Fast fMRI signals up to 1Hz vary across brain states and predict spontaneous neural activity

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Abstract:
fMRI signals were traditionally seen as very slow, with most resting-state studies only investigating signals slower than 0.1Hz, but task-based studies have shown that fMRI signals up to 0.75Hz reflect stimulus-induced neural activity. Here, we investigate whether high-frequency fMRI signals can index spontaneous neural activity across brain states. Using simultaneous EEG-fMRI in 21 humans drifting between sleep and wakefulness, we found an increase in fMRI spectral power during NREM sleep (compared to wakefulness) across frequency ranges as fast as 1Hz. Using machine learning, we found that these fast fMRI signals predict fluctuations in canonical neural rhythms measured with EEG, in subjects held-out from the training set. Since fMRI signals and neural rhythms are sensitive to systemic physiology, we tested whether this predictive fast fMRI information specifically represented neurovascular coupling, or was also present in the ventricles. We found that fMRI signals as fast as 0.9Hz (for alpha rhythm predictions) and 0.8Hz (for delta rhythm predictions) contained unique neural information above what was present in the ventricles. These results reveal that high-frequency spontaneous fMRI signals are coupled to neural activity that varies across brain states and index cognitive processes, pushing the boundaries of fMRI's abilities to reveal brain dynamics underlying cognition.

Introduction

fMRI is used to infer neural activity via the BOLD (Blood Oxygenation Level Dependent) signal, which was traditionally seen as very slow. As a result, fMRI studies sampled data in the order of seconds, and analyzed the BOLD signal using hemodynamic response functions that assume a sluggish BOLD response to neural events. While these approaches work well for blocked experimental designs, they can limit our ability to investigate faster and more naturalistic variations in neural activity underlying cognition. Task-based studies have shown that the BOLD signal can react much faster to stimulus-induced neural activity than previously thought, as fast as 0.75Hz in response to visual stimuli (Lewis et al., 2016). Furthermore, resting-state studies have detected spatially structured BOLD signals in high frequency ranges (Boubela et al., 2013; Chen & Glover, 2015). However, it is not known whether high-frequency spontaneous BOLD signals are coupled to spontaneous neural activity, such as the neural rhythms that vary across vigilance. Here, we use simultaneous EEG and fast fMRI to determine how fMRI dynamics up to 1Hz change across brain states, and predict variations in canonical EEG neural rhythms.

Results

We collected EEG and simultaneous fMRI (3T, 2.5mm isotropic voxels, TR=378ms) from 21 subjects naturally drifting in and out of sleep. Fig 1a shows data from a representative subject: as they drifted from wake to NREM sleep, several fMRI bands increased in power; meanwhile, the EEG showed an increase in delta power (1-4Hz, associated with memory consolidation and sleep quality) and a decrease in alpha power (8-12Hz, associated with attention and several other cognitive processes). To investigate fMRI power variations, we first calculated the fMRI spectrum in each parcellated fMRI region (Desikan et al., 2006) across wake and NREM sleep (manually scored), and found that fMRI power was significantly higher during sleep, as compared to wakefulness, in frequencies up to 1Hz (Fig 1b). This significant increase was present in many cortical and subcortical regions, but also in non-neuronal regions such as the 3rd ventricle, leaving open the possibility that this spectral difference was due to changes in systemic physiology during sleep rather than reflecting unique neural activity underlying brain states.

To identify how high-frequency fMRI signals are related to neural activity without assuming a specific relationship, we adapted an existing machine learning approach (Jacob et al., 2024). We trained neural networks (structure adapted from Syeda et al. (2023)) to predict the simultaneous EEG (Fig 1c). Occipital EEG power was calculated in 5s windows. Model predictors were sliding windows of 60 TRs (~22s) from 84 anatomically-parcellated fMRI regions (Desikan et al., 2006) covering nearly the whole brain, trained to predict the EEG point at the center of the window. EEG and fMRI data were normalized within each subject. Three subjects were iteratively held-out and performance (correlation between predictions and truth) was calculated on held-out subjects.

