

On the Etiology of Listening Difficulties in Noise Despite Clinically Normal Audiograms

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Many people with difficulties following conversations in noisy settings have “clinically normal” audiograms, that is, tone thresholds better than 20 dB HL from 0.1 to 8 kHz. This review summarizes the possible causes of such difficulties, and examines established as well as promising new psychoacoustic and electrophysiologic approaches to differentiate between them. Deficits at the level of the auditory periphery are possible even if thresholds remain around 0 dB HL, and become probable when they reach 10 to 20 dB HL. Extending the audiogram beyond 8 kHz can identify early signs of noise-induced trauma to the vulnerable basal turn of the cochlea, and might point to “hidden” losses at lower frequencies that could compromise speech reception in noise. Listening difficulties can also be a consequence of impaired central auditory processing, resulting from lesions affecting the auditory brainstem or cortex, or from abnormal patterns of sound input during developmental sensitive periods and even in adulthood. Such auditory processing disorders should be distinguished from (cognitive) linguistic deficits, and from problems with attention or working memory that may not be specific to the auditory modality. Improved diagnosis of the causes of listening difficulties in noise should lead to better treatment outcomes, by optimizing auditory training procedures to the specific deficits of individual patients, for example.

Key words: Auditory development and plasticity, Auditory processing disorder, Hidden hearing loss, Speech intelligibility in noise.

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INTRODUCTION

Perhaps 5% of children and younger adults (<60 years old) with “clinically normal” audiograms (i.e., tone thresholds better than 20 dB HL from 0.1 to 8 kHz) have difficulties understanding speech, particularly in noisy, reverberant or otherwise challenging listening environments (Hind et al. 2011). This should not be surprising, given that understanding speech in noise taxes our auditory and cognitive capacities much more than does detecting tones in quiet (Rudner & Lunner 2014). If anything, 5% could underestimate the prevalence of listening difficulties specific to noisy environments, as such people are less likely to be referred for or seek treatment than those with more pronounced hearing loss.

There are many possible causes of hearing difficulties in noise despite clinically normal audiograms. First, tone sensitivity better than 20 dB HL does not rule out potential pathology of the cochlea or middle ear. Recent findings that both noise exposure and aging can permanently destroy synapses between the inner hair cells (IHCs) and type I auditory nerve fibers (ANFs)—leading to a gradual degeneration of the denervated

ANFs but leaving the IHCs and hearing sensitivity intact—underscore the inability of the audiogram to detect certain types of peripheral loss (Kujawa & Liberman 2015). The term hidden hearing loss (HHL) has been coined with such peripheral loss in mind (Schaette & McAlpine 2011), but perhaps should extend to *all* possible types of hearing problems not captured by conventional clinical methods, including neurology. The term central auditory processing disorder (APD; Musiek & Chermak 2014) would then be reserved for neurologically confirmed lesions affecting the central auditory nervous system (CANS), unless specific deficits in central auditory processing (AP) could be confirmed by sensitive clinical tests that controlled for potential peripheral and cognitive confounds (Dillon et al. 2012). For example, deficits in binaural integration and sound localization (Cameron & Dillon 2008), often leading to impaired speech intelligibility in noise, could be a consequence of temporary periods of unilateral conductive hearing loss early in life, during bouts of otitis media with effusion (Kaplan et al. 2016). Likewise, AP deficits could result from chronic exposure to nontraumatic levels of noise (i.e., 50 to 70 dB SPL) during developmental sensitive periods and even in adulthood, degrading neural receptive fields and tonotopic maps in auditory cortex and subcortically (de Villiers-Sidani & Merzenich 2011; Gourévitch et al. 2014). Finally, listening difficulties might not be due to hearing problems at all, but to deficits in language comprehension, termed specific language impairment (Bishop 1997), or to deficits in attention or working memory that may not be particular to the auditory modality (Cacace & McFarland 2005). In this review, I discuss these possible causes of listening difficulties in spite of clinically normal audiograms, and examine established as well as promising new psychoacoustic and electrophysiologic approaches to differentiate between them, with the ultimate goal of better tailoring treatments to the specific deficits and needs of individual patients.

HIDDEN HEARING LOSS

“Clinically Normal” Audiograms

The average tone thresholds of healthy, normal-hearing young adults, measured in quiet, are defined to be 0 dB HL (hearing level) across audiometric frequency. SDs of the mean are 3 to 5 dB in the 0.1 to 8 kHz range (Wilber et al. 1988; Han & Poulsen 1998; American National Standards Institute 2010), only widening to about 10 dB at the highest audiometric frequencies (14 to 16 kHz). Thus, 95% confidence intervals (CIs) for normal tone thresholds are at most –10 to 10 dB HL up to 8 kHz. The current practice of classifying thresholds of 20 dB HL in the 0.1 to 8 kHz range (i.e., 4 to 6 SDs below average) as “clinically normal” therefore seems dubious at best.

Subjects with clinically normal audiograms typically perform very unevenly on more difficult listening tasks (Surprenant & Watson 2001; Kidd et al. 2007; Ruggles & Shinn-Cunningham

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2011; Ruggles et al. 2011; Bharadwaj et al. 2015). For example, in Speech-in-Noise (SIN) tests conducted on young adults (averaging 20 years) with normal audiograms, Surprenant and Watson (2001) obtained a 95% CI of 6 dB SNR (signal to noise ratio) for the 50% correct identification of low redundancy sentences, which corresponded to SIN scores of 82% at an SNR of -1.6 dB in the best 10% of listeners and only 38% at the same SNR in the worst 10%. In such young people, SIN scores tend not to correlate with tests of cognitive function (Akeroyd 2008), suggesting a potential HHL component instead. Highly variable performance on difficult listening tasks further weakens the case for using 20 dB HL as the cutoff for clinically normal hearing, especially for the purpose of establishing other clinical norms. Indeed, many people with listening difficulties and suspected APD (on the basis of normal audiograms and no apparent cognitive disorders) have SIN scores that are below average but within the wide normative range (i.e., z scores between -1 and -2 ; Ferguson et al. 2011).

The majority of people with thresholds between 10 and 20 dB HL have distortion product otoacoustic emission (DPOAE) amplitudes that are outside of the DPOAE normative range ($z < -2$), indicative of some degree of outer hair cell (OHC) dysfunction (Zhao & Stephens 2006; Job et al. 2007; Dhar & Hall 2011). DPOAEs are by-products of the frequency-specific and compressively nonlinear amplification of sound-induced cochlear vibrations by the OHCs, a process which increases both the sensitivity and the frequency resolution of hearing (Robles & Ruggero 2001; Moore 2007). Thus, even modest losses of OHCs, which are likely to leave audiometric thresholds within their wide clinically normal range, could contribute to hearing difficulties in noisy settings, where fine frequency resolution is especially important (Festen & Plomp 1983; Houtgast & Festen 2008; Badri et al. 2011). DPgrams can be more sensitive to OHC dysfunction (and to conductive hearing loss) than the audiogram, especially if individual baseline or pre damage DPgrams are available (see Fig. 1 for an example), and should always be performed to test for a potential OHC contribution to listening difficulties in noise. However, DPgrams and audiograms correlate only modestly with each other and with self-reported hearing loss (Dorn et al. 2001; Engdahl et al. 2013), in large part because OAEs are not very sensitive to damage to the IHCs or ANFs.

