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**REVIEW ARTICLE****Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy****Gary Rance<sup>1</sup> and Arnold Starr<sup>2</sup>**

The effects of inner ear abnormality on audibility have been explored since the early 20th century when sound detection measures were first used to define and quantify ‘hearing loss’. The development in the 1970s of objective measures of cochlear hair cell function (cochlear microphonics, otoacoustic emissions, summing potentials) and auditory nerve/brainstem activity (auditory brainstem responses) have made it possible to distinguish both synaptic and auditory nerve disorders from sensory receptor loss. This distinction is critically important when considering aetiology and management. In this review we address the clinical and pathophysiological features of auditory neuropathy that distinguish site(s) of dysfunction. We describe the diagnostic criteria for: (i) presynaptic disorders affecting inner hair cells and ribbon synapses; (ii) postsynaptic disorders affecting unmyelinated auditory nerve dendrites; (iii) postsynaptic disorders affecting auditory ganglion cells and their myelinated axons and dendrites; and (iv) central neural pathway disorders affecting the auditory brainstem. We review data and principles to identify treatment options for affected patients and explore their benefits as a function of site of lesion.

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**Abbreviation:** ABR = auditory brainstem response

**Introduction**

Neurologists have been well aware of ‘hearing’ impairments affecting the auditory nerve due to infections (e.g. lues), neoplasms (e.g. acoustic neuroma, brainstem meningiomas) and hereditary neuropathies (e.g. Friedreich ataxia and Charcot–Marie–Tooth disease) (Spoendlin 1974; Hallpike *et al.*, 1980; Nadol *et al.*, 2001). The development in the 1970’s of objective measures of ‘hearing’ using both averaged evoked potentials of auditory

nerve/brainstem pathways [auditory brainstem responses (ABRs), Starr, 1978] and objective measures of cochlear sensory hair cells (cochlear microphonics, Dallos and Cheatham, 1976; and cochlear otoacoustic emissions, Kemp, 1978) allowed the identification of hearing disorders due to auditory nerve dysfunction that were distinct from impairment due to sensory receptor loss. The hearing disorder accompanying auditory nerve abnormality reflects impaired processing of acoustic temporal cues which are critical for sound localization, discrimination of speech,

and identification of signals in background noise (Starr *et al.*, 1991; Rance *et al.*, 2004; Zeng *et al.*, 2005).

The diagnosis of ‘auditory neuropathy’ was proposed for patients with normal objective measures of hair cell activity (otoacoustic emission/cochlear microphonic) but abnormal auditory nerve functions (ABRs) as many also had clinical evidence of neuropathies affecting other cranial and/or peripheral nerves (Starr *et al.*, 1996; Fujikawa and Starr, 2000). Post-mortem examination of the cochlea from an individual with auditory neuropathy due to Charcot–Marie–Tooth disease (Type 1) (Starr *et al.*, 2003) showed marked loss of both auditory nerve fibres and ganglion cells whereas cochlear inner and outer hair cell counts were normal. These findings are similar to those reported by Spoendlin (1974) and Hallpike *et al.* (1980) in patients with hereditary neurological disorders and ‘unusual hearing loss’.

Auditory neuropathy is a common cause of hearing disorder. Approximately 1 in 7000 neonates evaluated through ‘new-born hearing screening’ is identified as having abnormal auditory nerve function (Rance and Starr, 2011). These children account for ~10% of permanent childhood hearing loss (Rance, 2005). Progressive forms of auditory neuropathy occur with a wide range of conditions including: mitochondrial disorders, genetic mutations affecting both synaptic and neural function, autoimmune abnormalities, toxic metabolic disorders, nutritional deficits and degenerative changes accompanying ageing and noise trauma (Starr *et al.*, 2000; Santarelli, 2010; Cacace and Pinheiro, 2011; Plack *et al.*, 2014; Starr and Rance, 2014). Supplementary Table 1 shows a representative sample of aetiologies associated with auditory neuropathy. Also shown are the peripheral, sensory and cranial neuropathies that often present in concert with the auditory disorder.

Over the past decade the term ‘auditory neuropathy spectrum disorder’ has been used for patients with abnormal ABRs and preserved cochlear hair cell responses. ‘Spectrum disorder’ may be appropriate for clinical conditions (such as autism) where objective measures are lacking and understanding of underlying aetiologies is limited. Recent advances in the auditory neuropathy field have, however, made the term redundant. In this review we address the clinical and pathophysiological features of auditory neuropathy using audiological, psychoacoustical and electrophysiological measures that distinguish between site(s) of abnormal function along the auditory nerve. These include: (i) presynaptic disorders affecting inner hair cells and ribbon synapses; (ii) postsynaptic disorders affecting unmyelinated auditory nerve dendrites; (iii) postsynaptic disorders affecting auditory ganglion cells and their myelinated axons and dendrites; and (iv) central neural pathway disorders affecting the auditory brainstem. We will identify treatment options that are useful in enhancing auditory signal processing for affected patients and explore their benefits as a function of site of lesion.

## Objective measures of cochlear hair cell and auditory nerve function

Objective measures of neural function provide the neurologist with tools to localize the site(s) of neurological disorder, quantify changes with time and treatment, and reveal underlying mechanisms. In particular the tests used to evaluate the auditory system include measures of function of sensory receptors, auditory nerve, auditory brainstem, and auditory cortex. They are relatively simple to perform and well tolerated by patients. These tests are outlined below.

### Cochlear hair cells

#### Otoacoustic emissions

Sound presented to a normal ear causes contraction of the cochlear outer hair cells due to conformation changes of the protein prestin (Liberman *et al.*, 2002). The contractions stiffen the basilar membrane and amplify its movement to reduce sound detection threshold and enhance frequency tuning. The mechanical amplification is accompanied by the production of cochlear pressure waves (‘acoustic emissions’) that are too faint for the subject to ‘hear’ but can be recorded by a microphone placed in the ear canal. The measure provides objective evidence of the functional integrity of outer hair cells (Kemp, 1978).

#### Cochlear microphonics

Cochlear microphonics are electrical potentials generated by depolarization and repolarization of both inner and outer hair cells that reproduce the acoustic wave forms of externally presented sounds (Dallos and Cheatham, 1976). They can easily be identified from scalp-recorded ABRs and are distinguishable from neural potentials in that they show a direct phase relationship with the stimulus waveform (Starr *et al.*, 1991). The term ‘microphonic’ was coined by Adrian (1930) as the potentials persisted to stimulus frequencies (e.g. 4 kHz) far above the upper firing rate limits of nerve fibres and remained even when the cochlea was cooled with ice.

#### Inner hair cell receptor summing potentials

The summing potential reflects the graded depolarization of inner hair cells to acoustic signals and is of largest amplitude when recorded via a needle electrode placed trans-tympanically on the cochlear promontory or round window (electrocochleography) (Durrant *et al.*, 1998). The amplitude and latency of the summing potential are objective measures of inner hair cell function.

## Auditory nerve and brainstem pathways

### Compound action potentials

The compound action potential reflects the response of auditory nerve fibres to transient signals such as acoustic ‘clicks’. The response can be identified as Wave I in scalp-derived ABRs, but is of much larger amplitude when recorded using transtympanic electrocochleography (Eggermont, 1976).

### Auditory brainstem response

The auditory brainstem response consists of five distinct peaks occurring in the first 10 ms after presentation of a brief auditory signal (Jewett and Williston, 1971). Wave I is generated by the VIIIth nerve close to the cochlea, Wave II is generated at the proximal portion of the VIIIth nerve, Wave III is generated in the region of the cochlear nucleus, and Waves IV and V are generated by the lateral lemniscus (Starr and Hamilton, 1976; Martin *et al.*, 1995). Neural conduction time along the auditory nerve and brainstem structures is reflected by the absolute latency difference between Waves I and V [normal:  $4.0 \pm 0.2$  ms (Starr and Achor, 1975)]. The relative amplitudes of wave components (V/I ratio) has been used as a measure of brainstem dysfunction (Rance *et al.*, 2008, 2012*d*). An abnormal increase in the amplitude ratio of Wave V/Wave I may also be useful in defining the presence of dendritic disorders of the auditory nerve (Kujawa and Liberman, 2009).

### Acoustic middle ear muscle reflex

The middle ear muscle reflex is a contraction of the stapedius muscle elicited by loud sounds causing movements of the tympanic membrane that can be detected by a microphone placed in the ear canal. The reflex arc involves auditory nerve, brainstem and facial nerve (Borg, 1973).

## Auditory neuropathy phenotype

Diagnosis of auditory neuropathy relies on (i) objective neurophysiological measures of cochlear hair cell and auditory nerve functions; (ii) imaging of auditory nerve/brainstem; and (iii) behavioural audiological measures. Figure 1 shows test results for an individual with unilateral auditory neuropathy who presented aged 37 years with ‘difficulties understanding speech in background noise’ and an inability to localize sounds. Sound detection thresholds for the left ear were within normal limits [ $\leq 15$  dB HL (decibels hearing level)]. For the right ear, a mild/moderate degree (predominantly low frequency) hearing loss was obtained. Acoustic middle ear muscle reflexes were present (in both the left and right ears) for stimuli presented to the left side, but absent (in both left and right ears) for signals presented to the right ear. Acoustic reflex absence is typical of

auditory neuropathy and is thought to be due to impaired synchrony of auditory nerve firing. In contrast, patients with auditory neuropathy have preserved middle ear reflexes to cutaneous stimulation of the face (Starr *et al.*, 1996, 1998).