Models were first trained under 3 conditions using all parcellated regions as the input with the following temporal treatments: fMRI high-passed above 0.2Hz, unfiltered fMRI (beyond the detrending done as part of the pre-processing), and a control condition in which the fMRI data were temporally shuffled. Predictions using the unfiltered fMRI replicated prior benchmarks (Jacob et al., 2024). The high-pass fMRI did not predict as well as unfiltered (as would be expected), but it still captured short- and long-range EEG dynamics and predicted better than control (Fig 1d, 1e).

This finding showed that fMRI signals above 0.2Hz are coupled to alpha and delta rhythms, but since these arousal-related rhythms are partially coupled to systemic physiology, we next sought to understand how much of the predictive fMRI information was specific to neurally-derived BOLD activity (rather than the components of the BOLD signal that reflect systemic physiology). We thus trained separate models using fMRI data from different groups of brain regions, using a progressively increasing cutoff for the highpass filter (Fig 1f). We used the following parcellated regions: all gray matter regions (76 features; 38 bilateral cortical and subcortical regions), the average of all cortical voxels (1 feature), white matter (2 features, one for each hemisphere), and ventricles (6 features). If the predictions yielded by the ventricles are outperformed by the other conditions, this suggests a presence of uniquely predictive neural information. The following neural conditions were used: first, all gray matter regions, representing region-specific predictive information. Second, since prior work showed that the global cortical average of the BOLD signal is coupled to oscillatory EEG activity (Fultz et al., 2019), we used the average of all cortical voxels as a separate neural condition, representing large, coordinated activity across the cortex. Prior work has also shown that these large BOLD increases in the cortical average reflect large inflow of blood into the brain (Fultz et al., 2019; Williams et al., 2023). Thus, we assumed this cortical average signal would be partially reflected in the white matter, and therefore we also included it as a condition.

The results (Fig 1f) showed that predictive information in the individual gray matter regions was degraded when the fMRI high-pass cutoff was above 0.3Hz (alpha predictions) and 0.2Hz (delta predictions), likely due to worse signal-to-noise ratios in these fast ranges. Ultra-high field fMRI acquisition may allow for faster information to be identified in individual regions. The cortical average predicted well at much faster high-pass cutoffs, and this predictive information was closely reflected in the white matter (particularly for delta predictions). The ventricles, on the other hand, predicted both EEG rhythms much more weakly than the cortical average, suggesting that neurovascular information is present in fMRI activity at least as fast as 0.9Hz (alpha) and 0.8Hz (delta). To ensure this is not due to decreased signal-to-noise in the ventricles, our future aims include assessing how well heart rate and respiration can predict these rhythms.

Alpha and delta rhythms index brain states that represent major shifts in attention and cognition. Our results show that high-frequency fMRI signals contain surprisingly rich information about these neural rhythms, with deep implications for evaluating fMRI temporal sensitivity and conducting future studies of fast, naturalistic neural processes.

