RELATIONS BETWEEN COCHLEAR SYNAPTOPATHY
AND AUDITORY DEFICITS IN HUMANS WITH
NORMAL AUDIOGRAMS

A thesis submitted to The University of Manchester
for the degree of Doctor of Philosophy
in the Faculty of Biology, Medicine and Health

HANNAH H GUEST
2018

SCHOOL OF HEALTH SCIENCES
Division of Human Communication, Development and Hearing
CONTENTS

CONTENTS .................................................................................................................... 2
ABSTRACT ...................................................................................................................... 3
DECLARATION ............................................................................................................... 4
COPYRIGHT .................................................................................................................... 4
1 BACKGROUND .......................................................................................................... 5
  1.1 Animal evidence for cochlear synaptopathy....................................................... 5
  1.2 Possible implications for human perception..................................................... 5
    1.2.1 Tinnitus........................................................................................................... 5
    1.2.2 Speech perception......................................................................................... 6
  1.3 Translational issues.............................................................................................. 7
    1.3.1 Interspecies differences............................................................................... 7
    1.3.2 Measuring cochlear synaptopathy............................................................... 7
    1.3.3 Estimating noise exposure.......................................................................... 8
  1.4 Synthesis of evidence......................................................................................... 8
2 AIMS & RATIONALE................................................................................................. 9
3 METHODS & RESULTS ............................................................................................ 10
  3.1 The Noise Exposure Structured Interview (NESI): An instrument for the comprehensive estimation of lifetime noise exposure......................................................................................... 11
  3.2 Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy ........................................................................................................... 12
  3.3 Tinnitus with a normal audiogram: Role of high-frequency sensitivity and reanalysis of brainstem-response measures to avoid audiometric over-matching......................................................................................... 13
  3.4 Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure ......................................................... 14
  3.5 Reliability and interrelations of seven proxy measures of cochlear synaptopathy .... 15
4 SUMMARY & FUTURE DIRECTIONS ......................................................................... 16
5 REFERENCES ............................................................................................................... 18

Word count: 29,642
ABSTRACT

In animals, noise exposure can destroy synapses between inner hair cells and auditory nerve fibres, without widespread loss of hair cells. This ‘cochlear synaptopathy’ does not permanently elevate cochlear thresholds, but does permanently reduce brainstem-response amplitudes at medium-to-high stimulus levels. If this pathophysiology manifests in humans, it might constitute a ‘hidden’ hearing loss, leading to auditory deficits despite normal audiometric thresholds. We recruited a cohort of adults with tinnitus and normal audiograms, and compared them with controls matched for age, sex, and audiometric thresholds. We also conducted a parallel study in adults with impaired speech perception in noise (SPiN) and normal audiograms. Measures of synaptopathy in both studies were the auditory brainstem response (ABR) and envelope-following response (EFR). Lifetime noise exposure was estimated using a detailed structured interview, which has since been developed into an instrument for use by other researchers. Neither study revealed any association of auditory deficits with measures of synaptopathy, although tinnitus was associated with greater lifetime noise exposure. Finally, we conducted a study assessing the reliability and interrelations of seven proxy measures of synaptopathy. Raw amplitude and threshold measures were highly reliable, but likely reflect myriad factors besides synaptopathy. Differential ABR and EFR measures were unreliable, and purported measures of synaptopathy did not correlate. Taken together, the results of the project provide no evidence that cochlear synaptopathy is a significant aetiology of tinnitus or impaired SPiN in humans with normal audiograms. However, in light of the uncertain validity of measures of synaptopathy, absence of evidence cannot be taken as evidence of absence.
DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Hannah Guest was the lead author of each of the five publications included in the thesis, and took the lead role in study design, data acquisition, and analysis.

COPYRIGHT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the “Copyright”) and she has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the “Intellectual Property”) and any reproductions of copyright works in the thesis, for example graphs and tables (“Reproductions”), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DoculInfo.aspx?DocID=24420), in any relevant Thesis restriction declarations deposited in the University Library, The University Library’s regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University’s policy on Presentation of Theses.

ACKNOWLEDGEMENTS

This project could not have taken place without the generosity of the Marston Family Foundation and the support of Action on Hearing Loss.

And it wouldn’t have been much fun without the support, advice, and good company of my friends and colleagues Chris Plack, Kevin Munro, Keith Wilbraham, Alex Sturrock, Sara Al-Hanbal, Richard Baker, Garreth Prendergast, Deb Hall, Andy King, Michael Stone, Shanelle Canavan, Becky Dewey, Sam Couth, Ghada BinKhamis, Becky Millman, Warren Bakay, Anisa Visram, Karolina Kluk, Tim Wilding, and Dan Owens-Cooper.
1 BACKGROUND

1.1 Animal evidence for cochlear synaptopathy

Seminal work in a mouse model by Kujawa and Liberman (2009) revealed that noise exposure can destroy synapses between inner hair cells (IHCs) and auditory nerve (AN) fibres, without widespread loss of hair cells. Evidence of this ‘cochlear synaptopathy’ has since been observed in rats, guinea pigs, chinchillas, and macaques (Hickox et al., 2017; Valero et al., 2017), and in relation to aging as well as noise exposure (Hickox et al., 2017). Moderate synaptopathy does not permanently reduce cochlear sensitivity, as measured via thresholds of the auditory brainstem response (ABR) and distortion-product otoacoustic emissions (DPOAEs). However, amplitudes of ABR wave I – reflective of AN activity (Melcher and Kiang, 1996) – are permanently reduced at medium-to-high stimulus levels (Kujawa and Liberman, 2009). There is also evidence to suggest that synaptopathy preferentially affects AN fibres with low spontaneous rates (low-SR fibres; Furman et al., 2013), which have high response thresholds (Liberman, 1978).

1.2 Possible implications for human perception

Given the striking animal data, it is important to determine whether synaptopathy manifests in humans. Common sources of recreational noise exposure, such as nightclubs and concerts, can involve exposure to greater sound energy than applied in animal models of synaptopathy (Beach et al., 2013). If synaptopathy occurs in humans, and leaves threshold sensitivity intact, then it could constitute a ‘hidden hearing loss’ (Schaette and McAlpine, 2011), perhaps leading to speech-perception difficulties and/or tinnitus in humans with normal audiograms.

1.2.1 Tinnitus

Subjective tinnitus is the perception of sound without an acoustic source, and is most often associated with hearing loss (NicolasPuel et al., 2002). Due in part to this association, tinnitus generation is widely thought to be triggered by loss of input to the central auditory system (Henry et al., 2014). Seemingly at odds with this theory, ~8% of tinnitus sufferers have normal pure-tone audiometric thresholds (Barnea et al., 1990). Cochlear synaptopathy might offer an explanation, since the condition can reduce AN activity without elevating cochlear thresholds.

Research in humans has yielded electrophysiological data consistent with reduced AN function in tinnitus, though not without exception and not without potential confounds. Schaette and McAlpine (2011) and Gu et al. (2012) reported that tinnitus was associated with decreased ABR wave I amplitude. However, high-frequency hearing thresholds were poorer in participants with tinnitus, potentially impacting wave I amplitude, which is dependent on basal generators (Don and Eggermont, 1978). Gilles et al. (2016) reported no wave I reduction, but measurement variability was very high, compromising statistical power. The Bayesian model of Bramhall et al. (2018) associated wave I amplitude with tinnitus, but the tinnitus and control groups differed markedly in sex.
composition and audiometric thresholds, and it is not clear that these confounds were adequately controlled. Paul et al. (2017) reported reduced amplitude of the envelope-following response (EFR) in tinnitus, but were later alerted to a crucial error in their statistical methods (failure to classify stimulus condition as a within-subject factor); upon correcting this error, no significant relation was evident (Roberts et al., 2018). Interestingly, it has become apparent that Schaette and McAlpine (2011) made precisely the same error as Paul and colleagues; consequently, the true p-value for the effect of tinnitus on wave I amplitude in their study was three times greater than reported (Schaette, personal communication, 2017), though still significant. Finally, Wojtczak et al. (2017) compared tinnitus and control participants using the acoustic middle-ear-muscle reflex (MEMR). Striking differences in reflex amplitude were seen between groups, though it should be noted that only the control group had normal hearing. (For further consideration of the literature on tinnitus with a normal audiogram, see Section 3.2.)

1.2.2 Speech perception

It has been suggested that cochlear synaptopathy, if it manifests in humans, might lead to deficits of speech perception in noise (SPIIN; Kujawa and Liberman, 2015; Bharadwaj et al., 2015). A small but significant proportion of patients attending audiology services report such difficulties, yet have normal audiometric thresholds (Stephens et al., 2003). This presentation has been given various labels over the decades, such as ‘obscure auditory dysfunction’ (Saunders and Haggard, 1989) and ‘King-Kopetzky syndrome’ (Hinchcliffe, 1992); here, it will be designated ‘SPIIN impairment with a normal audiogram’.

Synaptopathy’s preferential effects on low-SR fibres might have particular significance for listening in noise, due to the wide dynamic ranges of this fibre type (Schalk and Sachs, 1980). In listening situations with sound levels high enough to saturate the average rates of high-SR fibres, coding of sound is often assumed to rely on low-SR units (e.g. Kujawa and Liberman, 2015). If so, then destruction of these fibres might lead to significant SPIIN deficits. However, this reasoning has not gone unchallenged. Carney (2018) argued against a direct role for the average discharge rates of low-SR fibres in coding high-level sounds, positing that saturation of average rate might help, not hinder, the encoding of complex sounds by high-SR fibres. The reasoning of Kujawa and Liberman further rests on the assumptions that synaptopathy in humans preferentially affects low-SR synapses, and that low-SR fibres in humans have high thresholds and wide dynamic ranges; neither is certain (Hickox et al., 2017). If high-threshold fibres are not targeted in human synaptopathy, likely effects on perception are unclear. A simple model based on signal-detection theory suggests minimal effects on perception (Oxenham, 2016), while an alternative model suggests that ‘stochastic undersampling’ of sound might substantially degrade SPIIN (Lopez-Poveda and Barrios, 2013).

Evidence in humans is inconclusive. Bharadwaj et al. (2015) related EFR strength to behavioural measures of temporal coding and spatial speech perception, but the use of a low stimulus modulation rate casts doubt on the likelihood that results reflect synaptopathy (Shaheen et al.,
Similarly, Liberman et al. (2016) reported relations between noise exposure, SPiN, and an electrophysiological measure, but it is not entirely clear that results can be attributed to synaptopathy (Fulbright et al., 2017; Wang et al., 2018). Fulbright et al. (2017) measured ABR wave I amplitude at a range of stimulus levels and found that none related to SPiN. Large-scale studies have demonstrated no relation of noise exposure to SPiN performance (Prendergast et al., 2017; Grose et al., 2017; Yeend et al., 2017), nor to clinically significant SPiN difficulties (Stephens et al., 2003). All told, there is little evidence to support the notion that noise-induced cochlear synaptopathy is a major determinant of SPiN in humans with normal audiograms. However, with exception of Stephens et al. (2003), no study has sought participants with significant perceptual impairment. Hence, investigation in this population is an important research gap. For more detailed consideration of the literature on SPiN in relation to synaptopathy, see Section 4.4.

1.3 Translational issues

1.3.1 Interspecies differences

In rodents, cochlear synaptopathy can be induced by noise at sound levels similar to those encountered by humans at loud music events (Hickox et al., 2017; Beach et al., 2013). The human auditory system may be far more resilient. Large interspecies differences are evident even among existing animal models of synaptopathy (Shi et al., 2013; Valero et al., 2017). Using comparable temporary-threshold-shift data in rodents and humans, Dobie and Humes (2017) estimated that a two-hour exposure to 114 dB SPL might be necessary to induce synaptopathy in humans.

A second issue is the likelihood of accompanying audiometric loss. In animal models, synaptopathy without widespread hair-cell loss can be induced by carefully titrated noise exposures. Even so, some degree of attendant hair-cell loss is common, especially in the extreme cochlear base (Hickox et al., 2017). Since real-world exposures are far more varied, synaptopathy in humans with normal audiograms may be rare.

1.3.2 Measuring cochlear synaptopathy

If synaptopathy is a cause of auditory deficits, or even just an early marker for more impactful hearing damage in later years, then methods for measuring the extent of the pathology in humans are needed. The direct measures used in animals are not possible pre-mortem, so investigations in living humans rely on proxy measures. Numerous metrics are in use, but the validity of many is uncertain. Credible measures ought to have (i) sound reasoning to support their purported sensitivity to synaptopathy, (ii) sufficient reliability to discriminate between individuals, and (iii) validation in appropriate animal models – ideally in primates. As will be discussed in section 3.5, these characteristics are often lacking.

One possible complication affecting many proxy measures of synaptopathy is the potential influence of extended high-frequency (EHF) audiometric threshold elevation. Loss of hearing sensitivity at frequencies above 8 kHz has been associated with poorer SPiN (Badri et al., 2011; Yeend et al.,
2017) and greater noise exposure (Le Prell et al., 2013; Liberman et al., 2016). If this loss of sensitivity also impacts our measures of ‘synaptopathy’, then it represents an important potential confound. Troubling, then, that the most popular measure – the clickevoked ABR – features dominant contributions from high characteristic frequencies, including those above 8 kHz (Don and Eggermont, 1978). Moreover, this effect is magnified at high sound levels (Eggermont and Don, 1980), further complicating interpretation of much existing synaptopathy data. (For more on this issue, see Section 3.3.)

1.3.3 Estimating noise exposure

In animal models of synaptopathy, noise exposures are directly controlled; human studies of noise-induced synaptopathy are necessarily observational. In the future, research in humans may be aided by wearable technologies that allow an individual’s noise exposure to be measured over the long term; for now, lifetime noise exposure must be estimated via retrospective self-report. The accuracy of such estimates is limited by participant recall, but also by the quality of the data capture procedures. Few existing procedures give sufficient consideration to key features of exposure over the lifetime, such as frequency of occurrence of exposure, duration of each exposure, duration of overall period of exposure, and use of hearing protection. (For more detailed consideration of these issues, see Section 3.1.)

1.4 Synthesis of evidence

In animals, evidence of cochlear synaptopathy is compelling. Translation to humans is not straightforward, and the existence of synaptopathy in young, audiometrically normal adults is uncertain. If the condition manifests in this population, it might be associated with significant perceptual consequences. Investigations of the relations between synaptopathy and perception in humans with normal audiograms have yielded mixed results. Several studies have associated tinnitus with proxy measures of synaptopathy, but also with reduced high-frequency hearing sensitivity – a potential confound. Evidence linking measures of synaptopathy with SPiN is limited, though research in humans with significant perceptual impairment might be more fruitful. In summary, there is dear scope for further investigation of synaptopathy in humans with auditory deficits despite normal audiograms, with careful control of potential confounds. To provide confidence that results reflect underlying synaptopathy, such research would ideally demonstrate evidence of both enhanced noise exposure and reduced AN function in symptomatic individuals; hence, measures of each must be designed with care.
2 AIMS & RATIONALE

The aims of the research described in this thesis were to:

- Develop a comprehensive instrument for the estimation of lifetime noise exposure
- Test for evidence of cochlear synaptopathy in tinnitus with a normal audiogram
- Test for evidence of cochlear synaptopathy in SPiN impairment with a normal audiogram
- Investigate the reliability and interrelations of proxy measures of cochlear synaptopathy

The need to develop a comprehensive measure of noise exposure was recognised in the early days of the project, and an initial version of our procedure was created for use in the main studies (testing for evidence of noise-induced synaptopathy in humans with auditory deficits). Later, following data collection, the decision was made to refine the procedure into an instrument that could easily be employed by researchers elsewhere. Development of the Noise Exposure Structured Interview (NESI) was a collaborative effort, drawing on the insights of at least nine researchers with experience in gathering self-report estimates of lifetime noise exposure.

The heart of the PhD programme involved testing for evidence of cochlear synaptopathy in audiometrically normal humans with self-reported auditory deficits. To investigate two potential sequelae of synaptopathy – tinnitus and SPiN difficulties – we designed two cross-sectional studies, comparing the noise exposure and AN function of symptomatic individuals with those of controls. In order to maximise our chances of observing evidence of synaptopathy, we defined both health conditions strictly: tinnitus was prolonged spontaneous tinnitus, and SPiN impairment was defined based on self-report and laboratory performance. We also aimed to thoroughly control potential confounds of sex, age, and audiometric sensitivity.

Finally, we set out to interrogate our measures of synaptopathy more closely, along with a few others reported by investigators elsewhere. Having gained extensive experience in gathering EFR, ABR, and MEMR data, we were confident that seven measures of synaptopathy could be acquired at a single testing session, without unduly fatiguing the participant. Hence, in the two months available for testing, we could gather repeated measurements from ~30 participants, allowing us to assess both reliability and interrelations of the measures.
3 METHODS & RESULTS
3.1 The Noise Exposure Structured Interview (NESI): An instrument for the comprehensive estimation of lifetime noise exposure

Published in Trends in Hearing, October 2018
The Noise Exposure Structured Interview (NESI): An Instrument for the Comprehensive Estimation of Lifetime Noise Exposure

Hannah Guest1, Rebecca S. Dewey2,3,4, Christopher J. Plack1,5,6, Samuel Couth1, Garreth Prendergast1, Warren Bakay1, and Deborah A. Hall3,4,7

Abstract

Lifetime noise exposure is generally quantified by self-report. The accuracy of retrospective self-report is limited by respondent recall but is also bound to be influenced by reporting procedures. Such procedures are of variable quality in current measures of lifetime noise exposure, and off-the-shelf instruments are not readily available. The Noise Exposure Structured Interview (NESI) represents an attempt to draw together some of the stronger elements of existing procedures and to provide solutions to their outstanding limitations. Reporting is not restricted to prespecified exposure activities and instead encompasses all activities that the respondent has experienced as noisy (defined based on sound level estimated from vocal effort). Changing exposure habits over time are reported by dividing the lifespan into discrete periods in which exposure habits were approximately stable, with life milestones used to aid recall. Exposure duration, sound level, and use of hearing protection are reported for each life period separately. Simple-to-follow methods are provided for the estimation of free-field sound level, the sound level emitted by personal listening devices, and the attenuation provided by hearing protective equipment. An energy-based means of combining the resulting data is supplied, along with a primarily energy-based method for incorporating firearm-noise exposure. Finally, the NESI acknowledges the need of some users to tailor the procedures; this flexibility is afforded, and reasonable modifications are described. Competency needs of new users are addressed through detailed interview instructions (including troubleshooting tips) and a demonstration video. Limited evaluation data are available, and future efforts at evaluation are proposed.

Keywords

noise-induced hearing loss, self-report, occupational noise, risk, public health

Date received: 13 May 2018; revised: 24 August 2018; accepted: 27 August 2018

Background

Research into noise-induced hearing damage has proliferated in recent years. In part, this is attributable to endeavors to determine human physiological and functional correlates of noise-induced cochlear synaptopathy, as demonstrated in animal models (Liberman & Kujawa, 2017). Unlike this animal work, human research predominantly relies on retrospective self-report estimates of cumulative noise exposure. Accuracy of quantification is undoubtedly limited by respondent recall but also by data capture procedures. Numerous methods have been developed independently by different research teams, each to solve the same problems.
The first research gap is therefore the lack of standardization of procedure. The second research gap is the comprehensiveness of the estimation procedure itself. Existing procedures tend not to fully consider all of the factors that are important for eliciting an estimate of noise exposure over the lifespan (e.g., Bramhall, Konrad-Martin, McMillan, & Griest, 2017; Carter, Black, Bundy, & Williams, 2016; Dalton et al., 2001; Johnson, Cooper, Stamper, & Chertoff, 2017; Jokitulppo, Toivonen, & Björk, 2006; Liberman, Epstein, Cleveland, Wang, & Maisen, 2016; Moore, Zobay, Mackinnon, Whitmer, & Akeroyd, 2017; Neitzel, Seixas, Goldman, & Daniell, 2004; Spankovich, Le Prell, Lobarinas, & Hood, 2017; Yeend, Beach, Sharma, & Dillon, 2017). Figure 1 reports on these factors and summarizes the performance of existing methods. While some of the procedures appear more comprehensive than others, few allow public access to the instrument per se. This identifies the third research gap, which is lack of publication of the administrator instructions, record forms, checklists, and calculations of noise units, at least as an “off-the-shelf” solution that can readily be used, in a consistent manner, by researchers elsewhere.

The Noise Exposure Structured Interview (NESI) represents the first effort to go beyond simply describing a procedure for estimating lifetime noise exposure based on self-report, by offering a comprehensive and ready-made solution that we intend as a common standard for the field. This article presents the complete instrument, including a description of the procedure and all supporting materials for self-directed “training” and for administration. The NESI does not claim to contain completely novel elements; indeed, some of its elements are adopted from existing procedures, notably the Noise Exposure and Rating Questionnaire published in a Health and Safety Executive report (Lutman, Davis, & Ferguson, 2008), which was originally developed for the UK National Study of Hearing (A. C. Davis, 1995; Lutman & Spencer, 1991), and utilized in a number of other projects (e.g., Browning, 1986; Smith, Davis, Ferguson, & Lutman, 2000). Rather, the innovation and scientific value lie in the way the procedures are packaged together and integrated with novel elements, yielding an instrument that is comprehensive, clear, and not unduly time-consuming for the administrator.

Methods have been developed in an iterative manner using insights from at least seven coauthors and external colleagues who conducted “beta” testing of preliminary versions. Of the various preliminary versions (see e.g., Prendergast et al., 2017, 2018), those bearing closest resemblance to the current NESI are the versions reported by Guest, Munro, Prendergast, Howe, and Plack (2017) and Dewey et al. (2018), which differ from the NESI in terms of interview instructions and aspects.

![Figure 1. Performance of existing self-report measures of noise exposure.](image-url)
of the supporting documents, but would be unlikely to produce markedly different results. We define the current instrument as “NESI version 1,” in order to explicitly acknowledge the potential for subsequent refinement and revision, as deemed necessary. However, for brevity, the remainder of this article refers to the instrument simply as “the NESI.”

**Concept**

The structured interview aims to elicit data on the level and duration of noise exposures over the lifespan, along with usage and attenuation of hearing protection devices (HPDs). The great challenge when collecting such data is that exposure activities and patterns of exposure are unique to the individual and change over time. In addressing these problems, the NESI adopts an approach which is flexible but also highly structured.

Reporting is not restricted to prespecified exposure activities and instead encompasses all activities that the respondent has experienced as noisy (defined based on sound level estimated from vocal effort). Changing exposure habits over time are reported by dividing the lifespan into periods in which exposure habits were approximately stable, with life milestones used to aid recall. Within each life period, standardized methods are used in the estimation of sound level, duration, and attenuation of HPDs. A suggested means of combining these data is provided, based on total energy of exposure, along with a primarily energy-based method for incorporating firearm-noise exposure.

**Methods**

**Structure and Documentation**

Practical administration of the NESI requires three documents, supplied as Supplementary Material:

- The NESI worksheets (for recording recreational, occupational or educational, and firearm noise exposure; Supplementary Material 1).
- The NESI guidance (overview, instructions, recreational noise examples, speech communication table, personal listening device table, and hearing protection guide; Supplementary Material 2).
- The NESI example calculations (a spreadsheet demonstrating calculation of units of noise exposure; Supplementary Material 3).

Additional background materials are also supplied:

- Further information on the methods for estimating attenuation of HPDs (Supplementary Material 5).
- Further information on the methods for quantifying firearm noise exposure (Supplementary Material 6).

The methods by which noise exposure data are obtained and combined fall into seven basic categories: (a) identification of exposure activities, (b) segmentation of the lifespan, (c) estimation of exposure duration, (d) estimation of exposure level, (e) consideration of hearing protection, (f) quantification of firearm noise exposure, and (g) calculation of noise exposure units.

**Identification of Exposure Activities**

Restricting reporting to prespecified activities is common in measures of noise exposure, but risks underestimating the exposure of respondents who engage in activities that are less common, or less commonly associated with high sound levels. An additional risk is the overreporting of activities which can involve high sound levels but do not always do so (e.g., quieter bars and concerts). The NESI follows Lutman et al. (2008) in allowing the respondent to report all noisy (>80 dBA) activities that they have experienced (see also Smith et al., 2000). A “noisy” environment is defined as one in which the respondent would need to raise his or her voice to communicate (at a distance of 4 feet, communicating with a listening partner with normal hearing, with gestures and facial cues available to aid communication).

Although identification of exposure activities is ultimately determined by the respondent’s report, we have elected to provide prompts to expedite this process. Recreational Noise Examples (on p. 8 of Supplementary Material 2) are provided to the respondent early in the interview. These examples were derived from preliminary data from respondents with varying ages, backgrounds, and noise exposures, obtained using measures closely related to the NESI. Listed activities were those reported by 4 or more out of ~250 respondents. Crucially, this list of examples is not exhaustive, and respondents are explicitly instructed to also report any other activities they perceived as noisy (i.e., requiring a raised voice to communicate). Similarly, they are instructed to ignore any activities that appear on the list but which they did not perceive as noisy.

**Segmentation of the Lifespan**

Exposure habits vary across the lifespan. This can be true of not only choice of exposure activities but also frequency of occurrence, sound level, usage of hearing
protection, and so on. Reporting of current habits is likely to be unrepresentative of lifetime exposure patterns, especially in older respondents. One solution, utilized by Yeend et al. (2017) and Moore et al. (2017), is to segment the lifespan into decades and assess noise exposure habits in each. However, this framework is likely to compromise accuracy where exposure habits have changed markedly mid-decade, for example, if a respondent attended nightclubs from 18 to 22 (incurring 2 years of exposure in the second decade of life, and two in the third).

A more accurate approach is to segment the lifespan on the basis of exposure habits. Hence, the NESI prompts respondents to divide the lifespan into periods in which exposure habits were approximately stable (e.g., time spent as a university student). Patterns of exposure are then recorded for each life period separately, until reporting across the lifespan is complete. Since exposure habits may change for one activity but not others, life periods are identified for each activity separately.