The potential utility of OAEs in uncovering HHL can be extended by presenting moderately loud noise to the contralateral ear during OAE recording, which normally decreases DPOAE amplitudes by 1 or 2 dB (Kim et al. 2001; Butler et al. 2011), by activating the crossed medial olivocochlear (MOC) efferent pathway to suppress the OHC amplifier (Murugasu & Russell 1996). A recent study has suggested that the MOC efferents are activated by input from type II ANFs, which originate from the OHCs, rather than from type I ANFs, which originate from the IHCs (Froud et al. 2015). Thus, if DPOAEs are normal but are not contralaterally suppressible, this could indicate a problem with either the MOC efferent system or with type II ANFs, and not necessarily with type I ANFs as previously thought. However, the Froud et al. (2015) study remains controversial and more work is generally needed to identify the potential contributions of MOC dysfunction to hearing problems, both with and without threshold shifts (Mishra 2014). One possibility is that both the MOC and the LOC efferent systems (the lateral olivocochlear or LOC efferents contact the input terminals of the ANFs) play an oto-protective role, without which the cochlea becomes more vulnerable to both noise- (Maison et al.

2013) and age-related synaptopathy (Lieberman et al. 2014), as described in the “Cochlear Synaptopathy” section.

If “clinically normal” thresholds of 10 to 20 dB HL are in fact likely indicators of some degree of peripheral loss, do thresholds better than 10 dB HL guarantee normal peripheral hearing? The first and most obvious possibility is that measuring the audiogram to only 8 kHz (let alone to 4 kHz) may miss damage to the ultra-high-frequency basal turn of the cochlea. It has long been suspected that basal-turn hair cells, which at high SPLs are strongly stimulated not only by high-frequency but also low frequency sounds, are most vulnerable to noise trauma (Bredberg 1968). In a recent longitudinal study of teenagers who frequented discos, it was found that permanent threshold shifts (PTSSs) were most common and pronounced at 14 to 16 kHz (Biassoni et al. 2005; Serra et al. 2005). As an example, consider the “extended” audiogram of a young adult amateur musician (Fig. 2): thresholds mostly in the -5 to 5 dB HL range up to 10 kHz give way to a sloping bilateral loss of 45 to 50 dB at 16 kHz. While elevated thresholds above 10 kHz may have little direct impact on speech intelligibility (Boothroyd & Medwetsky 1992), they likely triggered a chronic, bilateral, hissing tinnitus, which this subject reliably pitch-matched to narrowband noise with a center frequency of 9 kHz, near the edge of the loss. In addition to potentially triggering a high-pitched tinnitus, noise-induced damage at ultra-high frequencies could increase the severity of future age-related losses at lower frequencies (Kujawa & Liberman 2006). More speculatively, damage at ultra-high frequencies might point to already present but still hidden losses in the speech frequency range, as discussed below.

Cochlear Synaptopathy

The audiogram is even less sensitive to partial losses of the IHCs or ANFs than to partial losses of OHCs. By partial losses, I mean that in every tonotopic region of the cochlea, there remain some normally functioning hair cells and nerve fibers; in other words, there are no “dead regions” (Vinay & Moore 2007). Schuknecht and Woellner (1953) reported long ago that cats could retain normal hearing sensitivity after a nearly complete bilateral sectioning of the auditory nerve, despite ANF losses of up to 80%. More recently, Lobarinas et al. (2013) found normal behavioral audiograms in chinchillas with carboplatin-induced IHC losses of also up to 80%; importantly however, tone thresholds in noise were elevated in these animals (Lobarinas et al. 2016). Similar findings were reported by Chambers et al. (2016) in ouabain-treated mice with up to 95% ANF loss. In all of these studies, the losses were distributed more or less evenly along the length of the cochlea, indicating that only a small percentage of surviving IHCs or ANFs is required for the preservation of normal tone thresholds in quiet, as long as the OHCs remain intact. A hallmark of human auditory neuropathy is that speech intelligibility, especially in noise, is substantially poorer than expected on the basis of the audiogram, which can remain in the clinically normal range (Starr et al. 1996; Zeng et al. 2005; Giraudet & Avan 2012). Again, understanding speech in noise can be challenging even for “normally-hearing” people (Ruggero 1992; Surprenant & Watson 2001; Joris et al. 2004; Kidd et al. 2007; Lopez-Poveda & Barrios 2013), whereas only about 20% of IHCs or ANFs appear to suffice for normal sensitivity to tones in quiet, providing that the losses are distributed along the cochlea and the OHCs are unaffected (Schuknecht & Woellner 1953; Lobarinas et al. 2013; Chambers et al. 2016).

