CODING-IN-NOISE DEFICITS AFTER EXPOSURE TO NOISE MIMICKING REAL-LIFE PARAMETERS

by

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ABSTRACT

Noise induced synaptopathy (NIS) has been thoroughly researched in animals since the first observation of significant synaptic loss without permanent threshold shift (PTS) in CBA mice after brief noise exposure. However, it remains a challenge to translate these animal findings to human data, since the noise used to establish NIS in previous animal studies is unlike the noise experienced by humans in everyday life. A total of 32 albino guinea pigs were separated into a control and a noise group. The noise group was exposed to noise mimicking what is experienced by humans (relatively low in level, fluctuated and intermittent) to investigate whether NIS without PTS could be established by such noise. It was also examined whether coding-in-noise deficits (CIND) are the major difficulty associated with NIS without PTS, which has previously been speculated based on evidence for disproportionate synaptic loss for auditory nerve fibers (ANFs) with low spontaneous rates (LSR). This was done by examining the impact of the NIS on temporal processing under masking. Furthermore, since robust evidence supporting CIND as the major problem associated with NIS is limited, the role of LSR ANFs in signal coding of high-level noise has been reexamined (see review (Carney, 2018)): the fluctuation profile model has been proposed to support a role for high-SR ANFs in the coding of high-level noise in combination with efferent control of cochlear gain. This study evaluated the role of temporal fluctuation in evoking efferent feedback and the effects of NIS on this feedback. Results showed that noise exposure experienced by humans in daily life is less effective in causing NIS, and that the NIS causes temporal processing deficits that are likely of a central origin. Additionally, results demonstrated no apparent evidence suggesting that NIS deteriorates the signal detection ability in noise using temporal cues. Finally, the results did not provide sufficient evidence supporting the MOC regulation in the fluctuation profile model.

LIST OF ABBREVIATIONS USED

ABR	Auditory brainstem response
AM	Amplitude modulation
ANF	Auditory nerve fiber
ANOVA	Analysis of variance
ASSR	Auditory steady state response
AVCN	Anteroventral cochlear nucleus
BBN	Broadband noise
BMF	Best modulation frequency
CAP	Compound action potential
CF	Characteristic frequency
CIND	Coding-in-noise deficits
CN	Cochlear nucleus
CS	Contralateral suppression
CtBP2	C-terminal binding protein 2
DCN	Dorsal cochlear nucleus
DPOAE	Distortion product otoacoustic emission
EAR	Efferent acoustic reflex
EFR	Envelope following response
F0	Fundamental frequency
FFT	Fast Fourier transformation
FIR	Finite impulse response
HC	Hair cell
IC	Inferior colliculus
IHC	Inner hair cell
I/O	Input/output
ITD	Interaural time difference
Leq	Long-term equivalent
L/M/HSR	Low/medium/high spontaneous rate
LOC	Lateral olivocochlear
LSO	Lateral superior olivary nucleus
MD	Modulation depth
MEM	Middle ear muscle
MF	Modulation frequency
MOC	Medial olivocochlear
MSO	Medial superior olivary nucleus
MTF	Modulation transfer function
nfEFR	Near-filed envelope following response
NIHHL	Noise induced hidden hearing loss
NIHL	Noise induced hearing loss
NIS	Noise induced synaptopathy
OAE	Otoacoustic emission
OC	Olivocochlear
OHC	Outer hair cell

PBS	Phosphate-buffered saline
PSD	Post-synaptic density-95
PTS	Permanent threshold shift
PVCN	Posteroventral cochlear nucleus
RM	Repeated measure
RMS	Root-mean square
SEM	Standard error of the mean
SGN	Spiral ganglion neuron
SNR	Signal-to-noise ratio
SOC	Superior olivary complex
TB	Tone burst
TMTF	Temporal modulation transfer function

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CHAPTER 1 INTRODUCTION

1.1 Overview and research questions

Noise induced hearing loss (NIHL) is typically defined by the permanent threshold shift (PTS) caused by noise exposure (Berger et al., 1978). In recent years, however, this concept has been expanded by the finding that noise damage to the ribbon synapses between the inner hair cells (IHC) and the spiral ganglion neurons (SGN) in the cochlea can occur without PTS (Hesse & Kastellis, 2019; Le Prell & Clavier, 2017; M. C. Liberman, 2015, 2017; Paul et al., 2017; Plack et al., 2014, 2016; Tepe et al., 2017). The damage to, and the loss of, the afferent synapses between the IHCs and the SGNs (which are also called ribbon synapses based on their structural characteristics), as well as the associated functional deficits are described by the concept of noise induced synaptopathy (NIS) (Chen, Shi, et al., 2019). NIS can occur with and without PTS. If such damage occurs without PTS, then the associated functional deficits are conceptualized by Noise Induced Hidden Hearing Loss (NIHHL), because such deficits are often subclinical and cannot be detected by routine audiological evaluations that are focused on threshold. However, the concept of NIHHL also covers the functional deficits that have central origins. NIHHL has been of special interest in the field of audiology, and it continues to gain attraction as its possible implications for humans become more apparent, since the damage to the ribbon synapses can affect the ability of the listener to process complex sounds such as speech (M. C. Liberman, 2015).

To date, although there have been a significant number of studies on the topics of NIS without PTS and NIHHL, many knowledge gaps remain. Such knowledge gaps serve as the basis of three research questions that were investigated in this study. The first

research question is understood by examining the animal studies on NIS without PTS in recent history (Chen, Shi, et al., 2019; Fan et al., 2020; Furman et al., 2013; Kaur et al., 2019; Kim et al., 2019; Kujawa & Liberman, 2009; L. Liu et al., 2012; Shi et al., 2013; Shi, Guo, et al., 2015; Shi, Liu, et al., 2015; Song et al., 2016; Zhang et al., 2020). The literature reveals that the noise used to cause the NIS in these experiments is unlike that which is experienced by humans in real life, making it difficult to use the animal data to predict or interpret human data. Therefore, the present study aimed to investigate if NIS without PTS can be established by noise exposure that mimics what is frequently experienced by humans.

The second research question, like the first, also stems from the fact that the experimental parameters used in the animal studies are unlike what are experienced by humans in real life. Currently, coding-in-noise deficits (CIND) are speculated as the major problem in subjects with NIS without PTS. However, no robust evidence has been found to support the occurrence of CIND either in animal studies or human research. One of the potential problems in the relevant research is with the use of masking. Many experiments used a stationary masker instead of a more realistic temporally fluctuated masker (Chen, Shi, et al., 2019; Fan et al., 2020; H. Liu et al., 2019; Ralli et al., 2019; Souchal et al., 2018; Zhang et al., 2020). When listening under temporally fluctuated maskers, subjects may detect the signals in the dips of the masker. Since the described signal detection relies on the temporal processing ability of the listener, a masking test using a temporarily fluctuated masker should reveal the connection between CIND and temporal processing ability. This study therefore examined the role of temporal

processing disorder in the coding-in-noise deficits that potentially result from NIS without PTS.

The third research question of the present study is primarily based on the challenges to the theoretical dependence of auditory nerve fibers (ANFs) with low spontaneous rates (LSR) in the signal coding of high-level sound against masking (see review by (Carney, 2018)). Carney discusses a fluctuation profile model to identify the role of ANFs with high spontaneous rates (HSR) in coding supra-threshold sounds, such as speech (2018). This is a compelling argument, especially considering its implications for current hypotheses on supra-threshold hearing in humans. Furthermore, Carney (2018) suggests that the fluctuation profile of ANFs is enhanced by the feedback control via medial olivocochlear (MOC) innervation. This study investigated the importance of signal fluctuation in the MOC-mediated cochlear suppression and the effect of NIS without PTS on it.

The current literature related to the outlined research questions is reviewed in the following subsections.

1.2 Noise exposure used in the studies of NIS without PTS in animals

In recent history, animal models have offered valuable insight on the subject of NIHHL (Chen, Shi, et al., 2019; Fan et al., 2020; Furman et al., 2013; Kaur et al., 2019; Kim et al., 2019; Kujawa & Liberman, 2009; L. Liu et al., 2012; Shi et al., 2013; Shi, Guo, et al., 2015; Shi, Liu, et al., 2015; Song et al., 2016; Zhang et al., 2020). The accumulated knowledge from the animal studies proves to be incredibly helpful in understanding NIS without PTS in animals. However, the studies are methodologically similar in terms the

noise presentation in the experiments, which creates a significant knowledge gap that makes translating the animal data to human data difficult.

Many of the animal studies induced the synaptic damage and loss with a single, brief exposure of stationary band noise at the upper limit of what will not create PTS (around 105 dB SPL for guinea pigs and rats, and 100 dB SPL for mice) (Furman et al., 2013; Kaur et al., 2019; Kujawa & Liberman, 2009; L. Liu et al., 2012; Lobarinas et al., 2017; Shi, Guo, et al., 2015; Zhang et al., 2020). For instance, in the study of Song et al. (2016), a single dose of broadband noise at 105 dB SPL was delivered to guinea pigs for 2 hours. A second example is given by the study of Zhang et al. (2020), in which, although multiple noise exposures were administered, the exposures were still brief (2 hours) and at a high sound level (106 dB SPL for guinea pigs and 100 dB SPL for mice). Moreover, broadband noise was once again used (white noise, in this case). Further, in the study by Lobarinas et al. (2017), rats were exposed to bandpass noise (8-16 kHz) of 106- or 109-dB SPL for 2 hours.

Therefore, due to the noise exposure administered in the outlined studies, it is argued that the noise used in the animal studies is unlike what human beings experience outside of a laboratory setting.

1.2.1 The noise experienced by humans in real life

Human beings are exposed to noise every day, which is concerning seeing as noise can cause hearing loss as well as non-auditory adverse effects such as communication problems (Basner et al., 2014; Nieuwenhuijsen et al., 2017; Stansfeld & Matheson, 2003; Zare Sakhvidi et al., 2018). Currently, the noise frequently experienced by humans that has raised the most concern comes from traffic (Münzel et al., 2017, 2020;

Nieuwenhuijsen et al., 2017; Zare Sakhvidi et al., 2018), recreational events (Fulbright et al., 2017; Ivory et al., 2014), industrial settings (Lie et al., 2016; Stucken & Hong, 2014), and military activities (Nakashima & Farinaccio, 2015; Pfannenstiel, 2014). For the purpose of this study, military activity is not considered because of its limited relevance to the general population. The remaining described settings, which strongly apply to the general human population, generate noise with certain properties that have not yet been exploited in animal studies on NIHHL.

First and foremost, the noise observed in traffic, industrial settings, and recreational events is generally of a much lower sound level than what has been used to cause NIS without PTS in animal studies, when the use of hearing preservation methods/devices is taken into consideration under current safety standards. For example, Lie et al. reported that industrial noise exposure causes between 7 and 21 % of hearing loss among workers, lowest in developed countries, where safety regulations regarding hearing protection are strictly enforced (2016). This is because such safety regulations ensure that the noise levels rarely exceed 90 dB SPL. Furthermore, the long-term equivalent (Leq) of noise generated by traffic is generally lower than 80 dBA. In such exposures, the noise level may frequently peak at very high levels (i.e., 110 dB SPL). However, those instances usually last only for a very short time period (Jagniatinskis et al., 2017; Oiamo et al., 2017).

A second discrepancy between the noise administered in animal studies on NIS without PTS and the noise experienced by humans is the temporal feature of noise. Not only is the noise produced in bars (Barlow & Castilla-Sanchez, 2012) or at sporting events (Masullo et al., 2016) likely to give a Leq of less than 90 dB SPL, but it is also

temporally fluctuating. Therefore, the animal studies that have previously administered stationary band noise were not realistic in the sense that the noise frequently experienced by humans fluctuates in temporal pattern.

The third discrepancy between the noise exposure experienced by laboratory animals in NIS studies and that which is experienced by humans in daily life is related to the first one. In the animal studies, the damaging amount of noise energy is delivered in a short period of time due to the use of high-level noise. However, in human experience, the same amount of noise energy is accumulated by repeated noise exposures with significant interruption between exposures. Such resting time would allow for the self-repair process to occur and therefore may change the development of NIS without PTS.

Theoretically, a possible argument against the need to test the establishment of NIS without PTS using noise that is more realistically experienced by humans stems from the "equal energy" hypothesis, which is a rule of thumb that some researchers use to estimate the amount of noise damage that would result from different sound levels. The hypothesis suggests that a low-level noise exposure would create an equal amount of damage or NIHL as a high-level noise exposure, if the duration of the low-level noise were extended by the amount to deliver an equal amount of noise energy. However, although research on NIS resulting from low-level noise exposure is rare, the few studies that have examined the idea refute the use of the equal energy hypothesis in studying NIS. In the study of Maison et al., noise of 84 dB SPL was presented continuously to CBA mice for 168 hours (2013). Such noise exposure caused significantly less ribbon synapse loss than that which was reported in the study by Kujawa & Liberman (2009), which presented 100 dB SPL for 2 hours to the same strain of mice. This is noteworthy

because the noise used in the study by Maison et al. (2013) has a total energy that is well above the equal noise dose of the noise used in the study by Kujawa & Liberman (2009). This finding not only suggests that the equal energy hypothesis is not applicable to NIS, but also that NIS is level dependent.

In summary, the noise used to establish NIS without PTS must have the following three properties in order to make the animal data applicable to humans: it must have a relatively low Leq, it must be temporally fluctuated, and it must be repeated intermittently over a long time.

1.3 Is coding-in-noise deficit the major problem in NIHHL?

CIND has been speculated as the major problem associated with NIHHL (Bharadwaj et al., 2014; C. Kohrman et al., 2020; De Siati et al., 2020; Furman et al., 2013; Huet et al., 2019; Kobel et al., 2017; Le Prell & Clavier, 2017; M. C. Liberman, 2017; M. C. Liberman & Kujawa, 2017; Plack et al., 2014). It is typically characterized as difficulty hearing speech in background noise. Therefore, this hearing deficit occurs at relatively high sound levels. There are several clues suggesting that those with NIS without PTS may experience CIND at high sound levels. First, animal data show that the ribbon synapses innervating ANFs with low spontaneous rates (LSR) are more sensitive to noise damage. Therefore, it is the LSR ANFs that lose their function from noise exposure (Fucci, McColl, et al., 1997; Fucci, Petrosino, et al., 1997; Furman et al., 2013; Song et al., 2016). Second, compared to ANFs with high spontaneous rates (HSR), LSR ANFs have a higher threshold and a larger dynamic range. Therefore, unlike the HSR ANFs, LSR ANFs do not become saturated from high-level sound (M. Liberman, 1982; M. C. Liberman, 1978; M. C. Liberman & Beil, 1979; Taberner & Liberman, 2005). Finally,

LSR ANFs appear to function better in signal coding against masking by strong background noise (Costalupes et al., 1984).

