Signs of noise-induced neural degeneration in humans

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Animal studies demonstrated that noise exposure causes a primary and selective loss of auditory-nerve fibres with low spontaneous firing rate. This neuronal impairment, if also present in humans, can be assumed to affect the processing of supra-threshold stimuli, especially in the presence of background noise, while leaving the processing of low-level stimuli unaffected. The purpose of this study was to investigate if signs of such primary neural damage from noise-exposure could also be found in noise-exposed human individuals. It was investigated: (1) if noise-exposed listeners with hearing thresholds within the "normal" range perform poorer, in terms of their speech recognition threshold in noise (SRTN), and (2) if auditory brainstem responses (ABR) reveal lower amplitude of wave I in the noise-exposed listeners. A test group of noise/music-exposed individuals and a control group were recruited. All subjects were between 18-32 years of age and had pure-tone thresholds ≤ 15 dB HL from 250-8000 Hz. Despite normal pure-tone thresholds, the noise-exposed listeners required a significantly better signal-to-noise ratio to obtain SRTN, compared to the control group. The ABR results showed significantly lower amplitude of wave I, in the left-ear, of the test group listeners. Significantly higher wave III and normal wave V were also found in the left ear of the test group listeners suggesting a compensated neural gain in the brainstem. Overall, the results from this study seem to suggest that noise exposure affects supra-threshold processing in humans before pure-tone sensitivity, raising suspicion to the hypothesis of primary neural involvement.

INTRODUCTION

For decades the outer hair cells (OHCs) have been presumed to be the primary targets of noise-exposure (Spoendlin, 1971; Lawner *et al.*, 1997), and the first auditory symptom has been assumed to be elevated pure-tone thresholds, showing a dip/noise-notch around 4 kHz. However, our current knowledge of noise-induced hearing loss is now questioned both in regards to the pathology, but also in respect to the perceptual consequences of the damage. Recent research on animal models (mice and guinea pigs) has suggested that noise exposure causing only a temporary

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threshold shift (TTS) can lead to primary and extensive damage of the afferent type I nerve fibres innervating the inner hair cells (IHCs), despite the recovery of pure-tone thresholds and no evidence of OHC and IHC loss (Kujawa and Liberman, 2009; Lin *et al.*, 2011; Furman *et al.*, 2013). Also, despite normalisation of the pure-tone thresholds the wave-I component of the auditory brainstem response (ABR) in response to supra-threshold stimuli (80 dB nHL) was found to be significantly reduced in the exposed animals. This reduction is assumed to reflect that fewer peripheral afferent nerve fibres fire synchronously in response to supra-threshold sound stimuli, supporting that noise-exposure causing a TTS can cause primary damage of the peripheral synapses and nerve fibres impairing only supra-threshold processing. This synaptic and neural damage seems to be of progressive nature causing a slow degeneration of the spiral ganglion cells (Kujawa and Liberman, 2009). For the remainder of this document this noise-induced neural damage will be referred to as noise-induced neural degeneration (NIND).

In 2013, Furman *et al.* further documented this NIND to be selective of the nerve fibres with low spontaneous firing rate, i.e., low spontaneous rate fibres (LSRFs), while leaving the high-spontaneous rate fibres (HSRFs) unaffected. This finding provides a physiological explanation to why NIND does not affect pure-tone sensitivity, but primarily affects supra-threshold processing. The HSRFs, found to be largely unaffected (Furman *et al.*, 2013), are responsible for the coding of low-intensity stimuli (Liberman, 1978; Taberner and Liberman, 2005). However, the LSRFs that are suggested to be the primary targets of noise-exposure (Furman *et al.*, 2013) are responsible for the coding of mid- to high-intensity stimuli (Liberman, 1978; Taberner and Liberman, 2005). In addition to coding supra-threshold stimuli, LSRFs have been suggested to have greater resistance to the limitations of saturation that can occur in the presence of high background noise levels (Costalupes *et al.*, 1984). This suggests the LSRFs to be important for the processing of auditory stimuli in the presence of high-level background noise. Thus, assuming acoustic overexposure also causes primary NIND of the LSRFs in humans, it can be hypothesised that the first signs of a noise-induced hearing impairment is supra-threshold processing difficulties, and not elevated pure-tone thresholds.

Signs of a disorder impairing only supra-threshold processing without affecting pure-tone thresholds have been documented in humans before and it has been referred to as, e.g., the "King-Kopetzky Syndrome" (KKS; Zhao and Stephens, 1996) or more recently as "hidden hearing loss" (Schaette and McAlpine, 2011). The main symptom of KKS is difficulties with speech in noise despite normal pure-tone thresholds (Zhao and Stephens, 1996). Based on the characteristics of LSRFs this deficit can also be assumed to occur in response to NIND.