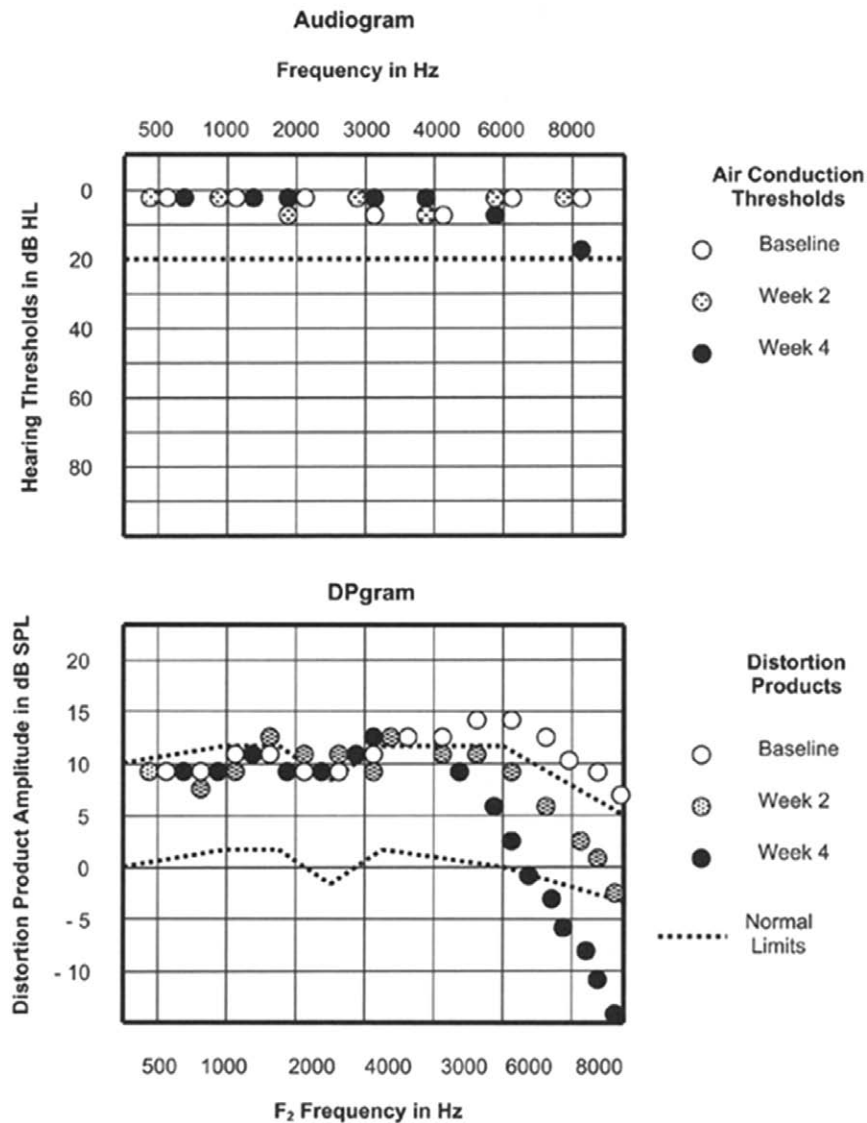


Fig. 1. Audiograms (top) and DPgrams (bottom; i.e., distortion product otoacoustic emission amplitudes vs. primary tone frequency) in a child with a brainstem tumor who underwent chemotherapy that included the ototoxic drug cisplatin. Adapted from Figure 7–4 in *Otoacoustic Emissions: Principles, Procedures, and Protocols*. San Diego, CA: Plural Publishing; 2011.

A seminal recent finding was that mice or guinea pigs exposed for 2 hr to octave-band noise at about 100 dB SPL suffered an irreversible loss of up to 50% of IHC synapses in frequency regions peaking just above the noise band, while hearing sensitivity decreased only temporarily (i.e., a temporary threshold shift or TTS) and recovered completely within a week or so of the 2-hr exposure (Kujawa & Liberman 2009; Lin et al. 2011). Furthermore, this synaptopathy led to a gradual degeneration of the denervated spiral ganglion cells, the cell bodies of the ANFs, whereas both IHCs and OHCs remained intact. (Of course, after louder and/or longer exposures, IHCs and especially OHCs would also be lost.) Each successive 2 hr, ~100 dB SPL noise dose, delivered a few weeks apart (to allow for complete recovery from TTS), added to the severity of the synaptopathy, and PTS did develop after the third exposure (Wang & Ren 2012). Longer exposures to 8 to 16 kHz noise at lower SPLs also caused significant (but less pronounced) synaptopathy in mice; this was shown after a 1-week exposure at 84 dB

SPL (Maison et al. 2013), and a 10-week exposure at 75 dB SPL (Pienkowski 2016). Fortunately, a recent mouse study showed that not all TTS-inducing noise exposures cause synaptopathy: 2 hr of 8 to 16 kHz noise at 91 dB SPL (versus 100 dB SPL) did not (Fernandez et al. 2015). In older mice never exposed to loud noise, synaptic and neural losses were also observed well before hair cell losses or PTS (Sergeyenko et al. 2013). Similar age-related (if not also noise-related) losses of IHC synapses and spiral ganglion cells were seen in human temporal bones, again in the absence of hair cell loss (Makary et al. 2011; Viana et al. 2015). All of these findings imply that IHC synapses are more vulnerable to both noise exposure and aging than the hair cells themselves. Synaptopathy is thus a likely candidate for at least some of the hearing difficulties experienced in noisy settings by people with a history of noise exposure, particularly the elderly, in spite of normal or near-normal hearing sensitivity (Kujala et al. 2004; Brattico et al. 2005; Humes et al. 2012; Kumar et al. 2012; Füllgrabe et al. 2014).

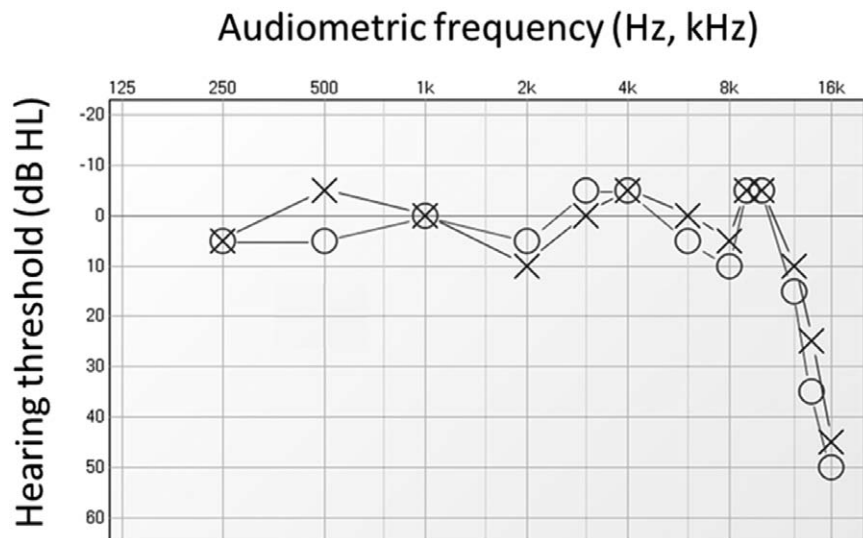


Fig. 2. Previously unpublished extended audiogram of a young adult amateur musician, recorded in our University clinic, showing elevated thresholds only above 10 kHz. This person had a chronic, bilateral, hissing tinnitus, which she reliably pitch-matched to narrowband noise with a center frequency of 9 kHz, near the edge of the hearing loss.

At present, an 8-hr daily exposure limit of about 85 dB A (A-weighted SPL) is thought to safeguard normal-hearing people from PTS (NIOSH 1998; OSHA 2002), with an additional 3 to 5 dB of noise allowed per halving of the exposure duration (i.e., 88 to 90 dB A for a 4-hr exposure, 91 to 95 dB A for a 2-hr exposure, etc., so that 100 dB SPL for 2 hr is in fact considered unsafe, whereas 91 dB SPL is not [cf. Fernandez et al. 2015]). However, as mentioned above, synaptopathy in mice can occur at noise levels in the 75 to 85 dB SPL range over longer exposure durations (Maison et al. 2013; Pienkowski 2016). Furthermore, mild TTS can be induced at relatively low exposure levels in humans (Ward et al. 1976): for example, 76 dB A for 8 hr of broadband noise, or just 65 dB A for 4 hr of octave-band noise centered at 4 kHz, the frequency range to which we are normally most sensitive. It is thus unclear if present occupational noise standards do in fact adequately safeguard against synaptopathy and eventual PTS.