On the other hand, the evidence confirming the speculation that subjects with NIS without PTS experience CIND is minimal in both animal and human studies. Furthermore, in human studies there exist more negative publications (Fulbright et al., 2017; Grinn et al., 2017; Grose et al., 2017; Guest et al., 2018; Le Prell & Clavier, 2017; Lobarinas et al., 2017; Prendergast et al., 2019; Prendergast, Guest, et al., 2017; Prendergast, Millman, et al., 2017; Valderrama et al., 2018; Yeend et al., 2017) than positive ones on the matter (Alvord, 1983; Grose et al., 2019; Kujala et al., 2004; U. Kumar et al., 2012; M. C. Liberman et al., 2016; Makary et al., 2011; Meehan et al., 2019; Schaette & McAlpine, 2011; Stamper & Johnson, 2015; Stone et al., 2008).

However, it should be noted that it is incredibly difficult to identify NIS in human subjects due to the lack of morphological information. It is also challenging to interpret human deficits associated with NIS without PTS (if they occur) as many of the reviewed studies relied on self-report to quantify the noise exposure endured by the subjects. Moreover, only functional methods can be used to evaluate NIS in human subjects. However, a reliable method that can quantify the functional deficits that occur as a result of the loss of ribbon synapses and ANFs is not yet available. Therefore, animal studies can still make a critical contribution to establishing such a method.

1.3.1 The effect of NIS without PTS on temporal processing ability

Although CIND has yet to be proven as the major problem resulting from NIS without PTS, such a hypothesis can be further investigated by simultaneously investigating the possible temporal processing deficits that may also arise from NIS without PTS.

The signal processing ability of the auditory system is highly distinguishable from that of other sensory systems, such as vision, due to its high temporal resolution (Hirsh, 1959; Leshowitz, 1971; Ronken, 1970). Temporal processing disorders have been reported in subjects with presbycusis (Gordon-Salant, 2005; Humes et al., 2012; Martin & Jerger, 2005; Pichora-Fuller & Souza, 2003; Schneider & Hamstra, 1999; Walton, 2010), also known as age-related hearing loss, and in subjects with auditory neuropathy (A. U. Kumar & Jayaram, 2005; Lobarinas et al., 2020; Narne, 2013; Vlastarakos et al., 2008). By definition, NIS is a type of auditory neuropathy.

Furthermore, it is highly probable that temporal processing deficits occur as a result of NIS. As described in Section 1.1, NIS is caused by noise damage to the ribbon synapses between the IHCs and the SGNs, which happens to be the first speed-limiting site of auditory processing. At these sites, the primary function of the presynaptic ribbons is to facilitate the neurotransmission through the synapses (Moser et al., 2006; Moser & Starr, 2016; Safieddine et al., 2012). Therefore, damage to the ribbons would give rise to further limitation of auditory processing speed, likely resulting in temporal processing disorders (Buran et al., 2010; Jing et al., 2013).

Moreover, a connection between NIS without PTS and temporal processing deficits was reported in the study of Song et al. (2016), which observed the change in coding function of single ANF units within one month of a noise exposure of 105 dB SPL for 2 hours. The noise exposure in this study, which was presented to albino guinea pigs, led to an initial synaptic loss of approximately 50%. Within the month following the noise exposure, along with partial recovery of the number of ribbon synapses, temporal coding deficits had developed. The temporal coding deficits manifested as the delayed

onset peak of ANF firing as well as reduced peak rate, indicating that the repaired synapses presented problems with encoding signal onset (Song et al., 2016). Additionally, a different study executed by the same researchers reported similar temporal processing deficits in guinea pigs exposed to the same noise in the study of the field responses from cochleae (Shi et al., 2013).

Temporal processing disorders resulting from noise exposure have also been investigated in human participants, both objectively and behaviorally. For instance, past objective studies have used ABR (auditory brainstem response) wave-V in order to identify temporal coding deficits in humans following noise exposure (Mehraei et al., 2016; Prendergast, Guest, et al., 2017). In the study by Mehraei et al., masking-induced wave-V latency shifting was of focus (2016). Not only is wave-V robust in humans, as it can be recorded at low stimulus levels and in background noise, wave-V latency shifting has also been found to correlate with the changes in ABR wave-I amplitude, which may indicate the number of functional ANFs. In normal subjects, wave-V latency is shifted in increasing levels of masking depending on absolute noise level and partially on signal-to-noise ratio (SNR) (Burkard & Hecox, 1983). It is likely that this shift reflects the activity of LSR fibers since they are more resistant to background noise (Costalupes, 1985) and have a delayed onset response compared to HSR fibers (Rhode & Smith, 1985). Therefore, it was postulated that the selective loss of LSR fibers from NIS should yield smaller ABR latency shifting as noise level increases, and that this latency shifting would correlate with perceptual measures of fine temporal encoding that rely on LSR responses (Mehraei et al., 2016).

Among the human participants in the study, those with small masking-induced wave-V latency shifting (which also likely indicates smaller ABR wave-I amplitude and a larger loss of synapses) performed poorer on a sound localization task requiring discrimination of interaural time differences (ITD) in sound envelopes (Mehraei et al., 2016). This result suggests that NIS may result in temporal processing deficits. In another objective study, a correlation was found between poor envelope following responses (EFR) and poor ITD threshold, which is representative of poor temporal resolution (Bharadwaj et al., 2015). These results further suggest that NIS may affect temporal processing ability, given that poor EFR has been found to be illustrative of NIS (Bharadwaj et al., 2014; Parthasarathy et al., 2019; Parthasarathy & Kujawa, 2018; Shaheen et al., 2015). Furthermore, a connection between CIND and temporal processing disorders has also been found in humans from behavioral studies. For example, in their study investigating the connection between temporal resolution and speech-in-noise scores, Snell et al. found that aged individuals with poorer gap detection thresholds showed significantly poorer word scores as the level of background babble increased (2002). These results suggest that temporal processing could play an important role in understanding speech in noise (Snell et al., 2002). The loss and/or unhealthy repair of the synapses innervating the LSR ANFs, to which the noise damage is biased (Furman et al., 2013; Song et al., 2016), plus the potential damage to the synapses innervating the M/HSR ANFs, may affect onset coding (Song et al., 2016) as well as envelope following ability to continuous sound (Bharadwaj et al., 2014).

Additional examples demonstrating that temporal processing deficits occur as a result of NIS in humans are given by the studies of Stone et al. (2008) and U. Kumar et

al. (2012). In the study by Stone et al., participants who had been exposed to noise had trouble discriminating a temporally fluctuating noise from a more stationary one (2008). The study by U. Kumar et al. compared the performance of noise-exposed train drivers to a control group in various temporal processing tasks including gap detection, modulation detection and duration pattern detection. Those in the noise-exposed group not only performed poorly in the temporal processing tasks, but such performance was also correlated with poor speech recognition in noise (U. Kumar et al., 2012).

On the other hand, reports refuting the connection between temporal processing deficits and CIND from NIS also exist. For instance, a study by Yeend et al., which examined the auditory processing abilities of middle-aged participants with normal hearing thresholds, assessed temporal processing using the threshold for detecting amplitude modulation (AM). In this study, no clear relationship between noise exposure and auditory perception was found (Yeend et al., 2017). Additionally, a study by Prendergast, Millman, et al. yielded similar results (2017). In this study, a significant but weak correlation was found between speech-in-noise deficits and temporal processing deficits in noise-exposed groups with normal hearing thresholds. Here, temporal processing ability was evaluated by AM tasks (Prendergast, Millman, et al., 2017). However, it should be noted that in both reviewed studies, self-report was depended upon to determine lifetime noise exposure and it may not be reliable.

1.3.2 Is temporal processing disorder a concern for evaluating CIND?

From the review above, it is clear that temporal processing deficits are likely a result of NIS without PTS, and could contribute, partially at least, to the CIND exhibited in individuals with NIS. Logically, the evaluation of CIND should take the temporal

processing deficits into account. Ultimately, the data presented in the reviewed literature indicates that temporal processing plays a role in detecting signals against background noise. As outlined in Section 1.2.1, the noise experienced by humans in real life is temporally fluctuated. In such noise, subjects use their temporal processing ability to detect the signal in the dips of the masker. Therefore, the masker used in experiments investigating coding ability against background noise should also be temporally fluctuated. When a stationary masker is used, it is not possible to take advantage of short gaps in the noise to aid detection, and thus might be equally challenging for subjects with and without temporal processing disorders. However, the use of a temporally fluctuated masker has been largely ignored in previous studies examining CIND, especially those with animal subjects. In many of the reviewed animal studies evaluating CIND, stationary noise was used as the masker (Chen, Xing, et al., 2019; Fan et al., 2020; Lobarinas et al., 2017; Zhang et al., 2020).

In the behavioral studies with human participants, although both stationary and fluctuated maskers (such as multi-talker babble) have been used in speech-in-noise tests in order to examine potential deficits in subjects with NIS without PTS, the temporal feature of the masker has never been the focus of the studies. Therefore, there is no comprehensive comparison of the masking effect from maskers with varying temporal features. For example, in the study by Prendergast, Millman, et al., stationary noise was used as the masker and there was no difference between the noise group and the control group in the speech-in-noise task (2017). In another study, Gilles et al. examined the effect of noise-induced tinnitus on speech-in-noise understanding in young adults. In this study, participants with noise-induced tinnitus showed worse speech-in-noise

performance than the non-tinnitus control regardless of whether the masker was stationary or fluctuated (Gilles et al., 2016). However, there was no control without noise exposure used in this work. Only the study by Kumar et al. (2012) appeared to confirm worse speech-in-noise performance in noise-exposed participants by using multi-talker babble as the masker. However, the effect of the temporal feature of the masker was not examined. It is therefore evident that a valid comparison cannot be made across the reviewed studies in order to identify the effects of different maskers, which is largely due to differences in research design.

To date, there is no comprehensive evaluation of whether a temporally fluctuated masker is superior to a stationary masker in a speech-in-noise test used to identify CIND in subjects with NIHHL. In the present study, the potential CIND resulting from NIS without PTS was re-evaluated by using fluctuating noise as the masker and comparing it with a stationary masker.

1.3.3 Auditory response to AM signals

Signal processing in the auditory system is often evaluated using amplitude modulated signals (Chen, Shi, et al., 2019; Joris et al., 2004; Moore, 1993; Walton, 2010). When recorded in the far field (e.g., clinically), such signals are typically referred to as auditory steady-state responses (ASSR) or envelope following responses (EFR) (De Siati et al., 2020; Picton et al., 2003). The responses in those tests are measured as the signals synchronized with the modulation frequencies and can therefore represent the ability of the neurons to follow the envelope of the signals. However, multiple generators such as hair cells, ANFs, and central auditory neurons contribute to EFRs recorded in far-field. The relative contribution from each of these different sources is determined primarily by

the modulation frequency (MF), as suggested by available data. For instance, EFRs elicited by low MFs (e.g., < 200 Hz) are dominated by cortical (Herdman et al., 2002; Kuwada et al., 2002) and subcortical (Parthasarathy, 2012; Picton et al., 2003) sources, whereas contribution from ANFs exists in EFR evoked by AM with MF close to 1 kHz (Shaheen et al., 2015).

Although single ANF units phase lock to AMs with a low-pass temporal modulation transfer function (TMTF) pattern (Johnson, 1980; Joris & Yin, 1992; Palmer & Russell, 1986; Rose & Weiss, 1988; Temchin & Ruggero, 2010; Weiss & Rose, 1988), it is very challenging to verify the phase locking to low MFs (i.e., below 400 Hz) via far-field recording. Instead, Shaheen reported that ANFs dominated the EFR peaks at MFs around 1 kHz in the TMTF (2015). In this study, EFR TMTF was compared between control and noise exposure groups (Shaheen et al., 2015). As shown in Figure 1 (Fig. 5 in the study by Shaheen et al. (2015)), Shaheen et al. found a significant decrease in the TMTF from the noise exposed group as compared with the control group for a 32 kHz carrier at around MF = 1 kHz (2015). This decrease was linked to NIS, which is significant at the high frequency region (32 kHz), but not at lower frequencies (e.g., 11.3 kHz and below). The noise exposure used in this study was similar to that used in the study by Kujawa and Liberman (2009), which was 2 hour-long octave band noise centered around 10 kHz at 98 dB SPL (Kujawa & Liberman, 2009).

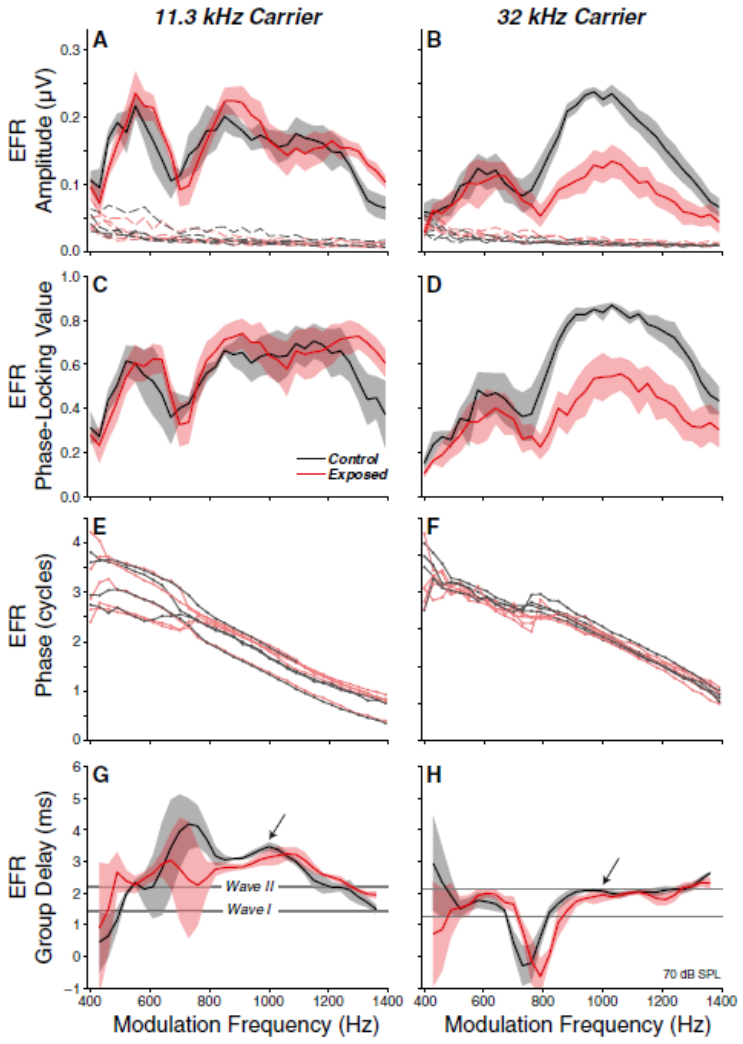

Figure 1: EFR comparison between control and noise groups (Shaheen et al., 2015).