The authors have observed an additional benefit of this approach: life events can be used as points of reference to improve quality of recall, as in the Noise History Calendar (Welch, John, Grynevych, & Thorne, 2011). Hence, the NESI provides fields for recording the timing of each exposure period and advises that any contemporaneous life milestones (e.g., graduation or change of workplace) be noted to assist recall (see Step 5 of the NESI instructions in Supplementary Material 2).

Estimation of Exposure Duration

To estimate total exposure duration within each life period, the interviewer requires information on typical duration and frequency of occurrence of exposures. Following Lutman et al. (2008), we have elected to express exposure frequency in weeks per year and days per week. Broader subdivisions (e.g., days per month and months per year) are inappropriate for some purposes, such as the reporting of occupational exposure patterns that remain constant from week to week.

However, recording of data in this format is not always straightforward. For example, a respondent might report engaging in an activity “twice a month.” In these cases, it falls to the interviewer to convert these data to fit the NESI framework (e.g., “twice a month” = 24 weeks per year × 1 day per week). The need to perform such conversions is highlighted in Step 7 of the NESI instructions (Supplementary Material 2).

Estimation of Exposure Level

Three basic approaches to the quantification of sound level are employed in existing self-report measures of noise exposure:

(a) No consideration of sound level; all exposure activities are weighted equally (e.g., Liberman et al., 2016; Moore et al., 2017).

(b) Sound level is estimated for each exposure activity using databases of sound level measurements (e.g., Bramhall et al., 2017; Johnson et al., 2017; Yeend et al., 2017).

(c) Sound level is estimated by the participant, based on communication difficulty (e.g., Guest et al., 2017; Jokitulppo et al., 2006; Keppler, Dhooge, & Vinck, 2015; Lutman et al., 2008).

Method (b) has some advantages, principally in reducing the time taken to complete the measure and in circumventing concerns about the accuracy of respondent estimates. However, we propose that method (c) may be preferable, for the following reasons:

- For some exposure activities, especially those associated with less commonplace occupations, no sound level measurements may be available.
- For activities that are included, the listed sound levels may not reflect the full range of levels possible for that activity and may therefore be misleading. For example, sound levels associated with sailing, listed at 45 dBA in the Noise Navigator database (Berger, Neitzel, & Kladden, 2015), were estimated to exceed 80 dBA by several preliminary NESI respondents.
- Within a single activity, a very wide range of sound levels is often listed, for example, 67 to 88 dBA for restaurants in the NOISE database (Beach, Gilliver, & Williams, 2013). A means of choosing among them, guided by the respondent, is required.
- Respondents are capable of estimating noise levels with reasonable accuracy, given a loudness rating scale based on communication difficulty (Beach, Williams, & Gilliver, 2012; Ferguson, Tomlinson, Davis, & Lutman, 2018).

Hence, the NESI procedure incorporates respondent-estimated sound level. The Speech Communication Table (Ferguson et al., 2018; Lutman et al., 2008) prompts the respondent to estimate the vocal effort that (s)he would require to communicate in a given environment, at a distance of 4 feet, assuming that the listener is not hearing impaired, is not wearing hearing protective equipment, and may be assisted by gestures and facial cues (see p. 9 of Supplementary Material 2). Note that only the hypothetical listener in this scenario is required to have normal hearing, not the talker (the NESI respondent), who may be hearing impaired. The present version of the table was adapted from that reported by Lutman and colleagues (see Supplementary Material 4).
Evaluation data have been obtained for the use of this procedure in estimating occupational noise levels (Ferguson et al., 2018), though not for recreational exposures and not for exposures in the distant past (see Evaluation section of the present article). We recognize that some NESI users may wish to adopt an alternative approach, such as using respondent estimates for only those activities omitted from databases of sound-level measurements. To facilitate this approach, the NESI worksheets (Supplementary Material 1) include extra fields for recording estimates from an alternative source.

Finally, for earphones or headphones used with personal listening devices (PLDs), we have developed the Personal Listening Device Table (p. 10 of Supplementary Material 2): a tool for estimating free-field equivalent output level based on typical volume control setting. Conversion values are based on approximate mean levels measured by Portnuff, Fligor, and Arehart (2011), using a range of devices coupled to stock earphones. These values are also consistent with EU standards governing maximum sound levels of PLDs (British Standards Institution, 2017). Note that the Personal Listening Device Table applies only to PLDs, not to earphones used with other devices (e.g., stereos or personal computers). For such exposures, sound level may be estimated by eliciting comparisons to other activities previously reported by the participant (e.g., “louder than”, “similar loudness to”, or “quieter than” an activity whose sound level has already been estimated).

It is important to note that, although we have attempted to provide sound-level estimation methods for most common noisy activities, omissions remain. For example, for musicians performing at amplified live-music events, sound from in-ear monitors contributes to personal exposure (Federman & Ricketts, 2008), yet levels could not be easily estimated using the NESI (nor, indeed, using any of the procedures reported in Table 1). Hence, caution and common sense must be employed when attempting to quantify the exposure of some music-industry professionals and students.

**Consideration of Hearing Protection**

HPDs reduce sound levels in the ear canal but may be worn inconsistently. Hence, to quantify their effects, the NESI examines the approximate proportion of time that HPDs were used, as well as their estimated attenuation. The former is estimated by the respondent; the latter is derived from attenuation ratings published by HPD manufacturers.

To assist the user in estimating the attenuation of HPDs, we have developed the NESI Hearing Protection Guide (pp. 11–12 of Supplementary Material 2). Several possible routes to an estimate are provided, since, in our experience, respondents vary greatly in their recollection of protector type, from vague descriptions of shape through to precise reports of make and model. Pictorial representations of protector types are provided, along with attenuation values for several popular HPDs, and guidance on estimating attenuation based on the product’s single number rating or noise reduction rating.

Supplementary Material 5 provides detailed information on the quantitative methods by which our attenuation estimates are derived, and the reasoning behind these methods.

**Quantification of Firearm Noise Exposure**

Over the decades, damage risk criteria have employed a variety of methods for quantifying firearm noise exposure. Early metrics based on peak level and duration have been succeeded by metrics based on the entire temporal waveform (R. R. Davis & Clavier, 2017). Prominent among the latter is A-weighted equivalent continuous 8-hr level (L_Aeq8hr), which has been recommended by the National Institute for Occupational Safety and Health (Murphy & Kardous, 2012), the American Institute of Biological Sciences (Wightman, Flamme, Campanella, & Luz, 2010), and Defence Research and Development Canada (Nakashima, 2015). One clear benefit of this metric is that it can be easily integrated with energy-based measures of continuous-type noise exposure (Nakashima, 2015).

However, a significant body of research indicates that impulsive noise is more damaging to the auditory system than continuous-type noise of equal energy (e.g., Dunn, Davis, Merry, & Franks, 1991; Hamernik & Qiu, 2001). In the context of damage risk criteria, there is growing support for energy-based metrics that are adjusted for the greater kurtosis (peakedness) of impulsive noise (e.g., R. R. Davis & Clavier, 2017; Murphy & Kardous, 2012). Sounds with greater kurtosis cause greater permanent threshold shift than Gaussian noise of equal energy (R. I. Davis et al., 2012; Hamernik, Qiu, & Davis, 2007). Adjusting noise metrics for kurtosis improves their capacity to predict permanent threshold shift in humans (Goley, Song, & Kim, 2011; Xie et al., 2016; Zhao et al., 2010). The NESI has adopted the kurtosis-corrected metric of Goley et al. (2011):

$$L'_{Aeq} = L_{Aeq} + 4.02 \times \log_{10}(\beta/\beta_G)$$

where L'_{Aeq} is kurtosis-corrected A-weighted equivalent continuous level, L_{Aeq} is uncorrected A-weighted equivalent continuous level, 4.02 is a constant derived from dose-response data in chinchillas, $\beta$ is the kurtosis statistic of the noise, and $\beta_G$ is the kurtosis statistic for Gaussian noise ($\beta_G = 3$).

Incorporation of firearm noise into the NESI can therefore be achieved by combining L_{Aeq} and $\beta$, as
measured at the shooter’s ear. Flamme, Wong, Liebe, and Lynd (2009) and Meinke et al. (2014) have reported these data for a variety of firearms. More specifically, Flamme et al. report A-weighted equivalent continuous 8-hr level ($L_{\text{Aeq}8\text{hr}}$): the A-weighted noise level that, if present over an 8-hr period, would contain the same sound energy as the firearm impulse. Due to a markedly bimodal distribution of $L_{\text{Aeq}8\text{hr}}$, we have elected to dichotomize these weapons into low-caliber (.22 and .17) rifles and all other hand-held firearms (with the exception of air guns, see later). Mean $L_{\text{Aeq}8\text{hr}}$ for each category has been combined with a kurtosis correction term, yielding kurtosis-corrected A-weighted exposure energy for each category. These values are presented for the NESI user as fractions of a NESI unit of noise exposure, which should be multiplied by the total number of rounds fired.

Exposures to air guns and exposures while wearing hearing protection are disregarded, due to their very low exposure energy. Quantitative justification for this decision is provided in Supplementary Material 6, as are details of all calculations outlined above. Exposure to impulsive noise from sources other than firearms (e.g., artillery and blast noise) is beyond the scope of the NESI.

Finally, it is worth noting that, for the sake of simplicity, NESI procedures for quantification of firearm noise are more rudimentary than those for continuous-type noise in recreational or occupational settings. The firearm noise worksheet (Supplementary Material 1) allows the respondent to estimate the total number of rounds fired in whatever manner they choose. (The field labeled “Additional information to assist recall” may be used to note number of rounds per session, sessions per year, etc.) This contrasts with the more prescriptive approach adopted in the other worksheets. In addition, as stated earlier, firearms are dichotomized, and exposures while wearing hearing protection disregarded. Although preliminary NESI respondents (who were generally UK residents) reported relatively little firearm exposure, we appreciate that other populations may be more highly exposed. Supplementary Material 6 provides guidance on implementing a more fine-grained approach, if required.

### Calculation of Noise Units

The NESI is primarily a procedure for collecting noise exposure data. However, a suggested means of combining these data is also provided, based on that of Lutman et al. (2008).

For exposure activities where no hearing protection was worn:

\[
\text{Units of noise exposure} = \frac{Y \times W \times D \times H}{2080} \times 10^{\frac{L - 90}{10}}
\]

For exposure activities where hearing protection was worn and reduced sound levels to $\leq 80$ dBA:

\[
\text{Units of noise exposure} = \frac{Y \times W \times D \times H}{2080} \times (P \times 10^{\frac{L - 90}{10}} + (1 - P) \times 10^{\frac{L - 80}{10}})
\]

where

- $Y$: years of exposure
- $W$: weeks per year of exposure
- $D$: days per week of exposure
- $H$: hours per day of exposure
- $P$: proportion of time that hearing protection was worn (from 0 to 1)
- $L$: sound level (dBA)
- $A$: attenuation of hearing protection

The resulting measure is linearly related to the total energy of exposure above 80 dBA. One unit is equivalent to one working year (2080 hrs) of exposure to 90 dBA (hence “$L$-90” in the above equations). The reasons for focusing on one working year and 90 dBA are largely historical: the equations were originally devised for the assessment of occupational noise exposure, at a time when 90 dBA represented an important legal limit. We have elected not to alter the calculations, so that NESI data may be comparable with data obtained using precursor measures. Firearm noise exposure is incorporated using a primarily energy-based metric (see Step 16 of Supplementary Material 2 and further details in Supplementary Material 6).

To aid investigators new to the NESI, an Excel spreadsheet with example calculations is provided (Supplementary Material 3). It is possible to remove the example data and replace with data from verum NESI respondents, and some users may opt for this approach. However, users are advised to carefully consider alternative ways to store and analyze the data.

### Application and Training

The NESI was developed for use in auditory research, but may have wider application, for example in non-auditory research fields and for clinical purposes. Piloting suggests that completion of the interview takes 10 to 25 min for most respondents, excepting those with extremely extensive or complex noise exposure histories. The instructions (Supplementary Material 2) and
demonstration video (https://youtu.be/bqgz7-_wmYA) provide guidance on maintaining interview duration within reasonable limits.

Competency in conducting the NESI requires thorough training and practice, due to the potential for interviewer behavior to influence reporting. To maximize both inter- and intrarater reliability, the user must develop a consistent “script” for each stage of the interview. The precise wording of the script may be chosen by the user but must express the points set out in the NESI instructions and be consistent across participants. We recommend that new users carefully study the worksheets, guidance, and additional background materials (Supplementary Materials 1–6 and video) and also conduct several mock interviews before embarking upon data collection.

We recognize that some users may wish to modify the NESI in order to address specific research questions (e.g., quantifying total duration of exposure above a given level or examining exposure at specific stages of the lifespan). The instructions provide guidance on some reasonable modifications and how they might be implemented (p. 7 of Supplementary Material 2). It would be good practice to disclose any deviations from the principal NESI methods when reporting the resulting data.

**Evaluation**

The advent of smart-watches and other technologies may soon allow for continuous, long-term, objective measurement of an individual’s noise exposure. For now, the absence of a gold-standard measure of lifetime noise exposure means that self-report metrics must be evaluated piecemeal.

A component of the NESI, the Speech Communication Table, has been evaluated via dosimetry in 15 workplace settings in which noise levels were greater than or equal to 85 dBA (Ferguson et al., 2018). In this study, 168 participants aged 16 to 25 years estimated noise exposure using a version of the Speech Communication Table and wore personal noise dosimetry badges to objectively measure the noise level in the same nominated occupational tasks. In terms of estimation, methods agreed to within ±3 dB in 56% of cases and within ±6 dB in 91% of cases (Ferguson et al., 2018). Lutman et al. (2008) therefore concluded that, “for group comparisons, noise level estimation from self-reported communication difficulty is appropriate” (p. 57). Note, however, that a limitation of this study is that exposures were purely occupational; recreational exposures might pose different challenges.

Feedback from NESI pilot users indicates interviewer confidence in the capacity of the procedures to enhance respondent recall. In preliminary data, exposure to a single activity was often recorded across multiple life periods, suggesting that this framework is of value in capturing changing exposure habits across the lifespan. Preliminary data also demonstrate the NESI’s capacity to distinguish those in noisy professions from other respondents (Figure 2).

![Figure 2. Noise exposure data from a cohort of 62 preliminary NESI respondents, obtained using a beta version of the NESI (Dewey et al., 2018). Nineteen were classed as music-industry workers, the remaining 43 were not. Music-industry workers encompassed professionals, teachers, trainees, and experienced amateurs in the following: musical performance, sound engineering, music production engineering, and disk jockeying. Density plots illustrate the distributions of (a) recreational noise exposure, (b) occupational noise exposure, and (c) total lifetime noise exposure. Note that, to allow plotting on a logarithmic scale, NESI scores of 0 have been adjusted to 0.001.](image)
Since recreational noise exposure is a major contributor to the lifetime noise dose, a priority for future research should be evaluation of the Speech Communication Table in recreational settings. In addition, evaluation of this procedure for sporadic or erstwhile exposures may be important, since accuracy of recall may diminish over time. It may also be valuable to determine both the intra- and interrater reliability of the NESI.

Conclusion

Development of the NESI represents an attempt to draw together some of the stronger elements of existing self-report procedures for estimating lifetime noise exposure and to supply novel solutions to their outstanding limitations. Its structure allows the report of an unrestricted range of noisy activities and of changing noise exposure habits over the lifetime, strengthened by a mnemonic approach. Methods are provided for estimating the sound levels of all exposure activities, not only those that are adequately represented in databases of sound-level measurements. Straightforward methods allow the effects of hearing protection to be quantified. An energy-based means of combining the resulting data—including exposure to firearm noise—is supplied. Since some users may wish to deviate according to research needs, the NESI affords the flexibility for reasonable modifications. Training of new users is aided by detailed instructions and a demonstration video. Of course, further evaluation of the NESI instrument is required, and suggestions as to useful modifications in future versions are welcome. Finally, the authors call for the open sharing of data obtained using the NESI, so that the power of large data sets might be harnessed.

Acknowledgments

The authors thank Mark Lutman, Melanie Ferguson, and Adrian Davis for insightful discussion on the procedures for estimating noise exposure using their Noise Exposure and Rating Questionnaire. The authors are grateful to Fred Marmel, Michael Stone, and Hannah-Sian McGuinness for providing valuable feedback on previous versions of the NESI.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Development of the instrument was funded by The Marston Family Foundation and Action on Hearing Loss, with support from the Medical Research Council UK (MR/L003589/1 and MR/M023486/1) and the NIHR Manchester Biomedical Research Centre. D. A. H. is an NIHR senior investigator.

ORCID iD

Hannah Guest @ http://orcid.org/0000-0002-4981-6663
Deborah A. Hall @ http://orcid.org/0000-0002-3804-1452

References


<table>
<thead>
<tr>
<th>Exposure activity</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of exposure period</strong> (e.g. age at start and age at end)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exposure duration</strong></td>
<td>Years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weeks per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hours per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exposure level</strong></td>
<td>Basis for estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimated level (dBA)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Optional:**

<table>
<thead>
<tr>
<th>Exposure level (alternate estimation method)</th>
<th>Basis for estimate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated level (dBA)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Use of hearing protection**

<table>
<thead>
<tr>
<th>Proportion of time worn (between 0 and 1)</th>
<th>Notes on type and attenuation of protector</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated attenuation (dB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category B: Occupational and educational noise exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID:</td>
<td>Date:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure activity</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

| Timing of exposure period  
(e.g. age at start and age at end) | | | | | | |
|------------------------------------|---|---|---|---|---|---|

| Exposure duration | Years | Weeks per year | Days per week | Hours per day | |
|-------------------|--------|----------------|--------------|--------------|

| Exposure level | Basis for estimate | Estimated level (dBA) | |
|----------------|---------------------|------------------------|

| Optional: Exposure level  
(alternate estimation method) | Basis for estimate | Estimated level (dBA) | |
|-----------------------------|---------------------|------------------------|

| Use of hearing protection | Proportion of time worn  
(between 0 and 1) | Notes on type and attenuation of protector | Estimated attenuation (dB) | |
|----------------------------|---------------------|-----------------------------|-----------------|---|

NESI Version 1 (2018)
| **Type of firearm** | | | | | | |
| **Additional information to assist recall** | | | | | | |
| **Total number of rounds fired without hearing protection** | | | | | | |

**Summary information**

<table>
<thead>
<tr>
<th><strong>Category A:</strong> Recreational noise</th>
<th><strong>Category B:</strong> Occupational and educational noise</th>
<th><strong>Category C: Firearm noise</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of worksheets used</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Person conducting interview</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overview</td>
<td>Introduction</td>
<td>Recreational noise exposure</td>
<td>Occupational and educational noise exposure</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>Outline how the NESI works</td>
<td>Identify exposure activities</td>
<td>Identify exposure activities</td>
</tr>
<tr>
<td></td>
<td>Explain which activities should be reported</td>
<td>For each activity, divide the lifespan into periods in which exposure habits were approximately stable</td>
<td>For each activity, divide the lifespan into periods in which exposure habits were approximately stable</td>
</tr>
<tr>
<td><strong>Recreational noise exposure</strong></td>
<td>- Estimate duration of exposure</td>
<td>- Estimate level of exposure</td>
<td>- Estimate duration of exposure</td>
</tr>
<tr>
<td></td>
<td>- Record use and type of <strong>hearing protection</strong></td>
<td></td>
<td>- Record use and type of <strong>hearing protection</strong></td>
</tr>
<tr>
<td><strong>Occupational and educational noise exposure</strong></td>
<td>- Identify exposure activities</td>
<td></td>
<td>- Identify exposure activities</td>
</tr>
<tr>
<td></td>
<td>For each activity, divide the lifespan into periods in which exposure habits were approximately stable</td>
<td></td>
<td>For each activity, divide the lifespan into periods in which exposure habits were approximately stable</td>
</tr>
<tr>
<td></td>
<td>- Estimate duration of exposure</td>
<td></td>
<td>- Estimate duration of exposure</td>
</tr>
<tr>
<td></td>
<td>- Estimate level of exposure</td>
<td></td>
<td>- Estimate level of exposure</td>
</tr>
<tr>
<td></td>
<td>- Record use and type of <strong>hearing protection</strong></td>
<td></td>
<td>- Record use and type of <strong>hearing protection</strong></td>
</tr>
<tr>
<td><strong>Firearm noise exposure</strong></td>
<td>For any exposures without hearing protection...</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Record type of firearm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estimate number of rounds fired</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>For each activity and life period, combine the above data into units of noise exposure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Use the [recreational noise examples](#) (page 8) to aid identification of noisy recreational activities
- Use the [speech communication table](#) (page 9) to estimate the sound level of free-field exposures
- Use the [personal listening device table](#) (page 10) to estimate the sound level from earphones/headphones
- Use the [hearing protection guide](#) (pages 11-12) to estimate the attenuation of hearing protectors
- Use the [worksheets](#) to record the respondent's noise exposure information
**Steps 1 to 2: Introducing the NESI**

1. Outline the purpose of the interview: to identify activities involving high sound levels and estimate the duration and level of exposure for each.

   **Suggested script:**
   The purpose of this interview is to estimate your lifetime noise exposure. We will identify activities that have caused you to be in noisy situations, then estimate how long you spent in those situations and how noisy they were.

2. Define the activities that should be reported: those with an estimated sound level exceeding 80 dBA.

   For free-field exposures, this is based on estimated vocal effort required to communicate (see *Speech Communication Table*). Instruct the respondent to report situations requiring a “raised voice” at a communication distance of 4 feet (1.2 m).

   For personal listening devices, instruct the respondent to report listening at volume control settings above 70% of maximum volume (see *Personal Listening Device Table*).

   **Suggested script:**
   I’ll explain what I mean by a “noisy” situation: It’s the kind of situation where, if you and I were 4 feet apart, you would have to raise your voice to communicate with me. [Interviewer gestures to indicate a distance of 4 feet.] Assume that I have normal hearing, that I am not wearing ear plugs or ear muffs, and that we are able to see each other’s faces and gestures clearly. Situations that are at least this noisy are the ones you should report. Quieter situations, which don’t cause you to raise your voice, can be ignored.

   Finally, there’s one other kind of noisy activity we’ll look at, and that’s listening through earphones or headphones with the volume control set quite high, above 70% of maximum volume.

   **Tip:**
   It is sometimes necessary to emphasise that the communication scenario used to estimate free-field noise levels is *hypothetical*.

   The respondent should imagine attempting to communicate with a listener without hearing protection, even if this scenario would be unlikely to occur in the environment in question.
Steps 3 to 11: Estimating recreational, occupational, and educational noise exposure

Record recreational exposures (Category A) first, followed by occupational and educational exposures (Category B). Interview methods are similar for the two categories.

3. Prompt the respondent to identify exposure activities. For Category A, these should be noisy activities that occurred recreationally; for Category B, noisy activities that occurred in the course of work or study.

Provide pen and paper and allow the respondent a few minutes alone to note exposure activities. For Category A, also provide the Recreational Noise Examples.

The respondent should use these notes later, to aid their recollection. The notes will not be analysed. They may add to the notes at any time.

4. Next, you will examine the identified exposure activities, one after another, estimating sound level, duration, and use of hearing protection for each one.

Encourage the respondent to report their most significant sources of noise exposure early in the interview.

5. Outline the process for recording exposure patterns across time: dividing the lifespan into periods in which exposure habits were approximately stable.

A single activity may be reported across multiple life periods if exposure habits have significantly altered.

If not, or if the respondent can't recall, then they should report average exposure habits for the entire period of exposure (e.g. age 18 to 45).

6. Prompt the respondent to identify a life period. Note the timing (e.g. “age 22 to 30”) in the second row of the worksheet. This information may be useful later in the interview, when checking for “gaps” in the exposure record (life periods which involved exposure, but haven’t yet been recorded).

Record the duration of this period in years. (This doesn't have to be a whole number.)

Tip:
In Category A, what appears initially to be a single “activity” may be divisible into more specific activities with differing sound levels and/or use of hearing protection (e.g. “metal bands” and “folk bands”). If the respondent is able to recall information about these exposures separately, then record them as separate activities.

Similarly, in Category B, make sure to distinguish between a job and an activity. One job may involve multiple activities, only some of which may be noisy.

Suggested script:
Now let’s look at one activity in detail. Which do you think has contributed most to your overall noise exposure?

Suggested script:
Now we need to estimate how long you have spent [engaging in the activity].

As a first step, I’ll ask you to think of a period of your life when your habits were fairly stable: a number of years where there weren’t major changes in how often you [engaged in the activity], or how noisy it was, or how long the noise lasted. You might need to divide your life into several periods. For example, if you [engaged in the activity] very frequently from 16 to 22 and less frequently from 22 to 30, we would look at each period separately.

Suggested script:
So, when it comes to [the present activity], which period of your life should we look at first?

Tip:
Encourage the participant to make use of relevant life milestones to structure their recollection (e.g. change of workplace, graduation from university).
7. For the activity and life period identified above, prompt the respondent to estimate weeks per year and days per week of exposure. (These don't have to be whole numbers.)

8. Prompt the respondent to estimate average hours per day of exposure. (This doesn't have to be a whole number.)

9. Prompt the respondent to estimate the typical sound level associated with the activity.

   Standard NESI procedure is to use the **Speech Communication Table** (for free-field exposures) or **Personal Listening Device Table** (for headphones/earphones attached to personal listening devices).

   Record the estimated sound level. Also record the information that provided the basis for this estimate (e.g. "shout from 2 feet" from the Speech Communication Table).

   Tip: Participants sometimes find it easier to express this information in alternative terms (e.g. days per month or days per year). The interviewer should allow this, then convert the information into weeks per year and days per week.

