victoria in consultation with Drs. Daniel Benoit and Amineh Koravand. Data collection for Milloy et al. (submitted) was carried out by Victoria in the laboratory of Dr. Campbell. Dr. Campbell and Dr. Tavakoli also trained Victoria with the operation and programming of their ERP systems. This allowed Victoria to train Masters students in Dr. Koravand's laboratory to carry out the remainder of the research. Thus data collection and programming of the stimulus presentation program for articles 2 and 3 were conducted by Audiology Masters student, Don Nguyen. Finally the data collection and recruitment for the tinnitus pilot Article 4 was completed by Audiology Masters student, Fauve Duquette-Laplante. All data analyses were completed by Victoria in consultation with Drs. Campbell and Tavakoli.

6 CHAPTER 6: Conclusion

The main objective of this Ph.D. thesis was to study the effects of neural gap detection on a tinnitus sample to isolate the possible confounding effects of attention and hearing loss underlying the conflicting evidence for the Turner "fill-in" hypothesis. To elucidate the effects of these factors, electrophysiological measures were proposed to map the response of the central auditory system to various gap durations. In order to do so, the methodology was optimised for time and efficiency by comparing the optimised paradigm to the oddball, using a narrower bandwidth stimulus at a higher intensity, and measured in the presence and absence of filler noise. These parameters were all tested on a normal hearing population prior to testing a pilot tinnitus group. In the normal hearing group, the MMN decreased proportionally with the duration of the gap. The optimised paradigm was successful in eliciting robust MMNs for gaps that could be detected behaviourally (i.e. supra-threshold gaps). When presented in the presence of a filler noise, the amplitude of the MMN and N1 decreased proportionally with the intensity of the filler.

The tinnitus sample showed the MMN amplitude increased proportionally to increasing suprathreshold gaps similar to the normal hearing group. The filler noises decreased the amplitude of the MMN simliar to the normal group. However in the high and low noise condition, the MMN did not decrease proportionally to the gap duration. Rather when presented with noise, the largest gap durations elicited smaller MMN amplitudes than medium gaps. This change in pattern may suggest underlying damage to the spontaneous rate fibers of the auditory nerve or synaptic ribbon loss effecting the tonotopic organization of the auditory cortex. It may also be an indication of the effect of residual inhibition. This leads to many questions about

whether other electrophysiological recordings of multiple gap durations, such as the Auditory Brainstem Response or Electrocochleography, may also show similar amplitude patterns. Results from a study we conducted adjacent to this thesis showed similar positive correlations between the gap duration and wave V amplitude in normal hearing participants (unpublished research conducted in association with Vivosonic Inc., Toronto), however further research is required on clinical populations with tinnitus.

The collection of findings presented in this thesis proposes that ERPs reveal an underlying organization of coding of gap durations at the level of the central auditory system that is undetected by behavioural testing of temporal resolution. Changes to the organized coding of gaps may be related to "hidden" nerve damage and thus functional hearing difficulties such as hearing in noise. Thus by using the electrophysiological measures presented in this thesis, it is possible that further information can be provided to show central changes of the auditory system related to temporal resolution or gap detection that has not been explored in clinical populations. This may have implications on our understanding of the mechanisms involved in populations reporting a variety of hearing problems and could lead to new objective measurement tools.

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APPENDIX

Appendix 1: Scoping review on the ABR

frontiers in Aging Neuroscience

REVIEW
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Auditory Brainstem Responses in Tinnitus: A Review of Who, How, and What?

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The auditory brainstem response (ABR) in tinnitus subjects has been extensively investigated over the last decade with the hopes of finding possible abnormalities related to the pathology. Despite this effort, the use of the ABR for tinnitus diagnosis or as an outcome measure is under debate. The present study reviewed published literature on ABR and tinnitus. The authors searched PubMed, MedLine, Embase, PsycINFO, and CINAHL, and identified additional records through manually searching reference lists and gray literature. There were 4,566 articles identified through database searching and 151 additional studies through the manual search (4,717 total): 2,128 articles were removed as duplicates, and 2,567 records did not meet eligibility criteria. From the final 22 articles that were included, ABR results from 1,240 tinnitus subjects and 664 control subjects were compiled and summarized with a focus on three main areas: the participant characteristics, the methodology used, and the outcome measures of amplitude and/or latency of waves I, III, and V. The results indicate a high level of heterogeneity between the studies for all the assessed areas. Amplitude and latency differences between tinnitus and controls were not consistent between studies. Nevertheless, the longer latency and reduced amplitude of wave I for the tinnitus group with normal hearing compared to matched controls was the most consistent finding across studies. These results support the need for greater stratification of the tinnitus population and the importance of a standardized ABR method to make comparisons between studies possible.

Keywords: tinnitus, ABR, review, brainstem, synaptopathy, meta-analysis, hearing loss

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INTRODUCTION

Tinnitus is known as a phantom sound that is perceived in the absence of an acoustic stimulation. It is described by patients in a variety of ways that can be as simple as a single pure tone and as complex as a combination of different sounds (Stouffer and Tyler, 1990). It can also be perceived differently in one ear, both ears or in the head, and can be modulated in some individuals by orofacial movements (Levine, 1999), touch, background noise, stress, anxiety, depression, and attention (Tyler et al., 2008).

Although, the pathophysiology of tinnitus is still not clear, various origins, and mechanisms have been described in the literature (Henry et al., 2014). The fact that tinnitus is not always suppressed when the cochlear nerve is sectioned suggests there are, at least, two distinct tinnitus sub-types:

cochlear tinnitus and central tinnitus (House and Brackmann, 1981; Berliner et al., 1992). Cochlear tinnitus can be defined as a tinnitus subtype that results from aberrant activity in the cochlear nerve (Noreña, 2011). Central tinnitus can be defined as a tinnitus subtype that does not result from an increase of activity (or synchrony) in the cochlear nerve but rather at cortical levels within the central auditory pathways (Noreña, 2011). In this latter subtype, the tinnitus perception may result from cortical changes associated with the reduction of sensory inputs due to hearing loss.

One technique used to assess the activation along the neural pathways between the eighth peripheral nerve of the cochlear nucleus up to the inferior colliculus is the Auditory Brainstem Response (ABR) (Melcher and Kiang, 1996). Auditory Brainstem Responses (ABRs) are acoustically stimulated signals that represent the synchronized neural activation along the neural pathways. A study investigating the generation sites of ABRs in cats revealed the first wave (I) of the ABR reflects activity of the spiral ganglion cells at the distal part of the eighth auditory nerve, wave II is predominantly from the globular cells in the cochlear nucleus, wave III is generated by the cochlear nucleus spherical cells and globular cells, and waves IV and V generate from the medial superior olive and its projections to the nuclei in the lateral lemniscus and the inferior colliculus (Melcher and Kiang, 1996). These electrophysiological responses are typically less than a microvolt in amplitude (Burkard and Secor, 2002; Chalak et al., 2013). The success of revealing true and reliable responses relies heavily on averaging techniques employed to reduce noise contamination thereby improving the signal to noise ratio (Burkard and Secor, 2002). ABRs have been used clinically for two main purposes: hearing threshold estimations and neurodiagnostics. Indeed, the ABR is a well known cost-effective test that is routinely used in clinical practice as an objective diagnostic measure for determining the presence of hearing loss in infants, young children and patients that are difficult to test behaviorally. More so, the ABR is an important clinical tool for identifying the presence of retrocochlear lesions, acoustic neuromas, and vestibular schwannomas (Kotlarz et al., 1992; Rupa et al., 2003). This is achieved by identifying waves I, III, and V peaks and comparing the absolute latency values to normative ranges for each wave. For example, the presence of an acoustic neuroma at the level of the auditory nerve could significantly delay neural conduction. As a result, the latency between waves I and V is usually extended from the normative value by more than 0.2 ms (Wilson et al., 1992). Normative ABR latency values, for clicks at 70 dB nHL, collected on the most reliable waves I, III, and V are, respectively, 1.66, 3.68, and 5.64 ms for the left ear, and 1.66, 3.65, and 5.59 ms for the right ear (Chalak et al., 2013). When comparing between genders of the same age, the latencies are shorter and the amplitudes are larger in women compared to men (Hultcrantz et al., 2006). Hearing loss of different configurations affect the ABR: high frequency hearing losses show a delayed wave V at low intensities and a greater degree of wave I delay at all intensities, low frequency hearing losses show an earlier wave V at low intensities (Keith and Greville, 1987; Watson, 1996). Furthermore, elevated hearing thresholds also reduce the amplitude of waves I and V using the click-ABR (Sand and Saunte, 1994) and wave V using tone-burst ABR when the tone-burst characteristic frequency falls within the frequency region of the hearing loss (Lewis et al., 2015). The ABR sensitivity and specificity for both hearing threshold estimations and neurodiagnostics, have been shown to be very high with values of 100 and 91% for the former (Hyde et al., 1990) and 88 and 92% for the latter (Bauch et al., 1996). ABR assessment is also used for the diagnosis of auditory neuropathy (Starr et al., 1996). In such a case, the function of the outer hair cell of the cochlea is mostly normal, irrespective of hearing thresholds, even though the ABR waves are absent due to a lack of synchronized neural activity or excessive auditory fatigue (see Giraudet and Avan, 2012). The ABR technique thus provides information about the integrity of the central auditory system and can be a valuable diagnostic tool. Moreover, ABRs are relatively easy to obtain from only a few electrodes and are mostly insensitive to cognitive states (e.g., attention or arousal) or even consciousness (Burkard and Secor, 2002).

In tinnitus research, ABRs have been used in a variety of ways in humans. ABRs have been used to differentiate peripheral from central lesion sites in patients (Kehrle et al., 2008), and to investigate tinnitus treatment efficacy following drug administration (Shulman and Seitz, 1981; Milicic and Alcada, 1999; Bayar et al., 2001; Gopal et al., 2015). ABRs have also been used to identify noise-induced hidden hearing loss. In brief, Kujawa and Liberman found that the ABR wave I amplitude of mice significantly decreased at moderately-high levels (above 70 dB) up to 2 months following noise exposure even when the auditory thresholds had recovered to normal values (Kujawa and Liberman, 2006, 2009). In addition to the amplitude reduction, damage to the synaptic ribbons of the inner hair cells and spiral ganglion cells were revealed, suggesting that reduced wave I amplitude may be indicative of auditory nerve deafferentation. The term "cochlear synaptopathy" was further proposed to describe damage at the cochlear synapse without loss of hair cells resulting in "hidden hearing loss," a functional hearing deficit without an elevation of audiometric thresholds (Liberman and Kujawa, 2017). In tinnitus patients with normal hearing (≤20 dB HL, Freq: 0.25–8 kHz), Schaette and McAlpine (2011) and Gu et al. (2012) showed similar reduced wave I amplitudes at high levels (80–90 dB SPL) compared to non-tinnitus matched controls, which were both interpreted as diminished activity of the low spontaneous rate auditory nerve fibers (LSR). Interestingly, the amplitude of wave V (measured baseline to peak) was reported to be significantly higher in only Gu et al. (2012). Schaette and McAlpine (2011) suggest the normal wave V amplitude, despite a reduction in wave I, is due to the central auditory system increasing its neural responsiveness to compensate for the reduced activity of the auditory nerve. Conversely, Gu et al. (2012) suggest that the higher amplitude of wave V is an artifact from the use of a lower frequency filter cutoff. Based on these findings, people suffering from tinnitus with normal audiometric thresholds show ABR amplitude changes that may be indicative of cochlear synaptopathy (reduced wave I) and the compensated responses of central/cortical regions (normal or elevated wave V). The increased responsiveness of central regions would generate

increased spontaneous activity leading to tinnitus generation. Hickox and Liberman (2014) attempted to link synaptopathy to the generation of tinnitus in noise-exposed mice. The mice exposed to loud noise displayed the typical auditory nerve degeneration (determined by ribbon counts), reduced wave I amplitude/enhanced wave V ABR responses, and subtle changes in the behavioral response of tinnitus that did not reached significance (using the gap prepulse inhibition acoustic startle reflex or GPIAS). Low efficacy of this particular behavioral technique (GPIAS) in CBA-mice might explain the failure of significant results (Yu et al., 2016). Using another strain with better GPIAS could maximize these effects and link wave I reduction to a behavioral measure of tinnitus in animals. Another animal study (Rüttiger et al., 2013), exposed animals to loud noise and separated them based on tinnitus behavior. They found that although the ABR waveform was generally reduced after the trauma for both groups, wave I did not significantly change amplitude after recovery. Interestingly, the tinnitus group showed reduced wave IV and V amplitude after recovery, which the authors proposed to arise from a failure to compensate for the cochlear loss at the central levels of the auditory system.