The goal of the current study was to investigate if signs of NIND could also be documented in humans with a history of acoustic exposure, and if this damage could potentially be linked to the diagnosis of KKS/hidden hearing loss. Using a combination of supra-threshold behavioral tests and electrophysiological measures we set out to test (1) if a test group with a history of acoustic exposure needs a better signal-noise-ratio (SNR) to understand speech in noise, compared to a control group,

with no history of acoustic exposure despite pure-tone thresholds ≤ 15 dB HL in all subjects, and (2) if the test group has lower amplitudes of the wave-I component of their ABR compared to the control group.

METHOD

Two groups (a test and a control group) of young normal hearing listeners between 18-32 years of age and with pure-tone thresholds < 20 dB HL from 250-8000 Hz were recruited and participated in the study. The listeners were classified and divided into groups based on their present and/or past experience working in noise or music exposure. Thorough questioning regarding acoustic exposure was always completed with each listener to ensure that the control group listeners had not been exposed to any longer lasting acoustic exposures. Control group listeners with large scale usage of MP3 players or similar exposures were excluded from the study. The control group consisted of listeners with no work-related acoustic exposure. The test group listeners however, represented listeners with a history of acoustic over-exposure from their work environment. Work-related acoustic overexposure was defined as a work environment with a level of noise or music so loud that the listener felt that it would be necessary to raise his or her voice in order to conduct a conversation. Furthermore a test group with listeners categorized as having a history of acoustic exposure had to have worked in this noise or music for at least 5 hours a day, 5 days a week, for at least 6 months. The test group listeners consisted mainly of professional musicians (14 out of 16) that were recruited from the Royal Danish Navy Band. The test group consisted of 16 listeners (12 men, 4 women), with a history of acoustic exposure from their workplace. The control group consisted of 16 listeners (12 men, 4 women) with no history of acoustic exposure.

Procedure and materials

All listeners completed a test session of 2 hours. Initially a questionnaire was filled out together with the researcher. Otoscopy was performed. Pure-tone audiometry was conducted for frequencies 250-8000 Hz in a double-walled sound-proof booth, using a GN Otometrics Madsen Astera Audiometer and Sennheiser HDA 200 circumaural earphones. Speech recognition thresholds (SRTs) and word recognition score in quiet were also measured, using the "Dantale I" material, to ensure normal hearing and processing of speech in quiet.

The speech material "Dantale II" (Wagener *et al.*, 2003) was applied for testing SRTs in noise (SRTN), to investigate if the test group listeners needed a better dB SNR, compared to the control subjects, to obtain 50% speech intelligibility in noise. The speech and noise signal were presented binaurally in the sound-field environment of the sound booth with the listener seated in the center between 5 loudspeakers. The speech signal was presented from a front loudspeaker (0° azimuth), and the noise was presented from two speakers at ± 45° and two at ± 135° azimuth. Each new session started with a SNR of 0 dB SNR, i.e. a noise level of 70 dB SPL and speech at 70 dB SPL. The noise level was kept at a constant level of 70 dB SPL while the speech presentation level was adjusted according to the

number of words repeated correctly in each sentence. Three training lists of 10 sentences each were always completed to familiarize the test subject with the material. The speech recognition threshold in noise was calculated from the subsequent sentences by adding the presentation levels from sentences 12-31 together, dividing by 20, and then subtracting the noise level giving the final result in dB SNR.

The measure of ABR was performed using the Interacoustics Eclipse ABR system (EP15/EP25). Disposable non-invasive electrodes were used for this purpose. Inverting electrodes were attached to the mastoids, a non-inverting electrode was placed on the middle of the forehead just below the hairline, and the ground electrode was placed just below the non-inverting electrode. An impedance of maximum 3 kΩ was always ensured. Click stimuli at a level of 90 dB nHL were presented with alternating polarity at a rate of 16.1/s through ER-3A insert earphones. A time window of 0-20 ms was used and 4000 sweeps were completed for all listeners. Amplitudes of wave I, III and V were measured from peak to following trough.

RESULTS

The statistical method "Mann-Whitney *U*" was applied to investigate significant differences between the two groups. As expected the measures of speech recognition threshold in noise showed a significant difference ($p < 0.001$) between the two groups, despite normal pure-tone thresholds in all the listeners. The test group listeners needed a significantly higher speech level to recognize 50% of the speech material in noise. Figure 1 shows the SRTN data for both groups. From this figure it is seen that the test group listeners generally required a higher presentation level of the speech signal to obtain their SRTN compared to the control group.