Given that clinically normal audiograms do not necessarily rule out synaptopathy as a possible contributor to listening difficulties in noise, how can this be done? Detecting IHC/ANF loss and differentiating it from OHC loss (e.g., to diagnose auditory neuropathy) has traditionally been the purview of the auditory brainstem response (ABR; Starr et al. 1996; Harrison 1998; Mills 2006; Picton 2011; Pienkowski & Ulfendahl 2011; Hall 2015). However, ABR audiograms can be unaffected in rodents with confirmed synaptic losses, despite the fact that ABR wave I amplitudes at mid to high SPLs are reduced (Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013). This can be explained by the finding that noise apparently destroys synapses mostly with high-threshold (low spontaneous rate) ANFs, while largely sparing synapses with low-threshold (high-spontaneous rate) ANFs (Furman et al. 2013). A loss of predominantly high-threshold ANFs has also been observed in aged gerbils raised in a quiet vivarium (Schmiedt et al. 1996). Unfortunately, wave I amplitudes are much less robust in scalp-recorded human ABRs than subcutaneously-recorded animal ABRs, especially at low to moderate stimulus levels. Nonetheless, two recent studies reported reduced ABR wave I amplitudes at high SPLs in groups of tinnitus patients with normal audiograms, compared with nontinnitus controls (Schaeffe

& McAlpine 2011; Gu et al. 2012). Most recently, Stamper and Johnson (2015) studied people with normal audiograms and varying degrees of self-reported chronic exposure to moderately loud noise in the 67 to 83 dB A range. They found significant negative correlations between the level of noise exposure and the ABR wave I amplitude evoked by high-level clicks and 4 kHz tone bursts, but not between the level of noise exposure and DPOAE amplitudes, suggesting that they may have been tracking the severity of noise-induced synaptopathy in their subjects.

Given the high variability of scalp-recorded human ABR wave I, a more reliable clinical metric of synaptopathy may be the wave V to wave I amplitude ratio, which is more consistent between normal-hearing subjects. The wave V/I ratio is predicted to increase in synaptopathy because whereas wave I amplitude should be reduced, wave V is likely to remain normal as a result of compensatory increases in auditory brainstem activity (Turrigiano 1999; Salvi et al. 2000; Schaeffe & McAlpine 2011; Chambers et al. 2016). Another approach is to record the amplitude of the auditory nerve compound action potential (CAP) with a tetrode in the ear canal or a tymptrode at the eardrum. The CAP is more robust than its ABR wave I counterpart (by virtue of being recorded closer to its cochlear source), and can often be measured reliably down to 0 dB nHL (normalized hearing level) in normal-hearing subjects. An interesting recently-revived scheme is to measure chirp-evoked CAPs in the presence of high-pass masking noise, using progressively higher noise cutoff frequencies to track the frequency specificity of the loss (Eggermont 1976; Earl & Chertoff 2012; Earl 2015). One could also use tip- or tymptrodes to measure the hair cell-generated summing potential (SP), and compare it to the amplitude of the neural CAP. (This SP/CAP ratio is currently used in the diagnosis of Meniere's disease [Lamounier et al. 2014]). A significant increase in the SP/CAP ratio, indicative of normal hair cells but impaired ANFs, was recently observed in a group of noise-exposed subjects with normal thresholds, compared with nonexposed controls (Epstein et al. 2016). However, an important complication here are the recent findings of Bourié et al. (2014), who showed that substantial ouabain-induced

ANF losses in guinea pigs can coexist with both normal CAP thresholds and suprathreshold CAP amplitudes. These data suggest that the contribution of high-threshold ANFs to CAP (or ABR wave I) amplitudes might be small, and that a substantial reduction of the CAP implies that low-threshold fibers must also have been denervated, which is surprising given that CAP/ABR thresholds remain normal.

Another window to a partial loss of high-threshold (and perhaps also low threshold) ANFs could be impaired temporal encoding fidelity. Individual ANFs can phase lock to sound pressure fluctuations of at most a few hundred Hz, a limit imposed by their maximal rate of spike firing. However, groups of ANFs can collectively phase lock to sound frequencies an order of magnitude higher (several kHz), as seen in cochlear microphonic recordings (Palmer & Russell 1986; Ruggero 1992). This collective phase-locking would suffer with a partial ANF loss (Joris et al. 2004; Lopez-Poveda & Barrios 2013). A recent study recorded ABRs to sinusoidally amplitude-modulated (AM) tones in noise-exposed mice, and found that decreases in envelope-following response parameters were better indicators of synaptopathy than decreases in tone-evoked ABR wave I (Shaheen et al. 2015). Amplitude modulation detection can also be assessed psychophysically, by measuring temporal modulation transfer functions for example (Viemeister 1979). Temporal modulation transfer functions show AM detection thresholds versus the modulation frequency, and are always low pass in character (i.e., it is easier to detect low- than high-frequency AM); this low-pass cutoff frequency should decrease with synaptopathy, although this remains to be tested. The most common behavioral metric of the auditory system's temporal acuity is gap detection in noise (Green 1971), variants of which can be studied electrophysiologically to facilitate comparisons with animal studies. For example, ABRs measured in a tone-on-tone burst forward-masking paradigm with a variable gap duration (2 to 64 msec) showed prolonged wave V latencies for short but not for long-duration gaps in older subjects with normal thresholds compared with younger controls (Walton et al. 1999). However, in seeming contrast to this finding, differences in wave V latencies between older and younger subjects with normal thresholds were not seen in standard click ABRs when the click presentation rate was increased from 11 to 75 Hz, although the older subjects did have significantly reduced wave I amplitudes (Burkard & Sims 2001). Most recently, Mehraei et al. (2016) demonstrated that noise-exposed synaptopathic mice showed smaller ABR wave 4 (analogous to human wave V) latency increases when measured in noise, compared with nonexposed controls, as would be predicted from a selective loss of high-threshold ANFs (Furman et al. 2013). In normal-hearing humans, smaller wave V latency increases in noise were correlated with poorer performance on a timing-based sound localization task, suggesting that masked ABRs could be another useful clinical metric of synaptopathy (Mehraei et al. 2016).