It is noteworthy that ABR wave amplitude may be altered by the number of neural components activated by the stimulation and/or the level of synchronization between them. As amplitude of wave I is mostly due to tightly synchronized activity at the level of the cochlear nerve, the reduction in amplitude noted previously at high intensities might indicate not only a loss of neural fibers but also a decrease of synchronization. Conversely, increased neural synchrony has been proposed as a potential mechanism of tinnitus generation (Eggermont, 1984; Moeller, 1984). It was postulated that increased synchrony of the spontaneous firing rate even at the peripheral level of the auditory nervous system could be sufficient to produce a perception of a sound in the absence of external stimulation. The higher wave V amplitude reported in tinnitus subjects might reflect increased neural synchronization at higher levels of the auditory system. In brief, changes in wave I might reflect damage to the periphery and the following wave modifications might reflect compensation mechanisms such as higher increased neural synchrony in tinnitus. Still, modifications of wave III and wave V amplitude might occur without being related to wave I alterations. In a recent study, decreases in the amplitude of waves III and V were not adequately explained by changes in wave I in older participants compared to younger ones (Konrad-Martin et al., 2012). In this study, the reduction of the peak amplitudes of waves III and V, seemed to be linked to the effects of aging, instead of wave I amplitude reduction (and latency shift), which is believed to be the consequence of reduced auditory nerve inputs.

The current purpose of the study was to review ABR findings on tinnitus to assess any consistencies across studies in terms of absolute wave amplitudes and latencies. As ABR waves are affected by hearing loss (Don et al., 1998), and tinnitus mechanisms may differ between normal hearing and hearing loss participants (Henry et al., 2014), studies were separated based on this variable. A potential decrease in wave I amplitude in tinnitus subjects with normal hearing is expected to be one of the most consistent findings across studies (Schaette and McAlpine, 2011; Gu et al., 2012). The current review might also bring insight on possible modifications of the other waves such as wave III and wave V, in populations reporting tinnitus. A careful analysis of studies on tinnitus and ABR from 1980 to 2016 was made and convergent evidence was extracted based on the population/sample (who?), the methodology (how?), and the outcome (what?). The investigated outcomes were related to the latency and amplitude of waves I, III, and V.

METHODS

Database Search

A scoping review of the literature was conducted using the method described by Arksey and O'Malley (2005). This approach uses a five stage framework that includes (1) identifying the research question, (2) identifying relevant studies, (3) selecting the study, (4) charting the data, and (5) collating, summarizing, and reporting the results. Statistics for each level of data collection are tabulated in the PRISMA schema (Moher et al., 2009; **Figure 1**).

A team approach to the process of the review was used to eliminate the level of error produced by a single individual and a second reviewer was used to independently analyze all the abstracts for inclusion (Levac et al., 2010). Given the high volume of articles yielded from the comprehensive search strategy, a "liberal accelerated" approach was used: the second reviewer analyzed only articles excluded by the first reviewer instead of the entire yield (Khangura et al., 2012).

The primary outcome of interest is measurement of the absolute peak amplitudes (peak to following trough) and latencies of the ABR waveform in tinnitus patients with and without hearing loss. Searches were conducted, between April 2015 and August 2016, by the principal investigator (V.M.) using the strategies detailed in Supplementary Table 1. In brief, the search terms (and their variations) used alone or in combination referring to tinnitus were: tinnitus, ear, buzz, ring, roar, click, pulsate, or pulse, and referring to the auditory brainstem measurements were: brainstem, brain, stem, auditory, response, potential, ABR, BAER, BSER, and evoked. The databases PubMed, CINAHL, Medline, PsycInfo, and Embase were searched separately and results were compiled in a Microsoft Excel (2011) spreadsheet where the search strategy yields were dated and organized (Supplementary Table 1). Gray literature which includes conference papers, master dissertations, and doctoral theses was also searched (October 2016) using ProQuest Dissertations and Theses Global and Conference Papers Index and added to the compiled list of articles. No conference papers, master dissertations, or doctoral theses were included in the final compilation as all those found were later published. Articles were limited to those published after 1980 as the waveforms were only just described in the 1970s by Jewett and colleagues and not yet applied to subjects with tinnitus (Jewett et al., 1970; Jewett and Williston, 1971). Any articles assessing populations with tinnitus due to underlying medical conditions were excluded for the purposes of this review (i.e., acoustic neuroma, otitis media, otitis externa, etc.). Excluding various comorbidities ensured the ABR outcomes

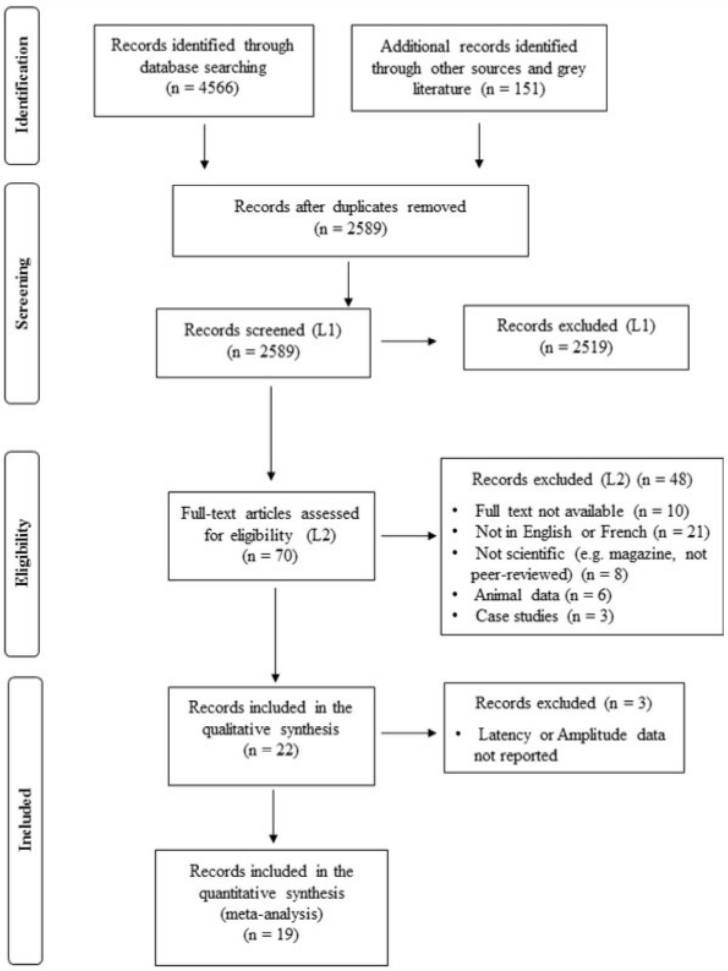

FIGURE 1 | Flowchart of study selection (PRISMA diagram).

reported were not due to known covariables. Any articles discussing ABRs for the purpose of measuring hearing loss such as threshold searching and newborn hearing screenings were also excluded. Preoperative and intraoperative ABRs were not included in this review as clinical populations with other underlying conditions, such as acoustic neuromas, or vascular abnormalities, are typically involved in these studies and are known covariables of ABR (Berliner et al., 1992; De Ridder et al., 2015).

The first screening (L1) consisted of excluding the articles that did not meet the criteria described in **Table 1** based on the analysis of title and abstract of the article. The second reviewer screened the articles rejected by the first reviewer. Both reviewers completed the second screening (L2) where eligibility was based on the analysis of the full text. The use of a language translator was not feasible for this study, therefore all texts written in languages other than French or English were eliminated. Three case-report studies, where a single participant was reported

TABLE 1 | Inclusion and exclusion criteria applied to the scoping review search.

	Inclusion criteria	Exclusion criteria
Population	Subjective tinnitus with or without hearing loss. This includes individuals with noise-induced hearing loss.	Subjective tinnitus with a history of ontological conditions (i.e., hypertension, tumors, demylenation, multiple sclerosis, Meniere's disease, auditory neuropathy, otitis media, otitis externa, middle ear pathologies etc.).
		Individuals with cochlear implants, CAPD, head trauma, psychological disorders, sudden hearing loss.
		Individuals with objective tinnitus or pulsatile tinnitus.
		Studies with a sample size of 1.
Evaluation	Auditory evoked potentials of the brainstem.	Long Latency Auditory Evoked Potentials (P1, N1, P2, N2); Event Related Potentials (MMN, P300, N400, P600 etc.). Auditory Steady State Responses, intraoperative ABR, preoperative monitoring, newborn hearing screening.
Publication type	Peer-reviewed journals only with articles published after 1980 in English or French.	Any unscientific papers: Magazine articles, conference proceedings, editorials, and manuals.
Outcomes	Measured peak amplitudes and latencies of the ABR wave.	

(Shulman and Seitz, 1981; Milicic and Alcada, 1999; Gopal et al., 2015), were removed from the remaining yield. The sample size was too small to significantly contribute to the analysis, and the purpose of these studies was mostly to measure the responsiveness to treatment.

After the two levels of title and abstract screening (L1) and full-text screening (L2) were completed, a narrative synthesis was used to organize key points of the data into two charts. Key points of interest included population (i.e., age, tinnitus etiology, tinnitus localization, and hearing status), technical information (i.e., transducer used, ABR system used, stimulus type, presentation levels, tinnitus characterization, and recording filters), and results.

Meta-Analysis of the Compiled Data

The results were compiled in Microsoft Excel (2011) for a meta-analysis of the data using two different methodologies. The first method (meta-analysis 1) consisted of compiling the latency and amplitude values from Waves I, III, and V for all the subjects, with or without tinnitus, from all the studies reporting these values. The mean values for absolute latency and amplitude, standard deviations, and sample size for each study were organized in a table as a function of the ABR waves. The results were also separated based on hearing status and reported tinnitus. For example, the results of the four groups were determined based on the participants having (a) normal hearing without tinnitus, (b) normal hearing with tinnitus, (c) hearing loss without tinnitus, and (d) hearing loss with tinnitus. In these cases, we used the normal hearing and hearing loss definitions established within each article. These definitions varied from one study to the other (see Section Results and Discussion). Meta-analysis calculations were carried out on these data to determine (a) the total number of subjects for all the studies separated by hearing status; (b) the total mean latency/amplitudes weighted according to sample size of each study; (c) the composite standard deviation calculated as a combination of all the groups from all the studies; (d) the 95% confidence interval (CI) determined based on the composite standard deviation; (e) the mean difference latency/amplitude (i.e., the mean latency/amplitude of the tinnitus group subtracted by the mean latency/amplitude of the non-tinnitus group) again weighted according to the sample size. The confidence interval was calculated using Microsoft Excel software and consisted of adding or subtracting the confidence value from the weighted mean. The confidence value was calculated based on the composite standard deviation and the total number of observations of the pooled data grouped in one of the categories: normal hearing, normal hearing and tinnitus, hearing loss, or hearing loss and tinnitus. Confidence intervals were chosen because the interval estimate obtained from this method is more informative for data comparison of future studies than a sample mean and *T*-test. The confidence level of the confidence intervals was set at 95%, which is the equivalent of $p < 0.05$.

The second method (meta-analysis 2) consisted of calculating the difference of the mean amplitude and latency for waves I, III, and V (and the 95% CI) between the tinnitus and control groups, only for studies with at least matched age and hearing status. This method was added to minimize the risk of identifying differences in population variables, assessment techniques or methodologies between tinnitus and control groups. The differences found with the second methodology are thus presumed to be the result of group differences as both groups were tested with very similar protocols.

RESULTS

Study Selection

A total of 4,566 articles were retrieved from the databases PubMed, MedLine, Embase, PsycINFO, and CINAHL. An additional 133 articles were found by manually searching citations from the reference lists of articles that met the eligibility criteria and another 18 from gray literature (i.e., doctoral theses and conference papers). After the duplicates were removed, 2,589 articles were screened by title and abstract and 70 of those articles were analyzed by reading the full text. Of the remaining articles, 22 were included in the qualitative narrative synthesis and 19 in the meta-analysis (see **Figure 1**). The most common objective of the studies is the assessment of possible changes to the ABR of tinnitus patients compared to those without tinnitus ($n = 19$)

TABLE 2 | Demographics include the number of subjects, the mean age, the tinnitus etiology, and localization and the hearing status criteria.

