Investigating the electrophysiological fingerprints of spontaneous fMRI activity

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Purpose: Although resting-state fMRI is widely used for investigating the functional organization of the human brain, the neural basis of spontaneous BOLD signal fluctuations is not fully understood [1]. Using simultaneous measurements of electrophysiology and fMRI, previous studies have reported a degree of correspondence between the fMRI signal and fluctuations in the power of local field potentials (LFP) within certain frequency bands (e.g. [2-6]). Power in the gamma range of the LFP (30-100 Hz) is the most consistently reported electrophysiological correlate of fMRI, though the strength of association is modest, explaining less than 25% of the temporal variance of the fMRI signal [1]. One primate study noted that fluctuations of power within a low frequency range (<15 Hz) also demonstrated correlations with the fMRI signal, though of smaller magnitude and less consistency across the different animals compared to those of the high-frequency (upper gamma) LFP [3]. Here, we investigate in further detail the contributions of high- and low-frequency LFP power fluctuations to the fMRI signal. Specifically, we examine whether these two frequency ranges account for overlapping temporal variance in the spontaneous fMRI signal or whether they are providing distinct and complementary information, and characterize spatial patterns in their relationship to fMRI signals across the brain.

Methods: Simultaneous LFP-fMRI recordings were carried out on macaque monkeys in the awake, un-anesthetized state, in a dark room (4.7T, voxel size=1.5mm^3 isotropic, TR/TE=2.6s/15.6ms, duration=30.33min per session, rCBV contrast using MION injection; details in [3]). Data for the present study consisted of 6 sessions from a subject previously shown to display correlations with the fMRI signal in both low and high frequency ranges of the LFP [3]. For this monkey, LFP signals were measured from a 32-channel subdural ECoG array (600um inter-contact spacing) positioned in the visual cortex (Fig.1). ***LFP analysis***: For each session, the mean power of the LFP data in the low (here, 3-7Hz; "LF") and high (40-80Hz; "HF") frequency bands was computed over segments of data corresponding to each fMRI TR using a Hanning-tapered Fourier transform. This resulted, for each electrode, in two time series that quantify variations in power within the LF and HF bands, respectively (denoted "LF and HF regressors"), sampled at the same rate as the fMRI signals. Regressors were standardized to unit variance and temporally delayed by 3 TRs (7.8s) to account for the hemodynamic response prior to comparison with fMRI [3]. ***fMRI analysis***: Pre-processing included motion coregistration, nuisance regression of 1st and 2nd-order polynomials and 6 motion parameters, spatial smoothing FWHM=3mm, and between-session alignment with rigid body transformation. Since rCBV was measured, the sign of the signal was inverted to be consistent with BOLD (i.e., increases in neural activity cause increases in signal). For ROI analyses, we derived time series from ICA components that were consistently identified across sessions [7] (Fig.1). ***Combined LFP-fMRI analysis:*** The relationship between the LF and HF power fluctuations and fMRI time series was quantified using temporal correlation and regression methods. Joint vs. distinct LF and HF correlates of the fMRI time series were quantified by considering (*i*) the mean over [standardized] LF and HF regressors, (*ii*) LF orthogonalized to HF, and (*iii*) HF orthogonalized to LF. In addition, the contribution of LF power *beyond* that of HF power to the fMRI signal at each voxel was statistically assessed by comparing nested linear regression models using an F-test, in which the full model included both LF and HF regressors and the reduced model included only HF regressors. The reverse, i.e. comparing the full model against one that includes only LF regressors, was also tested in order to determine contributions of HF power beyond that of LF.

Results:

1. Joint vs. independent contributions of low- and high-frequency LFP power to fMRI. Consistent with [3] and others, correlations with the visual cortex (ROI 1) in the fMRI data were highest with high frequency (gamma) LFP power (Fig.2A). Taking the *mean* of the LF and HF regressors yielded stronger correlations with fMRI compared to the HF regressor alone ($p<0.05$) in both ROIs (Fig. 2A,C), suggesting that the LF and HF bands are providing complementary information about the fMRI signal. In fact, for a network located outside of visual cortex (ROI2; Fig.2C), correlations were stronger for the LF band compared to HF, implying a spatial dependence of LF vs. HF effects.