One obstacle to the development of clinical tests of synaptopathy is difficulty quantifying a person's noise exposure history. This is easier in musicians, for example, but their hearing loss could be especially well hidden by their more "practiced ears" (or rather auditory brains; Moreno & Bidelman 2014; Alain et al. 2014), allowing them to hear comparatively well in noise in spite of synaptopathy. A better initial study group might be nonmusicians with normal audiograms in the speech range but elevated thresholds at ultra-high frequencies, as in Figure 2. Such audiograms may be more reliable indicators of noise trauma than questionnaires, and could prove to be simple but effective screeners for hidden losses at lower frequencies.

These or other ideas (Plack et al. 2014; Bharadwaj et al. 2014; Kujawa & Liberman 2015; Valero et al. 2016) could soon be used to diagnose noise- and age-related cochlear synaptopathy, and to correlate it with the extent of patients' listening difficulties in noise. Until then, the task of dissociating peripheral from central contributions to listening difficulties in noise will remain fraught with at least some uncertainty. Finally, although the prevalence of synaptopathy should increase with age, children unfortunately often listen to music or play video games at high volumes through earphones, and attend noisy school dances, concerts, sporting events, etc. (Keith et al. 2011; Taljaard et al. 2013; Carter et al. 2014), making them potentially vulnerable to noise-induced synaptopathy as well.

Central HHL

Hearing difficulties in spite of normal audiograms can also arise in the absence of any damage to the ear, including the hidden varieties discussed above, and in the absence of neurologically detectable CANS lesions. Animal studies have shown that exposure to moderately loud broadband noise during developmental sensitive periods can lastingly degrade cortical tonotopic maps and block the emergence of cortical neural tuning for complex sound features (Zhang et al. 2002; Chang & Merzenich 2003; Chang et al. 2005; de Villers-Sidani et al. 2008; Insanally et al. 2010; de Villers-Sidani & Merzenich 2011; Bureš et al. 2016). Less clear are the perceptual consequences of these cortical (and often also subcortical) changes. In one of the few studies addressing this important issue, Pan et al. (2011) exposed juvenile rats to pulses of broadband noise at 65 dB SPL and found that this led to impaired sound localization in adulthood. Very similar noise exposures early in life did not affect the adult rat's ability to discriminate human speech sounds (Ranasinghe et al. 2012), but did impair working memory as assessed in T-maze tasks (Ruvalcaba-Delgado et al. 2015). Note that although these studies only reported pre- and post-exposure ABR audiograms and not ABR wave I amplitudes, noise-induced synaptopathy is unlikely because exposure levels were only in the 60 to 70 dB SPL range. Furthermore, in these and other studies (Zhou & Merzenich 2007, 2009; Zhu et al. 2014), intensive perceptual training or environmental acoustic enrichment in adulthood was able to completely reverse the degraded cortical representations and sensory deficits resulting from developmental noise exposure and also from aging (de Villers-Sidani et al. 2010), encouraging the use of auditory training (AT) as a clinical treatment for central HHL (see the "Implications for AT" section).

The pinnacle of human auditory system development is language acquisition, which requires both passive listening (resulting in CANS specializations for discriminating phonetic contrasts in the native language, for example) and active engagement with language "tutors," a process reminiscent of song learning in birds (Kuhl 2004; Woolley 2012). Although the disruption of normal sound input (or of social contact) during sensitive periods can delay or even lastingly impair language and song acquisition (Kuhl 2004; Woolley 2012; Amin et al. 2013), it is presently unknown if moderate noise exposure during human infancy could lead to listening difficulties persisting into the grade school years. Neonatal intensive care units are one source of such nontraumatic but potentially CANS-altering noise (Brown 2009; McMahon et al. 2012). Another are broadband noise generators intended to help babies sleep, which many manufacturers recommend leaving on through the night during the first year of life. Despite

concerns about the high noise levels put out by some of these machines (Hugh et al. 2014), and the possibility that they could impair CANS development (e.g., <http://www.webmd.com/baby/news/20030417/white-noise-may-delay-infant-development>), their popularity appears to be on the rise.

Another example of abnormal sound input early in life that could potentially lead to longer-term listening difficulties is temporary unilateral conductive loss due to infection of the middle ear, a condition named amblyaudia in analogy to the better known amblyopia (Whitton & Polley 2011; Kaplan et al. 2016). Animal studies have shown that short periods of such conductive loss can alter CANS development and disrupt binaural integration and hearing in noise even after a complete reversal of the loss (Knudsen et al. 1984; Popescu & Polley 2010; Polley et al. 2013; Gay et al. 2014). While some residual conductive loss sometimes remains in older children and adults with a history of middle ear infection, especially those who required multiple intubations (typically 5 to 10 dB, especially above 4 kHz; Hunter et al. 1996), the bulk of the lingering difficulties hearing in noise is likely the result of impaired binaural hearing, as evidenced by poor performance on the masking level difference test (Lynn et al. 1981), for example (Teele et al. 1984; Pillsbury et al. 1991; Wilmington et al. 1994; Hall et al. 1995; Hogan & Moore 2003; Gray et al. 2009).

Abnormal sound input can also trigger long-lasting changes in the mature auditory brain, which maintains a lifelong capacity not only for perceptual learning but also for passive sound-driven plasticity (Pienkowski & Eggermont 2011, 2012; Eggermont 2014; Gourévitch et al. 2014). For example, adult cats exposed for several weeks or months to sharply band-limited, moderately loud noise showed a long-term suppression of auditory cortical responses to sound frequencies within the noise band, and an enhancement of responses to frequencies just above and below the noise band, in the apparent absence of hearing loss (Noreña et al. 2006; Pienkowski & Eggermont 2009, 2010a, b; Pienkowski et al. 2011). These cortical changes may be the neural correlates of the loudness rescaling demonstrated in normal-hearing human subjects after several weeks of wearing a noise generator or earplugs (Formby et al. 2003; Fournier et al. 2014).

Could working or living in moderately noisy environments lead to listening difficulties over time, even in the absence of synaptopathic-type losses? Kujala et al. (2004) reported electrophysiologic evidence of impaired syllable discrimination in quiet, but interestingly, not in noise, in 8 shipyard workers and 2 preschool teachers (23 to 36 years old) with an average 6 years of moderate occupational noise exposure but normal audiograms. The fact that syllable discrimination was impaired in quiet but not in noise suggests that synaptopathy was not a factor. Similar findings were described in a recent animal study by Zheng (2012): adult rats exposed to moderately loud broadband noise had impaired frequency discrimination in quiet but better discrimination in noise. These results suggest that while persistent exposure to moderately loud noise can lead to difficulties hearing in quiet (see also Zhou & Merzenich 2012; Kamal et al. 2013), noise at nonsynaptopathic levels can actually be useful for improving listening in noise. Such low level “sound therapy” has also been shown to reduce the impact of a traumatic noise exposure, and to potentially ameliorate tinnitus and hyperacusis (Noreña & Eggermont 2005, 2006; Noreña & Chery-Croze 2007; Schaette et al. 2010), providing that the noise spectrum is matched to the frequency range of the hearing loss and contains the pitch of the tinnitus.

