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Effects of Noise Exposure on Auditory Brainstem Response and Speech-in-Noise Tasks: A Review of the Literature

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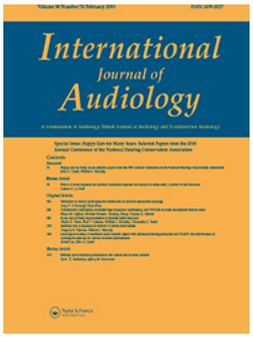

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REVIEW ARTICLE

Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: a review of the literature

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ABSTRACT

Objective: Short-term noise exposure that induces transient changes in thresholds has induced permanent cochlear synaptopathy in multiple species. Here, the literature was reviewed to gain translational insight into the relationships between noise exposure, ABR metrics, speech-in-noise performance and TTS in humans.

Design: PubMed-based literature search, retrieval and review of full-text articles. *Study Sample:* Peer-reviewed literature identified using PubMed search.

Results: Permanent occupational noise-induced hearing loss (NIHL) is frequently accompanied by abnormal ABR amplitude and latency. In the absence of NIHL, there are mixed results for relationships between noise exposure and ABR metrics. Interpretation of speech-in-noise deficits is difficult as both cochlear synaptopathy and outer hair cell (OHC) loss can drive deficits. Reductions in Wave I amplitude during TTS may reflect temporary OHC pathology rather than cochlear synaptopathy. Use of diverse protocols across studies reduces the ability to compare outcomes across studies.

Conclusions: Longitudinal ABR and speech-in-noise data collected using consistent protocols are needed. Although speech-in-noise testing may not reflect cochlear synaptopathy, speech-in-noise testing should be completed as part of a comprehensive test battery to provide the objective measurement of patient difficulty.

Abbreviations: ABR: auditory brainstem response; AP: action potential; BKB-SIN: Bamford-Kowal-Bench Speech-in-Noise; CAP: compound action potential; CEOAE: click-evoked otoacoustic emission; CHABA: Committee on Hearing, Bioacoustics, and Biomechanics; CRM: Coordinate Response Measure test; dB: decibel; dBA: A-weighted decibel; dB HL: decibel hearing level; dB nHL: decibel hearing level relative to a normal hearing population; dB S/B: decibel signal to babble ratio; dB SL: decibel sensation level (dB above threshold); dB SPL: decibel sound pressure level; dB peSPL: decibel peak-equivalent sound pressure level; DPOAE: distortion product otoacoustic emission; ECochG: Electrocochleography; EHF: extended high frequency; FFR: frequency following response; HINT: Hearing in Noise Test; HPD: hearing protection device; Hz: hertz; IHC: inner hair cell; kHz: kilohertz; LiSN-S: Listening in Spatialized Noise-Sentences High Cue Condition; NEQ: noise exposure questionnaire; NIHL: noise-induced hearing loss; NIOSH: National Institute on Occupational Safety and Health; NU-6: Northwestern University Auditory Test Number 6; OHC: outer hair cell; OSHA: Occupational Safety and Health Administration; PTS: permanent threshold shift; QuickSin: Quick Sentences in Noise; SNR: signal-to-noise ratio; SRT: speech recognition threshold; SSQ: Speech, Spatial, and Qualities of Hearing Scale; STS: standard threshold shift; TEN(HL): threshold equalising noise (specified as dB hearing level); TTS: temporary threshold shift; UTD: University of Texas at Dallas; WIN: Word-in-Noise test

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Introduction

Exposure to loud sound has the potential to damage cells in the inner ear. It has long been known that the outer hair cells (OHCs) are particularly vulnerable to noise injury (Wang, Hirose, and Liberman 2002; for review, see Hu 2012), as well as other diverse insults such as occupational chemical exposure (for review, see Morata and Johnson 2012) and ototoxic drugs including aminoglycoside antibiotics and chemotherapeutics (for review, see Campbell and Le Prell 2018). More recently, it has become clear that the synapses connecting the inner hair cells (IHCs) to the auditory nerve dendrites are also vulnerable to loss as a consequence of noise (for review, see Kujawa and Liberman 2015), aminoglycoside antibiotics (Hinojosa and Lerner, 1987) and aging (Sergeyenko et al., 2013).

Hearing loss that occurs after exposure to loud sound may recover, in which case it is a temporary threshold shift (TTS) or the hearing loss may not resolve, in which case it is a permanent threshold shift (PTS) (for review, see Ryan et al. 2016). The classic literature on human TTS includes the measurement of TTS 2 minutes after the end of the noise exposure (TTS_2) (Yates, Ramsey, and Holland 1976; Stephenson and Wall 1984). Threshold shifts at later times are a smaller, recovering, TTS (for review, see Ward 1970; Melnick 1991). It is more difficult to capture TTS_2 in animal studies given the need to anaesthetise the

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animal prior to testing. In this review, TTS_2 is used to denote classic 2-minute post-noise testing, and TTS without a specific time notation attached refers to a recovering TTS assessed at a longer post-noise time. A typical paradigm when using an animal model is to expose an awake animal to intense sound; post exposure, sound-evoked auditory brainstem response (ABR) thresholds are measured over the days and weeks after the noise exposure. Distortion product otoacoustic emission (DPOAE) thresholds may be monitored in place of or in combination with ABR thresholds, or DPOAE amplitude may be monitored. At the conclusion of the experiment, cochlear tissues are harvested and the OHC and IHC populations are counted.

One of the paradigms that has become increasingly common in recent years is the use of a short-term (two to four hours) sound exposure, with changes in both DPOAE and ABR thresholds and amplitude measured approximately 24 hours after the exposure and at one- to two-week intervals thereafter to monitor any permanent changes (Kujawa and Liberman 2006, 2009). Using such paradigms, there is now an elegant and convincing documentation of permanent auditory nerve synaptic pathology "hidden" behind normal hair cell counts, with a parallel decrease in ABR Wave I amplitude "hidden" behind normal threshold sensitivity. In this context, hidden synapse loss refers to a loss of synapses that occurs despite intact OHC and IHC populations – i.e. synapse loss cannot be inferred from the conventional OHC and IHC counts (as these cell counts are normal). The Wave I amplitude decreases have been termed "hidden hearing loss" as threshold measurements, the most common measurement of function, return to baseline, even though the amplitude of Wave I is decreased. The use of the term hidden hearing loss to specifically refer to decreased Wave I amplitude was proposed by Schaette and McAlpine (2011). Since then, this term has also sometimes been used within the literature to refer to auditory dysfunction that is speculated to accompany the cochlear synaptopathy and accompanying decreased Wave I amplitude (Kujawa & Liberman, 2015).

Taken together, after noise exposure resulting in TTS, but no OHC loss and no PTS, permanent decreases in the number of synaptic connections between the IHCs and auditory nerve fibres resulting in decreased Wave I amplitude can be substantive, but will go undetected and unreported based on conventional reporting that is limited to threshold measures and counts of IHCs and OHCs. Fundamental to the interpretation of hidden hearing loss, i.e. a cochlear synaptopathy-driven functional deficit, the test battery must document that the middle ear conduction system is intact, typically accomplished using tympanometry, and there must be documentation that the OHC population has not been compromised, in order to attribute any observed functional deficits to the inferred "hidden" synapse loss.

Effects of noise on cochlear hair cells

Noise exposure can result in stereocilia damage or, in more severe cases, mechanical trauma to the OHCs or the organ of Corti itself (Henderson, Hamernik, and Sitler 1974; Henderson and Hamernik 1986; Wang, Hirose, and Liberman 2002). Noise-induced damage to the OHCs compromises threshold sensitivity; the electromotile action of the OHC population provides up to 40 dB of gain and the OHCs are therefore labelled the "cochlear amplifier" (Dallos and Evans 1995; Dallos, Zheng, and Cheatham 2006; Ashmore et al. 2010). If the OHCs are damaged, the loss of the cochlear amplifier will result in a reduced input to the IHCs. The IHCs have typically been documented to be less vulnerable to noise injury than the OHCs (Wang, Hirose, and Liberman 2002; Chen and Fechter 2003); however, Mulders, Chin and Robertson (2018) recently argued that noise-induced injury to the IHCs plays a significant role in the Wave I amplitude reductions that are labelled hidden hearing loss. OHC loss shows only a moderate correlation with PTS, at least in part because OHCs may be present (living) but impaired (Chen and Fechter 2003).

With respect to monitoring noise-induced damage to the OHCs, a common strategy for monitoring OHC function is the use of DPOAE tests. Not only are DPOAEs well known for use identifying OHC damage due to cisplatin or aminoglycoside treatments (for recent review, see Campbell and Le Prell 2018), DPOAEs have shown high sensitivity to noise injury with deficits in DPOAE amplitude reportedly associated with occupational noise (Seixas et al. 2004; Korres et al. 2009; Seixas et al. 2012; Boger, Sampaio, and Oliveira 2017), recreational music player use (Santaolalla Montoya et al. 2008; Lee et al. 2014) and military service (de Souza Chelminski Barreto et al. 2011). Observations that noise-induced deficits in DPOAE and click-evoked otoacoustic emission (CEOAE) thresholds significantly exceeded noise-induced TTS have been used to suggest that OAEs are a more sensitive measure of noise injury than the audiogram itself (Attias and Bresloff 1996). DPOAE amplitude decreases may provide an early warning of pre-clinical damage and increased vulnerability for hearing loss (Lapsley Miller et al. 2006; Lapsley Miller and Marshall 2007). Despite their strengths and utility, it must be remembered that normal DPOAEs can be recorded even in the presence of OHC damage, and thus, normal DPOAEs do not necessarily imply the OHC population is not damaged (Subramaniam et al. 1994a, 1994b; Chen and Fechter 2003). Taken together, normal OAEs do not confirm the absence of OHC pathology, but they provide reasonable assurance that the cochlear amplifier is relatively intact.

Documentation of DPOAE amplitude as a measure of OHC integrity may be less important for inferences regarding cochlear synaptopathy if neural function is measured using higher level sound stimuli. At higher sound pressure levels, the OHCs do not provide any significant cochlear gain. Studies by Ruggero and Rich (1991), Fridberger et al. (2002), and Earl and Chertoff (2012) provide evidence that compromised OHC function does not significantly decrease the magnitude of auditory nerve output in response to high-intensity stimuli (for additional discussion, see Adelman, Weinberger, and Sohmer 2010). Thus, studies including high-level stimuli sufficient to "bypass" the influence of OHCs are less reliant on use of DPOAE data to confirm normal OHC function when attempting to make inferences about the integrity of the auditory nerve pathway. In essence, if the stimulus level used for ABR recordings is sufficiently intense to stimulate IHCs and trigger neural firing directly, the interpretation of changes in ABR amplitude may be less complicated. However, if higher-level sound is used as a stimulus, the medial olivochlear (MOC) efferent reflex (Müller et al. 2005; Sun 2008; Verschooten et al. 2017) and the middle ear reflex (Sun 2008) may be stimulated, either of which can have the net effect of reducing sound-driven auditory nerve discharge.

Pathological neural consequences of noise that induces TTS

Detailed reviews of the literature on noise exposure, cochlear synaptopathy and permanent auditory nerve pathology clearly describe the potential for permanent pathology in the ascending neural pathway in the absence of noise-induced PTS (for reviews, see Plack, Barker and Prendergast 2014; Kujawa and Liberman

2015; Hickox et al. 2017; Kobel et al. 2017; Liberman 2017; Liberman and Kujawa 2017; Barbee et al. 2018; Le Prell 2018). Whereas loss of cochlear OHCs results in poorer sound detection thresholds (hearing loss) (for review see Saunders et al. 1991), a significant proportion of the IHC population can be lost without comprising thresholds (Lobarinas, Salvi and Ding 2013). As noted above, pathology that is limited to the IHCs, their synaptic connections to the auditory nerve dendrites and the auditory nerve itself have therefore been described as "hidden" as these pathologies can occur in the absence of PTS (see Schaette and McAlpine 2011). In rodent models, noise exposure that induces a TTS of 40 dB or greater (measured the day after the noise exposure) has resulted in permanent auditory nerve injury in multiple studies, even though complete post-noise threshold recovery was observed.

Noise-induced cochlear synaptopathy has been observed across diverse animal models including mice (Kujawa and Liberman 2009; Wang and Ren 2012; Fernandez et al. 2015), guinea pigs (Lin et al. 2011; Furman, Kujawa, and Liberman 2013), chinchillas (Hickman et al. 2018), rats (Altschuler et al. 2018) and nonhuman primates (Valero et al. 2017). These exposures typically employ a short-term noise exposure, with rodent subjects typically exposed to octave band noise for two-hours. Across rodents, the two-hour duration sound exposure level needed to induce cochlear synaptopathy has varied, with higher sound levels needed in the guinea pig (106 dB SPL, see Lin et al. 2011) and rat (109 dB SPL, see Lobarinas, Spankovich, and Le Prell 2017) than in the mouse (100 dB SPL, see Kujawa and Liberman, 2009; Fernandez et al. 2015). In the absence of noise exposure, age-related cochlear synaptopathy is also reliably observed. This age-related pathology has been reported in mice (Sergeyenko et al. 2013), rats (Möhrle et al. 2016) and gerbils (Viana et al. 2015; Gleich, Semmler, and Strutz 2016). One significant issue that has been identified long after recovery from an earlier TTS is the long-term slowly progressive expansion of synapse loss from the immediately damaged higher-frequency regions (at 22.6 and 32 kHz in the mouse cochlea) to the previously intact lower-frequency cochlear regions (at 5.6 and 11.3 kHz in the mouse cochlea) (Fernandez et al. 2015). A second significant issue is the slowly progressive loss of spiral ganglion neurons, with the total observed loss exceeding the otherwise expected age-related decline in spiral ganglion numbers (Kujawa and Liberman, 2006; Lin et al. 2011). Multiple recent reviews of these pathological consequences are available (Kujawa and Liberman 2015; Liberman and Kujawa, 2017), including a recent review of the extent to which permanent auditory nerve pathology can occur in parallel with cochlear hair cell pathology (Hickox et al. 2017).

Based on the above results, it has been suggested that the risks of TTS in humans exposed to intense sound may be greater than previously assumed (Kujawa and Liberman, 2006; Kujawa and Liberman, 2009). In addition, there has been fairly broad speculation that hidden neuropathic damage (immediate cochlear synaptopathy followed by slow spiral ganglion cell loss) could explain the disproportionate difficulties experienced by some individuals processing speech in noisy environments (Kujawa and Liberman, 2009; Lin et al. 2011; Makary et al. 2011). The relationships between TTS_2, TTS recovery, auditory pathology and supra-threshold functional deficits are a topic of significant interest to scientists and clinicians, and there are concerns about the implications for occupational injury to workers who may be at risk for TTS (for additional discussion, see Kujawa and Liberman 2009; Kujawa 2014; Kujawa and Liberman 2015; Liberman and Kujawa 2017).

