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Investigating the Relationship between Subcortical and Cortical Auditory Processing

Sonia Varma, *The University of Western Ontario*

Supervisor: Johnsrude, Ingrid, *The University of Western Ontario*

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Abstract

The auditory system is highly integrative, with feedforward and feedback connections from periphery to cortex (and stages in between). In order to understand how the different levels of the human auditory system interact, it is necessary to simultaneously measure responses from multiple auditory levels. A novel stimulus was paired with electroencephalography (EEG) in 29 young, normal-hearing participants (17-34 years) to examine interactions among stages of the auditory pathway. Temporal regularity was manipulated by continuously accelerating and decelerating the rate of a click-train stimulus (i.e., ~3.5 Hz frequency modulation of the click rate). Adaptation of the brainstem (cochlear nucleus and inferior colliculus) response latencies was observed simultaneously with cortical phase-locking and sustained low frequency activity to the temporal regularity. However, no correlations were found between subcortical adaptation and cortical regularity responses, suggesting that these phenomena may be independent of one another.

Keywords

Brainstem, hearing loss, adaptation, audition, electroencephalography

Summary for Lay Audience

The present study investigates the relationship between responses from multiple levels of the human auditory system. Specifically, we investigate how processing of temporal, or timing-related, information is related in different auditory levels. Investigating the relationship between temporal processing in the different levels of the auditory system may be useful in understanding complex hearing impairments that are not detectable through standard clinical tests. The most common of these impairments is difficulty hearing speech in the presence of background noise. Using a unique stimulus capable of eliciting responses from multiple levels of the auditory system, and a technique capable of non-invasively recording electrical activity from the brain, we were able to observe temporal processing responses from subcortical and cortical auditory areas simultaneously and non-invasively. We did not find any relationship between processing in these areas, suggesting that temporal processing in the subcortical and cortical levels of the auditory system may be at least partially independent.

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List of Abbreviations

ABR…….....Auditory Brainstem Response

AC……Auditory Cortex

ANF……...Auditory Nerve Fibers

ASSR…….Auditory Steady-state Response

CN……Cochlear Nerve

ECOCHG……Electrocochleography

EEG……..…Electroencephalography

ERP…….Event-Related Potentials

FFR……..Frequency-Following Response

IC……..Inferior Colliculus

IHC……...Inner Hair-Cells

IOI…….Inter-Onset-Interval

OHC……Outer Hair-Cells

MGB……...Medial geniculate body

MMN…….....Mismatch Negativity

MOC…… Medial Olivocochlear

MOCR……...Medial Olivocochlear Reflex

SOC……...Superior Olivary Complex

SR…….…..Spontaneous Rate

Chapter 1

1. Introduction

The auditory system is a complex and interconnected circuit with multiple functional stages. Changes in temporal processing at one or many of these stages, or in the interactions between stages, may be implicated in complex hearing impairments that are not detectable using standard clinical tools such as audiometric thresholds. Temporal processing at multiple stages of the auditory system has been evaluated separately, but to the best of our knowledge, the relationship between different stages has not been investigated. An account of how temporal sensitivity is related across multiple levels of the auditory pathway may be useful in understanding complex hearing impairments. The aim of this work is to provide an integrated account of sensitivity to temporal information in multiple stages of the auditory system, and to examine how this sensitivity is related across stages.

1.1 Overview of the Auditory System

Ascending auditory pathway

Sound waves are carried by air and enter the ear through the pinna into the ear canal and finally the tympanic membrane (eardrum). Pressure changes in the ear canal cause the tympanic membrane to vibrate. These acoustic vibrations are carried to the cochlea (a fluid filled compartment) by the ossicles (3 tiny bones) (Sarrat et al., 1992). At the cochlea, acoustic vibrations are transduced into electrical activity. The cochlea contains the inner and outer hair cells. The inner hair cells (IHC) are responsible for converting vibrations of the basilar membrane (one of the two membranes spanning the length of the cochlea) into electrical activity (Hewitt & Meddis, 1991). In contrast, the outer hair cells (OHC) amplify the motion of the basilar membrane (Pujol, Carlier, & Lenoir, 1980), which improves sensitivity at the periphery. At the basilar membrane, frequency components of sounds are separated based on the characteristic frequency (CF) that a given region on the membrane is most sensitive to. The cochlea, and all ascending structures above it, maintain a tonotopic organization (frequency

dependent spatial arrangement of where sounds are processed) (Bourk, Mielcarz, & Norris, 1981; Clopton & Winfield, 1973; Liberman, 1982; Pantev et al., 1989).

The hair cells in the cochlea synapse with auditory nerve fibers (ANF). The majority of the ANF synapse with the inner hair cells (around 10-20 ANF per IHC). There are three types of afferent ANFs which are differentiated by their spontaneous discharge rates (SR) (Liberman, 1978): low-, medium-, and high- SR ANF. The AN then carries information to the cochlear nucleus (CN) in the brainstem (Webster, 1992) which has a role in frequency discrimination (Ayala et al., 2013). From here, information is sent to either the superior olivary complex (SOC), inferior colliculus (IC), or nuclei of the lateral lemniscus (Plack, 2018).

The SOC integrates signals from both ears, and plays a functional role in sound localization; it is the first point of binaural integration in the ascending auditory pathway (Goldberg & Brown, 1969; Hefner & Heffner, 1986; Tollin, 2003). Up until this point, signals from each ear remain separate; all the structures involved processed only signals entering from the ipsilateral side. Neurons from the SOC can project binaurally to either the IC or the lateral lemniscus (Malmierca & Hackett, 2010).

The nuclei of the lateral lemniscus receive signals from the CN and SOC, and projects to the IC (Webster, 1992). The IC is the point of integration for nearly all ascending nerve fibers, and plays roles in binaural hearing (Litovsky, Fligor, & Tramo, 2002), sound localization (Masterson, Jane, & Diamond, 1968), frequency discrimination (Ayala et al., 2013), and more. IC neurons project to the medial geniculate body (MGB) in the thalamus (Webster, 1992). Neurons from the MGB project to the auditory cortex (Plack, 2018).

Descending auditory pathway

There are also numerous efferent connections in the auditory system spanning from the cortex to cochlea (for detailed review see Saldaña, 2015). In contrast to the ascending auditory pathway, the descending auditory pathway is still poorly understood and research into this domain is in its early stages.

Efferent fibers exist in the auditory cortex (AC), SOC, IC and lateral lemniscus (Kelly & Wong, 1981; Saldana Feliciano & Mugnaini, 1996; Huffman & Henson, 1990). These projections are tonotopically organized (Huffman & Henson, 1990; Malmierca & Rees, 1996). AC efferents from layer V project to the ipsilateral and contralateral IC (Herbert, Aschoff, Ostwald, 1991), as well as the ipsilateral lateral lemniscus, SOC, and CN. Ipsilateral projections to the IC are more extensive than contralateral projections (Saldana Feliciano & Mugnaini, 1996). IC efferents project to the ipsilateral and contralateral SOC and CN. SOC efferents synapse with the both the IHC and OHC in cochlea by traveling down the AN (Warr and Guinan, 1979; Guinan, Warr, & Norris, 1983; Brown, 1987; Wilson et al., 1991; Warr, 1992; Guinan, 1996). SOC efferents (in addition to those from the IC and lateral lemniscus) can also synapse with the CN (Saldaña, 2015). MOC efferents project to the OHC, affecting frequency-specific sensitivity in the peripheral auditory system (Cooper & Guinan , 2006).

As both the ascending and descending auditory circuits are highly interconnected, with each stage playing important roles in hearing, it is important to consider the entire auditory system as a whole in order to understand hearing and hearing loss.

1.2 Hearing Loss

Hearing loss affects at least 78% of Canadians over the age of 60 (StatsCan, 2016). Generally, hearing loss is diagnosed using pure tone audiometry, which measures the lowest decibel (dB) level at which an individual can hear a set of given frequencies (often 250-8000 Hz) (Johnson, 1970) 50% of the time. The audiogram is a measure of loss of sensitivity, or threshold elevation, to sounds in quiet. Not all hearing impairments are apparent in the audiogram (Plack, Barker, & Pendergast, 2014), however. Hearing impairments to sounds above threshold can occur even in those with normal audiograms (Davis, 1989). These impairments include suprathreshold symptoms such as perceiving sounds at moderate intensities to be uncomfortably loud (hyperacusis) (Epstein, & Marozeau, J, 2010; Tyler et al., 2014), perception of noise or ringing in the ears (tinnitus) (Kiang, Moxon, & Levine, 1970) and impaired understanding speech in the presence of background sound (Pichora-Fuller, & Souza, 2003; Helfer, & Wilber, 1990).

1.3 Audiogram Insensitivity to Suprathreshold Hearing Impairments

Situational factors

Even in healthy ears, listening in quiet is very different from listening in natural settings, where multiple talkers, background noise, and room reverberation can provide additional challenges to hearing and comprehension (Cherry, 1953; Nabelek & Robinson, 1982). In real-word listening situations, sound levels are higher overall. Consequently, a larger percentage of ANF will respond, including low- SR fibers which respond selectively to high-threshold sounds. Evidence from animal studies suggests that these low SR-ANF are more susceptible to aging and noise exposure, and are consequently damaged earlier (Schmeidt, Mills, & Boettcher, 1996; Furman, Kujawa & Liberman, 2013). Since these fibers contribute less at lower sound levels (Costalupes, Young & Gibson, 1984), their dysfunction may only be problematic in listening situations with high over-all sound levels, without affecting thresholds in quiet (as measured on the audiogram).

In addition, these higher sound levels also broaden the spread of cochlear excitation along the tonotopic axis of the basilar membrane. It is therefore possible that, at higher intensities, neurons with characteristic frequencies different from the sound input are firing more, in addition to those matching the characteristic frequencies of the sound (Lin, Furman, Kujawa, Liberman, 2011). This reduces frequency specificity, which is important for speech perception and speech recognition in noise (Brokx & Nooteboom, 1982; Fu et al., 1998; Qin & Oxenham, 2003; Sickney et al., 2004).

Another distinction between listening in noise and in quiet is that there is weaker signal modulation in noisy situations (Dubbelboer & Houtgast, 2007). Spectro-temporal modulations in speech are demonstrably important for comprehension in human listeners (Elliot & Theunissen, 2009). When these modulations are reduced in noise, this can influence speech processing in a way that is not represented by threshold elevation in quiet (where signal modulation is absent).

Physiological factors

Beyond differences in listening conditions, suprathreshold symptoms of hearing impairments may have physiological underpinnings that are distinct from those that lead to loss of sensitivity at threshold. Specifically, loss of the inner and outer hair-cells, which underlies reduced threshold sensitivity, may not be the main or sole contributor to complex hearing impairments like difficulty perceiving suprathreshold sounds clearly.

