Despite the common occurrence of potentially synaptopathic noise levels in everyday occupational and recreational settings, and emerging evidence of noise-induced synaptopathy in our non-human primate cousins (Valero et al., 2017), and in normally-aged human post-mortem tissue (Wu et al., 2018), the prevalence of cochlear synaptopathy in humans and its contributions to perceptual deficits remains unknown.

In order to understand the perceptual consequences of cochlear synaptopathy, it is essential to combine physiological measures of synaptopathy with perceptual measures in the same individuals. One strategy to achieve this would be to perform behavioral measurements in animal models in which synaptopathy can be directly assessed using microscopy and immunolabeling. However, it is possible that the behavioral consequences in relatively simple tasks are weak (e.g., see Oxenham, 2016) and that more complex listening conditions need to be created for the functional deficits to be apparent (Bharadwaj et al., 2014; Plack et al., 2014), rendering behavioral measurement in non-human animal models challenging. An alternate strategy, is to use non-invasive physiological assays that are putative correlates of synaptopathy in behaving humans and compare these measures to perceptual performance. Considerable effort is currently directed towards this enterprise by the hearing-research community.

The notion of comparing physiological correlates of processing in the early parts of the auditory pathway to auditory perception is not new. Indeed, otoacoustic emissions (OAEs), the auditory brainstem response (ABR), and the auditory steady-state response (ASSR), can each be used to estimate a

suprathreshold ABR amplitude is a candidate non-invasive measure of synaptopathy. However, absolute ABR amplitudes do not appear reliable as a diagnostic in more genetically heterogeneous animals. For instance, in a genetically heterogeneous cohort of guinea pigs with similar levels of synaptopathy as in the CBA/CaJ mice, absolute ABR amplitudes did not predict synaptopathic damage; only when suprathreshold ABR amplitude reductions (relative to pre-exposure amplitudes in the same ears) were computed were the ABR measurements related to synaptopathy (Lin et al., 2011; Furman et al., 2013). This suggests genetic heterogeneity can contribute variability to measures of absolute ABR wave I amplitude that is not easily normalized out in humans. In aging mice where immonolabeling showed cochlear synaptopathy, suprathreshold ABR wave I amplitudes were reduced in a manner similar to that found in noise-exposed mice. However, the relationship between synaptopathy and the ABR was most robust when the wave I amplitudes were normalized by the summating potential (SP; Sergeyenko et al., 2013). These observations suggest that some normalization procedure that reduces other sources of variability could be important when trying to interpret ABR measures.

In humans with tinnitus despite normal audiograms, Schaette and McAlpine (2011) reported that ABR wave I amplitude, normalized by wave V amplitude was reduced. This was interpreted as evidence of deafferentation at the auditory nerve level where wave I is thought to originate, and a compensatory “central gain” at the level of the midbrain where wave V is thought to originate. A similar result was found in mice with altered startle response properties following deafferentwam(res)15(ea)ng ne20291(orig)uu8(ob)2suo8(by)-358(w)-9(av)51B.L3.-9obwasreseaewasudes heen(l)-32u((to)-291(orig)19(e3w)12

Badri et al., 2011). This raises the question of whether audibility in those frequencies is intrinsically important for speech-in-noise perception, or whether threshold elevation at those frequencies is a marker for other damage, including cochlear synaptopathy at lower frequencies.