PERIPHERAL HEARING LOSS, APD, OR COGNITIVE DEFICIT?

Lesions of the CANS, caused by neurodegenerative disease, stroke, tumor growth, head injury, etc., can lead to APDs without impacting hearing sensitivity (Musiek & Chermak 2014). Audiologic assessment for APD is presently indicated when listening difficulties occur in the apparent absence of peripheral hearing loss (but see the “Hidden Hearing Loss” section) and cognitive disorders. The American Academy of Audiology (2010) recommends that relevant psychologic/psychiatric assessments be performed first, so that information about potential attention, memory, and linguistic deficits is available to the audiologist before APD testing. However, as this is not always practical, the audiologist can perform basic tests of attention, memory, and linguistic abilities, such as continuous performance tests (Riccio et al. 2001) and the Second Comprehensive Test of Phonological Processing (CTOPP2; Wagner et al. 2013). If cognitive deficits are found, they should be controlled for in subsequent APD testing, as discussed further below.

Audiologic assessment for APD has traditionally consisted of psychoacoustic tests with reasonably good sensitivity and specificity for detecting frank lesions of the CANS (Musiek 1983a; Musiek & Pinheiro 1987; Jerger et al. 1988; Musiek et al. 1991, 2005, 2011; Rappaport et al. 1994; Hurley & Musiek 1997; Boscaroli et al. 2011; Musiek & Weihing 2011; Bamiou et al. 2012; Musiek & Chermak 2015). For example, in a recent study on 20 adult patients with neurologically confirmed bilateral cortical lesions that included auditory cortex (caused by epilepsy, stroke, tumors, or head trauma), and 29 age-matched controls, Musiek et al. (2011) reported a sensitivity of 80% and specificity of 93% for the dichotic digits (Musiek 1983b) and frequency patterns tests (Musiek 1994) when used as a two-test battery (i.e., failure required performance below the control group 95% CI on both tests). While these are useful numbers for screening purposes, justifying further psychoacoustic, electrophysiologic, and neurologic testing, it is unclear whether such a test battery could effectively predict the existence of CANS lesions in the general population of children and adults with listening difficulties, many or most of whom may instead have hidden peripheral losses or cognitive deficits.

A key factor influencing the diagnostic utility of any clinical test is the prevalence of the condition the test is designed to detect. If the prevalence is low, then the predictive power of a test with even high sensitivity and specificity may be poor. At present, the general prevalence of the types of CANS lesions used to validate the dichotic digits and frequency patterns test battery by Musiek et al. (2011) is difficult to estimate. As a hypothetical example, consider a prevalence of 10%, with the remaining 90% of cases of hearing problems despite normal audiograms attributable to HLL or to cognitive deficits. The conditional probability, $P(L|F)$, of a frank CANS lesion (L), given a failed APD test or test battery (F), also known as the positive predictive value, is given by Bayes' rule:

$$P(L|F) = P(L \cap F) / P(F),$$

where $P(L \cap F)$ is the joint probability of having a lesion and failing the test battery. If test sensitivity and specificity, as established in patients with confirmed CANS lesions, is 80% and 93%, respectively (Musiek et al. 2011), then $P(F) = 0.1(0.8)$

+ 0.9(0.07) = 0.143 (i.e., you can fail the test as a true positive or a false positive, respectively), and $P(L \cap F) = 0.1(0.8) = 0.08$ (i.e., the joint probability is just the probability of being a true positive). Finally, $P(L|F) = 0.08/0.143 = 56\%$. Thus, if a person failed the dichotic digits and frequency patterns test battery, he would have a roughly 50/50 chance of actually having a CANS lesion. On the other hand, if the prevalence of CANS lesions among people with listening difficulties and normal audiograms was only 1%, the positive predictive value of Musiek et al.'s (2011) test battery would drop to just 10%. The predictive value would also drop if HHL or cognitive deficits also resulted in poorer performance on such tests of "AP" (Smurzynski & Probst 1999; Neijenhuis et al. 2004; Glyde et al. 2013; Musiek & Chermak 2015).

A number of studies have reported that children who fail tests of AP are also likely to fail tests of cognition (Sharma et al. 2009, 2014; Miller 2011; Ahmed et al. 2014). For example, Sharma et al. (2009) found that in a sample of 68 children (7 to 12 years old) with suspected APD, almost half (47%) failed not just the AP tests but also the language and reading tests, whereas only 4% failed just the AP tests, 7% just the language tests, and 4% just the reading tests. A popular explanation for this apparent comorbidity has been that AP deficits, especially poor temporal acuity, can delay language acquisition and literacy (Tallal & Piercy 1973; Tallal 1980, 2004; Benasich & Tallal 2002; Banai et al. 2005; Ziegler et al. 2005, 2009; Boets et al. 2011; Hornickel et al. 2012; Hornickel & Kraus 2013; White-Schwoch et al. 2015). However, poor temporal acuity could also be a consequence of hidden peripheral losses (Lopez-Poveda & Barrios 2013), and cognitive deficits could drive poor performance on tests of AP. As reviewed by Rosen (2003) and substantiated by some of the more recent data (Amitay et al. 2002; Richardson et al. 2004; Dawes et al. 2009; Rosen et al. 2009; Watson & Kidd 2009; Bishop et al. 2012; Vandewalle et al. 2012), most children and adults with language and reading difficulties do not in fact appear to have impaired AP, and when they do, the deficits do not always include fast temporal processing. The current consensus seems to be that language and reading disorders more often result from impaired linguistic rather than auditory sensory processing (Bailey & Snowling 2002; Pennington & Bishop 2009). Figure 3 provides an intuitive guide to distinguishing between the two. Note that comparing performance on tests of AP that use speech versus nonspeech sounds is probably not sufficient to differentiate APD from linguistic disorders, as children with the latter tend to do poorly with both classes of stimuli (Loo et al. 2013).

