Response to Journal Club

We thank Holmes & Herrmann for their commentary on our paper, in which they highlight the importance of identifying subcortical and cortical sources of the FFR. We agree that the relationship between BOLD activity in the right planum temporale (PT) and the strength of the FFR's fundamental frequency (f0) that we reported does not by itself constitute unequivocal evidence that an FFR signal is being *emitted* by the identified region. As they emphasize, the observed correlation might be explained by a relationship between brainstem phase-locking and a neural correlate of pitch perception in the PT; indeed there is evidence that cortical evoked potentials are correlated with FFR strength (Musacchia et al., 2008).

The finding does, however, point to a role of right auditory cortex in the processing of periodicity that is related to the generation of FFR. In our previous MEG work (Coffey et al., 2016), data did suggest a right-lateralized cortical generator in the same vicinity, but its contribution to the EEG-FFR is unclear. Several papers have since appeared that suggest multiple separable generators are represented in EEG (e.g. Zhang and Gong, 2016; Tichko and Skoe, 2017). We readily agree that more work is needed to clarify the extent to which EEG-FFR captures multiple FFR sources. There are also likely to be descending influences on subcortical channels, especially in the context of plasticity and attention; future efforts should be directed towards disentangling the interplay between cortical and subcortical systems.

Holmes & Herrmann also note that the planum temporale is posterior to areas suggested as having phase-locking properties by previous work. Individual cortical folding patterns and BOLD activation vary considerably in this region. To enhance precise localization of purported cortical FFR generators (i.e. PT vs. Heschl's gyrus), other experimental designs and methodology would perhaps be more revealing, for example intracranial electrodes along the superior temporal gyrus with simultaneous FFR recording, or MEG or high-field fMRI designs that allow FFR-related areas to be identified at the individual level. Notwithstanding, results from our two independent datasets now point towards peri-primary cortex; these areas should therefore be included in future investigations aimed at localization.

Finally, the suggestion that older subjects' FFRs might be 'uncontaminated' by cortical activity is an interesting notion, though without a means of measuring cortical contributions, this line of questioning would run into similar interpretation challenges. However, it should be remembered that nearly all (human) FFR studies have used stimuli that have f0s within the very narrow range of frequencies (~70-300Hz, see Coffey et al., 2016, Supplementary Fig 1) - yet the FFR is correlated with myriad human behaviours, enhancements, and dysfunction. Rather than attempting to isolate 'pure' subcortical FFRs, it may be more productive to 1) develop new methods to explore the interactions of cortical and subcortical processing, and 2) consider the EEG-FFR as a useful window of observability of the auditory system's tuning and functioning before the signal is transformed into non-phase-locked neural code, whether it includes cortical contributions or not.

References

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