Speech discrimination score (monosyllabic words) for the (normal) left ear was 100%, and abnormal to stimulation of the right ear (12%). This latter result was far poorer than expected for a mild/moderate loss of sensory origin, where speech scores  $\geq 90\%$  are typical. Temporal processing ability was assessed using a ‘gap detection’ task where the shortest detectable silent period in a burst of noise was established. Detection threshold for the left ear was normal, but was significantly elevated for the right, showing a threshold of 11 ms—more than double that expected for a normal listener (Rance *et al.*, 2010*a*).

Cochlear sensory hair cell activities were normal bilaterally. Amplitudes of both outer hair cell responses (cochlear microphonics/otoacoustic emissions) and inner hair cells summing potentials were within normal limits.

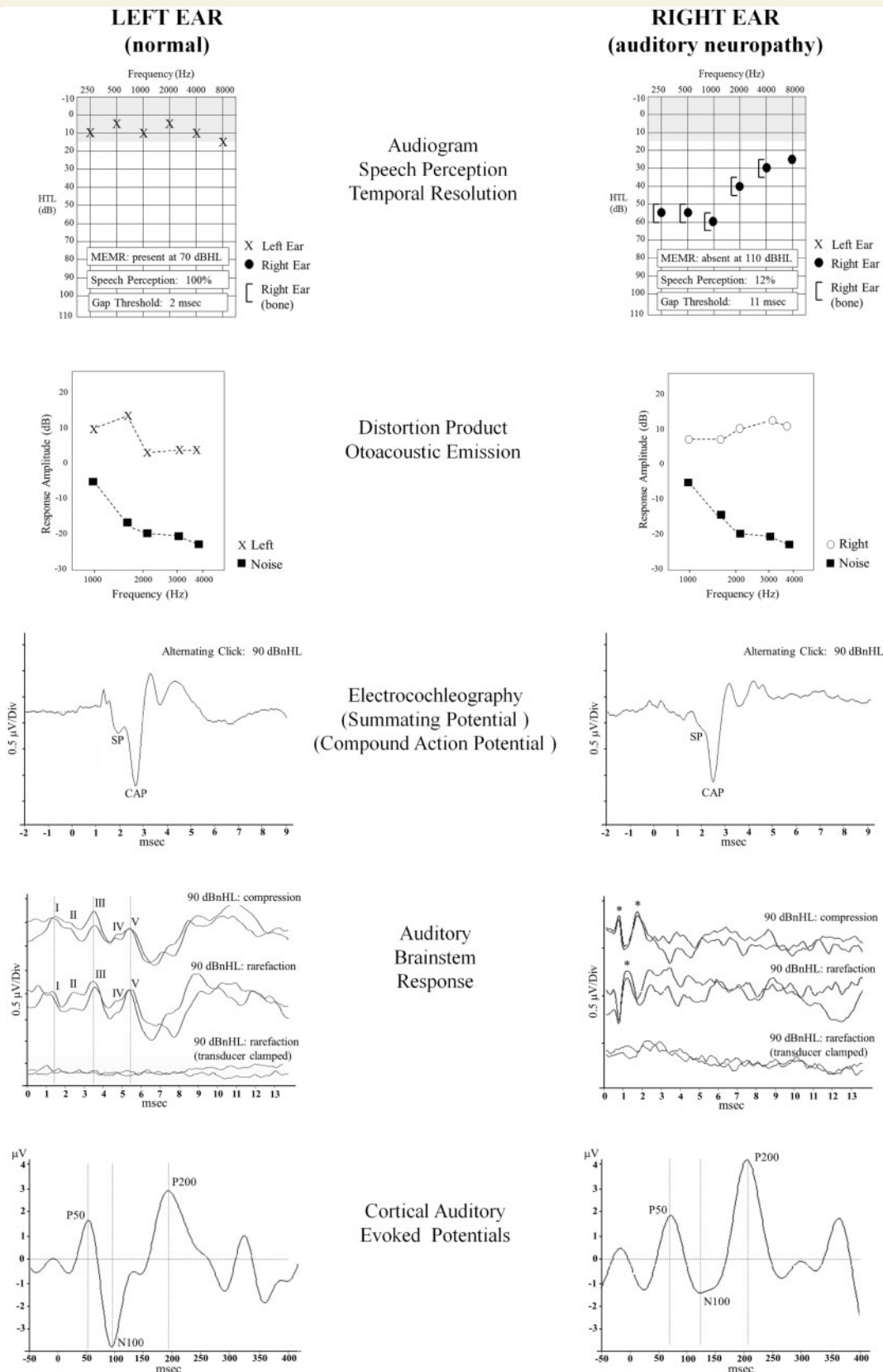
Auditory brainstem responses to left ear stimulation were normal. In contrast, right ear stimulation showed absent ABR neural components but present cochlear microphonic responses. The mismatch between preserved preneural activity (cochlear microphonic/otoacoustic emission) and absent auditory brainstem potentials are objective criteria for auditory neuropathy.

Cortical auditory evoked potentials of equivalent amplitude were obtained bilaterally even though ABRs were only recordable to stimulation of the left ear. The presence of these cortical responses reflects the different sensitivity of the auditory brainstem and cortex to temporal variation. Recording of the ABR is dependent on precise neural synchrony and the response is attenuated by temporal fluctuations of as little as 0.5 ms (Starr *et al.*, 1991). In contrast, cortical potentials of normal amplitude/morphology can be obtained even when temporal synchrony varies by 20 ms (Michalewski *et al.*, 1986). In the auditory neuropathy subject in Fig. 1, cortical peak latencies were present, but delayed to stimulation of the affected (right) ear by up to 25 ms (P50: 65 ms; N100: 125 ms), consistent with impaired processing of temporal cues at stimulus onset (Onishi and Davis 1968).

Most cases of unilateral auditory neuropathy are the result of auditory nerve hypoplasia (Buchman *et al.*, 2006). MRI scans of the brainstem and CT images of the cochleae were, however, normal in this patient.

## Disruption of auditory nerve activity

There are two basic mechanisms by which neural activity is disrupted in the auditory brainstem: (i) reduction of the number of activated auditory nerve fibres (deafferentiation); and (ii) reduction in the degree of neural synchrony



**Figure 1 Audiological and electrophysiological results for an individual with unilateral auditory neuropathy.** Findings contained in panels on the *left* were obtained for stimuli presented to the left (normal) ear. Panels on the *right* represent results for the right (auditory neuropathy) ear. The ‘audiogram’ is the pattern of behavioural sound detection thresholds displayed as a function of stimulus frequency. The shaded area represents the normal sensitivity range. Electrocochleography and ABR testing used acoustic clicks at maximum presentation levels [90 dBnHL (decibels normal hearing level)]. For the right side the ABR is absent but the cochlear microphonic (asterisks) is present. Note that the microphonic shows a phase reversal with change in stimulus polarity (compression/rarefaction) confirming that the potential is of pre-neural origin. The sinusoidal waveform disappears when the stimulus tube is clamped indicating that the potential is not stimulus artefact.