Audiometric monitoring for occupational noise-induced hearing loss

The federal noise regulations in the United States [i.e. 29 CFR 1910.95 enforced by the US Occupational Safety and Health Administration (OSHA)] and national regulations in other countries include annual audiometric testing requirements so that the development of NIHL can be detected and additional hearing loss prevented. Even if a worker wears a hearing protection device (HPD; typically earplugs or earmuffs), it is possible that annual audiometric testing will reflect temporary changes in hearing. Thus, if a new hearing loss is detected (relative to the baseline audiogram on file for that worker), there will be typically be some effort to complete a retest either immediately or after a noise-free interval to confirm the repeatability and/or permanence of the change.

Per 29 CFR 1904.10, hearing loss is required to be reported as an occupational noise injury when 1) a standard threshold shift (STS) is documented during annual audiometric testing (with STS defined as a permanent threshold change averaging 10 dB or more at the frequencies of 2, 3 and 4 kHz), 2) the average threshold at the 2, 3 and 4 kHz frequencies is 25 dB HL or poorer, and 3) exposure in the workplace may have caused or contributed to the hearing loss (OSHA 1983). Other agencies have provided different guidance in an effort to support earlier detection of NIHL. For example, the US National Institute on Occupational Safety and Health (NIOSH) advocates that a "significant threshold shift" be defined as a 15-dB threshold shift at 0.5, 1, 2, 3, 4 or 6 kHz, with an immediate retest used to confirm that the observed shift is not a function of test–retest reliability (NIOSH 1998). With earlier detection, earlier intervention is possible, with the goal of minimising additional hearing loss.

Although the OSHA regulations do not require testing at 8 kHz or above, poorer high-frequency hearing has been reported in workers exposed to occupational noise. Deficits have been reported within the extended high-frequency (EHF) range of 10 kHz and above in workers exposed to occupational noise (Hallmo, Borchgrevink, and Mair 1995; Korres et al. 2008; Riga et al. 2010; Mehrparvar et al. 2014), personal audio system device users (Le Prell et al. 2013; Sulaiman, Husain, and Seluakumaran 2015; Kumar et al. 2017), those with a history of musical training (Schmidt et al. 1994; Gonçalves et al. 2013; Liberman et al. 2016), frequent concert goers (Grose, Buss, and Hall 2017), those with acoustic trauma during military service (Balatsouras, Homsioglou, and Danielidis 2005; Buchler, Kompis, and Hotz 2012) and individuals with higher lifetime noise exposure (Prendergast et al. 2017a; Yeend et al. 2017). NIOSH recommends testing through 8 kHz. Inclusion of EHF frequencies above 8 kHz in monitoring programmes would require careful consideration of the effects of age at EHF frequencies, as these are significant (Stelmachowicz et al. 1989).

Although occupational noise reporting requirements are largely intended to capture the rate of new PTS injuries at the 2, 3 and 4 kHz frequencies (i.e. hearing loss meeting STS and other criteria laid out in 29 CFR 1904.10), there have also been efforts to understand and perhaps even regulate, noise injury based on TTS. For example, the Committee on Hearing, Bioacoustics, and Biomechanics (CHABA) proposed a limit for exposure to impulse noise (gunfire) based on generation of a specific amount of TTS, with the maximum allowable TTS defined as 10 dB at

1 kHz and below, 15 dB at 2 kHz, or 20 dB at 3 kHz and above (CHABA 1968, 1992). It has been suggested that these strategies have the potential for application to occupational noise as well. Specifically, Kryter et al. (1966) proposed that TTS_2 might serve as a measure "that will correlate with the ability of a single-day's exposure to produce a noise-induced, permanent threshold shift (NIPTS), if it is repeated on a near-daily basis, over a course of about ten years".

There are continued efforts to understand the extent to which TTS is predictive for a later PTS (Fritze 1981; Moshammer et al. 2015; Chan, Ho, and Ryan 2016). One potential application of this work is the screening of workers for TTS vulnerability to identify those at increased risk of PTS; this was suggested by Moshammer et al. (2015) based on their observation that workers with a larger TTS, as measured at least 10 min after a standardised noise exposure, also developed greater PTS during long-term follow-up (average follow-up time was 13 years, with testing at 3–5-year intervals). Taken together, although the cumulative effect of repeated daily occupational noise exposure on the auditory nerve currently remains unknown, it is clear that noise-induced cochlear synaptopathy has been observed in the absence of PTS in multiple animal models. If cochlear synaptopathy was to develop as a consequence of exposure to occupational noise, neither the threshold-based STS strategies mandated by OSHA nor the "red flag" early detection strategies recommended by NIOSH would be sensitive to IHC injury, cochlear synaptopathy or other hidden auditory nerve injuries (for additional discussion, see Kujawa and Liberman, 2009; Kujawa 2014; Kujawa and Liberman 2015; Liberman and Kujawa 2017). The translational relevance of cochlear synaptopathy to noise-exposed workers is a topic that remains actively under discussion (see Dobie and Humes 2017; Murphy and Le Prell 2017). While much of the literature on occupational NIHL is limited to threshold deficits, a number of studies include descriptions of ABR waveforms, perhaps providing an opportunity for potential insights into underlying noise-induced pathology.

Non-pathological TTS exposures

In studies in which rodent subjects have had a smaller TTS, i.e., a maximum of 20–30-dB TTS 24-hour post-noise, measurable synaptic pathology generally has not been documented (Hickox and Liberman, 2014; Fernandez et al. 2015; Jensen et al. 2015). Although it is appealing to infer that shorter or less intense exposures that result in these smaller TTS deficits are "safe" based on the lack of pathology in rodent models, the rodent studies have not been designed to allow broad conclusions regarding safety as they typically include only a single exposure. Because human exposures are likely to be repeated, from a practical perspective, an exposure is only "safe" if it can be repeated without injury emerging after subsequent exposures.

A small number of studies have combined repeated exposure paradigms with synapse counts in animal models (Wang and Ren 2012; Gannouni et al. 2015; Mannstrom, Kirkegaard, and Ulfendahl 2015). However, none of these repeated exposure paradigms were designed to provide insight into the effects of daily exposure to occupational noise over extended periods of time. Indeed, humans are likely to be exposed to intense sound repeatedly across their lifespan regardless of whether sound exposure is occupational, non-occupational or related to military service. Because the experimental data do not address whether repeated exposures, each resulting in a small, transient TTS, will ultimately result in permanent auditory nerve pathology akin to that associated with a single-larger TTS, the potential risk for human populations is a topic of interest.

Human cochlear synaptopathy: direct measurements and inferred pathology

The identification of noise-induced cochlear synaptopathy requires cochlear histology; thus, there are very few studies in which cochlear synaptopathy has been confirmed in humans. There is one report in which progressive age-related cochlear synaptopathy was suggested based on quantification of synapses in five human temporal bones from donors ranging in age from 54 to 89 years old (Viana et al. 2015). The observation of fewer synaptic connections in human temporal bones from older donors complements earlier reports describing age-related decreases in myelinated nerve fibres. Felder and Schrott-Fischer (1995), for example, reported an age-related loss of nerve fibres in nine temporal bones from eight temporal bone donors; this loss was in addition to the expected hair cell loss that was also observed. These early observations were extended by Makary et al. (2011), who documented selective age-related decreases in human cochlear spiral ganglion cell survival, in the absence of hair cell loss, in 100 temporal bones. The age-related neural and synaptic pathologies observed in human temporal bones parallel systematic observations of age-related cochlear synaptopathy in mice have not been exposed to noise and do not have other risk factors for hearing loss (Sergeyenko et al. 2013). The amplitude of Wave I of the ABR is highly correlated with synapse loss in mice (Sergeyenko et al. 2013). Thus, it is intriguing that age-related declines in ABR waveform amplitude in humans are well known from other human studies without histology components (Konrad-Martin et al. 2012; Skoe et al. 2015).

Speech-in-noise tests: a role in diagnosis of cochlear synaptopathy?

The role of IHC loss

The most commonly hypothesised functional effect of noise-induced neuropathic damage is difficulty understanding speech in noisy environments (Kujawa and Liberman 2009; Lin et al. 2011; Makary et al. 2011; see also the detailed discussions by Plack, Barker, and Prendergast 2014; Plack et al. 2016; Pienkowski 2017). Compelling evidence that selective loss of IHCs compromises hearing in noise was provided using carboplatin-induced lesions of the chinchilla IHC population in combination with a psychophysical tone in noise detection task (Lobarinas, Salvi, and Ding 2016). Consistent with this, Vinay and Moore (2007) interpreted elevated thresholds on the threshold equalising noise (specified as dB hearing level) [TEN(HL)] test as perhaps reflecting the loss of neural synchrony, as their participants were previously diagnosed with auditory neuropathy. During the TEN(HL) test, pure-tone targets are presented in background noise, with the background noise spectrally shaped to interfere with off-frequency listening (Moore et al. 2000; Moore, Glasberg, and Stone 2004). In contrast to these observations, modelling of the effects of synapse loss on basic perceptual tasks suggests that the effects of 50% loss of synapses would be barely measurable – for example, a just-noticeable difference of 1 dB is modelled to increase to 1.4 dB with 50% loss of synapses (Oxenham 2016). The recent detailed review by Carney (2018) argues against a direct role for cochlear synaptopathy in the coding of moderate to high-level speech sounds, pointing instead to

interactions between cochlear gain (by OHCs) and IHC saturation as well as central processing within the brainstem and midbrain.

The role of OHC loss

Because damage to the OHC population is often observed in parallel with neural or synaptic pathologies (for detailed review, see Hickox et al. 2017), the extent to which speech-in-noise test outcomes (or more generically, signal-in-noise test outcomes) will be influenced by OHC loss must be considered in parallel to considerations of the effects of cochlear synaptopathy. Measurements of auditory nerve discharge in response to vowel sounds (in animal models) clearly indicates that impairment of both the OHCs and the IHCs can contribute to degraded representation of speech sounds by the auditory nerve (Bruce, Sachs and Young 2003). There is also a fairly extensive literature that suggests OHC damage may directly contribute to speech-in-noise deficits (see, for example, Leger, Moore and Lorenzi 2012; Summers et al. 2013; Hoben et al. 2017). Indirectly supporting a role of the OHCs in perception of speech in noise, the MOC system, which modulates the OHC response to sound, may aid speech perception in noise (Kumar and Vanaja 2004).

Specifically probing the role of the OHCs, Lutman and Saunders (1992) reported no reliable differences in click-evoked OAEs when patients with complaints of difficulty understanding speech in noise (diagnosed as obscure auditory dysfunction) were compared to matched controls. As noted above, however, it is possible to obtain normal OAEs even in the presence of OHC damage, reducing confidence in assumptions that the OHC population had not been subtly damaged in the patients with obscure auditory dysfunction. Another possible approach is to use statistical techniques to account for OAE amplitude. For example, Ridley et al. (2018) assessed participants with diverse noise exposure and diverse thresholds using the TEN(HL) test and reported that deficits detecting tones in noise were greater than expected after statistically adjusting for the expected effects of threshold shift and OAE amplitude. Bramhall et al. (2015) also used statistical techniques to account for multi-variate interactions. They measured speech-in-noise using the Quick Sentences in Noise (QuickSin) test in addition to measuring the amplitude of Wave I of the ABR and found reduced ABR Wave I amplitudes as a function of increasing age. ABR Wave I amplitude was also associated with decreased performance on the QuickSin, but only in combination with poorer pure-tone thresholds. DPOAE data were not collected and the potential contributions of OHC loss are thus unknown.

The role of test difficulty

A major factor that must be taken into account in evaluating the literature for evidence of performance deficits is the specific perceptual task used in each investigation. A wide range of tests are available (for review and discussion, see Le Prell and Brungart 2016; Le Prell and Lobarinas 2016). Across tests, as the difficulty increases, performance of the participants decreases, and it is increasingly likely that subtle deficits will emerge even in normal hearing listeners when difficult listening tests are used (see Wilson, McArdle, and Smith 2007b).

One of the tests specifically targeted to children is the Bamford-Kowal-Bench Speech-in-Noise (BKB-SIN) test, in which the BKB sentence lists (Bench, Kowal, and Bambford 1979) are presented against four-talker babble with SNRs ranging from 21 dB SNR (easiest) to −6 dB SNR (hardest) (for review, see Etymotic Research 2005; Schafer 2010). Sentence levels systematically decrease from 96 dB SPL to 90 dB SPL, and the background babble level increases by 3 dB per sentence, making the test progressively harder with each additional sentence. A second commonly used sentence-based test is the Hearing in Noise Test (HINT), which also uses the BKB sentence-based speech materials, but with sentences presented at various sound levels in a background of spectrally matched masking noise presented at a fixed level of 72 dBA (Nilsson, Soli, and Sullivan 1994; Vermiglio 2008). The QuickSin is also a sentence-based test, with sentences presented at 70-dB HL, while the level of the four talker babble background is adjusted from 15-dB SNR (easiest) to 0-dB SNR (hardest) (Killion et al. 2004; McArdle and Wilson 2006). Finally, there are word-based tests, such as the Word in Noise (WIN) test. During testing with the WIN, NU-6 words are presented in multiple talker babble, with a female speaker against a background babble that includes six competing female voices. The babble is set at 80 dB SPL, and the target word levels decrease from 104 dB SPL (24 dB SNR) to 80 dB SPL (0 dB SNR) in 4-dB decrements, with five words per condition (Wilson, Carnell, and Cleghorn 2007a; Wilson and McArdle 2007). There are significant correlations with respect to performance across tests (Wilson, McArdle, and Smith 2007b). Although highly correlated, listeners typically do better on the BKB-SIN and the HINT (with sentences providing context) than the QuickSin or the WIN (which do not provide context from sentences) (Wilson, McArdle, and Smith 2007b). A suggested benefit of the WIN over the QuickSin is the reduced reliance on memory, cognition or other linguistic skills, as the participant repeats only the target word, rather than working to recall multiple words per sentence (Wilson, McArdle, and Smith 2007b).

Summary

The data generally suggest that damage to the OHCs and damage to the IHCs both have the potential to compromise speech-in-noise performance. To attribute deficits to cochlear synaptopathy, it is therefore necessary to exclude potential OHC pathology that could contribute to deficits on the speech-in-noise test, or otherwise correct for OHC dysfunction using statistical techniques. Caution is warranted as experimenters should assure deficits are related to poorer perceptual ability and not memory or cognition deficits. Taken together, the utility of speech-in-noise deficits as part of the differential diagnosis of the site of lesion within the organ of Corti remains questionable. As stated by Liberman and Kujawa (2017), this area of research is in its infancy, but is crucial to the translation of findings to humans.

