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Erratum and comment: Envelope following responses in normal hearing and in tinnitus

The envelope following response (EFR) is a response generated primarily by sources in the auditory midbrain when sounds are amplitude modulated (AM) at rates exceeding ~85 Hz. Recently the response has been used to probe neural differences between normal hearing subjects with and without tinnitus. We report here that our analysis of variance reported in Paul et al. (2017) comparing EFR amplitude between tinnitus and control subjects was incorrectly implemented in Matlab.¹ When corrected the probability of a Type I error for the main effect shown in Fig. 3b of our article increased from $p = 0.029$ to $p = 0.207$ ($p = 0.163$ for the quiet condition only). Correction brings our results into qualitative agreement with those of Guest et al. (2017) who found the EFR trending nonsignificantly lower in a large sample of tinnitus compared to control subjects also in quiet ($p = 0.10$). It appears that EFR amplitude tends to be smaller in tinnitus than control subjects, but overall group comparisons do not reach statistical significance.

We suggest here that this outcome may reflect the multi-determined nature of the EFR. Factors such as synaptopathy (Shaheen et al., 2015) and tinnitus-related neural noise (Roberts et al., 2015; Galazyuk et al., 2017) that impair neural phase locking in auditory pathways (thus reducing EFR amplitude) may be offset by other factors such as increased central gain (Schaeffe and McAlpine, 2011; Gu et al., 2012; Auerbach et al., 2014) and thalamo-cortical modulation of midbrain EFR generators (Asokan et al., 2017) that may increase the EFR when deafferentation is present. If so, comparisons of EFR amplitude between groups will depend on which of these factors contributes most to the EFR, with synaptopathy being one such factor identified by animal models of hidden hearing loss (Shaheen et al., 2015). Additionally, differences between human subjects in the sources and orientation of neural generators may increase between-subject variability (Roberts et al., 2015) and further impede the detection of group differences in EFR amplitude.

In contrast to the ambiguity of the sources of between-group differences in EFR amplitude, group differences in the effects of within-subject manipulations that are known to selectively affect a specific factor contributing to the EFR may be more revealing of neural differences between tinnitus and control subjects. Paul et al. (2017) conducted one such test by measuring behavioral and neural coding ability in the presence of narrow band noise (NBN) in tinnitus and control subjects with clinically normal hearing thresholds. The NBN was designed to suppress the contribution of auditory nerve fibers (ANFs) with low thresholds and high rates of spontaneous activity (high-SR fibers) to performance

(Costalupes, 1985) while leaving intact the contribution of ANFs with high thresholds and low rates of spontaneous activity (low-SR fibers, these fibers not saturated by the NBN). First, Paul et al. (2017) measured the ability of tinnitus and control subjects to detect the presence of amplitude modulation in a 5 kHz sound presented at 75 dB SPL in NBN (the 5 kHz sound was in the tinnitus frequency region of the tinnitus subjects). Tinnitus subjects were significantly poorer than controls at this task ($p = 0.016$) suggesting hidden low-SR synaptopathy in the tinnitus group. Next, Paul et al. measured the EFR evoked by the 5 kHz sound (AM at 85 Hz) in quiet where both fiber types were available to code AM, and again in NBN where low-SR fibers were expected to code AM. Paul et al. found that control subjects whose EFRs were reduced most by NBN (“EFR drop”) had poorer AM detection thresholds ($r = 0.45$, $p = 0.027$) than other control subjects. Simulation of the EFR by a well-established peripheral model of the cochlea showed that hidden low-SR synaptopathy was sufficient to explain poor AM coding in the control subjects. If the pattern of synaptic loss observed among controls is the same as that in tinnitus, similar findings would be expected in the tinnitus group. However, the relationship of EFR drop to AM detection thresholds trended in the opposite direction among tinnitus subjects ($r = -0.27$, $p = 0.368$) and differed significantly from that obtained in controls ($p = 0.047$). This result could not be simulated by the peripheral model unless, in addition to severe low-SR fiber loss in the tinnitus subjects, an increasing percentage of high-SR fibers was also removed from the simulation.

Based on these results, Paul et al. (2017) suggested that hidden damage to high-SR fibers adds tinnitus to deficient temporal processing caused by hidden low-SR synaptopathy in subjects with clinically normal hearing thresholds. High-SR synaptopathy would tend to reduce EFR amplitude measured in quiet in a group of tinnitus subjects compared to control subjects, consistent with the group trends reported by Paul et al. (2017) and Guest et al. (2017). However, expression of this difference between groups may be obscured by other factors that contribute to EFR magnitude such as those outlined above.

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