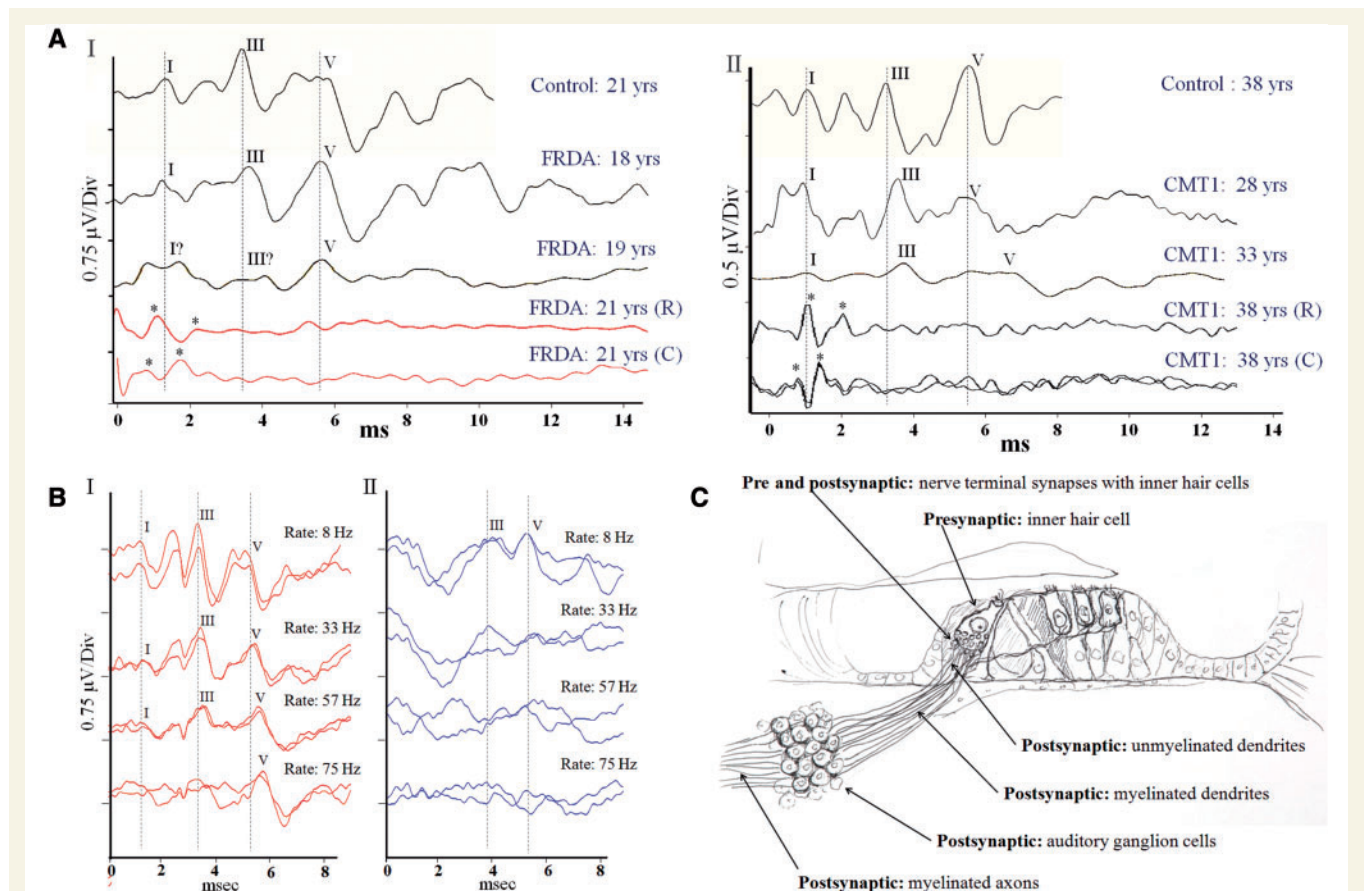
(dyssynchrony). Examples of each form are shown in Fig. 2A. Figure 2A(I) is from an individual with progressive axonal neuropathy (Friedreich ataxia). Figure 2A(II) is from an individual with progressive demyelinating disorder Charcot–Marie–Tooth disease (Type 1). Note that in the axonal case, ABR amplitudes decrease between age 18 and 19 years, but inter-peak conduction times are unaffected. Two years later (age 21) ABRs are absent but the cochlear microphonic (marked with asterisks) is preserved. In the individual with progressive demyelinating neuropathy, ABR interpeak latency increases over time from 4.5 ms at 28 years to 6 ms at 33 years. In addition, response amplitude decreases over time consistent with desynchronization of neural firing and/or loss of functioning nerve fibres.

Increasing the rate of stimulus presentation in subjects with normal hearing is accompanied by both an attenuation of ABR amplitudes and an increase in peak latencies (Fig. 2B). These effects are exaggerated in auditory

neuropathy due to both presynaptic (Wynne *et al.*, 2013; Santarelli *et al.*, 2015a) and postsynaptic disorders (Daly *et al.*, 1977; Pratt *et al.*, 1981; Fowler and Noffsinger, 1983). Figure 2B shows this rate effect in a 61-year-old individual with auditory neuropathy due to diabetic neuropathy.

## Auditory electrophysiological measures and site of lesion

Knowledge of the site(s) of lesion is important to define mechanisms of altered nerve function in auditory neuropathy and inform clinical management. Figure 2C shows the different sites of damage within and beyond the cochlea and Table 1 provides an overview of the different pathologic mechanisms known to produce the auditory neuropathy phenotype, their primary loci and the typical electrophysiological results.



**Figure 2 Auditory brainstem response patterns for patients with auditory neuropathy.** (A) Longitudinal ABR recordings for individuals with neurodegenerative disease. In both cases essentially normal sound detection and normal otoacoustic emission responses were preserved throughout the testing period. Panel I shows tracings obtained over 3 years from a patient with axonal neuropathy due to Friedreich ataxia (FRDA). Panel II shows recordings over 10 years from an individual with progressive demyelinating disorder [Charcot-Marie-Tooth disease Type I (CMT1)]. In both cases the ABR was unrecordable at final assessment, but the cochlear microphonic was preserved. (B) Auditory brainstem responses to acoustic click stimuli at presentation rates ranging from 8–75 Hz. Panel I shows tracings for a control subject with repeatable waveforms to each stimulus rate. Waves I, III and V are labelled when present. Panel II shows findings for a patient with diabetic neuropathy in whom ABRs are only identifiable to clicks at very slow rates (8 Hz). (C). Pre and postsynaptic sites of lesion associated with auditory neuropathy.

**Table 1** Auditory electrophysiological measures and site of lesion

Site of lesion	Pathological mechanism	Locus	Aetiology examples	Cochlear/auditory nerve activity				Key references
				CM	SP	CAP	ABR	
<b>Presynaptic</b>	Receptor disorder	Inner hair cell	Oxygen deprivation	Normal	Abnormal	Abnormal	Abnormal	Amatuzzi <i>et al.</i> , 2001
	Synaptic disorder	Ribbon synapse	Genetic <i>OTOF</i>	Normal	Normal	Abnormal	Abnormal	Starr <i>et al.</i> , 1998 Santarelli <i>et al.</i> , 2008
<b>Postsynaptic</b>	Diminished auditory nerve activity	Dendrites	Genetic <i>OPA1</i>	Normal	Normal	Abnormal	Abnormal	Huang <i>et al.</i> , 2009 Santarelli <i>et al.</i> , 2015c
		Dendrites and axons	Peripheral Neuropathy FRDA CMT2	Normal	Normal	Abnormal	Abnormal	Starr <i>et al.</i> , 1991; 1996 Rance <i>et al.</i> , 2008, 2012d
		Ganglion cells	Kernicterus	Normal	Normal	Abnormal	Abnormal	Rance <i>et al.</i> , 1999 Shapiro, 2003
	Dyssynchronous nerve activity	Myelin	CMT1	Normal	Normal	Abnormal	Abnormal	Rance <i>et al.</i> , 2012d
	Hypoplasia	Auditory nerve	Congenital malformation	Normal	Normal	Absent	Absent	Buchman <i>et al.</i> , 2006
	Conduction disorder	Brainstem	Acoustic neuroma Multiple sclerosis	Normal	Normal	Normal	Abnormal	Laury <i>et al.</i> , 2009 Chiappa, 1997

CAP = compound action potential; CM = cochlear microphonic; SP = summating potential.

## Presynaptic mechanisms of auditory neuropathy

### Cochlear inner hair cell dysfunction and/or loss

The cochlear inner hair cells are the primary point of contact between the sensory mechanism and the auditory nerve. Loss or dysfunction of these cells results in amplitude reduction or loss of the receptor summating potential and subsequent decrement of auditory nerve activity. This receptor disorder is typically associated with ‘sensory’ hearing loss, but the auditory neuropathy pattern arises when the outer hair cells are normal and can produce otoacoustic emissions and/or the cochlear microphonic.

Selective loss of cochlear inner hair cells as a cause of auditory neuropathy was reported by Amatuzzi *et al.* (2001) in premature infants with elevated/absent ABRs. Experimental animal studies also indicate that prolonged hypoxia, can have greater effects on inner, than outer hair cell survival (Shirane and Harrison, 1987; Billett *et al.*, 1989). However, both of these findings are inconsistent with results from adult temporal bones that have not shown isolated inner hair cell loss.

### Inner hair cell ribbon synapses

Deficits of neurotransmitter release from ribbon synapses are a major cause of deafness in neonates with abnormal ABRs (Del Castillo and Del Castillo, 2012; Moser *et al.*, 2013). The typical pattern of objective measures includes: normal summating potentials reflecting normal inner hair cell functions, abnormal compound action potentials reflecting reduced and/or varying time of activation of auditory nerve terminals and absent or abnormal ABRs (Santarelli *et al.*, 2008, 2015a).

Physiological studies of experimental animals with homozygous otoferlin (encoded by *OTOF*) mutations have shown impaired glutamate neurotransmitter release (Moser *et al.*, 2013). In humans, a particular mutation of *OTOF* is associated with relatively normal ‘hearing’ when afebrile but severely impaired sound detection and loss of both compound action potential and ABR potentials with slight elevations of core temperature (Starr *et al.*, 1998; Varga *et al.*, 2006). These patients show rapid adaptation of subjective loudness for steady tones consistent with impairment of neurotransmitter reuptake and/or release (Wynne *et al.*, 2013).

## Postsynaptic mechanisms

Disorders of auditory nerve function can occur at multiple sites along the auditory nerve including: (i) unmyelinated dendrites within the cochlea; (ii) myelinated dendrites and axons coursing centrally; and (iii) myelinated auditory ganglion cells. The loss of nerve fibres and ganglion cells is accompanied by a reduction in the amplitude of synchronous input.