Purpose of the current review

As outlined above, there is significant interest in the potential strategies for diagnosis of cochlear synaptopathy in human patients, and a need to define the risk factors for cochlear synaptopathy in humans. The issue of noise-induced cochlear synaptopathy has been discussed in the context of a public health issue, based on suggestions that much of the population is at risk given the prevalence of many common non-occupational leisure noise exposures (Jensen et al. 2015; Liberman 2015). The issue of noise-induced cochlear synaptopathy has also been discussed as a potential occupational health issue, in that the current noise regulations define a threshold-based monitoring approach that will not be sensitive for diagnosing cochlear

synaptopathy (Kujawa and Liberman 2009; Kujawa and Liberman 2015; Liberman and Kujawa 2017). Multiple research laboratories around the world have therefore initiated efforts to identify evidence that is consistent with cochlear synaptopathy and any accompanying supra-threshold deficits, with different electrophysiological tests and different functional tasks being used across laboratories and scientific teams (see data tables, below). The purpose of the summary tables provided in this review is to provide detailed information on study protocols and results within four specific topic areas: 1) the relationship between occupational noise exposure and ABR metrics, 2) the relationship between non-occupational noise exposure and ABR metrics, 3) the relationship between noise exposure history and speech-in-noise performance and 4) the relationship between noise exposure, TTS and ABR metrics.

Methods

Multiple PubMed literature searches were completed using diverse combinations of search terms including for example ABR and occupational noise, evoked potential and occupational noise, ABR and noise-induced hearing loss, evoked potential and noise-induced hearing loss, hidden hearing loss, cochlea and synaptopathy, noise-induced hearing loss and speech in noise, occupational noise and speech in noise, temporary threshold shift and hearing, temporary threshold shift and ABR, temporary threshold shift and evoked potential, temporary threshold shift and speech in noise, etc. PubMed is a free resource, developed and maintained by the National Center for Biotechnology Information at the National Library of Medicine. With more than 28 million citations available across thousands of journals, it provides a comprehensive search tool for articles dated back to at least 1966, with less consistent inclusion of references prior to that time. Although chapters, proceedings and government reports will not be identified via PubMed, peer-reviewed literature can be readily identified.

The author reviewed the resulting article title lists for relevance and carefully read abstracts of potentially relevant articles to determine whether the study included human participants with a history of noise exposure and then to confirm that the design included either sound-evoked auditory nerve response measurement (ABR or CAP) or a speech-in-noise test. All articles that appeared to be relevant were downloaded from the University of Texas at Dallas (UTD) library or requested through the UTD Inter-Library Loan service if the full-text was not available through the UTD library. Articles written in any language other than English were excluded from the full-text review. In addition to the PubMed search strategy, all full-text articles were reviewed for references to other published data relevant to the current review. Initial PubMed searches were completed in May of 2018; an additional search for new publications was completed in September 2018.

Noise exposure history was only grossly defined in the majority of the studies identified; in those cases where sound exposure levels or duration were provided by the authors, this information has been included in the data table. Although it would be helpful if noise exposures were characterised as short term/long term, continuous/intermittent/impulsive, single/repeated, with sound levels and sound spectra provided, very little information was provided in any of the retrieved studies discussed below. Variability in the accuracy of the noise exposure categorizations, including the accuracy of recall during the collection of self-reported noise exposure data, may contribute to differences in results across studies. Variable use of HPDs over the course of an occupational career, or across non-occupational events and activities, has the potential to influence deficits; reporting of HPD use is sporadic across reports, and even in those cases where HPD use was reported, it is not known if HPDs were used correctly or consistently.

Results

Relationship between occupational noise exposure and ABR metrics

A summary of the studies reporting ABR data for diverse noise-exposed worker populations is provided in Table 1. The most common test paradigm included the placement of electrodes on the forehead and mastoid and use of alternating polarity click stimuli. Stimulus presentation rates were variable, ranging from 10.3/sec to 71/sec. For the subset of studies reporting the total number of presentations averaged into the final response, 1024 and 2048 were most commonly reported. Only a small number of studies reported replication of the waveforms to assure repeatability. There was no consistent reporting convention for sound levels used during testing with five sound level measurement protocols (dB HL, dB nHL, dB SL, dB peSPL and dB SPL) used in the 13 reports listed in Table 1. As per Hall (1992, see Chapter 4: Effect of stimulus factors), the most common convention within a clinical setting is to report stimulus levels in dB nHL (dB relative to normal hearing population), but all five stimulus measurement strategies are appropriate. For typical click stimulus conditions (0.1 msec click presented at rate of 10–20/sec), a 0 dB nHL click would correspond to click levels of 36.4-dB peak SPL and 29.9 dB SPL (Hall 1992). If those conversion factors are applied to the sound levels listed in Table 1, then sound levels across studies were on the order of 70 dB nHL (Almadori et al. 1988; Chen, Chiang, and Chen 1992; Donaldson and Ruth, 1996; Thakur, Anand, and Banerjee 2004), 75 dB nHL (Attias and Pratt, 1984; Konrad-Martin et al. 2012), 80 dB nHL (Samelli et al. 2012; Karawani et al. 2015; Pushpalatha and Konadath, 2016) or 90 dB nHL (Attias et al. 1996; Noorhassim, Kaga, and Nishimura 1996; Xu et al. 1998).

Across studies, there were multiple reports that the latency for Waves I, III, and/or V were delayed in workers exposed to noise, with a smaller number of studies measuring or reporting the amplitude for Waves I, III or V. One exception to this pattern of results was observed for the professional musicians assessed by Samelli et al. (2012), with no significant deficits in ABR Waves I, III or V detected in professional musicians with or without hearing loss. A small number of additional studies assessed ABR metrics in military populations with a significant noise exposure history, but the effects of noise could not be readily extracted. First, a study by Attias et al. (1996), assessing the relationships between ABR amplitude and tinnitus, did not include a noise-free control group. Second, a study by Konrad-Martin et al. (2012), assessing the relationships between ABR amplitude and aging, reported that noise exposure was included in the statistical model, but the effects of noise were not specifically reported or discussed.

Although prolonged ABR waveform latencies were commonly reported across studies, most of these studies also reported that the noise-exposed worker cohorts had significant hearing loss. The presence of a permanent NIHL suggests OHC pathology accompanied any neuropathic change that might potentially be inferred from the ABR latency increases and other atypical ABR

Table 1. Relationship between occupational noise exposure and auditory brainstem response (ABR) metrics.

Author	Participants	Noise Exposure/Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Attias and Pratt (1984)	31 new employees, ages 18–21	Continuous engine noise of 112–117 dB(A) for 8 h/day; subjects self-reported HPD use	PTS at 4 kHz developed over 14 months	Not included	Forehead and mastoid electrodes; alternating polarity clicks; 10 and 55/sec, 75 dB HL, 1024 repetitions averaged, waveforms replicated Wave-I latencies prolonged after 14 months, at both 10 and 55/sec rates; Waves III and V were delayed only with 55/sec rate	Not included
Almadori et al. (1988)	54M patients ages 25–51 years with presumed NIHL; 15 age matched controls	At least 5-year occupational noise exposure	Bilateral and symmetric hearing loss in the 1–4 kHz range, ranging from less than 20 dB to 50–71 dB	Not included	Alternating polarity clicks; 21 and 51/sec, 70 dB nHL, 2048 repetitions averaged Latency values within normal limits for waves I, III, V Wave I missing in 10 cases, generally observed in ears with more hearing loss	Not included
Chen, Chiang, and Chen (1992)	112 employees (92M, 20F) ranging in age from 20–50 years and working at an airport in Kaohsiung, Taiwan; controls were 13M, 6F ranging in age from 25–45 years	Exposures were distributed across maintenance workers ($n = 23$), firemen ($n = 20$), policemen ($n = 24$), airline ground staff ($n = 34$) and civil servants ($n = 14$)	High frequency hearing loss observed in 65% of maintenance workers, 55% of firemen, 42% of policemen, 32% of ground staff, and 0% of civil servants.	Not included	Alternating polarity clicks; 13.3/sec, 70 dB SL, 2048 repetitions averaged Wave V latency values significantly prolonged in maintenance workers and firemen.	Not included
Attias et al. (1996)	13M career military personnel with NIT ages 21–45 years, 11 matched controls without NIT	All subjects were military personnel with well documented history of noise exposure	Notched audiometric configuration in both groups	Not included	Scalp and mastoid electrodes; 100 μsec alternating polarity clicks; 10.3/sec, 120 dB peSPL, 1024 repetitions averaged ABR Wave III amplitude larger in participants with tinnitus; no inclusion of noise-free control – effects of noise cannot be determined	Not included
Donaldson and Ruth (1996)	9M, 1F ages 33–54 years; normative data derived from Donaldson and Ruth (1993)	"significant history of noise exposure"	Slight, mild, or moderate hearing loss consistent with NIHL	Not included	Forehead and mastoid electrodes; 65 dB nHL (99 dB peSPL) rarefaction clicks; 27/s. Maskers presented at 57 dB SPL spectrum level, equivalent to 95 dB SPL in the wideband condition Noisier and less repeatable waveforms in NIHL group in both high-pass and band-pass conditions	Not included
Noorhassim, Kaga, and Nishimura (1996)	22M ranging from <50 years to >70 years old; mean = 62.1±9.9 yrs	Occupational exposure >90 dB(A), <10 years to >20 yrs exposure	All subjects had permanent NIHL	Not included	Forehead and mastoid electrodes; clicks; 10/sec, 90-100 dB HL, two replicated runs Eight ears (18.2%) with prolonged Wave-I latency; eight ears with missing Wave-I Ears with missing Wave-I were more likely to be from participants with severe hearing loss	Not included
Xu et al. (1998)	22M with NIHL ages 37–64 years (mean = 51 years), and 21M controls with an average age of 41 years	Various industries >85 dB(A), 10–40 years	SNHL at 4 kHz, with or without hearing loss at 1, 2 and 3 kHz	TEOAE with click at 85 dB, 260 sweeps;	Alternating polarity clicks; 21.3/sec, 90 dB nHL Wave I/V amplitude ratios decreased with increasing SNHL	Not included

(*continued*)

Table 1. Continued.

Author	Participants	Noise Exposure/Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
				TEOAE disrupted	Presence of Wave I decreased with increasing SNHL	
Fabiani et al. (1998)	130 athletes (104M, 26F) (mean age ~30 yrs old); 77 had thresholds ≤25 dB HL; 53 had thresholds ≥30 dB HL at one or more frequencies from 2–8 kHz	Athletes belonged to Italian National Teams of trap-shooting (FITAV), target shooting, (UITS), modern pentathlon, (FIPM) and triathlon (FISI)	Hearing loss was prevalent in sport shooters, including 35 athletes with severe high frequency hearing loss	Not included	Clicks; 24/sec, 100 dB SPL; 2000 responses averaged Latency of Waves I-V was measured but amplitude was not; ABR was absent in 19 ears and Wave V was delayed in 12 ears. Central and peripheral pathology inferred, and described as "hidden" behind the hearing loss	Not included
Thakur, Anand, and Banerjee (2004)	38M workers at Air India, Mumbai airport; 24 exposed to noise (mean age 48 years) and 14 controls (mean age 43 yrs)	24M with occupational exposure of 95–110 dB(A) for 7–8 hrs/day over 15–30 years; controls not exposed to noise exceeding 80 dB(A)	The majority of noise-exposed workers had mild or moderate hearing loss at 4 or 8 kHz, with no hearing loss in controls	Not included	Vertex and earlobe electrodes; 100-μsec clicks; 15/sec, 70 dB SL, 2000 repetitions averaged with repetition to assure repeatability ABR Wave III latency delayed in participants with noise exposure; ABR Wave V/I ratios not reliably different	Not included
Konrad-Martin et al. (2012)	131 veterans, age 26–71 years; mostly male sample with very few females	Noise index created from questionnaire on noise and HPD use in military, occupational, and recreational settings	Thresholds were <40 dB HL at 2 kHz, and <70 dB HL at 4 kHz	Not included	Mastoid and forehead surface electrodes; 100-μsec alternating polarity clicks; 11, 51, and 71/sec rates, 110 dB SPL, 1024 repetitions collected twice to verify replication then all 2048 runs averaged. Age related decreases in amplitude and increases in latency were detected for waves I, III, and V, with greatest effects of age observed at 11/sec rate; noise included in model but effects of noise not discussed in detail	Not included
Samelli et al. (2012)	32M aged 18–45 years with thresholds no poorer than 40 dBNA from 0.25–8 kHz no poorer; musicians subdivided as normal or hearing loss	16 professional musicians belonging to rock/pop bands for more than 5 years and having at least 2 h/wk exposure to amplified music; 16 controls	Musicians with hearing loss had poorer hearing at 2, 3, 12.5, 14, 16 and 18 kHz, relative to musicians without hearing loss and non-musician controls	TEOAE with clicks presented at 78–83 dB peSPL, 200 sweeps/ear; musicians poorer at 1, 1.5, 2, 3 and 4 kHz.	Mastoid and forehead surface electrodes; 0.1-μsec alternating polarity clicks; 19/sec rates, 80 dB nHL dB SPL, 2000 repetitions. No significant differences in ABR amplitude or latency for Waves I, III, or V.	Not included
Karawani et al. (2015)	82 workers with an average age of 38 years	Exposure was a combination of industrial (continuous noise exposure) and military (impulsive noise exposure); all participants were enrolled in annual audiometric monitoring programme	25 workers had normal hearing (thresholds ≤20 dB HL from 0.25–8 kHz); 57 workers had bilateral symmetrical NIHL including thresholds of 25 dB HL or poorer and notched configuration	Not included	Forehead surface electrode and two earlobe electrodes; 100-μsec rarefaction clicks and 1 and 2 kHz tone bursts; 13.3/sec, 80 dB HL decreasing to threshold, minimum of 2000 repetitions per level with more repetitions near threshold. In 24 ears with profound NIHL, brainstem responses to clicks and tone bursts could not be recorded, although auditory steady-state	Not included

(*continued*)

Table 1. Continued.