Recent investigations of the causes of suprathreshold symptoms of hearing impairments have suggested that degeneration of the synapses between IHCs and cochlear-nerve neurons (cochlear synaptopathy), induced by age and noise exposure, can occur even in the absence of hair-cell loss (Kujawa & Liberman, 2009). Work on animals shows that hair cell counts can remain intact while up to 50 percent of the cochlear synapses have degenerated (Kujawa & Liberman, 2009). Importantly, this synaptopathy can occur in response to exposures that are insufficient to induce permanent hair cell damage, leaving thresholds intact (Kujawa & Liberman, 2009). This work has been translated to humans: examination of human temporal bones demonstrates that synaptopathy occurs in humans as well (Viana et al., 2015).

Some evidence that suggests that synaptopathy may play a role in impaired perception of speech in noise (Kujawa & Liberman, 2015). This is because for sounds near threshold-level, a small increase in intensity can increase discharge rates in surviving fibers and spread activity onto additional fibers along the cochlea (Lin et al., 2011), 'blurring' activity and broadening auditory filters. Because synaptopathy selectively spares the high-SR, low-threshold fibers which are selectively recruited for sounds at low levels such as during audiometric testing, sensitivity at threshold may remain unaffected even with significant neuronal loss. Moreover, the low-SR high threshold ANF that are most susceptible to degeneration (Schmeidt, Mills, & Boettcher, 1996; Furman, Kujawa & Liberman, 2013) be involved in coding sounds in sustained background noise (Costalupes et. al, 1984). This is because background noise saturates the high-SR fibers, but the low-SR fibers have higher thresholds and wider dynamic ranges (Liberman, 1978; Schalk & Sachs, 1980) and are consequently less susceptible to this saturation.

In addition, responses of low-SR ANF are phase locked to the stimulus (Kiang, 1965; Johnson, 1980; Palmer & Russel, 1986) and, thus, provide information about sound frequency. Low-SR neuropathy has also been linked to binaural processing deficits (Bharadwaj et al., 2014; Bharadwaj et al., 2015), as well as impaired speech comprehension and use of timing and amplitude modulation information (Schmiedt et al., 1996)

Beyond speech comprehension impairments in noise, synaptopathy may be implicated in other distressing suprathreshold symptoms such as hyperacusis. Synaptopathy in mice is associated with hypersensitivity to sound, and hyperactivity in the auditory brainstem (Hickox & Liberman, 2013) which may underlie hyperacusis in humans. In fact, many studies have identified that amplification of synaptic gain in the auditory cortex can occur in response to reduced peripheral input – this has been interpreted as compensatory plasticity (Chambers et al., 2016; Möhrle et al., 2016 ; Salvi, Wang & Ding, 2000).

Synaptopathy, however, cannot explain all suprathreshold symptoms. Tinnitus, for example, has been linked to noise exposure but not synaptopathy in humans (Guest et al., 2017). Moreover, even for speech in noise impairments and hyperacusis, there is currently no direct evidence linking these impairments to synaptopathy. It is likely that these impairments actually reflect a more diverse set of pathologies, rather than a single peripheral change.

1.4 Auditory-System-Wide Dysfunction

The mechanisms underlying suprathreshold symptoms might involve more than a single change along the auditory pathway. Rather, these impairments may reflect dysfunctional interactions between stages of the auditory pathway.Given the interconnected nature of the auditory system, it is likely that the functional relationships between different stages of the auditory pathway are relevant for hearing.

Age and noise-exposure related changes have been documented at all stages of the auditory system (periphery, subcortical, and cortical). At the most peripheral levels, noise-exposure and normal aging can lead to hair-cell loss (Chen & Fechter, 2003), and degeneration of ANF (cochlear synaptopathy) (Kujawa & Liberman, 2009).

At the subcortical levels, age has been associated with reduced inhibition in the cochlear nucleus (Caspary et al., 2005). Moving upstream, age and noise exposure have been linked to delayed inferior colliculus responses (Mehraei et al.,2016), and impaired gap detection in inferior colliculus neurons (Allen et al.,2003; Williamson et al., 2015). At cortical levels, age and noise exposure have been linked to reduced inhibition (thought to underlie compensatory gain), and impaired detection of regularity (repeating patterns) in sound (Herrmann et al., 2016; Herrmann, Buckland, & Johnsrude, 2019). As mentioned earlier, compensatory plasticity occurs in the auditory cortex in response to reduced peripheral input (Chambers et al., 2016; Möhrle et al., 2016; Salvi et al., 2000). Work on chinchillas has demonstrated that, in quiet listening conditions, reductions in peripheral input are associated with smaller reductions in subcortical responses, and no reductions in cortical responses, suggesting that signals are amplified at higher levels of the auditory system (Salvi et al., 2017).

Dysfunction can occur selectively at some levels

Although abnormalities have been documented at all stages of the auditory system, impairment at one stage does not guarantee abnormality at all stages. A unique example of this is seen in auditory neuropathy disorder. Here, OHCs remain intact while peripheral auditory function is impaired (Berlin, 1999; Butinar et al., 1999; Starr et al., 1996). Auditory neuropathy patients demonstrate speech perception impairments that are disproportionally severe when compared to pure tone thresholds (Kaga et al., 1996; Starr et al., 1996; Butinar et al., 1999; Zeng et al., 1999; Sheykholeslami et al., 2001), and lack auditory nerve and brainstem responses (Starr et al., 1996; Berlin et al., 1988; Berlin, 1999). Moreover, some individuals with auditory neuropathy still display cortical responses; the presence of cortical responses have been associated with better speech intelligibility (Rance et al., 2002). Auditory neuropathy represents a clear instance where multi-level observations of the auditory pathway would be beneficial.

Interactions between stages of the auditory pathway

The documented abnormalities at multiple levels of the auditory system emphasize the importance of each stage of system in hearing. Building on this, the different stages of the

auditory pathway interact with one another, and these interactions can be abnormal. One such interaction is illustrated in the medial olivocochlear reflex (MOCR) feedback activity evoked in response to low level sound (10-20 dB). When activated, medial olivocochlear (MOC) fibers reduce the basilar membrane vibration at the characteristic frequency of the sound input (Murugasu & Russell, 1996). The MOCR has been implicated in improving perception in noise by increasing the signal-to-noise ratio in the auditory nerve response: specifically, by reducing the responsivity to background noise (Guinan, 2006 & 2010; Kujawa & Liberman, 2001). The MOCR provides an example of a functional interaction between stages of the auditory system (here, brainstem to cochlea) which also plays a role in hearing. Further, just as dysfunction can occur in several individual stages of the auditory pathway, the efferent activity of the MOC has been shown to be diminished in auditory processing disorders in which speech perception in noise is commonly impaired (Muchnik et al., 2004). Given that impairments can occur in not only the different stages of the auditory pathway, but also in the interactions between stages, it is important to consider the auditory system as a whole when investigating complex hearing impairments (such as those with suprathreshold symptoms).

1.5 Temporal Processing

Temporal processing refers to the auditory system's ability to process changes in the characteristics of sound over time. In the natural environment, these changes can occur extremely fast. For example, in speech, consonant and vowels are produced dozens of times per second (Plack, 2018). As a result, processing of speech information requires high temporal resolution. Temporal processing may therefore be an important factor in hearing impairments to speech in noise. Deficits in temporal processing have also been linked to other suprathreshold symptoms such as tinnitus (Turner et al., 2006; Turner & Parrish, 2008).

Temporal processing occurs at all levels of the auditory system: in the periphery (Fettiplace & Crawford, 1978; Geurts & Wouters, 2001; Møller, 1972), subcortical areas (Galbraith et al., 2000; Slee et al., 2005), and cortex (Hall et al., 2006; Talavage et al., 2004).

At the periphery, temporal processing of frequency information can be coded by firing rate up to approximately 5000 Hz (Rose et al., 1967). However, firing rate alone cannot explain all frequency coding that occurs in the auditory system. The human ear can hear sounds up to

20 000 Hz, which is far beyond the firing rate capacity of auditory nerve fibers. Above 5000 Hz, frequency may be coded using a 'place code' where different frequency tones stimulate different regions on the basilar membrane (Mather, 2006), as evidenced by the tonotopic organization of the membrane. Higher frequencies may also be coded according to the 'volley principle' (Wever, 1939); here, it is proposed that groups of neurons actually fire slightly out of phase with one another in order to produce faster nerve impulses than the maximum firing rate of any individual neuron allows. Frequency is clearly coded at higher levels of the auditory system as well, although the maximum firing rates of neurons are lower at these levels (Coffey, Musacchia, & Zatorre, 2017; Giraud et al., 2000; Nourski et al., 2014), suggesting that a different code may be employed.

At the subcortical and cortical levels, the sound envelope can also be encoded (Wang et al., 2013; Batra, Kuwada, Stanford, 1989; Nourski et al., 2009). The sound envelope refers to slow overall amplitude modulations in a waveform over time, which are distinct from the rapid pressure variations that give rise to the fine structure of sounds (i.e. frequency). Envelope-following responses represent processing of more complex sounds.

Several phenomena can be observed to evaluate temporal processing at the different levels of the auditory system. Here, we are interested in adaptation, regularity detection, and neural synchronization, which are all sensitive to temporal information

Adaptation

Adaptation refers to reduced neuronal responsiveness to repetitive stimulation (Grill-Spector, Henson, Martin, 2006). Adaptation can be measured as the difference in response to different presentations of the same stimulus (usually clicks or tone-bursts). When the stimulus is first presented, responses are unadapted. If the response to subsequent presentations of the same stimulus is reduced (or delayed), this is interpreted as adaptation (Grill-Spector et al., 2006; Herrmann et al., 2015). Often, an oddball stimulus sequence is used to investigate adaptation. The oddball sequence consists of multiple common (standard) tones and few, rarely occurring, deviants (oddballs). The responses to standard tones are consistently weaker than those to the deviants, exemplifying adaptation to the standard tones (Näätänen, 1992; Cowan et al., 1993). The time-scale of adaptation is measured by varying the intervals between

stimulus (click or tone) presentations, and observing the maximum interval for which adaptation is still observed. For adaptation to be observable, neurons in a given population must adapt and not fully recover from adaptation within the inter-stimulus interval used.

At the neural population level, there are two mechanisms that can underlie adaptation. The first involves fewer active neurons, while the firing rate remains constant. The alternative is number of active neurons remains constant, while the firing rate is reduced (Stephens et. al 1975). At the individual neuron level, adaptation can be a result of either a reduced firing rate, or an increased spike latency (Herrmann et al., 2015).

