

## Journal Club

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## Revisiting the Contribution of Auditory Cortex to Frequency-Following Responses

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Review of Coffey et al.

Human scalp-recorded frequency-following responses (FFRs), also known as auditory steady-state responses, capture neural responses that synchronize with sound periodicities. FFRs are believed to reflect activity from different combinations of neural generators, depending on the stimulation frequency. A long-standing belief is that auditory cortex is the primary generator of FFRs at modulation rates  $\sim 40$  Hz, but that cortical contributions are much weaker for modulation rates faster than  $\sim 70$  Hz. This belief is based on converging evidence from animal electrophysiology (Smith et al., 1975), source modeling of FFRs (Herdman et al., 2002; Bidelman, 2015), and estimations of response latencies (Herdman et al., 2002). Thus, FFRs at 70–150 Hz have been thought to predominantly reflect phase-locked activity in the brainstem.

FFRs at 80–140 Hz are sensitive to cognitive factors, including musical training (Musacchia et al., 2007) and language experience (Krishnan et al., 2009, 2010). These findings have sparked substantial

interest because they have been assumed to demonstrate that brainstem responses are dynamically modulated by experience, a characteristic that has traditionally been thought to be limited to cortex. Yet, an increasing body of converging evidence suggests that cortical activity may indeed contribute to FFRs at these rates. For example, the initial research into the locations of FFR generators (Herdman et al., 2002; Schoonhoven et al., 2003) found that cortical sources, albeit weaker than brainstem, contribute to FFRs at 80–96 Hz, a finding that has recently been corroborated (Coffey et al., 2016). Also, studies using electrocorticography (ECoG) (Nourski et al., 2013) demonstrate that neurons in Heschl's gyrus can phase lock to modulation rates up to 200 Hz. Consistent with these findings, an fMRI study (Giraud et al., 2000) showed that left superior temporal gyrus responds to stimuli with modulation rates up to 256 Hz. Together, these recent studies reignite the long-standing hypothesis that cortical phase-locking could potentially contribute to FFRs at rates for which FFRs are probably dominated by brainstem sources, calling into doubt the claim that modulations of FFRs are attributable to brainstem processing.

A new study published in *The Journal of Neuroscience* (Coffey et al., 2017) used the high spatial resolution of fMRI in combination with EEG to investigate the cortical correlates of EEG-recorded FFRs.

Coffey et al. (2017) presented speech and music stimuli to participants during two separate recording sessions: one EEG and one fMRI. In separate blocks, participants were presented with multiple repetitions of the speech (/da/ syllable) and music (piano tone) stimuli, which had harmonic structures related to a fundamental frequency of 98 Hz. BOLD activity in bilateral auditory cortices was extracted from the fMRI data. The EEG data were used to calculate FFR phase coherence at the fundamental frequency of the stimuli (i.e., 98 Hz). Coffey et al. (2017) found that the magnitude of BOLD activity in right planum temporale increased with greater FFR phase coherence for both the speech and music stimuli. Based on this correlation, the authors conclude that activity from auditory cortex likely contributes to FFRs at 98 Hz.

Coffey et al. (2017) make a novel contribution to the literature by measuring fMRI and EEG-recorded FFRs in the same participants. This is important because scalp EEG, which is currently the most common method for measuring FFRs, is sensitive to different neural responses and/or generators than ECoG (Buzsáki et al., 2012) and MEG (Ahlfors et al., 2010). Therefore, it is unclear whether the cortical sources identified with ECoG and MEG contribute to EEG-recorded FFRs at 70–200 Hz. Linking EEG-recorded FFRs to fMRI activity, which has high spatial resolution, is thus of great value for the quest

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to elucidate the neural generators of FFRs. In the following, we extend the discussion on the relationship between EEG-recorded FFRs and BOLD activity in planum temporale, in the context of putative FFR generators, and we suggest possible avenues for future research.