   Example: "Twice a month for 3 years" = 3 years × 24 weeks/year × 1 day/week

   Suggested script for free-field exposures:

   I'd like you to estimate how noisy it was when you [engaged in the activity] by answering this question: If you and I were 4 feet apart in that situation, which of the following would you need to do to communicate with me? [The interviewer presents the six options from the Speech Communication Table.] Assume that I have normal hearing, that I am not wearing ear plugs or ear muffs, and that we can see one another’s faces and gestures clearly.

   Tip: The **Personal Listening Device Table** applies only to portable devices such as personal music players and phones, not to stereos, PCs, or sound recording equipment. For such exposures, sound level may be estimated by drawing comparisons to other activities previously reported by the participant (e.g. "louder than", "similar loudness to", or "quieter than" an activity whose sound level has already been estimated).

   Tip: It is possible to obtain sound-level estimates from alternative sources. (See “Departing from NESI standard procedure” on page 7 of this guide.) Such estimates may be recorded in the grey-shaded fields on the NESI worksheets, which should otherwise be left blank.

10. For free-field exposures, obtain information on use of hearing protection: protector type, estimated attenuation, and proportion of time worn (ranging from 0 to 1).

    Use the **Hearing Protection Guide** to help identify protector type and estimate attenuation.

    Tip: The participant may express the proportion of time that hearing protection was worn as a percentage. Convert from percentage to proportion by dividing by 100 (e.g. 70% → 0.7).

    If hearing protection was never worn, record proportion of time worn as 0.

11. One worksheet column is now complete. Repeat steps 7 to 10 for each additional period of the respondent’s life which involved the present activity. Then repeat for each additional exposure activity.

    If you run out of columns, attach extra worksheets as needed.

    Tip: Be prepared to split the content of a column into multiple columns, if necessary. A respondent may initially report consistent exposure habits for a given activity, only for further questioning to reveal otherwise (e.g. changes in frequency of exposure, level of exposure, or use of hearing protection).
Steps 12 to 13: Estimating firearm noise exposure

12. Determine whether the respondent has ever used a rifle, shotgun, or handgun without hearing protection. (Exposures while wearing hearing protection should be ignored. Exposure to air guns should be ignored.)

Tip:
The NESI quantifies exposure to firearms only. Exposure to heavier weapons and blast noise is beyond the scope of the measure.

13. For exposures without hearing protection, record type of firearm and approximate number of rounds fired on the Category C worksheet. Low-calibre (.22 and .17) rifles are assigned fewer units of noise exposure than other firearms, so make sure to establish whether this type of firearm was used.

Tip:
Complete as many columns as are needed to capture the respondent's exposure history. More than one column may be completed per firearm type. Notes may be made in the “Additional information...” field to assist in estimating the total number of rounds fired (e.g. rounds per session and sessions per year). The contents of this field will not be analysed.

Steps 14 to 17: Recording and analysis

14. Complete at least one worksheet for each of the three categories. Even if the respondent reports no noise exposure in a given category, fill in the fields at the top right corner and retain the worksheet with the others.

If a respondent requires more than one worksheet for a given category, attach extra worksheets as required.

Tip:
Completion of the NESI takes 10-25 minutes for most respondents, excepting those with extensive or complex noise histories.

If an interview risks overrunning the available time, reinstruct the respondent to reduce the precision of their reporting. For example, rather than describing three life periods with slightly differing exposure habits, the respondent may report average exposure habits over one long period.

Do not adopt this approach with the earlier exposure activities in each category (i.e. those that contributed most to overall exposure). Instead, reserve this approach for later in the interview, when dealing with more minor sources of noise exposure.

The priority is to ensure that the interview is not cut off, and that all activities are reported across the full lifespan.

It is possible to implement a modified version of the NESI which incorporates firearm exposure while wearing hearing protection. (See “Departing from NESI standard procedure” on page 7 of this guide.)
15. Calculate units of recreational, occupational, and educational noise exposure.

Use the following formulae to generate noise units for each completed column on worksheets A and B.

The NESI example calculations spreadsheet shows how these formulae are applied, using example NESI data.

16. Calculate units of firearm noise exposure.

Use the following formula to generate noise units for each of the completed columns on worksheet C.

The NESI example calculations spreadsheet shows how this formula is applied, using example NESI data.

17. Add the units from all columns to yield total units of lifetime noise exposure, a measure linearly related to total energy of exposure above 80 dBA. One unit equates to one working year (2080 hours) of exposure to 90 dBA.

Alternate units may be generated. See “Departing from NESI standard procedure” on page 7 of this guide.
Departing from NESI standard procedure

Recommended procedure for administering the NESI is fully specified by:
- Steps 1 to 17 of the above guide
- The Recreational Noise Examples
- The Speech Communication Table
- The Personal Listening Device Table
- The Hearing Protection Guide

However, it is recognised that some users of the NESI may wish to modify elements of the procedure. Any such modifications must be disclosed when reporting data obtained using the NESI. Some anticipated modifications are outlined below, along with guidance on their implementation.

**Modification 1: Estimating exposure level**

NESI standard procedure involves estimating sound level using the Speech Communication Table and the Personal Listening Device Table.

It is possible to obtain sound-level estimates from other sources, e.g. databases of sound level measurements. The NESI worksheets include fields for recording an alternative estimate, so that either may be used in analysis.

**Modification 2: Altering the criterion sound level for exposure activities**

The NESI records all exposures with an estimated sound level >80 dBA, and the standard analysis generates noise units linearly related to total energy of exposure above this level. Some NESI users may wish to apply a higher criterion level in the course of analysis (e.g. analysing only exposures >100 dBA). Such users should implement this modification by amending the structure in which they store and process NESI data, so that inclusion of an activity in the overall NESI score is conditional upon sound level.

**Modification 3: Generating units of firearm noise exposure**

Standard NESI procedure assigns 1/16000 noise units to each round from a .22 or .17 rifle and 1/500 units to a round from any other handheld firearm, considering only those exposures incurred without hearing protection. These values are based principally on the approximate energy of such exposures, with an adjustment for the kurtosis of the sound waveform.

Alternate analysis methods are possible, e.g. assigning different values to different types of firearm, and/or incorporating exposures incurred with hearing protection. Users considering such modifications should refer to the NESI dissemination paper, which details the basis for the standard NESI weighting of firearm noise and outlines some possible modifications.

**Modification 4: Generating total units of lifetime noise exposure**

Standard NESI units of lifetime noise exposure are linearly related to the total energy of exposure above 80 dBA. One unit is equivalent to one working year (2080 hours) of exposure at 90 dBA.

Some NESI users may wish to generate an alternative measure, e.g. log energy of exposure, or total duration of exposure exceeding a criterion sound level, or total units of occupational noise exposure. Such users should implement this modification by amending the structure in which they store and process NESI data.

**Modification 5: Examining noise exposure during specific periods**

Standard NESI output is a measure of cumulative lifetime noise exposure.

Some users may wish instead to examine the timing of exposures (e.g. focusing on exposures during childhood, or exposures preceding the development of hearing deficits). In this case, the interviewer must ensure that the “Timing of exposure period” field is always completed, and should amend the structure in which they store and process NESI data, so that inclusion of an exposure in the overall NESI score is conditional upon timing.
Recreational Noise Examples

- Your interviewer has asked you to note any noisy activities you have experienced. Listed below are some common noisy activities, which may help to prompt your memory.
- **Remember what is meant by “noisy”:** situations causing you to raise your voice to communicate at a distance of 4 feet (1.2 m).
- **Do not restrict yourself to the activities on this list.** Also note any other noisy activities you have experienced.
- **Only note activities that you have found to be noisy.** If you have experienced an activity on this list but did not find it noisy, then ignore it.

### Live music
Examples:
- Concerts
- Festivals

### DIY noise
Examples:
- Power tools
- Powered gardening tools

### Nightlife
Examples:
- Nightclubs
- Bars
- Pubs

### Engine noise
Examples:
- Motorbikes
- Motorsports
- Motorboats

### Making music
Examples:
- Playing/singing in a group
- Playing/DJing/singing solo

### Sport-related noise
Examples:
- Sports matches
- Sailing

### Listening through earphones or headphones

### Cinema
## Speech Communication Table

A guide for estimating unknown noise levels (of a continuous type) based on speech communication difficulty.

Approximate communication-limiting noise levels are based on the scenario of one person communicating with another in an environment that they are both used to, assuming that the listener is not hearing impaired, is not wearing hearing protection, and may be assisted to some extent by gestures and facial cues.

<table>
<thead>
<tr>
<th>Vocal effort required</th>
<th>Estimated level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Talk normally</strong> from 4 feet (1.2 m)</td>
<td>≤80 dBA</td>
</tr>
<tr>
<td><strong>Raise voice</strong> from 4 feet (1.2 m)</td>
<td>87 dBA</td>
</tr>
<tr>
<td><strong>Talk loudly</strong> from 4 feet (1.2 m)</td>
<td>90 dBA</td>
</tr>
<tr>
<td><strong>Talk very loudly</strong> from 4 feet (1.2 m)</td>
<td>93 dBA</td>
</tr>
<tr>
<td><strong>Shout</strong> from 4 feet (1.2 m)</td>
<td>99 dBA</td>
</tr>
<tr>
<td><strong>Shout from 2 feet (0.6 m)</strong></td>
<td>105 dBA</td>
</tr>
<tr>
<td><strong>Shout in listener’s ear</strong></td>
<td>110 dBA</td>
</tr>
</tbody>
</table>
A guide for estimating the free-field equivalent output levels of earphones or headphones coupled to personal listening devices (e.g. phones and music players), based on the respondent's typical volume control setting.

<table>
<thead>
<tr>
<th>Volume control setting</th>
<th>Estimated level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70% of maximum</td>
<td>&lt;80 dBA</td>
</tr>
<tr>
<td>70% of maximum</td>
<td>82 dBA</td>
</tr>
<tr>
<td>80% of maximum</td>
<td>88 dBA</td>
</tr>
<tr>
<td>90% of maximum</td>
<td>94 dBA</td>
</tr>
<tr>
<td>Maximum volume</td>
<td>100 dBA</td>
</tr>
</tbody>
</table>

**Output-level warning messages in European devices**

Many personal listening devices sold in the European Union from February 2013 have settings designed to encourage listening levels below 85 dBA*. When sound levels reach 85 dBA, the listener is presented with a visual or audible warning message which they must acknowledge in order to access the upper portion of the volume control range.

Note that “maximum volume” in the above table does **not** refer to the sound level that elicits this warning message. “Maximum volume” refers to the true upper limit of the volume control range, accessed by acknowledging the message and further increasing the sound level.

If a respondent has encountered such warning messages, then their recollection of this phenomenon can sometimes assist in estimating sound level (for example, if they consistently chose not to exceed the 85 dB warning level).

A tool for estimating the attenuation of hearing protectors.

NESI “estimated attenuation” is derived from attenuation ratings reported by manufacturers: either the Single Number Rating (SNR), used primarily in Europe, or the Noise Reduction Rating (NRR), used in the US and elsewhere.

- If the specific model of protector is listed in this guide, simply read its estimated attenuation from the table
- If the specific model is not listed, but its SNR or NRR is known, calculate its estimated attenuation using the final table
- For all other hearing protectors, estimate attenuation based on the type of hearing protector

<table>
<thead>
<tr>
<th>Formable ear plugs</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M E-A-R Classic (SNR 28)</td>
<td>24 dB</td>
</tr>
<tr>
<td>Howard Leight Laser Lite (SNR 35)</td>
<td>31 dB</td>
</tr>
<tr>
<td>Moldex SparkPlugs (SNR 35)</td>
<td>31 dB</td>
</tr>
<tr>
<td>Hearos Xtreme Protection (NRR 33)</td>
<td>32 dB</td>
</tr>
<tr>
<td>3M 1000/1100 (SNR 37)</td>
<td>33 dB</td>
</tr>
<tr>
<td>Typical ear plug of this type</td>
<td>31 dB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flanged ear plugs</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M E-A-R Tri-Flange (SNR 29)</td>
<td>25 dB</td>
</tr>
<tr>
<td>Howard Leight Airsoft (SNR 30)</td>
<td>26 dB</td>
</tr>
<tr>
<td>Howard Leight Smartfit (SNR 30)</td>
<td>26 dB</td>
</tr>
<tr>
<td>3M E-A-R Ultrafit (SNR 32)</td>
<td>28 dB</td>
</tr>
<tr>
<td>3M E-A-R Tracer (SNR 32)</td>
<td>28 dB</td>
</tr>
<tr>
<td>Typical ear plug of this type</td>
<td>26 dB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-fidelity ear plugs</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etymotic ETY-Plugs (NRR 12)</td>
<td>11 dB</td>
</tr>
<tr>
<td>Alpine MusicSafe, gold filter (SNR 18)</td>
<td>14 dB</td>
</tr>
<tr>
<td>EarPeace, red filter (SNR 20)</td>
<td>16 dB</td>
</tr>
<tr>
<td>Alpine PartyPlug Pro (SNR 21)</td>
<td>17 dB</td>
</tr>
<tr>
<td>Eargasm (SNR 21)</td>
<td>17 dB</td>
</tr>
<tr>
<td>Typical ear plug of this type</td>
<td>16 dB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Push-in ear plugs</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M E-A-R Express Pod Plugs (SNR 28)</td>
<td>24 dB</td>
</tr>
<tr>
<td>3M E-A-R Skull Screw (SNR 32)</td>
<td>28 dB</td>
</tr>
<tr>
<td>3M No-Touch foam (SNR 35)</td>
<td>31 dB</td>
</tr>
<tr>
<td>Howard Leight TrustFit Pod (SNR 36)</td>
<td>32 dB</td>
</tr>
<tr>
<td>3M E-A-R Push-Ins (SNR 38)</td>
<td>34 dB</td>
</tr>
<tr>
<td>Typical ear plug of this type</td>
<td>31 dB</td>
</tr>
</tbody>
</table>
### High-attenuation earmuffs

<table>
<thead>
<tr>
<th>Product</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mpow (SNR 34)</td>
<td>30 dB</td>
</tr>
<tr>
<td>3M Peltor Optime III/105 (SNR 35)</td>
<td>31 dB</td>
</tr>
<tr>
<td>3M Peltor X-Series X5 (SNR 37)</td>
<td>33 dB</td>
</tr>
<tr>
<td>Fnova 34 dB (NRR 34)</td>
<td>33 dB</td>
</tr>
<tr>
<td>Pro For Sho (NRR 34)</td>
<td>33 dB</td>
</tr>
<tr>
<td>Typical earmuffs of this type</td>
<td>33 dB</td>
</tr>
</tbody>
</table>

### Low-attenuation earmuffs

<table>
<thead>
<tr>
<th>Product</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard Leight Impact Sport (NRR 22)</td>
<td>21 dB</td>
</tr>
<tr>
<td>3M Peltor Optime I (SNR 26)</td>
<td>22 dB</td>
</tr>
<tr>
<td>Silverline 633815 (SNR 27)</td>
<td>23 dB</td>
</tr>
<tr>
<td>Neiko 53925A (NRR 26)</td>
<td>25 dB</td>
</tr>
<tr>
<td>Silverline 633816 (SNR 30)</td>
<td>26 dB</td>
</tr>
<tr>
<td>Typical earmuffs of this type</td>
<td>23 dB</td>
</tr>
</tbody>
</table>

### Banded ear plugs

<table>
<thead>
<tr>
<th>Product</th>
<th>Estimated attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moldex 6700 Jazz-Band 2 (SNR 23)</td>
<td>19 dB</td>
</tr>
<tr>
<td>Howard Leight QB2HYG (SNR 24)</td>
<td>20 dB</td>
</tr>
<tr>
<td>Howard Leight QB1HYG (SNR 26)</td>
<td>22 dB</td>
</tr>
<tr>
<td>3M E-A-R Reflex, foam tips (SNR 26)</td>
<td>22 dB</td>
</tr>
<tr>
<td>Radians RB2120 RadBand 2 (NRR 25)</td>
<td>24 dB</td>
</tr>
<tr>
<td>Typical ear plugs of this type</td>
<td>22 dB</td>
</tr>
</tbody>
</table>

### Other protectors with known SNR or NRR

<table>
<thead>
<tr>
<th>Hearing protectors with known SNR</th>
<th>Estimated attenuation = SNR - 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing protectors with known NRR</td>
<td>Estimated attenuation = NRR - 1</td>
</tr>
</tbody>
</table>
NESI Supplementary Material: Adoption of the Speech Communication Table (SM4)

Source Version of the Speech Communication Table

The basis for the NESI Speech Communication Table is the version reported by Lutman et al. (2008), which has been lightly modified to suit the needs of the NESI (modifications are described below). Ferguson et al. (2018) have since reported evaluation data for a version closely resembling that of Lutman and colleagues, though it specifies six levels of vocal effort, rather than seven, and differs at the highest level of vocal effort. (For Lutman and colleagues, “shouting close to the listener’s ear” corresponds to “>110 dBA”, whereas for Ferguson and colleagues, “>110 dBA” corresponds to the level at which communication “close to the listener’s ear” is “impossible”.)

Modifications to the Speech Communication Table

The layout and wording have been altered, so that the expression of communication distance is more straightforward (expressed in words, rather than the use of multiple columns). Dotted lines emphasise the divisions.

Vocal effort is now expressed using verb-adverb phrases (e.g. “talk loudly”), rather than adjective-noun phrases (e.g. “loud voice”), which allows easier expression of the vocal-effort options by the interviewer.

The description of the communication scenario has been altered so that only the listener is free of hearing impairment, not the talker. (The talker in the scenario is the NESI respondent, who might be hearing-impaired, whereas the listener is a hypothetical listener with normal hearing.)

The very highest level of vocal effort (shouting into the listener’s ear) is now ascribed a sound level of 110 dBA, not >110 dBA as in Lutman et al. (2008). This slightly more conservative estimate more closely resembles that of Ferguson et al. (2018), but was chosen largely for pragmatic reasons. Since exposures at sound levels >110 dBA are rare (Berger et al., 2015), we consider some imprecision in these estimates acceptable.

Evaluation of the Speech Communication Table

Ferguson and colleagues conducted a large-scale evaluation of their version of the Speech Communication Table, using personal dosimetry measurements from 168 employees in 15 workplaces. A summary of results is given in the main NESI paper (see section on Evaluation).

References


Various types of hearing protection devices (HPDs) are available, differing widely in the attenuation they offer. Those with low-to-moderate attenuation do not guarantee residual sound levels <80 dBA in the ear canal when worn in high-noise environments. Hence, the type of HPD worn by the respondent should be taken into account when quantifying noise exposure.

Since attenuation ratings reported by HPD manufacturers are publicly available, we have sought to derive attenuation estimates from these values. Consequently, attenuation should be easily estimated for protectors reported by future NESI respondents. The table below outlines the basic characteristics of two widely used attenuation ratings and the means by which they are converted into NESI “estimated attenuation”.

<table>
<thead>
<tr>
<th>Region of use</th>
<th>Single Number Rating (SNR)</th>
<th>Noise Reduction Rating (NRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis for determining the attenuation rating</td>
<td>Mean and standard deviation of real-ear attenuation at threshold, measured for devices fitted by non-expert users</td>
<td>Mean and standard deviation of real-ear attenuation at threshold, measured for devices fitted by expert users</td>
</tr>
<tr>
<td>Simplified explanation of the rating calculation</td>
<td>Mean attenuation minus 0.84 standard deviations (i.e. the attenuation achieved by ~80% of users)</td>
<td>Mean attenuation minus two standard deviations (i.e. the attenuation achieved by ~98% of users) minus a 3 dB safety factor</td>
</tr>
<tr>
<td>Conversion to NESI “estimated attenuation”</td>
<td>Estimated attenuation = SNR − 4 dB</td>
<td>Estimated attenuation = NRR + 3 dB − 4 dB = NRR − 1 dB</td>
</tr>
</tbody>
</table>

Both conversions above involve subtraction of a 4 dB “derating” value, to account for real-world factors that reduce that reduce the attenuation of HPDs, as recommended by the UK Health and Safety Executive (Brueck, 2009).

The conversion from NRR also involves re-addition of the 3 dB “safety factor” already incorporated in the NRR, to bring the estimate closer in line with that obtained from the SNR. This approach may still be expected to yield a more conservative estimate of attenuation than the SNR, since it reflects the attenuation likely to be achieved by 98% of users, c.f. 80% for the SNR. However, the NRR measurement employs expert rather than naïve users, potentially ameliorating this disparity. In practice, we find that the estimates derived from SNR and NRR seldom differ by more than a few dB. Each is likely sufficiently accurate for the purposes of the NESI, since noise exposure incurred with HPDs contributed relatively little to the overall sound energy of pilot NESI respondents.

References

To account for the greater auditory hazard posed by impulsive sound, NESI has adopted the kurtosis-corrected noise metric of Goley et al. (2011):

\[
L'_{Aeq} = L_{Aeq} + 4.02 \times \log_{10} \left( \frac{\beta}{\beta_G} \right)
\]

where \(L'_{Aeq}\) is kurtosis-corrected A-weighted equivalent continuous level, \(L_{Aeq}\) is uncorrected A-weighted equivalent continuous level, 4.02 is a constant derived from dose-response data in chinchillas, \(\beta\) is the kurtosis statistic of the noise, and \(\beta_G\) is the kurtosis statistic for Gaussian noise (\(\beta_G = 3\)).

For impulses whose acoustic energy expressed as A-weighted equivalent continuous 8-hour level (\(L_{Aeq8hr}\)), the equation becomes:

\[
L'_{Aeq8hr} = L_{Aeq8hr} + 4.02 \times \log_{10} \left( \frac{\beta}{\beta_G} \right)
\]

Incorporation of firearm noise into the NESI can therefore be achieved by combining \(L_{Aeq8hr}\) and \(\beta\) for firearm impulses measured at the shooter’s ear. Flamme et al. (2009) and Meinke et al. (2014) have reported these data for a wide variety of firearms. Due to a markedly bimodal distribution of \(L_{Aeq8hr}\), we have elected to dichotomize these weapons into low-calibre (.22 and .17) rifles and all other hand-held firearms (excepting air guns). A single kurtosis correction factor has been applied to both categories, since this factor was found to differ little between firearms:

<table>
<thead>
<tr>
<th>Low-calibre (.22 and .17) rifles</th>
<th>Other hand-held firearms (except air guns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy of a round, expressed as (L_{Aeq8hr})</td>
<td>Mean = 66.7 dBA, SD = 2.5, (n = 5) (Meinke et al., 2014)</td>
</tr>
<tr>
<td>Kurtosis statistic</td>
<td>Median = 78.5, range = 20 to 220, (n = 10) (Flamme et al., 2009)</td>
</tr>
<tr>
<td>Kurtosis correction factor</td>
<td>Kurtosis correction factor = 4.02 (\times\log_{10} \left( \frac{\beta}{\beta_G} \right))</td>
</tr>
<tr>
<td>For the firearms reported by Flamme et al. (2009), mean kurtosis correction factor = 5.4 dBA (SD = 1.2)</td>
<td></td>
</tr>
<tr>
<td>Kurtosis-corrected A-weighted equivalent continuous 8-hour level ((L'_{Aeq8hr}))</td>
<td>(L'<em>{Aeq8hr} = L</em>{Aeq8hr} + 4.02 \times \log_{10} \left( \frac{\beta}{\beta_G} \right))</td>
</tr>
<tr>
<td>= 66.7 + 5.4</td>
<td></td>
</tr>
<tr>
<td>= 72.1 dBA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(L'<em>{Aeq8hr} = L</em>{Aeq8hr} + 4.02 \times \log_{10} \left( \frac{\beta}{\beta_G} \right))</td>
</tr>
<tr>
<td>= 81.8 + 5.4</td>
<td></td>
</tr>
<tr>
<td>= 87.2 dBA</td>
<td></td>
</tr>
<tr>
<td>Conversion to NESI units of noise exposure</td>
<td>NESI units of noise exposure</td>
</tr>
<tr>
<td>= 10 (\text{level} - 90)/10 (\times) hours / 2080</td>
<td></td>
</tr>
<tr>
<td>= 10 (\text{72.1} - 90)/10 (\times) 8 / 2080</td>
<td></td>
</tr>
<tr>
<td>= 0.000062 (\approx 1 / 16000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NESI units of noise exposure</td>
</tr>
<tr>
<td>= 10 (\text{level} - 90)/10 (\times) hours / 2080</td>
<td></td>
</tr>
<tr>
<td>= 10 (\text{87.2} - 90)/10 (\times) 8 / 2080</td>
<td></td>
</tr>
<tr>
<td>= 0.002213 (\approx 1 / 500)</td>
<td></td>
</tr>
</tbody>
</table>

Note that correcting for kurtosis in the above calculations involves adding 5.4 dB to the equivalent continuous level. Interestingly, Murphy and Kardous (2012) remark that “for occupational noise exposures with impulsive content, the rule of thumb is to add 5 dB to the continuous dose estimate to compensate for the increased risk” – an adjustment similar to that obtained via Goley and Kim’s kurtosis statistic.
Exceptions

We recommend that exposures incurred while wearing hearing protection be disregarded, due to their very low sound energy. Assuming protector attenuation of 30 dB, exposure to ~500000 such rounds would be required to accrue a single NESI noise unit.

Exposures to air rifles should also be disregarded, since all rifles tested by Lankford et al. (2016) were associated with a shooter-ear $L_{A_{eq,8hr}}$ below 54 dBA, yielding less than a billionth of a NESI noise unit.

Exposure to impulse noise from sources other than hand-held firearms (e.g. artillery and blast noise) is beyond the scope of the NESI.