Adaptation can occur at multiple locations along the auditory pathway (Dahmen et al., 2010; Dean et al., 2005,2008; Rabinowitz et al., 2011; Watkins & Barbour, 2008; Wen et al., 2009), and at multiple time-scales (Ulanovsky, Las, Farkas, & Nelken, 2004). The time-scale of short-term adaptation is different depending on the location at which adaptation is occurring; at lower levels, such as the auditory nerve, recovery from adaptation occurs much faster (in the order of 10s of milliseconds) (Westerman & Smith, 1984) compared to at the auditory cortex where recovery from adaptation may take a few 100 milliseconds after stimulation (Smith, 1977).

Human and animal work have demonstrated multiple forms of adaptation occurring at all auditory levels (for review see Pérez-González & Malmierca, 2014). Here we briefly summarize the nature and role of adaptation at peripheral, subcortical, and cortical auditory levels.

Adaptation across the auditory system

Adaptation can already be observed at the peripheral auditory system, in the auditory nerve, with a fast time-scale – recovery from adaptation has been observed in a few 10s of milliseconds in all species investigated to date (examples: Nomoto et al., 1964; Kiang et al., 1965; Feng et al., 1991). This adaptation may highlight the onset of novel stimuli. Interestingly, adaptation is stronger in low-SR ANF (Sumner and Palmer, 2012), the more vulnerable of the ANF to cochlear synaptopathy (Furman et al, 2013).

Similarly, firing rate adaptation has been observed in brainstem nuclei such as the cochlear nucleus (CN) (Boettcher, Salvi, & Saunders, 1990), superior olivary complex (SOC) (Finlayson & Adam, 1997), and the inferior colliculus (Ingham and McAlpine, 2004).

Like the auditory nerve fibers, recovery from adaptation at the CN can occur when inter-stimulus intervals are quite short, in just 10s of milliseconds (Boettcher, Salvi, & Saunders, 1990). Animal work has shown that sensorineural hearing loss increases recovery time from short-term adaptation at the CN (Walton, Frisina, & Meierhans, 1995), emphasizing the value of evaluating adaptation with respect to hearing impairment.

The SOC is the first site in the ascending auditory pathway where ipsilateral and contralateral inputs are integrated; neurons at the SOC are important for sound localization via extraction of binaural cues (Goldberg & Brown, 1969; Heffner & Heffner, 1986,1987). Here, there are neurons where adaptation occurs equally to both ipsilateral and contralateral inputs, as well as those demonstrating unequal degrees of adaptation to ipsilateral versus contralateral inputs (Finlayson & Adam, 1977). This will produce an imbalance in interaural differences in response magnitude which may affect sound localization accuracy, especially in noisy conditions where signals are not fully lateralized.

Moving up in the ascending auditory pathway, the inferior colliculus (IC) is an integration point for ascending and descending auditory inputs (Malmierca and Hackett, 2010; Malmierca and Ryugo, 2011). It displays firing rate adaptation in certain neurons (Ingham and McAlpine, 2004). Adaptation at the IC is much slower than those at lower levels (Yates et al., 1983, 1985; Westerman & Smith, 1987), suggesting that this adaptation is not simply inherited from lower levels. This, again, emphasizes the importance of a multi-level approach to investigating the auditory system.

Beyond firing-rate adaptation, some IC neuron populations have also been found to adapt to stimulus statistics, which would enhance processing of the most probable sounds (Dean et al., 2005). Further, IC neurons display what is known as stimulus-specific adaptation (SSA). Here, responses are reduced to a repeated stimulus, however, a novel stimulus will elicit rapid non-adapted responses from the same neurons (Perez-Gonzalez, Malmierca, Covey, 2005; Malmierca et al., 2009). SSA is thought to play a role in attention and deviance detection,

and so may be important in speech comprehension. The IC is the earliest stage of the ascending auditory pathway to display SSA (Lumani and Zhang, 2010; Zhao et al., 2011; Ayala and Malmierca, 2013; Ayala et al., 2013). SSA is also found in the auditory thalamus (Anderson, Christianson & Liden, 2009) and cortex (Ulanovsky et al., 2004).

Several forms of adaptation take place in the auditory cortex (AC). For example, SSA has been well documented in the AC (Szymanski et al., 2009; Farley et al., 2010; Tasseh Yaron, & Nelken, 2011; Ulanovski, Las, & Nelken, 2003), although recovery from adaptation takes longer at the cortex than at lower levels (Malmierca et al., 2009). Cortical adaptation is highly diverse, with recovery times from 5 ms to 150 ms (Ulanovsky et al., 2003, 2004; Malone et al., 2002, Condon & Weinberger, 1991).

Moreover, AC neurons, like those in the IC, also adapt to stimulus statistics (Ulanovsky et al., 2003). Adaptation at the cortex is thought to be important for protection against over-stimulation (Megela and Teyler, 1979), detection of auditory change (Ulanovsky et al., 2003, 2004), efficient stimulus encoding (Wark, Lunderstorm,& Fairhall 2007), and auditory attention (Fritz et al., 2007).

In summary, adaptation been observed across the auditory system, and may have numerous roles in auditory processing, especially of temporal information. Adaptation may be especially relevant to speech in noise impairments, given that if neurons remain adapted from background noise, they may not fire to relevant auditory information.

Temporal regularity

Beyond adaptation, temporal processing can be evaluated via neural responses to temporal regularity. Temporal statistical regularities are abundant in natural sound environments (repetitive auditory features) (Julesz, 1981; Portilla and Simoncelli, 2000; Geisler, 2008; McDermott Schemitsch, & Simoncelli, 2013; Theunissen and Elie, 2014). Perception of these regularities is important for speech comprehension (Idemaru & Holt, 2011; Giraud & Poeppel, 2012; Peelle & Davis, 2012; Baese-Berk et al., 2014). Like adaptation, sensitivity to temporal regularity also occurs at multiple levels of the auditory system (in the periphery, sub-cortex, and cortex) (Palmer, 1982; Pinheiro, Wu, Jen, 1991; Gaese & Ostwald,

1995). Processing at each of these levels can be observed in multiple ways. Here we focus on two neural phenomena that can be used to assess sensitivity to temporal regularity; the sustained response and entrained oscillatory activity.

Regularity detection (sustained) response

Processing of temporal regularities can be measured more directly by cortical responses marking the detection of repetitive auditory features. Recent research in this domain has found that listeners are sensitive to the onset of complex patterns (Barascud et al., 2016; Sohoglu and Chait, 2016; Southwell et al., 2017). This sensitivity emerges from the brain's propensity to represent stimulus statistics, even in the absence of behavioral relevance, and has been localized to the primary auditory cortex, hippocampus, and inferior frontal gyrus (Barascud et al., 2016). This sensitivity, known as the sustained response, is thought to underlie predictive capacity (Schroeder & Lakatos, 2009; Henry & Herrmann, 2014; Nobre & van Ede, 2018), which may be used to allocate resources for times when sounds are expected (Nobre, Coorea, & Coull.,2007), attend to select sounds (Bendixen, 2014), and detect changes in the environment (Bendixen, SanMiguel, & Schröger ,2012).

Neural synchronization

Another phenomenon sensitive to temporal regularity is the tendency for neural oscillations to synchronize with the temporal structure of sound (Lakatos et al., 2008, 2013; Nozaradan et al., 2011; Henry & Obleser, 2012; Costa-Faidella et al., 2017; ten Over et al., 2017). This phenomenon can be described as phase-locking or neural synchronization, and can occur at multiple levels of the auditory system (Rose, Brugge,& Anderson, 1967; Smith, Marsh, & Brown, 1975; Herdman et al., 2002). However, the time-scale at which neurons can synchronize varies greatly depending on where in the auditory system they are located. At the cochlea, neurons my fire up to 5000 time per second (Rose et al., 1967). In contrast, cortical neural activity has been documented synchronizing to frequencies up to 250 Hz (Coffey, Musacchia, & Zatorre, 2017; Giraud et al., 2000; Nourski et al., 2014). However, above 110 Hz, synchronization responses are thought to more strongly reflect brainstem contributions than cortical ones (Holmes et al., 2018); cortical contributions are strongest for modulation

rates at around 40 Hz (Bidelman, 2015; Herdman et al., 2002; Smith et al., 1975). This cortical synchronization is much slower than in neurons at the periphery.

Like adaptation, neural synchronization has also been linked to hearing. For example, reduced synchronization at cortex is linked to poorer speech comprehension (Peelle, Gross & Davis, 2012). As such, neural synchronization may be an objective marker of impaired speech comprehension in noise.

1.6 ERPs and Neural Oscillations

To evaluate the relationship in auditory processing between different levels of the auditory pathway, we will record whole-system electrophysiological responses using an electroencephalography (EEG) system with the integration of electrocochleography (ECochG). ECochG is similar to EEG, except that it recorded electrical potentials from the cochlea, not the scalp. It provides a more sensitive measure of the compound action potential (CAP) response of the auditory nerve, which reflects the synchronous firing of thousands of ANF (Ferraro, 2000).

This system allows us to observe subcortical adaptation and cortical processing of temporal regularity (here, frequency modulation). We evaluate event-related potentials (ERP), which represent neural activity in response to sensory, cognitive, or motor events (Coles & Rugg, 1995). ERPs are measured as small voltage changes (Blackwood and Muir, 1990), thought to represent the summed activity of many postsynaptic potentials of pyramidal cells produced by thousands to millions of neurons firing synchronously, and in similar orientations (Peterson Schroeder, & Arezzo 1995). Further, the neurons generating the ERP must also be perpendicular to the surface of the skull (as pyramidal cells are) (Peterson et al.,1995). The temporal resolution of ERPs permits measurement of brain activity at the order of milliseconds (Adrian & Yamagiwa, 1935; Li, McLennan, & Jasperm 1952). Further, there is no quantifiable conduction delay between the generation of brain activity and the potentials measured from the scalp (Nunez & Srinivasan, 2006)

Unfortunately, to determine where a potential was generated requires knowing the number of simultaneous active generators (Vaughan, 1982). This limits the spatial resolution

of ERPs. To resolve where a potential was generated, there are a few strategies one can employ. Animal and lesion studies, as well as neurosurgical recordings in humans suggest that at early levels (auditory nerve to inferior colliculus), the latency of responses (when the response occurs) can be used to estimate the origin of the response (Melcher & Kiang, 1966; Møller & Jannetta 1983).

Another way of localizing responses is by exploiting the discrepancies in neural oscillation rates between subcortical and cortical areas. By filtering out fast signals (over approximately 150 Hz) we are able to eliminate brainstem contributions while sparing cortical ones. Similarly, by filtering out signals below 150 Hz, we are able to eliminate cortical contributions and spare subcortical ones.