To disambiguate between the two competing interpretations for the correlation between the ABR and extended-high-frequency audiograms, the most direct test would be to compare the ABR amplitudes in animals with and without OHC loss in the hook region, and with and without broader cochlear synaptopathy, if at all such selective damage is achievable. The correct interpretation of the correlations is likely a combination of both of these views, with no strong evidence yet to support one view more than the other. In either of those cases, however, this extraneous factor of high-frequency OHC loss should be considered. One approach to circumnavigate this issue for the purpose of assaying cochlear synaptopathy would be to "regress out" (or otherwise statistically account for) the audiometric variations beyond 8 kHz from ABR measures. Any residual relationship between the ABR and risk factors such as noise-exposure and age can then be reasonably attributed to mechanisms distinct from OHC damage. However, this approach is likely too conservative because cochlear synaptopathy is correlated with OHC damage, and regressing out audiograms might attenuate the effects attributed to syanptopathy. This might contribute to an elevated rate of false negatives, i.e., a bias towards reporting a lack of correlation between ABR and noise exposure, or ABR and age. Nonetheless, measuring audiograms beyond 8 kHz would be useful in studies involving any cohorts of human subjects that are at risk for synaptopathy.

[illegible]

It is well known that the acoustic pressure and intensity of stimuli delivered to the ear can depend on the immittance properties of the outer and the middle-ear. Accordingly, calibration procedures of supra-aural, circum-aural, and insert ear-

significantly higher (= .0005), likely reflecting ear-canal filtering effects. Thus, when frequency-specific assessment is desired, we recommend that FPL-based calibrations be employed for assays of cochlear synaptopathy.

Discussion

Assays of suprathreshold hearing in humans, by virtue of being non-invasive, reflect population responses along the auditory pathway. Thus, in addition to the response properties of sin-

(Don and Eggermont, 1978). Here we illustrate this issue by comparing the relative amplitudes of wave I and wave V (i.e., the I/V amplitude ratio) for conventional broadband clicks and clicks that are high-pass filtered at 3 kHz. Stimuli in both cases were delivered at 80 dB above the detection thresholds for three pilot subjects. The broadband click level was comparable to standard 80 dB nHL clicks in intensity.

described in Bharadwaj and Shinn-Cunningham (2014). The multichannel EEG-based rankings are shown in Table 1 (bottom row) and correspond to a rank correlation of 85% (= .002) with MEG rankings. Note that rank correlations rather than Pearson correlations are reported here because test–retest rank correlation of absolute EFR amplitudes (i.e., measures on the same individuals in two separate sessions with EEG) tend to be 100%, whereas test–retest Pearson correlations are lower. The MEG-EEG comparisons suggest that

sleep and compare them to 600 trials where they were awake. The magnitudes were indistinguishable from each other with an across-subject Pearson correlation of 0.98. The noise fl

motivate strategies that may help mitigate them. While factors such as cochlear mechanical dispersion, audiometric loss at extended high frequencies, anatomical factors, and the stereotypical spectral response profile for the MEMR may be individual specific (and hence repeatable in a given individual), they nonetheless can obscure the effects of cochlear synaptopathy. Thus, a high degree of test–retest reliability by itself is insufficient for a candidate assay. The true test of whether a measure is potentially a good assay is whether the measure can capture individual variations in synaptopathy over and beyond the variance that is imposed by the host of extraneous variables. Indeed, by using methods that should mitigate the effects of some of these extraneous variables, we showed that the ABR wave I/wave V ratio for high-pass clicks, the wideband MEMR elicited by FPL-calibrated high-pass noise, and the modulation depth-dependence of the EFR elicited by modulated high-pass noise exhibit correlations with each other. This raises the possibility that cochlear synaptopathy might indeed be a widespread occurrence in humans – even those with normal hearing thresholds in ranges tested by typical audiometric screenings – and that the variations in the degree of synaptopathy might be the common factor resulting in correlations between these measures. Whether this is the case or not should be carefully explored in future studies. One line of investigation that would be particularly useful is to study these candidate non-invasive assays in genetically heterogeneous groups of animals where synaptopathy can be directly assayed using immunolabeling, and then comparing these metrics to the degree of synaptopathy observed.

For understanding of the prevalence and consequences of cochlear synaptopathy in humans, it is useful to separately consider those two aspects of the question, i.e., (1) Does synapto-

performance may be limited by “informational masking” (Brungart et al., 2006). Some studies that did

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