In contrast to Sharma et al. (2009), Gyldenkerne et al. (2014) reported that 57% of 101 children with listening difficulties (also 7 to 12 years old) failed an AP test battery, 50% failed the auditory and visual sustained attention test (Sandford

& Turner 1995), while 34% failed both. If AP and attention deficits were independent, the expected failure rate for both would be 29% (57% × 50%), not much less than the observed 34%, suggesting that AP and attention deficits can exist as largely independent conditions, with each contributing roughly equally to the case count of children with listening difficulties. In an interesting study, Moore et al. (2010) randomly sampled 1469 primary school children (6 to 11 years old) and found that the correlation between numerous metrics of AP and cognition was low ($0.1 < \rho < 0.3$, or at most about 10% of the variance in AP scores was explained by cognitive factors), as also reported by others (Riccio et al. 2005; Rosen et al. 2010; Gyldenkerne et al. 2014). (Note that in elderly adults, these correlations are typically higher, but then secondary to the effect of audiometric hearing loss [Akeroyd 2008; Humes et al. 2013]). Nevertheless, the bottom 5% of auditory performers in the Moore et al. study also had significantly lower cognitive scores than the top 95% or "typical" auditory performers, suggesting that auditory problems in the general primary school population could indeed be caused primarily by cognitive deficits. When the auditory tests were modified to control for cognitive confounds, by taking the difference scores of pairs of subtests that kept the cognitive load constant while varying the difficulty of the auditory task (as in the masking level difference test and the low cue versus high cue subtests of the Listening in Spatialized Noise-Sentences test [LiSN-S]; see below), the bottom 5% of auditory performers no longer had significantly worse cognitive scores than the top 95%. (A complementary strategy would be to keep the auditory difficulty constant across subtests while varying the cognitive load.) Moore et al.'s message was that applying uncontrolled tests of AP to the general primary school population would tend to catch children with cognitive issues rather than sensory ones. While these findings have been criticized on several grounds (Musiek & Chermak 2015), the general approach of employing subtest difference scores to control for cognitive confounds seems to be a very useful one, as further illustrated below.

A good example of defining a subtype of APD and creating a specific, controlled test to detect it was recently provided by Dillon and colleagues (Cameron & Dillon 2007a, b, 2008; Dillon et al. 2012). Their LiSN-S test, developed to detect deficits in binaural or spatial processing, is a twist on the masking level difference test (Lynn et al. 1981). In the LiSN-S, simple target sentences are presented binaurally and in phase through earphones, so that they are localized to the front of the listener. In the four subtests of the LiSN-S, illustrated in Figure 4, two distractor voices are either co-localized to the front, or lateralized to the sides; furthermore, the two distractors are produced either by the speaker of the target sentences or by different speakers. In addition to the individual subtest scores, three difference scores can be calculated (Fig. 4): "talker advantage" gives the amount of improvement when distractor voices are different from the target voice; "spatial advantage" gives the amount of improvement when distractors are lateralized relative to the target, analogous to masking level differences; "total advantage" combines both elements, but is not necessarily equal to the summed improvement of the talker and spatial advantages. The "high cue" subtest (Fig. 4), when both spatial and speaker cues are available, should be administered first, and a normal score would rule out difficulties using these cues to hear effectively in noise (unless the ability to use one cue was enhanced by a deficit in the ability to use the other). As reported in Dillon et al. (2012), of 183 children identified by teachers or parents as

Upon hearing a phrase, ask the following questions:

Did you hear it?	Can you explain what it means?
Can you repeat it?	Will saying it slower help?
Can you identify the first sound?	Will repeating it multiple times help?
Can you identify another sound you heard?	Will making it louder help?
If the answer to these questions is "yes"	If the answer to these questions is "no"

Then the problem is language processing, not auditory processing

Fig. 3. An intuitive guide to differentiating deficits in linguistic and auditory processing. Adapted from Richard (2013).

having difficulties hearing in noise, only 40 (22%) failed the high cue subtest. It is thus clear that many other auditory and cognitive factors contribute to listening difficulties in children. However, in most of the children who failed the high cue LiSN-S, a subsequent normal score on the low cue subtest (Fig. 4) ruled out cognitive issues, as the cognitive demands of the low and high cue subtests are essentially the same. Running the remaining two subtests and calculating the talker and spatial advantage difference scores could then partial out the contributions of talker and spatial cues to the abnormal total advantage score. When this was done, 32 children were found to have an abnormal spatial advantage while only 4 had an abnormal talker advantage. Thus, in this sample, spatial processing deficits were eight times more likely to contribute to listening difficulties than speaker discrimination deficits. Cameron et al. (2012) went on to show, albeit only in a small-sample study of 10 of the children with spatial processing deficits as diagnosed by LiSN-S, that their LiSN & Learn auditory training program, which specifically targeted the spatial deficits, led to improved LiSN-S spatial advantage scores, whereas a non-specific commercial auditory/reading training program (Earobics, Boston, MA) did not. These results support the strategy of subtyping APD and implementing deficit-specific remediation (see the “Implications for AT” section), a promising approach that has also been investigated and advocated by others (e.g., Moncrieff & Wertz 2008; Bellis & Bellis 2015).

In addition to psychoacoustic testing, electrophysiology can also be useful for differentiating auditory from cognitive contributors to listening difficulties in noise. As mentioned, the standard click- and tone ABR can be a sensitive and specific screener for lesions of the auditory nerve and brainstem (due to neuropathies, acoustic neuromas and other tumors, multiple sclerosis, infections, stroke, trauma, etc.), often even if thresholds are unaffected (Hosford-Dunn 1985; Hendrix et al. 1990; Levine et al. 1993; Starr et al. 1996; Häusler & Levine 2000; Litovsky et al. 2002; Cho et al. 2005; Church et al. 2007). In many cases, the lesions can then be confirmed by neuroimaging, particularly magnetic resonance imaging.

In recent years, the “complex” ABR (cABR), best studied using the syllable /da/, has been introduced as a potentially more sensitive metric of subcortical speech processing than the click or tone ABR (Skoe & Kraus 2010; Anderson & Kraus 2013a). The cABR normally resembles a low-pass-filtered version of the stimulus waveform, and can be analyzed to assess subcortical speech-encoding fidelity in both the time and frequency domains. For example, in a study of older adults (60 to 73 years old) with clinically normal audiograms, cABR amplitudes to /da/ presented either in quiet or in noise correlated strongly with HINT (hearing in noise test) scores (Anderson et al. 2011). The same was true in younger adults with normal self-reported hearing (Song et al. 2011), suggesting that the cABR could provide an objective, subcortical correlate of the large variability in SIN scores observed across young, apparently normal-hearing listeners (Surprenant & Watson 2001). Interestingly, in both young, normal-hearing (Song et al. 2012) and older subjects (Anderson et al. 2013), AT to improve hearing in noise led to more robust cABRs in noise, while musicians also showed better cABRs in noise compared with nonmusicians (Parbery-Clark et al. 2009; Bidelman & Krishnan 2010). The cABR could therefore potentially differentiate auditory from cognitive contributions to listening difficulties, although it could just as easily be affected by hidden deficits at the level of the cochlea and auditory nerve (see the “Cochlear Synaptopathy” section) as by deficits in brainstem processing.