To evaluate subcortical neural activity, we use an early latency (occurring within 10 ms after stimulus onset) ERP known as the Auditory Brainstem Response (ABR) (Jewett and Williston, 1971). The ABR is composed of at least 5 distinct ERP components. The earliest of these ERP components, Wave I (same as CAP from ECochG), is generated at the auditory nerve and represents a true action potential. All subsequent waves represent post-synaptic activity (Picton, 2010). For our purposes, we investigate Waves III and V of the ABR, thought to be generated at the cochlear nucleus and inferior colliculus respectively (Picton, 2010).

To evaluate cortical neural activity, we use a late latency (occurring over 100 ms after stimulus onset) ERP known as the sustained (as opposed to transient) response. The sustained response is thought to reflect the detection of regularity in a sound sequence (Barascud et al., 2016; Sohoglu and Chait, 2016; Southwell et al., 2017). This ERP is represented by a low frequency direct current power offset in magneto-/electroencephalographic activity sustained for the duration of the regularity. Enhancement of the sustained response amplitude is thought to reflect predictive capacity (Barascud et al., 2016; Heilbron and Chait 2017).

Beyond ERPs, EEG can also be used to monitory neural oscillatory activity. We are able to use EEG to monitor synchronization of neural oscillations to temporal regularities in sounds (Lakatos et al., 2008). This synchronizing activity is thought to be involved in the prediction of future sounds (Schroeder & Lakatos, 2009; Henry and Herrmann, 2014; Nobre

and van Ede, 2018), which may play a role in speech comprehension (Peelle and Davis, 2012; Doelling and Poeppel, 2015).

Evidence suggests that the sustained response and neural synchronization are related but are not the same. Both phenomena are sensitive to regularities in sounds; however, it is possible that neural synchronization is more sensory in origin, while the sustained response may be influenced by experiential factors (Herrmann & Johnsrude, 2018). We make use of both these cortical responses, along with the subcortical ERPs to evaluate system-wide auditory sensitivity to temporal regularity.

1.7 Difficulty of Simultaneous Recording

Given the potential importance of regularity processing to hearing, it would be useful to develop a system sensitive to temporal processing at multiple levels of the auditory system. Moreover, it is important that responses at these levels be examined simultaneously in order to minimize between-session and/or between-subject variability. However, simultaneous measurement of responses across levels is challenging because the response properties of neurons are drastically different at subcortical and cortical levels. Specifically, firing rates are much higher and refractory periods much shorter at subcortical compared to cortical levels. Consequently, synchronization and adaptation in subcortical versus cortical neurons occur at very different time scales, complicating simultaneous measurement of these processes.

Slugocki, Bosnyak, and Trainor (2017) designed a technique allowing simultaneous recording of subcortical (brainstem and thalamus) and cortical responses (primary and secondary auditory cortices). By using an amplitude modulated pure-tone carrier which deviated on 15% of trials, they were able to elicit responses from the inferior colliculus (500 Hz frequency-following response (FFR)), thalamus (80 Hz ASSR), and primary (40 Hz auditory steady-state response (ASSR)) and secondary (mismatch negativity (MMN), P3a, N1-P2 complex) auditory cortices. While their method is indeed innovative, and permits simultaneous recording from multiple auditory areas, their 80 Hz FFR may be contaminated by cortical contributions (Coffey et al., 2017; Holmes et al 2018). Moreover, their method evaluated a different set of responses than those of interest in the present study, and did not include responses from the CN. Specifically, at the subcortical levels, they were interested in

the FFR, and not adaptation of the ABR waveform components. At the cortical level, they also examined a response related to the detection of regularity; they investigated the MMN, and not the sustained response. The MMN marks the detection of sounds violating an established pattern (Paavilainen, 2013), indirectly demonstrates the auditory system's ability to process regularity, and is measured using the oddball paradigm. The MMN is measured as the difference between the response to the standard and oddball stimuli. However, the MMN as a marker of change detection is controversial, as some believe the MMN can be explained by simple adaptation (Jääskeläinen et al., 2004; for review see Escera & Malmierca, 2014). In contrast, however, the sustained response illustrates directly that the auditory system is capable of rapidly extracting regularities (Barascud et al.,2016).

While Slugocki's work is useful in lesion detection, understanding auditory learning, and even hearing loss diagnosis (2017), further investigation into the relationship between subcortical and cortical auditory processing is merited. Specifically, understanding if and how adaptation at subcortical levels is related to direct measures of cortical regularity processing is an important step towards understanding the mechanisms underlying suprathreshold symptoms.

The present study aims to simultaneously and non-invasively record and compare adaptation at the subcortical level with the sustained response and neural synchronization recorded in cortex, to the same stimuli. This will allow us to link different measures sensitive to the processing of temporal information in sound, across levels of the auditory system, and provide a multi-level physiological characterization of temporal processing in the auditory system.

1.8 Stimulating Regularity Responses

Although EEG does permit us to simultaneously record auditory-system-wide responses, the challenge is evoking simultaneous responses from subcortical and cortical levels because of the timing discrepancies between the responses from different levels. To resolve this, we make use of a novel stimulus, developed in the lab, made up of rapid instantaneous

clicks. Clicks are short duration sounds with abrupt onsets used to excite a broad range of ANF (Chertoff, Lichtenhan, & Willis, 2010). These individual clicks are presented within the order of milliseconds, fast enough to observe subcortical adaptation. The individual clicks are presented in such a way that they give rise to a 3.5 Hz frequency modulation, slow enough to elicit cortical synchronization and sustained activity. We evaluate adaptation of subcortical responses, and compare subcortical adaptation with cortical processing of temporal regularity (sustained response, and entrained oscillatory activity).

Chapter 2

2. Methods

2.1 Participants

Twenty-nine (mean: 20.41 years, range: 17-28 years, females: 21) healthy, English speaking adults participated in the experiment. Four additional participants took part in the experiment but were excluded due to >30% of data being contaminated by artifacts (N=2), or having a wave V latency more than 2 standard deviations above the mean for all subjects (N=2).

Participants did not report any neurological diseases or hearing problems. They gave written consent prior to the experiment and were either paid $CAD 5.00 per half hour for their participation or were given course credits for their introductory psychology course. For each participant, pure-tones audiometry was acquired for each ear at 0.25, 0.5, 1, 2,4, and 8 kHz. All participants but one showed normal hearing for all frequencies (i.e, <25 db HL). The one exception was not excluded based on audiometric thresholds because sound level was adjusted for each participant individually, they displayed an elevated threshold at 8 kHz only, and the statistical analysis of the data was unaffected by the inclusion/exclusion of this participant.

2.2 Acoustic stimulation and procedure

Prior to the EEG recording, otoscopy was performed on each participant to confirm that the tympanic membrane was intact and to ensure that the ear canal was not occluded by cerumen (ear wax). Sounds were presented to the right ear only via Etymotic ER1 headphones using a FIREFACE 400 sound card. A Cedrus StimTracker was used to track the sound presentation. Acoustic stimulation was designed using Psychtoolbox (version 3) on MATLAB.

For each participant, the sensation level for the stimulation was determined using the method of limits (Leek, 2001)**.** In this procedure, click trains were presented with a 0.01 second rise and fall. The entire sound (click train) lasted 15 seconds, with a 4.3 dB change (either

increase or decrease) per second. Sounds were presented in ascending and descending intensity, with 6 repetitions of each. Participants indicated with a keyboard button press when they could hear the clicks (for ascending trials) or when they could no longer hear them (for descending trials). The mean sound intensity at the time of the keyboard press for all trials was used to determine the individual sensation level. Acoustic stimulation for the experiment was presented at 60 dB above the obtained individual sensation level.

Prior to the experimental blocks, neural recordings were made using a standard clinical stimulation paradigm, and these could then be compared to recordings from experimental blocks. This was done to validate the use of our system for the recording of peripheral and subcortical potentials (Wave I/CAP, Wave III, and Wave V). To this end, 4000 clicks (0.1 ms duration, rectangle function) were presented with an inter-onset-interval (IOI) of 0.088 s (11.3 clicks per second). Clicks were presented with alternating polarity (every 10^{th} click). Stimulus polarity was alternated such that any stimulus artifact and cochlear microphonic (outer hair-cell contribution to ECochG) are minimized in the trial average (Eggermont, 2017). The clinical stimulation protocol lasted about 6 min.

Two stimulus conditions were presented in six experimental blocks (each block lasting approximately 6 min): an unmodulated control stimulus and a frequency-modulated stimulus (Figure 1). Unmodulated and modulated stimuli were each presented 24 times per block. Both stimulus conditions were presented in pseudo-random order such that a maximum of 3 stimuli of one condition could be presented in direct succession. For the unmodulated control stimulus, 140 clicks (0.1 ms duration, rectangle function, alternating polarity) were presented at an IOI of 0.04 s, resulting in a ~5.64 s stimulus. For the frequency-modulated stimulus, a click train of 27 clicks with an IOI of 0.04 s (i.e., identical to the unmodulated stimulus; lasting 1.08 s) was followed (without a gap) by accelerating and decelerating IOIs from 0.04 s to 0.004 s to 0.04 s (18 IOIs; logarithmically spaced; see also Herrmann et al., 2016). This modulated section of the stimulus consisted of 16 accelerating-decelerating cycles. The duration of the modulated stimulus (including unmodulated and modulated sections) was ~5.64 seconds. Stimuli were presented in alternating polarity. The modulated component of the stimulus gave rise to a 3.5 Hz frequency modulation. The unmodulated component (in the modulated stimulus) provides a period at which both unmodulated and modulated stimuli are identical,

allowing us to observe how responses diverge between the two conditions once modulations begin. The separate unmodulated condition eliminates contamination from the modulated sound onset at 1.08 seconds in the modulated condition.

During sound stimulation (in the clinical paradigm and experimental blocks), participants watched a muted movie of their choosing with subtitles. Participants were instructed to ignore the acoustic stimulation and watch the movie.

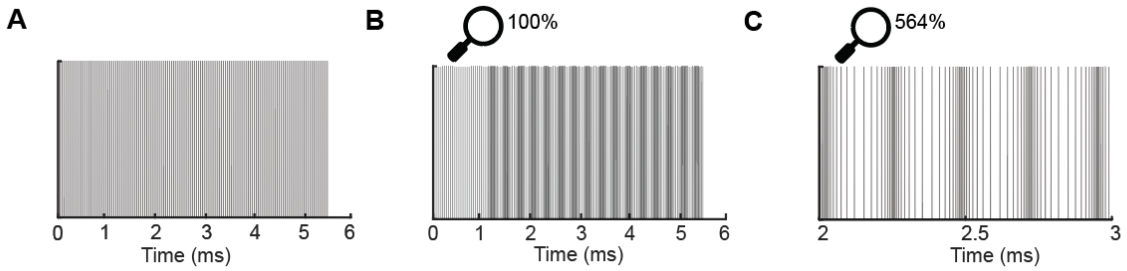

Figure 1. A. Plot of clicks over time in the unmodulated stimulus condition. Each vertical line on plot represents one click. B. Plot of clicks over time in the frequency modulated stimulus condition. Modulations begin at 1.08 s C. Zoomed in (564%) representation of the frequency modulated stimulus condition shown in B.