### Dendritic nerve terminals

Auditory nerve terminals within the cochlea are unmyelinated and synapse with inner hair cells. Their number, size and position relative to the hair cell vary systematically along the basilar membrane. Pathology affecting the dendritic nerve terminals results in a pattern of objective measures similar to those outlined for ribbon synapse disorders: i.e. normal summating potentials reflecting normal inner hair cell functions and absent nerve responses (compound action potentials). In an example of terminal dendritic abnormality (due to *OPA1* gene mutation), Santarelli *et al.*

(2015c) describe a prolonged low amplitude negative potential that adapts at high stimulation rates (consistent with a neural origin). Auditory brainstem responses are absent or abnormal.

Auditory nerve terminals within the cochlea become reduced in size and number in aged subjects and likely contribute to hearing loss during ageing (presbycusis) (Chen *et al.*, 2006). Dendritic damage from noise trauma has also been proposed by Liberman and colleagues from animal studies showing that dendrites swell and withdraw from synaptic connection with inner hair cells due to excessive neurotransmitter release (Kujawa and Liberman, 2009). The number of auditory ganglion cells gradually reduces over time and ABRs in these animals show a significant reduction of amplitude of ABR Wave I but not of Wave V. The effects of noise exposure and ageing on the auditory nerve terminals and has been named ‘cochlear neuropathy’ (Furman *et al.*, 2013). The term ‘hidden hearing loss’ has also been used reflecting the fact that patients may have a dendritic, postsynaptic disorder (and consequently suffer a range of perceptual deficits) while displaying sound detection thresholds within the normal range (Plack *et al.*, 2014).

### Axonal neuropathies

Axonal neuropathies reduce neural activity in the auditory nerve and brainstem without affecting cochlear hair cells [Fig. 2A(I)]. Patients with pathology restricted to the nerve should have normal summing potentials and reduced amplitude or absent compound action potential/ABR depending on the degree of deafferentiation (Table 1).

Friedreich ataxia is an hereditary degenerative disorder leading to loss of peripheral and cranial nerve fibres in which nearly all patients show the auditory neuropathy result pattern late in the disease process (Rance *et al.*, 2010a). Rance *et al.* (2008) found reduced ABR Wave V/I amplitude ratios (in patients who still had recordable potentials) consistent with axonal loss in the auditory nerve. Furthermore, Santarelli *et al.* (2015b) carried out objective measures of auditory function in such patients and found summing potentials to be of normal latency but reduced amplitude and compound action potentials absent and replaced by a prolonged negativity, suggesting that Friedreich ataxia may also result in a reduction of inner hair cell function producing reduced depolarization of terminal dendrites.

### Auditory ganglion cell disorders

There are ~25 000 bipolar auditory neural ganglion cells. Their viability is susceptible to a number of adverse metabolic factors including hyperbilirubinaemia (Shapiro, 2003). Objective measures of auditory function in jaundiced patients with auditory neuropathy (Santarelli and Arslan, 2002) show normal summing potentials consistent with normal inner hair cell function, absent compound action potentials replaced by low amplitude sustained

negativities characteristic of reduced neural dendritic responsiveness and absent ABRs.

### Myelin disorders

Some forms of auditory neuropathy may reflect the attenuation of synchronous neural discharges due to demyelination. The intermodal lengths in normal auditory nerve fibres are remarkably constant. However, slight changes of intermodal length introduced in regenerating demyelinated fibres could adversely affect neural synchrony (Waxman, 1977; Rasminsky, 1984; Uncini and Kuwabara, 2015). An example of a peripheral nerve disease with demyelination is Charcot–Marie–Tooth disease type 1. Auditory brainstem responses in patients so affected show prolonged conduction times between Wave I and III (VIIIth nerve to cochlear nucleus) but normal central conduction times between Waves III and V (cochlear nucleus to lateral lemniscus) suggesting demyelination affecting auditory nerve but not auditory brainstem pathways (Rance *et al.*, 2012d) [Fig. 2A(II)].

Demyelination disorders can accompany axonal damage. For example, Wynne *et al.* (2013) evaluated patients with a range of disorders consistent with nerve fibre abnormality and found ABRs were abnormal with both reduced amplitude and delayed I–V conduction times. When stimuli were repeated trains of clicks, ABRs to the initial click were normal, but responses became attenuated and delayed to subsequent stimuli suggesting the development of a ‘conduction block’ during repetitive stimulation (Rasminsky and Sears, 1972).

### Hypoplasia of auditory nerve

Congenital hypoplasia of the auditory nerve (or ‘cochlear nerve deficiency’) may be unilateral or bilateral and may occur in children with physiologically normal cochleae (Buchman *et al.*, 2006). Brainstem and auditory nerve images reveal either an ‘absent’ or ‘small’ auditory nerve (Buchman *et al.*, 2006; Jeong and Kim, 2013). Receptor summing potentials would be present, reflecting normal inner hair cell population and function, but compound action potentials and ABRs are typically absent (Table 1).

### Auditory nerve conduction disorders

Pontine angle tumours such as vestibular neuromas and meningiomas frequently present with a hearing disorder resembling auditory neuropathy due to compression of proximal auditory nerve. Auditory brainstem response results vary from complete absence to preserved waveforms with prolonged wave I–V conduction times. Removal of the tumour in some cases may result in normalization of the ABR, suggesting that the neural disruption was likely due to a conduction block of nerve fibres.

Multiple sclerosis is associated with demyelination of central auditory brainstem fibres. ABR Wave I is typically unaffected whereas central components (Waves III–V) can be absent or delayed in latency (Chiappa, 1997). As such,



multiple sclerosis is a brainstem disease that has many features similar to auditory nerve disorders.

## Perceptual deficits accompanying auditory neuropathy

### Sound audibility

Average sound detection thresholds (hearing levels) in both adult and paediatric populations are evenly distributed with ~10% showing thresholds within the normal range ( $\leq 15$  dBHL) and a similar proportion unable to detect high level ( $\geq 90$  dBHL) stimuli (Rance *et al.*, 1999; Sininger and Oba, 2001; Berlin *et al.*, 2010). Fluctuating sound detection has also been reported, particularly in individuals with OTOF mutations who can present with severe deficits when febrile that are promptly corrected when core temperature normalizes (Starr *et al.*, 1998). The mechanism in this case is not known, but would be consistent with impaired intracellular calcium ion regulation, which is essential for ribbon synapse transmitter release.

### Complex auditory signal processing

The perceptual consequences of auditory neuropathy are distinct from those associated with cochlear sensory hearing loss, reflecting their different pathological mechanisms. These differences and some of the behavioural measures used to quantify them are summarized in Table 2. Individuals with auditory neuropathy suffer disruption of the neural code resulting in a range of perceptual deficits including: inability to judge sound direction; impaired capacity to discriminate complex or rapidly changing sounds (such as speech); and a decreased ability to detect/discriminate signals in the presence of background noise (Starr *et al.*, 1991, 1996; Rance *et al.*, 2004, 2012e; Zeng *et al.*, 2005).

### Cochlear processing (frequency/intensity cues)

Outer hair cell loss results in disruption of cochlear-level processing of frequency and intensity cues. In listeners with sensory loss, disruption of the cochlear amplifier (mediated by contraction of the outer hair cells) impairs frequency resolution along the basilar membrane and also results in abnormal loudness growth (recruitment) (Evans and Harrison, 1976; Turner *et al.*, 1989). In patients with auditory neuropathy, in contrast, outer hair cell function is usually preserved and affected listeners typically show normal cochlear processing of frequency and intensity parameters (Rance *et al.*, 2004; Zeng *et al.*, 2005).

### Neural processing (temporal cues)

Disruption of neural firing patterns in auditory neuropathy is accompanied by abnormal percepts dependent on

auditory temporal cues. In normal listeners, auditory neurons encode the temporal features of sounds by synchronizing their firing (phase locking) to both the fine structure of the acoustic waveform and the overall signal envelope. This temporal coding is precise (sensitive to changes  $< 50 \mu\text{s}$ ) and is relatively unaffected by audibility changes that accompany cochlear sensory loss (Moore, 1995). Individuals with auditory neuropathy are, however, severely impaired and show a range of real-life listening consequences.

### Localization

Judging the direction of sound sources is achieved through comparison of subtle differences in the intensity and timing of acoustic signals reaching each ear. Localization of high frequency sounds is (primarily) based on interaural loudness differences and is relatively unimpaired by auditory neuropathy (Zeng *et al.*, 2005). Localization of low frequency sound sources, in contrast, is contingent on the ability to integrate timing differences of  $\sim 50 \mu\text{s}$  and is grossly impaired (Zeng *et al.*, 2005). Where normal listeners can identify sound direction changes of  $< 3^\circ$ , auditory neuropathy patients are typically unable to detect alterations of up to  $90^\circ$  (Table 2).