Author	Participants	Noise Exposure/Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
					responses (ASSR) were able to be obtained.	
Pushpalatha and Konadath (2016)	20M individuals ages 20–45 years, exposed to occupational noise; 20 control	Occupational noise exposure >85dB(A) for 0–5 years, 5–10 years, or >10 years	All hearing thresholds within 25 dB HL	Not included	Forehead and mastoid electrodes; clicks and CE-chirps; 11.1/sec, 80 dB HL Clicks: Wave-III amplitude smaller and latency delayed, Wave-V amplitude reduced. Chirps: Waves I, III, V latencies delayed; wave-V amplitude decreased	Not included

results listed in Table 1. Decreased DPOAE amplitude is well documented in noise-exposed populations (Seixas et al., 2004; Korres et al. 2009; Seixas et al. 2012; Boger, Sampaio, and Oliveira 2017). As seen in Table 1, many of the studies employing ABR metrics to assess potential effects of occupational noise exposures did not include the parallel collection of DPOAE data, complicating the interpretation of the observed changes in ABR amplitude and latency.

The clinical utility of DPOAEs was not generally recognised prior to the 1990s (Lonsbury-Martin and Martin, 1990), and thus, it is not surprising that DPOAEs were not conducted at least in the earlier studies listed within Table 1. Nonetheless, with stimulus levels of 70–100 dB nHL (i.e., approx 100–130 dB SPL), the studies listed in Table 1 presumably used stimuli that were sufficiently intense to stimulate IHCs and trigger neural firing directly via the passive mechanics of the basilar membrane. At these sound levels, the passive mechanics of the cochlea dominate after the active process has saturated (see models and discussion in Johnstone, Patuzzi, and Yates 1986), and thus one might speculate that neural pathology contributed to delayed ABR latencies and reduced ABR amplitudes, even if permanent threshold deficits were caused by undocumented OHC loss. Although speculative, this interpretation is consistent with the conclusion by Hickox et al. (2017) that OHC loss and cochlear synaptopathy are likely to occur in parallel. Given this interpretation of potential neural pathology in workers exposed to occupational noise, pre-clinical research in animal models should directly assess the potential for synapse loss with lower level repeated exposures modelled after occupational noise. Longitudinal studies of workers would also be helpful in determining effects of noise on the auditory nerve in workers exposed to occupational noise. Variation in vulnerability to NIHL is considerable in humans (see for example the 10th versus the 90th percentiles in International Standard Organization 2013) and variability is also well documented in animal models (Maison and Liberman 2000).

Relationship between non-occupational noise exposure and ABR metrics

Table 2 summarises methods and results from studies assessing potential cochlear synaptopathy in human participants using ABR Wave I amplitude as a metric. Whereas studies of cochlear synaptopathy in rodent models have typically relied on short-term noise exposure paradigms that induce a large TTS lasting at least 24 hours, many of the sounds that human populations are commonly exposed to are likely to induce a smaller and shorter duration TTS. Changes in hearing in those attending concerts or clubs are commonly on the order of 10 dB immediately after the event (Opperman et al. 2006; Derebery et al. 2012; Ramakers et al. 2016). Moreover, threshold recovery is likely to be complete within 24 hours of the event for most attendees (Grinn et al. 2017). Concerns about the hazards of the repetition of such exposure, in combination with other intense sound encountered on a regular basis, led Liberman (2015) to suggest that the cochlear synaptopathy observed in animals "raises questions about the risks of routine exposure to loud music at concerts and clubs and via personal listening devices". Similarly, Jensen et al. (2015) pointed to the increasing sales of portable listening devices and similarly suggested a population of at-risk adolescents based on the use of such devices. As per Table 2, this has resulted in a number of relatively more recent investigations focussing on

Table 2. Relationship between non-occupational noise exposure and auditory brainstem response (ABR) metrics.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Schaette and McAlpine (2011)	33 young adult females with or without tinnitus (average age within groups was 33 to 36 yrs old); participants had thresholds ≤20 dB HL from 0.125–8 kHz	Noise exposure history was not assessed	Five participants with tinnitus and three controls were unable to hear 16 kHz. Effects of noise on functional metrics could not be determined as noise exposure was not surveyed	Not included	Electrodes placed on both mastoids and on the high forehead. 50-μsec clicks; 11/sec, 90 and 100 dB SPL, minimum of 6000 repetitions averaged. ABR Wave I amplitude was significantly smaller in the tinnitus group; no differences were observed in Wave-V. Effects of noise on evoked potential amplitude could not be determined as noise exposure was not surveyed	Not included
Stamper and Johnson (2015a)	30 young adults (10M, 20F) ages 19 to 28 years (mean = 22.8 yrs) with thresholds ≤20 dB HL from 0.25–8 kHz	$L_{AEQ8760}$ assessed via NEQ: mean = 74.6, range = 67–83	.25–8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity	DPOAE at 1–4 kHz, 50–80 dB FPL: No statistically significant relationships between DPOAE amplitude and threshold	TM and Mastoid used for noninverting electrode; inverting electrode at forehead and ground at contralateral mastoid. 100-μsec clicks and 4 kHz tones; 11.3/sec, 70–90 dB nHL, two runs of 2000 repetitions, averaged. Statistically significant correlations between $L_{AEQ8760}$ observed when tests were conducted with mastoid electrodes but not TM electrodes. When reanalysed accounting for sex differences, effects limited to females (Stamper and Johnson2015b).	Not included
Liberman et al. (2016)	34 participants (19M, 15F) ages 18-41 yrs with thresholds <20 dB HL from 0.25 –8 kHz	Subjects divided as high-risk (15M, 7F) or low-risk (4M, 8F) based on self-reported exposure to sound and use of HPDs	High-risk group showed significant threshold elevation at all test-frequencies above 8 kHz	DPOAE at 0.5–12 kHz using F1 = 65/ F2 = 55 dB; DPOAEs present in all subjects with no significant group difference in amplitude	Extra-tympanic gold-foil wrapped electrodes with ground on forehead; 100-μsec alternating polarity clicks; 9.1 or 40.1/sec, 94.5 dB nHL. Statistically significant increase in SP in high-risk cohort, no reliable differences in AP; SP/AP ratio increased in high risk group	See Table 3
Bramhall et al. (2017)	100 participants ages 19–35 years with thresholds <20 dB HL from 0.25–8 kHz; 64 participants (37M, 27F) included in final analysis.	Subjects interviewed regarding occupational, military, and recreational lifetime noise history, and use of HPDs, using LENS-Q; subjects divided into four veteran/non-veteran and high-noise/low-noise subgroups	Veterans with high noise exposure had threshold elevations of ∼5 dB for 3, 4 and 6 kHz PTA; statistical comparisons not reported and threshold not included in Bayesian analysis of factors influencing ABR measurements	DPOAEs screened from 1.5–6 kHz; DPOAE amplitude not reliably different across groups	Extra-tympanic gold-foil wrapped electrode with reference on high forehead and ground on low forehead; tonebursts varied in duration and level across frequencies (1, 3, 4 and 6 kHz); 11.1/sec, all tones included 110 dB p-pe SPL condition, some included 60, 70, 80, 90 and 100 dB p-pe SPL. ABR Wave-I amplitude reduced in veteran high noise and non-veteran firearm group at 110 dB p-pe SPL across frequencies with no differences in the amplitude of waves III or V.	Not included
Fulbright et al. (2017); for additional discussion see Fulbright (2016)	60 participants (26M, 34F) from 18-28 yrs old with thresholds ≤25 dB HL from 0.25 – 8 kHz	$L_{AEQ8760}$ assessed via NEQ: mean = 78.6, range = 64-87 Post-hoc analysis included assignment to high-risk and low-risk groups based on self-report	.25-8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity	DPOAE screened from .5-8 kHz using F1 = 65/F2 = 55 dB SPL, and F1 = 53/ F2 = 35 dB SPL: DPOAE amplitude not reliably related	Electrodes placed at high and low forehead and ipsilateral earlobe; 100-μsec rarefaction clicks; 21.1/sec, 70, 80, 90, and 99 dB nHL, minimum of 2000 repetitions. Tones were 4 kHz alternating polarity, 27.1/sec, 90 dB nHL; electrode configurations included earlobe electrode as per clicks, and	See Table 3

(*continued*)

Table 2. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
		of a previous TTS after a loud event.		to noise exposure history.	tiptrode ear canal electrode. Females had larger Wave I amplitudes than males. No relationships between noise exposure history and ABR Wave-I amplitude were detected. No differences between high risk and low risk groups were detected.	
Grinn et al. (2017)	32 participants (13M, 19F) from 21-27 yrs old with thresholds ≤25 dB HL from 0.25 – 8 kHz	$L_{AEQ8760}$ assessed via NEQ: mean =79.3, range =57-87	.25-8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity.	DPOAE screened from 1-8 kHz using F1 = 55/F2 = 45 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	Tiptrode ear canal electrodes placed in both ears and electrodes placed at high and low forehead; alternate polarity clicks and 2, 3, and 4 kHz tone bursts; 11.7/sec, 70, 80, 90, and 99 dB nHL, 500 repetitions with replication. Females had larger Wave I amplitudes than males. No relationships between noise exposure history and ABR Wave-I amplitude were detected.	See Table 3
Prendergast et al. (2017a)	126 participants (51M, 75F) ages 18-36 yrs with thresholds <25 dB HL from 0.25 – 8 kHz	Lifetime noise exposure questionnaire modified from Lutman et al. (2008)	No statistically significant relationships between noise exposure history and threshold sensitivity from 0.25 to 8 kHz; 16 kHz thresholds elevated as a function of noise history in females, but not males	TEOAEs screened from 1.5-4 kHz at 83 dB peSPL; TEOAE amplitude not reliably related to noise exposure history	Electrodes placed at high forehead, seventh cervical vertebra and both mastoids; 100-μsec alternating polarity clicks; 11/sec, 80 and 100 dB peSPL presented dioticly; 7480 repetitions per stimulus condition. Females had larger amplitudes and shorter latencies than males. No relationships between noise and ABR amplitude or latency were detected. No relationships between noise and ABR Wave I:V amplitude ratio were detected	Described in Prendergast et al. (2017b); see Table 3
Spankovich et al. (2017); for additional discussion see Spankovich (2010)	40 participants (18M, 22F) from 18-28 yrs old with thresholds <25 dB HL from 0.25 – 8 kHz; participants with type 1 diabetes mellitus were included as high risk group	$L_{AEQ8760}$ assessed via NEQ: mean = 74.1, range = 66-83 Noise Exposure History (NEH) (modified from Neitzel et al., 2004a; 2004b; Seixas et al.,2004), General Noise Survey (GNH) (following Jokitulppo et al.,1997; 2006), and Adolescents Habits and Hearing Protection Use (AHH) (see Olsen,2004) also used.	.25-8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity	Click-evoked TEOAEs screened at 80 dB peak SPL; TEOAE amplitude not reliably related to noise exposure history. DPOAE screened from .5-8 kHz using F1 = 65/F2 = 55 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	Four electrode montage including vertex, both ears, and high forehead; 100-μsec clicks; 27.7 and 77.7/sec, 50, 65, and 80 dB nHL, 2048 repetitions, at least two runs averaged. Females had larger amplitudes and shorter latencies than males. No relationships between noise and ABR amplitude or latency were detected; no relationships between noise and wave V/I ratio were detected.	Not included
Grose, Buss, and Hall (2017)		Self-reported event attendance: High	The only observed relationship was poorer threshold	DPOAE screened from .5–8 kHz using	Tiptrode ear canal electrodes placed in both ears and electrodes placed at	See Table 3

(*continued*)

Table 2. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
	61 participants (32M, 29F) ages 18–35 years with thresholds ≤20 dB HL from 0.25–8 kHz	Noise group included 31 participants (21M, 10F) who had attended ≥ 25 loud music events in past year, and ≥ 40 loud music events in past two years. The control group included 30 participants (11M, 19F) with median 2-year event attendance of 4 loud events (range =0–30 loud events)	sensitivity at 16 kHz in the High Noise group; no statistically significant differences were observed from 0.25–11.2 kHz.	F1 = 65/F2 = 55 dB SPL; additional L1 and L2 levels were: 65:65, 63:60, 61:55, 59:50, 57:45, 55:40, 53:35, 51:30, 49:25 and 47:20: DPOAE amplitude was not reliably different between the two noise exposure groups.	high and low forehead; 100-μsec alternating polarity clicks; 7.7/sec, 95 and 105 dB nHL, 2048 repetitions with replication were run. ABR Wave-I amplitude had a larger average value in the control group, although the difference was not statistically significant. After normalising as Wave I/V ratio, there was a statistically significant difference with controls having a larger I/V ratio than high noise participants.	
Prendergast et al. (2018)	30 female participants ages 19–34 years with thresholds <25 dB HL from 0.25–8 kHz	Lifetime noise exposure questionnaire modified from Lutman, Davis, and Ferguson (2008), and described in Guest et al. (2017); subjects were divided into high noise and low noise groups.	The high-noise group had higher (poorer) thresholds at 16 kHz in the left ear but not the right ear; ABRs were acquired from the right ear.	DPOAEs screened from 1 -8 kHz at 70 dB SPL; DPOAE amplitude was not reliably different as a function of noise exposure history.	Electrode placed at high forehead and contralateral mastoid; reference electrode was either earcanal Tiptrode or ipsilateral mastoid. Stimuli: 100-μsec alternating polarity clicks; 11/sec, 80 dB nHL (115.5 dB peSPL); minimum of 6000 repetitions per stimulus condition. No relationships between noise exposure history and ABR Wave-I amplitude, wave-V amplitude or SP amplitude were detected. No relationships between noise exposure history and SP/AP amplitude were detected. ABR Wave-I amplitude was highly reliable; neither SP nor SP/AP ratio were reliably replicated.	Not included
Skoe and Tufts (2018)	73 participants ages 18–24 years with thresholds ≤25 dB HL from 0.25–8 kHz	Participants wore a dosimeter for one week and were grouped as low noise (10M, 19F; average daily dose ≤ 20%), moderate noise (average daily dose between 20 and 100%), or high noise (4M, 22F; exposures exceeding 100% on two or more days).	There were no statistically significant differences in threshold sensitivity from .125 to 8 kHz for low noise versus high noise groups.	Not included	Electrodes placed at vertex, forehead, and right earlobe; 100-μsec rarefaction clicks; 3.4, 6.9, 10.9, 15.4, 31.25, 46.5, 61.5 and 91.24/sec, 75 dB nHL, at least 2000 repetitions were run. ABR Wave-I could not be resolved in a subset of participants when rates were ≥ 46.5/sec. There were no statistically significant differences in amplitude of ABR Waves I, III, or V for high-noise and low-noise groups, even when controlling for sex. Latency of ABR Waves I, III and V was later in high-noise than low-noise groups, with biggest differences observed at Wave-V.	Not included