Study	Subjects	Mean age in years (Range)	Tinnitus characterization	Tinnitus localization	Hearing status criteria	Results: latency	Results: amplitude
NOISE-INDUCED ETIOLOGY							
Attias et al., 1993	Tinnitus ($n = 12$) Controls ($n = 12$) Matched: Age, HL severity and configuration	Not mentioned (26-45) Not mentioned (26-45)	Pitch Matching Loudness Matching	Bilateral ($n = 12$)	Audiometrically matched, No definition Noise induced hearing loss	No differences	No differences
Attias et al., 1996	Tinnitus ($n = 13$) Controls ($n = 11$) Matched: Age and Hearing	35 (21-45) Not mentioned (age and hearing matched)	Pitch Matching Loudness Matching Tinnitus severity profile	Unilateral ($n = 8$) Bilateral ($n = 5$)	Normal hearing: ≤20 dB HL, Freq: 0.25–2 kHz Hearing loss: 20–45 dB HL, Freq: 2–8 kHz	No differences	Enhanced Wave III amplitude
Gilles et al., 2016	Tinnitus ($n = 19$) Controls ($n = 23$) Matched: Age, Sex, and Hearing	~23 (SD: 2.4)	VAS–Loudness TQ	Head ($n = 1$) Unilateral ($n = 2$) Bilateral ($n = 16$)	Normal hearing (<25 dB HL, Freq: 0.25–16 kHz?) Hearing loss (>25 dB HL, Freq: 0.25–16 kHz?) HF tested (up to 16 kHz)	No differences	No differences
Santos-Filha et al., 2014	Tinnitus ($n = 30$) Controls ($n = 30$) Matched: Age, Sex, Hearing	41 (27-50) 41.6 (27-50)	VAS—Severity	Bilateral (67%) Unilateral (33%)	Normal hearing (<25 dB HL, Freq: 0.25–8 kHz)	No differences	Not reported
IDIOPATHIC ETIOLOGY							
Cartocci et al., 2012	Tinnitus ($n = 10$) Controls ($n = 14$) Matched: Age, Sex, Hearing	43.9 (SD: 11.0) 45.1 (SD: 11.9)	Not reported	Unilateral ($n = 5$) Bilateral ($n = 5$)	Normal hearing (≤20 dB HL, Freq: 0.125–8 kHz)	Longer Wave V and III–V	Not reported
Mahmoudian et al., 2013	Tinnitus ($n = 44$) No Controls	43.45 (18-65)	Not reported	Unilateral ($n = 19$) Bilateral ($n = 25$)	Included Hearing levels (≤30 dB HL, Freq: 0.5–2 kHz and <60 dB HL, Freq: 4–8 kHz)	No latency changes	III/V and I/V ratio modifications following electrical RI
Maurizi et al., 1985	Tinnitus ($n = 54$) No Controls	Not mentioned (23-78)	Residual Inhibition	Unilateral ($n = 54$)	Classification of hearing loss: 1) ≤20 dB HL, Freq: 0.5–4 kz 2) 21–49 dB HL, Freq: 0.5–4 kHz and >50 dB HL, Freq: 0.5–4 kHz	Prolonged Wave V in tinnitus ears vs. control ears	Not reported
McKee and Stephens, 1992	Tinnitus ($n = 18$) Controls ($n = 19$) Matched: Age and Hearing	26 (18-37) 27.5 (17-38)	Not reported	Head ($n = 2$) Unilateral ($n = 2$) Bilateral ($n = 14$)	Normal hearing (≤20 dB HL, Freq: 0.25–8 kHz) HF tested (up to 18 kHz)	No differences	Not reported
Nemati et al., 2014	Tinnitus ($n = 25$) Controls ($n = 16$) Matched: Age, Sex, Hearing	34.4 (20-57) Not mentioned (matched)	Not reported	Unilateral ($n = 19$) Bilateral ($n = 6$)	Normal hearing (<25 dB HL, Freq: 0.25–8 kHz)	No differences	Amplitude ratio V/I larger
Singh et al., 2011	Tinnitus ($n = 25$) Controls ($n = 20$) Matched: Age, Sex, Hearing	32 (18-45) Not mentioned (matched)	Not reported	Unilateral ($n = 19$) Bilateral ($n = 6$)	Normal hearing (<25 dB HL, Freq: 0.25–8 kHz)	Longer Wave I Shorter Wave V Shorter I–II and I–V	Not reported

(Continued)

TABLE 2 | Continued

Study	Subjects	Mean age in years (Range)	Tinnitus characterization	Tinnitus localization	Hearing status criteria	Results: latency	Results: amplitude
HETEROGENEOUS ETIOLOGY							
Kim et al., 2016	Tinnitus (n = 123) No Controls	53.5 (SD: 13.4)	VAS—Discomfort Minimum masking level Residual inhibition THI Pitch matching	Unilateral (n = 79) Bilateral (n = 44)	Audiometric configurations: 1) Flat 2) High frequency gently sloping 3) High frequency steeply sloping	Prolonged latencies I, III and V for steeply high frequency hearing loss group	Not reported
ETIOLOGY NOT MENTIONED							
Barnea et al., 1990	Tinnitus (n = 12) Controls (n = ??) Matched: Age, Sex, Hearing	35 (21-45) Not mentioned (matched)	Pitch matching Loudness matching	Unilateral (60%) Bilateral (40%)	Normal hearing (≤20 dB HL, Freq: 0.25–8 kHz) HF tested (up to 20 kHz)	No difference	No differences
De Lavernhe-Lemaire and Beutter, 1989	Tinnitus (n = 164) Controls (n = 57) Not Matched	Not mentioned	Not reported	Unilateral (n = 112) Bilateral (n = 52)	Not mentioned	Longer Wave I, but decreased inter-peak I–V	Not reported
De Lavernhe-Lemaire and Beutter, 1990	Tinnitus (n = 139) Controls (n = 20) Not Matched	27-74	Not reported	Unilateral (n = 93) Bilateral (n = 46)	Not mentioned	Not reported	Decrease wave I and III amplitude
Gerken et al., 2001	Tinnitus (n = 9) Controls with normal hearing (n = 11) Controls with hearing loss (n = 8) Controls-elderly (n = 7) Not Matched	45.7 (26-68) 28 (22-37) 40.9 (23-53) 63.6 (60-68)	Pitch matching Loudness matching Minimum masking level	Not mentioned	Normal hearing (≤15 dB HL, Freq: 0.5–8 kHz) Hearing loss (>15 dB HL, Freq: 0.5–8 kHz)	Problem tinnitus group longer wave VII	No differences
Gu et al., 2012	Tinnitus (n = 15) Controls (n = 21) Matched: Age, Sex, Hearing	42 (SD: 6) 43 (SD: 7)	Pitch matching Loudness matching Minimum masking level Residual inhibition	Head (n = 4) Unilateral (n = 2) Bilateral (n = 9)	Normal hearing (≤20 dB HL, Freq: 0.25–8 kHz) HF tested (up to 16 kHz)	No latency differences	Reduced wave I and enhanced wave V
Ikner and Hassen, 1990	Tinnitus (n = 35) Controls (n = 35) Matched: Age, Sex, Hearing	40 36	Not reported	Not mentioned	Normal hearing (<20 dB HL, Freq: 1–4 kHz)	Longer wave I, III, V, and III–V interval	Not reported
Kehrle et al., 2008	Tinnitus (n = 37) Controls (n = 38) Matched: Age, Sex, Hearing	36 (SD: 7.2) Not mentioned (matched)	Not reported	Unilateral (n = 13) Bilateral (n = 24)	Normal hearing (<25 dB HL, Freq: 0.5–8 kHz)	Longer Wave I, III, V, and III–V	Ratio V/I
Kehrle et al., 2016	Tinnitus (n = 84) Controls (n = 47) Matched: Age, Sex, Hearing	37.2 (18-48) 35.7 (18-48)	VAS— severity Pitch matching Loudness matching THI	Unilateral (n = 26) Bilateral (n = 58)	Normal hearing (≤25 dB HL, Freq: 0.25–8 kHz)	Abnormal for wave I, wave III, wave V, inter-peak I–III, inter-peak III–V, Inter-peak I–V	Not reported

(Continued)

TABLE 2 | Continued

Study	Subjects	Mean age in years (Range)	Tinnitus characterization	Tinnitus localization	Hearing status criteria	Results: latency	Results: amplitude
Lemaire and Beutter, 1995	Tinnitus (n = 355) Controls (n = 129) Not matched	52.1 (SD: 16.4) <25	Pitch matching Loudness matching	Unilateral (n = 220) Bilateral (n = 135)	Normal hearing (<20 dB HL, Freq: ??)	Longer for 0–I and I–V on the tinnitus affected side	Reduced Wave I, III, and sometimes V
Rosenhall and Axelsson, 1994	Tinnitus with hearing loss (n = 57) Tinnitus with normal hearing (n = 56) Controls with hearing loss (n = 166) Controls with normal hearing (n = 54) Matched: Age, Sex, Hearing	57.2 (SD: 10.6) 42.1 (SD: 13.8) Not mentioned (matched) Not mentioned (matched)	Not reported	Unilateral (n = 30) Bilateral (n = 83)	Normal hearing (<20 dB HL, Freq: 0.125–2 kHz and <35 dB HL, Freq: 4–8 kHz) Hearing loss (45–60 dB HL, Freq: 4 kHz)	Longer Wave I, III, and V	Not reported
Schaette and McAlpine, 2011	Tinnitus (n = 15) Controls (n = 18) Matched: Age, Sex, Hearing	36.3 (SD: 2.6) 33.2 (SD: 1.9)	Modified tinnitus spectrum	Not mentioned	Normal hearing (≤20 dB HL, Freq: 0.25–8 kHz) HF tested (up to 16 kHz)	Not reported	Reduced Wave I. No change Wave V

SD, Standard deviation; dB, decibels; HL, hearing loss; Freq, frequency; n, number of subjects; VAS, visual analog scale; TQ, Tinnitus Questionnaire; THI, Tinnitus Handicap Inventory; HF, high frequency; thresholds above 8 kHz.

for the purpose of distinguishing between peripheral and central tinnitus or identifying lesions or deafferentation of the auditory nerve. Other objectives were to compare the ABR to tinnitus perception ($n = 1$), emotions ($n = 1$), and the behavioral effects of residual inhibition ($n = 1$).

Population Characteristics

Characteristics of the populations tested in the 22 studies are shown in **Table 2**. Nineteen out of the 22 studies had a control group. The matching procedures varied between the studies, if mentioned at all. In 12 studies subjects were matched by sex, age, and hearing status, in three studies by age and hearing only and in four studies not matched (see **Table 2**). The mean age of the tinnitus and control groups was 40.1 and 38.0 years old, respectively, but varied widely between the studies ranging from 18 to 78-year-old participants. Since the data were not reported for smaller age groups, this data could not be separated into more narrowly defined age divisions. The tinnitus etiology was characterized as noise-induced for five of the studies, idiopathic for six studies, and not mentioned for the remaining 11 studies. Seventeen studies assessed patients with both bilateral or unilateral tinnitus, two studies used either bilateral tinnitus (Attias et al., 1993) or unilateral tinnitus exclusively (Maurizi et al., 1985) and three studies did not mention the lateralization of the tinnitus. Gender of the population was reported in 19 of the 22 studies of which five separated ABR data for males and/or females.

Hearing status was reported in all except two studies (De Lavernhe-Lemaire and Beutter, 1989, 1990). Among the studies that evaluated hearing, 17 studies used hearing status as a way to match controls to the tinnitus group. Three articles (Maurizi et al., 1985; Mahmoudian et al., 2013; Kim et al., 2016) did not have a control group and focused their comparisons on subgroups of tinnitus patients based on the configuration of the audiogram. These 17 studies either ensured that they used only a normal hearing population for both the tinnitus and control groups ($n = 12$), or a mixture of normal hearing and hearing loss for the control and tinnitus groups, matched based on the degree of hearing loss ($n = 5$). These studies used average audiometric thresholds of ≤15 dB HL ($n = 1$), <20 dB HL ($n = 3$), ≤20 dB HL ($n = 6$), <25 dB HL ($n = 5$), ≤25 dB HL ($n = 1$) as the criteria for normal hearing for the standard clinical frequencies. One study did not mention the criteria used to define normal hearing (Attias et al., 1993). Still, the frequency by which the audiometric criteria for normal hearing were applied varied from one study to the other. Indeed, there were typically defined from 0.25 to 8 kHz ($n = 9$), 0.125 to 8 kHz ($n = 1$), or 0.5 to 8 kHz ($n = 2$). Some studies limited the frequencies to a narrower range ($n = 5$). Of the five studies that used hearing loss populations, hearing loss was either undefined (Ikner and Hassen, 1990; Attias et al., 1993), defined within a limited range (i.e., 20-45, 21-49, 31-60, or 45-60 dB HL), or an unlimited range (i.e., above 15, 25 or 50 dB HL). A small number of studies ($n = 5$) tested frequencies above 8 kHz (Barnea et al., 1990; McKee and Stephens, 1992; Schaette and McAlpine, 2011; Gu et al., 2012; Gilles et al., 2016) (see also **Table 2**).