More recently, Parthasarathy and Kujawa conducted a study re-evaluating the EFR contributors (2018). In order to isolate the EFR responses generated by ANFs, ouabain was applied to the round window (Parthasarathy & Kujawa, 2018), which deactivates ANFs without altering outer hair cell functions (Lang et al., 2011; Yuan et al., 2014). The ouabain application did increase the ABR wave-I threshold, and it did not change the distortion product otoacoustic emission (DPOAE). Further, the utilization of ouabain decreased EFR amplitudes in response to AM with a MF of 1024 Hz, but not to AM with a MF of 4096 Hz. Therefore, EFRs elicited by a MF around 1 kHz likely

originate primarily from ANFs, while the response to a higher MF arises from hair cells (HC) (Parthasarathy & Kujawa, 2018).

As mentioned above, EFRs at MFs lower than 400 Hz were not observed in the reviewed studies by Shaheen et al. (2015) and Parthasarathy and Kujawa (2018). Such practice is due to the likelihood that the EFRs at lower MFs would be dominated by a central origin.

Additionally, modulation depth (MD) is another factor that is critical in detecting coding problems in NIS without PTS. AM tones presented at high intensities and low modulation depths theoretically challenge ANFs with high spontaneous rates (SR), low thresholds, and narrow dynamic ranges, since modulations may occur across levels at which the ANFs' rate-level functions are saturated. This idea is depicted in Figure 2, in which typical rate-level functions for both low and high SR ANFs are given along with a high-sound level AM signal. Especially when the MD is small (indicated by the red dashed curve), the fluctuation of sound is in the saturated range of HSR ANFs. As outlined in a study by Bharadwaj et al., when an AM signal is presented at high sound level and with a small MD, phase locking to AM is more challenging for HSR ANFs (Bharadwaj et al., 2014). In such a situation, AM responses are considered to primarily reflect LSR, high threshold ANFs, which has led to increased interest in the use of high-level AM signals with shallow modulation for evaluating possible NIS associated with the selective loss of the LSR ANFs.

Further, LSR fibers are also thought to be more important for signal coding in high levels of background noise (Joris & Yin, 1992; Kobel et al., 2017; M. C. Liberman & Kujawa, 2017; Moser & Starr, 2016; Plack et al., 2016), due to their robustness with

respect to masking (Costalupes, 1985; Young & Barta, 1986). AM responses should therefore be better equipped to detect coding deficits in noise compared to transient responses such as ABR and compound action potential (CAP), which are dominated by the onset responses from the HSR fibers (Bourien et al., 2014). This inference is supported by the Shaheen et al. study, which found a more significant decrease in EFR phase locking than ABR wave-I amplitude in CBA mice with cochlear synaptopathy (2015).

However, using the above technique of recording responses to AM at a high sound level in combination with masking, studies by Chen, Xing, et al. (2019) and Zhang et al. (2020) were unable to find a significant difference in the responses of guinea pigs with NIS compared to normal controls (Chen, Xing, et al., 2019; Zhang et al., 2020). It is possible that the negative results may be related to the use of stationary noise as the maskers in these studies.

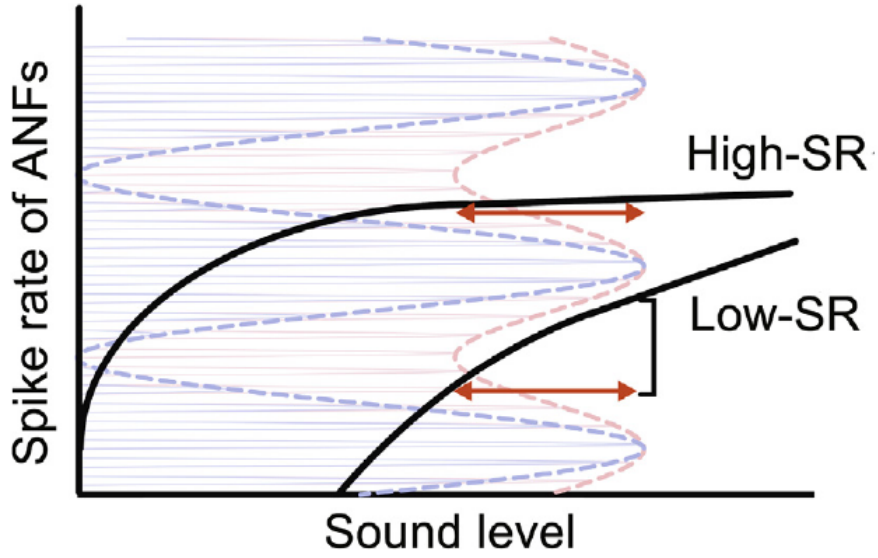

Figure 2: Illustration of how sound level and MD impact the coding of amplitude changes in an AM tone by HSR and LSR ANFs.
Notes: When the AM tone is presented at a high sound level and with a small MD, the amplitude fluctuation is in the range of sound where the rate-level functions of the HSR ANFs are saturated. Therefore, the HSR ANFs cannot detect such fluctuation.

1.4 A challenge to the dependence of signal coding at high sound level on LSR ANFs

As described in Section 1.3, CIND at high sound level is expected to be the major problem in subjects with NIS without PTS based on the dominant role of LSR ANFs in signal coding at high sound level. However, as reviewed above, no robust evidence supporting the existence of CIND in subjects with NIS without PTS has been found in either animal or human studies. This negative result challenged the entire idea about CIND in connection with the selective loss of LSR ANFs and the specific function of that group of ANFs. In a recent review, Carney presented a comprehensive evaluation of this idea (2018). Specifically, the argument targets the assumption that it is the difference in dynamic ranges of L/MSR ANFs compared to those of HSR ANFs that makes L/MSR ANFs favorable candidates for encoding supra-threshold stimuli. Carney argues that, in

order to encode sound level with average rates, several requirements must be met, and such requirements are not met by the responses of L/MSR ANFs (2018). In other words, it is insufficient to conclude that L/MSR ANFs support perception exclusively at high sound level solely based on the fact that only this group of ANFs changes their average discharge rates at supra-threshold levels (Carney, 2018).

The first requirement that fails to be met by L/MSR ANFs is that changes in average rate must be larger than the variance of the rate in order to code changes in level (Carney, 2018). It is well understood that rate variability increases as the rate increases with sound level (Delgutte, 1996; Heinz et al., 2001; Siebert, 1965; Steven Colburn et al., 2003; Viemeister, 1988; Winter & Palmer, 1991). Therefore, it is not only required that the rate changes with sound level but that the rate accelerates upward in order to compensate for increasing rate variability (Carney, 2018). However, such rate-level function is not observed for any type of ANF. Furthermore, the typical wide dynamic range of LSR fibers does not exist in those with characteristic frequencies (CF) below 1500 Hz (M. C. Liberman, 1978; Winter & Palmer, 1991).

The second requirement is that average rates must be consistent in different stimulus contexts in order to code level. However, since the dynamic range in any rate-level function is continuously changing based on the recent activity of that neuron, there is no simple correspondence between an ANF's average rate and the stimulus level (Carney, 2018).

The third requirement is for the SR to be stable over time if sound level were coded by the change in rate with respect to SR. In reality, SRs continuously and

randomly fluctuate by a considerable amount (Jackson & Carney, 2005; Teich et al., 1990).

The fourth requirement is that a rate-based code for sound level must be maintained along the ascending auditory pathway. However, in the cochlear nucleus (CN), there is no evidence of high-threshold neurons with wide dynamic ranges that project a rate-based code for complex sound. The CN is just one synapse along the ascending pathway toward the major brainstem and midbrain targets essential for perception (Carney, 2018).

The final requirement outlined by Carney is that the rate code should be robust in background noise as well as in a context of time-varying level, including roving-level paradigms (2018). Carney (2018) argues that the power spectrum model of hearing (Patterson & Moore, 1986), which drives rate-based codes for spectral amplitude, fails to explain the results of key experiments. For example, the ability to detect tones in noise in a roving level paradigm (Kidd Jr. et al., 1989).

1.4.1 Fluctuation profile model for signal coding at high sound level

In order to explain the role of HSR ANFs in coding of complex signals such as speech, which typically occurs at 65-75 dB SPL, Carney discussed a fluctuation profile model (2018). The model provides a potential mechanism for HSR ANFs that are saturated in terms of average rate to instead convey information from the speech spectrum by responding differently to the temporal fluctuations in the stimulus across frequencies. Such response fluctuations are ultimately a result of the modulation produced by the interaction of harmonics in speech, which presents temporal fluctuation in its amplitude. It is understood that ANF firings phase-lock to all of the low-frequency fluctuations, such

as the fundamental frequency of speech (Joris et al., 2004). Since the sound level at the formant peaks in speech is high, the ANFs with a CF at the formant peaks are likely saturated, while the ANFs with a CF at the troughs may not be, depending on the overall level of speech. Therefore, the temporal fluctuations in ANF responses across auditory channels mirror the spectrum of speech—larger fluctuation is seen at the formant troughs and smaller fluctuation is seen at the formant peaks. This is clearly illustrated by Fig. 2 in Carney's review (2018), which has been referenced in this report as Figure 3.

Furthermore, Carney suggested that the fluctuation profile of ANFs is enhanced by the feedback control of the auditory efferent system (2018). Specifically, such enhancement would occur via MOC innervation in which the MOC signals would act to reduce cochlear gain in the presence of high-level sound or background noise. The reduction of cochlear gain would reduce the amount of IHC saturation in channels with relatively low spectral amplitudes, effectively increasing the differences in fluctuation amplitude across frequency channels (Carney, 2018). In combination with the fluctuation profile model, Carney further speculated that the temporal fluctuation in ANF response is an important factor in this control: those ANFs in the channels of formant peaks have less fluctuation, which results in a weaker MOC excitation and therefore less cochlear gain reduction, while those ANFs in the channels of troughs would have stronger fluctuations and then excite MOC neurons more strongly, resulting in a greater decrease of cochlear gain.

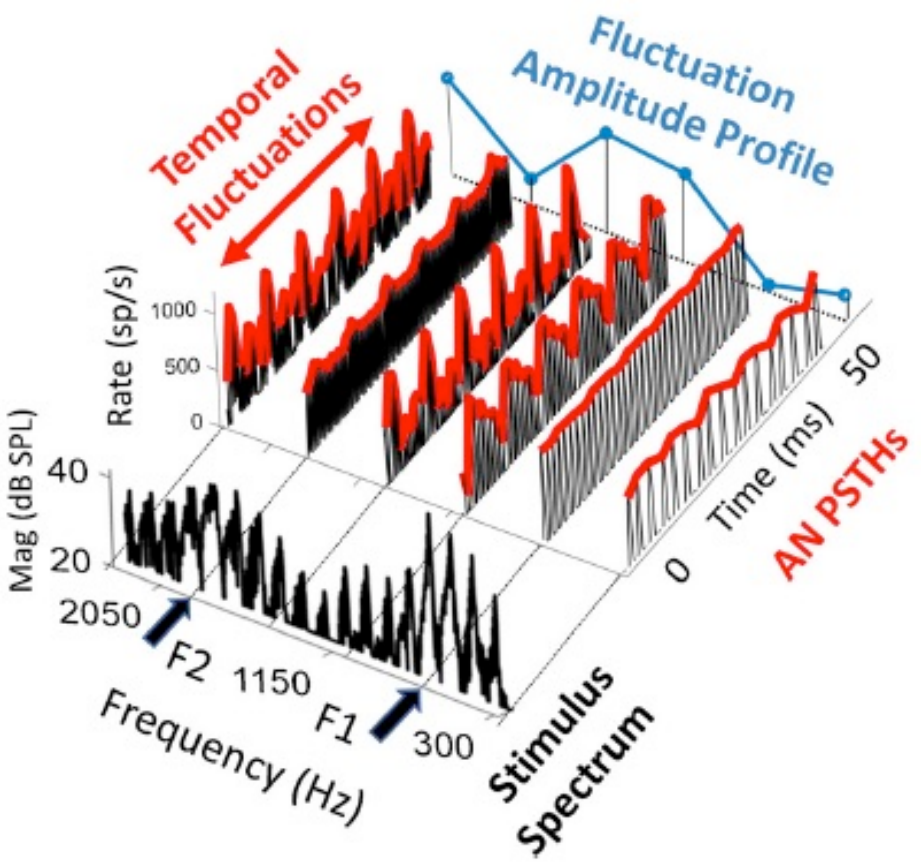

Figure 3: The fluctuation profile model by Carney (2018).
Notes: This model shows the spectrum of the vowel /æ/ in the foreground, along with model HSR AN peristimulus time histograms (PSTH) for several CFs spanning two spectral peaks in the vowel. The two formant frequencies are given by F1 (700 Hz) and F2 (1800 Hz). The blue line in the background shows the AN fluctuation amplitudes across. Note that the dips in the fluctuation amplitude profile are aligned with the spectral peaks (Carney, 2018).

Four arguments supporting the existence of the described fluctuation profile enhancement via MOC innervation are presented. First, it is known that inferior colliculus (IC) neurons have bandpass modulation transfer functions (MTF) with a best modulation frequency near the fundamental frequency (F0) of male speech (Carney et al., 2016; Krishna & Semple, 2000). Second, MOC neurons also have bandpass MTFs, indicating that they are likely excited by descending inputs from IC neurons (Gummer et al., 1988). Third, Carney proposes that these inputs from IC neurons carry signals appropriate to enhance fluctuation profiles as previously outlined: frequency channels

with strong fluctuations, corresponding to the troughs of speech, would excite MOC neurons and therefore decrease cochlear amplification. On the other hand, channels driven by weak fluctuations, corresponding to formant peaks, would result in greater cochlear amplification (Carney, 2018). Lastly, the L/MSR ANFs provide a significant input to MOC neurons via the small cell cap of the anteroventral cochlear nucleus (AVCN) (Ye et al., 2000). In this CN region, neurons have wider dynamic ranges (Ghoshal & Kim, 1996) and exclusively receive input from L/MSR ANFs (Leake & Snyder, 1989; M. C. Liberman, 1991; Ryugo, 2008). Therefore, the loss of L/MSR ANFs impair efferent control, which may reduce the effectiveness of a fluctuation profile-driven system (Carney, 2018).

Although Carney's review offers a substantial amount of evidence supporting the fluctuation profile model, several concerns and unresolved issues remain (2018). First, when the fluctuation is emphasized in this model, the level-dependent responses of the HSR ANFs are of focus, while the contribution from the LSR ANFs is ignored. Specifically, if the contribution from the LSR ANFs were to be considered, the fluctuation profile would be less sharp since LSR ANFs are not saturated at the formant peaks. This should be the case in individuals without NIS, in which LSR ANFs function properly.

Furthermore, Carney's model (2018) focuses on the feedback loop from the ANFs to the MOC via the CN and the IC but does not fully consider the loop via the lower brainstem of the ANFs to the CN to the MOC directly. It is possible that the lower loop may be more efficient in MOC activation, and that it may not be fluctuation dependent.