(*continued*)

Table 2. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Valderrama et al. (2018)	74 participants (37M, 37F) from 29–55 yrs old; 84% had normal thresholds (≤20 dB HL from 0.25–6 kHz) and 12% had near normal thresholds (≤25 dB HL up to 2 kHz, ≤30 dB HL at 3 kHz, _ 35 dB HL at 4 kHz, and ≤ 40 dB HL at 6 kHz. Thresholds were assessed to 12.5 kHz.	Lifetime noise exposure was calculated using online surveys that assess both occupational and leisure noise (following Beach et al., 2013; Yeend et al., 2017)	.25–12.5 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity; Although noise exposure history and high frequency thresholds were not related, poorer high frequency thresholds were related to poorer speech-in-noise performance and greater self-reported listening difficulty.	DPOAE screened from 1–12 kHz using F1 = 65/F2 = 55 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	Electrodes placed at high forehead, middle forehead, ipsilateral mastoid, and ipsilateral gold TIPtrode in ear canal. Stimuli: 113-μsec rarefaction clicks; 39.1/sec, 108.5 dB peSPL (75 dB nHL); 12,500 repetitions per stimulus condition. There were statistically significant associations between lifetime noise exposure and ABR Waves I, III, and V amplitudes and latencies. The authors cautioned that significant individual variability was observed and statistical significance relied on inclusion of a single subject with extremely low noise exposure and very large ABR waveform amplitudes.	See Table 3
Bramhall et al. (2018)	74 participants ages 19–35 yrs; this report describes a subset of participants assessed by Bramhall et al. (2017).	Subjects interviewed regarding occupational, military, and recreational lifetime noise history, and use of HPDs, using LENS-Q; LENS-Q noise score not considered as part of analysis.	All participants had thresholds <20 dB HL from 0.25–8 kHz; thresholds not included in analysis.	All participants had normal DPOAEs. DPOAEs averaged from 3–8 kHz were not correlated with Wave-I amplitude at 4 kHz.	Extra-tympanic gold-foil wrapped electrode with reference on high forehead and ground on low forehead; 4 kHz toneburst; 11.1/sec, 110 dB p-pe SPL. The probability of reporting tinnitus increased as Wave I amplitude decreased.	See Table 3
Ridley et al. (2018)	33 participants. 13 participants (6M, 7F) ages 23-48 years old had normal hearing (≤15 dB HL from 0.25–8 kHz). 20 participants ages 35–64 years old (10M, 10F) had SNHL (thresholds >15 dB at 4 kHz).	$L_{AEQ8760}$ assessed via NEB: mean =75.2, range =66.8–86.5		DPOAE screened at F2 = 1 kHz and F2 = 4 kHz using F1 = 61 dB SPL and F2 = 55 dB SPL. DPOAE amplitude was correlated with threshold.	Electrodes placed at vertex, forehead, and in the ear canal (Tiptrode); 1 and 4 kHz tonebursts; 27/sec, 80 and 100 dB peSPL, at least 4000 repetitions were run. SP was identified by two waveform reviewers working together as SP was difficult to identify. There were no statistically significant differences in amplitude of ABR Waves I, III, or V for high-noise and low-noise groups, even when controlling for sex. Latency of ABR Waves I, III, and V was later in high-noise than low-noise groups, with biggest differences observed at Wave-V.	See Table 3

participants with less noise exposure, better hearing thresholds and intact DPOAE function.

Consistent with the results summarised in Table 1, the most common test paradigm involves placement of electrodes on the forehead and mastoid and use of alternating polarity click stimuli, although the use of foil-wrapped "TipTrode" ear canal electrodes is increasingly common and a number of studies now include tone bursts in addition to click stimuli. The total number of presentations averaged into the final response was highly variable across studies, with stimulus averaging ranging from 500 (Grinn et al. 2017) to 12,500 (Valderrama et al. 2018). As discussed by Valderrama et al. (2018), averaging across larger numbers of stimulus presentations improves data quality, with improved signal to noise ratios (SNR) for waveforms. According to Hall (1992), the most robust improvement in SNR is obtained over the initial 1000 sweeps (from the start of averaging to the completion of 1000 sweeps), with lessor improvement from 1000 to 2000 sweeps. However, near threshold, as many as 4000 sweeps may be necessary to accurately distinguish small neural responses from the noise floor (for discussion see Chapter 5, Effect of acquisition factors, in Hall 1992).

Stimulus rates were also highly variable. Although most studies used either 11/sec or 27/sec rates, Skoe and Tufts (2018) assessed responses with stimulus presentation rates ranging from 3.4/sec to 91.24/sec. For click rates of 3.1 to 21.1/sec, AP amplitude and latency should be relatively constant, but amplitude progressively decreases and latency progressively increases as click rates increase from 31.1 to 91.1/sec (Hall 1992; for illustration of these changes, see his Figure 4–21). Effects of click rate on ABR Wave I amplitude and latency are similar; responses are generally equivalent when click rates are below 20/sec but as click rates increase, amplitude and latency progressively change for Waves I, III and V (Hall, 1992; for illustration of these changes, see his Figure 4–22).

As shown in Table 2, there have been mixed results across studies assessing potential relationships between non-occupational noise exposure and ABR Wave I amplitude. Several studies assessing this phenomena obtained results that were consistent with synaptic and/or auditory nerve pathology based on observations of decreased ABR Wave I amplitude as a function of noise exposure (Stamper and Johnson, 2015a; Bramhall et al. 2017; Valderrama et al. 2018). The decreased Wave I amplitudes observed by Stamper and Johnson (2015a) were generally attributed to recreational noise, which was estimated based on self-reported exposure in the past 12-months. The decreased Wave I amplitudes observed by Valderrama et al. (2018) were observed in association with increasing lifetime noise exposure, which accrues both as a function of leisure and work-related activities, although the relationship was no longer statistically significant if a single outlier was removed from the analysis. In contrast, the decreased Wave I amplitudes reported by Bramhall et al. (2017) were generally attributed to recreational firearm use (civilians) or service-related firearm use (military personnel), with participants distributed into four discrete groups based on use of firearms and exposure to other intense sound.

In addition to reports of associations between Wave I amplitude and historic noise exposure, data expressed as normalised evoked potential metrics (such as the SP/AP ratio, and ABR Wave V/I ratio) have been interpreted as reflecting potential noise-induced cochlear synaptopathy and/or auditory nerve pathology (Liberman et al. 2016; Grose, Buss, and Hall 2017). The decreased SP/AP ratios observed by Liberman et al. (2016) were generally attributed to musical rehearsals and performance associated with enrolment in a music conservatory, whereas the decreased Wave V/I ratios reported by Grose, Buss, and Hall (2017) were specifically attributed to frequent concert attendance (which was one component of the enrolment criteria). In another recent study with normal hearing participants, the latency of the ABR waveforms was delayed even though amplitude did not appear to have been affected by previous noise exposure (Skoe and Tufts 2018); participants in this investigation were distributed within low-noise and high-noise groups based on the results of one-week of body worn dosimetry data collection.

In contrast to these positive results, a number of other studies have not found evidence of decreased ABR Wave I amplitude or changes in latency as a function of either lifetime noise exposure or the previous 12-month exposure period. In studies completed by Spankovich et al. (2017), Fulbright et al. (2017), Grinn et al. (2017) and, most recently, Ridley et al. (2018), noise exposure was estimated following Stamper and Johnson (2015a), with noise exposure over the previous 12 months surveyed using the Noise Exposure Questionnaire (NEQ) and changes from previous years queried. No relationships between noise exposure and Wave I amplitude were detected in any of these studies. A comprehensive series of studies completed at the University of Manchester used detailed interview data to calculate a single comprehensive lifetime noise score (Guest et al. 2017; Prendergast et al. 2017; Prendergast, Millman et al.,2017b; Guest et al. 2018; Prendergast et al. 2018). No relationships between noise exposure and Wave I amplitude were detected in any of these studies. As part of the comprehensive analysis by Prendergast et al. (2017a), it was noted that initial observations suggested that ABR wave V latency increased with increasing noise exposure (for the 80 dB peSPL click) and that frequency following response (FFR) signal-to-noise ratios decreased as a function of noise exposure (in males but not females), but neither of these correlations remained significant after controlling for the effects of age. Given observations of age-related synaptopathy in the absence of noise exposure, it is critical to adjust for age when samples with a wide age range are recruited. As per Table 2, most studies have recruited participants in their 20's–30's, with a smaller number of studies enrolling participants in their 40's or 50's.

Relationship between noise exposure and speech-in-noise performance

The most commonly hypothesised functional effect of noise-induced neuropathic damage is difficulty understanding speech in noisy environments (Kujawa and Liberman 2009; Lin et al. 2011; Makary et al. 2011; see also the detailed discussions by Plack, Barker, and Prendergast 2014; Plack et al. 2016; Le Prell and Clavier 2017; Pienkowski 2017; Le Prell 2018). Table 3 therefore includes a summary of studies that have assessed the relationships between speech-in-noise and noise exposure history. Although some of these studies included ABR assessments (and those studies are therefore repeated from Table 2), the collection of ABR data was not required for inclusion in Table 3. The literature search strategy for Table 3 was specifically based on speech-in-noise deficits analysed as a function of noise exposure history. If other signal-in-noise tests were completed in parallel with speech-in-noise tests, those results are also listed in Table 3. However, a systematic search and review of outcomes across all articles reporting signal-in-noise outcomes were outside the scope of the current review and studies that included signal-in-noise tests, but not speech-in-noise tests, are not included here.

Table 3. Relationship between noise exposure history and speech-in-noise test metrics.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Alvord (1983)	20 participants: 10 Male subjects ages 23–57 years working in high noise occupations; 10 controls (7M, 3F) ages 30–58 years reported no history of intense noise exposure	High noise occupations included jet mechanics, firing range instructors, and helicopter crew members;	Threshold sensitivity was ≤20 dB HL from .25–4 kHz and ≤30 dB HL at 8 kHz; noise-exposed participants had 5–10 dB poorer thresholds across all tested frequencies.	Not Included	Not Included	Monosyllabic words were presented at 60 dB HL with background noise set for 10 dB SNR. There was a statistically significant difference between groups, with the controls achieving ∼80% correct performance whereas the noise-exposed group had ∼70% correct performance.
Kujala et al. (2004)	20 participants ages 20–36, including 10 noise-exposed participants (9M, 1F) and 10 control participants (9M, 1F)	Noise-exposed participants worked in shipyard ($n = 8$, 95–100 dB(A), HPDs worn) and day-care ($n = 2$, 67–75 dB(A), no HPD use). Controls worked in quieter jobs.	No statistically significant group difference detected; threshold data were not presented and no enrolment criteria were listed.	Not Included	Not Included	Subjects performed complex visual tracking task while distractor syllable (/pa/) was repeated. Subjects' responded as quickly as possible when presented with a deviant syllable (/ka/) or novel sound (telephone ringing, door slamming, etc.). The stimulus level was 70 dB SPL; white noise background was delivered at 15 dB SNR. The noise-exposed workers did more poorly on the visual tracking task and had poorer signal in noise identification as shown by fewer correct target detections (69% hit rate versus 42% hit rate).
Stone, Moore, and Greenish (2008)	A subset of 26 participants aged 16–47, including 6 noise-exposed participants (5M, 1F) and 10 control participants (5M, 5F). Thresholds were ≤ 15 dB HL at enrolment	Noise-exposed participants went to concerts and clubs (>105 dB(A) for ≥45 min at least once/ week without hearing protection). Controls had only occasional event attendance.	No statistical comparisons reported; threshold data presented in report reveal ∼5 dB better thresholds in noise-exposed participants at 4 kHz.	Not Included	Not Included	Subjects discriminated Gaussian noise from low-noise noise which had same long-term power spectrum but less amplitude (envelope) fluctuation. The noise-exposed participants performed more poorly than controls at sensation levels below 20 dB SL, with no group differences at higher sound levels.
Kumar, Ameenudin, and Sangamanatha (2012)	118 participants: 28 noise exposed workers ages 30–40 ($n = 13$), 41–50 ($n = 9$), and 51–60 ($n = 6$) years; 30 age matched controls per age group	Noise-exposed participants were railway train engine drivers exposed to noise [Leq of 86 dB(A)] for 8–10 h/ day for >10 years	Threshold data were not presented; hearing threshold sensitivity was <25 dB HL from .25–8 kHz.	Not Included	Not Included	Speech-in-babble task and gap detection, modulation detection, and duration pattern (temporal processing tasks) were assessed. Noise-induced deficits on temporal processing tasks varied with age and with task; noise-exposed groups had statistically significant deficits on the speech-in-babble task were across age groups.
Hope, Luxon, and Bamiou (2013)	20 participants: 10 Male Royal Air Force aircrew pilots and 10 Male administrators, ages 24–39 years; thresholds ≤ 20 dB HL from .5 to 4 kHz	Noise-exposed Royal Air Force pilots had a minimum of 500 flying hours; Royal Air Force administrator controls had no history of noise exposure	Pure tone average at .5, 1, 2 and 4 kHz was ∼2 dB poorer in noise-exposed pilots but differences were not statistically significant	Click-evoked TEOAEs screened at 80 dB; TEOAE amplitude deemed normal if SNR ≥ 6 dB and reproducibility criteria were met; TEOAE amplitude was ∼4 dB larger in noise-exposed pilots with statistically significant	Not Included	Tests were binaural and included temporal processing (backward masking tests), spectral processing (simultaneous masking tests), frequency discrimination, auditory attention, and recognition of speech-in-noise (vowel–consonant–vowel test in International Collegium for Rehabilitative Audiology (ICRA) noise). Noise-exposed pilots had statistically significant deficits in their speech-in-noise test results, with no statistically significant differences on any of the temporal processing tests.