2.3 EEG recording

Electroencephalograms (EEG) were recorded using a 16-channel ActiveTwo BioSemi system. Acoustic stimulation for all 7 blocks consisted of 0.1 ms clicks presented a 60 dB above a participant's individual sensation level. The sampling rate was 16,384 Hz (BioSemi; 3334 Hz low-pass filter). Participants were seated in comfortable chair in a sound-attenuated and electrically shielded booth. Additional surface electrodes were placed on both mastoids and earlobes. The 16 channels were referenced online to the CMS electrode located adjacent

to CZ. The EEG recording system also had ECochG implemented using an individual electrode custom-made from a Biosemi electrode and a clinical ECochG electrode (Etymotic Research INC.). The custom-made electrode interfaces with the Biosemi amplifier and provides the connection to an in-ear Etymotic eartip that is covered in gold foil for the measurement of ECochG (tiptrode). The gold foil tiptrode was inserted into the participant's ear canal and referenced online to the CMS electrode.

2.4 EEG Analysis

Offline data analysis was carried out using MATLAB software (MathWorks, Inc.). Raw data were notch filtered with a 60-Hz band-stop, elliptic filter to remove line noise.

Subcortical recordings

Data from 16 scalp electrodes were re-referenced to the averaged mastoids, and the data from the in-ear tiptrode was re-referenced to the contralateral (left) ear lobe. Raw data were high-pass filtered at 130 Hz (2743 points, Hann window) and low-pass filtered at 2500 Hz (101 points, Hann window). Data were divided into epochs ranging from -2 ms to 10 ms time-locked to the click onset. Epochs were rejected if the amplitude range exceeded 60 μV in the Cz and C3 electrodes. These electrodes were selected because sounds were presented monaurally to the right ear only, eliciting responses that are localized around the center to left side of the head. The rejection criteria were applied only to the time-window following stimulus onset (0-10 ms), so as to not reject trials based on any stimulus artifact in any single trial. This was done because single-trial artifacts would be averaged out as trials are averaged together due to alternating polarity of the stimuli.

To examine the relationship between click presentation rate and subcortical responses, clicks from the modulated trains were identified based on the IOI between them and the preceding click. Responses to modulated clicks (12 ms time window around click onset) were averaged together based on IOI in bins of 3 individual IOIs, in a moving-window fashion. For example, the first average would consist of the first 3 IOIs; the second average would consist of the second, third, and fourth IOIs; the third average would consist of the third, fourth, and

fifth IOIs and so forth such that all individual IOIs are represented in at least one of the IOI bins. In each window, all IOIs are weighted equally.

To validate the use of our stimulus as a means of eliciting subcortical responses, we isolated unmodulated clicks from the experimental condition and compared the responses to them to those evoked by the clicks in the clinical validation stimulus. Clicks in the experimental blocks with a 40 ms interval between them were isolated and responses (12 ms time window around click onset) to them were averaged together. The average response from these clicks was compared visually to the average response to the clicks of the clinical validation stimulus.

We evaluated auditory nerve and cochlear nucleus activity using the in-ear tip-trode. Stimulus artifact and the cochlear microphonic (generated by outer hair-cell activity) were removed by averaging responses across both polarities. To evaluate the subcortical electrophysiology, we investigated the Auditory Brainstem Response (ABR) recorded from Cz and C3 electrodes. For this experiment, the waves of interest were waves I, generated at the auditory nerve, III, generated at the cochlear nucleus, and V, generated at the inferior colliculus (Picton, 2010).

These waves were identified based on the morphology and time of appearance (Picton, 2010). We were unable to obtain peripheral responses from the auditory nerve using the ABR (wave I) or in-ear tiptrode. As a result, peripheral responses were not included in any further analysis. This was, however, unsurprising as the human wave-I response magnitude is quite small, and is often difficult to assess (Sohmer & Feinmesser, 1973). Moreover, reduced human ABR amplitudes can occur in normal-hearing individuals with larger head diameters (Mitchell, Phillips, & Trune, 1989; Trune, Mitchell, & Phillips, 1988). In regard to the CAP, which is often used to supplement the wave I, we used a non-invasive extra-tympanic set-up, which did not penetrate the tympanic membrane. Moreover, it is likely that our stimulus presentation was not intense enough to elicit these small magnitude responses. We were, however, unable to increase the stimulation intensity as the fast presentation rate of our clicks increases the perception of loudness, possibly resulting in discomfort to the participants. Waves III and V were present in the majority of subjects and were included in subsequent analysis.

Statistical analyses

Individual ABR Wave IIIs were extracted from data recorded using the in-ear tiptrode for each IOI in the modulated condition by extracting the largest peak within the time-window during which a Wave III would be expected. We calculated this time window as -0.5 to 0.5 ms around the manually extracted Wave III peak latency from the ABR average waveform of all IOIs. This peak value was extracted based on absolute and peak-to-peak latencies, as well as morphological criteria (Picton, 2010). Only subjects with a visible Wave III in the clinical condition (N=21) were included for this analysis. The in-ear tiptrode was used, as opposed to scalp electrodes, to maximize the size and reliability of response.

For each subject, a linear fit was applied to the relationship between IOI and wave III latency and amplitude, to index sensitivity of adaptation to IOI. The slope of the linear fits for each subject were then tested against 0 using a two-tailed t-test.

Individual ABR Wave Vs were extracted from C3 and Cz electrodes using the same method, with the exception that the time window for the Wave V is -0.7 ms to +0.7 ms around the grand average peak. Moreover, 29 rather than 21 subjects presented a Wave V. The same analysis as was performed on the Wave III was applied to the relationship between IOI and Wave V latency and amplitude to estimate the degree of subcortical adaptation in inferior colliculus.

Cortical recordings

Cortical analysis was only performed on the 6 experimental blocks, and not the clinical validation, as the validation stimulus lacks a frequency modulated component (or any other detectable pattern/regularity). Further, the clicks in the clinical stimulus were presented at a slower rate than those in the unmodulated part of the modulated stimulus; consequently, the clinical stimulus cannot be used for unmodulated versus modulated comparisons.

Data from 16 scalp electrodes were re-referenced to the averaged mastoids. Responses were extracted to the first click in each click train marking the onset of either the modulated or

unmodulated stimuli. Data were low pass filtered at 22 Hz (2001 points, Kaiser). Data were then down-sampled from 16384 Hz to 1024 Hz prior to high pass filtering. Data were high-pass filtered at 0.7 Hz (2449 points, Hann window), and then divided into epochs ranging from -1 s to 6.6 s time locked to stimulus onset.

To investigate the sustained neural activity high-pass filtering was omitted (all other analyses remained the same). This is necessary to investigate the sustained response, as the response is a very low-frequency signal reflecting a DC shift (Barascud et al., 2016; Southwell et al., 2017).

Independent Components Analysis (ICA; runica method, Makeig at al., 1996; logistic informax algorithm, Bell and Sejnowski, 1995) was computed using Fieldtrip software (v2017b). Components containing eye blinks were rejected, and the data were then projected onto the original electrodes. For non-high-pass filtered data, independent components were generated from the high-pass filtered data. The components to be rejected were decided based on these high-pass filtered data components. The corresponding components were rejected from the non-high-pass filtered data. Trials were rejected if the amplitude difference between the highest peak and lowest trough exceeded 200 microvolts in any of the electrodes.

Statistical analyses

For our cortical analysis, we examined both low frequency sustained activity (sustained response) and neural synchronization (phase-locking).

Sustained Response

Single-trial time courses were averaged for each condition (modulated and unmodulated). Response time courses for each electrode were baseline corrected by subtracting the mean amplitude of the pre-stimulus window (-1 s to 0 ms) from the amplitude at each time point. Signals were averaged across a fronto-parietal electrode cluster (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4), and the mean amplitude was calculated within the time window for which a temporal regularity could occur, that is, the time window in which the frequency modulation takes place in the modulated condition (1.08 to 5.64 s). The sustained response was

compared between the unmodulated and modulated stimulus conditions. The amplitude of the sustained response was compared via a two-tailed t-test during the time window in which temporal regularity (frequency modulation) could occur.

Neural Synchronization

Neural synchronization was investigated using Inter-Trial Phase Coherence (IPTC) (Lachaux et al., 1999). A fast Fourier transform (including Hann window taper) was calculated for each trial and channel during the time window in which regularity (frequency modulation) could occur (1.08 to 5.64 s). The resulting complex numbers (representing sine wave amplitudes) were divided by their respective magnitudes to normalize them. The normalized numbers were then averaged across trials, and their absolute value, which could be between 0 and 1 (0 means no coherence while 1 means maximum coherence) was used as the Inter-Trial-Phase-Coherence (ITPC). ITPC was calculated for frequencies within the range of 1 to 12 Hz. For statistical analyses, ITPC was averaged across the fronto-parietal electrode cluster (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4).

ITPC was compared between the unmodulated and modulated stimulus conditions. The magnitude of ITPC was compared via a two tailed t-test for the 3.45 to 3.55 Hz frequency window around the modulation frequency of the modulated stimulus (3.5 Hz).

Correlations

Pearson's correlations were calculated between the degree of subcortical adaptation, estimated using the slopes of the linear regression lines for wave III and V latency shifts, and regularity encoding, estimated using the extent of cortical synchronization of temporal regularities (the magnitude of ITPC difference between modulated and unmodulated sections) and as the sustained response amplitude difference between ITPC to modulated and unmodulated sections. Pearson's correlations were also calculated to compare adaptation slopes at the subcortical level with one another (wave III and wave V).

Chapter 3

3. Results

3.1 In-lab developed stimulus elicits comparable responses to standard clinical stimulus

To validate the use of our recording paradigm for obtaining responses from peripheral and subcortical auditory areas, we compared the responses to the unmodulated portion of the experimental stimulus to those from the clinical validation stimulus. Figure 2 depicts the grand average time courses elicited by the average of all clicks for each stimulus condition. Both stimulus conditions reliably elicited peaks at 4 and 6 ms corresponding to waves III and V (from the cochlear nucleus and the inferior colliculus, respectively). However, no reliable wave I/CAP was observed for clicks in either condition. This may have been due to the relatively low intensity of our clicks, as increasing the intensity of the stimulus evokes larger ABR responses (Picton, 2010). Note that we could not increase the intensity of our clicks as their fast presentation rate increases perception of loudness. Increasing the intensity of the clicks would have result in discomfort to the participants, and was thus avoided.