Finally, in the majority of available studies that have investigated the efferent control of cochlear responses such as DPOAE suppression (Atcherson et al., 2008; Chambers et al., 2012; Chéry-Croze et al., 1993; Danesh & Kaf, 2012; Kujawa et al., 1993; Sun, 2008; Zhang F et al., 2007), CAP suppression (Chabert et al., 2002; Kawase & Liberman, 1993; May & McQuone, 1995; Najem et al., 2016; Popelár et al., 2001; Puria et al., 1996), and masking release (Mertes et al., 2018; Nieder & Nieder, 1970), stationary signals were used as the suppression signals. In those instances, it should be the average rate of ANF firing that most significantly influences MOC activation since a higher level of contralateral suppression (CS) signal exerts a larger suppression on DPOAEs (Moulin et al., 1993; Zhang F et al., 2007) and CAP (Puria et al., 1996). If temporal fluctuation in stimuli plays a dominant role in activating efferent control, as suggested above, fluctuated stimuli at lower levels would induce stronger MOC activation and therefore larger gain reduction due to the fluctuation of the ANF responses. Higher-level stimuli, on the other hand, would be less effective in MOC activation since the ANF responses are saturated at high sound level even though the stimuli are fluctuated with time. This idea remains purely speculation as it has not been verified. In one study, an AM signal was used to evoke contralateral suppression on otoacoustic emissions (OAE). Although the result showed that the suppression increased with modulation depth, the suppression was observed at only one suppressor level (Maison et al., 1997). Level effects on efferent suppression of cochlear responses have yet to be observed using a fluctuating signal as the suppression signal.

1.4.2 Does NIS without PTS change the cochlear efferent control?

The hypotheses that have been formulated from Carney's discussion of the fluctuation profile model (2018) guided the present study in examining the possible effects of NIS without PTS on the cochlear efferent control. The current literature on the cochlear efferent system will be reviewed below, followed by a report of the literature supporting the potential impact of NIS on the cochlear efferent system.

Neural circuits for efferent acoustic reflex

The cochlear efferent system is part of the acoustic reflex loop that is initiated by the input from ANFs to the brainstem and then to the cochlea. This part of acoustic reflex is different from the middle ear acoustic reflex in that it occurs via olivocochlear (OC) neurons, which are in the perinuclei of the superior olivary complex (SOC). In order to differentiate this acoustic reflex from that of the middle ear, the efferent control to the cochlea is referred to as efferent acoustic reflex (EAR). Furthermore, although centrifugal control from the auditory cortex, specifically the IC, to the OC neurons exists, the olivocochlear reflex via the lower brainstem is better understood and is likely stronger in the control of cochlear function (Guinan, 2006).

There are two groups of OC neurons, which have been identified and named based on their origins, pathways, targets, and functions (Guinan et al., 1983; W. B. Warr & Guinan, 1979). The two types of OC neurons and their cochlear bundles are described as lateral olivocochlear (LOC) efferents and medial olivocochlear (MOC) efferents. LOC efferents originate from small neurons in and near the lateral superior olivary nucleus (LSO), they have unmyelinated axons, and they terminate on the dendrites of the auditory nerve radial afferent fibers beneath the IHCs. On the other hand, MOC efferents originate

from larger neurons located medially, ventrally, and anteriorly to the medial superior olivary nucleus (MSO). MOC efferents have myelinated axons and terminate on the bodies of the outer hair cells (OHC).

To date, the descending portion of the EAR circuit has been well documented (W. B. Warr, 1992), while the ascending portion of the pathway (from the CN to the MOC neurons) remains to be understood. As outlined by Guinan, MOC neurons primarily receive input from contralateral posteroventral cochlear nucleus (PVCN) neurons (2006). Since the main innervation from the MOC to the cochlea crosses the midline, the ipsilateral MOC EAR circuit, which is stronger, occurs via a double cross. For example, consider the right side as shown in Figure 4: to form the double cross, the first cross occurs along the pathway from the right CN to the left MOC and the second cross occurs from the left MOC back to the right cochlea. Therefore, this double cross is the reason why the ipsilateral MOC EAR circuit is roughly 3 times as strong as the contralateral one in most species examined (Abdala, 1996; Gifford & Guinan, 1987; M. C. Liberman & Brown, 1986; Maison et al., 2003; Robertson & Gummer, 1985). However, it is easier to examine cochlear suppression by the MOC efferent via the contralateral pathway. This is due to the difficulty of differentiating the role of the ipsilateral stimuli in producing responses from suppression.

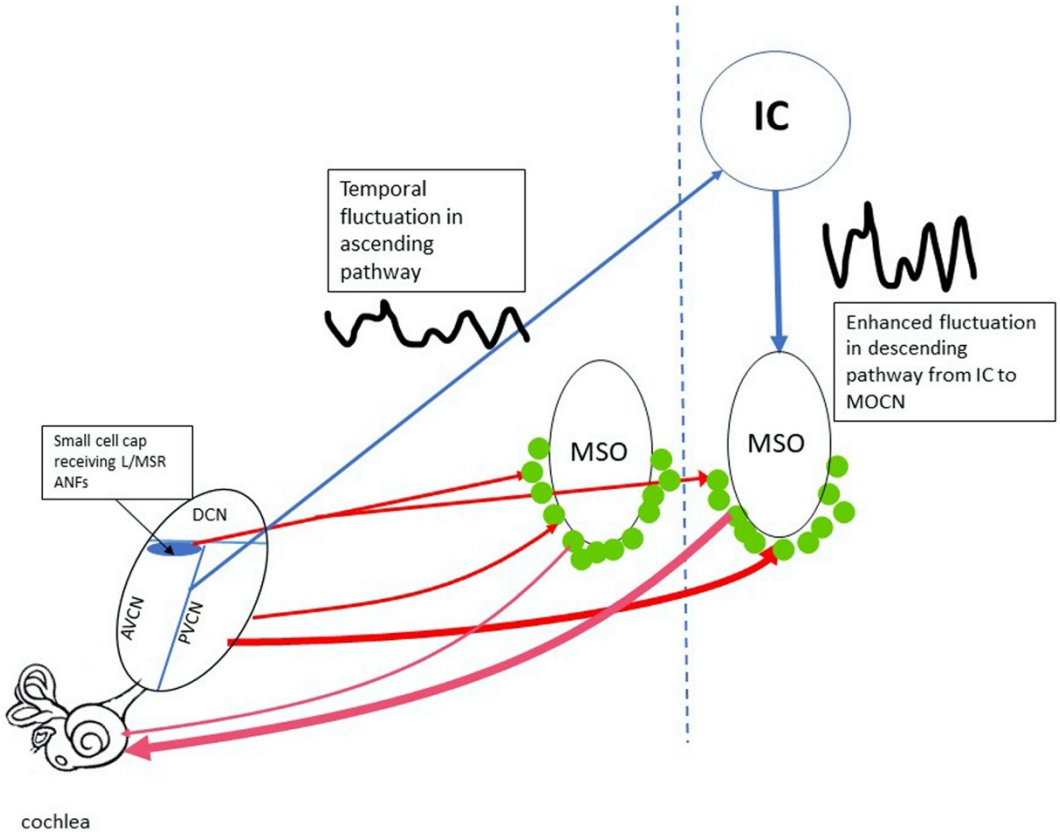

Figure 4: The efferent feedback loops controlling the OHC gain.
Notes: The short loops going through the lower brainstem are marked by red lines. The thickness of the line represents the relative strength in the typical loop from PVCN to MOC neurons (green dots). The loop from the small cell cap in AVCN to the MOC neurons is thought to be selective receiving input from L/MSR ANFs. The relative strength of this loop is unknown. The long feedback loop (blue lines) includes the projection from both AVCN and PVCN cores to IC, which is sensitive to the low-frequency temporal fluctuation. The fluctuation is inherited and enhanced in the descending projection from the IC to MOC neurons. Abbreviations: AVCN/PVCN, anterior/posterior ventral cochlear nucleus; DCN, dorsal cochlear nucleus; MOCN, medial olivocochlear neurons; MSO, medial superior olivary nucleus; IC, inferior colliculus.

As outlined in Section 1.4.1, the MOC efferent control can occur through different loops: one is the loop via the lower brainstem (from the ANFs through the CN and then directly to the MOC), and the other is the midbrain loop (from the CN to the IC and then to the MOC). Although there exists direct innervation from the CN to the MOC in the lower brainstem loop (Robertson & Winter, 1988), its relative significance is unclear in terms of its role in EAR compared to the longer midbrain loop. Compared with the innervation from sources such as the IC, there is uncertainty surrounding the density

of the direct projection in the lower brainstem loop. In a study by Gummer et al., a few medial efferent neurons showed a short latency (5 ms), which is consistent with a direct input from CN neurons to MOC neurons (1988). However, the group delays measured from MTFs were longer for most neurons (8.2 ± 1 ms), indicating that the activation of most MOC neurons may be mediated by a chain including one or more neurons between the CN and MOC (Gummer et al., 1988). Alternatively, the long group delays may be accounted for a direct CN connection plus a long delay in medial efferent dendrites.

Furthermore, MOC neurons mainly receive projection from the PVCN, as reviewed above (Guinan, 2006). Input to MOC neurons from the AVCN is also suggested to be part of the EAR circuitry, although it has only been noted in a few reports. One study, for example, provided evidence based on fiber degeneration experiments (W. E. Warr et al., 1982). Moreover, the projections in question have been found to travel to the MOC via the small cell cap in the marginal shell of the AVCN (Ye et al., 2000). However, the relative significance of the projections from the AVCN and PVCN in the EAR circuit is yet to be determined.

Finally, as for the LOC acoustic reflex, several pieces of evidence suggest that it exists even though it has never been demonstrated. The LOC neurons receive input from the PVCN, and LOC neurons can be activated by sound (Adams, 1995). The LOC acoustic reflex should be predominantly ipsilateral since the innervation and the sound activation are greatest on the ipsilateral side, and LOC neurons' projections are nearly completely uncrossed. However, little else is known about the function of LOC acoustic reflex.

Potential impact of NIS without PTS on EAR function

As outlined by Carney, the type I afferent ANFs are categorized by their spontaneous rate, and there is evidence for a special role of the L/MSR ANFs in the EAR. The L/MSR ANFs are known to carry significant level information that is important for the gross adjustment of cochlear gain based on overall sound level (2018). This makes sense considering the potential role of MOC EAR, which is the regulation of OHC gain in response to input sound. Furthermore, the functional categorization of ANFs based on SR emphasizes the importance of the projection from the AVCN to the MOC, which was demonstrated in a study by Ghoshal et al. (1996). In their study, Ghoshal et al. found that the majority of neurons in the AVCN small cell cap in cats have a low SR and very wide dynamic ranges (1996). Such finding is consistent with the fact that the inputs to the neurons in the AVCN small cell cap exclusively come from L/MSR ANFs (Leake & Snyder, 1989; M. C. Liberman, 1991; Ryugo, 2008). This is different from the neurons in the AVCN core, which exhibit narrow dynamic ranges (Ghoshal & Kim, 1996). However, it is unclear whether PVCN neurons also receive input from L/MSR ANFs, and whether neurons in the AVCN core project to MOC neurons. It is also not clear regarding the dominance of the projection from AVCN versus PVCN in the EAR loop.

In terms of the LOC efferent, its main function is considered to be the mitigation of damage to ANFs from excessive activation by traumatic sounds (Guinan, 2018). Specifically, since the LOC neurons synapse on the dendrites of ANFs beneath the IHCs, the LOC efferent has been shown to protect the afferent IHC-SGN synapses. This particular role of the LOC efferent is incredibly important, especially with the recent demonstration that auditory neuropathy is a common result of even mild acoustic over-

stimulation (Guinan, 2018). Furthermore, the protection of the synapses between the IHCs and the SGNs by the LOC efferent has been directly shown in a study by Maison et al. (2013). In this study, control mice showed no synaptic loss after 168 hours of noise presented at 84 dB SPL, while the mice that underwent deefferentation surgery showed a synaptic loss of 40% in response to the same noise (Maison et al., 2013). In accompaniment to protection of the IHC-SGN synapses, a second function of the LOC efferent has been discovered. As a way of maintaining the SGN afferent dendrites and synapses, the LOC efferent has been shown to either suppress or enhance afferent excitability depending on acoustic stimulation. This regulation of afferent excitability by the LOC efferent presumably occurs at the site of synaptic contact on the peripheral SGN afferent dendrite (Reijntjes & Pyott, 2016).

In subjects with NIS without PTS, the potential change in EAR is likely due to the change in the ascending pathway resulting from the damage and loss of functional ANFs. Since the synaptic loss is biased to L/MSR ANFs, which are more dynamic in their responses to high level sound, the fluctuation profile model should work better in subjects with NIS. On the other hand, the fluctuation profile should be less sharp between formant peak and trough frequencies in control subjects, because the L/MSR ANFs can provide fluctuated responses at the formants.

As described in Section 1.4.1, MOC EAR can be activated by acoustic stimulation, which produces suppression on various cochlear responses including OAE (Jacobson et al., 2003; Komazec et al., 2003) and CAP (Stronks et al., 2010). This is most easily achieved by the contralateral suppression (CS) paradigm. According to Carney's model, a high-level temporally fluctuated CS signal (such as an AM tone) should produce

less MOC activation, and therefore less suppression on OAE and CAP, due to the saturation of the ANF responses, which results in a smaller fluctuation and therefore less activation of MOC. Note that this idea differs from previous reports, in which stationary CS signals were used and high-level tones exerted stronger CS (Moulin et al., 1993; Zhang F et al., 2007). In one study, efferent suppression of OAEs was observed using an AM signal to evoke contralateral suppression. However, while the result showed that the suppression was increased with modulation depth, the suppression was observed at only one suppressor level (Maison et al., 1997). Level effects for efferent suppression of OAE and CAP with fluctuated suppressors have never been observed.

Furthermore, since noise exposure selectively damages LSR ANFs, the fluctuation profiles should become stronger in subjects with NIS. In other words, since there would be a larger difference between the formant peak and trough (or high- and low-level sound) channels, there would be more of a chance that a high-level AM tone would produce less CS compared to a low-level AM tone. However, this has never been evaluated in any published report. More importantly, if the fluctuation profile is the major mechanism for high-level speech coding, then such coding should be better in subjects with NIS. This would offer a partial explanation for the reports contradicting the idea that humans who potentially have NIS without PTS will also present with poor speech perception abilities.

As a final note, it would not be surprising if the level effect of AM CS is not as predicted, since the LSR ANFs may not be lost permanently in subjects with NIS. This idea comes from the study by Song et al. (2016), which examined the effects of noise damage on guinea pig ANFs using single unit recording. In the study, the SR distribution

returned to normal one week after the noise along with the partial recovery of synaptic density per IHC (Song et al., 2016).

1.4.3 The concerns of methods evaluating MOC efferent functions

As outlined in Section 1.4.1, there are three main methods used to evaluate the efferent effect on cochlear function, all of which observe the suppression of cochlear responses resulting from the activation of the MOC efferent by acoustic signals. These three methods include the observation of OAE suppression, CAP suppression, and masking release of CAP and speech perception. Due to its relevance to the current study, CAP suppression is detailed below.

