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Envelope following responses, noise exposure, and evidence of cochlear synaptopathy in humans: Correction and comment

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Abstract: A correction and comment are provided for a recent article by Paul, Waheed, Bruce, and Roberts [(2017). J. Acoust. Soc. Am. **142**(5), EL434–EL440].

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The envelope following response (EFR) evoked by stimulation rates >80 Hz has been suggested to be sensitive to the loss of low-spontaneous rate (low-SR) cochlear synapses following noise exposure (Bharadwaj *et al.*, 2014; Bharadwaj *et al.*, 2015; Paul *et al.*, 2017a). Paul *et al.* (2017b) examined the EFR evoked in three narrowband background noise (NBN) conditions that increased in level such that the contribution of high-spontaneous rate (high-SR) synapses to AM encoding should have been progressively suppressed. The aim was to determine if young adults (aged 18 or 19) with more reported noise exposure history had weaker EFRs in background NBN, suggesting low-SR synaptopathy. We note here that our analysis of variance (ANOVA) reported in that study comparing EFR amplitude between high and low noise exposure groups was incorrectly implemented in the MATLAB statistics toolbox.[1] After correction, the probability of a type I error for the main effect shown in Fig. 2(b) of our article increased from $p = 0.029$ to $p = 0.19$. Thus while the EFR magnitude across all conditions expressed in dB signal-to-noise ratio (SNR) was descriptively smaller across all stimulus conditions in the high exposure group, the effect was not significant as measured by an ANOVA.

A challenge in measuring EFRs is to disentangle factors related to the state of cochlear synapses from other sources of variability affecting the response. For example, recording factors such as noise artifacts and EEG channel impedance contribute to the EFR magnitude, as well as individual factors such as head size and the geometry of neural generators of evoked responses (Roberts *et al.*, 2015). A suggested approach to mitigate unwanted sources of EFR variability is to evaluate the response as a relative within-subject measure, for example, the slope of a line fit across several stimulus conditions evoking the EFR (Bharadwaj *et al.*, 2015) or the difference between two conditions of background noise (Paul *et al.*, 2017a; Roberts *et al.*, 2018). In this way the EFR is "self-normalized" and may better reflect suprathreshold encoding factors rather than the overall magnitude of each person's response (Bressler *et al.*, 2018). Paul *et al.* (2017a) accordingly examined the effect of the EFR evoked in 40 dB spectrum level NBN relative to a quiet baseline, and found that EFRs that were more sensitive to noise had poorer behavioural detection of AM in noise that matched low-SR synaptopathy simulated in a well-established model of the auditory periphery (Zilany *et al.*, 2014).

Considering this practice, we used a linear mixed effects (LME) model to perform a *post hoc* analysis of data from Paul *et al.* (2017b). LME models have the advantage of examining in how several categorical and continuous variables may affect the EFR across different conditions in a within-subjects design (Magezi, 2015). The LME was implemented in the MATLAB statistics toolbox setting the response variable as the EFR in each NBN condition relative to quiet, giving a negative value when the EFR decreased in NBN. Stimulus condition (25, 40, and 45 dB spectrum level NBN), gender, age, high frequency audiogram (audiogram averaged across ears and from 9 to 16 kHz), and noise exposure group (high and low) were treated as fixed effects. Each subject was set as a random intercept, and condition per subject was set as a random slope.

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The LME model results found that the coefficient for stimulus condition was significantly different from zero [$\beta = -1.78$, SE = 0.36, $t(69) = -4.96$, $p < 0.001$]. This result means that the effect of NBN on the EFR increased with increasing NBN spectrum level, as was expected. The grouping variable for noise exposure history approached significance [$\beta = -2.74$, SE = 1.46, $t(69) = -1.88$, $p = 0.064$], suggesting an increased effect of NBN on the EFR in those subjects reporting a history of greater noise exposure. Interestingly, the coefficient for high-frequency audiogram was also significant [$\beta = +0.35$, SE = 0.15, $t(69) = 2.39$, $p = 0.02$], revealing a smaller effect of NBN on the EFR when high-frequency thresholds were elevated. A second model excluding the grouping variable of noise exposure was also calculated. A comparison of the two models by a likelihood ratio test approached significance [$\chi^2(1) = 3.3$, $p = 0.068$].

Because high-SR fibers tend to become fully saturated at around 40 dB sound pressure level (Costalupes, 1985), a NBN of this spectrum level may be the optimal point for separating contributions of on-band high-SR from low-SR synapse contributions to AM encoding. As mentioned above, Paul *et al.* (2017a) found that individuals with EFRs more degraded in 40 dB NBN had poorer behavioural detection of 19 Hz AM in the same background noise. Because of this precedent, using data from Paul *et al.* (2017b) we evaluated the EFR in 40 dB NBN relative to quiet as the sole response variable in a fixed effects model, treating noise exposure group, age, gender, and high-frequency audiogram as fixed effects. The only coefficient significantly different from zero was the noise exposure grouping [$\beta = -4.06$, SE = 1.84, $t(20) = -2.21$, $p = 0.039$]. This result suggests that with increasing noise exposure history, fewer low-SR fibers were available to support AM coding in quiet, such that coding was dependent on high-SR fibers. Thus, when the NBN saturated the high-SR fibers, a larger drop in EFR was produced than in subjects with less noise exposure history. Comparison of an alternative model excluding the noise exposure grouping was significantly different from the model including noise exposure group [$\chi^2(1) = 4.5$, $p = 0.034$]. Separate models considering these fixed effects on response variables of 25 and 45 dB NBN did not reveal noise exposure effects reaching significance. A possible explanation for these results is that the 25 dB spectrum level NBN may not be sufficient to suppress contributions from high-SR fibers that are presumed to be proportionally healthier in both noise exposure groups. At an NBN level of 40 dB, the on-band high-SR and low-SR contributions may be optimally separated such that changes in the extent of low-SR synaptopathy can be inferred from the susceptibility of the EFR to background noise. The 45 dB spectrum level NBN could have degraded additional low-SR fiber contributions beyond saturation of high-SR synapses such that the effect of low-SR loss on the EFR was obscured.

We conclude by suggesting that the effect of young adults' lifetime noise exposure history on subcortical AM encoding in background noise may be best expressed in conditions in which contributions from noise-susceptible low-SR synapses are separated from those of high-SR synapses that are less vulnerable (e.g., 40 dB NBN). This conclusion results from the above follow-up analysis of data reported in Paul *et al.* (2017b) and requires further testing.

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[1]We thank Christopher Plack for calling our attention to the potential problem.

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