Characteristics of the Assessment and ABR Technique

Tinnitus was characterized in only 12 of the studies (see **Table 2**). Of these studies, four used a visual analog scale to determine either loudness ($n = 1$), severity ($n = 2$), or discomfort ($n = 1$), and eight used matching psychoacoustic procedures for loudness and pitch or a variation called the modified tinnitus spectrum procedure where pitch and loudness are rated (see **Table 2**). Residual inhibition was measured in three studies. The characteristics of the assessment and the ABR technique can be found in **Table 3**. The most commonly reported systems used to acquire the ABR were the Nicolet CA-1000 ($n = 4$) and the Bio-Logic NavPro or Traveler Express ($n = 5$). Transducers used were typically the supra-auricular headphones TDH-39(P) ($n = 6$) and TDH-49 ($n = 4$), or the insert headphones ER-3(A) ($n = 3$) with the exception of one study that used high frequency Sennheiser HDA-200 circumauricular headphones (Gu et al., 2012). The stimulus type was largely broadband clicks ($n = 19$) with a typical duration of 0.1 ms ($n = 16$) presented at a rate of 10–31 clicks per second. Exceptionally, one study used 0.05 ms clicks (Schaette and McAlpine, 2011) and another study used 3 ms tone bursts (Gerken et al., 2001). Presentation levels were generally high (>80 dB) and were either expressed in HL ($n = 8$), nHL ($n = 6$), or SPL ($n = 7$). Of the six studies reporting stimulus level in dB nHL, three reported using their own subjects to determine the minimum click intensity in dB SPL that elicited a behavioral response (Maurizi et al., 1985; Gu et al., 2012; Mahmoudian et al., 2013). When filter characteristics were reported ($n = 16$), the cutoff frequency of the high-pass filters ranged from 5 to 200 Hz and from the 1,500 to 5,000 Hz for the low-pass filters. Contralateral masking was used in 5 studies, all of which used a white noise at an intensity of 55 dB nHL (Gilles et al., 2016) or 50 dB HL (De Lavernhe-Lemaire and Beutter, 1989, 1990; Lemaire and Beutter, 1995; Kehrle et al., 2008).

Latency was reported in all studies except for De Lavernhe-Lemaire and Beutter (1990) and Schaette and McAlpine (2011). The most common outcome was no change in latency ($n = 9$) or an increase in the latency of waves I ($n = 8$), III ($n = 5$), and V ($n = 7$) for the tinnitus group (See **Table 2**). Only one study reported a decrease in wave V latency. Other latency changes for the tinnitus group varied considerably from increased interlatencies between waves III–V ($n = 4$), I–V ($n = 1$), and I–III ($n = 1$) to decreased interlatencies between waves I–II ($n = 1$) and I–V ($n = 3$). Out of the 12 studies that reported amplitude, four did not report any changes. The others reported the tinnitus group amplitudes either increased for waves III ($n = 1$), or decreased for waves I ($n = 4$), III ($n = 2$) and V ($n = 2$). Amplitude ratios were reported in four studies: V/III ($n = 1$) and V/I ($n = 3$). Gilles et al. (2016) was the sole study that reported the latency and amplitude of waves II and IV.

Meta-Analysis 1: Quantitative Analysis of ABR Latency and Amplitude Changes Separated by Hearing Status

The data of the 19 studies were compiled: a total of 1,240 subjects included in the tinnitus population and 664 control subjects were found. Three studies were not included because they have not reported any amplitude or latency data in format suitable for the analysis (see **Figure 1**). A summary of the mean latency and amplitude pooled from all studies is presented in **Table 4**. Each ear was treated as a separate data point when available in the literature. The raw latency and amplitude values for all the studies are available in Supplementary Table 2. **Table 4** shows that for the normal hearing populations, there is no significant difference between the tinnitus and non-tinnitus groups. The difference in mean latency for the normal hearing tinnitus group was 0, 0.01, and 0.03 ms higher than the control group for waves I, III, and V, respectively. For the hearing loss populations, the tinnitus group lower limit (95% CI) values of 1.75 (I), 3.83 (III), and 5.80 (V) ms were significantly higher than the upper limit (95% CI) values of 1.62 (I), 3.76 (III), and 5.68 (V) ms for the non-tinnitus groups. When comparing hearing loss groups, the tinnitus groups were 0.21, 0.15, and 0.22 ms delayed for waves I, III, and V compared to the group without tinnitus. Amplitudes for the normal hearing population were 0.04 μV lower for the wave I, and 0.02 and 0.01 μV higher for waves III, and V, respectively, for the tinnitus group. The hearing loss population showed 0.1, 0.09, and 0.06 μV lower wave I, III, and V amplitudes for the tinnitus group. Amplitudes were significantly different for the hearing loss population but not significantly different for normal hearing populations. Nevertheless, the wave I amplitude reduction in the tinnitus with normal hearing compared to the normal hearing controls was close to significance with a higher limit of the 95% CI of 0.24 μV compared to 0.23 μV 95% CI lower limit for the controls.

Meta-Analysis 2: Quantitative Analysis of ABR Latency and Amplitude Mean Difference between Tinnitus and Matched Control Groups Separated by Hearing Status

The mean differences in latencies and amplitudes between the tinnitus group and the matched controls (age and hearing status) were extracted when possible. For the latencies, the extraction of the mean difference was possible for only 10 out of the 15 studies that minimally matched their controls for age and hearing status. From the five excluded studies, one study did not report latencies (Schaette and McAlpine, 2011) and four studies provided insufficient information for data extraction (i.e., only the tinnitus data were presented, standard deviation was omitted, etc.; Barnea et al., 1990; McKee and Stephens, 1992; Rosenhall and Axelsson, 1994; Nemati et al., 2014). To note, only two studies out of the 10 studies that were kept for the latency meta-analysis did not include gender in their matching procedure (Attias et al., 1993, 1996). Interestingly, they were also the two studies with the highest degree of variability for both latency and amplitude analysis. For amplitudes, the number of included studies is even lower with five studies included in the second meta-analysis. Given that the amplitudes of waves III and V are poorly reported, the analysis was made on wave I only. Overall, similar problems extracting sufficient information were found for both the amplitude and latency data.

TABLE 3 | Characteristics of the Auditory Brainstem Responses methodologies used including the latency and amplitude outcome results.

Study	ABR system	Transducer	Polarity	Stimulus type	Presentation level(s)	Recording filters (Hz)
Attias et al., 1993	Microshev-4000 System	Not reported	Alternating	Broadband clicks, (0.1 ms duration 10 clicks/s)	120 dB SPL	200–3,000
Attias et al., 1996	Not mentioned	TDH-49	Alternating	Broadband clicks, (0.1 ms duration 10.3 clicks/s)	120 dB peSPL	100–2,000
Barnea et al., 1990	Microshev-2000	TDH-49	Alternating	Broadband clicks, (0.1 ms duration, 10 clicks/s)	120 dB SPL	200–2,000
Cartocci et al., 2012	Epic Plus	Not reported	Alternating	Broadband clicks, (0.1 ms duration, 11 clicks/s)	90 dB HL 80 dB HL	150–1,500
De Lavernhe-Lemaire and Bautter, 1989	Nicolet CA-1000	TDH-39P	Alternating	Broadband clicks, (0.1 ms duration, 11.1 clicks/s)	90 dB HL	150–1,500
De Lavernhe-Lemaire and Bautter, 1990	Nicolet CA-1000	TDH-39P	Alternating	Broadband clicks, (0.1 ms duration, 11.1 clicks/s)	90 dB HL	150–1,500
Gerken et al., 2001	Tucker-davis FT5 Grass P511k	ER2 inserts	Not reported	Tone bursts (1–8 kHz) (3 ms duration, 9.7 clicks/s)	112.5 peak dB SPL	1–3,000
Gilles et al., 2016	Bio-Logic with Nav Pro	ER-3A	Alternating	Broadband clicks, (0.1 ms duration, 31 clicks/s)	80 dB nHL	100–3,000
Gu et al., 2012	Tucker-Davis Medusa	HDA-200	Condensation	Broadband clicks, (0.1 ms duration, 11 clicks/s)	30, 50, 70, 80 dB nHL	5–5,000
Ikner and Hassen, 1990	Nicolet CA-1000	TDH-39	Condensation	Broadband clicks, (0.1 ms duration, 21.9 clicks/s)	75 dB nHL	Not reported
Kehrle et al., 2008	Amplaid Mk-15	TDH-50P	Alternating	Broadband clicks, (0.1 ms duration, 12 clicks/s)	80 dB HL	100–2,500
Kehrle et al., 2016	Biologic Navigator Pro AEP	E-A-RTONE 3A	Rarefaction	Broadband clicks, (0.1 ms duration, 21.1 clicks/s)	80 dB HL	100–3,000
Kim et al., 2016	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Lemaire and Beutter, 1995	Nicolet CA-1000	TDH-39P	Alternating	Broadband clicks, (0.1 ms duration, 11.1 clicks/s)	90 dB HL	150–1,500
Mahmoudian et al., 2013	Bio-Logic with Nav Pro	ER-3	Alternating	Broadband clicks, (0.1 ms duration, 11.1 clicks/s)	20 dB over the AEP threshold level	30–3,000
Maurizi et al., 1985	Amplaid MK 6	TDH-49	Rarefaction	Broadband clicks, (0.1 ms duration, 21 clicks/s)	60 dB nHL	200–2,000
McKee and Stephens, 1992	Biologic Evoked Potential System	Not reported	Not reported	Broadband clicks, (0.1 ms duration, 19.1 clicks/s)	85 dB HL	Not reported
Nemati et al., 2014	ICS CHARTR	Not reported	Alternating	Broadband clicks, (duration not reported, 11.1 clicks/s)	90 dB SPL	Not reported
Rosenhall and Axelsson, 1994	Madsen 2250 ERA	Not reported	Rarefaction	Broadband clicks, (duration not reported, 20 clicks/s)	80 dB nHL	150–2,000
Santos-Filha et al., 2014	Bio-Logic Traveler Express	TDH-39	Rarefaction	Broadband clicks (0.1 ms duration 19 clicks/s)	80 dB HL	Not mentioned
Schaette and McAlpine, 2011	Medelec Synergy T-EP system	TDH-49	Not reported	Broadband clicks, (0.05 ms duration, 11 clicks/s)	90 and 100 dB SPL	100–1,500
Singh et al., 2011	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

dB, Decibels; HL, hearing loss; SPL, sound pressure level; TDH, Telephonics supraauricular headphones; ER, Etymonic insert earphones; HAD, Sennheiser circumauricular headphones.

TABLE 4 | Summary table of the meta-analysis (1) of the mean latency and amplitude of waves I, III, and V for tinnitus and non-tinnitus groups separated by hearing status.

	Tinnitus			No tinnitus		
	I	III	V	I	III	V
NORMAL HEARING						
Mean latency (ms)	1.59	3.73	5.61	1.59	3.72	5.58
Standard error	0.02	0.02	0.02	0.01	0.02	0.02
95% CI	1.55–1.62	3.69–3.76	5.56–5.65	1.58–1.61	3.68–3.75	5.53–5.62
N-value	142	142	152	490	118	132
Mean Amplitude (μV)	0.21	0.34	0.43	0.25	0.32	0.42
Standard error	0.01	0.01	0.02	0.008	0.009	0.01
95% CI	0.19–0.24	0.31–0.36	0.39–0.48	0.23–0.26	0.30–0.34	0.40–0.44
N-value	105	75	75	248	212	212
HEARING LOSS						
Mean latency (ms)	1.77	3.86	5.84	1.56	3.71	5.62
Standard error	0.007	0.02	0.02	0.03	0.03	0.03
95% CI	**1.75**–1.78	**3.83**–3.89	**5.80**–5.88	1.5–**1.62**	3.66–**3.76**	5.57–**5.68**
N-value	1,407	369	385	69	69	69
Mean Amplitude (μV)	0.15	0.19	0.33	0.25	0.28	0.39
Standard error	0.004	0.004	0.005	0.04	0.03	0.03
95% CI	0.14–**0.16**	0.18–**0.20**	0.32–**0.34**	**0.17**–0.32	**0.23**–0.34	**0.34**–0.45
N-value	831	919	919	34	34	34

Confidence intervals (CI) and number of observations (n-value) are presented for each group. Bolded values are significant (comparing the limits of the 95% CI of the tinnitus to the no tinnitus group). Number of observations was obtained by adding the reported number of subjects or ears of each study within the group.