It should be noted that, in any evaluation of MOC efferent function, it is critical that the effects of the middle ear muscles are ruled out. In order to distinguish efferent effects from middle ear muscle (MEM) effects, which can be activated by ipsilateral or contralateral sound, several methods can be used. Such methods include vestibular neurectomy (in which olivocochlear efferent fibers exit the brain with the vestibular nerve), using subjects with weak or absent MEM reflexes, and/or measuring the medial efferent reflex effect in the high frequency region where the conduction of sound is not influenced by MEM (MEM is low frequency biased) (Büki et al., 2000).

Pertaining to the described methods for evaluating MOC efferent function, a notable concern of the present study is that only stationary signals have been used to activate the MOC efferent system in the past. **Thus far, there are no data indicating whether signals fluctuating in amplitude, such as AM signals, would produce CS more effectively than stationary signals**. **Furthermore, there is also no indication of whether the level dependence of using an AM signal is opposite to what is reported**

using stationary signals, as we postulate from the fluctuation profile model. The present study therefore aimed to provide insight to the model.

CAP suppression

The effect of CS has been observed on CAP in a number of studies (Chabert et al., 2002; Kawase & Liberman, 1993; May & McQuone, 1995; Najem et al., 2016; Popelár et al., 2001; Puria et al., 1996). In the study by Puria et al., which observed the effect of CS on both DPOAE and CAP, a larger suppression was seen on CAP than on DPOAE by the same CS (1996). This result is shown in Figure 5 (Puria et al., 1996).

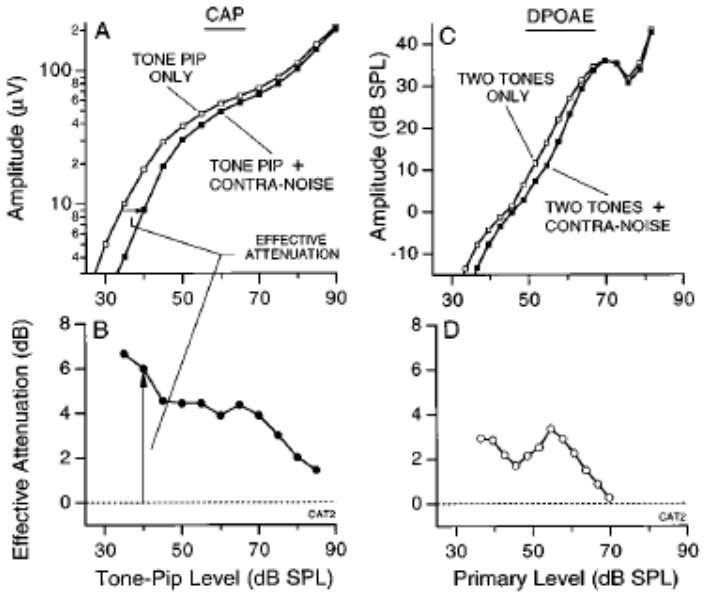

Figure 5: Comparison of CS on CAPs (left) and DPOAEs (right), measured in the same animal approximately 0.5 days apart.
Notes: A: CAP amplitude as a function of tone-pip level for ipsilateral tone pips at 4.0 kHz, and CS at 80 dB SPL broadband noise (BBN). B: Effective attenuation of CAP as a function of tone-pip level, computed from the data in panel A. The vertical arrow indicates the measurement shown by the horizontal arrow in panel A. C: DPOAE amplitude as a function of primary level for ipsilateral tones only and for ipsilateral tones plus 80 dB SPL contralateral noise. D: Effective attenuation as a function of primary level for the data from panel C (Puria et al., 1996).

1.5 The present study

Three main methodological concerns surrounding NIS without PTS were at the center of the present study. First, there are knowledge gaps that make the translation of animal data to human data difficult, since most animal studies have invoked NIS by using noise unlike what is experienced by humans in real life. The present study therefore used low-level (Leq of roughly 90 dB SPL) repeated noise (with adequate intervals) that fluctuates in level (not stationary).

Second, the majority of previous studies examining the CIND associated with NIS without PTS used stationary maskers. The present study used a temporally fluctuated masker in order to mimic the masking experienced in real life. Its effect was compared to that of a stationary masker to evaluate the role of temporal processing disorder in CIND. This design was also used to examine the potential connection between temporal processing disorders and CIND.

Finally, the model discussed in the review by Carney (2018) presents a significant number of postulations that have yet to be verified. The present study tested the fluctuation profile model in subjects with NIS without PTS; specifically, the importance of signal fluctuation in the MOC-mediated cochlear suppression. By measuring CS on CAP, it was examined whether the fluctuated CS signals produced a different level effect than the stationary CS signals, as hypothesized from the fluctuation profile model.

This work has been peer reviewed and published in *Frontiers in Neuroscience* (Xia et al., 2022). Our team has also published a review summarizing the status of research in NIS and NIHHL, much of which shares content with this thesis. This review can also be found in *Frontiers in Neuroscience* (Ripley et al., 2022).

CHAPTER 2 METHODOLOGY

2.1 Outline of subjects and main procedures

This study was completed in two stages. In the first stage, a total of 20 adult albino guinea pigs (Hartley) were obtained from Charles River, Canada for this study; 12 in the control and 8 in the noise groups respectively. At the midpoint of data collection in this stage, we realized that the upper end of the MF setting (1113 Hz) in the EFR testing was not high enough to show the drop off of the low-pass TMTF with MF, and the parameters of the signal used for transient CAP were not ideally set. Therefore, we modified the recording settings for EFR and CAP at the halfway point of the experiment in the first stage. Moreover, the sample size for CAP in both groups was small due to failure with some animals. Therefore, 12 more guinea pigs were studied in the second stage; 8 were used to replace the control group and other 4 were added to the noise group. I was involved in the data collection in the first stage. The data analysis of this thesis, however, utilized all the data collected. The sample size for each measurement was labelled based on the data points that were successfully recorded.

Shortly after the animals were recruited (at the age of 1.5-2.5 months), their external ears were checked for abnormality. The animals were then tested with frequency specific ABR to ensure normal hearing sensitivity. In this baseline test, EFR was also measured in far-field only. Following the baseline test, the animals in the noise group were subjected to a noise exposure over a 1-month period. A one-month rest period was then given to them after the noise exposure. Two months after the baseline test (or one month after the noise), ABR and EFR were repeated on the animals in each group, followed by a set of near-field recordings from the round window, including transient

CAP and AM CAP (or near-field EFR (nfEFR)). Following this terminal evaluation, the animals were sacrificed, and their cochleae were harvested for a morphological evaluation of ribbon synapse count. All the procedures were approved by the University Committee of Laboratory Animals (protocol# 20-024).

2.2 Noise exposure

Multi-talker noise of a male human speech was modified to shift the frequency band to 2-16 kHz using Matlab. To do this, a zero-phase 1000-point finite impulse response (FIR) filter was used to filter the multi-talker babble into 19 third-octave bands with center frequencies ranging from 125 Hz to 8 kHz. Then, a white noise was filtered into 19 sixth-octave bands from 2 to 16 kHz. In each speech band, the amplitude envelope was extracted by calculating the absolute value of the Hilbert transform of the filtered band. Each speech envelope was then bandpass filtered between 2 and 50 Hz to eliminate envelope fluctuations outside of the range of frequencies that reflect human articulatory movements. Next, from each third-octave speech band, the filtered envelope was used to modulate the corresponding sixth-octave noise band. The sixth-octave filter that was used to extract the noise prior to modulation was then used to refilter each modulated noise band. The purpose of this step was to remove any out-of-band energy introduced by the envelope shaping. Then, each noise band was scaled to have the same root-mean square (RMS) amplitude as the speech band from which their modulations were derived. Finally, the 19 modulated noise bands were summed to produce the modified 2-16 kHz multi-talker babble (Dorman et al., 1997).

The multi-talker noise was presented in a sound booth via a four-speaker array (Pyramid TW-67 Super Tweeters; Brooklyn, NY, USA), which was suspended 40 cm

above the table floor where the animal cage was placed. Throughout the noise exposure, the animals were awake and unrestrained in a metal wire cage inside the sound booth with free access to water and food (Chen, Xing, et al., 2019; Zhang et al., 2020). The animals were exposed to the noise, with an Leq of 90 dB SPL, for 8-12 hours per day on every other day to allow one day of rest following each episode of noise exposure. The total duration of the noise exposure was 122 hours, making the total energy of the noise roughly equal to the 2-hour exposure at 106 dB SPL that was used in previous studies with guinea pigs (Fan et al., 2020; Furman et al., 2013; Shi et al., 2013; Song et al., 2016; Zhang et al., 2020).

2.3 ABR and EFR

All electrophysiological evaluations were performed in an electromagnetically shielded sound booth. Guinea pigs were anesthetized with a mixture of ketamine and xylazine by intraperitoneal injection for the ABR and EFR baseline tests. The initial dose was 40 and 10 mg/kg for ketamine and xylazine, respectively, and 1/3 of the initial dose was added as needed to maintain the anesthesia between stages 2 and 3. This was judged by the toe-pinching reflex. Throughout the experiment, the body temperature of the animal was kept at 38 °C with a thermostatic heating bad. In the terminal evaluation, all the tests were completed with the animals under urethane (i.p., 1.5 g/kg).

An auditory signal processing station (RZ6) from Tucker-Davis Technologies (TDT System III; Alachua, FL, USA) was used to generate the signals for auditory stimulation and to record the biological responses. The acoustic signals for all the auditory responses were delivered in open field via a broadband speaker (FT28D, Fostex). The maskers for EFR recording were also delivered in open field via an

additional FT28D speaker. The signals for contralateral suppression were delivered via a MF1 (TDT) speaker via tubing in closed field.

Both ABR and EFR were recorded with three subdermal electrodes, with the recording electrode inserted at the vertex and the reference and grounding electrodes positioned posterior to the external auditory canals. The biological signals picked up by the electrodes were sent to an RA16PA preamplifier, which amplified the signal 20 times.

2.3.1 ABR testing

ABR was evoked by 10-ms tone bursts (TB) with a rise/fall time of 0.5 ms. The TBs were presented at 21.1 /s and the ABR thresholds were examined from 1 to 32 kHz in octave steps. For each trial, the response was averaged 1000 times, or less if a clear and stable response was reached. At each frequency, TBs were presented in a descending sequence from 90 dB toward the threshold, which was defined as the lowest sound level at which a repeatable wave-III is visible.

2.3.2 EFR testing

EFR was evaluated as phase-locked responses to 16 kHz AM tones that were presented at the moderately high level of 75 dB SPL. The AM tones were presented in a sweeping pattern, and they had a duration of 500 ms and a rise/fall time of 5 ms. The modulation frequency (MF) was initially set from 113 to 1113 Hz in 100 Hz steps to get a TMTF, which was evaluated at two MDs (30% and 60%) respectively. Since it was determined that the 1113 Hz cut-off was often not enough to show a clear drop-off of the low-pass TMTFs, the highest MF was extended to 1513 Hz. The data reported in this thesis all used the range of MF from 113 to 1513 Hz.

The EFR was sampled at 24.414 kHz over a 500-ms time window to cover the length of the stimuli. The response of the first 50 ms was set to zero to avoid the impact of the onset response. In each trial, EFR was averaged 50 times and the averaged waveform in the time domain was converted into the frequency domain by a Fast Fourier Transformation (FFT), with a frequency resolution of 1.5 Hz (12407/8096). The spectrum peak at each MF was measured as the phase-locked response if the amplitude was at least 3 dB above the noise floor around the frequency in question.

Following the testing in quiet, the masking effect on EFR was evaluated at the best MF (BMF), i.e., the MF at which the greatest response occurred. The EFR at BMF was repeated separately under each of the two maskers: one stationary and the other temporally fluctuated. The stationary masker was broadband noise (high-pass filtered white noise with a low cut-off at 4 kHz) and the amplitude fluctuated masker was the same multi-talker noise that was used for the noise exposure. The Matlab-generated sound file of each masker was played out from the sound card of the computer that controlled the TDT system and was delivered in open field via a FT28D speaker at 75 dB SPL (yielding a 0 dB signal-to-noise ratio).

To mitigate the impact of random change in EFR with time, each masked EFR was sandwiched between two control recordings (without masking). The two EFRs before and after the masked EFR were averaged as the control for the calculation of the masking effect, which was presented as the reduction of EFR by the masker in dB. This strategy was also used for the recording of near-field EFR (nfEFR).

2.4 CAP and nfEFR from round window

Both the transient CAP and the cochlear response to AM, which is defined as nfEFR, were tested in the terminal evaluation. Under the anesthesia of urethane (i.p., 1.5 g/kg), a silver ball electrode was placed on the round window membrane after the mastoid was surgically opened. To secure the electrode in place, the silver wire was fixed to the mastoid with dental cement. The other end of the silver wire as well as the reference and grounding electrodes were connected to the preamplifier and then to the TDT system, the same way as for the ABR and EFR recording. A plastic tube was embedded through the dental cement to provide ventilation of the middle ear, which prevented the buildup of negative pressure. During the surgery and recording, the animal was placed on a thermostatic heating pad to maintain the body temperature at 38 °C.

The nfEFR was measured and analyzed the same way as the scalp EFR, except the number of averages in each trial was 25 instead of 50 due to the larger signal-to-noise ratio (SNR) in the near-field recording. The masking effect on nfEFR was observed as it was for the scalp EFR, that is, at the BMF under the respective high-pass and multi-talker noise maskers. Both the AM signal for evoking the EFR and the masker were delivered in open field via two FT28D speakers at 0 dB SNR.

The transient CAP was evoked by 16 kHz TBs across 90-10 dB SPL to obtain I/O functions. The stimuli were delivered in open field via a FT28D speaker. The effect of contralateral suppression (CS) was observed in the CAP. The CS signal was delivered in closed field via a MF-1 speaker with tubing that was inserted into the contralateral ear. Three types of signals were used as CS stimuli: (1) 16 kHz tone without modulation, (2) 16 kHz tone modulated by 93 Hz MF with 30%, and (3) 60% MDs. With each type of CS

signal, the CS effect was observed at three CS levels: 75-, 63-, and 51-dB SPL respectively. Therefore, CS effect was observed under 9 conditions (3 types × 3 levels).

In order to mitigate the impact of random variation of the CAP with time, the control CAP (with no CS) was done before and after each test condition with CS (the two controls sandwiched the recording with CS). The two controls were averaged for the calculation of the CS effect, which is the difference in the CAP amplitude in dB with and without CS.

The CAP was also tested in response to clicks at the beginning and the end of the CAP test to index the status of the ear and the round window electrode.