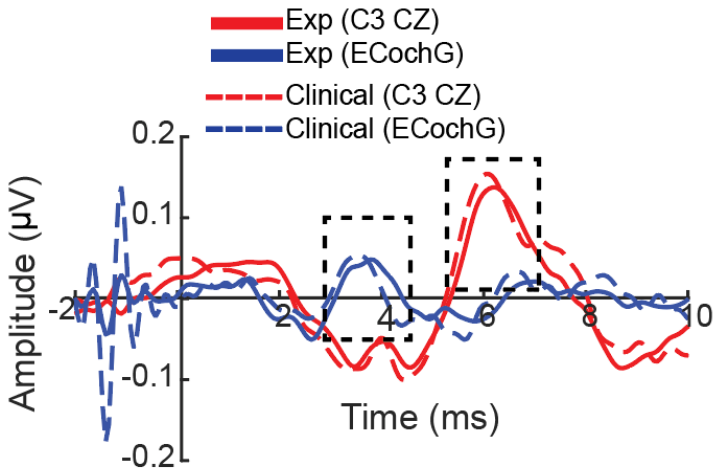

Figure 2. Average time courses of Auditory Evoked Potentials (AEP) from average signal across C3 and Cz electrodes to the unmodulated stimulus from the experimental blocks (red solid line) compared to the same electrodes from the clinical validation stimulus (red dashed line). Data from the in-ear ECochG electrode also is plotted in blue (solid for experimental; dashed for clinical validation). Black dashed boxes are used to highlight peaks corresponding to Waves III (left box) and V (right box).

Individual time-courses evoked by both the modulated (grant average of clicks from all 8 IOI bins) and unmodulated clicks were also extracted for each participant and used to ensure participants displayed clear ABRs. Nearly all participants demonstrated a clear wave V (N=28). Note that while not all participants displayed a wave III, this was consistent across all IOI bins. Participants who displayed wave V's with a latency exceeding 2 standard deviations from the mean wave V latency were excluded from all subsequent analysis (N=2). Participants who did not display a wave III in response to the average of all **modulated** clicks were not included in analysis pertaining to IOI effects on the wave III.

3.2 Subcortical Responses

IOI affects wave III latency, but not amplitude

Figure 3 A. shows the ECochG time-courses elicited by the modulated clicks averaged across all participants. Separate time-courses for each of the 8 unique IOIs used to evoke responses are displayed. Individual amplitudes and latencies for each participant were extracted, and a linear function was fit for both amplitude and latency values as a function of IOI. The slope values from the linear fits for latency as a function of IOI were significantly different from 0 (t= -2.1060, df =20, p= 0.048), but the slope values from the linear fits for amplitude as a function of IOI were not. The degree of latency adaptation for each individual participant was estimated from the slope of their regression line. The slope was negative for the majority of participants (Figure 3 B).

IOI affects wave V latency, but not amplitude

Figure 3 A. shows the ABR time-courses elicited by the modulated clicks averaged across all participants. Individual amplitudes and latencies for each participant were extracted, and a linear function was fit for both amplitude and latency values as a function of IOI. Slope values from the linear fits for latency as a function of IOI were significantly different from 0 (t= -7.519, df =28, p= 3.4394e-08), but the slope values from the linear fits for amplitude as a function of IOI were not. The degree of latency adaptation for each individual participant was estimated from the slope of their regression line. The slope was negative for all participants except two (Figure 3 C).

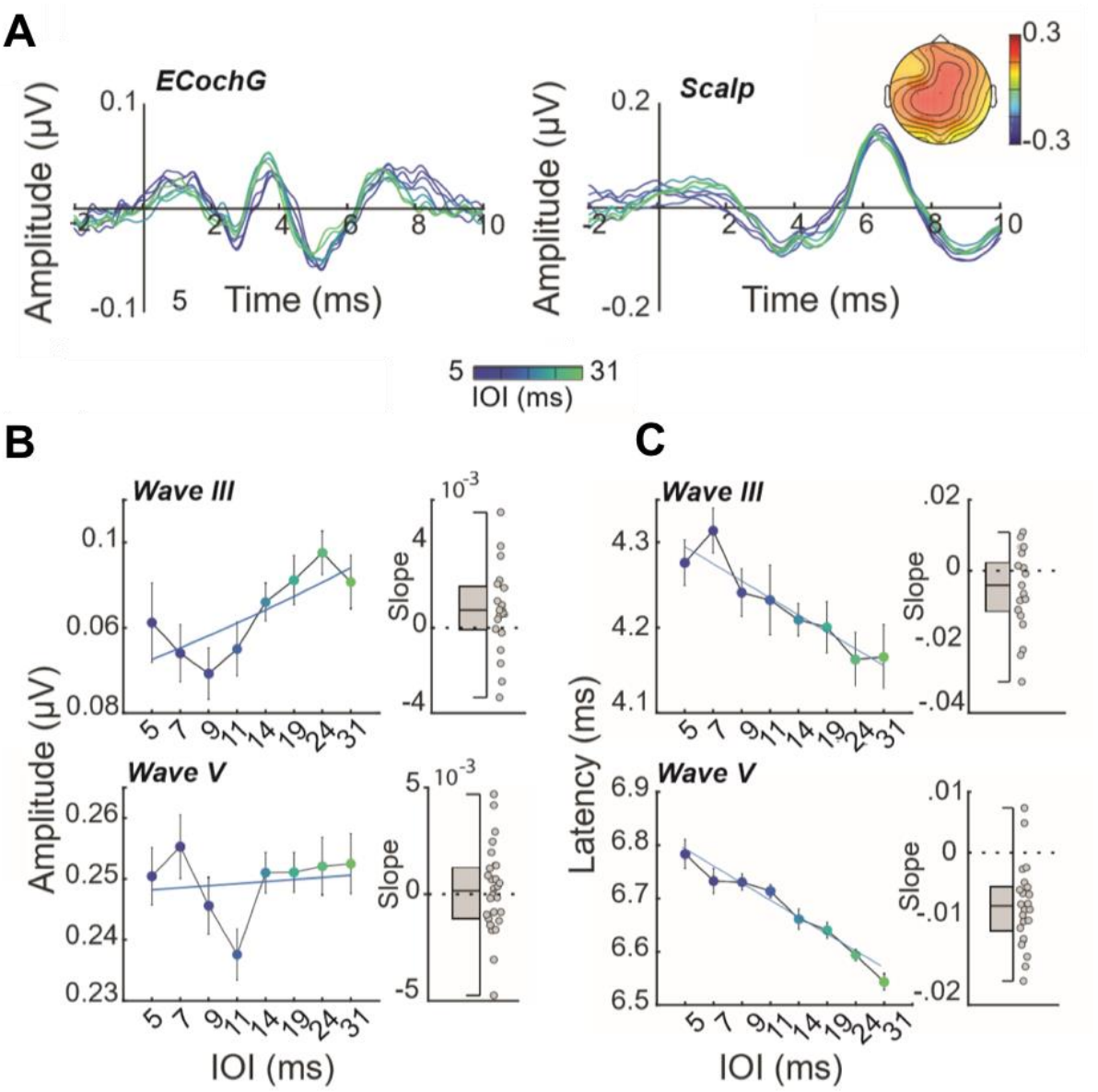

Figure 3. A. Right panel shows the average time-courses across all participants displaying wave III (N=21) from the ECochG tip-trode. Left panel shows the average time-courses across all participants (N=29) for each of 8 unique Inter-onset intervals (IOIs) (see color legend) from the average across C3 and CZ electrodes B. Plots of Wave III (top panel) and V (bottom panel) amplitude over IOI. Coloured circles in the plot on the left correspond to aligning IOIs, and are consistent with the coloured traces in 3A. Individual slope values (taken from each participant's linear equation) are plotted in the right-hand panels. C. Plots of wave III (top panel) and V (bottom panel) latency over IOI with regression line. Individual slope values are plotted in the right-hand panels.

3.3 Cortical Responses

Low frequency sustained activity in the cortex is enhanced by temporal regularity

Low-frequency sustained activity was compared between the unmodulated and modulated stimulus conditions. Figure 4 shows a comparison of the amplitude of the EEG activity between the modulated and unmodulated conditions. The mean amplitude of the EEG signal during the time window in which a temporal regularity could occur (1.08 to 5.64 s) was significantly lower in the modulated condition than in the unmodulated condition; $t(28)=2.7$, $p<0.013$. This indicated that the sustained response to the modulated stimulus was enhanced (more negative) relative to the unmodulated stimulus.