(*continued*)

Table 3. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
				differences for the right ear.		
Liberman et al. (2016)	34 participants (19M, 15F) ages 18–41 years with thresholds <20 dB HL from 0.25–8 kHz	Subjects divided as high-risk (15M, 7F) or low-risk (4M, 8F) based on self-reported exposure to sound and use of HPDs	High-risk group showed significant threshold elevation at all test-frequencies above 8 kHz	DPOAE at 0.5–12 kHz using F1 = 65/ F2 = 55 dB; DPOAEs present in all subjects with no significant group difference in amplitude	See Table 2	Northwestern University List 6 (NU-6) words presented at 35 dB HL; white noise presented at 35 dB HL (0 dB SNR) and 30 dB HL (5 dB SNR). NU-6 words time compressed (45% or 65%) and reverberation added (0.3 s). Participants in high-risk group had significantly poorer scores than participants in low risk group.
Prendergast, Millman et al et al. (2017b)	138 participants (56M, 82F) ages 18–36 years with thresholds <25 dB HL from 0.25–8 kHz; included all participants described in Prendergast et al. (2017a)	Lifetime noise exposure questionnaire modified from Lutman et al. (2008)	The only observed relationship was between 16 kHz threshold and amplitude modulation detection: at 80 dB SPL, detection thresholds improved with increasing 16-kHz thresholds, with reduced relationships after controlling for lower-frequency thresholds.	TEOAEs screened from 1.5–4 kHz at 83 dB peSPL; TEOAE amplitude not reliably related to noise exposure history.	Participants tested in evoked potential portion of the study are described in Prendergast et al. (2017a); see Table 2	Digit triplet test: three spoken digits with varied sound levels presented sequentially in background noise at 40 or 80 dB SPL. SNRs vary from −24 to −3 in three dB steps. Co-ordinated response measure speech task performed at 40 and 80 dB SPL with maskers in different locations and at different SNRs. Frequency difference limens, intensity difference limens, interaural phase difference discrimination, amplitude modulation detection thresholds, localisation and musical consonance task also assessed. Some weak trends noted, with more noise-exposed participants having better function in some but not all trends.
Fulbright et al. (2017); for additional discussion see Fulbright (2016)	60 participants (26M, 34F) from 18–28 years old with thresholds ≤25 dB HL from 0.25–8 kHz	$L_{AEQ8760}$ assessed via NEQ: mean =78.6, range =64–87 Post hoc analysis included assignment to high-risk and low-risk groups based on self-report of a previous TTS after a loud event.	.25–8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity	DPOAE screened from .5–8 kHz using F1 = 65/ F2 = 55 dB SPL, and F1 = 53/ F2 = 35 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	See Table 2	Word in Noise (WIN) test used; Babble fixed at 80 dB SPL and SNR adjusted from 24 to 0 dB in 4 dB steps to determine 50% correct threshold. NU-6 words also presented at 80 dB HL in competing broadband noise presented at 50 or 60 dB HL. Temporal summation assessed using 4-kHz tones with durations of 3, 30 and 300 msec. There were no statistically significant relationships between supra-threshold tasks and noise exposure history, or ABR Wave-I amplitude.
Grinn et al. (2017)	32 participants (13M, 19F) from 21-27 yrs old with thresholds ≤25 dB HL from 0.25–8 kHz	$L_{AEQ8760}$ assessed via NEQ: mean =79.3, range =57–87	.25–8 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity.	DPOAE screened from 1–8 kHz using F1 = 55/ F2 = 45 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	See Table 2	Words in Noise (WIN) test used; Babble is fixed at 80 dB SPL and speech level is adjusted from 24 dB SNR to 0 dB SNR in 4 dB steps to determine 50% correct speech reception threshold. There were no statistically significant relationships between word in noise identification and noise exposure history.
Yeend et al. (2017)	122 participants (59M, 63F) from 30–57 years old; 71% had thresholds ≤20 dB HL from 0.25–6 kHz; 21% had	Lifetime noise exposure was calculated using online surveys that assess both	.25–12.5 kHz: No statistically significant relationships between noise exposure history and threshold	DPOAE screened from 3–12.5 kHz using F1 = 65/ F2 = 55 dB SPL:	Not Included	Listening in Spatialized Noise-Sentences High Cue Condition (LiSN-S), National Acoustic Laboratories Dynamic Conversations Test (NAL-DCT), Temporal

(*continued*)

Table 3. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
	thresholds ≤40 dB HL up to 6 kHz; 8% had one or two thresholds above 40 dB HL. Thresholds were assessed to 12.5 kHz.	occupational and leisure noise (following Beach et al.,2013; Williams et al.,2015)	sensitivity; Although noise exposure history and high frequency thresholds were not related, poorer high frequency thresholds were related to poorer speech-in-noise performance and greater self-reported listening difficulty.	DPOAE amplitude not reliably related to noise exposure history.		Fine Structure task, Threshold-equalising noise test, and amplitude modulation thresholds, were also assessed. There was no evidence that noise exposure history was associated with auditory processing ability or speech in noise identification.
Grose et al. (2017)	61 participants (32M, 29F) ages 18–35 years with thresholds ≤20 dB HL from 0.25–8 kHz	Self-reported event attendance: High Noise group included 31 participants (21M, 10F) who had attended ≥ 25 loud music events in past year, and ≥ 40 loud music events in past two years. The control group included 30 participants (11M, 19F) with median 2-year event attendance of four loud events (range =0–30 loud events)	The only observed relationship was poorer threshold sensitivity at 16 kHz in the High Noise group; no statistically significant differences were observed from 0.25-11.2 kHz.	DPOAE screened from .5-8 kHz using F1 = 65/ F2 = 55 dB SPL; additional L1 and L2 levels were: 65:65, 63:60, 61:55, 59:50, 57:45, 55:40, 53:35, 51:30, 49:25, and 47:20: DPOAE amplitude was not reliably different between the two noise exposure groups.	See Table 2	Speech tests included filtered phoneme recognition and speech-in-noise recognition. Psychoacoustic tests included temporal modulation detection, spectral modulation detection, and sensitivity to interaural phase. There were no relationships between noise exposure history and supra-threshold function on any of the above tests.
Guest et al. (2018)	85 participants ages 18–40 years recruited as controls or speech-in-noise (SPiN) impaired; enrolled participants were matched based on age, sex, and threshold. All thresholds ≤20 dB HL from 0.25–8 kHz	Structured lifetime noise exposure questionnaire described in Guest et al. (2017). Noise exposure did not differ between SPiN impaired groups and controls.	There were no statistically significant differences in threshold sensitivity from .125 to 14 kHz for speech-in-noise (SPiN) impaired groups versus controls.	Not included	See Table 2	Of 32 participants self-reporting speech in noise (SPiN) impairment, 16 were verified as impaired-based on Coordinate Response Measure (CRM) test performance at 90th percentile relative to controls. SPiN impairment was not associated with lifetime noise exposure, nor with any evoked potential measurements.
Le Prell et al. (2018)	74 participants (14M, 60F) ages 18–27 years; Although participants were not required to have "normal" hearing, all but two had thresholds ≤ 25 dB HL from .25 to 8 kHz.	Exposure to loud recreational sound was common, with bars or dance clubs and music players being the two most commonly reported sources of loud sound.	There were no statistically significant relationships between noise exposure history and threshold sensitivity.	DPOAE screened from 2–8 kHz using F1 = 55/ F2 = 45 dB SPL and F1 = 45/ F2 = 35 dB SPL. There were no statistically significant relationships between noise exposure history and DPOAE amplitude.	Not included	Words in Noise (WIN) test used; Babble is fixed at 80 dB SPL and speech level is adjusted from 24 dB SNR to 0 dB SNR in 4 dB steps to determine 50% correct speech reception threshold. There were no statistically significant relationships between noise exposure history and performance on the WIN.

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Table 3. Continued.

Author	Participants	Noise Exposure/ Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Valderrama et al. (2018)	74 participants (37M, 37F) from 29-55 yrs old; 84% had normal thresholds (≤20 dB HL from 0.25 – 6 kHz) and 12% had near normal thresholds (≤25 dB HL up to 2 kHz, ≤30 dB HL at 3 kHz, _ 35 dB HL at 4 kHz, and ≤ 40 dB HL at 6 kHz. Thresholds were assessed to 12.5 kHz.	Lifetime noise exposure was calculated using online surveys that assess both occupational and leisure noise (following Beach et al.,2013; Yeend et al.,2017)	.25-12.5 kHz: No statistically significant relationships between noise exposure history and threshold sensitivity; Although noise exposure history and high frequency thresholds were not related, poorer high frequency thresholds were related to poorer speech-in-noise performance and greater self-reported listening difficulty.	DPOAE screened from 1-12 kHz using F1 = 65/ F2 = 55 dB SPL: DPOAE amplitude not reliably related to noise exposure history.	See Table 2	High cue condition in Listening in Spatialized Noise-Sentences High Cue Condition (LiSN-S). Masker presented at 61 dB SPL; unamplified sentences presented at 68 dB SPL initially, with levels adjusted for audibility using NAL-RP prescription. There was a statistically significant interaction between central gain (amplitude difference between Waves I and V), conduction speed (latency difference between Waves I and V) and LiSN-S performance.
Bramhall et al. (2018)	74 participants ages 19–35 years; this report describes a subset of participants assessed by Bramhall et al. (2017).	Subjects interviewed regarding occupational, military, and recreational lifetime noise history, and use of HPDs, using LENS-Q; LENS-Q noise score not considered as part of analysis.	All participants had thresholds <20 dB HL from 0.25–8 kHz; thresholds not included in analysis.	All participants had normal DPOAEs. DPOAEs averaged from 3-8 kHz were not correlated with Wave-I amplitude at 4 kHz.	See Table 2	All participants performed at close to 100% on speech perception in quiet tasks at both 60 dB HL and 90 dB HL sound levels, with no relationship with wave I amplitude. ABR wave I amplitude was not correlated with speech perception in noise, as measured by the WIN test.
Ridley et al. (2018)	33 participants. 13 participants (6M, 7F) ages 23-48 yrs old had normal hearing (≤15 dB HL from 0.25 – 8 kHz). 20 participants ages 35-64 yrs old (10M, 10F) had SNHL (thresholds >15 dB at 4 kHz).	$L_{AEQ8760}$ assessed via NEB: mean =75.2, range =66.8-86.5		DPOAE screened at F2 = 1 kHz and F2 = 4 kHz using F1 = 61 dB SPL and F2 = 55 dB SPL. DPOAE amplitude was correlated with threshold.	See Table 2	Thresholds in noise measured using the Threshold-equalising noise (TEN) (HL) test described by Moore et al. (2004). The TEN masker was set at 70 dB HL

To be included in Table 3, normal (or near normal) hearing for participants was required. Certainly, there are a number of studies in which workers with permanent NIHL have poorer word-in-noise test outcomes (Smoorenburg 1992; Leensen, de Laat, and Dreschler 2011; Leensen et al. 2011; Jansen et al. 2014). Some of these deficits are related to audibility of the test signals, although even after correcting for audibility, deficits are often detected (for discussion, see Le Prell and Brungart 2016). Table 3 specifically illustrates the various patterns of deficits that have been reported in worker populations with small (i.e., 5–10 dB) deficits relative to controls (Alvord 1983; Kujala et al. 2004; Kumar, Ameenudin, and Sangamanatha 2012; Hope, Luxon, and Bamiou 2013), and other populations with normal hearing.

The studies by Fulbright et al. (2017), Grinn et al. (2017), Le Prell et al. (2018) and Bramhall, Konrad-Martin, and McMillan (2018) used the relatively difficult WIN test (described above). There were no relationships between WIN threshold and noise exposure history (Fulbright et al. 2017; Grinn et al. 2017; Le Prell et al. 2018) or WIN threshold and Wave I amplitude (Bramhall, Konrad-Martin, and McMillan 2018). In the studies by Yeend et al. (2017) and Valderrama et al. (2018), the Listening in Spatialized Noise – Sentences High Cue Condition (LiSN-S) was used. During the LiSN-S test, two-talker masker noise is presented at 61 dB SPL 90 degrees relative to the listener, and the target speech is delivered at 68 dB SPL, 0 degrees relative to the listener. Neither study reported relationships between LiSN-S performance and noise history, although Valderrama et al. (2018) did report that longer ABR interpeak latencies and reduced central gain (less growth of Wave-V amplitude relative to Wave-I amplitude) was associated with poorer performance on this test. As part of a comprehensive test battery, Yeend et al. (2017) also completed the National Acoustic Laboratories Dynamic Conversations Test (NAL-DCT), a temporal fine structure task, the TEN test, and an amplitude modulation test. There was no evidence that noise exposure history was associated with auditory processing ability on any of these tests.

One of the most carefully controlled investigations to date is that of Guest et al. (2018). They recruited individuals self-reporting deficits perceiving speech in noise, verified deficits using the Coordinate Response Measure (CRM) test and assessed relationships between both self-reported and verified speech-in-noise deficits and ABR Wave-I amplitude, as well as lifetime noise exposure history, with no statistically significant relationships detected. During the CRM test, participants must listen for a colour and number in the presence of 80 dB SPL background noise. Masker noise is delivered via two speakers each at 60 degrees relative to the listener, and the target speech is delivered at 0 degrees relative to the listener, with the level varied in 2-dB increments to determine threshold. The CRM test was also used by Prendergast, Millman et al. (2017). No differences were detected on the CRM test, or a variety of other tests including the digit triplet test, during which three spoken digits with varied sound levels are presented sequentially in background noise at 40 or 80 dB SPL. Frequency difference limens, intensity difference limens, interaural phase difference discrimination, amplitude modulation detection thresholds, localisation and musical consonance task were also assessed, with no statistically significant findings although some weak trends were noted on some measures.

Grose et al. (2017) used the BKB sentences with the target words filtered from 1–2 kHz or 3000–6000 kHz and corresponding speech-shaped noise with an equivalent spectral envelope as a masking stimulus. The filtered speech was presented at 60 and 80 dB SPL, and the level of the background babble varied in 2 dB steps to determine threshold. No differences in performance on the BKB sentences were detected when those with a history of frequent concert attendance (defined as at least 25 concerts within the past year, and at least 40 within the past two years) were compared to those with minimal concert attendance. Other psychoacoustic tests completed as part of the study by Grose et al. (2017) included temporal modulation detection, spectral modulation detection and sensitivity to interaural phase, with no relationships with concert attendance detected.

In contrast to these largely negative findings, Liberman et al. (2016) reported poorer speech-in-noise performance in participants with more noise exposure using a difficult custom task, including the identification of NU-6 words at 35 dB HL at an SNR of 0 dB or 5 dB, with or without digital time compression (45% or 65% of original duration), and with 0.3-sec reverberation added. Participants in that study had poorer hearing at frequencies above 8 kHz and a larger SP/AP ratio, which was driven by decreased SP amplitude in the higher-noise participants (Liberman et al. 2016). Given these results, it seems possible that studies using the most difficult listening tasks may show greater sensitivity for detection of the relationships of interest. For example, the study of deficits on an envelope-processing task in a group exposed to concert noise revealed poorer performance in concert-goers than controls, but only when the tests were conducted at levels below 20 dB SL; there were no deficits detected when the listening test was performed at higher sound sensation levels (Stone, Moore, and Greenish 2008). Consistent with the hypothesis that only the most difficult tests will reveal deficits, there was limited evidence for changes in function on a signal-in-noise test when rats were tested in difficult listening conditions before TTS was induced and after thresholds had recovered to baseline (Lobarinas, Spankovich, and Le Prell 2017). Functional changes were only induced in those cases in which TTS was robust (40–50 dB, 24-hour post-noise), and listening in noise deficits were only observed at the subset of frequencies at which a permanent noise-induced decrease in ABR Wave I amplitude was measured. Moreover, deficits were measured only in the most difficult SNR conditions.