2.5 Synapse count observation

The morphological evaluation was carried out in accordance with previously published procedures (Chen, Xing, et al., 2019; L. Liu et al., 2012; Shi et al., 2013; Song et al., 2016; Zhang et al., 2020). To begin, the cochlear tissues were dissected after being fixed with 4% paraformaldehyde in phosphate-buffered saline (PBS). They were then permeabilized with 1% Triton X-100 in PBS for 1 hour, incubated in 5% goat serum in PBS for an additional 1 hour, and then incubated overnight at 4 °C with primary antibodies against both C-terminal binding protein 2 (CtBP2) and post-synaptic density-95 (PSD95) (mouse IgG1 to CtBP2; BD Biosciences, Franklin Lakes, NJ, USA: cat. # 612044, 1:200; mouse IgG2a to PSD95; Millipore, Billerica, MA, USE: cat. # MAB1596, 1:600). After the reaction, the tissues were washed and treated with the corresponding secondary antibodies (A21124 and A21131, respectively; Invitrogen, Carlsbad, CA, USA) at room temperature for 2 hours, and then mounted on microscope slides.

A confocal laser-scanning microscope (LSM 710 META; Zeiss, Shanghai, China) with a 63× water-immersion objective was used to obtain confocal images at specified frequency positions based on frequency-distance mapping (Viberg & Canlon, 2004). Next, image stacks were exported to ImageJ image-processing software (National Institutes of Health, Bethesda, MD, USA). In order to obtain the puncta densities, over 10 successive IHCs at each frequency position of the cochlea were selected to count the puncta of CtBP2 and PSD95.

2.6 Data analysis

The ABR and EFR were repeated at two time points (a baseline and an end test) in each of the control and noise groups, forming 4 data sets labelled as Ctrl-young and Ctrl-old in the control group, and Pre-noise and Post-noise in the noise group. Due to unexpected recording problems, useful data was not obtained from every subject. The exact sample size was specified in each test result, either by the number in the brackets in the figure legends or as stated in the figure description.

All data in this report are presented as means ± standard error of the mean (SEM). To analyze the data, the data were first evaluated for normality and equal variance. Parametric tests would be performed for data passing the normality and equal variance tests, otherwise, non-parametric tests would be applied. All statistics were done using SigmaPlot 14. For data with multiple factors, analyses of variance (ANOVA) were followed by *post hoc* pairwise evaluations. $P < 0.05$ was used as the criterion for significance.

CHAPTER 3 RESULTS

3.1 ABR

Figure 6 shows the ABR thresholds measured at the young age (1.5-2 months old), and 2 months later (4-5 months old) from the control group and the noise group, respectively. The ABR-frequency curves measured from the control group at the two time points were largely overlapping, indicating that there was no age effect on the ABR threshold. This was verified by a two-way repeated measure (RM) ANOVA within the control group against the factors of time and frequency. No significant age (time) effect was seen in this analysis ($F_1 = 0.712$, $p = 0.422$). A two-way ANOVA was conducted to compare the Ctrl-old and Post-noise data sets (with frequency as a co-variant) to determine whether noise exposure had any impact on thresholds. No significant effect of group was seen between the two data sets, suggesting no PTS ($F_1 = 0.156$, $p = 0.694$).

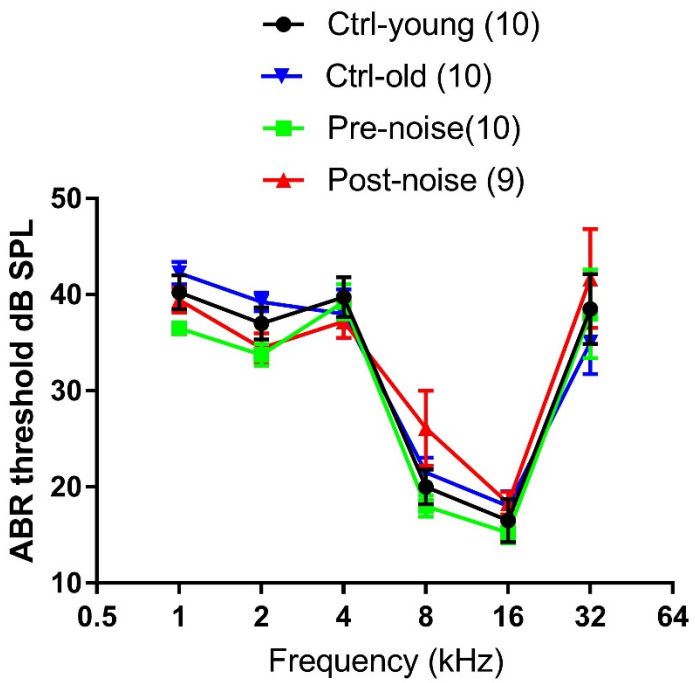

Figure 6: The effect of age and noise on ABR thresholds.
Notes: Ctrl-young and Pre-noise were the baseline thresholds taken at 1.5-2 months of age from both the control and noise groups before the noise exposure. Ctrl-old was measured at 4-5 months old of age (from the control group), which matched the age of the noise group for the ABR tested one month after the noise exposure (Post-noise).

3.2 Synapse count observation

Figure 7 shows representative images of immunostaining against CtBP2 (red dots) and PSD (green dots) from both a control animal and a subject exposed to the noise (one month after). The images were taken from the high frequency region of the cochlea. The images show that the synaptic puncta are distributed mostly along the bottom of IHCs in the control, while the distribution is less organized in the noise-exposed cochlea.

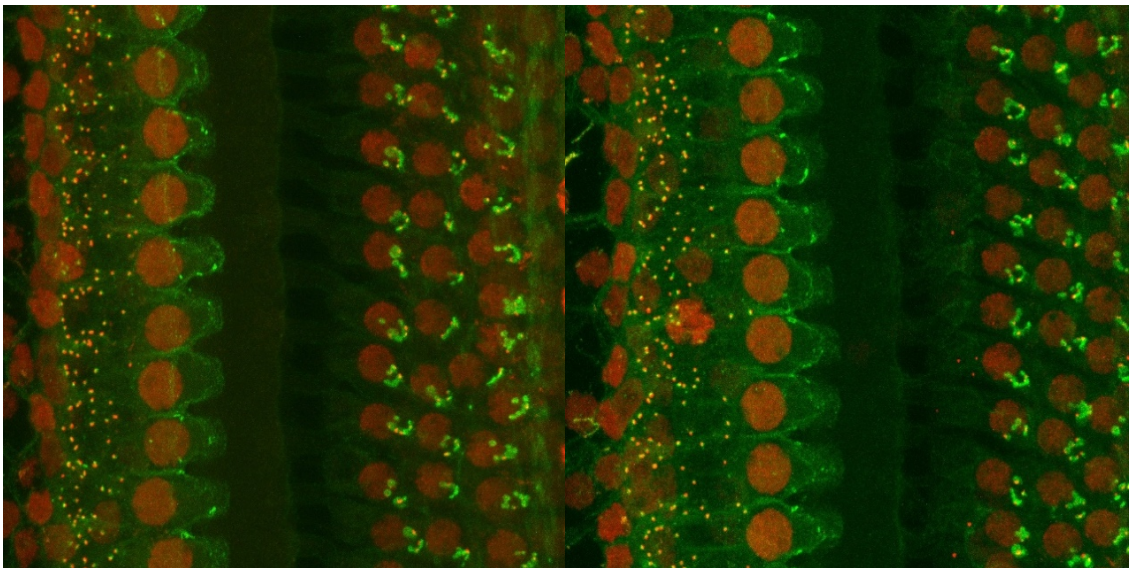

Figure 7: Representative images of immunostaining against CtBP2 (red dots) and PSD (green dots).
Notes: Left: control animal. Right: noise-exposed animal (one-month post-noise exposure). The images, taken from the high frequency region of the cochlea, show that the distribution of the puncta is less organized in the noise-exposed cochlea.

Figure 8 compares the ribbon densities (stained against CtBP2) across groups. The data from a previous study were taken for the synaptic counts after a brief-noise exposure at a higher level (106 dB SPL, 2h; Noise 1) to compare with the low-level noise (~90 dB SPL) given periodically over one month and with roughly equal dose in the present study (122 hours, Noise 2). Since the ribbon puncta are paired with PSDs (Figure 7), the ribbon counts were used to indicate the number of synapses. This practice is supported by previous studies, which have shown that the number of CtBP2 puncta and the postsynaptic puncta are similarly changed following noise damage (Maison et al., 2013; Shi et al., 2013, 2016; Wang et al., 2015). Figure 8A shows the ribbon density-frequency map (or density cochleogram). Figure 8B compares the density averaged over the high-frequency region (above 4kHz). This average is 18.15 ± 0.387 in the control group and 15.18 ± 0.185 in the group exposed to the brief noise (dropped by 16% as compared to the control). This value was 16.99 ± 0.12 in the present study after the long-

term noise exposure (Noise 2, dropped by 6.2%). A one-way ANOVA on rank (Kruskal-Wallis) shows a significant overall difference across the groups ($H_2 = 19.79$, $p < 0.001$). *Post hoc* pairwise tests (Dunn's method) show significant difference between the groups of Ctrl and Noise 1 ($Q = 4.445$, $p < 0.001$) and between the groups of Noise 1 and Noise 2 ($Q = 3.029$, $p < 0.007$), but not between the groups of control and Noise 2 ($Q = 1.983$, $p = 0.142$).

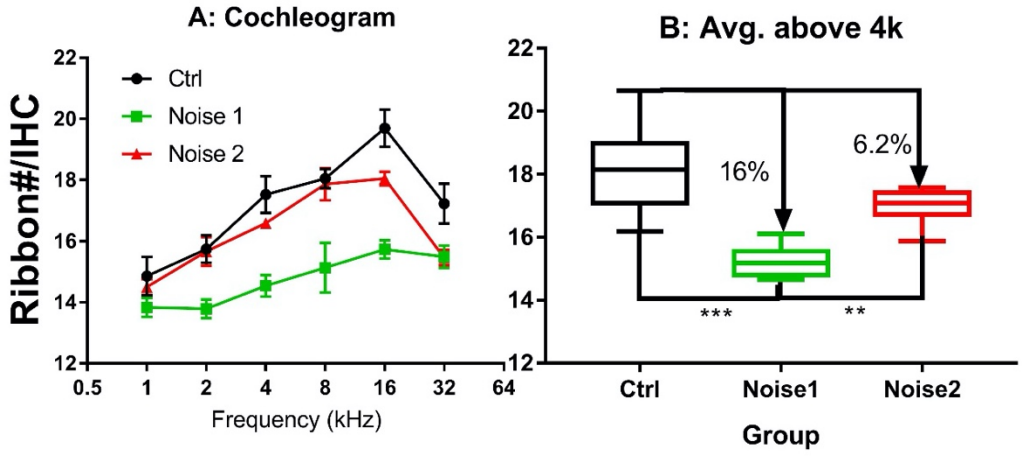

Figure 8: Synapse density comparison across groups (n = 8 in every group).
Notes: The synapse density is calculated from ribbon (Ctbp2). Noise 1 refers to a brief noise at 106 dB SPL for 2hrs (data taken from a previous study (Song et al., 2016)). Noise 2 is the noise exposure examined in the present study (fluctuated multi-talker noise, repeated over a period of 1 month for totally 122 hours with an Leq of roughly 90 dB SPL). The density was compared between groups. ***: $p < 0.001$, **: $p < 0.01$.

3.3 EFR and nfEFR

3.3.1 Temporal modulation transfer functions

Figure 9 shows the impact of noise and age on the TMTF as assessed via EFR. The TMTFs for 30% MD and 60% MD signals from the two groups at the two time points are given in Figure 9A and 9B, respectively. The TMTFs measured with 60% MD were largely overlapped between the Ctrl-old and Post-noise data at high MFs, while the Post-

noise TMTF measured by 30% MD diverged from that of the Ctrl-old, with the largest difference at 1213 Hz of MF. At this MF, the difference between the data sets was statistically significant as shown by a Mann-Whitney Rank Sum Test ($T = 59$, $p = 0.013$).

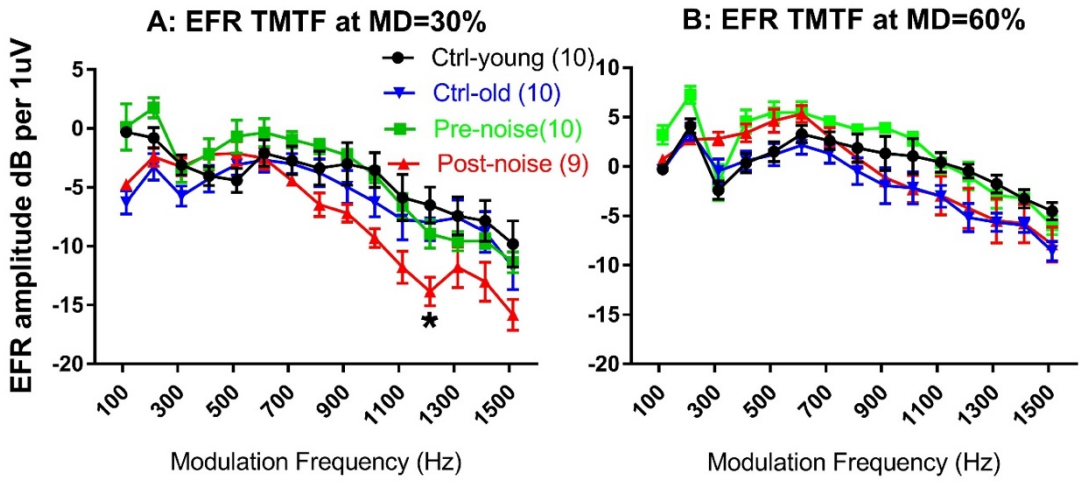

Figure 9: The impact of age and noise on EFR TMTFs measured in response to AM at 30% (A) and 60% (B) MD.
Notes: The Post-noise TMTF curve obtained with 30% MD appeared diverge from the Pre-noise and Ctrl-old TMTFs. A significant difference in the EFR amplitude was seen between the Ctrl-old and Post-noise TMTFs at the MF of 1213 Hz MF (*: $p < 0.05$).

Figure 10 shows the TMTFs of nfEFR. Since the nfEFR can only be recorded in the terminal test, they are compared between the old age data set without noise exposure (Ctrl-old) and the old age data set post-noise exposure (Post-noise). Unlike the TMTFs in the far-field recording, those obtained in the near field are largely overlapped between the control and the noise groups.