2. Spatial patterns of low- and high-frequency LFP contributions to fMRI. Fig. 3 shows, at every voxel, the number of sessions in which fluctuations in low-frequency LFP power contributed additional information (accounted for significantly greater temporal variance) in the fMRI data beyond fluctuation in high-frequency LFP power (top row); and vice versa (bottom row). Distinct spatial patterns are evident, with HF being most consistently correlated (beyond LF) with fMRI signals in the visual cortex, and LF being a stronger predictor in more distant regions.

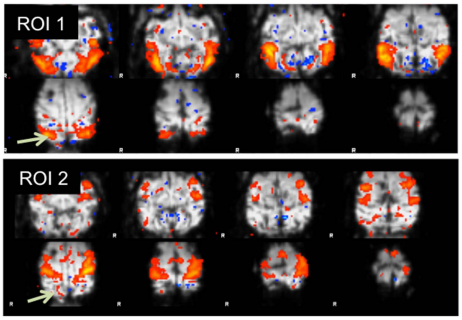

Fig. 1. (***above***) Consistent networks resulting from ICA analysis of the fMRI data, which define the ROIs used in Fig.2. Electrode position indicated with arrows.

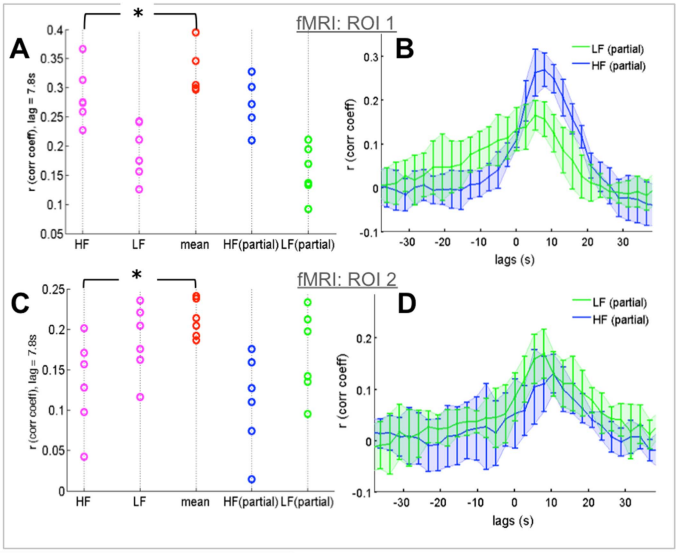

Fig. 2. (***right)*** Correlations between band-limited LFP power and the fMRI time series from ROI 1 (in *A,B*) and ROI 2 (in *C,D)*. In 2A and 2C, correlation values are shown for the HF and LF regressors (magenta), their mean (red), and when orthogonalized to one another (blue, green). Circles represents different sessions. Fig.2(B,D) depict the cross-correlation functions of the orthogonalized LF and HF signals with fMRI over a range of time lags, averaged over sessions (N=6).

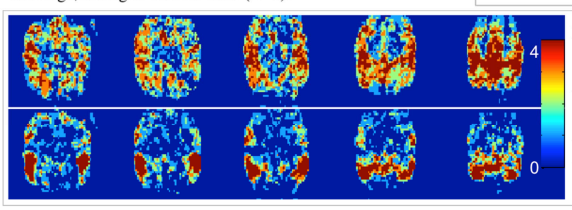

Fig. 3. Value at each voxel indicatesthe number of sessions where LF power explained significant ($p<0.01$, F-test) additional variance in the fMRI signal beyond HF power (top); and vice versa (bottom).

Discussion & conclusions: This study aims to increase our understanding of the neural basis of the BOLD signal in the wakeful, resting-state condition, examining distinct effects of low- and high-frequency LFP power fluctuations in simultaneous LFP-fMRI data. While HF (gamma) power had the strongest relationship with fMRI signals in visual cortex (location of the electrode), LF power fluctuations were found to explain significant additional temporal variance, suggesting that LF fluctuations are not simply conveying redundant (and lower-SNR) information. Moreover, LF effects were dominant in regions outside the visual cortex, consistent with findings that LF may reflect longer-range cortical processes [8]. Results also support the notion that electrophysiological correlates of fMRI arise from processes involving multiple distinct frequency bands [4,9].

References: [1] Leopold & Maier (2012) [2] Shmuel & Leopold (2008) [3] Scholvinck et al (2010) [4] Magri et al (2012) [5] Nir et al (2008) [6] Keller et al (2013) [7]http://www2.fmrib.ox.ac.uk/analysis/research/melodic[8] Buzsaki et al (2004) [9] Mantini et al. (2007).