For the latency mean differences, the meta-analysis revealed that only three studies out of 10 found a significantly prolonged wave I in the tinnitus group compared to controls and two other studies were close to significance (**Figure 2**). To note, two of the studies that are not close to significance were the only ones that tested participants (tinnitus and controls) with hearing loss (**Figure 2**, white diamonds), all the other studies used normal hearing individuals for both the tinnitus and control groups (**Figure 2**, black diamonds). As previously mentioned, they were also the two only studies that did not match their groups on the basis of gender. For wave III and V latencies, significantly prolonged latencies were found in three studies for the former and four for the latter. Kehrle et al. (2008, 2016) were the only studies that showed all three waves were significantly prolonged although Ikner and Hassen (1990) reported a similar trend. Interestingly, none of the studies with a specific noise induced tinnitus etiology inclusion criteria reported a significant latency effect for any of the waves (**Figure 2**, studies in Bold).

For the mean amplitude differences, the second meta-analysis revealed that only two studies out of five found a significant reduction of wave I (see **Figure 3**). Two of the studies that did not report significant reduction of wave I amplitude tested noise-induced hearing loss participants with and without tinnitus (**Figure 3**, white diamonds). Gilles et al. (2016) reported a tendency of the wave I amplitude to be increased in the tinnitus group, although this did not reach significance (**Figure 3**).

DISCUSSION

The aim of the present scoping review was to investigate whether consistent ABR abnormalities are prevalent in populations with tinnitus. Although there is increasing interest in the use of ABRs for measuring auditory function in tinnitus individuals, the present scoping review found that the evidence of abnormalities within this population is sparse. Only 22 studies corresponding to the broad inclusion and exclusion criteria were found. Of these 22 studies, only 19 used control groups to make their comparisons. The present review unfortunately indicates that the tested tinnitus populations (i.e., *who*) are typically poorly defined across ABR studies as the vast majority did not report tinnitus etiology, assess and/or report the psychoacoustic properties of tinnitus, did not measure high frequency thresholds (above 8 kHz) and used various definitions of normal hearing and/or hearing loss. In regards to the methodology used (i.e., *how*), the ABR system, the type of transducer, the presentation level and the filtering strategies varied significantly across the studies. Still, the results of these studies (i.e., *what*) showed significant changes in amplitude and/or latency for high intensity stimulation levels as the current review did not assess low stimulation levels. In addition to this, longer latency and reduced amplitude of wave I for the normal hearing tinnitus group compared to hearing matched controls was consistently shown across numerous studies. Since high sound levels of stimulation were used in most studies, these results might indicate cochlear nerve fiber degeneration, a loss of neural synchrony, or both. These results will be further discussed by looking at the population characteristics, the various techniques and assessments, and the outcomes of the included studies. Based on these results, recommendations for future studies will be made as well as a description of the future direction of electrophysiology in tinnitus research.

Heterogeneous Population Characteristics

One of the issues found by the current review is the poorly defined and undefined tinnitus population tested. Many of the studies reported the tinnitus from their test groups were either subjective or idiopathic. The vast majority did not report the tinnitus etiology at all. Only four studies chose noise-induced tinnitus as their sample population of which two included sensorineural hearing loss participants. Interestingly, none of the studies on noise-induced tinnitus reported any significant effects on wave latencies and amplitudes with the only exception being Attias et al. (1996) who found higher wave III amplitude in the tinnitus group compared to age and hearing matched controls. These null results contrast the findings by Gu et al. (2012) and Schaette and McAlpine (2011) showing reduced wave I amplitude in human tinnitus subjects, as well as animal studies showing decrease ABR wave I amplitudes at high stimulation levels after noise exposure without significant hearing threshold shifts (Kujawa and Liberman, 2006, 2009). Still, these human studies did not mention the etiology of the tinnitus nor did they classify their subjects as having noise-induced tinnitus. Conversely, the

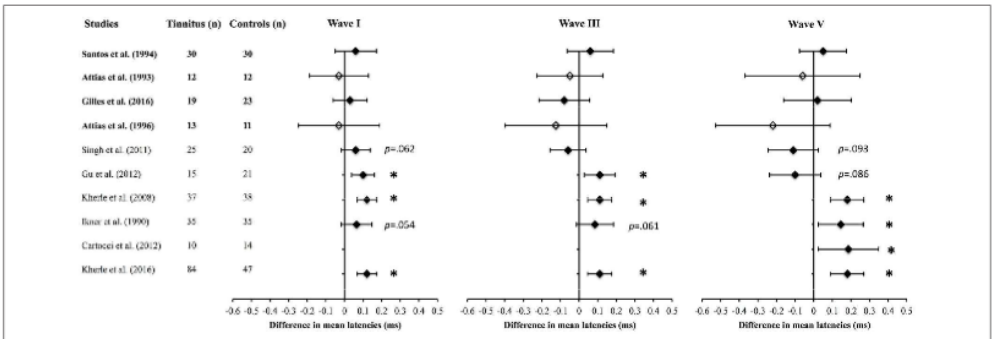

FIGURE 2 | Meta-analysis (2) of the net difference in latencies for Wave I, III, and V (95% CI) between tinnitus and control groups when matched for hearing status. Black diamonds represent studies with normal hearing participants and white diamonds studies with hearing loss participants. The studies in bold included only noise-induced tinnitus. *Asterisks represent significant differences ($p < 0.05$).

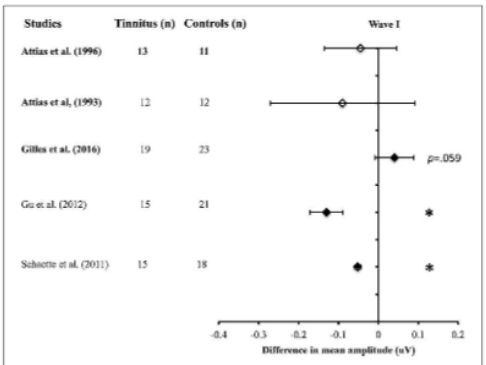

FIGURE 3 | Meta-analysis (2) of the net difference in amplitudes for Wave I (95% CI) between tinnitus and control groups when matched for hearing status. Black diamonds represent studies with normal hearing participants and white diamonds studies with hearing loss participants. The studies in bold included only noise-induced tinnitus. *Asterisks represent significant differences ($p < 0.05$).

Kujawa and Liberman (2006, 2009) animal studies did not assess tinnitus. Thus, the direct link between ABR abnormalities obtained in noise-induced animals and humans is not completely elucidated. Indeed, a recent study investigating ABRs in a young adult cohorts with normal audiograms but exposed to noise, did not find any significant reductions of wave I (Prendergast et al., 2017). More so, a recent study on a young adult sample (early 20's) of noise-induced tinnitus found no differences in the amplitude and latency of any of the ABR waves (Gilles et al., 2016). In that study, the ABR was assessed only on a subgroup of tinnitus and controls subjects. Their participants were matched for age, sex, and hearing thresholds for pure tones of 1–4 kHz only. Since a measure of synaptopathy such as the AP/SP ratio of the electrocochleography and very high frequency thresholds have been shown to be correlated (Liberman et al., 2016), it is thus possible that the tinnitus group had better thresholds at very high frequencies (>8 kHz) than the controls, and less synaptopathy. Still, this would be very unlikely considering that tinnitus subjects usually display more hearing loss than controls for those high frequencies when matched for normal thresholds at conventional frequencies (Fournier and Hébert, 2013). One possible interpretation of these results is that it takes some time, maybe years, for the nerve fibers to degenerate and therefore to effect the ABR responses. Another possibility is that ABRs are not sensitive enough to reveal synaptopathy and/or that synaptopathy loss is not necessary to develop tinnitus. Also, differences across species have been noted in the development of synaptopathy (Prendergast et al., 2017): losses of cochlear synapses have been shown to be irreversible in rodents but not in guinea pigs (although their function remained abnormal) (Liu et al., 2012; Shi et al., 2013; Song et al., 2016). Thus, one has to be cautious when comparing results from different animal species and, even more cautious, when translating such results to human listeners.

Very few studies assessed ABR wave characteristics between tinnitus and controls with hearing loss. Considering that tinnitus is often associated with hearing loss and remains rare in individuals with normal hearing, why have so few studies assessed ABR abnormalities in tinnitus participants with significant hearing loss? It is well known that two of three individuals with hearing loss will go on to develop tinnitus (Hoffman and Reed, 2004). It is possible these studies purposefully avoided recruiting participants with hearing loss in order to prevent known confounding effects of hearing loss on the ABR. However, ABR abnormalities in individuals with hearing loss might nevertheless help reveal certain underlying neural mechanisms responsible for tinnitus generation. To date, the only reported significant effect in this

specific population is higher wave III amplitude (Attias et al., 1996).

We conducted the first meta-analysis to demonstrate the effects of tinnitus within a large clinical population separated based on hearing loss. The advantage of such an approach is that the population is more comparable to what would be seen in a clinical setting, and the higher power, due to the large sample size, increases the chances of revealing tinnitus-related cofactors, such as hearing loss, whilst reducing the effects of random variables not related to tinnitus (i.e., gender, thickness of the scalp, transducer frequency response). This analysis shows increased latencies and reduced amplitudes for all three waves (I, III, and V) for tinnitus subjects compared to controls (**Table 4**) with hearing loss. However, these results must be interpreted cautiously as the number of subjects with tinnitus was five to 20 times higher than the number of controls depending on the wave. This imbalance of the number of subjects is the result of compiling all the data available from the entire yield of studies even though four studies did not report a control group. These ABR effects did not survive the second meta-analysis where only studies with matched control groups were used: the only two studies that used matched hearing loss control groups did not report any significant changes (Attias et al., 1993, 1996). It can be argued that the longer latencies and lower amplitudes found in the first meta-analysis may be the result of the compiled tinnitus group having a greater degree of hearing loss than controls (for amplitude: Sand and Saunte, 1994; for latency: Keith and Greville, 1987). The possibility of a gender and/or an aging bias could also account for the differences obtained in meta-analysis one.

The present review highlighted some variability in the criteria used to define normal hearing and an even larger variability in defining hearing loss. Future studies should define normal hearing as thresholds of less or equal to 15 dB HL minimally at all standard clinical frequencies thus from 250 to 8,000 Hz (Clark, 1981). More so, the measurements of high frequency thresholds (>8 kHz) need to be undertaken as significant threshold elevation for those frequencies (10–16 kHz) have been recently shown and interpreted as an early sign of synaptopathy in humans (Liberman et al., 2016). More so, high frequency hearing loss (>8 kHz) in tinnitus patients with conventional normal hearing (250– 8,000 Hz) have been reported (Fournier and Hébert, 2013; Vielsmeier et al., 2015). It is thus crucial to control for high frequency thresholds, at least up to 16 kHz, when comparing tinnitus subjects to controls in order to distinguish with confidence the presence of synaptopathy. Participants should be separated and grouped based on the presence of hearing loss. In addition to this, the degree (mild, moderate, severe, or profound), the origin (cochlear vs. neural), and the configuration (flat, high, or low frequency slope, notch) of the hearing loss should be clearly defined and reported.