For the ABR a significant difference of the wave amplitudes could only be documented from the left ear between the two groups. Significantly lower wave I amplitudes ($p < 0.05$) were documented from the left ear of the test subjects (M = 0.253 μV, SD = 0.107) compared to the control subjects (M = 0.326 μV, SD = 0. 092). Further analysis of the left ear ABR amplitudes showed the opposite tendency for the subsequent wave III amplitudes. The test group had significantly higher amplitude ($p < 0.05$) of wave III (M = 0.431 μV) compared to the control group (M = 0.344 μV). For wave V no significant difference was observed between the two groups. The amplitudes of wave I and III for the two groups are displayed in Fig. 2, panels A and B.

DISCUSSION

The SRTN results confirmed that the noise-exposed test group listeners needed a significantly higher speech level to recognize 50% of a speech signal in noise. This result cannot be regarded as an effect of impaired pure-tone sensitivity as normal pure-tone sensitivity (pure-tone thresholds ≤ 15 dB HL) was documented only minutes prior to the measure of SRTN. This finding could thus be assumed to reflect NIND affecting processing of supra-threshold stimuli in background noise.

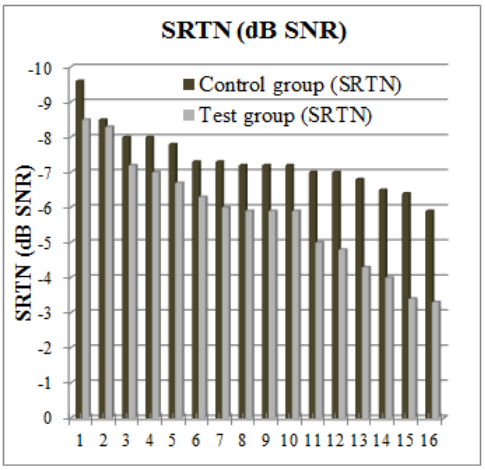

Fig. 1: The SRTN data for both groups arranged from smallest to highest value (dB SNR). The light grey pillars reflect data from the test group listeners and the dark represent the data from the control group. The height of the pillars reflect the level by which the speech signal could be reduced compared to the noise level (70 dB SPL), while still recognizing 50% of the speech.

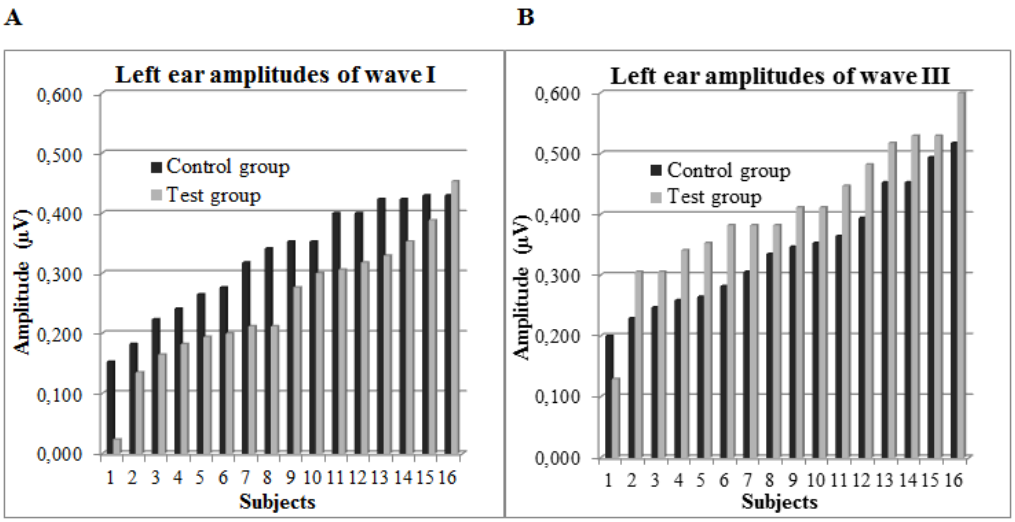

Fig. 2: Left ear ABR amplitudes of wave I and III across test and control listeners, arranged from smallest to highest value (µV). The left side (panel A) reflects the wave I amplitudes, and the right (panel B) reflects the amplitudes of wave III in response to a 90 dB nHL click. The light grey pillars reflect data from the test group and the dark pillars represent the control group.

