Direct measurement of delta frequency oscillations using fMRI

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Introduction: Oscillatory neural activity is frequently observed in electrophysiological recordings, which have identified important roles for rhythms between 0.1–500 Hz in cognition and consciousness (1). The hemodynamic response is generally thought to be sluggish, limiting the ability of fMRI to directly resolve oscillations at these frequencies. However, fMRI exhibits sufficient trial-to-trial precision to resolve small differences in onset times across the brain. Short (< 2 s) inter-stimulus intervals (ISIs) are still avoided due to the time needed for the hemodynamic response to recover following the prolonged post-stimulus undershoot. Even in event-related experimental designs, stimulus presentation is randomized to ensure that identical stimuli are not repeated at short ISIs, so the fundamental stimulus frequency remains low. We investigated whether BOLD responses can track high-frequency periodic stimuli, using V1 as a model system.

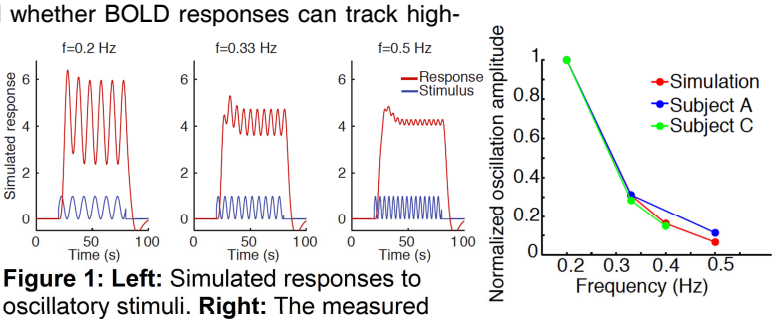

Figure 1: Left: Simulated responses to oscillatory stimuli. **Right:** The measured BOLD oscillations track stimulus frequency, with amplitude decreasing at high frequencies as predicted by the linear model.

Methods: Three subjects gave informed consent and were scanned on a 3T Siemens Trio scanner with a 32-channel head coil array. Acquisition targeted the calcarine sulcus, acquiring 5 oblique unaccelerated gradient-echo EPI slices with 2.5 mm isotropic resolution, a TE of 28 ms, echo-spacing of 0.52 ms, and a TR of 246 ms using a 30° flip angle. Stimuli consisted of a 12 Hz counterphase flickering radial checkerboard displayed for 4 minutes. Stimulus contrast was modulated at a frequency of 0.2 H z, 0.33 Hz, 0.4 Hz, or 0.5 Hz, resulting in a stimulus whose intensity varied periodically over time, oscillating between a gray screen and a high-contrast checkerboard. Contrast modulation was imposed as either a sinusoidal wave or as a square wave. Triggered analyses averaged the BOLD timecourse on every cycle, discarding the first two cycles to avoid transient effects. Averages included only visually responsive voxels identified in a single 0.2 Hz run that was not used in further analysis.

Results: We simulated a predicted BOLD response to the oscillatory stimuli by convolving the SPM two-gamma hemodynamic function with the stimulus contrast modulation waveform. While the initial activation at stimulus onset remains large as frequencies increase from 0.2 Hz to 0.33 Hz, the predicted amplitude of the continuous oscillation decreases by a factor of 3 (**Fig. 1**). We measured the BOLD response amplitudes from responsive voxels to test whether we could nonetheless resolve a continuous oscillation in the BOLD signal. We found that as expected, a large (4–8%) transient response occurred at the onset of the oscillatory stimulus, followed by a plateau. The periodic triggered average showed that the 0.2 Hz, 0.33 Hz, and 0.4 Hz stimuli elicited clear oscillatory responses in the BOLD fMRI within this plateau, and the amplitude of these signals matched predictions from the linear model (**Fig. 1**). In addition, we studied 0.5 Hz responses in one subject and found that even this high frequency resulted in a strong, matched oscillation in V1 (**Fig. 2**). Stimulating with a square wave instead of a sine wave at 0.33 Hz resulted in a phase shift of 780–798 ms in the BOLD response (**Fig. 3**), indicating that these oscillatory responses are sensitive to stimulus dynamics.

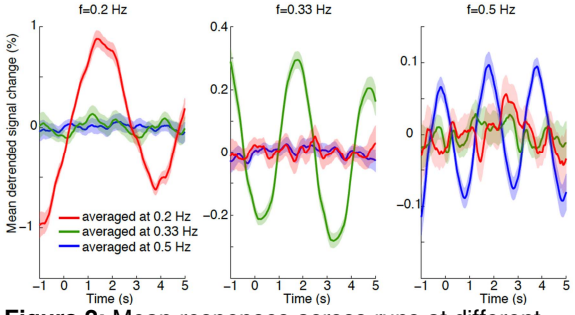

Figure 2: Mean responses across runs at different frequencies in Subject C demonstrate that BOLD oscillates at the stimulus frequency, up to 0.5 Hz.

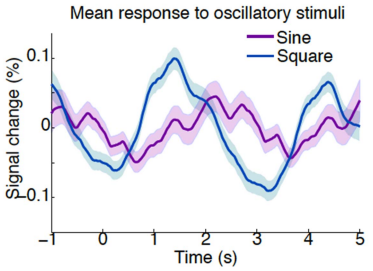

Figure 3: Mean responses show that both sine and square wave stimuli elicit BOLD oscillations at 0.33 Hz, but with a phase offset of 780-798 ms (range across subjects).

Discussion: We found that periodic stimuli can reliably elicit a BOLD oscillation at frequencies up to 0.33 Hz, and preliminary results suggest this extends up to at least 0.5 Hz. The linear convolution model predicts a decrease in BOLD oscillation amplitude across frequencies that resembles the measured changes, suggesting that the amplitude of the oscillatory BOLD response to rapid stimulus changes may exhibit a higher degree of linearity than transient responses (2). However, the phase offset of this oscillation differs substantially depending on the type of stimulus used, and this phase shift was not predicted by the convolution model, suggesting modifications may be needed to account for these temporal dynamics. Additional data and future studies at high fields will help determine whether 0.5 Hz is the fastest frequency that can be resolved, or whether even higher temporal resolution is achievable with increased measurement sensitivity, enabling fMRI to directly measure cortical oscillations.

References:

1. Buzsáki G, Draguhn A. Science 2004;304:1926–1929.
2. Pfeuffer J, et al. Neuroimage 2003;18:990–1000.