Comparing previous studies, there seems to be some discrepancy in the cortical regions proposed to contribute to FFRs. Coffey et al. (2017) found correlations between FFR phase coherence and the magnitude of BOLD activity in planum temporale, which is posterior to Heschl's gyrus and has, to our knowledge, not previously been shown to phase lock to stimulus rates as fast as 98 Hz. Critically, phase-locked activity in planum temporale is not the only explanation for the observed correlation. For example, the Coffey et al. (2017) motivation for linking BOLD activity to EEG phase coherence comes from animal work showing that extracellularly recorded local field potentials (which are closely related to EEG signals) are related to BOLD signal magnitude (Goense and Logothetis, 2008; Magri et al., 2012). However, studies examining this relationship have calculated local field potential power instead of phase-locked activity. The precise relationship between neural phase-locking, the BOLD signal, and power and phase coherence values extracted from EEG and local field potential recordings is unclear; thus, greater BOLD activity may not be directly related to stronger EEG phase coherence.

Instead of reflecting phase-locked activity in planum temporale, the observed correlation between FFRs and BOLD activity might be explained by a relationship between the precision of brainstem phase-locking and a neural correlate of pitch perception in planum temporale. Greater phase locking at lower levels of the auditory pathway (which would give rise to greater FFR phase coherence) could enhance representations of pitch (Gockel et al., 2011), leading to greater BOLD activity in planum temporale without changes in cortical phase-locking. Importantly, fMRI will pick up on any activity that is correlated with changes in FFRs, which may differ from the activity that underlies FFRs. Thus, correlations between FFRs and BOLD activity do not necessitate planum temporale contributions to FFRs.

Furthermore, the degree to which phase-locked neural activity in auditory cortex is inherited from subcortical (e.g., brainstem) structures is not fully understood. A likely scenario is that phase-locked brainstem activity feeds forward to cortical

structures, albeit likely with weaker phase-locking higher up the auditory pathway. Coffey et al. (2017) only analyzed BOLD activity in auditory cortex; thus, the extent to which subcortical BOLD activity correlates with EEG-recorded FFRs is unknown. Under the assumption that only brainstem generators contribute to FFRs, correlations with cortical activity may arise due to inherent correlations between neural responses at different stages of auditory processing. Future studies linking both subcortical and cortical activity to EEG-recorded FFRs are necessary to improve understanding of the relative strengths of brainstem and cortical contributions.

Experiments examining FFRs in older people might be useful for providing another perspective on neural generators of FFRs and for examining the sensitivity of brainstem activity to experience. FFRs to sounds with modulation rates of 100–400 Hz are commonly reduced (but present) in older people (Purcell et al., 2004; Anderson et al., 2012). Animal studies suggest that age-related reductions in FFRs occur in subcortical brain regions, for example, in the inferior colliculus (Shaddock Palombi et al., 2001; Herrmann et al., 2017). Reduced subcortical phase-locking will reduce the phase-locked information that is fed forward to auditory cortex; hence, the neural generators of FFRs may be different in older than younger people. Given that cortical contributions to FFRs >70 Hz are likely small even in younger people, it is possible that reduced phase-locking in older people may cause cortical contributions to be absent in FFRs >70 Hz. Thus, it would be interesting for future studies to compare the neural generators of FFRs in younger and older people. If cortical contributions are much weaker in older individuals, this finding might inspire future studies to examine experience-dependent modulations of brainstem processing by measuring FFRs in older people who have accumulated a lifetime of experience but whose FFRs might be uncontaminated by cortical activity.

In conclusion, Coffey et al. (2017) contribute to the reemerging question of whether cortical activity contributes meaningfully to FFRs at modulation rates commonly assumed to evoke activity dominated by brainstem sources. This debate is fundamental, given that recent studies have assumed that modulations of FFRs (e.g., by experience) reflect changes in brainstem responses. The results of Coffey et al. (2017) are consistent with the idea that cortical activity contributes to FFRs. However, whether cortical activity

is detectable in EEG-recorded FFRs is unclear: the auditory cortical regions proposed to contribute differ between studies and the relative strengths of brainstem and cortical contributions remain a topic of debate. In the meantime, to ensure that modulations of FFRs can be attributed to brainstem activity, careful assessment of putative cortical generators is necessary. For example, high-density EEG recordings could be used to estimate the contribution of different sources to FFR modulations. This emerging movement in the literature will undeniably improve knowledge of the neural generators of FFRs and of brainstem processing.

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