### Rapid changes in complex signals

Temporal resolution affects the ability to perceive (or track) rapid signal changes and is disrupted by auditory neuropathy. For example, identification of brief silent periods in a continuous signal is impaired and auditory neuropathy-patients typically require gaps two to five times longer than normal listeners (Table 2). Similarly, the ability to track rapid signal changes is affected. Most auditory neuropathy listeners, for example, are unable to identify amplitude fluctuations occurring over a time period  $< 10$  ms, where normal subjects can track changes lasting  $< 2$  ms (Table 2). As many of the cues that differentiate speech sounds occur over this time course, speech understanding may be significantly affected. For example, the only acoustic cue marking the difference between voiced and unvoiced stop-consonants (such as /t and d/ and /p and b/) is the duration of the gap between consonant burst and the accompanying vowel. These gaps last only around 30–70 ms and are typically indistinguishable to listeners with auditory neuropathy (Rance *et al.*, 2008, 2010a).

Disordered processing of auditory temporal cues is a consequence of both pre- and postsynaptic neuropathy. Presynaptic auditory neuropathy (for example due to OTOF mutation) disrupts neurotransmitter release, reuptake, or storage, affecting both the number of activated fibres and the consistency of fibre discharge (Glowatzki and Fuchs, 2002; Glowatzki *et al.*, 2008). Similarly, postsynaptic disorders reduce both the number of activated fibres and (particularly in cases where myelin is affected) the temporal synchrony of their firing (Waxman 1977).

Psychophysical measures of auditory nerve function cannot distinguish between pre- and postsynaptic neuropathies as both affect temporal processing to a similar degree

**Table 2 Behavioural measures of auditory function and typical outcomes for listeners with normal hearing, cochlear-sensory loss and auditory neuropathy**

Percept	Assessment		Stimulus	Results		Key references
	Locus	Assessment		Normal	Cochlear sensory loss	
Sound audibility	Cochlea	Audiogram (sound detection threshold)	Pure tones (250 Hz–8 kHz)	≤ 15 dBHL	<b>Abnormal</b> (20–120 dBHL +)	Rance <i>et al.</i> , 1999
	Cochlea	Difference limen (threshold for detection of pitch change)	High freq tones (≥ 1 kHz)	< 100 Hz	<b>Abnormal</b> (100–150 Hz)	Sininger and Oba, 2001
Frequency discrimination	Cochlea + neural	Intensity difference limen (threshold for loudness change)	Low freq tones (< 1 kHz)	< 10 Hz	<b>Abnormal</b> (> 80 Hz)	Rance <i>et al.</i> , 2004
	Cochlea	Loudness growth function (dynamic range: 'just audible' to 'uncomfortable')	Tones	< 3 dB	Normal	Zeng <i>et al.</i> , 2005
Intensity discrimination	Cochlea	Difference limen (threshold for timing change)	Tones	90 dB	<b>Abnormal</b> (recruitment) 20–70 dB	Zeng <i>et al.</i> , 2001
	Neural	Difference limen (threshold for timing change)	Gap detection (silent period in a continuous sound)	≤ 5 ms	Normal	Starr <i>et al.</i> , 1996
Temporal discrimination	Neural	Difference limen (threshold for timing change)	Amplitude modulation detection (rapid intensity changes) [e.g. 150 Hz]	Change in amplitude (≤ 10%)	<b>Abnormal</b> (> 20 ms)	Zeng <i>et al.</i> , 2005
	Neural	Difference limen (threshold for timing change)	Amplitude modulation detection (rapid intensity changes) [e.g. 150 Hz]	Change in amplitude (≤ 10%)	<b>Abnormal</b> (> 50% [–6 dB])	Rance <i>et al.</i> , 2004
Localization	Brainstem (binaural integration)	Difference limen (threshold for sound direction change)	High frequency signals	< 3°	Normal	Zeng <i>et al.</i> , 2005
	Cochlea-brain	Word or sentence discrimination	Low frequency signals	< 3°	Normal	
Speech perception	Brainstem (binaural integration)	Word or sentence discrimination	Speech in quiet	≈ 100%	<b>Abnormal</b> (> 90°)	
	Cochlea-brain	Word or sentence discrimination	Speech in noise (e.g. 0 dB SNR where speech and noise are the same level)	≈ 50%	<b>Abnormal</b> (50–80%)	Starr <i>et al.</i> , 1996
Spatial streaming	Brainstem (binaural integration)	Speech perception advantage (dB) when signal and noise are spatially separated	Target speech and competing noise originating from different azimuths (typically separated by 90°)	≥ 10 dB	<b>Abnormal</b> (0–30%)	Roush <i>et al.</i> , 2011
	Brainstem (binaural integration)	Speech perception advantage (dB) when signal and noise are spatially separated	Target speech and competing noise originating from different azimuths (typically separated by 90°)	≥ 10 dB	<b>Abnormal</b> (5–10 dB)	Zeng and Liu, 2006

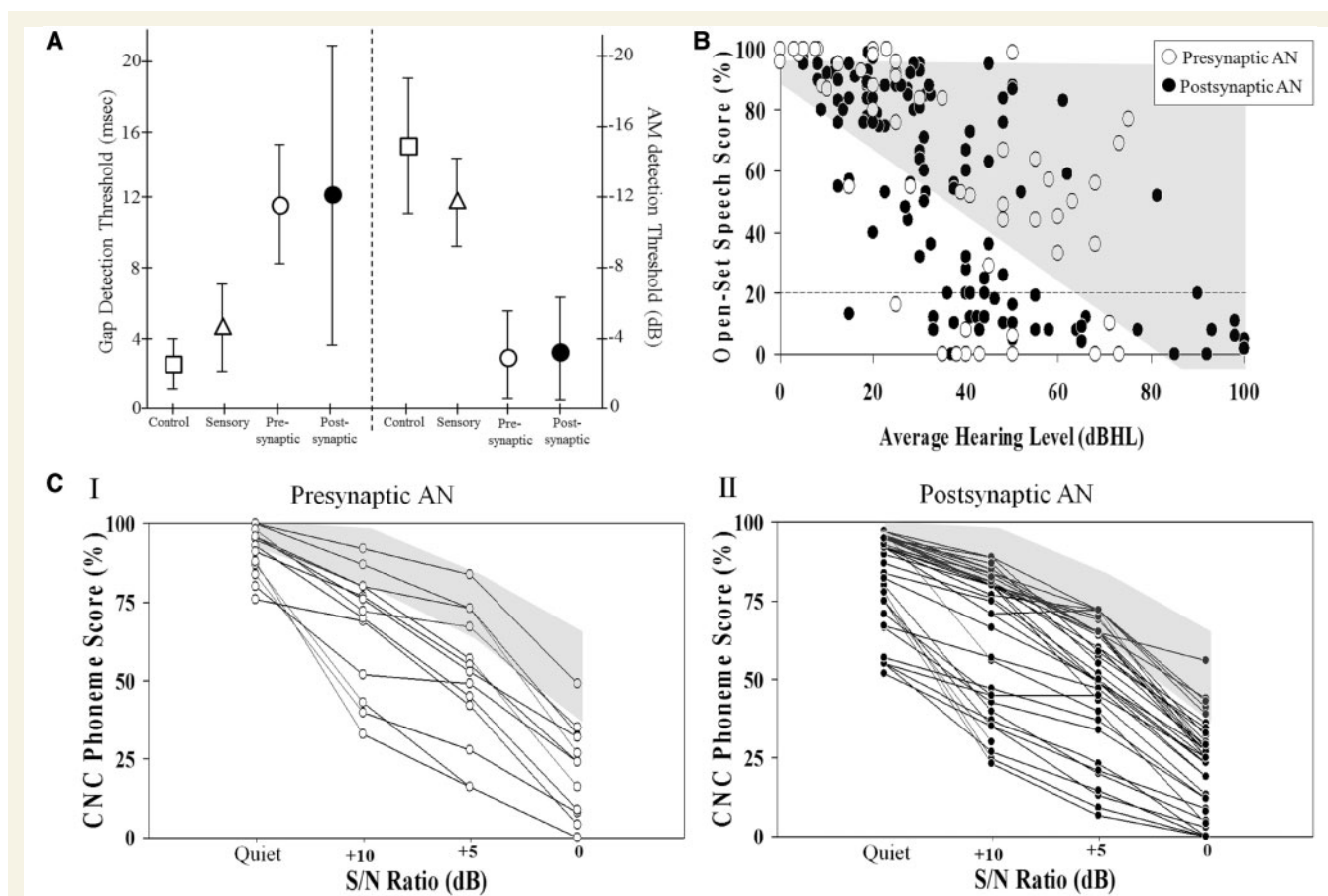
SNR = signal-to-noise ratio. Text in bold highlights absent or abnormal findings.

(Fig. 3A). They can, however, distinguish between auditory neuropathy and cochlear sensory loss. For the patients with auditory neuropathy represented in Fig. 3A, 29/35 (83%) showed gap detection ability outside the 95% performance range for sensory loss and 31/32 (97%) showed detection of rapid amplitude modulation outside the sensory loss range.