The studies included in Table 3 include quantitative speech-in-noise tests; efforts to assess self-reported difficulty hearing in noise have also been used, both in an effort to understand the prevalence of this clinical complaint (Gilliver et al. 2017) and in efforts to recruit participant populations with deficits (Guest et al. 2018). Statistically significant associations between exposure to noise and self-reported hearing difficulty were detected in a large epidemiological analysis, suggesting potential utility for qualitative metrics (Spankovich et al. 2018). One survey that has been used to explore potential relationships between ABR Wave I amplitude and perceived difficulties in noise is the Speech, Spatial, and Qualities of Hearing Scale (SSQ), developed by Gatehouse and Noble (2004) and used by Yeend et al. (2017) and Prendergast, Millman et al. (2017). The SSQ qualitatively assesses perceived hearing difficulty in settings ranging from ideal listening conditions (one-on-one conversation in quiet listening conditions) to difficult listening conditions (group conversations in noisy environments). Neither Yeend et al. (2017) nor Prendergast, Millman et al. (2017) found statistically significant relationships between lifetime noise exposure and overall SSQ scores. Efforts to validate self-reported difficulty using the SSQ against quantitative speech-in-noise test measures have had limited success (Banh, Singh, and Pichora-Fuller 2012; Fredriksson et al. 2016). Taken together, at this time, there is no "gold

standard" for either qualitative speech-in-noise surveys or quantitative speech-in-noise testing (for discussion, see Le Prell and Lobarinas 2015; Le Prell and Brungart 2016; Le Prell and Clavier 2017; Le Prell 2018).

Relationship between short-term noise exposure resulting in TTS and ABR amplitude change

In contrast to the studies described in Tables 1–3, in which noise exposure was assessed retrospectively, creating the opportunity for errors in subject recall to confound results, there are a small number of studies in which temporary changes in ABR Wave-I amplitude have been documented in humans after controlled noise exposures. These studies are described in Table 4. Unfortunately, there have been virtually no efforts to document changes in OHC function using OAEs in these TTS studies (with the exception of Grinn et al. 2017, who found no reliable deficits in either OAE or ABR-Wave-I amplitude at the one-day post-noise test), preventing any insight into whether compromised OHC function contributed to the observed changes in sound-evoked ABR. Similarly, there has been virtually no effort to identify potential supra-threshold deficits in any of these TTS studies; supra-threshold deficits could include tinnitus, hyperacusis, listening in noise deficits, temporal processing deficits, localisation errors or other auditory processing deficits. Because cochlear synaptopathy, when observed in animals, is both immediate and permanent, it seems unlikely that any of the studies listed in Table 4 provide evidence of a temporary cochlear synaptopathy, as all changes in evoked potential metrics fully recovered. Temporary injury to the OHCs during the period of post-noise deficits is the more parsimonious interpretation based on well-documented recovery of the OHC population after mild or moderate noise exposures.

The data from Lichtenhan and Chertoff (2008) are particularly notable here given the unique design of their study (i.e. experimentally controlled/standardised noise bandwidth to induce TTS in humans) and their detailed description of noise-induced changes in the sound-evoked compound action potential (CAP). Here, the CAP provided a measurement of the sound-evoked auditory nerve response using tympanic electrodes rather than the more distal electrode placements used during ABR tests. Lichtenhan and Chertoff (2008) reported that CAP amplitude in response to high-level sound stimuli was less impacted by TTS than when induced by lower-level sound stimuli. They inferred that at the lower stimulus levels, at which healthy OHCs amplified the cochlear response prior to noise exposure, post-noise CAP deficits were potentially a consequence of OHC trauma. In contrast, for CAP responses to the higher stimulus levels outside the range at which cochlear amplification occurs, noise-induced CAP deficits were not observed; post-noise CAP amplitude was equivalent to pre-noise baseline measures at the higher sound levels. Level-dependent analyses such as this are potentially helpful in distinguishing potential OHC pathology from potential IHC, synapse or auditory nerve pathology.

Discussion

Relationships between occupational noise and ABR metrics (Table 1)

The studies listed in Table 1 clearly demonstrate that deficits in the amplitude and latency of ABR Wave I have been detected in a variety of studies enrolling workers exposed to occupational noise as participants. The lack of DPOAE data precludes the distinguishing of effects of OHC loss and cochlear synaptopathy or progressive loss of spiral ganglion cells. However, detection of deficits at higher stimulus levels, at which the passive mechanics of the cochlea dominate after the active process has saturated, allows speculation that neural pathology contributed to delayed ABR latencies and reduced ABR amplitudes, even if permanent threshold deficits were caused by undocumented OHC loss. There is an urgent need for research in animal models using exposures that model occupational noise injury and assess the potential for synapse loss with lower-level repeated exposures. Within subjects, ABR waveforms are highly reliable (Grinn et al. 2017; Prendergast et al. 2018), and longitudinal studies of workers are needed.

Relationships between non-occupational noise and ABR metrics (Table 2)

Table 2 documents a small number of studies that have revealed associations between noise exposure and deficits in the amplitude and latency of ABR Wave I (Stamper and Johnson, 2015b; Bramhall et al. 2017; Valderrama et al. 2018) or other related metrics (Liberman 2015; Grose, Buss and Hall 2017). However, a number of studies treating noise exposure as a continuous variable, rather than dichotomising subjects into groups, failed to find any relationships between noise history and Wave I amplitude (Fulbright et al. 2017; Grinn et al. 2017; Prendergast et al. 2017a; Spankovich et al. 2017). Taken together, it seems likely that outcomes in studies such as these are highly dependent on both the specific protocols and the noise exposure of the enrolled participants. A major unknown is the role of high frequency loss, at frequencies above 8 kHz, in the above results, as hearing loss at the higher frequencies was consistently observed across studies.

Relationships between noise exposure and speech-in-noise metrics (Table 3)

The studies listed in Table 3 were highly variable with respect to outcomes. Several studies enrolling workers exposed to occupational noise, who had not yet developed significant hearing loss, revealed differences between the noise-exposed workers and controls (Alvord 1983; Kujala et al. 2004; Kumar, Ameenudin, and Sangamanatha 2012; Hope, Luxon, and Bamiou 2013). A study employing an extremely difficult speech in noise test revealed deficits associated with musical training (Liberman 2015), whereas a second study comparing frequent concert goers to those rarely attending concerts found no differences in speech in noise function (Grose, Buss, and Hall 2017). As in Table 2, a number of studies treating noise exposure as a continuous variable failed to find any relationships between noise history and outcomes on speech in noise tests (Fulbright et al. 2017; Grinn et al. 2017; Prendergast, Millman et al. 2017; Yeend et al. 2017; Valderrama et al. 2018). It is likely that outcomes in studies such as these are highly dependent on both the specific protocols and the noise exposure of the enrolled participants.

Short-term noise, TTS and ABR amplitude change in humans (Table 4)

The studies listed in Table 4 are important in that the noise insults were clearly defined and constant across participants, eliminating the significant unknowns associated with subject recall. If the short-term noise exposure paradigms used in these

studies revealed permanent changes in ABR Wave I or associate metrics, in the absence of changes in OAEs, cochlear synaptopathy would be suggested. Most studies did not include OAEs; however, none of these studies revealed permanent changes in ABR Wave I or associated metrics, suggesting cochlear synaptopathy was unlikely. Those results are not surprising, as none of the studies listed in Table 4 resulted in the larger and longer lasting TTS deficits that have been associated with cochlear synaptopathy in animal models. In animal studies in which cochlear synaptopathy has been documented, the pathology has been both immediate and permanent.

It seems reasonable to speculate that the temporary changes in ABR Wave-I amplitude reported in Table 4 could reflect temporary decreases in OHC gain, while OHCs recover from reversible injuries. TTS studies completed using a music player model revealed decreases in DPOAE amplitude that paralleled changes in threshold sensitivity, with recovery of DPOAE amplitude and audiometric thresholds proceeding in parallel across the post-music test times (Le Prell et al. 2012; Le Prell et al. 2016). Alternatively, the temporary changes reported in Table 4 may reflect a reversible auditory nerve dendritic swelling in the absence of synapse loss. Swelling of the auditory nerve dendrites under the IHCs has been shown to be reversible after infusion of excitotoxic substances such as AMPA and kainite (Pujol et al. 1990; Puel et al. 1994, 1995). Recovery of both auditory nerve dendrite swelling and AP (or ABR Wave-I) amplitude is also observed after noise exposure (Puel et al. 1998; Yamasoba et al. 2005). Recovery of the swelling and regained growth of ABR amplitude, with complete return to baseline, is observed even when swelling is induced for extended periods during chronic infusion of excitotoxic substances such as AMPA (Le Prell et al. 2004). In other words, excitotoxicity induced by noise or chemicals (AMPA, kainite) presumably has not resulted in permanent cochlear synaptopathy as the amplitude of the auditory nerve evoked responses returns to baseline. Taken together, additional research combining ABR and OAE protocols will be necessary to understand the likely pathology associated with TTS in humans participating in studies such as those in Table 4.

Additional comments on the differential diagnosis of cochlear synaptopathy

Given that a confirmed diagnosis of cochlear synaptopathy requires post-mortem histological analysis, there has been and will continue to be significant interest in the development of an *in vivo* test battery that would allow cochlear synaptopathy to be correctly inferred based on patterns of results across tests. To identify *selective* cochlear synaptopathy (a loss of synapses in the absence of middle ear and OHC pathology), the test battery must document that the middle ear conduction system is intact, typically accomplished using tympanometry, and there must be documentation that the OHC population has not been compromised. If cochlear synaptopathy occurs in parallel with OHC loss, diagnosis will be more difficult. These issues are of significant interest not only scientifically, to improve research design, but also to audiologists and otolaryngologists (Lin 2016; Hall 2017) who commonly report interest in cochlear synaptopathy as it relates to patient complaints and patient care. Given the variety of test batteries and test protocols being used across research studies, what can be inferred at this time, regarding clinical and scientific best practices?

As a starting point for patient care, the Joint Audiology Committee on Clinical Practice Algorithms and Statements is helpful (American Speech Language Hearing Association 1999); this committee included representatives from the American Speech-Language-Hearing Association (ASHA), the American Academy of Audiology (AAA) and the Department of Veterans Affairs (VA). With the caveat that the components of the assessment are dictated by patient need and may vary across patients, the following examination components have been identified: history, appropriate physical examination (eg otoscopy), cerumen management, air conduction pure-tone thresholds with appropriate masking, bone conduction pure-tone thresholds with appropriate masking, speech thresholds with appropriate masking, speech recognition measures with appropriate masking, acoustic immittance (tympanometry/acoustic reflex thresholds), acoustic reflex decay, rehabilitative needs assessment, communication inventory, otoacoustic emissions, high-frequency audiometry and either speech or pure-tone Stenger.

For differential diagnosis of cochlear synaptopathy, a careful patient history, otoscopy, and tympanometry, will be the basic starting point, to gain insight into patient risk factors, and the health and function of the outer and middle ear conductive system. Pure-tone air and bone conduction are also warranted, to determine the extent to which patient complaints are related to audibility issues, which may be appropriate to resolve with amplification. Completion of both air and bone testing will provide insight into conductive and sensorineural components of any observed hearing loss and guide recommendations. Pure-tone testing should include EHF audiometry given the reliable observation of high-frequency hearing deficits in association with Wave I amplitude deficits.

Speech detection thresholds can be measured as part of a conventional clinical test battery for the purpose of validating pure-tone threshold measurements ("cross-check principle") and word recognition in quiet can be considered, but these tests likely are not critical for differential diagnosis of cochlear synaptopathy. Word recognition scores are a supra-threshold test, commonly completed at 40 dB above the SRT, to determine the patient's best possible performance in easy listening conditions. Speech recognition thresholds (SRT) can also be measured; this test uses spondee words, which have two syllables pronounced with equal emphasis ("toothbrush"). The SRT is the minimum signal level at which the listener can correctly identify 50% of the speech material presented (Plomp and Mimpen 1979).

OAE tests

Over the course of this review, there has been significant discussion of the use of OAEs to assess the health of the OHCs. Given that the amplitude of these emissions varies across a 40-dB range even within normal hearing listeners, screening is not adequate; a diagnostic protocol should be used. As new equipment allowing higher frequencies to be routinely tested becomes available, testing through 12 kHz has begun to be incorporated into research protocols and should be considered as part of both research and clinical test batteries in order to gain insight into the health of the basal cochlea. With a baseline established, changes in cochlear health over time can be monitored (assuming patients have intact hearing and/or intact DPOAEs at these higher frequencies; if responses are absent at baseline, tests do not need to be repeated). In research studies where data are considered at the group level, rather than on an individual basis, protocols using multivariate statistical analyses in an effort to control for differences in DPOAE strength should be considered (following Bramhall et al. 2017; Bramhall, Konrad-Martin, and

Table 4. Relationship between short-term noise exposure resulting in temporary threshold shift (TTS) and auditory brainstem response (ABR) amplitude changes.