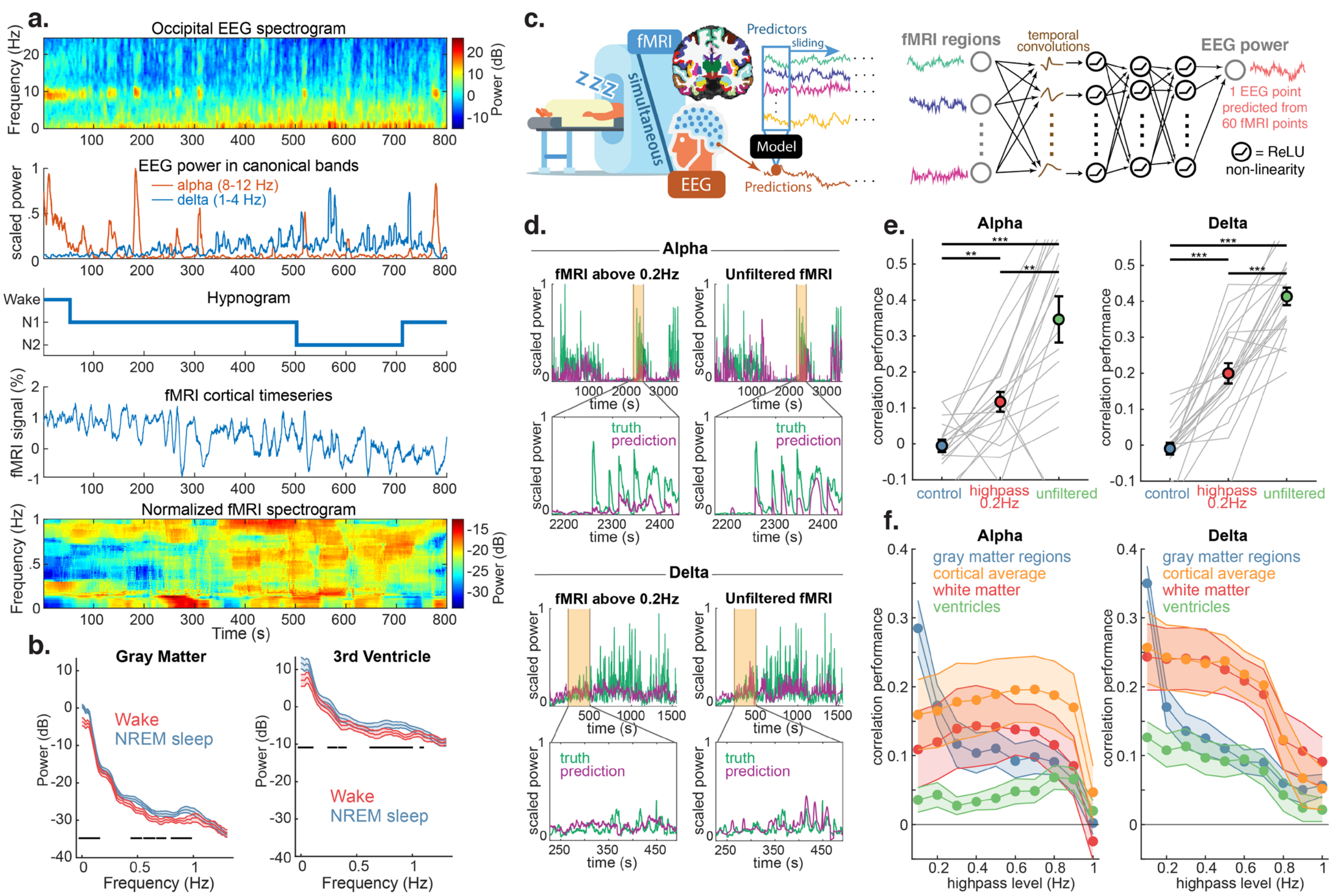

Fig 1: fMRI activity up to 1Hz changes across states and predicts EEG power. **a**. Representative variations in EEG and fMRI as a subject transitions from wake to NREM sleep. **b.** Group-level variations (n=21) show significantly higher fMRI power during NREM sleep across several frequency bands (black bars indicate p<0.05, Benjamini-Hochberg correction) in both gray matter and ventricles. **c.** We trained neural networks to predict EEG power from fMRI to determine if this high-frequency fMRI activity reflects neural activity and not just systemic changes in physiology. **d.** Representative occipital EEG power predictions (on a held-out subject) using high-pass filtered fMRI and unfiltered fMRI as predictors. **e.** Correlation between predictions (on held-out subjects) and ground truth using unfiltered fMRI, high-pass filtered fMRI, and temporally shuffled fMRI (control). Means with SEM. Gray lines are predictive performance on held-out subjects. **f.** Correlation between predictions (on held-out subjects) and ground truth using fMRI signals from different brain regions, high-passed above progressively higher levels. Means with SEM.

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