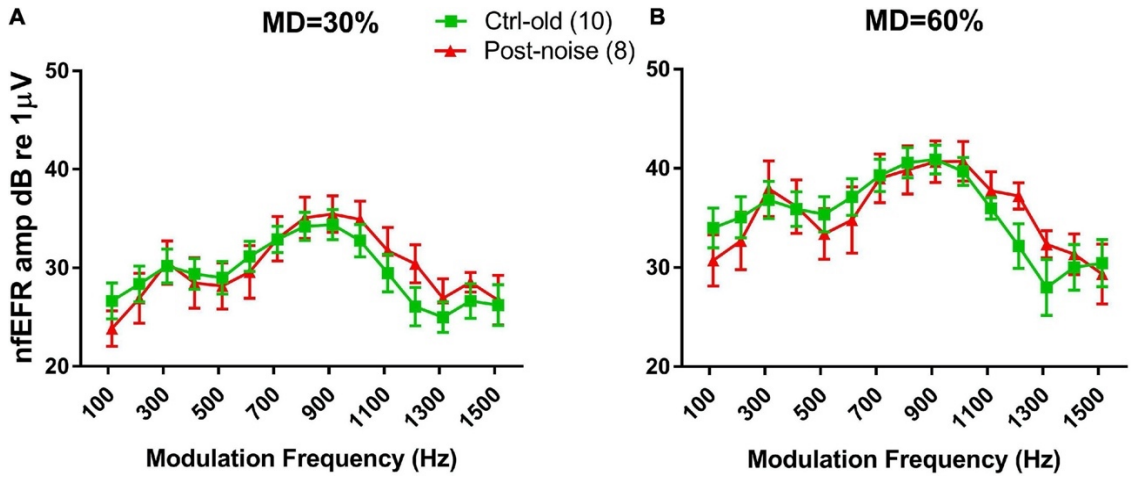

Figure 10: TMTFs of nfEFRs at 30% MD (A) and 60% MD (B).
Notes: The results are largely overlapped between the groups.

3.3.2 Effect of stationary and temporally fluctuated maskers

Figure 11 shows the masking effect by each of the two maskers and the difference between the two maskers in both EFR (11A, 11B and 11C) and nfEFR (Figure 11D, 11E, and 11F). The effect of each masker at the best modulation frequency of each subject was calculated as the difference of the response amplitude with and without masking, or the attenuation of the response by the masker in dB. Universally, the masking effect was much larger when the stationary masker was used than when the modulated masker was used. For example, under 30% MD in the post-noise testing (Figure 11A), the effect of masking on EFR amplitude using multitalker noise was 0.753 ± 0.328 dB, while the effect of masking using the high-pass masker was 5.318 ± 0.66 dB. A paired t-test indicated that this difference was significant (t = 6.625, p < 0.001). However, the difference between the two maskers (Figure 11C) did not show much variation between the groups and between the two tests within each group. For instance, the difference between the two maskers with respect to their effects on the EFR at 30% MD in the post-noise test was not significantly smaller than in the pre-noise control (3.509 ± 0.569 versus

4.564 ± 1.842, paired t-test: t = -1.185, p = 0.27). This negative result is inconsistent with the idea that noise-induced synaptic damage impairs signal coding in modulated maskers.

The effect of masking on nfEFR by the two maskers was also shown at two MDs (Figure 11D and 11E, respectively for 30% and 60% MD). Similar to the result in EFR, the masking effect of the high-pass noise appeared to be larger than that of the modulated masker and the masking effect by the two maskers appeared to be larger in the Post-noise data set. A two-way ANOVA was performed at each modulation depth for the factors of group and masker type. The analysis revealed a significant effect of both masker type (F_1 = 7.401 and p = 0.010 for MD = 30%, F_1 = 15.716 and $p < 0.001$ for MD = 60%), and grouping (F_1 = 6.458 and p = 0.016 for MD = 30%, F_1 = 8.339 and p = 0.007 for MD = 60%).

The *post hoc* comparisons (Holm-Sidak method) revealed a significant effect of grouping within the stationary masker for both 30% MD (t = 2.175, p = 0.037) and 60% MD (t = 2.622, p = 0.013) (marked by "#" in Figure 11D and 11E). Further, for 30% MD, a significant effect of masker type was seen within the Post-noise data set (t = 2.183, p = 0.036). For 60% MD, a significant effect of masker type was seen within the Ctrl-old data set (t = 2.358, p = 0.025) as well as within the Post-noise data set (t = 3.210, p = 0.003).

The difference in masking effect on nfEFR between the two maskers (Figure 11F) was also examined by a two-way ANOVA. A significant effect was found for group (F_1 = 4.192, p = 0.049), but not for the factor of modulation depth. However, the *post hoc* comparisons (Holm-Sidak method) revealed no significant difference between groups within either of the modulation depths (30% MD; t = 1.330, p = 0.193, 60% MD; t = 1.566, p = 0.127).

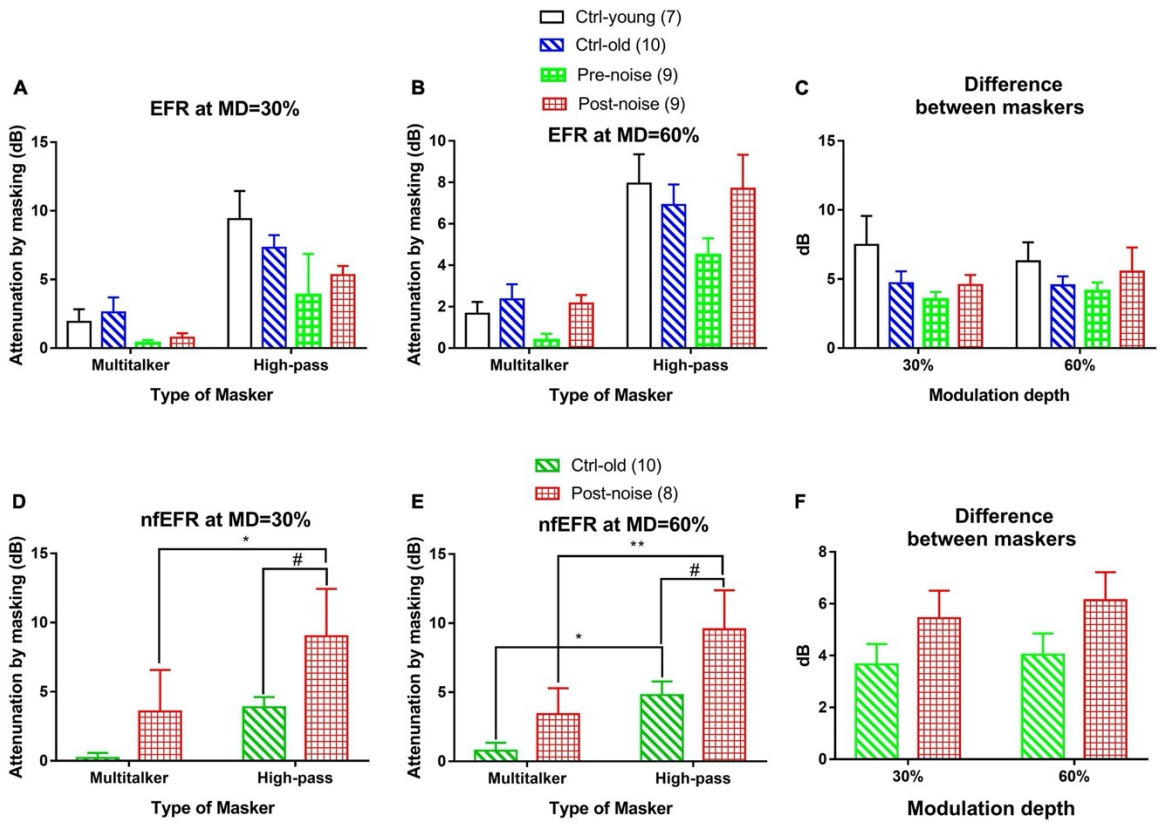

Figure 11: The masking effect by both the fluctuated (multi-talker) and stationary (high-pass) maskers at the two MDs (30% (A and D) and 60% (B and E)) for both the EFR (A and B) and nfEFR (D and E), as well as the difference in the masking effect between the two maskers (C for EFR and F for nfEFR).
Notes: Overall, the high-pass noise produced more masking than the multitalker noise. No significant difference was seen between the two maskers with respect to EFR amplitude (C). For the nfEFR, the high-pass noise resulted in a greater masking effect for the noise group than for the control (# in D and F). The difference between the two maskers in nfEFR (F) was much larger in the noise group as seen in the two-way ANOVA. However, *post hoc* tests found no significant differences within each MD. The number of "*" shows the significance level of the post-hoc comparisons within each group, while the number of "#" shows the significance level of the post-hoc comparisons within each masker: one for $p < 0.05$, two for $p < 0.01$, and three for $p < 0.001$.

3.4 Transient CAP and contralateral suppression

The transient CAP was measured in response to 16 kHz TBs. Figure 12A shows the CAP waveform from one subject across the sound levels between 20- and 90-dB SPL. The peak-to-peak value was read from the first negative peak to the next positive peak. Since the CAP was contaminated by summating potential at sound levels above 70 dB SPL, the

input/output (I/O) function was measured up to this level. Figure 12B shows the typical CS effect on an exemplary CAP I/O function. The suppression by three CS signals were quite similar and the suppression was larger at lower level of TBs evoking CAP.

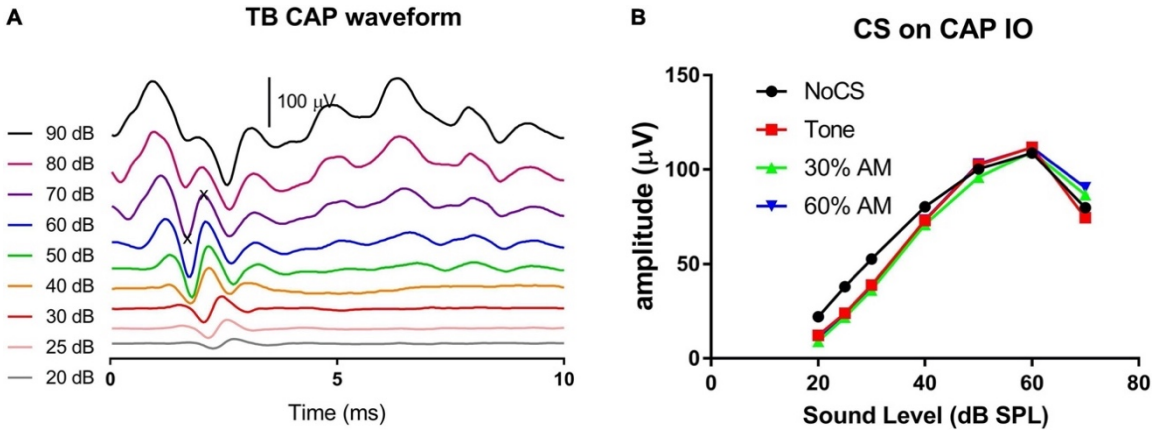

Figure 12: CAP waveforms across sound levels (A) and the exemplary CS effect on CAP I/O functions (B).
Notes: Three CS signals (tones, AM with 30% and 60% modulation depths respectively) were all presented at 75 dB SPL. They show a similar CS effect, which is larger at lower levels of tone bursts evoking CAP. The CAP amplitude was measured between "x" symbols (A).

The CS effect was calculated in dB by using the formula 20log(CAP with CS/CAP without CS). Since the CS effect is more significant at the lower levels, the low-level average was calculated across the TB levels of 30-, 25- and 20-dB SPL. Figure 13A, 13B, and 13C show the CS effect by each of the three CS signal types (16 kHz stationary tone, and that tone amplitude modulated by 30% and 60% respectively). In each of them, the CS effects at three CS signal levels (75-, 63- and 51-dB SPL) were presented. Overall, three trends can be seen for the CS effect across the level and the type of CS signal: (1) larger CS effect is seen with higher level CS, no exception for fluctuated CS signal (AM tone) as expected by the fluctuation profile model, (2) there is no obvious difference in CS effect across the CS types. (3) CS effects were not reduced but rather

increased in the noise group; suggesting that the NIS did not impair MOC regulation on cochlear gain. Since the CAP suppressions by the two lower CS signals are very small, further analysis was focused only on the CS effect produced by CS signal at 75 dB SPL to show the potential impact of CS types and groups (Figure 13D). A two-way ANOVA was performed for this purpose, which revealed a significant effect of group ($F_1 = 18.823$, $p < 0.001$) but no significant effect of CS type ($F_2 = 1.747$, $p = 0.199$). *Post hoc* comparisons were then performed (Holm-Sidak method), which revealed a significant difference between the Ctrl-old and the Post-noise data within the TB signal type ($t = 2.227$, $p = 0.031$) and within the 30% AM signal type ($t = 3.316$, $p = 0.002$).

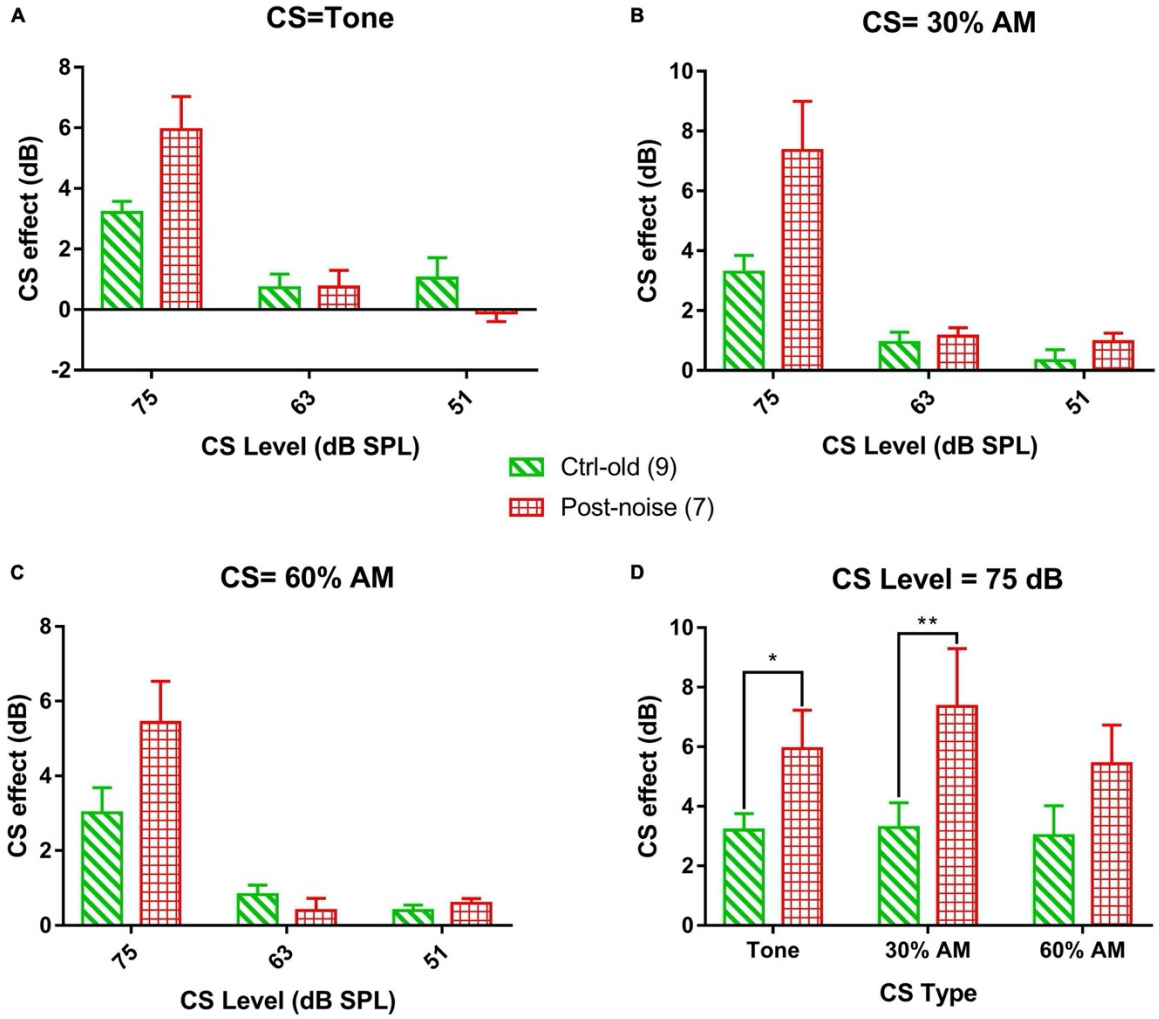

Figure 13: The CS effect on transient CAP in response to 16 k TB at the low-level average (the average of the stimulation levels of 20-, 25- and 30-dB SPL).
Notes: The CS signals are 16 k TB, and AM with 30% and 60% modulation respectively across three levels (75-, 63- and 51-dB SPL). A-C: the effect of CS levels on the CAP across groups, showing a decreased CS effect with decreasing of CS level, consistent across the three types of CS signals. D: comparison of CS effect across CS types and groups with 75 dB SPL CS signals.