## Speech perception

The major functional consequence of auditory neuropathy is impaired understanding of speech. Cochlear sensory loss also affects speech perception, but to a lesser extent, and

with degree of deficit closely related to reduced signal audibility. That is, ears with poorer sound detection thresholds suffer greater speech understanding difficulty. Figure 3B reflects this relationship with the shaded area representing the 95% performance range for speech perception (in quiet). In patients with auditory neuropathy, this audibility/speech perception relationship does not apply. Instead, degree of temporal processing disruption is typically the limiting factor (Rance *et al.*, 2004, 2010a, 2012d; Zeng *et al.*, 2005). As such, auditory neuropathy listeners often report that they can ‘hear’ speech, but ‘can’t understand what is said to them’. Individuals with pre- and postsynaptic abnormality are similarly affected (Fig. 3B).



**Figure 3 Auditory perceptual findings in patients with auditory neuropathy.** (A) Temporal processing in individuals with cochlear-sensory hearing loss and patients with pre- and postsynaptic auditory neuropathy. Based on data presented in Starr *et al.*, 1996, Zeng *et al.*, 1999; Rance *et al.*, 2004, 2010a, 2012d, e; Dimitrijevic *et al.*, 2011; Wynne *et al.*, 2013. Both pre- and postsynaptic auditory neuropathy groups showed poorer gap detection threshold than controls ( $P < 0.01$ ). Both pre- and postsynaptic auditory neuropathy groups showed poorer amplitude modulation (AM) detection (150 Hz) threshold than controls ( $P < 0.001$ ). (B) Open-set speech perception score plotted against average hearing level for individuals with auditory neuropathy due to presynaptic (open circles) and postsynaptic (closed circles) mechanisms. Based on data presented in Starr *et al.*, 1991, 1996, 1998, 2003; Rance *et al.*, 1999, 2004, 2007, 2008, 2012c, d, 2014; Miyamoto *et al.*, 1999; Zeng *et al.*, 2005, Zeng and Liu, 2006; Dimitrijevic *et al.*, 2011; Santarelli *et al.*, 2015a. The grey area represents the 95% performance range for ears with cochlear sensory hearing loss (Yellin *et al.*, 1989). Thirty-eight per cent (61/159) of auditory neuropathy listeners show speech understanding outside this range. A score of  $< 25\%$  represents speech perception insufficient to support normal conversation. (C) Open set speech perception scores for patients with auditory neuropathy with normal sound detection thresholds. Shown are scores for consonant-vowel nucleus-consonant (CNC) words presented in quiet and at +10 dB, +5 dB and 0 dB signal-to-noise ratios. The shaded area represents the 95% performance range for age-matched controls. Panel I shows findings for individuals with presynaptic auditory neuropathy. Panel II shows findings for postsynaptic auditory neuropathy. Based on data from Zeng and Liu, 2006; Rance *et al.*, 2007, 2008, 2012c, d, 2014.

## Speech processing in noise

In addition to suffering signal distortion in quiet listening conditions, listeners with auditory neuropathy experience extreme difficulties in background noise (Fig. 3C). Three possible explanations for this phenomenon are: (i) impaired ‘gap listening’; (ii) rapid loudness adaptation; and (iii) disrupted spatial streaming.

### Gap listening

Disruption of the temporal code in auditory neuropathy listeners affects the ability to separate sounds occurring sequentially (Zeng *et al.*, 2005). In everyday listening, where levels of background noise fluctuate, this may impair the listener’s ability to use brief gaps in the noise to access the speech signal and optimize perception (Alcántara *et al.*, 2004).

### Adaptation

Abnormal adaptation of signal loudness during constant stimulation has been reported for some forms of auditory neuropathy, particularly that associated with ribbon-synaptic disorder (Santarelli *et al.*, 2008; Wynne *et al.*, 2013). In affected listeners, the presence of continuous background noise could result in both an increase in activation threshold and a rise in degree of neural dyssynchrony.

### Spatial streaming

In everyday circumstances, auditory signals emanate from different directions and sound localization cues may be used to separate a signal of interest from the background noise. This phenomenon has been referred to as ‘spatial streaming’ or the ‘cocktail party’ effect (Micheyl *et al.*, 2007). Auditory neuropathy disrupts the ability to prioritize a particular signal based on its location and consequently, patients with auditory neuropathy obtain  $\approx 5$  dB less benefit from spatial streaming than normal listeners (Rance *et al.*, 2012*e*). This degree of deficit is functionally significant, and likely to increase stress and impact cognitive function in everyday (noisy) listening situations (Hetu *et al.*, 1990).

Patients with pre- and postsynaptic auditory neuropathy show similar speech-in-noise deficits (Fig. 3C), but both are distinguishable from listeners with normal auditory function. While many of the individuals represented in Fig. 3C demonstrated relatively unimpaired speech perception in quiet conditions, 46/52 (88%) were outside the normal range for speech presented in ‘everyday’ levels of background noise [0 dB SNR (decibels signal-to-noise ratio)].

## Pathophysiology and intervention

### Improving the acoustic signal

Perception of complex sounds in auditory neuropathy listeners is limited by the degree of neural disruption. As temporal deficits are a cardinal feature of all types of

auditory neuropathy, the effects of (acoustic) interventions have been broadly similar for both pre- and postsynaptic forms.

Listening and communication in background noise may be improved by increasing the level of the speech signal relative to the noise. This may be achieved by: (i) configuring the listening environment to minimize the noise; (ii) amplifying the speaker’s voice via a loudspeaker; or (iii) recording the speaker’s voice via a microphone near the mouth and transmitting the signal directly (via radio waves) to a receiver in the listener’s ear. This approach significantly improves the signal-to-noise ratio and has benefitted children with auditory neuropathy, improving both communication and academic outcomes (Rance *et al.*, 2010*b*).

Conventional hearing aids may be used to amplify the acoustic signal and improve speech audibility for listeners with auditory neuropathy, but these devices are often not helpful as making sounds louder does not improve the processing of auditory temporal cues (Starr *et al.*, 1996; Rance *et al.*, 2002; Rance, 2005; Berlin *et al.*, 2010; Roush *et al.*, 2011; Ching *et al.*, 2013). Digital speech processing hearing aids with algorithms capable of accentuating temporal differences may be beneficial (Zeng *et al.*, 2001). For example, timing cues can be enhanced by exaggerating the sound level changes that occur in natural acoustic signals. This process, known as ‘amplitude expansion’ has been tested in patients with auditory neuropathy, but is not yet commercially available (Narne *et al.*, 2008).

## Cochlear implantation and auditory neuropathy

Cochlear implantation is currently the intervention option of choice for most patients with auditory neuropathy. Multi-channel implantation is a surgical intervention in which stimulating electrodes are placed within the cochlear scala tympani. Current flow between electrodes activates the auditory nerve at various sites including myelinated dendrites, auditory ganglion cells and auditory axons. Most patients with sensory hearing loss are benefitted sufficiently to converse on the telephone, and most (children) demonstrate normal rates of speech, language and academic achievement (Leigh *et al.*, 2013).

In contrast, cochlear implant outcomes in patients with auditory neuropathy are variable. The majority benefit and achieve speech understanding, language development and communication outcomes equivalent to their peers with cochlear sensory loss (Trautwein *et al.*, 2001; Madden *et al.*, 2002; Shallop, 2002; Mason *et al.*, 2003; Zeng and Liu, 2006; Rance and Barker, 2009; Teagle *et al.*, 2010; Santarelli *et al.*, 2015*c*). A significant proportion ( $\approx 25\%$ ), however, obtain minimal benefit from the cochlear implantation, failing to achieve functionally useful hearing and showing no improvement on their preoperative auditory capacity (Gibson and Sanli, 2007; Teagle *et al.*, 2010; Roush *et al.*, 2011).

The efficacy of cochlear implantation in auditory neuropathy is closely related to the site(s) of lesion. This has been most obviously demonstrated for cases with congenital atrophy of cochlear nerve, where the relative diameter of the auditory and facial nerves is a predictor of cochlear implant outcome (Buchman *et al.*, 2006; Walton *et al.*, 2008; Teagle *et al.*, 2010; Jeong and Kim, 2013). Most affected children show little or no sound awareness post-cochlear implant, but occasional cases are benefitted (Walton *et al.*, 2008; Young *et al.*, 2012) (Fig. 4). Close examination of MRI and CT scans in implant candidates with auditory neuropathy is essential as <10% of cases with cochlear nerve deficiency achieve significant speech perception ability (Table 3).

The relationship between auditory neuropathy locus and cochlear implant outcome for other pathologies is less predictable. Figure 4 shows postoperative speech perception scores for all published auditory neuropathy cases where aetiology was reported ( $n = 101$ ). The data are segregated based on whether the patient history suggested a pre- or postsynaptic mechanism. The benefits for individuals with presynaptic auditory neuropathy were similar to those described for candidates with cochlear sensory-type hearing loss (Leigh *et al.*, 2011; Dowell, 2012). Results for postsynaptic cases were variable, but on average poorer than for presynaptic patients (presynaptic:  $76.0 \pm 15.8\%$ ; postsynaptic:  $33.3 \pm 35.0$ ,  $P < 0.001$ ). A breakdown of cochlear implant-outcomes based on aetiology is shown in Table 3.