Potential Limitations and Alternative Methods

It is important to note that our energy-based metric represents a single approach to the quantification of firearm noise exposure, which may not agree with other measures of auditory hazard. For example, in UK law, the threshold beyond which employers must provide hearing protection is a peak level of 135 dBC or a daily average level of 80 dBA (Health and Safety Executive, 2005). A low-powered Remington 514 rifle produces a peak sound level of 139.6 dBA, but its energy, expressed as $L_{A_{eq,8hr}}$, is only 63.8 dBA (Meinke et al., 2014). Even after adding a 5.4 dB correction for kurtosis, as in the NESI, 12 rounds could be fired from the Remington before the corrected $L_{A_{eq,8hr}}$ exceeded 80 dBA. Hence, it is plausible that our energy-based approach might under-weight firearm noise. At present, all that can be confidently stated is that energy-based metrics of impulsive noise are increasingly advocated as a basis for firearm-noise damage risk criteria (e.g. Murphy and Kardous, 2012), and that correcting energy-based metrics of impulsive noise for kurtosis improves their ability to predict noise-induced auditory damage (e.g. Zhao et al., 2010). In short, kurtosis-corrected energy appears a plausible metric, but would surely benefit from further evaluation.

Future NESI users may wish to distinguish between different types of hand-held firearm when quantifying exposure, rather than accepting the dichotomous categorisation used here. Such users should obtain the equivalent continuous level of a round fired from the weapon in question, as measured at the shooter’s ear. They may then combine it with the 5.4 dB kurtosis correction factor and convert into NESI units of noise exposure, as demonstrated in the above calculations.

Another potential limitation is our exclusion of exposures incurred while wearing hearing protection. If HPDs worn during firearm exposure provide substantially less than 30 dB of attenuation, then such exposures might make a meaningful contribution to lifetime noise exposure. If users wish to incorporate these exposures into the NESI, they may obtain an estimate of the attenuation provided by the equipment and use it to modify the equivalent continuous level, before combining this value with the kurtosis correction factor and converting to NESI units of noise exposure.

References


3.2  Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy

Published in Hearing Research, February 2017
Research paper

Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy

Hannah Guest a,⁎, Kevin J. Munro a, c, Garreth Prendergast a, Simon Howe b, Christopher J. Plack a, d

a Manchester Centre for Audiology and Deafness, University of Manchester, Manchester Academic Health Science Centre, UK
b Audiology Department, James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
c Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
d Department of Psychology, Lancaster University, Lancaster, UK

Article info
Article history:
Received 13 August 2016
Received in revised form 6 December 2016
Accepted 8 December 2016
Available online 11 December 2016

Keywords:
Tinnitus
Cochlear synaptopathy
Hidden hearing loss
Auditory brainstem response
Envelope following response
Noise-induced hearing loss

Abstract
In rodents, exposure to high-level noise can destroy synapses between inner hair cells and auditory nerve fibers, without causing hair cell loss or permanent threshold elevation. Such “cochlear synaptopathy” is associated with amplitude reductions in wave I of the auditory brainstem response (ABR) at moderate-to-high sound levels. Similar ABR results have been reported in humans with tinnitus and normal audiometric thresholds, leading to the suggestion that tinnitus in these cases might be a consequence of synaptopathy. However, the ABR is an indirect measure of synaptopathy and it is unclear whether the results in humans reflect the same mechanisms demonstrated in rodents. Measures of noise exposure were not obtained in the human studies, and high frequency audiometric loss may have impacted ABR amplitudes. To clarify the role of cochlear synaptopathy in tinnitus with a normal audiogram, we recorded ABRs, envelope following responses (EFRs), and noise exposure histories in young adults with tinnitus and matched controls. Tinnitus was associated with significantly greater lifetime noise exposure, despite close matching for age, sex, and audiometric thresholds up to 14 kHz. However, tinnitus was not associated with reduced ABR wave I amplitude, nor with significant effects on EFR measures of synaptopathy. These electrophysiological measures were also uncorrelated with lifetime noise exposure, providing no evidence of noise-induced synaptopathy in this cohort, despite a wide range of exposures. In young adults with normal audiograms, tinnitus may be related not to cochlear synaptopathy but to other effects of noise exposure.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Subjective tinnitus — the perception of sound without an acoustic source — is most often associated with hearing loss (Nicolas-Puel et al., 2002; Sanchez et al., 2005). It is widely agreed that these phenomena are related, with hearing loss usually regarded as a trigger for neuroplastic changes in the central auditory system, giving rise to the tinnitus percept. While these central

Abbreviations: ABR, auditory brainstem response; AN, auditory nerve; EFR, envelope following response; SR, spontaneous rate; TNA, tinnitus with a normal audiogram
⁎ Corresponding author. Manchester Centre for Audiology and Deafness, HCDH Office, Ellen Wilkinson Building, University of Manchester, Oxford Road, Manchester M13 9PL, UK.
E-mail address: hannah.guest@manchester.ac.uk (H. Guest).

0378-5955/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
fibers, yet leave inner and outer hair cells macroscopically intact. Termed “cochlear synaptopathy”, this primary deafferentation has also been observed in noise-exposed guinea pigs (Lin et al., 2011) and in aging mice without significant noise exposure (Sergeyenko et al., 2013). Crucially, the pathology does not compromise sensitivity to low-level sounds, seemingly due to preferential loss of AN fibers with low spontaneous firing rates (SRs) and high thresholds (Furman et al., 2013). Consistent with low-SR fiber loss, abnormal auditory processing is evident at higher sound levels. Synaptopathic ears exhibit permanent reductions in the amplitude of wave I of the auditory brainstem response (ABR) to tone bursts with moderate-to-high sound levels (Kujawa and Liberman, 2009).

Similar electrophysiological evidence of deafferentation has been reported in humans with TNA. Schaette and McAlpine (2011) recorded ABRs to clicks with high sound levels and demonstrated reductions in wave I amplitude in TNA subjects relative to audiogram-matched controls. The results were interpreted as evidence of deafferentation consistent with cochlear synaptopathy: a “hidden hearing loss” which might resolve the enigma of TNA. The absence of any tinnitus-related reduction in ABR wave V was tentatively attributed to increased central gain in the auditory brainstem, suggested as a mechanism of tinnitus generation. Gu et al. (2012) reported similar findings in subjects with near-normal hearing.

However, the latter study demonstrated significant wave I amplitude reductions only for the highest stimulus level used, 120 dB peSPL, and not for lower levels more comparable with those of Schaette and McAlpine (< 100 dB peSPL). Missing ABR data at this high stimulus level led to reduced participant groups with unmatched audiograms at high frequencies (tinnitus had systematically poorer mean thresholds above 8 kHz). This disparity may have accounted for the group difference in ABR amplitude, since wave I is dominated by the responses of high frequency AN fibers (Don and Eggermont, 1978). Schaette and McAlpine’s tinnitus and control groups also differed in high frequency sensitivity. Mean 12 kHz threshold was elevated by 3.5 dB in the tinnitus group, and thresholds at even higher frequencies were not reported. Additionally, a recent study by Gilles et al. (2016) found no wave I amplitude reduction in young people with tinnitus, though statistical power was compromised by high measurement variability. Given the growing interest in cochlear synaptopathy in humans, the evidence for its role in tinnitus could benefit from careful confirmation.

Investigation of the condition in living humans is necessarily indirect and requires a sensitive, non-invasive measure. The transient-evoked ABR may offer limited sensitivity to synaptopathy in humans, despite clear correlations with the pathology in rodent models. ABR amplitudes are highly variable, influenced by factors such as head size, cochlear dispersion, and skull thickness (Michalewski et al., 1980; Trune et al., 1988; Don et al., 1994), which might obscure the effects of synaptopathy. Differential ABR measures may minimize the influence of these non-synaptopathic factors (Plack et al., 2016), but recent evidence suggests a more fundamental shortcoming of the ABR. Recordings in gerbils and guinea pigs after ototoxic exposure indicate that AN fibers with the lowest SRs do not contribute to the compound action potential, equivalent to ABR wave I (Bourien et al., 2014). The low-SR fibers affected in animal models of synaptopathy exhibit a somewhat wider range of firing rates than those described by Bourien and colleagues (Furman et al., 2013). Nevertheless, the former exhibit relatively weak onset responses (Taberner and Liberman, 2005), limiting their contribution to the ABR (Shaheen et al., 2015).

In contrast, low-SR fibers surpass high-SR fibers in their synchronization to amplitude-modulated stimuli (Joris et al., 2004). Hence they make robust contributions to the subcortical envelope following response (EFR): a sustained response representing neural synchrony to the envelope of an amplitude-modulated stimulus. Relatively high modulation frequencies are necessary to elicit the subcortical EFR. At lower frequencies, below 80 Hz, responses are dominated by cortical generators (Kuwada et al., 2002). Using EFR stimuli optimized to enhance the contribution from the AN, Shaheen et al. (2015) demonstrated that EFR amplitude afforded greater sensitivity to noise-induced cochlear synaptopathy in mice than ABR amplitude. An additional strategy to enhance the sensitivity of the EFR was devised by Bharadwaj et al. (2015), who reasoned that stimuli with high sound levels and shallow modulations should be weakly encoded in synaptopathic ears, due to saturation of high-SR fibers and consequent reliance on low-SR units. To reduce variability from non-synaptopathic sources that might affect raw EFR amplitude, the researchers computed the slope of the function relating EFR amplitude to stimulus modulation depth. This measure was shown to correlate with behavioral measures of temporal coding and auditory selective attention in audiometrically normal humans, with synaptopathy proposed as a potential underlying cause. Hence carefully designed EFR measures may be of value in the identification of cochlear synaptopathy in humans.

Finally, previous studies associating TNA with evidence of cochlear synaptopathy have not obtained measures of lifetime noise exposure. Indeed, to the authors’ knowledge, no previous study has reported that TNA is associated with elevated noise exposure compared to audiogram-matched controls. It is therefore unclear whether the reported electrophysiological effects in TNA are caused by the same mechanisms demonstrated in rodent models of noise-induced synaptopathy.

The fourfold aims of the present study were: (a) To determine whether TNA is associated with greater lifetime noise exposure; (b) To provide a further test of the hypothesis that TNA is associated with ABR effects consistent with cochlear synaptopathy, controlling for high frequency sensitivity; (c) To determine whether TNA is associated with temporal coding deficits consistent with synaptopathy; (d) To examine the relations between electrophysiological measures of synaptopathy and lifetime noise exposure.

2. Material and methods

2.1. Participants

Control participants were recruited from the University of Manchester staff and student populations (via poster and on-line advertising) and from the general Manchester population (via on-line advertising). Tinnitus participants were recruited from the same sources, with the addition of patients identified by local audiology services. All participants were required to exhibit bilaterally normal pure tone audiometric thresholds (< 20 dB HL at 0.25–8 kHz) and middle ear function (compliance 0.3–1.6 mℓ; middle ear pressure –50 to +50 daPa). All were without history of head trauma, middle ear surgery, neurological disorder, and ototoxic exposure.

Tinnitus participants (n = 20, female = 10) were aged 25.7 ± 1.3 years (mean ± standard error of the mean). All reported prolonged spontaneous tinnitus that was stable (> 4 months) and non-pulsatile. Tinnitus characteristics are summarized in Table 1. The mean Tinnitus Functional Index (TFI) score was 33 (± 7), which corresponds to “moderate” problems with tinnitus on average (Henry et al., 2016).

Control participants (n = 20, female = 10, mean age = 25.5 ± 1.3 years) were individually matched with tinnitus participants on the basis of age (to within 18 months) and sex. Mean audiometric thresholds were matched between groups to within 2.3 dB at all
test frequencies from 0.25 to 14 kHz, after averaging the left and right ear thresholds. At the extended high frequencies (10 and 14 kHz), the group means differed by < 1 dB (Fig. 1).

Sample size was selected to provide 80% power (α = 0.05, one-tailed) to detect the ABR effect size demonstrated by Schaette and McAlpine (2011) for a 100 dB peSPL stimulus. It should be noted that the previous study recruited only female participants, whereas the present study recruited a mixed sex sample, potentially filled (see 3.2 and 4.2 for post hoc power analysis).

2.2. Noise exposure history

2.2.1. General procedure

Each participant provided a detailed history of lifetime noise exposure via structured interview, based on the procedure described by Lutman et al. (2008). For all exposures estimated to exceed 80 dBA (see 2.2.3), data were gathered on estimated sound level, total duration of exposure, and use of personal hearing protection. The participant provided information first on occupational noise exposure, followed by social noise exposure. The duration of the structured interview ranged from 5 to 45 min. Example noise exposure data for a single participant are given in Table 3 of Supplementary Material.

2.2.2. Determination of activities incurring noise exposure

The participant was asked to recall activities that routinely involved exposure to sound levels ≥ 80 dBA (see 2.2.2). A list of the most common social activities involving noise was provided (given in Lutman et al., 2008). Each activity identified by the participant was marked as an entry in their noise record, and associated information sought on duration and sound level. An activity was treated as a single entry only if it entailed approximately consistent sound levels throughout all exposures. If the sound level varied, then the exposures were broken down into two or more activities (e.g. “loud bars” and “quieter bars” or “metal gigs” and “rock gigs”).

2.2.3. Estimation of sound level

For free-field exposures, sound levels were estimated based on vocal effort required to hold a conversation at a distance of 1.2 m. Reported vocal effort was converted to dBA level using a speech communication table (Lutman et al., 2008; see Table 2 of Supplementary Material). For example, if the participant recalled that it was necessary merely to “raise one’s voice” to hold a conversation (rather than “talk very loudly” or “shout”), an estimated level of 87 dBA was selected. Information was also provided on use of personal hearing protection: type, attenuation (if known), and proportion of time worn during each activity. When attenuation was unknown, it was estimated from type of protector (see Lutman et al., 2008).

For exposures incurred through use of personal music players, the participant reported the typical setting of the volume control on their device, expressed as a percentage of the maximum setting. This value was converted to a free-field equivalent output level, based on the output levels measured by Portnuff et al. (2011) across a variety of devices coupled to stock earphones (see Table 2 of Supplementary Material).
2.2.4. Estimation of exposure duration
For a given activity, the participant identified a time period (usually a number of years) during which they had engaged in the activity with approximately uniform regularity. The participant then estimated the number of hours per day, days per week, and weeks per year of exposure during that period, allowing calculation of total hours of exposure. Often, the participant would report having engaged in an activity more frequently during one period than another. Hours of exposure would be calculated for each period separately, then summed. Additionally, where hearing protection had been worn only part of the time, it was necessary to calculate the protected and unprotected exposure durations.

2.2.5. Calculation of units of noise exposure
For each activity in the noise record, duration, level, and protector attenuation were combined to generate units of noise exposure based on the equal energy principle:

\[ U = 10^{\left(\frac{L - A}{90}\right) \times 10} \times T / 2080 \]

where:
- \( U \) = units of noise exposure
- \( L \) = level (dBA)
- \( A \) = attenuation of ear protection (dBA)
- \( T \) = total exposure time (hours)

The units from all exposures, regardless of whether they occurred in social or occupational settings, were summed to yield the total units of lifetime noise exposure. The resulting measure is linearly related to the total energy of exposure above 80 dBA.

2.3. Behavioral testing
Participants were seated in a double-walled sound-attenuating booth, providing responses using a button (pure tone audiometry) or mouse and computer monitor (high-frequency audiometry). Air conduction pure tone audiometric thresholds were obtained in accordance with British Society of Audiology recommended procedures (British Society of Audiology, 2011) at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz, using a GSI Arrow audiometer, TDH-39 supra-aural headphones, and MX-41 ear cushions. High-frequency thresholds were obtained using a three-interval, three-alternative, forced-choice paradigm, with stimuli delivered through Sennheiser HDA 200 circum-aural headphones driven by an E-MU 0202 external audio interface. In order to minimize the influence of threshold microstructure and ear canal resonance, stimuli were 1/3-octave bands of noise centered at 10 and 14 kHz. Steady-state noise levels were 80 dB, with the addition of 10 ms raised-cosine onset and offset ramps. Stimulus level was varied adaptively using a two-down, one-up rule. Threshold was attained using three initial turnpoints (6 dB step size) and eight subsequent turnpoints (2 dB step size). The stimulus level at the final eight turnpoints was averaged to obtain threshold. Thresholds were obtained for each ear separately and then averaged across ears. Prior to testing, each participant performed a practice run containing at least three turnpoints.

2.4. Auditory evoked potentials

2.4.1. General procedure
Participants reclined comfortably with eyes closed in a double-walled sound-attenuating booth. Auditory stimuli were delivered through EARtone 3A insert earphones with mu-metal and aluminum shielding, driven by an Avid FastTrack C400 external audio interface (48 kHz output). Evoked responses were recorded using the BioSemi ActiveTwo measurement system, with active electrodes at Cz, C7, and both mastoids. Common Mode Sense and Driven Right Leg electrodes were located on the low forehead and electrode offsets were maintained within ±40 mV throughout each recording. Bioelectric activity from each electrode was digitized at a sampling rate of 16384 Hz and processed off-line in MATLAB (The Mathworks Inc., 2013). EEG data files incorporated stimulus timing information by means of a custom trigger box connecting the external audio interface to the BioSemi USB interface.

2.4.2. Auditory brainstem response
Digital stimuli were single-polarity high-pass filtered clicks (first-order butterworth, 2.4 kHz cutoff). Due to the low-pass response of the ER3A inserts, the stimuli in the ear canal had a 10 dB bandwidth extending from about 1.2 to 4.7 kHz (measured in a Gras IEC60711 occluded-ear simulator coupled to ER3A insert earphones). In order to minimize recording time, presentation alternated between ears, at a rate of 7.05 per second in each ear, so that a click in one ear was followed after approximately 71 ms by a click in the other ear. This gave an overall presentation rate of 14.1 per second per ear and a total of 7040 presentations per ear. The inter-stimulus interval was jittered by a maximum of 10%, so as to prevent accumulation of stationary interference. In order to stimulate low-SR fibers, a presentation level of 102 dB peSPL (peak-to-peak) was selected, 2 dB higher than the maximum level used by Schaepte and McAlpine (2011).

Activity between Cz and ipsilateral mastoid was filtered (30–1500 Hz; fourth-order butterworth) and divided into epochs extending from 10 ms pre-stimulus to 13 ms post-stimulus, after correcting for the 0.8 ms acoustic delay introduced by the sound tube. Post-hoc artifact rejection eliminated epochs whose RMS amplitude exceeded the mean by more than two standard deviations. The remaining epochs were averaged and corrected for any linear drift by subtracting a linear fit to the pre-stimulus baseline.

Waves I and V of the ABR were identified and quantified automatically in MATLAB (The Mathworks Inc., 2013), based on waveform characteristics within specified time windows. The window for wave I extended from 1.55 to 2.05 ms after stimulus peak and the window for wave V from 5.1 to 6.5 ms. The trough of wave I was required to occur 0.3 to 1.0 ms after its peak. The peak and trough of wave I were defined as local maxima and minima. Wave V required more subtle denotation, in order to appropriately interpret waveforms featuring a prominent wave IV or blended wave IV/wave V complex. Hence the peak of wave V was defined as either a local maximum or a downward inflection point on a falling portion of the waveform (a maximum in the first derivative where the first derivative < 0). Wave I amplitude was measured from peak to following trough. Wave V was measured from peak to baseline, in order to capture the gradual rise in amplitude from pre-stimulus baseline to wave V peak observed in all waveforms (presented in Supplementary Material). Post-hoc subjective review verified that all waveforms had been appropriately interpreted by the peak-picking algorithm. The resulting amplitudes and latencies were averaged across left and right ears for each participant.

2.4.3. Envelope following response
Subcortical ERPs were recorded using the variable-modulation-depth paradigm described by Bharadwaj et al. (2015). Stimuli were 75 dB SPL transposed tones (Bernstein and Trahiotis, 2002) with a 4000 Hz carrier and 100 Hz modulator (Fig. 2). Stimulus duration was 400 ms with the addition of 15 ms onset and offset ramps. Off-frequency contributions were attenuated by notched-noise

**Supplementary Material.**
leading to higher values of the difference measure in synaptopathic ears.

For each trial, rather than being frozen between trials. Stimuli were 800 Hz centered on 4000 Hz) applied at a signal-to-noise ratio (SNR) of 20 dB (broadband RMS). The noise was realized separately for each trial, rather than being frozen between trials. Stimuli were of two modulation depths (0 dB and –6 dB re: 100% modulation) and each was presented in two polarities. The resulting four stimuli were presented in the sequence: 0 dB; inverted 0 dB; –6 dB; and inverted –6 dB. The average inter-stimulus interval was 400 ms, jittered by up to 10%. This sequence was presented 630 times.

Activity in the vertical channel from Cz to C7 was divided into epochs extending from 4 to 404 ms after the end of the stimulus onset ramp. Post-hoc artifact rejection eliminated epochs whose RMS level exceeded the 99th percentile for the recording. The remaining epochs were averaged and the opposing-polarity averages added to give the response to the temporal envelope. Response spectra were analyzed to yield EFR amplitude at the 100 Hz modulation frequency, as well as a differential measure equal to the difference in EFR magnitude (in dB) at the two stimulus modulation depths (Fig. 2). The EFR difference measure is closely related to that of Bharadwaj et al. (2015) - the slope of the function relating EFR amplitude to modulation depth - though slope was defined by a three-point function in the previous study. Unlike the other electrophysiological measures, the EFR difference measure was expected to increase due to synaptopathy, since ears with depleted low-SR fibers should exhibit particularly weak encoding of shallow modulations. In order to compute the difference measure for a given participant, significant 100 Hz EFR peaks were required in response to both modulation depths (defined as > 3 dB SNR, with noise being estimated from the mean amplitude in 10 adjacent frequency bins).

Development of Bharadwaj et al. (2015) - the slope of the function relating EFR amplitude to modulation depth - though slope was defined by a three-point function in the previous study. Unlike the other electrophysiological measures, the EFR difference measure was expected to increase due to synaptopathy, since ears with depleted low-SR fibers should exhibit particularly weak encoding of shallow modulations. In order to compute the difference measure for a given participant, significant 100 Hz EFR peaks were required in response to both modulation depths (defined as > 3 dB SNR, with noise being estimated from the mean amplitude in 10 adjacent frequency bins).

2.5. Statistical analysis

Statistical analysis was performed using R (R Core Team, 2015). All significance tests were conducted two-tailed. Data were checked for normality and homogeneity of variance prior to testing, and non-parametric tests applied where necessary. No data points were missing for any variable, therefore analyses were based on a total sample size N = 40, divided evenly between tinnitus and control groups. For supplemental sex-separated analyses, the four subgroups (tinnitus male, tinnitus female, control male, and control female) were each sized n = 10.

3. Results

3.1. Noise exposure history

Participants with TNA reported greater lifetime exposure than controls to sound levels over 80 dBA, Wilcoxon-Mann-Whitney U = 283, p = 0.02. However, as can be seen from Fig. 3, the spread of exposure values was greater for the TNA group, with some tinnitus participants presenting exposure scores in the same range as those of controls.

3.2. Auditory brainstem response

All participants produced unambiguous ABRs bilaterally, with waves I and V clearly evident at appropriate latencies. (Automatically interpreted waveforms are presented in Supplementary Material. Grand average waveforms are displayed in Fig. 4A.) Resulting amplitude and latency data are given in Table 4 (Supplementary Material).

As can be seen from Fig. 4B, the amplitude of ABR wave I was not significantly reduced in participants with tinnitus relative to controls, t(37.0) = –0.11, p = 0.91, Student’s t-test. Note that had a one-tailed test been applied to these data, the result would have remained non-significant, p = 0.46. Measurement variability was low (coefficient of variation 0.26 in controls, 0.30 in tinnitus), giving statistical power of 90% (α = 0.05, one-tailed) to detect the 26% reduction in wave I amplitude for tinnitus versus controls reported by Schaette and McAlpine (2011) for a 100 dB peSPL click.

In an attempt to manage non-synaptopathic sources of variability in ABR amplitude, we computed the ratio of wave I to wave V amplitude, thought to provide a measure of central gain in the auditory brainstem (Schaette and McAlpine, 2011). This self-normalized difference measure did not differ significantly between groups, Wilcoxon-Mann-Whitney U = 192, p = 0.84. Nor did the amplitude of wave V, t(34.7) = 0.60, p = 0.55, Student’s t-test. Supplemental sex-separated analyses revealed no significant effects of tinnitus on wave I amplitude (female p = 0.56, male p = 0.54, Student’s t-tests) nor on wave I/V amplitude ratio (female p = 0.52, unequal variance t-test; male p = 0.44, Wilcoxon-Mann-Whitney test).

3.3. Envelope following response

EFRs to stimuli of both modulation depths exceeded the noise floor for all participants, allowing analysis of both EFR amplitude....
Fig. 4. ABRs in response to 102 dB peSPL clicks for tinnitus and control groups. A: Grand average waveforms. Shaded areas correspond to the standard error of the mean. B: Wave I and wave V amplitudes, presented as mean ± standard error of the mean.

Fig. 5. EFR measures for tinnitus and control groups, presented as group mean ± standard error of the mean. A: EFRs to transposed tones with a shallow (–6 dB) and full (0 dB) modulation depth. The tinnitus-related reduction in response amplitude is non-significant. The lines connecting the responses illustrate the “EFR slope” measure devised by Bharadwaj et al. (2015), though defined by a two-point function. B: The difference in EFR amplitude (in dB) at the two modulation depths. The hypothesized enhancement in the tinnitus group is not evident.

3.4. Correlations between noise exposure and electrophysiological measures

Pearson’s product–moment correlation coefficients were computed to test the linear relations between log-transformed units of lifetime noise exposure and the various measures of neural function (Fig. 6). No association was evident between noise exposure and the amplitude of ABR wave I, $r = 0.15$, $p = 0.36$, nor between noise exposure and the ratio of wave I to wave V amplitude, $r = 0.15$, $p = 0.35$. Nor did noise exposure relate to EFR amplitude at a shallow modulation depth, $r = 0.01$, $p = 0.94$, or to the EFR difference measure, $r = –0.16$, $p = 0.31$. Note that in the latter case, it is predicted that the measure should increase with increasing noise exposure.