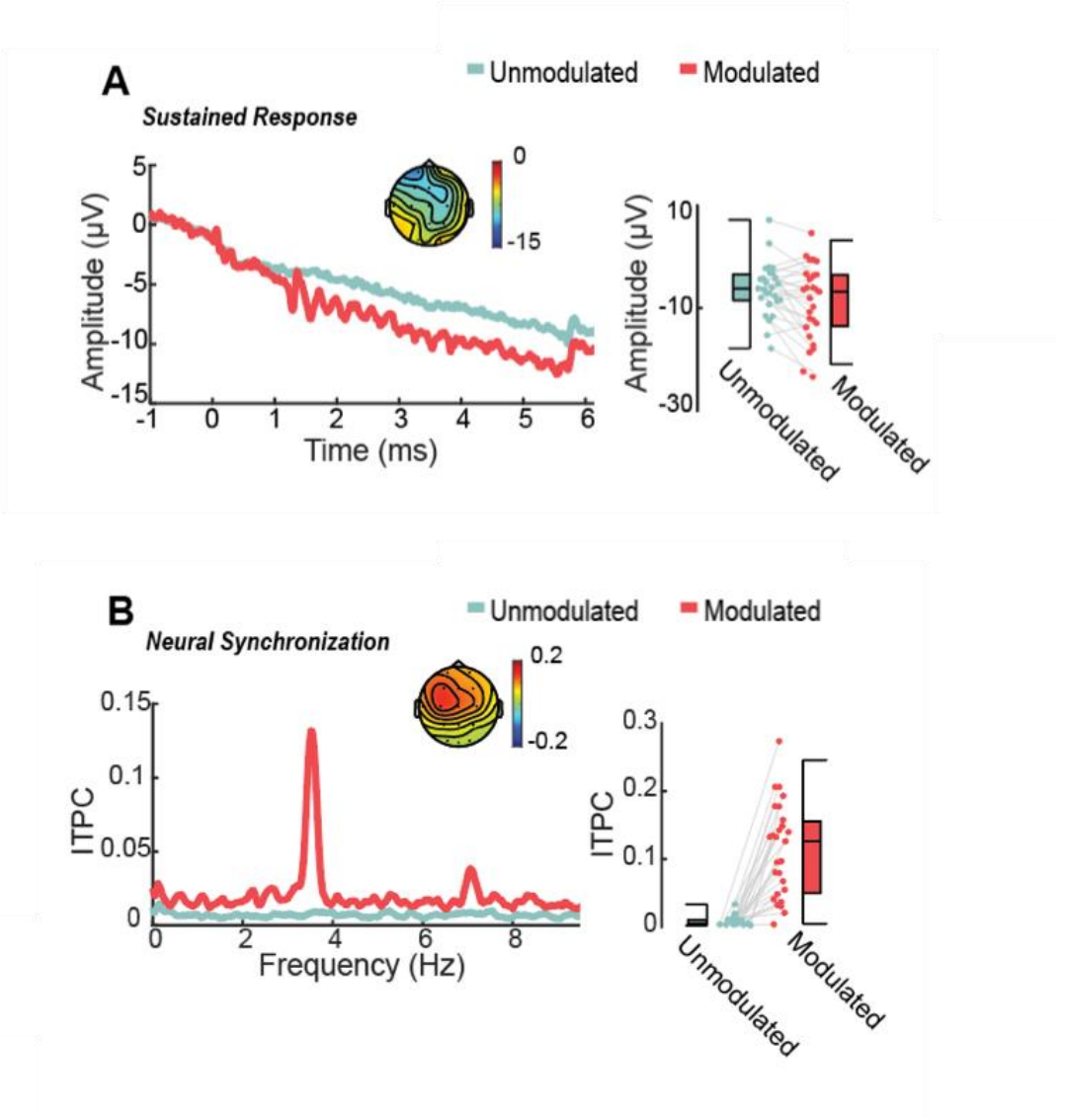

Figure 4 A**.** Low-frequency sustained activity in cortical responses to both unmodulated (blue) and modulated (pink) stimulus conditions. Individual amplitude values for both conditions were evaluated during the time window at which temporal regularity could occur (1.08 s to 5.64s). Individual amplitude values for both conditions are plotted on the panel to the right**.** B. Inter-trial phase coherence is represented for cortical responses to both unmodulated (blue) and modulated (pink) stimulus conditions. Individual IPTC values for both conditions were calculated for a 3.45-3.55 Hz frequency window, to evaluate neural synchronization at the stimulus modulation frequency (3.5 Hz). Individual IPTC values for both conditions are plotted on the panel to the right.

Cortical neural oscillations synchronize with stimulus frequency

Cortical processing of temporal regularity (here, frequency modulation) was investigated as the degree of neural synchronization, or phase-locking, to the modulation frequency (3.5 Hz) in the modulated stimulus condition. Figure 5 compares the ITPC magnitude of the unmodulated and modulated conditions. A large peak can be observed in the ITPC spectrum for the modulated condition at around 3.5 Hz, which reflects the stimulus. There was a significant difference in the mean magnitude of ITPC during the frequency window reflecting the stimulus modulation (3.45 to 3.55 Hz) in the modulated and the unmodulated stimulus conditions; $t(28) = -7.58$, $p= 2.9211e-08$. This indicates that neural activity synchronizes with the frequency modulation in the sound.

3.4 Correlations among neural measures

Figure 5.A shows a matrix representing the strength of Pearson's correlations (r^2) for all neural measures: average wave III amplitude, average wave III latency, average wave V amplitude, average wave V latency, slopes of the regression lines for IOI effects on wave III and V amplitudes and latencies, ITPC difference between the modulated and unmodulated conditions at the modulation frequency and harmonic, and sustained response difference between the modulated and unmodulated conditions. Multiple comparisons were corrected for using a False Discovery Rate (FDR) correction. No across level (subcortical vs cortical) correlations were significant. The only significant correlations were between the latency of the wave III with its amplitude ($r^2= -0.77$, $p= 0.0015$), and between latency of the wave V with its amplitude ($r^2= -0.64$, $p= 0.0044$).

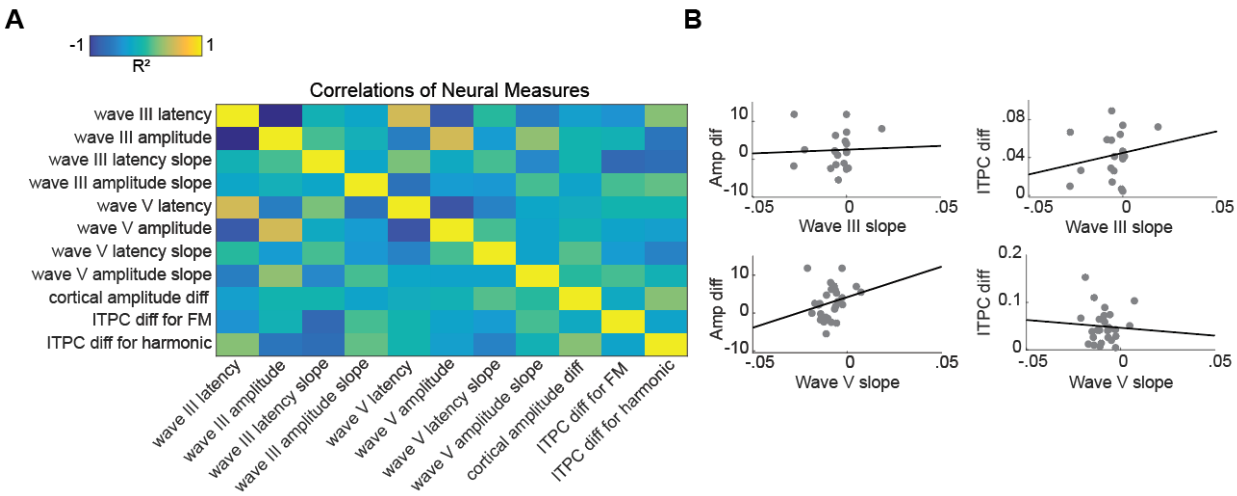

Figure 5. A. Matrix of correlations among neural measures. B. Sample of correlations between: magnitude of sustained response (measures as amplitude difference between modulated and unmodulated conditions) and wave III latency shift (measured by the slope of the IOI by latency relationship), magnitude of sustained response and wave V latency shift, magnitude of phase-locking (measured by the difference in inter-trial phase coherence at 3.5 Hz between the modulated and unmodulated conditions) and wave III latency shift, and magnitude of phase-locking and wave V latency shift.

Chapter 4

4. Discussion

The current experiment investigated the relationship between temporal processing in subcortical (CN and IC) and cortical auditory levels. Specifically, temporal sensitivity at subcortical levels was measured via adaptation of neural response (here, ERPs), and at cortical levels by both sustained activity reflecting repetition detection and by neural synchronization. Responses were measured simultaneously and non-invasively in humans using an integrated EEG-ECochG system. The experiment made use of a novel stimulus paradigm in which clicks were presented with steadily decreasing and then increasing IOIs, such that the stream was frequency modulated at 3.5 Hz. This stimulus was capable of eliciting subcortical ERPS (ABR waves III and V) and cortical responses (sustained ERP and neural synchronization).

4.1 Validation of system

To use our system to evaluate subcortical temporal processing via adaptation, we first needed to validate its ability to elicit subcortical responses. To do this, we included a validation block in our experiment which consisted of a standard clinical stimulus commonly used for recording subcortical ERPs. This stimulus was compared to our unmodulated experimental stimulus in the experimental block. Both the validation and unmodulated stimuli were isochronous clicks, but the clicks in unmodulated experimental stimulus were presented at over twice the rate of the validation stimulus. This comparison illustrated that both the clinical stimulus and our in-lab developed stimulus were able to reliably evoke waves III and V of the ABR, but not wave I.

4.2 Absence of Wave I

Neither the validation nor experimental stimulus was able to elicit the wave I (AN) response, even in the ECochG channel, which was closest to the generator in the auditory nerve. The magnitude of human wave I is quite small (Sohmer & Feinmesser, 1973), often making it difficult to record using an extra-tympanic system like ours. Moreover, as our system was designed to record cortical signals, it made use of an electrode cap which stayed in place using a jaw strap. The cap and jaw strap may contribute to minute muscle movements and tension that (negatively impact) the ECochG signal. The relatively low click intensity may have also contributed the absence of wave I. We were unable to increase the sound intensity any further as the fast click presentation rate already increases the perception of loudness. (this is discussed further in the limitations section).

Although wave I recordings would have allowed for more exhaustive system wide comparisons, our experiment is still valuable without the inclusion of a peripheral component. Simultaneous observation of temporal processing at the subcortical and cortical levels is an important step towards understanding suprathreshold symptoms of hearing impairments.

4.3 Subcortical adaptation

We measured sensitivity to temporal information indirectly, by evaluating subcortical adaptation. Subcortical adaptation (CN and IC) was evaluated using the change in response to successive click stimuli at different IOIs. The responses of interest were the waves III and V of the ABR, generated at the CN and IC respectively. We observed adaptation of latencies in both CN and IC such that latencies were longer when neurons had less time to recover from adaptation. Single-neuron recordings from the inferior colliculus in rats demonstrate both reduced firing rates and longer first-spike latencies to repetitive stimulation (Herrmann et al., 2015). Our electrophysiological data, however, demonstrated only adaptation of ABR latencies, and not amplitudes. At the single-neuron level, the first spike latency of most auditory neurons are time-locked to sound onset (Heil, 2004). It is possible that latency delays occur because the sound onset occurs during the relative refractory period of the neuron, and the response is thereby delayed until the relative refractory period is over and all sodium

channels have recovered. However, as the relationship between single neuron recordings and far-field potentials is still unknown, it is uncertain why electrophysiological recordings from the brainstem do not demonstrate amplitude adaptation (which would reflect firing-rate more directly). Still, our findings were line with previous accounts of IOI affecting wave V latency, but not amplitude (Lasky, 1984; Suzuki, Kobayashi & Takagi, 1986).

4.4 Sustained response

We evaluated cortical detection of temporal regularity via a sustained low frequency activity. We observed an enhancement of this sustained activity in response to the frequency modulated (temporally regular) sequences in our stimulus, which is in line with previous literature (Barascud et al., 2016; Sohoglu and Chait, 2016; Southwell et al., 2017; Herrmann & Johnsrude, 2018).

4.5 Neural synchronization

We evaluated cortical processing of temporal regularity via neural synchronization of EEG activity to the modulation frequency of our stimulus. Synchronization of neural activity to the modulation frequency is thought to facilitate the prediction of future sounds (Schroeder and Lakatos, 2009; Henry and Herrmann, 2014; Nobre and van Ede, 2018). We found that cortical neural oscillations synchronized with the frequency modulation in our temporally regular condition, which is in line with what we would expect based on previous findings (Schroeder and Lakatos, 2009; Henry and Herrmann, 2014; Nobre and van Ede, 2018).