Finally, while both pre- and post attentive auditory cortical evoked potentials (e.g., middle latency response, late potentials, P300) and electroencephalograms have been studied in children with listening difficulties despite normal thresholds (e.g., Jirsa & Clontz 1990; Purdy et al. 2002; Sharma et al. 2006; Schochat et al. 2010; Gilley et al. 2016), it’s not yet clear if cortical recordings could be useful in differentiating between sensory and cognitive contributions to listening difficulties in noise, given the intertwined nature of cortical processing (Medwetsky 2011; Poremba & Bigelow 2013; Steinschneider 2013).

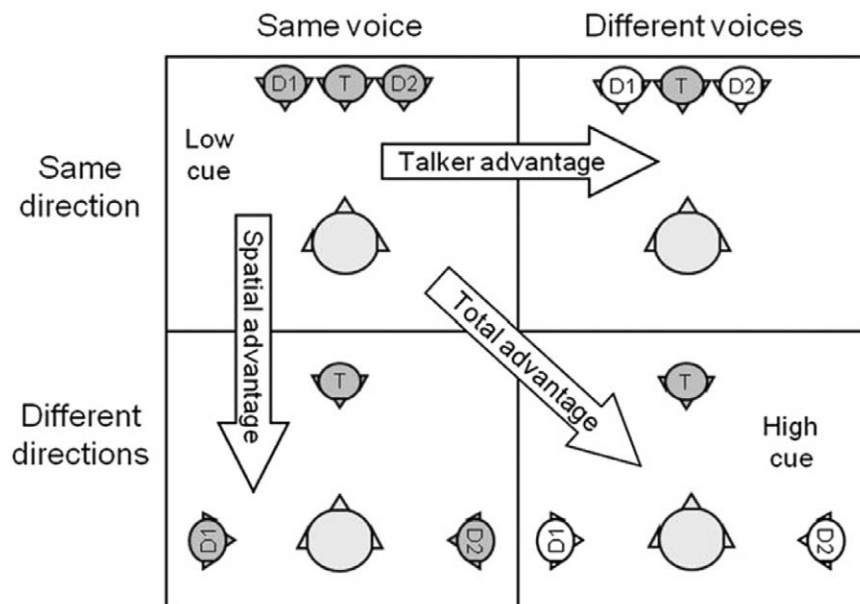


Fig. 4. Subtests of the LiSN-S test. See text for explanation. Adapted from Figure 2 in *J Am Acad Audiol*, 2012;23, 97–105. LiSN-S, listening in spatialized noise-sentences.

IMPLICATIONS FOR AT

Animal studies have demonstrated that perceptual training leads to rapid improvements in task performance, initially by shifting neural receptive fields to expand the “representational area” of the trained parameter in sensory-motor cortex (Recanzone et al. 1992, 1993; Fritz et al. 2003; Bao et al. 2004; Polley et al. 2006; Atiani et al. 2009; Bieszczad & Weinberger 2010; Whitton et al. 2014), and then by consolidating a more efficient representation from the expanded one (Molina-Luna et al. 2008; Bajo et al. 2010; Reed et al. 2011). Such demonstrations of CANS plasticity have provided the rationale for the rapid emergence of commercial computer-based AT programs for people both with and without audiometric hearing loss, with considerable evidence for their efficacy (Sweetow & Palmer 2005; Moore et al. 2009; Anderson & Kraus 2013b; Henshaw & Ferguson 2013). In a recent study, Loo et al. (2016) randomized 39 children (7 to 11 years old) diagnosed with APD into an intensive (3 months, 5 days/week) AT group, consisting of a variety of SIN listening tasks, or a standard treatment-only control group. Only the AT group showed improved hearing in noise, as assessed using the LiSN-S. Furthermore, the improvement correlated with better scores on the Children’s Auditory Processing Performance Scale questionnaire (Smoski et al. 1992), and were retained for at least 3 months after the completion of training. The Loo et al. (2016) study suggests that children diagnosed with APD using conventional clinical methods can benefit from intensive speech-based AT.

An intriguing question is the extent to which AT could be even more efficacious if the specific deficits underlying the APD (or the listening difficulties more generally) are targeted. To the extent that hearing in noise involves a wide range of AP and cognitive skills, generic speech-based training could provide benefits for a wide range of patients with listening difficulties, including those with purely cognitive issues. In fact, in a study of older adults with mild hearing loss who underwent phoneme discrimination training, reductions in self-reported hearing disability best correlated with training-induced improvements in attention and working memory, not auditory skills (Ferguson et al. 2014). Nevertheless, it is reasonable to suppose that deficit-specific training should result in maximal improvement in the ability to hear in noise (Cameron et al. 2012). For example, training a person with a binaural integration deficit on sound localization tasks should improve hearing in noise more than training on phonemic discrimination tasks.

CONCLUDING SUMMARY

Many people with tone thresholds in the wide “clinically normal” range have considerable difficulty understanding speech in noisy environments. In the apparent absence of cochlear damage and of cognitive disorders, such people have traditionally been subject to psychoacoustic tests of “AP,” and diagnosed with APD on failing one or more of them (American Speech-Language-Hearing Association 2005; American Academy of Audiology 2010; British Society of Audiology 2011; Wilson & Arnott 2013). However, there is a strong possibility that certain configurations of noise- and age-related peripheral loss, “hidden” from the audiogram and other conventional clinical tests, could also account for many cases of listening difficulties and for failure on some of the tests of AP (see the “‘Clinically Normal’ Audiograms” and “Cochlear Synaptopathy” sections). The same is true of deficits in attention,

working memory or linguistic abilities (see the “Peripheral Hearing Loss, APD, or Cognitive Deficit?” section). Furthermore, impaired AP could also be a consequence of abnormal patterns of sound input (e.g., auditory deprivation, persistent background noise), especially during developmental sensitive periods but also in adulthood, even in the absence of peripheral losses (including the hidden variety) and of frank lesions affecting the CANS (see the “Central HHL” section). Promising new tests to uncover hidden peripheral losses, and tests of central auditory function that better control for peripheral and cognitive confounds could soon translate to improved differential diagnosis of the causes of hearing difficulties in noise. It will then remain to determine how best to tailor the promising tool of AT to the specific deficits of individual patients (see the “Implications for AT” section).

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Erratum

Background Noise Degrades Central Auditory Processing in Toddlers: Erratum

In the article that appeared on page e342 on of the November/December 2015 issue of *Ear and Hearing* “Background noise degrades central auditory processing in toddlers”, there is an error. The correct signal to noise ratio between the syllable stimuli and cafeteria noise is 20 dB, not 15 as reported in the article on page e345. This error does not change the results of the research. The authors sincerely apologize for this error.

Reference:

Niemitalo-Haapola, E., Haapala, S., Jansson-Verkasalo, E., & Kujala, T. (2015). Background noise degrades central auditory processing in toddlers. *Ear Hear*, *36*, e342–e351.