4. Discussion

4.1. A role for noise exposure in tinnitus with a normal audiogram

Reported lifetime noise exposure of tinnitus subjects exceeded that of controls, despite close matching on the basis of sex, age, and audiometric thresholds. To the authors’ knowledge, these data represent the first published evidence implicating noise exposure in tinnitus without threshold elevation. Previous research has associated excessive noise exposure and tinnitus in normally hearing young people (Davis et al., 1998; Meyer-Bisch, 1996) but not through comparison with audiometrically matched controls. Hence noise exposure in previous reports may have been related to tinnitus through sub-clinical threshold changes.

In contrast, our tinnitus group exhibited no significant reduction in hearing sensitivity at any of 10 measurement frequencies between 0.25 and 14 kHz. Though we cannot rule out the existence of narrow audiometric “notches” in our tinnitus subjects, undetected by standard audiometry (Zhao et al., 2014), these findings nonetheless cast new light on the hazards of noise to the auditory system. It seems that excessive noise exposure can induce changes in auditory function that spare the audiogram, even at high frequencies, and yet may lead to disturbing perceptual consequences.

4.2. No ABR evidence for tinnitus-related or noise-induced synaptopathy

The nature of these noise-induced changes is very much less clear, since our measures revealed no evidence for cochlear synaptopathy in TNA. In particular, the expected reduction of ABR wave I amplitude was not observed. This finding stands in contrast with those of Schaette and McAlpine (2011), whose TNA subjects exhibited reduced wave I amplitudes relative to matched controls: reductions of 25% and 26% at 90 and 100 dB peSPL, respectively. Fig. 7 compares Schaette and McAlpine’s 100 dB data with the data obtained in the present study.

Type II error is unlikely to account for these divergent findings, since post-hoc power analysis for the present study indicates 90% power to detect a 26% reduction in wave I amplitude (see Section 3.2). This is despite inclusion of participants of both sexes, which might reasonably be expected to increase ABR amplitude variability. The present study’s wave I amplitude data are less variable than those of Schaette and McAlpine, perhaps due to the use of research-grade recording equipment. Therefore, other possible explanations for our null result must be considered.

It is plausible that differences in participant age between the two studies are responsible, an explanation which would have important implications for our understanding of both cochlear synaptopathy and tinnitus heterogeneity. Participants in the present study were considerably younger (mean tinnitus age 25.7 years, control 25.5 years) than those of Schaette and McAlpine (mean tinnitus age 36.3 years, control 33.2 years). It may be that cochlear synaptopathy is a significant etiology of TNA in older humans, but not among the very young, in whom other etiologies dominate.

It is therefore notable that evidence of human cochlear synaptopathy in relation to noise exposure is considerably less
concrete than the evidence in relation to aging. Age-related loss of spiral ganglion cells was observed by Makary et al. (2011) in a large study of human temporal bones without significant hair cell loss. Parallel findings in mice (Sergeyenko et al., 2013) and preliminary synaptic counts in humans (Viana et al., 2015) strongly suggest that this decline is the delayed sequel to age-related cochlear synaptopathy progressing throughout the lifespan. In contrast, research relating human AN function to noise exposure has relied on electrophysiological measures, with mixed results. The results of the present study show no relation of lifetime noise exposure to ABR wave I amplitude, nor to ABR wave I/V amplitude ratio. Previously, Stamper and Johnson (2015a) reported a negative relation between noise exposure (estimated over the previous 12 months) and ABR wave I amplitude, but results were confounded by sex. Subsequent sex-separated analysis revealed that the correlation was present only in females in response to a 120 dB peSPL stimulus (Stamper and Johnson, 2015b). Using electrocochleography in college students, Liberman et al. (2016) found no significant association between reported noise exposure and the amplitude of the compound action potential (equivalent to ABR wave I), although a noise-related enhancement of the summating potential was observed. In a large study of 126 normally hearing young listeners, Prendergast et al. (2016) demonstrated no relation between lifetime noise exposure and wave I amplitude or EFR synchronization strength.

One explanation for this pattern of results is that audiometrically normal humans do not exhibit substantial synaptopathy solely as a result of noise exposure. Other possible explanations exist, such as insensitivity of electrophysiological measures (discussed later in Section 4.2) and diverse genetic susceptibility to synaptopathy in humans, who might have “tough” and “tender” ears (Henderson et al., 1993). However, it remains plausible that synaptopathy arises in humans due primarily to aging, or to an interaction between aging and noise exposure (as demonstrated in mice by Fernandez et al., 2015). This manifestation would represent a divergence from mouse models, but increasing evidence suggests that such inter-species differences are to be expected. Noise-induced synaptopathy in guinea pigs requires higher sound levels than in mice and long-term degeneration of spiral ganglion cells is less pronounced (Lin et al., 2011). In stark contrast with mouse data, guinea pig synapses damaged by noise appear largely repairable (Liu et al., 2012; Shi et al., 2013), leading to only transient changes in the distribution of spontaneous rates among AN fibers (Song et al., 2016). Early indications from a macaque model suggest that primates may exhibit even greater resistance to noise-induced synaptopathy (Burton et al., 2016).

Alternatively, it is conceivable that synaptopathy exists in audiometrically normal young humans, but is limited to extremely basal cochlear regions. This possibility is suggested by differences in ABR stimulus bandwidth between the present study and that of Schaette and McAlpine (2011). In order to limit the unwanted influence of very high frequency audiometric loss, we selected stimuli with a 10 dB bandwidth extending from 1.2 to 4.7 kHz. By comparison, our measurements indicate that the 10 dB bandwidth of Schaette and McAlpine’s 100 dB clicks extends to 7.1 kHz (recorded in a Bruel and Kjaer 4153 artificial ear coupled to TDH-49 headphones). The high presentation level of our stimuli ought to elicit the “half-octave basalward shift” in the travelling wave, leading to strong excitation of characteristic frequencies up to approximately

![Fig. 6. Relations between lifetime noise exposure and electrophysiological measures of cochlear synaptopathy, including both raw amplitude measures and self-normalized difference measures. Shaded areas represent 95% confidence limits of linear regression lines for all subjects. Marginal density plots represent tinnitus and control group distributions. No significant correlation is evident between noise exposure and any electrophysiological measure. A: ABR wave I amplitude. B: ABR wave I/V amplitude ratio. C: EFR amplitude at a shallow (–6 dB) modulation depth. D: Difference in EFR amplitude (in dB) at two stimulus modulation depths. Note that D was hypothesized to exhibit a positive relation, whereas negative relations were expected in A to C.](image-url)
7 kHz. With the addition of upward spread of excitation, the stimulated region should encompass the 3–6 kHz characteristic frequency region where early noise damage is usually manifest (Coles et al., 2000). Nevertheless, it remains possible that synaptopathy existed in our tinnitus cohort, but was restricted to even higher frequencies. Participants generally reported tinnitus with a high frequency percept and tinnitus pitch was not measured.

A crucial and related issue is that of high frequency audiometric loss and its influence on ABR wave I. It is possible that the ABR findings of Schaette and McAlpine (2011) and Gu et al. (2012) reflect basal loss of sensitivity in tinnitus participants, rather than an audiometrically “hidden” hearing loss. Failure to replicate these findings might indicate robustness of our methods against the unwanted influence of audiometric loss, given the audiometric and stimulus differences between the present study and the previous reports. Wave I of the ABR is dominated by contributions from high frequency portions of the cochlear partition, where reduced dispersion enhances the synchrony of neuronal firing (Don and Eggermont, 1978). At high stimulus levels, upward spread of excitation involves increasingly basal generators (Eggermont and Don, 1980). Hence the unambiguous interpretation of wave I amplitude may require careful control of audiometric thresholds at frequencies well beyond the bandwidth of the ABR stimuli. The present study used not only a narrower stimulus bandwidth than the previous studies, but closer audiometric matching (group means differed by < 1 dB at 10 and 14 kHz). Schaette and McAlpine’s groups differed in audiometric sensitivity at 12 kHz, where mean threshold for the tinnitus group was 3.5 dB higher than for controls. Missing data (from five tinnitus subjects and three control subjects) prevented comparison at higher frequencies. Similarly, Gu et al. (2012) reported a significant reduction in wave I amplitude only for their 120 dB peSPL stimulus, for which missing ABR data led to systematic differences between groups in high frequency hearing sensitivity (tinnitus group had ~ 10 dB higher thresholds at 14 kHz). The band-limited ABR stimuli used in these studies fall within the low-frequency tails of high-frequency AN fiber tuning curves, and hence the response of these fibers should be relatively unaffected by outer hair cell dysfunction at least (Liberman and Dodds, 1984). However, it remains possible that tinnitus-related ABR differences in previous reports were at least partially driven by basal loss of sensitivity.

Finally, it is worth considering that absence of ABR evidence for tinnitus-related synaptopathy might reflect insensitivity of the ABR rather than absence of synaptopathy. In addition to the variability of ABR amplitude, which has many sources and might obscure neuropathic effects, the findings of Bourien et al. (2014) cast doubt on the fundamental contribution of low-SR fibers to ABR wave I (see Section 1). Ongoing attempts to develop more sensitive electrophysiological measures of cochlear neuropathy are clearly warranted.

4.3. No EFR evidence for tinnitus-related or noise-induced synaptopathy

Several alternatives to the ABR have been proposed as viable measures of synaptopathy in humans, including the amplitude ratio of the compound action potential to the summing potential (Liberman et al., 2016) and round window neural noise (Batrel et al., 2016). Among them, the EFR has shown promise in both animals and humans and has the advantage of being recordable non-invasively, without the use of ear canal or transtympanic electrodes. However, the relation of the EFR to AN function is difficult to interpret, since contributions from different auditory centers are not separated in time as they are for the ABR, and the resulting response is dependent on neural function central to the AN. Additionally, and in common with the ABR, EFR amplitude reflects many non-synaptopathic sources of variability. Hence researchers have sought innovative EFR measures with enhanced sensitivity to synaptopathy. The difference measure devised by Bharadwaj et al. (2015) – the slope of the function relating EFR amplitude to stimulus modulation depth - was intended as a sensitive, self-normalized measure of low-SR fiber loss. EFR slope was shown to correlate with behavioral measures of temporal coding and auditory selective attention, with individual differences tentatively attributed to synaptopathy (Bharadwaj et al., 2015).

The present study utilized an EFR difference measure very closely related to that of Bharadwaj and colleagues: the difference in EFR amplitude (in dB) at two stimulus modulation depths. Many stimulus characteristics were also shared with the previous study: level, duration, carrier frequency, modulation frequency, and off-frequency masking characteristics. Yet this measure was not associated with tinnitus status, nor with lifetime noise exposure. These results might be taken to indicate lack of noise-induced or tinnitus-related cochlear synaptopathy in our cohort. However, it is also possible that this pathology is not, after all, a major source of individual differences in EFR slope. The hypothesized sensitivity of the measure to synaptopathy relies upon several assumptions, including preferential damage to low-SR fibers in humans and saturation of high-SR units by stimuli with shallow modulations. There is some evidence, for example, that the high-SR fiber dynamic range for modulated stimuli considerably exceeds that for steady-state stimuli (Smith and Brachman, 1980). Interpretation of the present results would be aided by validation of the EFR slope measure in an animal model of synaptopathy.

Methodological differences between the present study and that of Bharadwaj et al. (2015) are also to be considered, though they appear unlikely to compromise sensitivity. The earlier study computed slopes using a minimum modulation depth of ~8 dB, employing multichannel recording and principal component analysis to enhance response SNR. The present study used a single channel and selected a ~6 dB minimum modulation depth to ensure that all responses exceeded the noise floor. However, Bharadwaj and colleagues reported that temporal perceptual performance correlated not only with EFR slope but also with raw EFR amplitude for a ~4 dB depth, implying that extremely shallow modulations were not an essential stimulus feature.

In addition to the EFR difference measure, the present study also analyzed straightforward EFR amplitude. EFR amplitude was not associated with lifetime noise exposure and did not differ significantly between tinnitus and control groups. Data from a mouse model indicate that EFR amplitude can be a robust measure of

![Fig. 7. ABR data from the present study, elicited using 102 dB peSPL clicks, presented alongside those of Schaette and McAlpine (2011), elicited using 100 dB peSPL clicks. Points and error bars represent the mean ± standard error of the mean. A: The raw amplitude of ABR wave I. B: The ratio of wave I amplitude to wave V amplitude.](image-url)
cochlear synaptopathy, but suggest that some features of our stimuli (and those of Bharadwaj et al., 2015) were suboptimal (Shaheen et al., 2015). The researchers used fully modulated EFR stimuli, optimized to enhance the contribution of the AN, and found that synaptopathy led to greater changes in EFR amplitude than in EFR phase locking value or ABR amplitude. Optimum sensitivity was achieved with high modulation frequencies (~1 kHz), which limited the influence of more central nuclei. In contrast, the present study used a much lower modulation frequency and likely elicited the responses of higher centers, where the effects of deafferentation might be mitigated by enhanced central gain (Brotherton et al., 2015; Chambers et al., 2016). Hence the present EFR amplitude data must be interpreted with caution. The observed trend for lower amplitudes in TNA was not significant, but it is possible that stimuli with higher modulation rates might have been more effective in revealing AN temporal coding deficits. Future investigation of cochlear synaptopathy in humans might be well served by optimized EFR measures paralleling those applied successfully in rodent models.

4.4. Conclusions

The ABR and EFR results of the present study provide no evidence for cochlear synaptopathy in young humans with tinnitus and normal audiometric thresholds. Nor do these electrophysiological measures relate to lifetime noise exposure, providing no evidence for noise-induced synaptopathy in this cohort. It is important to emphasize, however, that our results do not imply that synaptopathy is not prevalent in humans. It is possible, for example, that synaptopathy would have been measurable in an older population, through assessment of characteristic frequencies above 7 kHz, or through use of a more sensitive measure.

Tinnitus participants are, as a group, more noise exposed than controls, though also more heterogeneous in this regard. Uncertainty about mechanisms notwithstanding, the findings relating noise exposure and TNA have important implications. Even in tinnitus sufferers whose audiometric thresholds are indistinguishable from those of controls, symptoms may arise from subclinical damage due to excessive noise exposure.

Acknowledgments

The authors are grateful to two anonymous reviewers for constructive comments on an earlier version of the manuscript. The authors are also grateful to Dr Hari Bharadwaj for providing EFR recording software, and to Keith Wilbraham, Dr Michael Stone, and Dr Richard Baker for essential technical advice. The research was supported by an Action on Hearing Loss studentship, funded by the Marston Family Foundation, and by the Medical Research Council UK (MR/L003589/1).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.heares.2016.12.002.

References


Schaeffer, R., 2014. Tinnitus in men, mice (as well as other rodents), and machines. Hear. Res. 311, 63–71.


3.3 Tinnitus with a normal audiogram: Role of high-frequency sensitivity and reanalysis of brainstem-response measures to avoid audiometric over-matching

Published in Hearing Research, December 2017
Letter to the Editor

Tinnitus with a normal audiogram: Role of high-frequency sensitivity and reanalysis of brainstem-response measures to avoid audiometric over-matching

In Guest et al. (2017), we tested for associations between tinnitus and electrophysiological measures of cochlear synaptopathy in young humans with normal hearing sensitivity. Tinnitus and control groups were matched closely for age, sex, and audiometric thresholds up to 14 kHz. The groups did not differ significantly in auditory-brainstem-response (ABR) or envelope-following-response (EFR) measures of synaptopathy.

The matching of audiograms at extended high frequencies (EHFs) was intended to prevent confounding effects of EHF audiometric loss on brainstem-response measures. Such effects are, in our view, a potential pitfall in synaptopathy research, which tends to employ high stimulus levels that likely elicit contributions from the extreme cochlear base (for example, 120 dB pSPL in Gu et al., 2012; 130 dB pSPL in Liberman et al., 2016). Derived-band responses in humans indicate that ABR wave I is dominated by high-frequency generators, including those above 8 kHz (Don and Eggermont, 1978; Hardy et al., 2017), and increasingly so at high stimulus levels (Eggermont and Don, 1980). Hardy et al. (2017; personal communication, 10/02/17) recently demonstrated that both wave I amplitude and the ratio of wave I amplitude to wave V amplitude are reduced when noise high-pass filtered at 8 kHz is added to remove contributions from EHF regions. Their findings raise questions about apparent evidence for cochlear synaptopathy in humans, since such evidence has often been accompanied by EHF audiometric deficits (Gu et al., 2012; Liberman et al., 2016; Schaeffer and McAlpine, 2011), or even deficits at standard audiometric frequencies (Bramhall et al., 2017).

However, it has come to our attention that control of auditory-metric factors in our tinnitus study might have come at a cost. Hickox et al. (2017) note that many animal models of synaptopathy additionally produce some degree of basal hair-cell loss. Liberman et al. (2016) posit that “high-frequency threshold elevation will be correlated with mid-frequency cochlear synaptopathy”. If this expectation is justified, then over-matching of audiometric thresholds in our study might have risked obscuring genuine differences in auditory nerve function between groups. Future research might usefully address this issue by allowing variation in EHF audiometric thresholds and preventing their direct influence on proxy measures of synaptopathy through the application of high-pass masking.

Though we did not adopt this approach in our study, we reasoned that reanalysis without EHF matching might shed new light on our findings. Our decision to match thresholds up to 14 kHz may have been overzealous, since our stimuli possessed a narrower bandwidth than those of some previous studies (Gu et al., 2012; Schaeffer and McAlpine, 2011) and a far lower level than one study (Gu et al., 2012). The combination of restricted bandwidth, moderate stimulus level, and audiometric matching (to within 1 dB at 14 kHz) may have represented an excessively cautious approach.

Therefore, we repeated our original ABR and EFR analyses with groups matched solely for age and sex. Two participants were added to the tinnitus group (both female, with prolonged spontaneous tinnitus of >15 years duration) and the resulting 22 participants were matched with 22 controls drawn from a reservoir of 41 potential matches. This reservoir was composed of our original control group plus controls from a later study investigating listening difficulties and synaptopathy, whose measures encompassed those employed in the tinnitus study. Selection of controls was conducted via optimal pair matching using the “optmatch” R package (Hansen and Klopfer, 2006). Recruitment of tinnitus and control participants was based on normal pure-tone audiometry between 0.25 and 8 kHz, normal middle ear function, normal otological history, and age (18–40 years), but was otherwise unrestricted. Although we can’t discount possible biases related to participants’ willingness to participate, we consider that these groups are essentially a random sample of normal-hearing people with and without tinnitus in this age range.

The resulting groups are each 55% female and have similar mean ages (tinnitus 26.6 years, control 26.5 years), but differ substantially in EHF sensitivity (Fig. 1). Group comparisons of ABR and EFR measures of synaptopathy reveal no significant associations with tinnitus, just as in the original analyses (Fig. 2). This is true of both raw amplitude measures and self-normalized difference measures: $p > 0.23$ (two-tailed) in all cases, as determined by independent-samples t-tests and mixed two-way ANOVA.

Hence, we find no indication that the null results of our study were a consequence of audiometric over-matching. Our original conclusion stands, namely that we find no evidence for cochlear synaptopathy in tinnitus with a normal audiogram. The results also suggest that our ABRs and EFRs were not substantially affected by EHF audiometric function, presumably due to the combination...
of restricted stimulus bandwidth and relatively low presentation level. However, we caution that this may not be true of other ABR and EFR measures, and that careful control of EHF contributions should be a priority in synaptopathy research. Without such efforts, it will not be possible to establish whether EHF audiometric loss is a marker or a mimic of cochlear synaptopathy.

Acknowledgments

This research was supported by an Action on Hearing Loss studentship, funded by the Marston Family Foundation, and by the Medical Research Council UK (MR/L003589/1).

References


Hardy, A., de Boer, J., Krumholz, K., 2017. Improving auditory brainstem responses for evaluating the neural gain hypothesis. In: Presented at the BSA Basic Auditory Science Meeting, Nottingham, UK.


Hannah Guest*, Kevin J. Munro
Manchester Centre for Audiology and Deafness, University of Manchester, Manchester Academic Health Science Centre, UK
NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK

Christopher J. Plack
Manchester Centre for Audiology and Deafness, University of Manchester, Manchester Academic Health Science Centre, UK
NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK

Department of Psychology, Lancaster University, Lancaster, UK

* Corresponding author. Manchester Centre for Audiology and Deafness, Ellen Wilkinson Building, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.
E-mail address: hannah.guest@manchester.ac.uk (H. Guest).

4 October 2017
Available online 14 October 2017
3.4 Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure

Published in Hearing Research, July 2018
Research Paper

Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure

Hannah Guest a, b, *, Kevin J. Munro a, b, Garareth Prendergast a, b, Rebecca E. Millman a, b, Christopher J. Plack a, b, c

* Manchester Centre for Audiology and Deafness, University of Manchester, Manchester Academic Health Science Centre, UK
b NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK
c Department of Psychology, Lancaster University, UK

ABSTRACT

In rodents, noise exposure can destroy synapses between inner hair cells and auditory nerve fibers (“cochlear synaptopathy”) without causing hair cell loss. Noise-induced cochlear synaptopathy usually leaves cochlear thresholds unaltered, but is associated with long-term reductions in auditory brainstem response (ABR) amplitudes at medium-to-high sound levels. This pathophysiology has been suggested to degrade speech perception in noise (SPiN), perhaps explaining why SPiN ability varies so widely among audiometrically normal humans. The present study is the first to test for evidence of cochlear synaptopathy in humans with significant SPiN impairment. Individuals were recruited on the basis of self-reported SPiN difficulties and normal pure tone audiometric thresholds. Performance on a listening task identified a subset with “verified” SPiN impairment. This group was matched with controls on the basis of age, sex, and audiometric thresholds up to 14 kHz. ABRs and envelope-following responses (EFRs) were recorded at high stimulus levels, yielding both raw amplitude measures and within-subject difference measures. Past exposure to high sound levels was assessed by detailed structured interview. Impaired SPiN was not associated with greater lifetime noise exposure, nor with any electrophysiological measure. It is conceivable that retrospective self-report cannot reliably capture noise exposure, and that ABRs and EFRs offer limited sensitivity to synaptopathy in humans. Nevertheless, the results do not support the notion that noise-induced synaptopathy is a significant etiology of SPiN impairment with normal audiological thresholds. It may be that synaptopathy alone does not have significant perceptual consequences, or is not widespread in humans with normal audiograms.

© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Some individuals exhibit pure tone audiometric thresholds within the clinically normal range, yet report deficits of speech perception in noise (SPiN). This profile describes a small but significant proportion of patients attending audiology services; amongst patients referred for hearing difficulties, subsequent findings of normal hearing thresholds have been reported in 5–8.4% (Saunders, 1989; Stephens et al., 2003). This presentation has been designated variously as “selective dysacusis” (Narula and Mason, 1988), “obscure auditory dysfunction” (Saunders and Haggard, 1989), “King-Kopetzky syndrome” (Hinchcliffe, 1992), “auditory disability with normal hearing” (King and Stephens, 1992), “idiopathic discriminatory dysfunction” (Rappaport et al., 1993), and “auditory processing disorder” (British Society of Audiology APD Special Interest Group, 2011). The present text...
will eschew these labels in favour of a descriptive term, “SPiN impairment with a normal audiogram”.

The relatively high prevalence of this clinical presentation has prompted a significant body of research into the underlying causes. Large-scale studies have revealed a heterogeneous condition, most probably with major contributions from psychological factors, alongside (or in combination with) auditory deficits (Saunders and Haggard, 1992; Zhao and Stephens, 2000). Even in those patients with genuinely impaired SPiN, there are many possible etiologies, including minor pathology of the middle ear or cochlea, impaired central auditory processing, and deficits of attention, memory, and/or language (for a review, see Pienkowski, 2017).

It is possible that new insight into SPiN impairment with a normal audiogram may be offered by the recent emergence of a pathophysiology termed “cochlear synaptopathy”: loss of synapses between inner hair cells and auditory nerve (AN) fibers, which can occur without widespread hair cell loss or permanent threshold elevation. Originally induced in mice by exposure to high-level noise (Kujawa and Liberman, 2009), synaptopathy has since been observed in noise-exposed guinea pigs, rats, and macaques, and in aging mice without purposeful noise exposure (for a summary of histological evidence, see Hickox et al., 2017). The synaptic damage appears to preferentially affect AN fibers with low-to-moderate spontaneous rates (low-SR fibers; Furman et al., 2013), which have high response thresholds (Liberman, 1978). Cochlear thresholds are not permanently altered by the condition, though some loss of sensitivity at the highest frequencies can occur due to accompanying hair cell loss at the extreme cochlear base (Hickox et al., 2017). However, synaptopathy is associated with significant reductions in the amplitude of the auditory brainstem response (ABR) at moderate-to-high sound levels (Kujawa and Liberman, 2009).

It has been suggested that the suprathreshold effects of synaptopathy might also extend to auditory perception (Bharadwaj et al., 2014; Kujawa and Liberman, 2015; Plack et al., 2014). Kujawa and Liberman hypothesized that loss of low-SR fibers might largely explain why audiometrically normal individuals differ so widely in their SPiN abilities. The authors reasoned that, as background noise levels increase, humans must rely increasingly on these fibers, due to their large dynamic ranges and reduced susceptibility to noise masking. Accordingly, Lobarias and colleagues (2017) have reported evidence consistent with perceptual effects of synaptopathy in rats. Noise exposures causing large temporary threshold shifts (TTS) led to post-TTS impairment of signal detection in noise and reduced ABR wave I amplitude. Deficits were limited to specific frequencies and low signal-to-noise ratios (SNRs) and were not well predicted by ABR effects, reducing confidence that the two were directly related. Nevertheless, the results provide the first experimental indication that noise exposure can alter hearing in noise while leaving threshold sensitivity intact.

Research in humans has yielded some evidence consistent with the existence of perceptually consequential synaptopathy. As will be outlined below, a number of studies have associated SPiN with noise exposure, with electrophysiological measures assumed to be sensitive to synaptopathy, or with both factors. However, other studies have revealed no such association. Moreover, some of the reported relations are not clearly reflective of underlying AN deficits and may be consistent with other pathologies.