ABR was measured to acquire objective and physiological evidence of NIND. It was hypothesised that the test group would present with lower amplitudes of the wave-I component reflecting reduced neural synchrony. The results of the ABR measurements did in fact confirm the anticipated hypothesis. Significantly lower amplitudes of wave I were found in the left ear of the test group listeners. However, no statistically significant difference was documented from the right ear. With the hypothesis only confirmed for the left ear, it can be questioned whether this asymmetric finding reflects NIND, or if it is merely a coincidence or an error. It can be argued that the asymmetry could be a potential consequence of using professional musicians in the test group. Musicians cannot be expected to be evenly exposed on each ear, thus symmetric NIND cannot be expected. Also, there have been findings suggesting the left ear to be more vulnerable to noise damage than the right ear. Binaural noise exposure has been shown to cause more severe TTS on the left ear compared to the right (Pirilä, 1991). Furthermore, tinnitus which is a common consequence of acoustic overexposure (Palmer *et al.*, 2002) has also been suggested to be more common in the left ear (Axelson and Ringdahl, 1989). Also, greater efferent activity of the medial olivocochlear bundle (MOCB) has been indicated on the right ear (Bidelman and Bhagat, 2015) and this right ear efferent activity has furthermore been suggested to be greater in musicians vs. non-musicians (Micheyl *et al.*, 1997). The MOCB has been shown to have a protective role of the ear against noise exposure (Maison *et al.*, 2013). Thus, it can be speculated that the majority of the test group listeners have greater protection against acoustic exposure from the efferent MOCB on the right ear, providing a potential explanation to why signs of NIND were only indicated from the measures of the left-ear ABR. This is highly speculative and more research is needed to explain this asymmetric finding. It cannot be affirmed with certainty that the findings of poorer SRTN and lower amplitudes of wave I in the test group is caused by NIND.

Despite the asymmetry of the findings and the lack of correlation between the scores of SRTN and the wave-I amplitudes, there are still findings raising suspicion that NIND is the potential contributor of these results. Findings of significantly enhanced wave-III amplitudes of the left ear ABR of the test group listeners can potentially support the findings of poorer SRTN and lower wave I amplitudes to be a result of NIND. Decreased synchronous sound evoked activity in the auditory nerve (reflected as a reduced wave I amplitude), as a result of loss of LSRFs has been found to lead to a compensated neural gain (hyperactivity) in the brainstem (Hickox and Liberman, 2014; Knipper *et al.*, 2013; Schaette and McAlpine, 2011). This pathological increase in the response gain is reflected in the ABR as normal or increased amplitudes of waves III and V in the presence of reduced amplitude of wave I. In the current test group with reduced amplitude of wave I, wave III was significantly enhanced in the left ear and wave V showed no significant difference between the two groups. In the presence of the significantly reduced wave-I amplitudes of the test group, the enhanced wave III and normalised wave V can be suggested to reflect compensated neural gain in the brainstem in the response to NIND. However, the results must still be analysed with caution as there are

limitations of this study. Factors such as the exposure characteristics (duration, level, etc.), environmental differences and genetic factors are not accounted for or controlled. With the spiral ganglion cell (SGC) loss suggested to be slowly progressive over many years, the time elapsed since the initial exposure could play a role in the magnitude of the SGC loss. Thus, some test group listeners may suffer more progressed NIND than others while a few may have no NIND at all, despite a somewhat similar type of acoustic exposure in the test group (14 from the same workplace). Also, with no objective measure of the work-related exposure level of the test group listeners, it cannot be proven that the test group has been exposed to damaging levels and durations. However, the results do show significant deviations of supra-threshold processing in the test group listeners with a history of working in acoustic exposure compared to the control listeners with no reported history of acoustic exposure. It can thus be argued that these findings, despite not knowing the exact levels of the exposure, are a result of an exposure severe enough to affect supra-threshold processing of the left ear, suggested here to be perhaps the most vulnerable ear to noise exposure, and thus suggest NIND.

In conclusion, the test group listeners with a history of acoustic overexposure were found to need significantly higher SNRs to recognise 50% of a speech signal in noise despite normal pure-tone sensitivity. They also showed significantly reduced wave-I amplitudes of the left ear ABR. In the presence of pure-tone thresholds ≤ 15 dB HL and signs of compensatory neural gain in the brainstem (i.e., enhanced amplitude of wave III) which is found to accompany loss of LSRFs, these findings of lowered wave-I amplitudes and poorer SRTN can be suggested to reflect signs of NIND in the test group. This study cannot proclaim NIND in human listeners. However, it does show signs of impairments in agreement with the pathology of NIND in listeners with a history of acoustic overexposure. Thus these results can support the possibility that acoustic overexposure can also lead to NIND in humans. This study implicates the need of more research towards exploring this pathology and the potential auditory consequences in humans.

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