## Presynaptic auditory neuropathy and cochlear implantation

Individuals thought to have the presynaptic form of auditory neuropathy have consistently shown good cochlear

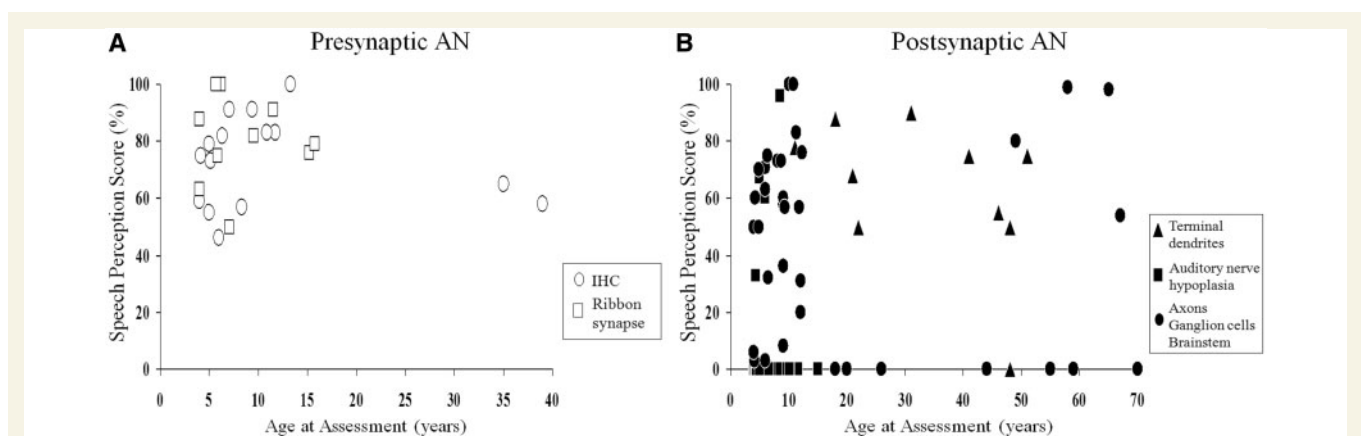
implant outcomes, reflecting the fact that direct electrical stimulation up to the level of the spiral ganglion bypasses the peripheral sensory system (Clopton *et al.*, 1980; Linthicum *et al.*, 1991; Fayad and Linthicum, 2006). Electrically evoked auditory potentials (compound action potential/ABR) are typically present indicating an increase in both the number of fibres activated and/or their synchrony of discharge, and cochlear implant programming levels (the amount of current required to elicit an auditory sensation) are normal (Table 3). Individuals with auditory neuropathy thought due to inner hair cell loss/dysfunction or abnormality of the inner hair cell ribbon synapse have all shown significant perceptual benefit (Fig. 4) and relatively normal rates of communication/language development (Rodriguez-Ballasteros *et al.*, 2003; Rouillon *et al.*, 2006; Gibson and Sanli, 2007; Jeong *et al.*, 2007; Rance and Barker, 2009; Santarelli *et al.*, 2011; Breneman *et al.*, 2012).

## Postsynaptic auditory neuropathy and cochlear implantation

Patients with postsynaptic auditory neuropathy show a range of cochlear implant outcomes reflecting the multiple possible sites of lesion, different pathological mechanisms and variable degrees of neural disruption. At best, affected individuals are afforded speech perception equivalent to their peers with sensory hearing loss. At worst, they achieve no auditory percept to electrical stimulation, or reasonable sound detection but no functionally useful hearing (Table 3).

### Dendritic disorder

All but one of the reported cases with abnormality of the terminal dendrites have benefitted from cochlear



**Figure 4** Open-set speech perception scores for auditory neuropathy patients who have received a cochlear implant in one or both ears. Individuals with confounding factors (such as cognitive deficit or known developmental delay) were excluded as were patients with prelingual auditory neuropathy implanted after the age of 6 years. (A) Individuals with aetiologies likely to result in presynaptic auditory neuropathy. (B) represents those with aetiologies likely to produce postsynaptic auditory neuropathy. Based on: Rance *et al.*, 1999; Rance and Barker, 2009; Miyamoto *et al.*, 1999; Mason *et al.*, 2003; Starr *et al.*, 2004; Rouillon *et al.*, 2006; Jeong *et al.*, 2007; Bradley *et al.*, 2008; Brookes *et al.*, 2008; Helbig *et al.*, 2009; Huang *et al.*, 2009; Oker *et al.*, 2009; Kang *et al.*, 2010; Colletti *et al.*, 2013; Kutz *et al.*, 2011; Breneman *et al.*, 2012; Young *et al.*, 2012; Govaerts *et al.*, 2003; He *et al.*, 2014; Mukherjee *et al.*, 2013; Santarelli *et al.*, 2015c.

**Table 3 Cochlear implant outcomes in auditory neuropathy.**

Site of Lesion	Locus	Aetiology	Reported patients (n = 101)	Electrically Evoked Potentials		CI current levels	Open-Set Speech Perception %	References
				ECAP	EABR			
Presynaptic	Cochlear IHC	Hypoxia	13	Normal	Normal	Normal	46–100	Rance and Barker, 2009 Breneman <i>et al.</i> , 2012
		DIAPH3 mutation	2	*	Normal	*	58–65	Starr <i>et al.</i> , 2004
	IHC ribbon synapse	OTOF mutation	10	Normal	Normal	*	50–100	Santarelli <i>et al.</i> , 2011 Breneman <i>et al.</i> , 2012
Postsynaptic	Dendrite	OPA I mutation	10	<b>Abnormal</b>	Normal	*	50–90	Huang <i>et al.</i> , 2009 Santarelli <i>et al.</i> , 2015c
	Dendrites and axons	Hereditary peripheral nerve disorders	FRDA	1	*	*	20	Miyamoto <i>et al.</i> , 1999
DDON			1	*	*	<b>Elevated</b>	0	Brookes <i>et al.</i> , 2008
CMT1			1	*	*	*	54	Goswamy <i>et al.</i> , 2012
	Ganglion cells	Kernicterus	21	Normal	<b>Variable</b>	<b>Normal or elevated</b>	0–100	Rance and Barker, 2009 Breneman <i>et al.</i> , 2012
	Auditory nerve	Congenital hypoplasia	32	<b>Typically absent</b>	<b>Typically absent</b>	<b>No response at max. Levels (&gt;90%) cases</b>	0 in most (>90%) cases	Buchman <i>et al.</i> , 2006 Young <i>et al.</i> , 2012
	Brainstem	Acoustic neuroma	10	*	<b>Abnormal</b>	*	0–99	Helbig <i>et al.</i> , 2009 Mukherjee <i>et al.</i> , 2013

CI = cochlear implant; CMT1 = Charcot–Marie–Tooth disease; DDON = deafness-dystonia-optic neuropathy (Mohr-Tranebjaerg) syndrome; EABR = electrically evoked auditory brainstem response; ECAP = electrical compound action potential; FRDA = Friedreich ataxia; IHC = inner hair cell; OPA I = optic atrophy I (autosomal dominant optic atrophy). Bolded cells indicate absent or abnormal findings.

\*No published data available.

implantation (Santarelli *et al.*, 2015c). This reflects the fact that implant-generated stimulus can bypass these peripheral processes stimulating the ganglion directly (Linthicum *et al.*, 1991). Electrically evoked ABRs are normal and excellent speech perception is typical (Huang *et al.*, 2009; Santarelli *et al.*, 2015c).

### Disorders affecting auditory nerve/brainstem

Cochlear implant outcomes for pathologies affecting the distal myelinated dendrites, ganglion cells/axons of the cochlear nerve and the central auditory pathways have varied considerably, reflecting the fact that the implant-generated signal in such cases must pass through a diseased system. Electrical evoked potentials in this population are often absent or abnormal suggesting significant degrees of deafferentation and/or desynchronized neural activity. Temporal resolution may also be affected as a consequence. Where Starr *et al.* (2004), for example, found normal (<10 ms) electrical gap detection thresholds in patients with presynaptic auditory neuropathy (due to DIAPH3 mutation), subsequent studies involving postsynaptic patients have revealed elevated gap thresholds suggesting that deficits in the neural code may not be overcome by cochlear implantation (He *et al.*, 2013).

The literature describing cochlear implant outcomes for most aetiologies affecting the auditory nerve/brainstem is sparse with only isolated patients described in most instances (Table 3). Findings for individuals with both deafferentiating and demyelinating neuropathies have, however, tended to be abnormal suggesting that candidature in these populations should be approached with caution.

Outcomes in ears with pontine angle tumours vary according to size and treatment history. Tumour excision is

typically a contraindication for cochlear implant as the nerve is rarely left intact (Lustig *et al.*, 2006; Trotter and Briggs, 2010). Cochlear implantation in untreated ears is, however, becoming more common in cases where the neoplasm is small and stable (Suryanarayanan *et al.*, 2010). Results in patients implanted with tumour *in situ* have been mixed (Helbig *et al.*, 2009; Mukherjee *et al.*, 2013) with ~50% of cases showing no speech perception ability.