Considering first the evidence in relation to noise exposure, several studies have reported poorer SPiN performance in occupationally noise-exposed individuals than in controls, though with possible contributions from uncontrolled audiometric hearing loss. Alvord (1983) reported that noise-exposure was associated with poorer discrimination of high-frequency monosyllables, but also with substantially poorer mean pure-tone thresholds (by 9.5 dB at 4 kHz). In the sentence recognition data of Kumar et al. (2012), audiometric thresholds merely fell in the range –10 to 25 dB HL and were neither matched between groups nor reported. In Hope et al. (2013), thresholds at individual frequencies were not reported or analyzed, nor measured beyond 4 kHz, and the apparent association between noise exposure and syllable recognition would not survive correction for multiple comparisons.

More recently, Yeend et al. (2017) investigated the effects of lifetime noise exposure on auditory processing in a large cohort (n = 122) with normal or near-normal audiometric thresholds. The survey of noise exposure incorporated both occupational and leisure noise exposure during each decade of life, with consideration given to duration and level of exposure and to the effects of hearing protection. Participants also completed several measures of temporal and spectral processing and two SPiN tasks. No relation of noise exposure to any perceptual measure was evident.

Perhaps most relevant to the present research is the large-scale clinical study reported by Stephens et al. (2003), examining self-reported noise exposure in patients with King-Kopetzky syndrome (that is, SPiN impairment with a normal audiogram). The study recruited a very large SPiN-impaired cohort (n = 110), though “normal hearing” was defined less strictly than in most synaptopathy research (≤20 dB HL at 0.5–4 kHz and ≤30 dB HL at 0.25–8 kHz). Controls (n = 70) met the same audiometric criteria and had similar age and sex distributions. Participants completed an etiological-factors questionnaire with a principal focus on noise exposure history. SPiN impairment was not associated with noise exposure.

Other researchers have sought to relate SPiN primarily to electrophysiological measures of synaptopathy. Bharadwaj et al. (2015) demonstrated correlations between the subcortical envelope-following response (EFR) and behavioral measures of temporal coding, including a spatial digit-discrimination task reliant on temporal cues. Bharadwaj and colleagues recorded EFRs to various modulation depths, allowing computation of a difference measure designed to emphasize the contributions of low-SR fibers. The resulting correlations suggest that perceptual abilities are partially determined by individual differences in temporal coding fidelity early in the neural pathway. Cochlear synaptopathy was suggested as a possible mechanism underlying this variability, an interpretation bolstered by marginal associations with a rudimentary measure of noise exposure.

Bramhall et al. (2015) analyzed relations between ABR wave I amplitude and sentence perception in noise in a large cohort of listeners with a broad array of audiometric profiles. A substantial subset exhibited normal or near-normal hearing sensitivity. ABR amplitude was correlated with SPiN, but the correlation was driven by audiometric differences; linear mixed-effects modelling revealed no main effect of ABR amplitude on performance, either in the full group or in the subset with acute hearing sensitivity.

Finally, several recent studies have combined measures of noise exposure, SPiN, and brainstem-response amplitudes with the explicit aim of investigating noise-induced synaptopathy. The first, conducted by Liberman et al. (2016), divided 34 students into high- and low-risk groups based on a short questionnaire assessing noise exposure habits. The high-risk group exhibited poorer word recognition in noise, along with elevated values of an electrocochleographic measure: the ratio of summing potential amplitude to action potential amplitude (SP/AP ratio). Results were interpreted as evidence of noise-induced synaptopathy with effects on SPiN. However, the high-risk group exhibited a substantial deficit in extended-high-frequency (EHF) audiometric sensitivity relative to the low-risk group (~20 dB at 16 kHz). Basal dysfunction may have influenced the electrocochleographic results, since stimuli were presented at an extremely high level, 130 dB peSPL.
Consistent with this interpretation, the resulting enhancement of SP/AP ratio in the high-risk group was driven largely by higher SP (a primarily pre-neural potential), with no significant reduction evident in AP (reflective of AN activity). Speech stimuli were delivered at 35 dB HL, a sound level insufficient to emphasize the contributions of high-threshold fibers and perhaps more sensitive to other pathologies.

Prendergast et al. (2017b) used a detailed structured interview to quantify lifetime noise exposure in 141 audiometrically normal young listeners. Participants completed SPiN tasks which varied in sound level and reliance on spatial cues, allowing computation of within-subject difference measures designed to enhance sensitivity to synaptopathy (Plack et al., 2016). Additional psychoacoustic tasks included frequency and intensity difference limens, inter-aural phase difference discrimination, and amplitude modulation detection. After correction for multiple comparisons, noise exposure exhibited no significant relation with any behavioral measure. ABR and EFR measures in a near-identical cohort were previously reported (Prendergast et al., 2017a) and were not associated with noise exposure.

Grose et al. (2017) administered a similarly extensive test battery in two groups of audiometrically normal young people, differing greatly in their exposure to loud music events. High-noise participants (N = 31) had attended a median of 90 such events in the preceding two years, while low-noise participants (N = 30) had attended four. The high-noise group demonstrated a reduction in ABR wave I amplitude, though this would not survive correction for multiple comparisons and was accompanied by an EFR audiometric deficit (~10 dB at 16 kHz), whose effects on the ABR are unknown. Noise exposure was not significantly associated with wave I amplitude, ABR amplitude, ABR slope, or with performance on any listening task, including sentence recognition in noise. The authors concluded that, even if noise-induced synaptopathy is manifest in humans, its perceptual consequences may be so insignificant as to elude detection.

Grinn et al. (2017) investigated effects of recreational noise exposure both retrospectively and prospectively, assessing auditory function before and after a loud music event and also obtaining self-report of noise exposure over the past 12 months. AP amplitude, SP/AP ratio and SPiN were not associated with previous-12-months’ noise exposure, nor reduced following a single exposure. However, it is not clear that a single exposure would be expected to cause measurable synaptopathy, given that participants had experienced many such exposures. Additionally, statistical power in the retrospective analysis was limited by the small sample (n = 32).

Fulbright et al. (2017) also recorded previous-12-months’ noise exposure, this time from 60 young, normally hearing participants. Participants also underwent tests of word recognition (in broadband noise and in multitalker babble) and ABRs at 70, 80, 90, and 99 dB nHL. ABR wave I amplitude was not significantly related to noise exposure, nor to perceptual performance.

Taken together, evidence for noise-induced synaptopathy as a determinant of speech perception appears tenuous. One possible explanation is that researchers have not purposely recruited individuals with significant deficits of speech perception, leading to cohorts with relatively homogeneous perceptual performance. Investigation of synaptopathy in individuals with SPiN impairment therefore represents an important gap in the literature. Careful control of audiometric thresholds should also be a priority, since audiometric influences on both electrophysiological and perceptual measures are possible. Interpretation of much existing synaptopathy research is complicated by this potential confound (Guest et al., 2017b).

The present study aimed to test for associations between SPiN impairment with a normal audiogram and (a) ABR measures of cochlear synaptopathy, (b) EFR measures of synaptopathy, and (c) lifetime noise exposure. We reasoned that such associations would together constitute plausible non-invasive evidence for noise-induced cochlear synaptopathy, if audiometric, sex, and age differences between groups were minimized. To enhance the likelihood of observing such evidence, the research questions were addressed primarily in a cohort with “verified SPiN impairment”: that is, presenting with both self-reported and laboratory-measured SPiN deficits.

2. Material and methods

2.1. Participants

Control participants were recruited from the University of Manchester staff and student population (via poster and on-line advertising) and from the general population of Greater Manchester (via on-line advertising). Participants with SPiN impairment were recruited from local audiology services and from the sources above. All were aged 18–40 and were fluent English speakers, either monolingual or early bilingual (acquired both languages by age 12 years). All exhibited normal otoscopic findings, normal pure-tone audiometric thresholds (<20 dB HL at 0.25–8 kHz), and reported no history of middle-ear surgery, neurological disorder, head trauma, or ototoxic exposure. For all but two participants, tympanometric results were within clinically normal limits (compliance 0.3–1.6 cm³, pressure −50 to +50 daPa). The exceptions were one control participant (2.4 cm³ compliance unilaterally) and one participant with SPiN impairment (0.2 cm³ compliance bilaterally). In both cases, bone conduction audiometry revealed no significant air-bone gaps (<5 dB at all but two test frequencies, and <10 dB at all test frequencies) and acoustic reflex testing at 1 and 2 kHz yielded thresholds <95 dB HL bilaterally.

Potential recruits to the SPiN-impairment group (n = 47) were recruited based on self-report of significant difficulties understanding speech in complex auditory environments (more than their peers) and subsequently provided a brief history of the nature and time course of their hearing deficits (summarized in supplementary material, Table SM1). Fifteen were excluded at the screening stage on the basis of audiological history, middle ear function, and/or pure-tone audiometry. The remaining 32 comprised the reported-SPiN-impairment group. Of these, 16 progressed to a verified-SPiN-impairment group, based on a laboratory SPiN measure (see Section 2.2.2). Eleven participants with reported SPiN impairment and six participants with verified SPiN impairment also reported tinnitus. Potential control participants (n = 38) reported no self-perceived auditory deficits (significant listening difficulties or tinnitus). Controls drawn from this initial group were matched with SPiN-impaired participants on the basis of age, sex, and audiometric thresholds (Section 2.6 provides information on matching).

In the study’s main analysis (see Table 1), participants with verified SPiN impairment were compared with controls matched for audiometric thresholds up to 14 kHz. The decision to focus on participants with verified SPiN impairment was motivated by evidence that some individuals with reported SPiN impairment underestimate their hearing ability (Saunders and Haggard, 1992). The decision to match audiograms to 14 kHz was motivated by concerns over a possible confound, since loss of basal sensitivity might be associated with poorer perceptual performance (Yeend et al., 2017) and affect electrophysiological responses (Don and Eggermont, 1978; Harby et al., 2017). Section 2.6 describes two supplementary analyses, which address parallel research questions using (a) the cohort with “reported SPiN impairment” (n = 32), and (b) non-audiogram-matched controls.
2.2. Perceptual measures

2.2.1. Audiometry

Methods were as reported in Guest et al. (2017a). Pure-tone air-conduction thresholds at 0.25—8 kHz were obtained in accordance with British Society of Audiology (2011) recommended procedures. EHF thresholds at 10 and 14 kHz were obtained using 1/3-octave noise bands, in order to limit the influence of ear canal resonances and threshold microstructure (periodic fluctuations in threshold with small changes in signal frequency). At both standard and extended high frequencies, thresholds were obtained for each ear separately, then averaged between ears.

2.2.2. Speech perception in noise: the coordinate response measure (CRM)

We aimed to design a SPiN measure that (a) possessed key attributes of the challenging listening situations reported by individuals with impaired SPiN and normal audiograms, and (b) emphasized the auditory structures and processes thought to be impaired by cochlear synaptopathy. In pursuit of the first aim, the measure incorporated meaningful speech stimuli (as opposed to nonsense syllables), high overall sound levels, competing talkers, and spatial cues. The latter three attributes were also expected to enhance sensitivity to synaptopathy, since loss of low-SR fibers should degrade the subtle temporal and level cues required to encode spatial information, especially at high sound levels. To enhance the specificity of the measure to auditory deficits, we selected a closed-set task incorporating simple vocabulary, in common with Bharadwaj et al. (2015). This was intended to reduce the influence of linguistic factors, rendering the measure appropriate for use in multilingual populations and relatively insensitive to SPiN deficits arising from language disorders.

Speech stimuli and speech maskers were CRM phrases, of the form "Ready {call-sign}, go to {color} {number} now". During practice, these comprised nonsense syllables, and were later expanded into real speech. Each trial included three CRM phrases, of the form "Ready {call-sign}, go to {color} {number} now", spoken by native British-English talkers (Kitterick et al., 2010). Each trial consisted of two CRM phrases: the first, which alternates between numerals (1–4) and letters (A–D), is thought to assess high-level cognitive skills such as mental flexibility, though correspondence of performance to any discrete cognitive domain is uncertain (Crowe, 1998). Prior to testing, participants completed short practice versions of each part.

2.3. Educational level and cognitive ability

Since cognitive factors may contribute to SPiN deficits (Pienkowski, 2017), brief assessments of educational attainment and cognitive function were conducted. Participants reported the highest educational level at which they had studied and whether or not they had completed the course of study in question. Based on this report, they were assigned to one of the following ordinal categories: doctoral graduate, doctoral student, master's graduate, master's student, bachelor's graduate, bachelor's student, or no higher education. Participants also completed both parts of the neuropsychological Trail Making Test, using pen and paper and following the protocol of Bowie and Harvey (2006). Participants drew lines to connect pseudo-randomly distributed numerals and letters in a specified order, proceeding as rapidly and accurately as possible. The first part, in which numerals are connected in ascending order, is thought to assess psycho-motor speed and visual search skills. The second, which alternates between numerals and letters (1-A-2-B-3-C, etc.), is thought to additionally assess higher level cognitive skills such as mental flexibility, though correspondence of performance to any discrete cognitive domain is uncertain (Crowe, 1998). Prior to testing, participants completed short practice versions of each part.

2.4. Lifetime noise exposure: the noise exposure structured interview (NESI)

Methods were as reported in Guest et al. (2017a). In summary, the NESI directs respondents to (i) identify occupational and/or recreational noisy activities (>80 dBA) in which they have engaged; (ii) for each activity, identify life periods in which exposure habits have been approximately stable; (iii) estimate exposure duration for each period, based on frequency of occurrence and duration of a typical exposure; (iv) estimate exposure level, based on vocal effort required to hold a conversation or, for personal listening devices, typical volume control setting; (v) report usage and type of hearing protective equipment. The resulting data from all activities and life periods are combined to yield units of lifetime noise exposure, a measure linearly related to the total energy of exposure above 80 dBA. Further details are provided in the supplementary material (Table SM2 lists the conversion values used in estimating sound level; Table SM3 provides the NESI calculation for a single participant).
2.5. Electrophysiological measures

Methods were largely as reported in Guest et al. (2017a) and are stated in full on page 6 of the supplementary material, with key elements summarized below.

2.5.1. Auditory brainstem response

Stimuli were filtered clicks designed to focus excitation on the characteristic frequencies typically affected by early noise-induced cochlear damage. The stimuli had a 10 dB bandwidth extending from 1.2 to 4.7 kHz (as recorded in a Gras IEC60711 occluded-ear simulator) and were delivered at 102 dB peSPL, sufficient to elicit the half-octave basilar shift in the travelling wave (McFadden, 1986) and provide strong excitation of characteristic frequencies between approximately 2 and 7 kHz. Each ear received 7040 stimuli at a rate of 7.05/second. Recording montage was Cz to ipsilaterial mastoid and responses were band-pass filtered between 50 and 1500 Hz. Waves I and V of the averaged waveform were identified by a peak-picking algorithm (wave I falling at 1.55–2.05 ms after stimulus peak, wave V at 5.1–6.6 ms). Post-hoc subjective review verified that the algorithm had appropriately interpreted all waveforms (presented in full on pages 7 and 8 of the supplementary material). For all participants but one, the amplitudes of wave I (peak-trough) and V (peak-baseline) were obtained for both ears, then averaged between ears. For one participant (a member of the reported-SPiN-impairment group but not the verified-SPiN-impairment group), only the left ABR was analyzed, due to a technical fault during recording.

2.5.2. Envelope-following response

Stimuli were transposed tones (Bernstein and Trahiotis, 2002) with the same carrier frequency, modulation frequency, off-frequency masking characteristics, presentation level, stimulus duration, and ramp duration as used by Bharadwaj et al. (2015). Inter-stimulus interval was 400 ms and the recording channel was Cz to C7. The tones were of two modulation depths: 0 dB (full modulation) and −6 dB (shallow modulation). This approach allowed computation of an EFR difference measure: the difference in response amplitude (in dB) at the two stimulation modulation depths. This measure is closely related to the “EFR slope” metric of Bharadwaj and colleagues, though based on a two-point function, and reflects the assumption that synaptopathy preferentially affects high-threshold AN fibers and should therefore preferentially degrade the encoding of stimuli with shallow modulations. A schematic illustration of the difference measure is provided in Fig. 1. Since it is possible that responses to both modulation depths might be impaired by synaptopathy, raw response amplitude was also analyzed.

2.6. Analysis

The main analysis compared participants with verified SPIN impairment (n = 16) with controls (n = 16) matched on the basis of age, sex, and audiometric thresholds up to 14 kHz. Controls (n = 4) with poor SPIN performance (CRM thresholds >90th percentile) were excluded from the reservoir of potential matches. Matching aimed to minimize the difference in mean 14 kHz thresholds between the groups while allowing mean age to differ by no more than 1 year. Characteristics of the resulting groups are reported in Table 1. Each research question was addressed in R (R Core Team, 2015) by way of independent-samples Student’s t-test, unequal variance t-test, or Wilcoxon-Mann-Whitney test, as appropriate. All significance tests were two-tailed. The exception was the EFR analysis, which employed a mixed two-way ANOVA with group as the between-subjects variable and stimulus modulation depth as the within-subject variable.

Two supplementary analyses were performed. The first compared participants with reported SPIN impairment (n = 32) with age-, sex-, and audiogram-matched controls (n = 32). This approach allowed our research questions to be addressed in a SPIN-impaired sample defined by self-report, which is arguably more relevant to clinical presentations of SPIN impairment than a sample defined by lab-measured performance. The second was a comparison of the verified-SPIN-impairment group with controls matched only for age and sex, not for audiometric thresholds (controls were selected to provide optimal age-matching, allowing thresholds to vary freely.) This approach was informed by the suggestion that high-frequency audiometric loss might be a biomarker for cochlear synaptopathy at lower frequencies (Liberman et al., 2016), meaning that audiometric over-matching might obscure relations between SPIN impairment and synaptopathy. Core outcomes of these supplementary analyses are reported in the main text, while figures and further statistics are reported on pages 1 and 2 of the supplementary material.

3. Results

3.1. Audiometry

For the groups used in the main analysis, audiometric thresholds were closely matched. The difference in mean threshold between verified-SPIN-impairment and control groups was <2 dB for pure tones at 0.25–8 kHz (Fig. 2A) and <2.2 dB for EHF thresholds at 10 and 14 kHz (Fig. 2B). Similar results were obtained in the first supplementary analysis, comparing the reported-SPIN-impairment group with controls. For the final supplementary analysis, participants with verified SPIN impairment and controls were not purposely audiogram-matched, yielding groups whose mean thresholds differed by 3.1 dB at 8 kHz, 4.2 dB at 10 kHz, and 5.6 dB 14 kHz, but differed little at lower frequencies (see page 2 of the supplementary material for audiograms).

3.2. Speech perception in noise

SPIN performance among participants with reported SPIN impairment exhibited substantial inter-subject variability (Fig. 3). CRM thresholds ranged from −21.4 dB (surpassing even the best-
performing control) to 0.4 dB (a deficit of 17 dB relative to median control threshold). Only half of the participants with reported SPiN impairment (n = 16) met the criterion for inclusion in the verified-SPiN-impairment group, consistent with past reports of underestimation of hearing ability in this population (Saunders and Haggard, 1992).

3.3. Educational level and cognitive ability

Verified-SPiN-impairment and control groups were similarly educationally diverse, with no indication of higher educational status among the control participants. Analysis by Wilcoxon-Mann-Whitney test indicated no significant between-groups differences in the distributions of participants among the educational categories (U = 105, p = 0.37). The time taken to complete Part B of the Trail Making Test did not differ significantly between groups (t(30) = -0.71, p = 0.49), providing no indication of cognitive contributions to SPiN impairment. The same patterns of educational and cognitive results were obtained in both supplementary analyses (see pages 1 and 2 of the supplementary material).

3.4. Lifetime noise exposure

Fig. 4 illustrates NESI units of lifetime noise exposure. Note that these units (presented here on a logarithmic scale) are linearly related to total energy of exposure and range from 0.1 to 90, indicating a wide range of exposures in this cohort (a factor of 900 in energy between the lowest and highest exposed). Noise exposure did not differ significantly between participants with verified SPiN impairment and controls (U = 125, p = 0.93, Wilcoxon-Mann-Whitney test), a finding repeated in both supplementary analyses (see pages 1 and 2 of the supplementary material).

3.5. Auditory brainstem response

Fig. 5 illustrates the ABR data obtained from participants with verified SPiN impairment and closely audiogram-matched controls. ABR wave I amplitude did not differ significantly between the groups (t(30) = 0.7, p = 0.49). A second ABR measure was also computed: the ratio of wave I amplitude to wave V amplitude, which has been suggested as a self-normalized measure of AN function with potentially enhanced sensitivity to synaptopathy (Schaette and McAlpine, 2011). No association with verified SPiN difficulties was evident (U = 128, p = 0.99, Wilcoxon-Mann-Whitney test). Neither wave I amplitude nor the ratio measure differed between groups in either supplementary analysis (see pages 1 and 2 of the supplementary material).
3.6. Envelope-following response

Response SNR exceeded 6 dB for 100% of EFRs at the full stimulus modulation depth, and for 91.4% at the shallow modulation depth (90.6% of SPiN-impaired participants, 92.1% of controls). In the main analysis (and in both supplementary analyses), response amplitudes (expressed in dB re: 1 μV) were normally distributed at both modulation depths in both participant groups, and hence were analyzed by a mixed two-way ANOVA, with group as the between-subjects factor and stimulus modulation depth as the within-subject factor. The model revealed a highly significant effect of stimulus modulation depth ($F(1,30) = 333$, $p < 0.001$), but no significant effect of group ($F(1,30) = 0.00$, $p = 0.99$) and no significant interaction effect ($F(1,30) = 0.01$, $p = 0.92$). Hence, as can be seen from Figure 6, verified SPiN impairment was not associated with reduced EFR amplitude, nor with rapid declines in amplitude with decreasing modulation depth. These results were echoed in both supplementary analyses (see pages 1 and 2 of the supplementary material).

4. Discussion

Humans with impaired SPiN and normal audiometric thresholds were matched with controls on the basis of age, sex, and audiometric sensitivity. In the main analysis, SPiN impairment was defined both by self-report and laboratory SPiN performance, and audiometric thresholds were matched closely up to 14 kHz. This design was chosen because some apparently SPiN-impaired patients underestimate their listening abilities (Saunders and Haggard, 1992) and because even minor high-frequency hearing loss may impact electrophysiological measures of synaptopathy (Verhulst et al., 2016; Hardy et al., 2017). In addition, one supplementary analysis defined SPiN impairment solely by self-report and a second supplementary analysis allowed audiometric thresholds to differ between groups. SPiN impairment was not associated with lifetime noise exposure, nor with any ABR or EFR measure of synaptopathy, despite small standard errors. These findings were consistent across all three analyses.

Such uniformly null results appear at odds with the notion that noise-induced cochlear synaptopathy is a significant etiology of impaired SPiN with a normal audiogram. The present study is, to the authors’ knowledge, the first to investigate synaptopathy in individuals with significant listening difficulties. However, its results accord with an existing body of literature that finds little evidence for relations of SPiN to noise exposure and AN function, or finds evidence that could reasonably be attributed to pathologies other than synaptopathy. Links between brainstem response measures and perceptual performance have been reported by some (Bharadwaj et al., 2015; Liberman et al., 2016), but not others (Bramhall et al., 2015; Fulbright et al., 2017). Reported relations of SPiN to occupational noise exposure are complicated by the possible influence of audiometric deficits (Alvord, 1983; Kumar et al., 2012; Hope et al., 2013). Two small studies of college students found no relation of noise exposure to SPiN (Le Prell and Lobarias, 2016; Grinn et al., 2017). In a third, noise exposure was associated with poorer SPiN, but at a low sound level unlikely to emphasize low-SR fibers (Liberman et al., 2016). A clinical study of SPiN impairment in 110 patients with normal audiograms demonstrated no relation to noise exposure history (Stephens et al., 2003). Finally, large-scale studies aiming to investigate noise-induced synaptopathy have revealed no effects of noise exposure on a broad array of perceptual measures (Prendergast et al., 2017b; Gröse et al., 2017; Fulbright et al., 2017; Yeend et al., 2017).

The dearth of consistent evidence for perceptually consequential synaptopathy in humans is surprising, given histological evidence for the pathophysiology in animal models. Possible explanations for the present results must be considered carefully. Chief among them are: (a) cochlear synaptopathy is not widespread in young people with normal audiometric thresholds; (b) cochlear synaptopathy does not substantially degrade SPiN; (c) our measures of cochlear synaptopathy and noise exposure are not sufficiently sensitive.

4.1. Possibility A: cochlear synaptopathy is not widespread in young people with normal audiometric thresholds

In numerous rodent models, cochlear synaptopathy has been induced in young animals by exposure to high-level noise, without permanent elevation of cochlear thresholds. Translation of these findings to humans may not be straightforward. In animals, exposures are carefully titrated so as to maximize synaptopathy without widespread hair-cell loss; even so, some loss of sensitivity tends to result, albeit restricted to the extreme cochlear base (e.g. Kujawa and Liberman, 2009; Liberman et al., 2015; Shaheen et al., 2015). Since human exposures are far more diverse, synaptopathy without audiometric loss may be rare. Susceptibility to synaptopathy may also be far lower in humans than in rodents, since inter-species differences are apparent even among animal models. In comparison to in-bred mice, guinea-pigs incur synaptopathy at higher sound levels (Furman et al., 2013; Shi et al., 2013) and their synapses appear to regenerate in the weeks following exposure (Shi et al., 2013). In macaques, a high sound level of 108 dB SPL produced relatively modest synaptic loss (12–27% in basal regions), accompanied by mild outer hair cell loss (Valero et al., 2017). Based on analogous TTS studies in mice and humans, Dobie and Humes (2017) estimate that noise-induced synaptopathy in humans might require a 2-h exposure level of ~114 dB SPL. In light of probable human resilience to synaptopathy, the findings of Maison et al. (2013) gain fresh significance, since they suggest that longer-duration exposures to moderate sound levels are also synaptopathic. However, it is not clear that synaptopathy was present in the latter study: synaptic densities of exposed animals were similar to those of control animals in previous studies (Le Prell and Brungart, 2016).