Author	Participants	Noise Exposure/Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Mills et al. (1970)	28-yr old male with normal hearing from 0.125–4 kHz, and 25 dB HL threshold at 6 kHz	octave-band noise centred at 0.5 kHz and presented at 81.5 dB SPL for 48 hours (exposure 1) and 92.5 dB SPL for 29.5 hrs (exposure 2)	TTS asymptote reached at approx. 8 hrs; TTS_4 at 0.75 kHz was 10.5 dB (exposure 1) and 27.5 dB (exposure 2). Complete recovery required 3-6 days	Not included	Vertex; 0.75 kHz tone, 20 msec or 200 msec; 1 sec inter-stimulus interval; 60 repetitions averaged Threshold shift paralleled behavioural shift but slope of the N_1–P_2 input-output function did not change	Not included
Sohmer and Pratt (1975)	10 adults with normal hearing	White noise, 117 dB SPL (90 dB SL), 15-min	TTS_2 on the order of 15 dB for clicks, with recovery within 30-60 min	Not included	Scalp and ear lobe clip electrodes; clicks; 10/sec, 60 dB SL, 512 repetitions averaged Temporary N_1 amplitude decrease, Temporary N_1 latency increase; The largest changes were observed immediately post-exposure, with rapid recovery from 3-30 min post noise	Not included
Botte et al. (1976), Botte et al. (1979)	5 young adults with normal hearing	1 kHz tone, at varied level and duration, ranging from 90 dB for 30 min to 95 dB for 85 min, used to induce TTS_2=20 dB at 1.5 kHz	TTS_2 on the order of 20 dB at 1.5 kHz, with recovery within 80 min	Not included	Vertex and ear lobe electrodes; 1.5 kHz tone Temporary N_1–P_2 amplitude decrease; the largest changes were observed 2-5 min post-exposure, with rapid recovery from 10-80 min post noise	Not included
Klein and Mills (1981)	5 young adults with thresholds of 7 dB HL or better from 0.25 to 8 kHz	narrow-band noise centred at 2.6 kHz and presented at 86 dB(C) for 4 or 8h; if TTS was <25 dB at 4h, the exposure was 8h	Maximum TTS of 28 dB measured at 3.5 kHz (testing began 20-min post-noise, with tuning curve tests followed by evoked potentials)	Not included	Forehead, ear canal near TM, and mastoid electrodes; 3.6 kHz tone; 21/sec, 61, 76, and 91-dB pe SPL; maximum of 4096 repetitions averaged One subject had decreases in Wave-I amplitude outside of test-retest values	Not included
Fialkowska et al. (1983)	22 young normal hearing persons	octave band noise centred at 2.8 kHz, 108 dB SPL	TTS of 15-35 dB at 4-6 kHz across subjects (Post-noise time not specified)	Not included	ABR: Forehead and mastoid electrodes, ECoG: silver ball electrode close to TM and mastoid electrode; Both ABR and ECoG: 4 kHz tone burst; 10/sec, 10 dB nHL (20 dB SPL) to 100 dB nHL (220 dB SPL); ABR: 2048 repetitions, ECoG: 512 repetitions Wave-I, III, and V latencies prolonged during TTS but only at lower intensities; CAP and Wave-I amplitude decreased	Not included
Attias and Pratt (1986)	All subjects included in Attias and Pratt (1984) (31 new employees, ages 18-21)	TTS induced by 95-dB HL pink noise for 15-min	TTS was 15±7 dB immediately post exposure	Not included	Forehead and mastoid electrodes; alternating polarity clicks; 10 and 55/sec, 75 dB HL, 1024 repetitions averaged, waveforms replicated Wave I, III, and V latencies were prolonged during TTS; amplitude was deemed "too variable to be suitable for further description"	Not included
Nam and Won (2004)	10 healthy adults (8M, 2F) ages 22 to 40 yrs (mean =26.9± 5.7) with no history of hearing loss	3 consecutive hours in computer arcade at 90.3-105.3 dB SPL (mean =91.5±4.5 dB)	TTS at 0.5, 1, 2 and 4 kHz was 5.8±2.8 dB immediately post-exposure; largest TTS (average: 10 dB) observed at 4 kHz	Not included	Extra-tympanic gold-foil wrapped electrodes; alternating polarity clicks; 7/sec, 90 dB; statistically significant increase in SP, no reliable change in AP, thus, SP/AP ratio increased; no reliable correlations between TTS and change in SP or change in SP/AP ratio	Not included

(*continued*)

Table 4. Continued.

Author	Participants	Noise Exposure/Noise Survey	Hearing Threshold	OAE amplitude	ABR amplitude and latency	Speech in Noise Testing
Lichtenhan and Chertoff (2008)	39 normal hearing participants ages 20 to 38 yrs: 25 dB HL or better from 0.25–8 kHz	N = 27 exposed to 115 dB SPL narrow band noise centred at 2 kHz for 15 min; n = 6 unexposed controls	TTS 30-60 sec post-noise ranged from 10-30 dB at 4 kHz in all but one subject; that subject improved by 5 dB post-exposure	Not included	Custom TM electrode, forehead, and ipsilateral ear lobe; alternating polarity clicks; 11.1/sec, 75–125 dB peSPL; CAP at lower SPLs more affected than CAP at higher SPLs; modelling suggests fewer responding neurons and less synchronous response at lower SPLs post-noise	Not included
Grinn et al. (2017)	32 participants (13M, 19F) from 21–27 years old with thresholds ≤25 dB HL from 0.25–8kHz	Prospective monitoring of changes in function the day after a loud event and one-week later. Noise dose was calculated based on SLM app data and duration of exposure.	No statistically significant relationships between noise dose and threshold shift the day after the event from .25 to 8 kHz; most noise-induced TTS had recovered.	DPOAE from 1-8 kHz with F1 = 55/F2 = 45 dB SPL: No statistically significant relationships between noise dose and DPOAE changes the day after the event.	Tiptrode ear canal electrodes placed in both ears and electrodes placed at high and low forehead; alternate polarity clicks and 2, 3, and 4 kHz tone bursts; 11.7/sec, 70, 80, 90 and 99 dB nHL, 500 repetitions with replication. No systematic changes in ABR Wave-I amplitude were observed the day after the recreational noise exposure.	Words in Noise (WIN) test used; Babble is fixed at 80 dB SPL and speech level is adjusted from 24 dB SNR to 0 dB SNR in 4 dB steps to determine 50% correct speech reception threshold. Temporary deficits on the WIN were observed with increasing deficits as noise dose increased. Performance returned to baseline one week post noise.

McMillan 2018). Such protocols are of significant interest as DPOAE amplitude can vary across a wide range even within a highly homogeneous normal-hearing population. For example, Le Prell et al. (2018) recently documented DPOAE amplitudes over a 30-dB range within a primarily female, Caucasian sample of young adults. Limiting the already homogeneous sample to just those participants with thresholds of 10 dB HL or better, DP amplitude still ranges from 0 dB SNR (responses indistinguishable from the noise floor) to as much as 40 dB above the noise floor, with the majority of the data ranging from 10 dB SNR to 30 dB SNR (see Figure 2 in the report by Le Prell 2018, for illustration).

Middle ear reflex tests

Although there is not yet sufficient evidence to advocate middle ear reflex testing for the purpose of diagnosing cochlear synaptopathy, testing should be considered as part of the comprehensive battery. The comparison of ipsilateral and contralateral evoked responses from the two ears has long provided not only a cross-check of the audiogram, but also insight into potential conductive, cochlear and retro-cochlear pathologies (Jerger, Jerger, and Hall 1979; Prasher and Cohen 1993; Neary et al. 1996). New wideband acoustic immittance devices increase the speed and power of such tests (Schairer et al. 2013). With respect to the differential diagnosis of cochlear synaptopathy, the amplitude of the middle ear muscle reflex has been successfully associated with cochlear synaptopathy in mouse models (Valero, Hancock and Liberman 2016; Valero et al. 2018). Middle ear muscle reflexes are weak, or absent, in a subset of the population (Flamme et al. 2017; McGregor et al. 2018), leading several investigators to suggest that noise exposure resulting in cochlear synaptopathic injury could provide one explanation for individual variability in human participants (Wojtczak, Beim, and Oxenham 2017; McGregor et al. 2018). There is also the thought that the amount of energy reaching the cochlea is a function of the wide band reflectance or admittance. If more energy is reaching the cochlea, then there is a greater risk of exposure. Consistent with these suggestions, reflex decay has been associated with speech recognition impairment and hearing loss in noise exposed workers (Duarte et al. 2015). As additional data begin to emerge in humans, it will be important to carefully consider the interpretation of any detected correlations. It is not only clear that noise exposure can compromise middle ear reflex amplitude (Valero, Hancock, and Liberman 2016; Valero et al. 2018), but also that a more robust middle ear reflex more effectively reduces the transmission of noise to the inner ear (Karlovich et al. 1977; Borg, Nilsson, and Engstrom 1983). Based on those data, the acoustic reflex has been suggested to directly mediate vulnerability to TTS_2 (Karlovich et al. 1977) as well as permanent NIHL (Borg, Nilsson, and Engstrom 1983) in noise-exposed patients and populations.

ABR and other evoked potentials

A major unknown at this time is the specific sound-evoked potentials that might be used during differential diagnosis of cochlear synaptopathy. There is a strong correlation between cochlear synaptopathy and the amplitude of Wave-I of the ABR in rodent ears in which OHC function is intact (Sergeyenko et al. 2013), but human patients and participants have diverse risk factors for OHC loss and the OHC population may be damaged. Although the amplitude of Wave-I of the ABR serves as

the gold standard within animal models, this has not been accepted as best practice for either human research studies or clinical test batteries used by those attempting differential diagnosis of patients. In addition to ABR protocol differences, differences in the specific populations and methods used to estimate previous noise exposure almost certainly contribute to the mixed outcomes across humans studies.

A number of alternative evoked potential metrics continue to be evaluated for potential use in human test batteries. Wave-V of the ABR, for example, has been suggested as a metric for cochlear synaptopathy in humans, with the specific measures utilised to date including measurement of ABR Wave-V latency (Verhulst et al. 2016; Skoe and Tufts 2018), ABR Wave-V latency during masking noise (Mehraei et al. 2016), and ABR Wave-V latency changes during forward masking (Mehraei et al. 2017). Although there have been reports in which the amplitude of ABR Wave-I relative to the amplitude of ABR Wave-V shows deficits (Verhulst et al. 2016; Grose, Buss, and Hall 2017), any Wave-I reliability issues presumably also impact this measure. However, it is worth note that Prendergast et al. (2018) carefully measured test–retest reliability for Waves I and V, and the SP, and found that the amplitudes of Waves I and V were highly reliable within subjects, whereas SP amplitude was less reliable. Several investigators have normalised the amplitude of the AP relative to the amplitude of the SP (i.e. SP/AP ratio) (Nam and Won, 2004; Liberman et al. 2016; Ridley et al. 2018); if the SP is not reliable, this metric will be less useful. Other evoked potential assessments considered to date include the FFR (Prendergast et al. 2017a), and the envelope following response (EFR) (Bharadwaj et al. 2015; Shaheen et al. 2015; Grose, Buss, and Hall, 2017; Guest et al. 2017; Paul, Bruce, and Roberts 2017; Guest et al. 2018), although statistically significant differences have not been detected either as a function of lifetime noise exposure (Prendergast et al. 2017a) or frequent concert/musical event attendance (Grose, Buss, and Hall 2017).

Speech in noise tests

A final consideration is the use and interpretation of speech in noise tests both in research studies and in patient care. Recommendations for speech in noise testing were long ago provided by Carhart and Tillman (1970), and these tests continue to be widely advocated as a metric that better captures real-world patient complaints regarding difficulties understanding speech in noisy backgrounds (Soli 2008; Wilson 2011; Vermiglio et al. 2012; Brungart, Sheffield, and Kubli 2014). As argued above, speech in noise deficits can emerge with either OHC loss or IHC loss/auditory nerve dys-sychrony. Thus, speech in noise deficits are not confirmatory for cochlear synaptopathy. However, regardless of whether speech in noise difficulties are ultimately determined to be caused by OHC pathology, cochlear synaptopathy or some combination of cumulative pathological changes in the inner ear, the patient's complaints should be assessed, and the only way to quantify their difficulty is to complete speech in noise testing. With a baseline in hand, increasing deficits can be detected, and, equally important, benefits of amplification or rehabilitation can be documented. It is important that efforts continue with respect to better understanding the relationships between noise exposure and auditory dysfunction in difficult listening environments. The identification of specific functional impairments as a consequence of noise exposure, emerging prior to permanent threshold shift, has the potential to guide new evidence-based screening and monitoring strategies regardless of whether the specific functional deficits are a consequence of OHC loss or cochlear synaptopathy.

Conclusions and challenges to the field

New data from animal subjects exposed to chronic noise through daily exposure paradigms are urgently needed as occupational exposure is composed of lower daily doses repeated on a daily basis over weeks, months and years. The extent to which synaptic pathology, OHC loss or mixed pathologies, will be induced by these chronic exposure histories is not known, as this condition has not been tested in animal studies (for discussion, see Dobie and Humes 2017; Murphy and Le Prell 2017). Non-occupational noise history generally has not been associated with decreasing ABR Wave I amplitude (Fulbright et al. 2017; Grinn et al. 2017; Prendergast et al. 2017a; Spankovich et al. 2017), although repeated exposure to loud music (Liberman et al. 2016; Grose, Buss, and Hall 2017) and exposure to firearm discharge (Bramhall et al. 2017) appear to be associated with changes in auditory nerve discharge in human participants. Although ABR amplitude in humans is more variable than that observed in rodents, ABR Wave-I amplitude appears to have high test–retest reliability (Prendergast et al. 2018) and it can be reliably monitored longitudinally within subjects for potential changes over time (Grinn et al. 2017). Longitudinal data are urgently needed to understand the potential for reduction of human ABR Wave-I amplitude or other derived measures as a function of aging or noise exposure. Diverse subject populations are needed, to fully characterise where risk begins, and how risk grows, with different real-world exposures and diverse real-world risk factors. Although the time, cost, equipment and training necessary for the collection of ABR data make it unlikely that such monitoring could readily be adopted as a monitoring tool across hearing loss prevention programmes (for discussion, see Skoe and Tufts 2018), such data have the potential to significantly contribute to our understanding of the mechanisms of noise injury. Speech in noise data is also urgently needed. Scientific documentation of deficits as a consequence of noise exposure is a necessary precursor for evidence-based suggestions for updated testing requirements. In addition to continued efforts to understand the extent to which noise exposure history affects speech in noise understanding, the relationships between noise exposure and high-frequency hearing loss should also continue to be explored.

A final caveat and call for research involves the need to assess the potential for spontaneous recovery of synapses. Although this generally has not been documented in pre-clinical noise-induced cochlear synaptopathy models using rodents as subjects, there are a small number of studies reporting recovery of the synaptic ribbons over a one-month period following noise exposure (Liu et al. 2012; Shi, Liu, He, et al. 2013; Shi, Liu, Wang et al. 2015). As discussed by Liberman and Kujawa (2017), additional research will be necessary to reconcile the differences in results across studies. If cochlear synaptopathy is ultimately determined to be reversible, the potential for temporary cochlear synaptopathic damage will be difficult, if not impossible, to distinguish from temporary OHC damage and temporary excitotoxic swelling. Finally, regardless of whether cochlear synaptopathy is induced by noise, or a function of aging, new research is necessary to fully identify mechanisms associated with drug-induced regeneration of synapses (Wan et al. 2014; Wan and Corfas 2015; Suzuki, Corfas, and Liberman 2016). These observations of synaptogenesis raise hope that a "cure" could be available, if human cochlear synaptopathy becomes possible to diagnose

using test batteries including elements such as those described here.

Declaration of interest

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