CHAPTER 4 DISCUSSION

The fundamental goal of this study was to address several gaps in the current knowledge of NIS without PTS and NIHHL, which gave way to three main objectives: (1) determine if significant NIS without PTS can be established using noise exposure mimicking that which is experienced by humans (temporally fluctuated, low-level noise that is repeated over time); (2) determine if the noise exposure in (1) impairs temporal processing and, if so, verify if the temporal processing impairment deteriorates signal detection ability in fluctuated noise; and (3) determine if the fluctuation profile of ANFs is important in the MOC EAR, as measured by CS on CAP, and determine if the level-suppression relationship differs between stationary and fluctuated CS signals.

It was hypothesized that (1) NIS without PTS would be established by the reduction in synapse density. However, compared to brief high-level noise exposure (106 dB SPL, 2 hours), it was expected that significant but much less synaptic loss would be induced by the fluctuated, low-level noise via repeated exposure (90 dBA, 122 hours), which is roughly equal in total energy to the 106 dB 2-hour noise. This hypothesis was based on previous studies suggesting that the "equal energy" hypothesis does not work for noise-induced synaptic loss (Kujawa & Liberman, 2009; Maison et al., 2013). (2) The noise exposure in this study would impair temporal processing, which would hinder the ability of the animals with NIS to detect signals in fluctuated noise. As a result, the difference in masking effect between the stationary and fluctuated maskers would be smaller in subjects tested after the noise exposure. This hypothesis was made based upon the fact that animals can use temporal cues to encode signals under masking. This is shown by a much smaller masking effect by the fluctuated masker compared to the

stationary masker. Further, should this ability be deteriorated by NIS without PTS, the difference in masking effect between the two maskers would be reduced in subjects with the NIS. This prediction is based upon two assumptions about the effect of masking in the subjects with the NIS: (i) the masking effect of the stationary masker would not be changed by the NIS, (ii) the masking effect by the fluctuated masker would be increased. (3) The fluctuation in the response of the ANFs plays an important role in activating MOC control on OHC function. This would be indicated by fluctuated CS signals producing a stronger CS effect as compared to the stationary CS stimulation, and by an increase of CS effect with decreasing sound level when a fluctuated CS signal is used.

The major findings of the present study include: (1) Significantly less synaptic loss occurred by the fluctuated, repeated noise exposure at low level in the present study as compared to the loss after a brief high-level noise used in previous studies (Figure 8). However, it is likely that the noise exposure in the present study did cause NIS without PTS. (2) Temporal processing deficits were seen in scalp EFR as indicated by (i) the reduced overall amplitude, (ii) a larger drop off of EFR with increasing MFs (Figure 9). However, such changes were not seen in nfEFR, suggesting a central origin of the changes in the scalp EFR. (3) Overall, the masking effect of the fluctuated masker was smaller than that of the stationary masker in both the control recording and in the tests after the NIS was established. Since the comparison was done using the same signal-to-noise ratio in both masking conditions, the result suggests that animals can use temporal dips to detect an AM signal under masking. However, in the measurement of scalp EFR, in which deterioration of temporal processing was evident, the NIS did not result in changes to the masking effect difference between the two maskers, as predicted by our

hypothesis. We also noticed an increased masking effect by the two maskers in the test with the subjects with NIS, conflicting with our assumption that the masking effect of the stationary noise would remain unchanged in the subjects with the NIS. The increase in the masking effect is parallel between the two maskers in the NIS subjects as compared with the control recording before the noise exposure. On the other hand, the masking effect difference in nfEFR was larger in the nfEFR of the noise group, which was also opposite to our hypothesis. These results did not provide clear evidence supporting the connection between temporal processing disorders and CIND. (4) There was no evidence supporting the importance of fluctuated input in ANFs to the MOC regulation on OHC functions. This was indicated by the lack of difference in CS effect between stationary and fluctuated CS signals as well as the fact that the CS effect was always larger with a higher level of CS, regardless of whether the CS signal was fluctuated or stationary. These results are discussed in detail below.

4.1 Can NIS be established using noise exposure like what is experienced by humans?

There are two main factors to consider when quantifying NIS accompanied by NIHHL. First, the damage to and loss of the afferent synapses between the IHCs and the SGNs. Second, the absence of PTS. In the present study, PTS was absent as indicated by the full recovery of the ABR thresholds. First, it was determined that there was no impact of age, which was evident by the overlapped threshold-frequency curves within the control group between the two time points tested (Ctrl-young and Ctrl-old, Figure 6). Further, although the Post-noise ABR thresholds were visually elevated at 8 kHz, a two-way ANOVA

against the factors of test time and frequency (within the noise group) deemed this elevation insignificant.

It was also determined that the noise exposure used in this study (multi-talker noise at 90 dBA, 122 hours) did cause permanent synaptic loss, although significantly less so compared to the brief high-level noise delivered in a single dose in previous studies (106 dB, 2 hours). This was determined by the synapse density observation, which showed that the average density in the subjects exposed to the brief noise (Noise 1) in a previous study dropped by 16% compared to the control group, while the group exposed to noise in the current study (Noise 2) dropped only by 6.2% compared to the control group. Further, post-hoc pairwise tests following the one-way ANOVA on rank showed a significant difference between the groups of Ctrl and Noise 1 and between the groups of Noise 1 and Noise 2, but not between the groups of Ctrl and Noise 2. These results were expected according to the idea that the "equal energy" hypothesis does not work for noise-induced synaptic loss. Although the 6.2% drop in the synaptic density in the present study was not statistically significant, we do think that NIS was established. This is supported by the fact that the initial synaptic loss, if evaluated shortly after noise exposure, is much larger than the permanent loss that is evaluated weeks after the noise exposure due to the synapses' ability to self-repair, as reported in previous studies (L. Liu et al., 2012; Shi et al., 2013; Song et al., 2016). For example, in the study from which the synaptic count data was borrowed in this thesis, the initial loss of the ribbon synapses was ~50%. The synaptic loss was reduced to ~16%, which is 1/3 of the initial loss. If such ratio remains the case in the present study, then the initial loss would be close to 20%. The existence of the NIS in the present study is also supported by the possibility that the

repaired synapses may not be completely healthy. Rather, some coding deficits may exist in association with the recovery of the synaptic count (Chen, Shi, et al., 2019; L. Liu et al., 2012; Shi et al., 2013; Song et al., 2016). Further, functional deficits were also observed in the present study. Therefore, it is likely that the noise exposure did cause NIS without PTS by way of damage to the synapses.

4.2 Temporal processing impairment: was it present and did it cause CIND?

4.2.1 Evidence of temporal processing deficits as indicated by TMTFs

To address the question of whether temporal processing was impaired after the noise exposure given in this study, the TMTFs of both EFR and nfEFR were examined for signals modulated at 30% and 60% MD. Initially, a visual inspection of the EFR TMTFs indicated that there was a drop in the TMTF of the group exposed to the noise compared to the control group, largest at the MF of 1213 Hz. A Mann-Whitney Rank Sum Test performed at this MF showed a significant difference between the Ctrl-old and Post-noise data sets for the 30% MD signal only (Figure 9A). This suggests that temporal processing deficits were present as the result of the NIS. Change in the far-field EFR TMTF by noise was also reported in mice in the study by Shaheen et al. (2015) outlined in Section 1.3.3, which showed band-pass TMTFs with a peak close to 1000 Hz MF. The ANF origin of this peak response was supported by its disappearance (or reduction) following the establishment of NIS. However, in the present study, the TMTFs of guinea pigs appeared to be low-pass in nature. In addition to the species difference, the EFRs in the study by Shaheen et al. (2015) were evaluated with an AM signal at 100% modulation, and the NIS in that study was much more severe than in the present report.

The negative result at 60% MD (Figure 9B) supports the idea that functional impairment of L/MSR ANFs is responsible for the described deficits. This is due to the idea that HSR ANFs are unable to phase lock to a high-level signal with a small MD because the amplitude fluctuation is in the range of sound where the rate-level functions of the HSR ANFs are saturated (Bharadwaj et al., 2014). Thus, since the results showed temporal processing deficits for the 30% MD signal only, the L/MSR ANFs must have been impaired, because HSR ANFs could not have phase-locked to such signal, because the small fluctuation of the sound level is in the range of the saturation of those ANFs when the AM signal is presented at 75 dB SPL. Conversely, the larger MD of 60% could have been coded by the HSR ANFs because the larger AM fluctuation causes the sound level change to be in the range where these ANFs are not saturated.

As for the nfEFR TMTFs, different results were obtained compared to those of the EFR TMTFs. At both MDs, the TMTFs from the two groups were largely overlapped, suggesting that the difference between groups shown by the EFR TMTFs (Figure 10A and 10B) is likely an indication of a central origin for the temporal processing deficits seen in EFR.

4.2.2 Stationary versus fluctuated masking effects on EFR and nfEFR

Testing signal perception or coding with masking present is one of the most common ways to evaluate hearing in noise. To assess the ability of signal coding in noise using temporal cues, the masker should be temporally fluctuated to allow for the detection of signal in the temporal dips of the masker. However, this parameter has been ignored or has been evaluated in a noncomprehensive manner in previous studies (Chen, Xing, et al., 2019; Ralli et al., 2019; Souchal et al., 2018; Zhang et al., 2020). In the present study, the

magnitude of the masking effect by a stationary masker was compared to that of a fluctuated masker. It was hypothesized that if NIS without PTS reduces the ability to detect signal in the dips of a masker, the masking effect by the fluctuated masker would be increased so that the difference between the two maskers would be decreased. However, this was not the case in the present study: the masking effect by both maskers on EFR were increased as tested at the old age in both groups (aside from a small decrease at the old age in the control group with the stationary masker), although the increases were not statistically significant (Figure 11A and 11B). The near-parallel increases in the masking effect by the NIS resulted in no significant between-masker difference across the groups in EFR (Figure 11C). In nfEFR, a similar trend was seen with the parallel increases of the masking effect by the NIS in comparing the two maskers. This rejects our assumption that the masking effect by the stationary masker would not be changed by the NIS. Although the similar increase of the masking effect between the maskers by the NIS was seen in nfEFR (Figure 11D and 11E, showing the larger attenuation of nfEFR by the masking), a larger, rather than smaller, between-masker difference was seen in the subjects with the NIS (Figure 11F). This is opposite to the hypothesis that the NIS would deteriorate signal detection using temporal cues (which should be evident from a largely increased masking effect by the fluctuated masker) and therefore reduce the between-masker difference. Therefore, the present study shows no clear evidence to suggest that NIS deteriorates the signal detection ability in noise using temporal cues. It is important to note that the amplitudes of nfEFR were reduced in the subjects with the NIS (shown in Figure 11D and 11E as the larger attenuation in the Post-noise data). This is consistent with previous studies using high-level noise exposure

(Chen, Xing, et al., 2019; Zhang et al., 2020), although the synaptic loss in the present study was much less. A question that remains to be explored in future work is whether a larger increase in the masking effect by the temporally fluctuated masker would be seen in subjects with more severe NIS than what was established in the present study.

4.3 Did CS on CAP reveal the importance of the fluctuation profile of ANFs in the MOC EAR?

CS on CAP was compared across stationary and fluctuated CS signals to verify our hypothesis that extended from the fluctuation profile model and the suggested role of the fluctuation in MOC control of cochlear function, as reviewed by Carney (2018). In the fluctuation model, ANFs around formant peaks have smaller or no fluctuation due to saturation and therefore would produce less excitation of MOC neurons, resulting in less gain reduction. If the fluctuation is critical in the MOC control, then a fluctuated stimulus (such as an AM signal) would produce a stronger gain reduction via MOC feedback, which should be testable by contralateral suppression (CS) on CAP.

The results of the present study did not show a significant difference in the CS effect between the stationary and fluctuated CS signals (Figure 13A, 13B, and 13C). Furthermore, the CS effect was always larger by a higher level of CS signal, which is opposite to the prediction by the fluctuation profile model (Carney, 2018). It is also worth noting that the CS effects were not reduced but rather increased in the noise group; suggesting that the NIS did not impair MOC regulation on cochlear gain (Figure 13D).

Overall, these results provide no evidence supporting the MOC regulation in the fluctuation profile model. However, this negative result may not be sufficient to fully reject the role of temporal fluctuation in the efferent control mediated by MOC neurons.

It is likely that the feedback loop relying upon average rate, rather than fluctuation, exists. It is therefore difficult to uncover the role of fluctuation in the MOC efferent from a loop that does not require fluctuation.

4.4 Conclusion

The present study showed that the fluctuated, intermittent noise exposure experienced by humans in daily life is less effective in causing NIS without PTS. It was also demonstrated that NIS without PTS and NIHHL may not be as problematic as previously thought. Considering the smaller amount of NIS established by the noise exposure in this study, the observed temporal processing dysfunction may have been limited and not reflective of NIS and NIHHL that is possible with a stronger noise exposure. Notably, while temporal processing deficits were seen in the far-field EFR TMTF, corresponding changes to the nfEFR TMTF were not seen, suggesting a central origin for the temporal processing changes. Conversely, only the near-field measures of the effect of masking on EFR revealed a greater masking effect with NIS, suggesting a peripheral origin for this effect along with central compensation. This result devalues the effectiveness of far-field EFR in assessing the coding deficits associated with NIS. Furthermore, the observed temporal processing deficits did not appear to be related to the masking effect, given the different origins and the lack of any significant difference between the masking effect found with a stationary versus fluctuated masker. The role of the temporal processing deficits in CIND should be evaluated in more detail in subjects with more severe NIS without PTS. Finally, the results of CS on CAP did not support the role of temporal fluctuation in the MOC efferent control on cochlear gain.

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