Evidence for noise-induced synaptopathy in audiometrically normal humans relies on non-invasive proxies, and remains inconclusive. An apparent negative relation between ABR wave I amplitude and previous-12-months’ noise exposure was sex-confounded (Stamper and Johnson, 2015a). Upon reanalysis, the relation remained only for females at the highest stimulus level; males exhibited an opposing trend (Stamper and Johnson, 2015b). Basal influences are unknown, since EHF audiometric thresholds were not measured. The high-noise participants of Liberman et al.
(2016) did not demonstrate significantly reduced AP amplitude, and it is not clear that their enhanced SP/AP ratio is more consistent with synaptopathy than other forms of cochlear damage. Prendergast et al. (2017a) found no electrophysiological evidence for noise-induced synaptopathy in a cohort of 126, using both ABR and EFR measures. The Bayesian regression analysis of Bramhall et al. (2017) associated noise exposure with wave I amplitude, but it is not clear that audiometric and sex confounds were adequately controlled. An informative prior was not specified for the expected effects of sex on amplitude, despite a pronounced correlation between sex and noise-exposure group. Audiometric thresholds were omitted from the model entirely, despite a 7.3 dB disparity between the highest- and lowest-exposed groups. Guest et al. (2017a) found no association between lifetime noise exposure and ABR or EFR measures of synaptopathy. The high-noise group in the study by Grose et al. (2017) exhibited lower values of the ABR wave I/V amplitude ratio ($p = 0.03$, uncorrected), though not of ABR wave I amplitude, nor any EFR measure. In the data of Spankovich et al. (2017), noise history was not associated with ABR wave I amplitude, nor wave I/V amplitude ratio, measured using both high and low click rates. Grinn et al. (2017) observed no relation between ABR wave I amplitude and noise exposure, either reported for the previous 12 months or incurred at a single loud-music event, though the sample was small ($n = 32$). In Fulbright et al. (2017), previous-12-months’ noise exposure was not associated with ABR wave I amplitude at any of four stimulus levels. Whilst histology provides support for the existence of age-related synaptopathy in humans (Makary et al., 2011; Viana et al., 2015), evidence in relation to noise exposure is less convincing, reducing confidence that synaptopathy is prevalent in young, audiometrically normal humans.

4.2. Possibility B: cochlear synaptopathy alone does not substantially impair SPiN

Kujawa and Liberman (2015) hypothesized that synaptopathy might explain SPiN deficits in humans with normal audiograms, citing the likely importance of low-SR, high-threshold fibers for listening in background noise. However, this reasoning rests upon the assumptions that synaptopathy in humans preferentially affects low-SR fibers, and that low-SR fibers in humans possess high response thresholds. The latter assumption, in particular, may be unfounded. Hickox et al. (2017) note that the low-SR/high-threshold relation observed in the AN fibers of mice, gerbils, guinea-pigs, and cats may not hold true in primates. Single-unit recordings from the AN fibers of macaque monkeys have demonstrated no systematic relation between SR and threshold (Joris et al., 2011).

If synaptopathy in humans does not preferentially affect high-threshold fibers, then its impact on perception may be limited. Oxenham (2016) devised a simple model based on signal detection theory to predict the effects of mixed-SR synaptopathy on tone detection in quiet and in noise and on the discrimination of frequency, intensity, and inter-aural time differences. For all measures, a 50% loss of AN fibers was predicted to produce barely measurable effects on performance. On the other hand, Lopez-Poveda and Barrios (2013) have suggested that widespread synaptic loss might degrade SPiN regardless of fiber type, by leading to a “stochastically undersampled” neural representation of the sound waveform. However, the vocoder used to test this hypothesis may not have meaningfully simulated the effects of synaptopathy (Oxenham, 2016).

Finally, it is important to note that myriad factors besides cochlear function influence speech perception, including the function of the central auditory pathways, linguistic abilities, attention, and working memory (Pienkowski, 2017; Yeend et al., 2017). Even if cochlear synaptopathy has effects on SPiN, and especially if these effects are modest, it is conceivable that they might be eclipsed by variability in other factors.

4.3. Possibility C: our measures of cochlear synaptopathy and noise exposure are insufficiently sensitive

Of the dependent measures employed in the present study, the NESI appears most questionable, given the inherent inaccuracy and unreliability of retrospective self-report (Sallis and Saelens, 2000). However, cross-sectional investigations of noise-induced synaptopathy are bound to rely on such data, at least in societies where workplace regulations limit the contribution of occupational noise to the lifetime noise dose. A reasonable question, then, is how the design of the NESI compares to the alternatives, and especially to those measures successfully associated with putative measures of synaptopathy.

Bharadwaj et al. (2015) employed a rudimentary noise metric that was supplementary to the study’s main measures, but whose methods were clearly reported. Participants rated their degree of exposure for four common noisy activities, along with their past experience of TTS. Scores were combined by weighting all categories equally. A much wider range of potentially noisy activities is surveyed by the Noise Exposure Questionnaire (Stampfer and Johnson, 2015a; Johnson et al., 2017), which also considers frequency and duration of exposure and use of hearing protection. However, these data are obtained for only the past 12 months of exposure. Hence, the measure is unsuitable for assessing cumulative exposure, and is likely to be especially inappropriate for use with respondents whose exposure habits have changed markedly over the years. The brief questionnaire administered by Liberman et al. (2016) addressed both social and occupational noise exposure. For each, it sought information on number of years of exposure, proportion of time that hearing protection was used, and descriptions of exposure activities. It did not include questions on typical duration of each exposure, frequency of occurrence, or estimated sound level, and it is not clear how participants were to report multiple exposure activities. Finally, it is not clear how the data were combined to decide allocation to the high- or low-risk group; if quantitative methods were used, they were not reported. In contrast, the LENS-Q measure of Bramhall et al. (2017) is quantitative and well defined, but is effectively a measure of firearm exposure, discounting other forms of noise. Duration of each exposure is not considered, so a rifle round with a peak level of 160 dB SPL is equated to a long-duration exposure at 160 dB SPL. Put another way, one such rifle round is equated to one million heavy metal concerts (with a level of 100 dB SPL). This relative weighting is not supported by damage risk criteria (Nakashima, 2015).

The NESI aims to provide a more comprehensive measure of noise exposure, though administration can be time-consuming (5–35 min in the present study, depending on the extent and complexity of the respondent’s noise history). Information is sought on all noisy activities experienced by the respondent, regardless of whether they are commonplace or unconventional and whether they occurred in occupational or recreational settings. For each activity, exposure habits may be expected to change across the lifespan. Hence, the NESI adopts a flexible, mnemonistic approach, examining various life periods in which exposure habits were relatively stable. For each life period, rigorous methods are then applied in the estimation of sound level, duration, and usage and attenuation of hearing protection. Ultimately, a clearly defined method, based on the equal energy hypothesis, is used to combine the resulting data. Despite these properties, the NESI necessarily
remains an inaccurate metric and it may therefore be important that our participants presented an extremely wide range of noise exposures, such that genuine differences were unlikely to be obscured by measurement error. Confidence in this interpretation—and in the measure—is bolstered by a previously reported association between tinnitus and noise exposure, as quantified using the NESI (Guest et al., 2017a).

ABR wave I amplitude may also be subject to doubt as a measure of synaptopathy in humans, despite clear correlations with synaptic loss in animal models (e.g., Kujawa and Liberman, 2009). In humans, the measure is contaminated by many non-synaptopathic sources of variability (Mitchell et al., 1989) and it has been suggested that within-subject difference measures might be necessary to emphasize AN function (Plack et al., 2016). However, such reasoning seems unlikely to account for the present results. In participants with SPiN difficulties, neither wave I amplitude nor wave I/V amplitude ratio was significantly reduced, despite small standard errors. Moreover, a trend was observed for higher wave I amplitude in those with SPiN difficulties (0.31 ± 0.03 μV) than in controls (0.27 ± 0.02 μV). A more fundamental defect of the ABR measures may be that wave I amplitude is not, after all, sensitive to loss of low-SR fibers. Bourien et al. (2014) demonstrated in the gerbil that fibers the lowest stimulation rates do not contribute to the compound action potential (equivalent to ABR wave I). A reasonable explanation is whether previously reported associations between wave I amplitude and noise exposure in humans (Bramhall et al., 2017; Stamper and Johnson, 2015b) reflect factors other than synaptopathy. Uncontrolled high-frequency or EHF audiometric loss may play a role (Guest et al., 2017b), since wave I is dominated by basal contributions (Don and Eggermont, 1978; Hardy et al., 2017), increasingly so at high stimulus levels (Eggermont and Don, 1980).

The EFR is thought to receive more robust contributions from low-SR fibers (Shaheen et al., 2015) and has some validation in animal models (Parthasarathy et al., 2017; Shaheen et al., 2015). Like the ABR, the EFR can be implemented using within-subject difference measures, in order to limit variability from non-synaptopathic factors. The present study used the variable-modulation-depth paradigm of Bharadwaj et al. (2015), which seeks to emphasize contributions of high-threshold fibers. Presence of SPiN difficulties was not associated with more steeply declining response strength, nor with reduced response strength overall. However, it is possible that our EFR stimuli—in common with those of other studies in humans—were inappropriate for the detection of synaptopathy. In animals, stimulus modulation rates of ~1 kHz are required to elicit substantial AN contributions and disclose synaptopathy (Parthasarathy et al., 2017; Shaheen et al., 2015). Use of such high rates in humans presents significant challenges, potentially limiting the utility of the EFR as a measure of synaptopathy.

5. Conclusion

In individuals with impaired SPiN and normal audiograms, we find no evidence of enhanced lifetime noise exposure, nor of reduced brainstem response amplitudes. These results persist regardless of whether SPiN impairment is defined solely by self-report or confirmed by laboratory measures of SPiN. It is possible that the ABR and EFR measures offer limited sensitivity to cochlear synaptopathy, perhaps due to measurement variability from other sources or to limited contributions from low-SR AN fibers. Likewise, it is possible that the self-report measure of noise exposure lacks validity, despite its comprehensive nature and a previously reported association with tinnitus. Nevertheless, the resoundingly and uniformly null findings frustrate the notion that noise-induced cochlear synaptopathy is a significant etiology of SPiN impairment with a normal audiogram. It may be that synaptopathy alone does not have significant perceptual consequences, or is not widespread in humans with normal audiograms.

Acknowledgments

The authors are grateful to Dr Hari Bharadwaj and two anonymous reviewers for providing constructive comments on earlier versions of this manuscript. The research was supported by an Action on Hearing Loss studentship, funded by the Marston Family Foundation, and by the Medical Research Council UK (MR/L003589/1).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heares.2018.03.008.

References


Hardy, A., de Boer, J., Krumholz, K., 2017. Improving auditory brainstem responses for clinical testing: the gain hypothesis [poster]. In: IBA Basic Auditory Science Meeting, Nottingham, UK.


3.5 Reliability and interrelations of seven proxy measures of cochlear synaptopathy

Submitted to Hearing Research, September 2018
Reliability and interrelations of seven proxy measures of cochlear synaptopathy

Hannah Guest a,*, Kevin J. Munro a,b, Garreth Prendergast c, Christopher J. Plack a,c

aManchester Centre for Audiology and Deafness, University of Manchester, Manchester Academic Health Science Centre, UK
bManchester University NHS Foundation Trust, UK
cDepartment of Psychology, Lancaster University, UK
*Corresponding author. Email: hannah.guest@manchester.ac.uk

Abstract

Investigations of cochlear synaptopathy in living humans rely on proxy measures of auditory nerve function. Numerous procedures have been developed, typically based on the auditory brainstem response (ABR), envelope-following response (EFR), or middle-ear muscle reflex (MEMR). Validation is challenging, due to the absence of a gold-standard measure in humans. Some metrics correlate with synaptic survival in animal models, but translation between species is not straightforward; measurements in humans are likely to reflect greater error and greater variability from non-synaptopathic sources. The present study assessed the reliability of seven measures, as well as testing for correlations between them. Thirty-one young women with normal audiograms underwent repeated measurements of ABR wave I amplitude, ABR wave I growth, ABR wave V latency shift in noise, EFR amplitude, EFR growth with stimulus modulation depth, MEMR threshold, and an MEMR across-frequency difference measure. Intraclass correlation coefficients for ABR wave I amplitude, EFR amplitude, and MEMR threshold ranged from 0.85 to 0.93, suggesting that such tests can yield highly reliable results, given careful measurement techniques. The ABR and EFR difference measures exhibited only poor-to-moderate reliability. No significant correlations, nor any consistent trends, were observed between the various measures, providing no indication that these metrics reflect the same underlying physiological processes. Findings suggest that many proxy measures of cochlear synaptopathy should be regarded with caution, at least when employed in young adults with normal audiograms.

Keywords: Cochlear synaptopathy; Hidden hearing loss; Auditory nerve; Auditory brainstem response; Envelope-following response; Middle-ear muscle reflex

Abbreviations: ABR, auditory brainstem response; AN, auditory nerve; AP, action potential; CF, characteristic frequency; EFR, envelope-following response; ICC, intraclass correlation coefficient; MEMR, middle-ear muscle reflex; RMS, root mean square; SD, standard deviation; SNR, signal-to-noise ratio; SP, summing potential; SR, spontaneous rate

1 Introduction

Seminal work in a mouse model demonstrated that noise exposure can destroy synapses between cochlear inner hair cells and auditory nerve (AN) fibers, without widespread hair-cell loss (Kujawa and Liberman, 2009). Direct evidence of cochlear synaptopathy has since been observed in rats, guinea pigs, gerbils, and macaques (Hickox et al., 2017; Valero et al., 2017). In affected animals, cochlear thresholds are left largely intact, yet auditory brainstem response (ABR) amplitudes are reduced at moderate-to-high stimulus levels (Hickox et al., 2017). Synaptopathy may preferentially affect the subset of AN fibers with low spontaneous firing rates (low-SR fibers; Furman et al., 2013), which have high response thresholds (Liberman, 1978). It is thought that the pathophysiology might have significant perceptual consequences, including deficits of speech perception in noise and tinnitus (Plack et al., 2014).

Naturally, researchers worldwide have hastened to investigate whether cochlear synaptopathy manifests in humans. The vast majority of studies have not employed histological techniques, relying instead on non-invasive proxy measures of cochlear synaptopathy. A wide variety of such measures are reported in the literature, generally based on the ABR, envelope-following response (EFR), or acoustic middle-ear muscle reflex (MEMR).

Most widely used is the amplitude of ABR wave I, which reflects the summed activity of AN fibers (Medcher and Kiang, 1996). When measured in response to high-level stimuli, wave I is assumed to include substantial contributions from high-threshold fibers. Accordingly, in animal models of synaptopathy, wave I amplitude is reduced at medium-to-high stimulus levels (Kujawa and Liberman, 2009). However, sensitivity of the measure to low-SR damage has been questioned, due to the delayed onset responses of this fiber type (Bourien et al., 2014). Moreover, ABR amplitudes in humans exhibit greater between-subject variability than in rodents, attributable to many factors unrelated to synaptopathy, such as head size, sex, cochlear dispersion, physiological noise, and pre-neural dysfunction (Plack et al., 2016). Within-subject difference measures may be of value in managing this variability.

One candidate measure is the ratio of wave I amplitude to wave V amplitude (Schaette and McAlpine, 2011). Sensitivity of the measure to synaptopathy rests on the assumptions that (i) the amplitudes of both waves are equally affected by non-synaptopathic sources of variability, and (ii) the amplitude of wave V is not reduced by synaptopathy, due to enhanced neural gain in the auditory brainstem. The first assumption, in particular, may not hold, since the two waves differ in terms of the cochlear regions represented in the response. Experiments using high-pass masking have shown that wave I is dominated by contributions from high characteristic frequencies (CFs), including those >8 kHz, while wave V is dominated by CFs <2 kHz (Don and Eggermont, 1978; Hardy et al., 2017). Consequently, the wave I/V amplitude ratio may be highly sensitive to high-frequency audiometric deficits. Since the clinically normal audiometric range spans 30 dB, “normalization” of wave I by wave V may not be meaningful, even in humans with normal audiograms.

An alternative difference measure, obtained using intra-canal electrodes, is the ratio of summing-potential amplitude to action-potential amplitude (SP/AP ratio; Liberman et al., 2016). Since the SP is a pre-synaptic potential, Liberman and colleagues reasoned that it should...
provide a means of normalizing the AP (equivalent to ABR wave I). However, this rationale requires that the SP and AP be similarly affected by differences in pre-neural function, which may not be so. Generation of the SP is complex, featuring contributions from inner and outer hair cells that vary across frequency and level (Durrant et al., 1998). It is important to understand how these potential sources of variability affect the resulting difference measure, especially if it is to be applied in humans with known audiometric deficits, as in Liberman et al. (2016). Use of the measure is further complicated by the extreme stimulus levels required to reliability elicit the SP (130 dB peSPL in the work of Liberman and colleagues).

A more straightforward measure is growth of ABR wave I amplitude with stimulus level. In a number of animal models of synaptopathy, ABR wave I growth functions have been shown to exhibit abnormally shallow slopes, with the greatest decrements in amplitude observed at the highest stimulus levels (e.g. Kujawa and Liberman, 2009). However, a potential practical issue is that measurement requires that ABR wave I be consistently evident at a range of stimulus levels, without exceeding comfortable loudness levels. Some researchers have questioned whether this is feasible, even in young humans with normal hearing (Mehraei et al., 2016).

In light of concerns about wave I measurement, Mehraei and colleagues devised a latency-based ABR measure: the shift in wave V latency with increasing background noise level. Sensitivity to synaptopathy rests on the assumption that the (low-SR) fibers most affected by synaptopathy have both longer response latencies and greater resistance to noise masking than the remaining fibers. Hence, in healthy ears, increasing noise levels should lead to rapidly increasing dominance of the ABR by low-SR fibers, causing ABR latency to increase markedly with noise level. In synaptopathic ears, which are assumed to have fewer low-SR fibers, the increase in latency should be less pronounced. Consistent with this reasoning, Mehraei et al. (2016) demonstrated smaller latency shifts in mice with noise-induced synaptopathy than in controls. A parallel experiment in humans showed that the measure was correlated (p = 0.036, uncorrected) with ABR wave I growth. However, in light of the small sample size (n = 10), replication is required.

Less commonly used than the ABR is the envelope-following response (EFR), a sustained neural response to the envelope of an amplitude-modulated (AM) stimulus. Since synchronization to AM tones is particularly strong in low-SR fibers, it has been suggested that the EFR might feature greater contributions from low-SR fibers than the transient-evoked ABR (Shaheen et al., 2015). Accordingly, animal models have demonstrated good sensitivity of EFR measures to synaptopathy, though only at very high stimulus modulation rates, around 1 kHz (Shaheen et al., 2015; Parthasarathy et al., 2017b).

Human synaptopathy research has also employed a variety of EFR difference measures, such as change in EFR amplitude with increasing level of background noise or with modulation depth (Bharadwaj et al., 2015). As with the ABR difference measures, these metrics aim to reduce variability from non-synaptopathic sources, based on assumptions about the relative contributions of high- and low-SR fibers in the various stimulus conditions. However, to our knowledge, such measures lack validation in animal models. Indeed, Parthasarathy et al. (2017a) found that EFRs at a range of modulation depths were equally impacted by synaptopathy.

A more recent addition to the battery of potential measures of synaptopathy is the acoustic MEMR: the involuntary contraction of the stapedius muscle in response to high-level sound stimuli. The afferent portion of the reflex arc may be driven by medium- and low-SR fibers (Valero et al., 2018). Accordingly, Valero and colleagues showed that cochlear synaptopathy in mice was more readily detected by MEMR measures than by ABR wave I amplitude. Sensitivity was maximized by use of threshold (rather than amplitude) measures, and by use of a high-frequency narrowband (rather than broadband) elicitor.

In summary, numerous procedures have been suggested and/or employed as proxy measures of cochlear synaptopathy in humans. The notion that all measures reflect the same underlying physiological processes is untested. Moreover, the use of multiple measures and conditions, even within a single study, inflates the potential for false discovery, if appropriate correction is not undertaken. These issues complicate interpretation of existing synaptopathy data in humans. Clarification of the situation is made challenging by the absence of a gold-standard, direct measure of synaptopathy in living humans. One important course of action should be thorough validation of promising measures in appropriate animal models, ideally in primates. Another is to investigate the reliability of measures in humans, to determine their capacity to discriminate among members of the target population despite measurement error. A third is to observe the extent to which the measures correlate, since correlations should be observed among sensitive measures of synaptopathy. The present study aims primarily to assess the reliability of seven proxy measures of synaptopathy (see Table 1), with a secondary aim of describing correlations between measures.

## 2 Material and methods

### 2.1 Participants

Target sample size (following attrition) was set at 30, sufficient to estimate the intra-class correlation coefficient (ICC) for ABR wave I amplitude with a 95% confidence interval (CI) of ~0.2. Forty-one women aged 18 to 30 were recruited via advertising on the University of Manchester website. They reported no history of middle-ear surgery, hearing loss, neurological disorder, ototoxic exposure, or head trauma. Ten were excluded due to presence of wax in the ear canal (n = 7), abnormal audiogram (n = 1), Eustachian tube dysfunction (n = 1), or self-reported sound intolerance (n = 1). The remaining 31 exhibited normal otoscopic findings, normal pure tone audiometric thresholds (≤20 dB HL at 0.25 to 8 kHz), and normal tympanometric results (compliance 0.3-1.6 cm3, pressure -50 to +50 daPa). Their mean age was 24.4 years (standard deviation [SD] =

<table>
<thead>
<tr>
<th>ABR wave I amplitude</th>
<th>Growth of ABR wave I amplitude with stimulus level</th>
<th>ABR wave V latency shift in noise</th>
<th>EFR amplitude</th>
<th>Growth of EFR amplitude with stimulus modulation depth</th>
<th>Acoustic MEMR threshold</th>
<th>MEMR across-frequency threshold difference</th>
</tr>
</thead>
</table>

**Table 1: Proxy measures of cochlear synaptopathy**
ActiveTwo measurement system recorded from active electrodes at Cz, C7, and the mastoid of the stimulated ear. Common Mode Sense and Driven Right Leg electrodes were attached at mid-forhead and electrode offsets remained within ±40 mV throughout all recordings. Data streams from all three electrodes were saved for offline analysis, along with stimulus-timing information received from the external audio interface via a custom-made trigger box.

Previous researchers have reported difficulty in obtaining clear responses in some of our electrophysiological measures (e.g. Mehraei et al., 2016). The present study adopted a three-fold approach to this issue. Firstly, extensive piloting and optimization of all measures was used to determine stimulus parameters that would produce clear responses in most young people with normal hearing. Achieving this result without using very high sound levels was made a priority, not least because comfortable stimuli may be expected to relax participants and reduce physiological noise. Secondly, the recording environment was carefully prepared to maximize participant comfort: lights were dimmed; air temperature was maintained at 25°C; a chair was selected which reclined to horizontal and offered excellent neck support; a choice of blankets was offered, to ensure a comfortable body temperature for each individual. Finally, extensive pre-recording counselling was provided (lasting ~15 minutes), with the aim of allaying any potential concerns and uncertainties. Counselling addressed the following issues: (i) purpose and basic setup of the recording; (ii) skin preparation, electrode placement, electrode removal, and clean-up; (iii) ear tip insertion and associated sensations; (iv) duration of each stimulus; (v) sound quality of each stimulus, described candidly; (vi) the need for a relaxed state during the majority of the recording; (vii) what to do in the case of difficulties or questions; (viii) what to do in the case of emergency. Participants were encouraged to ask questions, and – if they wished – to sample the recliner and/or stimuli prior to recording. These precautions, though unsophisticated, led to extremely low-noise recordings, yielding measurements with excellent reliability.

2.6 ABR wave I amplitude and growth

Following the methods of Mehraei et al. (2016), stimuli were monaural 80 µs broadband clicks, delivered at a rate of 9/s. The inter-stimulus interval was jittered by up to 20 ms, in order to prevent the accumulation of stationary interference. Based on extensive piloting, click levels of 90, 96, and 102 dB peSPL were selected, with the aim of ensuring both participant comfort and clear wave I presence at all stimulus levels. The resulting three stimuli were interleaved on a click-by-click basis throughout the recording. Participants received 5200-5600 presentations at each level.

Bioelectrical activity between Cz and ipsilateral mastoid was filtered between 50 and 1500 Hz (fourth-order butterworth). Epochs were extracted (10 ms pre-stimulus to 10 ms post-stimulus) and rejected if activity exceeded the mean for the recording by more than two SDs. The remaining epochs were averaged and the resulting ABR corrected for any linear drift by subtracting a linear fit to the pre-stimulus baseline. Peak-to-trough wave I amplitudes were obtained using an automated peak-picking algorithm. The algorithm defined the peak of wave I as a local maximum occurring within a pre-specified time window. For stimuli delivered at 90 dB peSPL, the window was 1.7–2.5 ms after stimulus peak; at 96 dB peSPL, 1.6–2.3 ms; at 102 dB peSPL,
1.45-2.15 ms. If no maximum was found (as was true in one of 183 waveforms), wave I peak was taken to be the highest point of the waveform within the time window. The trough of wave I was defined as the lowest point of the waveform occurring 0.3-0.7 ms after the peak of wave I. Post-hoc subjective review verified that the algorithm had appropriately interpreted all waveforms, with the exception of one; for this waveform, the timing of the window was advanced, due to an unusually short-latency response.

Wave I growth was computed as in Mehraei et al. (2016), by fitting a straight line through the response amplitudes at the three stimulus levels, yielding a measure expressed in µV/db. It should be noted that this approach would not be expected to control variability with multiplicative – rather than additive – effects on wave I amplitude.