One other recommendation is to recruit tinnitus participants based on tinnitus etiology (or report etiology) and/or psychoacoustic measurements in order to separate the test groups. This in turn might show ABR related patterns within each subgroup that would be otherwise masked by the heterogeneity of the sample. Few studies used characteristics of the tinnitus perception, such as pitch and loudness matching of the tinnitus percept or residual inhibition, as a means to separate various tinnitus subtypes. For instance, Noreña et al. (1999) classified the late auditory evoked potentials in three tinnitus subgroups based on their self-reported changes of tinnitus perception in relation to noise. They were classified as having decreased, increased, or unchanged tinnitus perception in the presence of noise. Based on this classification, they found that patients with decreased tinnitus perception in noise had greater intensity-dependence and longer N1 latency than the subgroup that reported increased tinnitus perception. Within the included ABR articles for this review, Maurizi et al. (1985) used residual inhibition (RI); a known phenomenon where a temporary reduction in the loudness or even disappearance of tinnitus follows the cessation of a masking noise, to stratify unilateral tinnitus into positive or no RI subgroups. They found wave I was prolonged for the positive RI group and wave V was prolonged for the no RI group of the tinnitus ear compared to the contralateral ear. They also performed ABR testing before and after treatment for each group. Interestingly, they found that after masking, the positive RI group's longer wave I latency had disappeared but the no RI group's wave V latency did not change. Stratification of the tinnitus test population based on psychoacoustic methods and added information on the tinnitus etiology would be crucial for future studies on auditory evoked potentials.

To note, only one study reported a potential adverse effect of the ABR on tinnitus subject. Indeed, Gu et al. (2012) reported that they could not complete the ABR assessment in 10 participants because they did not tolerate the stimulus intensity level. The co-occurrence of hyperacusis, which is defined as a hypersensivitity to moderate to loud sounds, and tinnitus have been shown to be very high (Hébert et al., 2004, 2013; Dauman and Bouscau-Faure, 2005). Still, the Gu and colleagues group is the only one to have reported that the hypersensitivity was detrimental for the assessment. From all the studies found in the current review, four measured hyperacusis in different ways within their sample: one used the Khalfa questionnaire (Gilles et al., 2016) and the others used loudness discomfort levels (LDL) (Gerken et al., 2001; Cartocci et al., 2012; Gu et al., 2012). It is not known whether hyperacusis was detrimental for the ABR assessment in those studies, as none reported it. Future studies should address the potential adverse effects of ABR testing such as discomfort or pain on tinnitus patients with and without hyperacusis. A potential cut-off on a hyperacusis questionnaire or on a psychophysical method such as LDL could be used to triage those participants for which the procedure is judged to be safe from those at risk of discomfort.

Various Techniques and Assessments

Several techniques and assessments revealed by the review may have impacted the ABR results. One suspect issue occurs with the type of transducer. Out of the studies that reported the type of transducer used, 11 used various types of supra-auricular headphones while only four used insert earphones. According to Van Campen et al. (1992), insert earphones such as the ER-3A insert earphones can increase interaural attenuation, ambient noise attenuation, patient comfort, and eliminate ear canal collapse. Their study measured the acoustic output of TDH 39P, TDH 49P, and ER-3A inserts earphones on a KEMAR mannequin

and used the same transducers for measuring click ABRs on normal hearing adults. One of the main differences they showed was that both TDH earphones had greater ringing than ER-3As for stimulus intensities down to 15 dB nHL. In addition to this, when tested on normal hearing adults, the insert earphones elicited a wave V that was significantly more delayed by 1.15 and 1 ms when stimulated at 40 dB nHL than the TDH earphones. Additionally, ER-3A earphones produced a significantly smaller wave I but similar wave V amplitude at 80 dB nHL than the TDH earphones, resulting in a greater V/I amplitude ratio. Given these differences, comparing data between insert and TDH earphones may be problematic.

Another potential issue comes from the frequency response of using various transducers with different response bandwidths. For example, the frequency response of an ER-3A earphone to a 500 Hz tone at 118.5 dB SPL is flat up to 4 kHz (E-A-R® Tone™ calibration specification sheet). This contrasts the Sennheiser HDA-200 headphones used by Gu et al. (2012) that was reported to have a bandwidth up to 8 kHz or the TDH 49 headphones that stimulate up to 7.1 kHz (Guest et al., 2016). Derived band measurements of the ABR to click stimuli show that wave I is mostly generated by characteristic frequencies above 2 kHz however wave V can be evoked by lower frequencies (Don and Eggermont, 1978; Abdala and Folsom, 1995). This may mean that the frequency response of the transducers used may influence the intensity of certain frequencies that may differ between studies. This variability may also contribute to the differences in latencies and amplitudes reported.

Heterogeneous Outcomes

The results found from the 22 studies were quite heterogeneous. For latencies, nine studies reported no change for any of the waves compared to nine who reported increased latency for waves I, V, and VII. Still, most well-controlled studies with appropriate matching procedures reported longer latencies for tinnitus compared to controls with wave I being the most consistently affected wave (**Figure 2**). A significant latency shift for all the three waves was found in Kehrle et al. (2008, 2016) and close to significance in Ikner and Hassen (1990) study. In these cases, the latency shift seen for waves III and V are not likely to be the result of the delayed wave I latency (due to neural damage) following through the other waves because the inter-peaks (I–V, III–V) were reported as abnormal in those same studies (see **Table 3**). These results might be related to a lack of central compensation in tinnitus individuals as suggested by Rüttiger et al. (2013).

Similar discordances were found within the amplitude data: four studies did not find any changes in amplitude for tinnitus, four reported decreased wave I, and either a decreased, an increased or even no modifications of the following amplitudes of waves III and V. Overall, only two of the five well-controlled studies reported decreased wave I amplitude. In addition to this, two well-controlled studies reported a higher V/I ratio (Kehrle et al., 2008; Nemati et al., 2014). More well-controlled studies are thus needed to clarify the presence of synaptopathy, as measured by wave I amplitude, in tinnitus patients. The large variability within the two studies with hearing loss tinnitus subjects prevent any conclusions that the trend towards lower wave I amplitude is due to an actual effect in tinnitus.

These mixed amplitude results may be related to the relative contribution of each type of nerve fibers (i.e., low-, medium-, and high-spontaneous rate) on the ABR signal. All the reviewed studies used high intensity stimuli that can be presumed to saturate the HSR fibers revealing potential difference linked only to LSR fibers. However, the specific contribution of each neural population (i.e., low-, medium-, and high- spontaneous rate) on the ABR waveform is not known. Substantial damage, for example to LSR fibers, may contribute to changes in the ABR amplitude in addition to the high spontaneous rate fibers. Bourien et al. (2014) have recently demonstrated that LSR fibers might have a negligible contribution to wave I ABR by measuring the compound action potential after selective damage to the LSR auditory nerve fibers of gerbils. They suggested that wave I reduction might be the result of damage to medium spontaneous rate fibers, which are usually mixed with LSR fibers in previous studies. It is also possible that damage to the LSR and MSR fibers varies across the length of the basilar membrane in such a way that the regions corresponding to certain frequencies have less damage than other areas. One way to target regions specifically affected by synaptopathy is to use specific frequencies or tone bursts, however narrowing the stimulus to include fewer frequencies may further reduce the number of responding fibers. For example, Gerken et al. (2001) used 10 tone bursts (1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 kHz) at a level of 112 dB SPL to elicit the ABR in a tinnitus and non-tinnitus population with and without hearing loss. They found no significant differences for the ABR amplitude and latencies (Wave I, III, V) of the tinnitus group compared to the non-tinnitus subjects. Still, they did not use any matching procedures to compose their groups and included only nine tinnitus subjects with hearing loss. It may be interesting to replicate the Gerken et al. (2001) study on normal hearing populations (for all frequencies up to 16 kHz) with and without tinnitus, and with appropriate matching procedures (gender, age, and hearing status) for different intensity levels, for different frequencies (from low to high, including tinnitus pitch) in order to compare the response of the HSR, MSR, and LSR fibers.

Since the search for this review was conducted, two more articles on ABR and tinnitus populations have been published: Ravikumar and Murthy (2016) and Guest et al. (2016). Both studies compared tinnitus populations with normal hearing to normal hearing matched controls. Normal hearing was not defined in the former, and was defined as pure tone thresholds of ≤20 dB HL at 0.25–8 kHz for the latter. Latencies of wave I, III, and V were significantly ($p = 0.05$) prolonged (Ravikumar and Murthy, 2016) and wave V amplitude was higher but not significant (Guest et al., 2016). The latter study also reported no differences in the amplitude of wave I and found there was no correlation between the amplitude of wave I and history of noise exposure.

Recommendations for Future Studies on ABR

Clear and simple recommendations for future ABR investigations on tinnitus can be determined from these

findings with the aim of improving future reviews on the subject, showing more reliable evidence of tinnitus, and making it easier to replicate previous studies. Most imperatively, it is highly encouraged that researchers report all the data collected including latencies and amplitudes of all the waves in a format that is suitable for meta-analysis. The meta-analysis of the current study was difficult particularly when latency or amplitude data was left unreported. From 22 studies found on ABR investigations of tinnitus in humans, only 10 studies could be used for the second meta-analysis to compare the mean difference of latencies between tinnitus and controls. Unfortunately, this represented <50% of all the studies found. For amplitude, even fewer studies were retained (n = 5), which represents <25% of all the studies. The mean and standard deviation of the latencies and amplitudes of the waves found within their paradigm for the tinnitus and control groups should be reported separately. Negative and non-significant results should always be reported in a similar fashion.

Secondly, all future ABR protocols should at least include control groups matched for gender, age and hearing status for sufficient control over these covariables. As mentioned previously, the two studies displaying the greatest variability for latencies and amplitudes in the second meta-analysis (Attias et al., 1993, 1996) did not match for gender between groups. Still, when comparing more recent studies to older ones, there appears to be a clear trend toward the use of more restrictive matching procedures. It is further suggested that hearing be assessed and matched for frequencies up to at least 16 kHz between groups. Studies should recruit participants with similar tinnitus etiologies (e.g., noise trauma) and include psychoacoustic measurements such as pitch and loudness matching, minimum masking level and residual inhibition. Future research should also consider separating participants into narrower age bands or at least separate younger and older subjects into two different groups. The two studies reporting reduced wave I in tinnitus (Schaette and McAlpine, 2011; Gu et al., 2012) tested participants approximately 10 years older on average than the study of Gilles et al. (2016) which included only participants below the age of 30. The absence of synaptopathy using wave I amplitude has also been reported in a study on noise-exposed young adults (mean age of 23, ranging from 18 to 36 years old), however tinnitus was not assessed (Prendergast et al., 2017). It is thus recommended that an age cut-off around 30 years old be used for future work. A sample size of at least 30 subjects per group is also recommended in order to reduce variability of the measures and to increase statistical power. Regarding the technical aspects of ABR measurement, insert headphones are preferred over circumauricular ones in order to optimize interaural attenuation, ambient noise attenuation, and to reduce the risk of ear canal collapsing. The frequency response of the transducer should also include as many frequencies above 2 kHz as possible.

Future Directions

Since the key publication of animal research demonstrating evidence of cochlear synaptopathy after noise exposure (Kujawa and Liberman, 2006, 2009), there has been a growing interest in improving ABR measurements in humans. Reliable ABR waveforms can sometimes be difficult to obtain mostly because of high inter-subject variability due to factors such as small signal to noise ratios, head shape, sex, as well as the various methodological concerns described above. Many research groups have attempted to address these issues by either improving the methodology of the click or tone-burst ABR method or by proposing new methods of assessment. For example, one study used an electrode placed on the tympanic membrane (TM) in order to improve the signal to noise ratio (Stamper and Johnson, 2015). Using a similar electrode tip on the TM, another group used electrocochleography instead of ABR to show significant differences in the SP/AP ratio between high and low noise exposure risk groups of participants (Liberman et al., 2016). This finding still needs to be replicated, but electrocochleography could potentially become a standard measure of synaptopathy instead of the classical ABR. Another group showed delayed wave V ABRs when responding to clicks in background noise as evidence of the presence of synaptopathy in animals and humans (Mehraei et al., 2016). The use of envelope following responses (EFR) with amplitude-modulated tones in notched noise with varying modulation depth have also shown deficits that are consistent with synaptopathy (Bharadwaj et al., 2015). All these new techniques could easily be applied to tinnitus participants. This in turn can bring new insight on a possible role, if any, played by cochlear synaptopathy in the generation of tinnitus. More so, the application of a paradigm to desynchronize neural activity may help reveal potential tinnitus mechanisms. Indeed, when click-rate is increased, the nerve fibers appear to have more difficulty synchronizing their discharge to the stimulus, resulting in smaller ABR amplitudes and prolonged wave V latencies (Konrad-Martin et al., 2012). Higher synchronous activity at higher levels of the auditory system related to tinnitus might thus only be revealed when using high click-rates.