The most widely reported aetiology associated with postsynaptic auditory neuropathy is perinatal kernicterus. Cochlear implant outcomes within this group have varied considerably. Some cases have required high current levels to obtain an auditory percept and have shown abnormal electrical auditory brainstem potentials (Rance *et al.*, 1999), while others have demonstrated relatively normal responses. Perceptual outcomes have been diverse with some cases (~50%) achieving significant open-set speech discrimination and others performing at near chance levels (Rance *et al.*, 1999; Vermeire *et al.*, 2003; Jeong *et al.*, 2007; Rance and Barker, 2009; Breneman *et al.*, 2012).

That cochlear implant outcome in a deafferentiating disorder (such as kernicterus) should be poor in some instances seems obvious. A more pertinent question is why might implantation be successful in some cases. Temporal bone examination in deceased implant recipients has revealed that spiral ganglion cell survival is not directly related to implant performance and suggested that excellent perceptual outcomes can be achieved with only 10% of the normal population (Fayad *et al.*, 1991; Linthicum *et al.*, 1991; Fayad and Linthicum, 2006). As such, only those cases with near complete deafferentation are likely to show elevated threshold levels and impaired

speech understanding to electrical stimulation of the auditory nerve.

## Future directions

### Auditory neuropathy as a biomarker for neurodegenerative disease

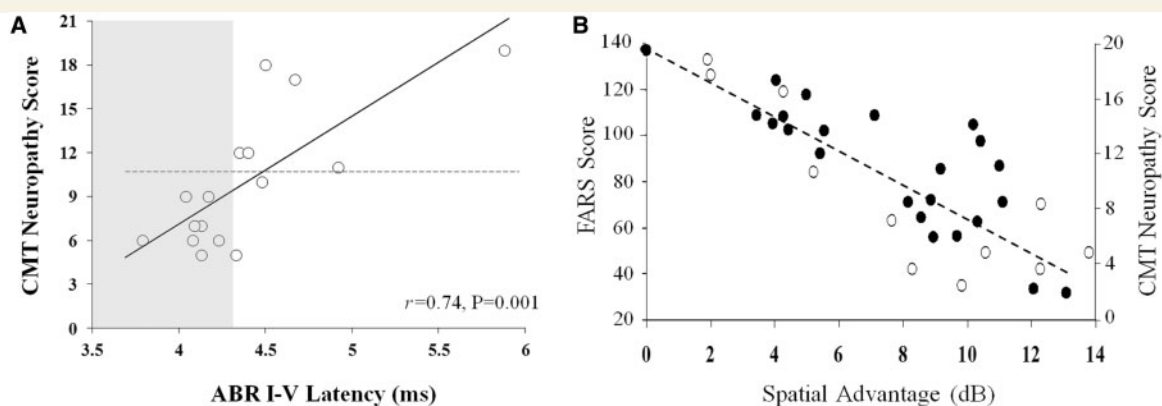
The sensitivity of the auditory system to disruptions in the neural code means that hearing difficulty (particularly affecting speech understanding) is often the first symptom to present in individuals with neurodegenerative conditions (Starr *et al.*, 1996). Recent work suggests that changes in auditory function can be used to track the natural history of disease progression. Cross sectional data have shown correlations between overall disability levels and neural conduction velocity (ABR Wave I–V interpeak latency), auditory temporal processing and speech perception ability in patients with Friedreich ataxia and Charcot–Marie–Tooth disease (Rance *et al.*, 2008, 2010a, 2012e) (Fig. 5). Furthermore, within-subject changes in auditory function over time have mirrored disease progress in patients with both of these conditions (Rance *et al.*, 2012a, e). These findings suggest that measures of auditory neuropathy may also be suitable as biomarkers and recent trials have shown functional hearing improvement in Friedreich ataxia participants undergoing therapeutic intervention (Yiu *et al.*, 2015).

### Clinical challenges

Determination of cochlear implant suitability is a major clinical challenge for auditory neuropathy patients too young to undergo behavioural psychophysical assessment.

As some children with auditory neuropathy do as well with hearing aids as the average implantee (Rance and Barker, 2009; Ching *et al.*, 2013), there is a need to develop non-volitional measures of auditory capacity that can inform management decisions in the first months of life (Yoshinaga-Itano *et al.*, 1998). Cortical auditory evoked onset potentials appear likely candidates as objective measures of auditory processing. Despite an absent or abnormal brainstem response, young patients with auditory neuropathy generally show reliable cortical potentials. In adult patients the ‘acoustic change complex’ can be elicited by stimulus changes (such as temporal gaps, intensity changes and frequency variation) and their thresholds are consistent with those obtained psychophysically (Michalewski *et al.*, 2009; Dimitrijevic *et al.*, 2011). As such, they offer the possibility of objective evaluation of auditory capacity (and potential for acoustic amplification benefit) in infancy (He *et al.*, 2015).

In this review we concluded that the site of dysfunction along the auditory nerve and brainstem pathways is crucial in determining cochlear implant outcome for individuals with auditory neuropathy. There is a need for techniques that can better identify both the site and degree of abnormality in individual patients. MRI is useful for children with hypoplasia, but is not diagnostically helpful for other forms of auditory neuropathy. The next generation of imaging technologies may offer greater insights into the fine structure of the nerves (fibre density/degree of myelination etc.). Diffusion tensor imaging (DTI) is one such technique that can characterize white matter structures by measuring the diffusion of water molecules in the brain (Basser *et al.*, 1994). Most studies in the auditory system have focused on the projections between inferior colliculus and cortex, where microstructural neuronal changes have been observed with ageing (Profant *et al.*, 2014). As yet,



**Figure 5 Auditory dysfunction and disease progression in neurodegenerative disorder.** (A) The relationship between overall disability level for the children with CMTI (Charcot–Marie–Tooth Disease Neuropathy Score) and auditory neural conduction time (ABR Wave I–V interpeak latency). Individuals with ABR latencies within the normal range (shaded) all showed only ‘mild’ effects on clinical examination and a range of neurophysiologic measures (Shy *et al.*, 2005), whereas those with abnormal auditory nerve conduction all experienced more advanced symptoms. Data from Rance *et al.* (2012d). (B) Binaural speech processing ability plotted as a function of overall disease progress in patients with Friedreich ataxia (filled circles) where spatial advantage is plotted against Friedreich Ataxia Rating Scale (FARS) score, and in participants with CMTI (open circles) where spatial advantage is plotted against Charcot–Marie–Tooth Neuropathy Score (CMTNS). Data from Rance *et al.* (2012e).

there have been no reports of DTI findings in patients with auditory neuropathy, but recent work in normal listeners has shown correlations between binaural temporal processing ability and the connectivity strength of auditory fibre tracts in the auditory brainstem (Wack *et al.*, 2014).

Electrical ABR measurement does not address the issue of site of lesion, but the presence of this response is strongly correlated with positive cochlear implant outcome (Walton *et al.*, 2008). Unfortunately the individual must have already undergone the invasive and expensive procedure to establish if the implant-generated response is present. Pre-operative transtympanic electrical auditory brainstem response (where the electrical stimulus is presented via a needle electrode resting on either the cochlear promontory or round window) has proven to be helpful as a pre-operative option in some hands (Gibson and Sanli, 2007), but electrical current distribution with this technique can be unpredictable and results have not consistently predicted cochlear implant outcomes (Nikolopoulos *et al.*, 2000).

Management of patients with auditory neuropathy identified with a poor cochlear implant prognosis also remains a challenge. Electrical stimulation (at the cochlea) may not be the best option for some individuals with auditory nerve abnormality, particularly for those with auditory nerve deficiency where current findings suggest that <10% of cases are afforded useful hearing. Brainstem implants are an alternative approach, used primarily in cases where the nerves are damaged following surgical removal of bilateral acoustic neuroma. Brainstem implantation has struggled to gain clinical acceptance as most patients have shown limited perceptual advantage (Otto *et al.*, 2002; Schwartz *et al.*, 2008), but there is a growing literature suggesting modest benefits in children with auditory neuropathy (Colletti *et al.*, 2004, 2013).

## Summary

Auditory neuropathy represents a nexus between the disciplines of audiology, otology and neurology. Advances in our understanding of auditory neural function have underpinned significant changes in the ways auditory clinicians approach diagnostic testing and intervention in individuals with permanent hearing impairment. Similarly, awareness of the sensitivity of the auditory system to subtle neural changes can inform the management of patients in the neurology clinic. A constant theme running through the auditory neuropathy literature over the past 25 years has been that patients are idiosyncratic, showing varying degrees of 'deafness' despite a common pattern of physiological findings. As outlined in this review, diagnostic techniques have improved, allowing differentiation of sensory receptor, synaptic, auditory nerve and brainstem disorders, but developing methods that can define both the site(s) and degree of dysfunction remains a challenge for the future.

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## Supplementary material

Supplementary material is available at *Brain* online.

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