2.7 ABR wave V latency shift in noise

Following the methods of Mehraei et al. (2016), stimuli were monaural 80 µs broadband clicks embedded in broadband noise. Clicks were delivered at 93 dB peSPL and noise at 42, 54, and 66 dB SPL (as measured at the output of the transducer), with the aim of ensuring substantial shifts in latency for all participants without risking erasure of the response. Clicks were delivered at a rate of 9/s, jittered by up to 20 ms. Presentation of the three noise levels was interleaved throughout the recording. Each block of noise had a duration of 2s, including 10 ms onset and offset ramps. The offset ramp of each block was concurrent with the onset ramp of the next. Following the onset of each noise block, 80 ms elapsed before presentation of the first click. Participants received 3600-4000 presentations at each noise level.

Bioelectricity between Cz and ipsilateral mastoid was filtered between 50 and 1500 Hz (fourth-order butterworth). Epochs were extracted (10 ms pre-stimulus to 10 ms post-stimulus) and rejected if root-mean-square (RMS) activity exceeded the mean for the recording by more than two SDs. The remaining epochs were averaged and the resulting ABR corrected for any linear drift by subtracting a linear fit to the pre-stimulus baseline. Wave V latencies were obtained using an automated peak-picking algorithm. The algorithm defined the peak of wave V as the highest-amplitude local maximum occurring within a pre-specified time window. For responses obtained at a noise level of 42 dB SPL, the window was 5.7-6.9 ms after stimulus peak; at 54 dB SPL, 5.9-7.1 ms; at 66 dB SPL, 6.1-7.3 ms. Post-hoc subjective review verified that the algorithm had appropriately interpreted 97% of waveforms; for the remainder, picked peaks were manually corrected. ABR latency shift in noise was computed by fitting a straight line through the latencies of wave V at the three noise levels. Note that the three peak-picking windows overlapped substantially, and that no constraint was placed on the temporal order of the three peaks; nothing in the algorithm prevented a decrease in latency with noise level. This relatively unrestrictive approach was designed to ensure that the algorithm did not simply “force” plausible values of the latency-shift measure, thereby artificially inflating reliability. Despite this precaution, recorded values were predominantly positive (see section 3.2.3).

2.8 Envelope-following response

Stimuli were diotic 75 dB SPL transposed tones (Bernstein and Trahiotis, 2002) with carrier frequency 4000 Hz and modulation rate 105 Hz. In order to attenuate off-frequency contributions, as in Bharadwaj et al. (2015), tones were presented concurrently with a notched-noise masker (20-10000 Hz; notch width 800 Hz, centered on 4000 Hz), realized separately for each trial and applied at a signal-to-noise ratio (SNR) of 20 dB (broadband RMS). Stimuli had a duration of 400 ms, with the addition of 10 ms onset and offset ramps, and were presented at a rate of 1.25/s. Inter-stimulus interval was jittered by up to 20 ms. Tones were of two modulation depths: 0 dB (full modulation) and -6 dB (shallow modulation). Each of these tones was presented 990 times, half in each polarity. The resulting four stimuli were interleaved throughout the recording, in the sequence 0 dB; -6 dB; 0 dB inverted; -6 dB inverted.

Bioelectricity between Cz and C7 was extracted for epochs extending from 8 to 408 ms after the end of the stimulus onset ramp. For each stimulus modulation depth and polarity, epochs were rejected if their RMS activity exceeded the 90th percentile for the recording. The remaining epochs were averaged and the responses to opposing polarities summed, emphasizing the response to the temporal envelope of the stimulus. Each resulting EFR was subjected to a discrete Fourier transform to yield the response amplitude (at the 105 Hz modulation frequency) and an estimate of the noise floor (based on activity in 10 adjacent frequency bins: 87.5-97.5 Hz and 112.5-122.5 Hz).

Following Bharadwaj et al. (2015), we analyzed not only EFR amplitude but also a difference measure: the difference in EFR amplitude between the two stimulus modulation depths. This measure is closely related to the “EFR slope” reported by Bharadwaj and colleagues, though based on a two-point rather than a three-point function. Sensitivity to synaptopathy rests on the assumption that high-threshold fibers are preferentially damaged, and that these fibers are especially important for the encoding of stimuli with shallow modulations. Hence, ears with synaptopathy should exhibit unusually steep EFR growth with modulation depth.

2.9 Middle-ear muscle reflex thresholds

Middle-ear muscle reflex thresholds were measured monaurally using a GSI Tymstar diagnostic middle-ear analyzer. The probe was encompassed in a Grason KR-Series clinical ear tip and delivered a probe tone at 226 Hz. Stimuli were ipsilateral pulsed pure tones at 1, 2, and 4 kHz with a duration of 1.5 seconds. Prior to measurement, the participant was instructed on the following: (i) basic setup and purpose of the test; (ii) sound quality of the stimuli; (iii) timing of the stimuli; (iv) timing of the response periods; (v) importance of artifact-free response periods; (vi) possible sources of measurement artifact (e.g. swallowing, movement, vocalization); (vii) test duration; (viii) importance of avoiding loudness discomfort; and (ix) verbal and non-verbal means of halting the test.

Reflex thresholds were determined by observing changes in middle-ear compliance following presentation of the stimuli. A reflex response was defined as a reduction in compliance of 0.02 ml or greater with appropriate morphology and no evidence of significant measurement artifact. If significant measurement artifact was observed during the response period, the presentation was repeated. For each threshold measurement, stimulus level commenced at 70 dB HL and ascended in 5 dB steps until a response was observed. Stimulus level then decreased by 10 dB and ascended in 2 dB steps until threshold was obtained. Threshold was defined as the lowest stimulus level at which three clear responses were observed over the course of three, four, or five artifact-free presentations. In addition to
the thresholds at each frequency, we also analyzed a difference measure: the difference (in dB) between the thresholds at 1 and 4 kHz. It was reasoned that this measure might offer sensitivity to noise-induced damage, which tends to predominantly affect the 3-6 kHz region (Coles et al., 2000).

MEMR data are missing for one participant, due to poor fit of the probe tip in the ear canal. For another participant, an adequate fit was obtained at the first session but could not be achieved at the second; her MEMR data are omitted from the reliability analysis.

2.10 Analysis

Test-retest reliability of each measure was assessed by computation of an ICC: the ratio of true variance to the sum of true variance and error variance. The specific form of ICC employed was a one-way, random-effects, single-rater ICC - denoted ICC(1,1) by Shrout and Fleiss (1979). Use of a one-way, random-effects model yields a more conservative estimate of reliability than other forms of ICC, and effectively regards each test session for each participant as a separate random judge sampled from the population, acknowledging that different test sessions involve differences in time of day, participant state, electrode placement, and so on. In Sections 3 and 4, descriptors of reliability (“moderate”, “good”, etc.) follow the conventions of Koo and Li (2016).

3. Results

3.1 Measures of cochlear mechanical function

Figure 1A illustrates pure-tone audiometric thresholds, which were ≤20 dB HL for all participants at frequencies from 0.25 to 8 kHz. Figure 1B illustrates DPOAE amplitudes at 2.8, 4, and 6 kHz – frequencies that fall within the range typically associated with noise-induced hearing damage (Coles et al., 2000). At these frequencies, 97% of response SNRs (not shown in the figure) exceeded 6 dB.

3.2 Reliability of proxy measures of synaptopathy

3.2.1 ABR wave I amplitude

Figure 2C shows wave I of the ABR in response to 102 dB peSPL clicks for all participants. Mean wave I amplitude was 0.40 µV (range 0.17 to 0.67). Figure 2D compares the amplitudes recorded at the first and second test sessions. Reliability was good, nearing excellent: ICC = 0.85 (95% CI = 0.71-0.93).

3.2.2 ABR wave I growth

The change in wave I amplitude with increasing stimulus level was always positive, with exception of one participant, who presented near-zero growth at both test sessions. The growth of amplitude with stimulus level is also apparent in the grand average waveforms (Figure 2, upper panels). Mean growth was 0.02 µV/dB (range -0.0002 to 0.04). Reliability of the measure (Figure 2E) was moderate, nearing poor: ICC = 0.52 (95% CI = 0.21-0.74).

3.2.3 ABR wave V latency shift in noise

Figure 3A presents grand average ABRs at the three noise levels. In 97% of measurements, response latency increased with noise level, as expected. Mean latency shift was 0.024 ms/dB (range -0.01 to 0.064). Reliability of the measure (Figure 3B) was poor: ICC = 0.45 (95% CI = 0.12-0.69). In

After confirming normality of distribution, possible relations between the various proxy measures of synaptopathy were assessed by computation of Pearson’s correlation coefficients (see Section 3.3 for comparisons).
3.2.4 EFR amplitude

Response SNR exceeded 6 dB for 100% of responses to the fully modulated stimulus and for 87% of responses to the shallow stimulus modulation depth. Mean EFR amplitudes (Figure 4A) at the full and shallow depths were -15 and -20.9 dB re: 1 µV, respectively. Reliability at the full modulation depth (Figure 4B) was excellent: ICC = 0.93 (95% CI = 0.86-0.97). Reliability at the shallow depth (Figure 4C) was good, nearing excellent: ICC = 0.85 (95% CI = 0.71-0.92).

3.2.5 EFR difference measure

The change in EFR amplitude with increasing modulation depth was always positive, with exception of one participant, who presented near-zero values at both test sessions, despite response SNRs >6 dB. Mean difference in response amplitude between the modulation depths was 5.87 dB. Reliability of this EFR difference measure was moderate, nearing poor: ICC = 0.54 (95% CI = 0.24-0.75).

3.2.6 MEMR thresholds

Mean thresholds measured at 1, 2, and 4 kHz were 85.3, 86.6, and 90.0 dB HL, respectively. For six participants, thresholds at 4 kHz exceeded the maximum output of the middle-ear analyzer (100 dB HL) at one (n = 3) or both (n = 3) test sessions. These participants were omitted from the 4 kHz reliability analysis; for the purposes of the correlational analysis, the affected thresholds were ascribed a value of 102 dB HL.

Reliability of the 1 kHz thresholds (Figure 5A) was good, nearing excellent: ICC = 0.89 (95% CI = 0.78-0.95). Reliability of the 2 kHz thresholds (Figure 5B) was excellent: ICC = 0.90 (95% CI = 0.80-0.95). Reliability of the 4 kHz thresholds (Figure 5C) was good, nearing excellent: ICC = 0.88 (95% CI = 0.75-0.95). Values of the MEMR difference measure (4 kHz threshold – 1 kHz threshold) ranged from -10 to 18 dB; reliability was good, nearing excellent: ICC = 0.85 (95% CI = 0.68-0.93).

3.3 Relations between measures of synaptopathy

Eighteen comparisons were conducted, illustrated in Figures 6, 7, and 8.

3.3.1 ABR amplitude measures vs ABR latency shift in noise

No significant relation was evident between ABR wave V latency shift in noise and either ABR wave I amplitude or ABR wave I growth (Figure 6).

3.3.2 ABR measures vs EFR measures

Six comparisons were conducted, pairing each of the two EFR measures with each of the three ABR measures (see Figure 7). Four yielded no significant relation. Comparison of ABR wave I amplitude with the EFR difference measure yielded a marginally significant correlation ($r = -0.36, p = 0.05$, uncorrected), but this relation was clearly too weak to survive correction for multiple comparisons. A stronger correlation was evident between EFR amplitude and ABR latency shift in noise; however, this relation ran in the opposite-from-predicted direction, and would not withstand correction in any case.
3.3 ABR measures vs MEMR measures

MEMR thresholds at 4 kHz and the MEMR difference measure were each compared with the three ABR measures (Figure 8, upper six panels). No significant correlations were evident.

3.3.4 EFR measures vs MEMR measures

The two MEMR measures were compared with the two EFR measures (Figure 8, lower four panels). No significant correlations were evident.

4 Discussion

4.1 Highly reliable measures of ABR and EFR amplitude are possible in humans

The reliability of ABR wave I amplitude is not widely documented in the literature; past research has tended to focus on latency measures. Bidelman et al. (2018) assessed the reliability of ABR amplitude, but only for wave V, which was found to be moderately reliable (ICC = 0.65). However, a previous study by our lab examined the test-retest reliability of ABR wave I amplitude using clinical recording equipment and yielded an ICC of 0.85 (Prendergast et al., 2018). The present study differed in methodology (e.g. use of research-grade recording equipment and a lower click level), yet produced a near-identical ICC. Our findings suggest that the amplitude of ABR wave I can be a highly reliable measure, if care is taken to ensure consistency in electrode placement, participant state, and other factors influenced by the investigator. Since lower reliability has been reported elsewhere, researchers adopting ABR amplitude measures would be well advised to undertake preliminary assessments of the reliability of their own ABR measurements.
Results for EFR amplitude were even more favourable: good-to-excellent reliability, depending on stimulus modulation depth. These values are in line with those reported by Bidelman et al. (2018) for frequency-following-response amplitude. It is worth noting that our EFRs were obtained using a simple, single-channel recording setup, suggesting that multi-channel recordings are not necessary to ensure response reliability.

### 4.2 Differential ABR and EFR measures exhibit poor reliability

The reliability of the ABR and EFR difference measures was poor-to-moderate, despite good-to-excellent reliability of the raw ABR and EFR measures. Of course, reliability depends on not only the magnitude of measurement error, but also the heterogeneity of the true values in the study population. If a difference measure is effective in eliminating non-synaptopathic sources of variability and is applied in a homogeneous population, varying little in presence of synaptopathy, then both between-subject variance and reliability are bound to be low. Hence, it is reasonable to ask whether the low reliability observed in the present study is predominately the result of low true variance, rather than high measurement error. This appears to be true in the case of the EFR difference measure, whose between-subject SD (2.9 dB) is far lower than that of raw EFR amplitude (5.1 dB), despite similar within-subject SDs (~1.8 dB). The same is not true of the ABR growth measure; when expressed as the amplitude difference (in μV) corresponding to a 12 dB increase in stimulus level, this measure’s between-subject SD is slightly lower than that of raw wave I amplitude (0.11 c.f. 0.13 μV), but its within-subject SD is markedly higher (0.78 c.f. 0.49 μV).

However, regardless of its sources, the low reliability of all three difference measures casts doubt on their value, at least when used in samples similar to our own. Previous studies have employed these difference measures in small (n ≈ 30) samples of normally hearing young adults, and reported possible evidence for synaptopathy (Bharadwaj et al., 2015; Mehsraei et al., 2016). Yet the consistently low ICCs reported here suggest that all three difference measures lack the capacity to distinguish powerfully between members of such populations. The EFR measure might be more valuable in populations with greater true variance – perhaps older adults, and/or those with a greater range of noise exposures – and all would have greater utility in much larger samples. Nevertheless, we urge caution to investigators considering the use of these difference measures in young humans with normal audiograms, and to those interpreting the results of such measures.

### 4.3 Highly reliable MEMR threshold measures are possible in humans

MEMR thresholds, measured using a clinical middle-ear analyzer, exhibited excellent or near-excellent reliability. Previous research in adult humans has indicated somewhat poorer reliability, especially for tests conducted on different days (Chermak et al., 1983). These results suggest that careful measurement techniques may be important in ensuring reliable responses (see Section 2.9).

The present study elicited MEMRs using pure-tone stimuli, based on the reasoning that synaptopathy might be most prevalent in the 3-6 kHz region, where early noise damage is often manifest (Coles et al., 2000), and that use of a broadband elicitor might dilute its effects. This reasoning is supported by MEMR findings in a mouse model (Valero et al., 2018), in which sensitivity to synaptopathy was greater with narrowband than broadband stimuli. It is notable that pure-tone thresholds were measurable in the majority of our participants, even at 4 kHz, where thresholds tend to be higher than at lower frequencies (Gelfand, 2009). Other investigators might opt for broadband stimulation, especially in older participants, since it typically produces lower thresholds (Keefe et al., 2010); the present data cannot speak to the reliability of the broadband MEMR.

We also assessed the reliability of a difference measure, comparing thresholds at 1 and 4 kHz. The mouse data of Valero et al. (2018) suggest that such a measure might have value: synapse loss was highly correlated with MEMR threshold when elicitor frequency lay in a synaptopathic region (r = 0.89) and uncorrelated in a lower frequency region (r = 0.17). In the present data, the difference measure exhibited good reliability, nearing excellent.

### 4.4 Purported proxy measures of cochlear synaptopathy do not correlate

We observed no correlations of interest between any of our proxy measures of cochlear synaptopathy. This was despite high reliability of the raw threshold and amplitude measures and use of a sample resembling those of previous studies of synaptopathy in humans. Of the 18 comparisons, two yielded apparent correlations: one that trended in the predicted direction but was marginal, and one that opposed the predicted relation; neither would withstand correction for multiple comparisons. Hence, we find no evidence that any of the measures assess the same underlying physiological processes. Of course, our sample size was small, and it is possible that correlations might have been evident with a greater number of participants. However, it is notable that even consistent trends are not evident in the data.

The lack of correlation between ABR latency shift in noise and ABR wave I growth contrasts with the findings of Mehsraei et al. (2016), who reported a significant correlation ($r^2 = 0.44\; p = 0.036$, uncorrected). The two studies differ principally in sample size: n=31 in the present study, n=10 in the previous study. The present data for ABR latency shift in noise were also obtained using a higher click level (93 c.f. 80 dB peSPL), though it is unlikely that this factor could reduce sensitivity to synaptopathy. The studies used similar noise levels: Mehsraei and colleagues presented noise at 42, 52, 62, 72, and 82 dB SPL and analyzed whichever conditions produced clear responses, most often 42-62 dB SPL (Mehraei, personal communication, February 2017). Finally, it is worth noting that wave I growth could only be measured in a subset of the participants enrolled by Mehsraei and colleagues, and the resulting growth values are an order of magnitude lower than those of the present study.

Two broad explanations exist for the absence of correlations observed in our data: (a) young women with normal audiograms lack variance in synaptopathy, and (b) most or all of the measures investigated in this study are insensitive to synaptopathy in humans. Possibility (a) should not be discounted. Human ears may possess superior resistance to synaptopathy, given known interspecies differences (Dobie and Humes, 2016). Moreover, some degree of hair-cell loss is often present in animal models of synaptopathy (Hickox et al., 2017); since real-world noise exposure differs greatly from carefully titrated laboratory exposures, synaptopathy in humans without audiometric
loss may be rare. However, as noted in Section 4.2, previous publications have reported possible evidence for synaptopathy in cohorts similar to that of the present study (Bharadwaj et al., 2015; Stamper and Johnson, 2015; Mehraei et al., 2016). Hence, it is important to consider possibility (b), namely that most of the measures used in this study do not index synaptopathy. A logical question, then, is which of the procedures constitute plausible measures of synaptopathy.

The amplitude and growth of ABR wave I have been shown to relate to synaptopathy in numerous animal models. In humans, wave I amplitude is influenced by many sources of variability besides AN function, but can at least be measured reliably. Growth of wave I theoretically offers a means of managing non-synaptopathic variability, thereby offering greater sensitivity to loss of high-threshold fibers. However, our data indicate that this measure exhibits substantially poorer reliability, underpinned largely by measurement error.

ABR latency shift in noise is similarly unreliable and less well validated, but has at least been shown to relate to synaptopathy at the group level (Mehraei et al., 2016). However, it is not clear that, in humans, the shift in wave V latency has its basis in the auditory periphery. Increasing noise levels lead not only to longer wave V latencies but also to longer wave I-V interpeak intervals (Burkard and Hecox, 1987; Gott & Hughes, 1989; Burkard and Sims, 2002). Moreover, Burkard and Hecox saw greater increases in the wave III-V interval than the wave I-III interval, casting further doubt on Mehraei and colleagues' peripheral interpretation. Confidence in wave V latency shift as a measure of synaptopathy would be strengthened by improved understanding of its potential bases in the central auditory system.

Interpretation of EFR measures of synaptopathy is similarly complicated by the issue of central influences. Since the EFR is a sustained response, it combines contributions from a variety of generators (Krishnan, 2006). In animal models, very high modulation rates (~1 kHz) are required to emphasize AN contributions and provide sensitive detection of synaptopathy (Shaheen et al., 2015; Parthasarathy et al., 2017b). Human EFR studies of synaptopathy have used far lower modulation rates (Bharadwaj et al., 2015; Grose et al., 2017; Guest et al., 2018), yielding responses that are likely dominated by higher centers.

MEMR thresholds can be highly reliable in humans and have been shown to correlate closely with synaptic survival in mice (Valero et al., 2018). A shortcoming of these measurements in humans is that between-subject variability – likely due to factors besides synaptopathy – is extremely high: in the present cohort, 1 kHz thresholds spanned a 24 dB range. Our across-frequency difference measure, which was designed to manage this variability, is highly reliable. However, validity of the difference measure rests on the assumption that thresholds at 1 and 4 kHz are not differentially affected by factors other than synaptopathy, and this is by no means certain. The high thresholds observed in some participants at 4 kHz might reflect synaptopathy; alternatively, they might reflect other factors that vary across frequency, such as reflex adaptation (Gelfand, 2009) or differences in pre-neural function.

5 Conclusion

The number of proxy measures of cochlear synaptopathy employed in humans has exploded in recent years, extending into double figures. Here, we investigated the reliability and interrelations of several of these measures, in a cohort of young, audiometrically normal women. Results indicate that raw ABR and EFR amplitudes can be highly reliable, given careful measurement techniques, as can MEMR thresholds. In contrast, all differential ABR and EFR measures exhibited poor or near-to-poor reliability. No significant correlations were evident between measures, despite their application in a sample resembling those of previous studies reporting possible evidence for synaptopathy. These findings suggest that many proxy measures of cochlear synaptopathy should be regarded with caution, at least when employed in young adults with normal audiograms.

Acknowledgments

This research was funded by The Marston Family Foundation and Action on Hearing Loss, with support from the Medical Research Council UK (MR/L003589/1) and the NIHR Manchester Biomedical Research Centre.

References


4 SUMMARY & FUTURE DIRECTIONS

Contrary to expectations, our research has uncovered no evidence for cochlear synaptopathy in relation to tinnitus or SPiN impairment. Tinnitus and SPiN impairment were strictly defined. Electrophysiological recordings were of high quality, yielding highly reliable ABR and EFR amplitudes. Great care was taken to prevent confounding by sex, age, and audiometric acuity.

Our negative tinnitus findings contrast with several positive reports. However, as outlined in Sections 1.2.1, 3.2, and 3.3, control of potential confounds in those studies was incomplete. One possibility is that loss of basal sensitivity was a confound in the previous studies, influencing both tinnitus generation and measures of AN function. However, it is important to consider that EHF hearing loss might be a biomarker for synaptopathy at lower frequencies. In order to understand whether such loss is a marker or a mimic of synaptopathy, future researchers should perhaps allow EHF audiometric thresholds to vary freely, but prevent their influence on measures of synaptopathy through the use of high-pass masking noise.

Another possibility is that our tinnitus cohort were too young to have developed significant synaptopathy. Participants were, on average, 10 years younger than those in Schaette and McAlpine (2011), 16 years younger than in Gu et al. (2012), and 20 years younger than in Wojtczak et al. (2017). Perhaps synaptopathy in humans cannot be induced by noise exposure alone, occurring instead as a result of ageing, or of interactions between ageing and noise exposure. Hence, future research in an older age group might be of value. Investigation of age-related changes in susceptibility to tinnitus might also be warranted. One approach would be to seek information on noise exposure history and tinnitus onset in a large sample, investigating whether development of tinnitus depends not only on quantity of noise exposure but also the age at which exposures were incurred.

One hint at the existence of ‘hidden’ hearing damage is the relation we observed between tinnitus and noise exposure, despite close audiometric matching between groups. Excessive noise exposure does appear capable of inducing changes to the auditory system that can lead to tinnitus, without altering hearing sensitivity. However, the nature of the damage is unclear; it does not appear to impact AN function, at least as measured by the ABR and EFR. It is conceivable that noise-induced changes may take place in more central auditory structures. In any case, there may be value in conducting future research involving the subset of tinnitus cases that are specifically noise-induced.

In contrast, our SPiN-impairment study revealed no links to noise exposure, nor to electrophysiological measures of synaptopathy. As outlined in Section 4.4, these findings mostly accord with the existing literature, though our study was the first to seek evidence of synaptopathy in a cohort with significant perceptual impairment. Our null results in relation to SPiN are perhaps unsurprising. Some models suggest that synaptopathy should have minimal effects on perception, and SPiN ability is influenced by a vast array of factors besides AN function. Even if synaptopathy
manifests in humans, its effects might be dwarfed by variability in other factors. Future research could perhaps look for synaptopathy in older age range, as in tinnitus research, but culprits other than synaptopathy should also be sought.

Finally, our project has highlighted some of the complications involved in measuring AN function and noise exposure in humans. In Section 3.5, we showed that differential ABR and EFR measures exhibit poor reliability—far lower than that of raw amplitude measures. The excellent reliability of MEMR thresholds is encouraging, especially given their superior sensitivity to synaptopathy in animals. However, as with ABR and EFR amplitudes, they are likely sensitive to a wide range of factors besides synaptopathy, limiting their utility; improved understanding of non-synaptopathic sources of variability is needed. The absence in our data of correlations between measures—or even consistent trends—is disconcerting, though such relations might be evident in a larger sample. Taken together, findings suggest that proxy measures of synaptopathy in humans deserve greater scrutiny. Given their uncertain validity, and often very high sound levels, we ought to be alert to the possibility that human synaptopathy research is doing more to cause subclinical hearing damage than to elucidate it.

Quantification of lifetime noise exposure has its own challenges. Exacerbating the inherent inaccuracy of retrospective self-report is the incompleteness of many existing self-report procedures. In developing the NESI, we have attempted to combine some promising methods into a comprehensive instrument, but evaluation will certainly be necessary. Validation of the method for estimating sound level in recreational settings should be a priority, but more extensive evaluation of the NESI would be preferable, perhaps capitalising on new technologies to conduct long-term measurements of personal noise exposure. It is, of course, possible that the results of these evaluations will show that radical revisions to the procedures are required; all the same, publication of the instrument is a step in the right direction.
REFERENCES