Finally, ABRs have more recently been used not only to understand the pathophysiology of tinnitus but also objectify its presence in individuals. The gap-in-noise ABR (or GIN-ABR) has been used in animal subjects with different background noise frequencies before and after tinnitus induction by salicylate (Lowe and Walton, 2015). Using this method, they found a significant reduction in gap detection after salicylate treatment for only the 16 kHz background noise condition. The authors concluded that since salicylate is known to produce a 16 kHz tinnitus percept that appears to fill the gap, the GIN-ABR may be effective for objectifying the presence of tinnitus in animals. This in turn may be a promising new avenue for future auditory brainstem research applied to humans with tinnitus.

AUTHOR CONTRIBUTIONS

All the authors contributed to this work. VM and AK provided the original conception and design of the study. VM and PF worked on data acquisition, analysis, and interpretation. They both wrote the manuscript. DB, AN, and AK provided

intellectual feedback and revised the content of several previous versions of the manuscript. All authors (VM, PF, DB, AN, and AK) approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00237/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer NKE and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

Appendix 2: REB certification

File Number: H06-14-35 **Date (mm/dd/yyyy):** 06/19/2017

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Amineh	Koravand	Health Sciences / Others	Supervisor
Daniel	Benoit	Health Sciences / Physiotherapy	Co-Supervisor
Kenneth B.	Campbell	Social Sciences / Psychology	Co-investigator
Paniz	Tavakoli	Social Sciences / Psychology	Co-investigator
Eric	Zorbas	Health Sciences / Others	Co-investigator
Victoria	Milloy	Health Sciences / Others	Student Researcher
Don	Nguyen	Health Sciences / Others	Student Researcher

File Number: H06-14-35

Type of Project: Independent Student Project

Title: Effects of Auditory Evoked Potentials on the Severity of Tinnitus

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
08/07/2017	08/06/2018	Renewal

Special Conditions / Comments:
N/A

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File Number: H06-14-35 **Date (mm/dd/yyyy):** 06/19/2017

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: https://research.uottawa.ca/ethics/forms.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: https://research.uottawa.ca/ethics/forms.

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5387 or by e-mail at: ethics@uOttawa.ca.

Signature:

[redacted]

Mélanie Rioux
Ethics Coordinator
For Catherine Paquet, Director of the Office of Research Ethics and Integrity

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Appendix 3: Consent forms

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Effect of Auditory Evoked Potentials on the severity of tinnitus

Consent form

I, _____, hereby accept to participate in the research project as described in this form. I have carefully read the content of this letter and understand that I will be completing a questionnaire regarding my hearing history and tinnitus history, after which I will be participating in various audiometric tests. The first consists of a basic hearing test and the second includes measures of auditory brain responses. These measures will be carried out during a single testing session lasting approximately 2-3 hours. An audiologist (the principal investigator of this project) is responsible for the data collection.

The risks related to these tests have been explained to me, and I fully understand them. I have also received a detailed explanation of the expected results. I had ample opportunity to ask questions, in which case adequate answers were provided. Furthermore, I am aware that I will constantly have the opportunity to ask questions during the tests and to receive appropriate answers. I understand that I may choose to withdraw from this research study at any time, for any reason. By participating in this study, I will be contributing to the development of evaluation tools in the field of tinnitus research.

If my candidacy cannot be retained because I do not meet the audiometric criteria, I will be referred, if necessary, to one of the following audiology services:

- Ottawa Hospital
  - General Campus, 501, Smyth Road (613) 737-8899
  - Civic Campus, 1053, Carling Avenue (613) 798-5555
- Advanced Hearing Clinic
  - 1657 Carling Ave, Ottawa (613) 728-4327
- Hearing Health Clinic/Clinique de santé auditive
  - 260 Centrum Boulevard, Orléans (613) 837-9902
- Centre hospitalier de Gatineau
  - 909 Boul. de la Vérendrye O., Gatineau (819) 561-8100
- Centre hospitalier de Hull
  - 116 Boul. Lionel Émond, Gatineau (Secteur Hull) (819) 595-6300
- Polyclinique de l'oreille
  - 120 Boul. de l'Hôpital, Gatineau (819) 561-0002
  - 290 Boul. St-Joseph, Gatineau (Secteur Hull) (819) 776-0163

In order to ensure data confidentiality, only the researchers mentioned below will have access to the collected data. I understand that, under no circumstances, will my identity be revealed and that a number assigned to my file will ensure this anonymity.

Finally, I am aware that the collected data will be locked away under lock and key in the hearing science laboratory located in room 1117, at the Roger Guindon campus, and that they will be destroyed five years after the publication of results.

For additional information regarding this research, I may contact any of the researchers involved in this study, Amineh Koravand, Victoria Milloy, Daniel Benoit, Kenneth Campbell, Paniz Tavakoli or Eric Zorbas. Their contact information is found below.

For all information, requests or complaints regarding the ethical conduct of this study, enquiries can be addressed to the Protocol officer for ethics in research at the following contact information: Protocol officer for ethics in research, University of Ottawa, Tabaret Hall, 550 Cumberland, room 154, Ottawa, Ontario K1N 6N5, phone number: (613) 562-5387, e-mail: ethics@uottawa.ca. There are two copies of the consent form, one of which I may keep.

I will be provided with compensation for my time and travel regardless of whether I decide to participate or withdraw from the study. Should I withdraw, my data will be destroyed and not used.

I consent to participating in this research project:
Researcher's signature: _____ Date: _____

Participant's signature: _____ Date: _____

I would like to receive a summary of the results of this research.

Please send it to the following address:

_____

_____

_____

☐ I do not want to receive a summary of the results of this research.

☐ I authorize the researchers to solicit my participation in future studies.

Names of researchers:

Amineh Koravand, Ph.D., Victoria Milloy, Ph.D.(C) Daniel Benoit, Ph.D., Kenneth Campbell, Ph.D., Paniz Tavakoli, Ph.D.(C), Eric Zorbas, B.Sc. Don Nguyen, B.Sc, and Fauve Duquette-Laplante, B.Sc. University of Ottawa, Faculty of Health Sciences, School of Rehabilitation Sciences, 451 Smyth Road, Ottawa, Ontario, K1H 8M5. Phone number: (613) 562-5800, ext. [redacted]

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Effet des potentiels évoqués auditifs sur la séverité de l'acouphène

Formulaire de consentement

Je, _____, suis invité(e) à participer au projet de recherche décrit dans la lettre d'information ci-jointe. J'en ai lu attentivement le contenu et je comprends que j'aurais à compléter un questionnaire concernant mon histoire auditive et mon histoire de l'acouphène, et que j'aurais ensuite à participer à deux tests audiométriques. Le premier test est un dépistage auditif et l'autre a pour but de mesurer la transmission neurale de l'acouphène. Ces mesures se dérouleront pendant une session d'environ 2-3 heures. Un audiologiste (la chercheure principale de ce projet) sera responsable de la collecte de données.

Les risques reliés à ces tests m'ont été expliqués et je les comprends bien. J'ai aussi reçu une explication détaillée au sujet des résultats attendus. J'ai eu l'occasion de poser des questions, pour lesquelles j'ai obtenu des réponses satisfaisantes. De plus, je sais que j'aurai la possibilité de poser des questions, et de recevoir les réponses, à n'importe quel temps durant la session de tests. Je sais aussi qu'en tout temps, je suis libre de me retirer de ce projet de recherche, peu importe la raison. Ma participation à cette étude sera profitable puisqu'elle contribuera au développement d'outils d'évaluation de l'acouphène.

Si ma candidature ne peut être retenue parce que je ne réponds pas aux critères audiométriques, je serai référé(e), si nécessaire, à un des services d'audiologie suivants :

- Hôpital d'Ottawa,
  - Campus Général, 501 rue Smyth (613) 737-8899
  - Campus Civic, 1053 avenue Carling (613) 798-5555
- Clinique de Advanced Hearing
  - 1657 avenue Carling, Ottawa (613)728-4327
- Clinique de Santé Auditive
  - 260 Centrum Boulevard, Orléans (613) 837-9902
- Centre hospitalier de Gatineau
  - 909 Boul. de la Vérendrye O., Gatineau (819) 561-8100
- Centre hospitalier de Hull
  - 116 Boul. Lionel Émond, Gatineau (Secteur Hull) (819) 595-6300
- Polyclinique de l'oreille
  - 120 Boul. de l'Hôpital, Gatineau (819) 561-0002
  - 290 Boul. St-Joseph, Gatineau (Secteur Hull) (819) 776-0163

Afin d'assurer la confidentialité des participants, seuls les chercheurs mentionnés ci-bas auront accès aux données recueillies. Je comprends que, sous aucun prétexte, mon identité ne sera révélée et qu'un numéro sera assigné à mon dossier afin d'assurer cet anonymat.

Finalement, je suis conscient(e) que les données seront conservées sous clef dans les laboratoires du local 1117, du Pavillon Roger Guindon, et qu'elles seront détruites cinq ans après la publication des résultats de ce projet.

Pour de plus amples informations concernant cette recherche, je peux contacter les chercheurs associés à cette étude, soit Amineh Koravand, Victoria Milloy, Daniel Benoît, Kenneth Campbell, Paniz Tavakoli ou Eric Zorbas dont les coordonnées apparaissent ci-bas.

Pour des informations, requêtes ou plaintes concernant la déontologie associée au processus de cette étude, il faut s'adresser à la responsable de l'éthique aux coordonnées suivantes: Responsable de l'éthique en recherche, Université d'Ottawa, Pavillon Tabaret, 550 rue Cumberland, pièce 154, Ottawa, Ontario K1N 6N5, tel: (613) 562-5387, courriel: ethics@uottawa.ca. Deux copies du présent formulaire de consentement sont disponibles, dont une que je peux conserver.

Je recevrai une compensation pour mon temps et le voyage même si je me retire de l'étude. Si je me retire, toutes mes données soient détruites et ne seront pas utilisées.

Je consens à participer à ce projet de recherche:

Signature du participant: _____ Date: _____

Signature du chercheur : _____Date: _____

☐ J'aimerais une copie des résultats du présent projet de recherche S.V.P l'envoyer à l'adresse suivante:

_____

_____

☐ Je ne désire pas de copie du présent projet de recherche.

☐ J'autorise les chercheurs à communiquer avec moi pour des études futures.

Noms des chercheurs:

Amineh Koravand Ph.D., Victoria Milloy Ph.D. (c) et Daniel Benoit Ph.D., Kenneth Campbell, Ph.D., Paniz Tavakoli, Ph.D.(c), Eric Zorbas, B.Sc. et Don Nguyen, B.Sc. Fauve Duquette-Laplante, B.Sc. Université d'Ottawa, Faculté des Sciences de la Santé, École des sciences de la réadaptation, 51 rue Smyth, Ottawa, Ontario K1H 8M5. Numéro de téléphone: (613) 562-5800, ext. [redacted]

Appendix 4: Information letter

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Université d'Ottawa
Faculté des sciences de la santé

École des sciences de la réadaptation

University of Ottawa
Faculty of Health Sciences

School of Rehabilitation Sciences

Effects of Auditory Evoked Potentials on the Severity of Tinnitus

Information letter

Names of researchers: Victoria Milloy, Ph.D.(c), Amineh Koravand, Ph.D., Daniel Benoit, Ph.D., Kenneth Campbell, Ph.D., Paniz Tavakoli, Ph.D.(c), Eric Zorbas, B.Sc., Don Nguyen, Fauve Duquette-Laplante
Institution, Faculty, Department: University of Ottawa, Faculty of Health Sciences, School of Rehabilitation Sciences, 451 Smyth Road, Ottawa, ON K1H 8M5
Phone number: (613) 562-5800 ext. [redacted]
Fax number: (613) 562-5428
E-mail: [redacted]

The Auditory Evoke Potentials are a tool used to measure the integrity of an individual's auditory nerve to cortex. The test requires the listener to sit in a chair while the test is conducted. Several electrodes are placed on the head. A set of insert headphone are inserted in the ears of the listener and a continuous recording of 80 dBA clicks is administered.

The measured responses (known as auditory evoked potentials) originate from the auditory nervous system's structures following the presentation of an acoustic stimulus. These structures include the cochlea, auditory nerve, auditory brainstem, medial geniculate body, thalamus, and the auditory cortex. The potentials are depicted as peaks and troughs with specific amplitudes and latencies. Shorter latencies are produced by structures of the auditory nervous system that are more peripheral, such as the cochlea, whereas higher order structures such as the auditory cortex provide the longest latencies. A plethora of previous studies have shown differences in AEPs in tinnitus participants compared to a control group at different points along the central auditory nervous system [electrocochleography (Majumdar et. al., 1983), auditory brainstem responses (Schaette and McAlpine, 2011; Gu et. al., 2012), middle latency responses (Singh et. al., 2011; Gerken et. al, 2001), and long latency responses (Pineda et. al., 2008; Delb et. al., 2008; Strauss et. al., 2008)].