4.6 Correlations of neural measures

Although we did not find any correlations between subcortical and cortical sensitivity to temporal regularity, we cannot claim that the two stages are completely independent from one another. It is possible that subcortical adaptation is independent, or partially independent, from cortical synchronization and sustained activity. However, it is also possible that these processes are related in an indirect or non-linear way, which we were unable to measure. More work is required to fully understand the relationship between subcortical adaptation and cortical markers of temporal regularity.

4.7 Limitations

Because of our fast click presentation rate, we were unable to increase the intensity of our clicks as this would also increase the subject's perception of loudness, possibly resulting in discomfort. ABR variability is affected by intensity such that clicks presented at higher intensities reduce the response variability (Picton, 2010; Burkard, Eggermont, & Don, 2007). Although we observed a robust Wave V (IC), Wave III (CN) was more variable, and this variability may have been reduced if the click intensity had been increased. This is also likely a factor in our inability to obtain any reliable wave I (AN) responses. Nevertheless, we were still able to evaluate subcortical adaptation, at the CN and IC, as well as cortical sustained activity and neural synchronization to temporal regularity. Consequently, we were able to measure sensitivity to temporal structure at the subcortical and cortical levels simultaneously and non-invasively in humans.

4.8 Implications

Our stimulus and system can be used to evaluate system-wide auditory responses simultaneously and non-invasively in humans. To our knowledge, this experiment is the first to employ a stimulus capable of eliciting subcortical ERPs in addition to neural synchronization and sustained activity at cortex, allowing us to simultaneously examine sensitivity to regularity at multiple levels. Although Slugocki and collogues (2017) were able to successfully record responses from the brainstem, thalamus, and primary and secondary auditory cortices, their method evaluates a different set of responses and did not investigate adaptation of subcortical responses. They did find that the latency of the brainstem FFR predicts the phase delay of the auditory cortex response (40 Hz ASSR), and that the amplitude of the brainstem FFR predicts the latency of the cortical N1 response. This suggests that subcortical and cortical processing are related. In contrast, the present study found no relationship between the subcortical and cortical responses that were investigated. However, as the present investigation focused on different aspects of subcortical and cortical auditory processing, it is possible that some aspects of subcortical and cortical auditory processing are

correlated while others are not. Specifically, subcortical adaptation may be independent from cortical processing of temporal regularity (as measured via the sustained response and entrainment of neural oscillatory activity), while subcortical FFRs appear to be correlated with cortical ASSRs and N1.

In addition, our stimulus could be useful in future investigations on top-down processing in the auditory system, where attention is manipulated during stimulus presentation. This would be interesting as top-down processing in the human auditory system is still poorly understood, but is clearly an important determinant of auditory perception.

This stimulus can also be applied to investigate differences in temporal processing across groups (older vs younger, hearing impaired vs healthy control). Previous investigations have shown that age affects responses in the subcortical (Willot, Parham, & Hunter, 1988; Parthasarthy, Herrmann, & Bartlett, 2019) and cortical (Herrmann et al., 2016; Herrmann, Buckland, & Johnsrude, 2019) auditory areas. Simultaneous measurement of responses from multiple levels of the auditory system might thereby yield important information about how the relationship between temporal processing across levels differs in groups with different hearing abilities like older versus younger listeners. Finally, this stimulus can be applied to investigate cortical gain in the auditory system by manipulating encoding of sounds at the peripheral level (perhaps by using ear-plugs to reduce peripheral input).

4.9. Conclusion

In summary, the current experiment investigated the relationship between sensitivity to temporal regularity in subcortical (CN and IC) and cortical auditory levels using a novel stimulus capable of simultaneously eliciting subcortical ABRs (which can demonstrate adaptation) and cortical regularity responses. No clear relationship between subcortical and cortical sensitivity to temporal regularity was observed suggesting that subcortical adaptation may be independent from regularity processing at the cortical levels. The use of this novel stimulus as a tool for investigating auditory system-wide (subcortical and cortical) regularity responses was validated. This stimulus can be used for future investigations of top-down processing in the auditory system, compensatory gain, and comparisons between hearing

impaired and normal hearing subjects. More broadly, this work provides an early step towards characterizing the relationship between multiple structures/stages of the auditory pathway, which is an important direction if we are to understand complex age and noise-exposure related hearing impairments.

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Curriculum Vitae

Sonia Varma

EDUCATION

UNIVERSITY OF WESTERN ONTARIO, London, Ontario 2017- Present
Masters of Science in Neuroscience

- Research focus on efferent connections in the aging human auditory cortex

UNIVERSITY OF OTTAWA, Ottawa, Ontario 2013-2017
Honours Bachelors of Science in Psychology

- Magna Cum Laude
- Dean's Honour's List

RESEARCH EXPERIENCE

UNIVERSITY OF WESTERN ONTARIO, London, ON September 2017- Present
Graduate Level Researcher

- **Project: Investigating Relationship between Subcortical and Cortical Auditory Processing**
- Conducted extensive literature review
- Administered electroencephalography and audiometric tests to subjects
- Performed data analysis using Matlab

UNIVERSITY OF OTTAWA, Ottawa, ON September 2016- July 2017
Research Assistant and Data Analyst

- **Project: Predicting Learning Using Markers in Brain Activity**
- Administered psychological tests to subjects
- Use event-related brain potentials (ERPs) to examine the extent of information processing
- Performed data and statistical analysis

UNIVERSITY OF OTTAWA, Ottawa, ON May 2016- July 2017
Honours Thesis Student and Research Assistant

- **Project: The Effects of Sleep Onset on Auditory Processing**
- Conducted overnight sleep lab EEG recording with no supervision
- Collected electrophysiological data from subjects during the waking and sleep onset periods
- Performed statistical analyses, and prepared the results for both a poster and final honours paper

UNIVERSITY OF OTTAWA, Ottawa, ON January 2016- May 2016
Volunteer Lab Assistant

- **Project: The Effects of Sleep Onset on Auditory Processing**
- Administered psychological tests to adolescent subjects
- Use event-related brain potentials (ERPs) to examine the extent of information processing
- In charge of monitoring EEG recordings, setting up and cleaning EEG equipment, and analysing EEG data

ROYAL OTTAWA: INSTITUTE OF MENTAL HEALTH, Ottawa, ON August 2015-August 2016
Research Assistant

- **Project: The Effects of Anxiolytic Botanicals on Fear Memory Extinction in Rats**
- Tested the effects of anxiolytics on rats using known animal models for PTSD
- Fed and attended to lab animals several times a week
- Required to thoroughly understand the use of animal models for psychological disorders
- Presented results in 2016 UROP Symposium

ACUITY RESEARCH GROUP, Ottawa, ON September 2015- September 2017
Field Researcher

- Administered written and oral questionnaires at Ottawa festivals and events such as CityFolk and Blues Fest
- Required to work efficiently and professionally in a fast paced and noisy environment
- Maintained the confidentiality of responders

PROFESSIONAL EXPERIENCE

UNIVERITY OF WESTERN ONTARIO, London ON September 2017- Present
Graduate Teaching Assistant

- Instructed weekly tutorials to class sizes of up to 30 students
- Held weekly office hours to facilitate student learning
- Marked and reviewed exams and assignments

UNIVERSITY OF OTTAWA, Ottawa ON September 2016- April 2017
Undergraduate Opportunity Program Leader

- Delivered presentations encouraging students to partake in undergraduate research
- Managed booth at University open house and answered student and parent questions
- Educated undergraduate students on research opportunities at the University of Ottawa

UNIVERSITY OF OTTAWA HEALTH SERVICES, Ottawa, ON May 2015- April 2017
Peer Educator

- Educated students about the health services available on campus
- Administered carbon monoxide tests to students
- Educated students about the effects of alcohol and tobacco products

T&J NGUYEN DENTAL CENTRE, Ottawa, ON July 2013- September 2015
Administrative Assistant

- Scheduled and canceled patient appointments
- Answered patient questions in an efficient and professional manner
- Organized clinic files and documents

EXTRA-CURRICULAR EXPERIENCE

LET'S TALK SCIENCE, London, ON September 2017- present
Volunteer

- Delivered basic science tutorials for elementary school classrooms
- Judged posters at elementary school science fairs
- Facilitated science related activities and games at camps and schools

UWO EQUITY COMMITEE, London, ON September 2017- present
Committee Member

- Organized campus events to promote student equity
- Interviewed faculty and students to create profiles for committee web page
- Created a best-practice resource for supervisors of international graduate students

UWO ACADEMIC COMMITEE, London, ON December 2017- present
Committee Member

- Reviewed abstracts for local research conferences
- Provided feed-back to unsuccessful conference applicants
- Attended monthly meeting to plan academic events for graduate students

INTERNATIONAL EXPERIENCE

FLORIANA ELEMENTARY SCHOOL**,** Narsipur, India June 2014- August 2014
Teaching Assistant

- Responsible for teaching English to 4th-6th grade students
- Conducted one on one tutoring sessions for students in need of extra help
- Organized weekly activities to facilitate learning in fun and innovative ways

AWARDS AND CERTIFICATIONS

- Recipient of Ontario Graduate Scholarship ($15,000)
- Recipient of Western Ontario Graduate Scholarship ($4,000)

- Recipient of the Undergraduate Research Opportunity Program (UROP) Scholarship ($1,000)
- Laureate of the Undergraduate Research Opportunity Program (UROP) competition (First place)
- Recipient of University of Ottawa Merit Scholarship ($1,000/ academic year)
- WHMIS and WSPS Certification
- Lab Safety Certification
- Ontario Secondary School Diploma
- Diplôme d'études en langue française
- Semi-finalist in Poetry Nation's National Amateur Poetry Contest 2016

PEER-REVIEWED PUBLICATIONS AND PRESENTATIONS

Varma, S., Purcell, D., Johnsrude, I., & Herrmann, B. (2019, May) *Investigation of the relationship between subcortical neural responses and cortical processing of temporal regularity.* Poster presented at the International Hearing Loss Conference, Niagara-on-the-Lake, ON.

Varma, S., Herrmann, B., Johnsrude, I. (2019, February) *Investigation of the neurl processes underlying hearing from periphery to brain.* Poster presented at the 48th Lake Ontario Visionary Establishment, Niagara Falls, ON.

Tavakoli, P., **Varma, S**., & Campbell, K. (2017). Highly relevant stimuli may passively elicit processes associated with consciousness during the sleep onset period. *Consciousness and cognition*.

Varma, S., Richards, C., Merali, Z., & Kent, P. (2016, March). *The effects of anxiolytic botanicals on fear-memory extinction in rats.* Poster presented at the 5th annual University of Ottawa Undergraduate Research Symposium, Ottawa, ON.