During this study, you will be asked to:
1) Take part in a basic hearing test, divided into four parts. A questionnaire regarding your hearing history will be completed and an otoscope (an instrument equipped with a light) will be used to visualize your auditory canals and eardrums. A second instrument

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will be used to evaluate the pitch and intensity of the tinnitus Finally, in order to establish your hearing thresholds, you will be asked to detect soft sounds of different frequencies presented under headphones;
2) Lay relaxed in a chair while watching a NetFlix film of your choice while a recording of the brain is made. A cap with several electrodes will be placed on the head and gel will be inserted through the cap.
3) Using the same setup, you will be asked to perform a discrimination task.

These steps will be performed by the principal investigator who is also an audiologist.

If your candidacy cannot be retained because you do not meet the audiometric criteria, an appointment with a local audiologist will be recommended.

You are free to withdraw from this research project at any time. In this case, any results or information gathered will not be used for the project and will be deleted or discarded immediately. Results and information gathered will be used solely for the purpose of this research project and will be kept confidential. In order to ensure anonymity, only codes will be associated with the results obtained throughout this study. Only the researchers involved in this study will have access to the collected data, which will be locked away in a cabinet in the laboratory and destroyed five years after the publication of results.

Potential risks involved in this research are minimal. Sterilized probe tips are inserted at the entrance of the external auditory canal in order to assess the eardrum's mobility. The probe then varies the pressure in the ear canal, which can result in slight discomfort for some individuals. However, this test presents no danger for the eardrum since the probe tip is placed at the outer edge of the canal and is sterilized to avoid any risk of contamination. Furthermore, all sound stimuli will be below the occupational limit for sound exposure. By participating in this study, you will be contributing to the development of evaluation tools in the area of tinnitus.

For additional information, comments or worries, please contact one of the researchers (contact information above). For all information, requests or complaints regarding the ethical conduct of this study, please address your enquiries to the Protocol officer for ethics in research, University of Ottawa, Tabaret Hall, 550 Cumberland, room 154, Ottawa, Ontario K1N 6N5, phone number: (613) 562-5387, email : ethics@uottawa.ca. Please keep a copy of the information letter for your records.

uOttawa

Université d'Ottawa
Faculté des sciences de la santé

École des sciences de la réadaptation

University of Ottawa
Faculty of Health Sciences

School of Rehabilitation Sciences

L'effet des potentiels évoqués auditifs du tronc cérébral sur la sévérité de l'acouphène

Lettre d'information

Noms des chercheurs : Victoria Milloy, Ph.D. (c), Amineh Koravand, Ph.D., Daniel Benoit, Ph.D., Kenneth Campbell, Ph.D., Paniz Tavakoli, Ph.D. (c), Eric Zorbas, Don Nguyen, Fauve Duquette-Laplante
Institution, Faculté, Département : Université d'Ottawa, Faculté des Sciences de la Santé, École des sciences de la réadaptation, 451 rue Smyth, Ottawa, ON K1H 8M5
Numéro de téléphone : (613) 562-5800 poste [redacted]
Télécopieur : (613) 562-5428
Adresses de courrier électronique : [redacted]

Les potentiels évoqués auditifs (PÉA) sont un outil pour évaluer l'intégrité du nerf auditif de la cochlée jusqu'au cortex. Pour réaliser le test, le participant doit être assis sur une chaise pendant environ 60 minutes. Plusieurs électrodes sont placées sur la tête de l'individu: une sur le front et une derrière chaque oreille. Des écouteurs sont insérés dans les oreilles du participant et un bruit continu, qui ressemble à des clics à un niveau de 80 dBA, est administré.

Suite à la présentation d'un stimulus acoustique, les structures du système nerveux auditif produisent une réponse que l'on peut mesurer (des potentiels évoqués auditifs). Ces structures auditives comprennent la cochée, le nerf auditif, le tronc cérébral, le corps géniculé médial, le thalamus, et le cortex auditif. Les potentiels sont représentés par des pics et des creux avec des amplitudes et des latences spécifiques. Des latences plus courtes sont produites par des structures du système nerveux auditif plus périphérique, comme la cochlée, tandis que des latences plus longues sont créées par des structures plus proches au cortex. Plusieurs études précédentes démontrent la différence entre les potentiels auditifs évoqués par des participants avec des acouphènes et ceux d'un groupe témoin, à différents points tout au long du système nerveux auditif central [les réponses de l'éléctrocochléographie (Majumdar et coll., 1983), des potentiels évoqués auditifs du tronc cérébral (Schaette et McAlpine,

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2011; Gu et coll., 2012), des potentiels évoqués auditifs à moyenne latence (Singh et coll., 2011; Gerken et coll., 2001), et des potentiels évoqués auditifs à longue latence (Pineda et coll., 2008; Delb et coll., 2008; Strauss et coll., 2008)].

Pendant cette étude, on vous demandera de:
1) Participer à un dépistage auditif divisé en quatre sections. Vous devrez compléter un questionnaire de votre histoire auditive, et participer à une évaluation de votre conduit auditif externe utilisant un otoscope (un instrument équipé d'une lumière). Un deuxième instrument sera utilisé pour évaluer le ton (la hauteur) et l'intensité de votre acouphène. Finalement, pour établir votre capacité auditive, vous devrez détecter des sons doux à des fréquences différentes qui vous seront présentés à travers des écouteurs.
2) Rester assis sur une chaise en regardant un programme NetFlix de votre choix pendant l'enregistrement des réponses de votre cerveau. Un casque avec plusieurs électrodes sera placé sur votre tête. Les électrodes seront remplies de gel.
3) En utilisant la même configuration, effectuer une tâche de discrimination.

Ces procédures seront administrées par la chercheure principale qui est également une audiologiste.

Au cas où votre candidature ne peut pas être retenue, parce que vous ne rencontrez pas les exigences de l'étude, nous vous conseillerons de prendre rendez-vous avec une clinique audiologique de la région.

Vous êtes libres à vous retirer du projet de recherche à n'importe quel moment. Dans ce cas, vos résultats et vos informations ne seront pas utilisés pour le projet et seront supprimés ou détruits immédiatement. Si vous choisissez de rester dans le projet, vos informations resteront confidentielles et ne seront utilisées que pour le projet de recherche. Pour garder votre nom anonyme, vos résultats ne seront identifiés qu'avec un code. Seulement les chercheurs, nommés ci-dessous, auront accès à vos données. Toutes vos données seront gardées sous clé dans une armoire dans le laboratoire de l'université d'Ottawa, et seront détruites cinq ans après la publication des résultats.

Les risques potentiels dans ce type de recherche sont minimaux. Des sondes stérilisées sont insérées dans l'entrée du canal auditif externe pour mesurer la mobilité de la membrane tympanique. Par la suite, la sonde changera la pression de l'air dans le canal auditif externe, ce qui peut causer de l'inconfort pour certains individus. Cependant, ce test ne présente aucun danger pour la membrane tympanique, car la sonde est insérée au bord externe du conduit auditif et la sonde

est stérilisée pour empêcher des risques de contamination. De plus, tous les sons présentés seront sous la limite occupationnelle pour l'exposition au son. Par votre participation dans cette étude, vous allez contribuer au développement d'outils d'évaluation dans le domaine de l'acouphène.

Pour de plus amples informations, ou pour partager vos commentaires ou inquiétudes, veuillez contacter un(e) des chercheures (information ci-dessus). Pour toutes autres informations, demandes ou plaintes concernant la conduite éthique de cette étude, veuillez contacter l'agent du protocole pour l'éthique en recherche, université d'Ottawa, pavillon Tabaret, 550 rue Cumberland, pièce 154, Ottawa, Ontario K1N 6N5, téléphone: 613-562-5387, courriel: ethics@uottawa.ca.

Veuillez garder une copie de cette lettre d'information dans vos dossiers.

Appendix 5: Recruitment poster

Université d' University of Ottawa

If you have good hearing and/or tinnitus?

This message is for you!!

RECRUITMENT FOR A STUDY

Effect auditory evoked potentials on the severity of tinnitus

We are looking for adults wishing to participate in a research study on the effects of tinnitus.

To participate, you must:

- **Have either good hearing and/or tinnitus** (auditory screening done during the evaluation session)
- Be between 18 and 60 years of age
- Have no known medical conditions related to your hearing

If you meet the specific eligibility criteria*, you will be asked to:

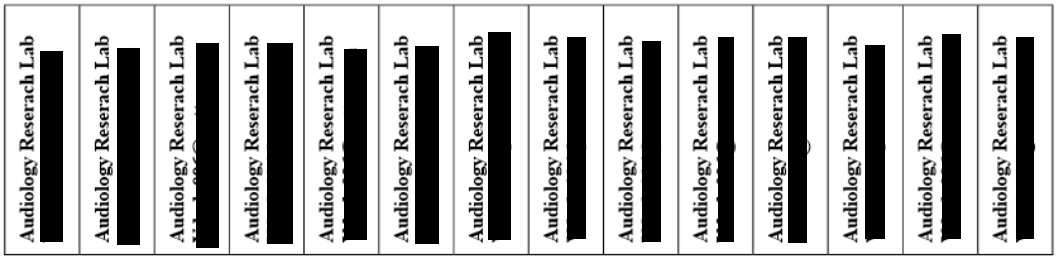
- Listen to sounds presented in quiet (hearing screening test)
- Listen to a clicking noise while laying in an armchair

* Please note that during the auditory screening and questionnaires your candidature for the study will be determined. Not all participants will be selected to participate in the study should they not meet the specific eligibility criteria.

The testing session will take place at Roger Guindon Hall of the University of Ottawa. During this session, a hearing-screening test will be performed as well as an electrophysiological test. The evaluation session will take approximately 60 minutes.

If interested in participating, please leave your contact information at the following number or email address and one of the researchers involved in the study will contact you as soon as possible: [redacted]

Name of researchers: Victoria Milloy, M.Sc., Amineh Koravand, Ph.D., Daniel Benoit, Ph.D., University of Ottawa, Faculty of Health Sciences, School of Rehabilitation Sciences, 451 Smyth Road, Ottawa, Ontario, K1H 8M5. Phone number: (613) 562-5800, ext. [redacted] Fax number: (613) 562-5428.



Université d'
University of
Ottawa

Avez-vous une bonne audition et/ou un acouphène ?

Ce message est pour vous!!

LE RECRUTEMENT POUR UNE ÉTUDE

Effet des potentiels évoqués auditifs sur la sévérité d'un acouphène

Nous cherchons des adultes qui veulent participer dans un projet de recherche sur les effets des acouphènes.

Pour participer, il faut que vous :

- **avez une bonne audition et/ou un acouphène** (un dépistage auditif sera administré pendant la session d'évaluation)
- avez entre 18 et 60 ans
- n'avez aucune condition médicale connue qui peut affecter votre audition.

Si vous avez satisfait les critères d'éligibilité spécifiques*, il vous sera demandé de :

- écouter les sons présentés dans un environnement calme (dépistage auditif)
- écouter un son qui ressemble à un clic pendant que vous êtes assis dans un fauteuil.

* Il est à noter que pendant le dépistage auditif et les questionnaires de l'histoire auditive, votre candidature sera déterminée. Tous les participants ne seront pas nécessairement choisis pour l'étude, car il faut satisfaire les critères d'éligibilités spécifiques.

Les sessions d'évaluations auront lieu au pavillon Roger Guindon à l'université d'Ottawa. Pendant la session, un dépistage auditif sera administrer et ensuite un test éléctrophysiologique. La session d'évaluation prendra environ 60 minutes.

Si vous êtes intéressé(e)s à participer, veuillez laisser vos coordonnées par téléphone ou par courrielle avez une des chercheuses de cette étude. Quelqu'une vous répondrez le plutôt possible.[redacted]

Noms de chercheurs/ses: Victoria Milloy, M.Sc., Amineh Koravand, Ph.D., Daniel Benoit, Ph.D., université d'Ottawa, Faculté des Sciences de la Santé, École des sciences de la réadaptation, 451 rue Smyth, Ottawa, Ontario, K1H 8M5. Téléphone: (613) 562-5800, ext.[redacted] Télécopieur: (613) 562-5428.

Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]	Audiology Reserach Lab [redacted]