Neural activity associated with spontaneous eye opening and closure in the awake macaque

Catie Chang[1], David A Leopold[2], Hendrik Mandelkow[1], Marieke L Schölvinck[3], and Jeff H Duyn[1]

[1]*Advanced MRI Section, Laboratory of Functional and Molecular Imaging, NINDS, NIH, Bethesda, MD, United States,* [2]*Section on Cognitive Neurophysiology and Imaging, Laboratory of Neuropsychology, NIMH, NIH, Bethesda, MD, United States,* [3]*Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society, Frankfurt am Main, Germany*

Purpose: While there is strong evidence that spontaneous fMRI signals and their emergent correlation patterns have a neural basis, the specific neuronal and physiological contributions to this phenomenon are unresolved. In addition to the anatomically constrained correlation patterns ('resting-state networks') that are largely shaped by the underlying structural connectivity, there exist more global, spatially widespread fluctuations that may be associated with endogenous shifts in vigilance/arousal state [e.g.,1,2]. Here, we investigated the spatial and temporal relationship between neural activity and a behavioral index of vigilance state (spontaneous eye open/closure in darkness) using simultaneous fMRI and electrophysiological data from unanesthetized macaques in the resting state.

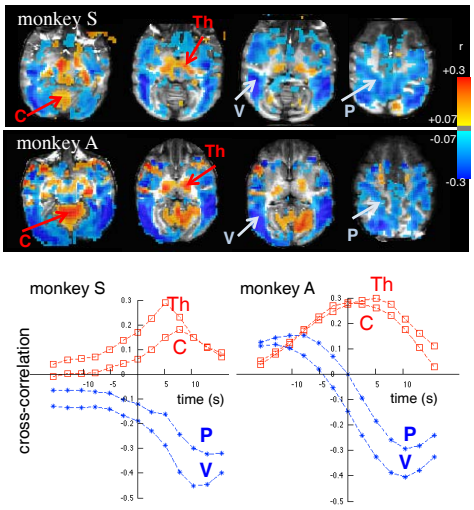
Methods: Simultaneous LFP-fMRI data were acquired from macaque monkeys in the awake, un-anesthetized state, in a dark room (4.7T, voxel size=1.5mm^3 isotropic, TR/TE=2.6s/15.6ms, duration=30.33min per session, rCBV contrast using MION injection; details in [3]). Data for the present study consisted of 12 sessions from two monkeys (N=8, N=4; monkey S,A respectively), with electrodes recorded in V1, V4 (monkey S) and Frontal, Parietal sites (monkey A). ***Eye signal analysis:*** Behavioral data were obtained from infrared camera monitoring of the face during the scan. A signal indicating the degree to which the eyes were open ("eye signal") was constructed by extracting the height of a bounding box around the pupil at each movie frame, and taking its median value within each 2.6-s TR. This yielded a regressor sampled at the same rate as the fMRI time series. For comparison, we also considered a binary eye signal (1=open, 0=closed) based on independent, manual scoring of the eye camera videos. ***fMRI analysis***: Pre-processing included motion co-registration, 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. ***LFP analysis***: For each session, the mean power of the LFP signal within each frequency band of interest was computed over segments of data corresponding to each fMRI TR. For further analysis, eye, LFP, and fMRI signals were concatenated across all sessions within each monkey.

Results:

1. Spontaneous eye opening/closure in darkness has widespread correlation with fMRI signals. **Fig. 1** depicts voxel-wise correlations with the eye signal, where the latter was first convolved with a canonical hemodynamic response function [4]. Both monkeys showed widespread inverse correlations with the eye signal across the cortex. Focal areas where the fMRI signal increased in proportion with eye opening were also observed and were consistent across monkeys, localized to the thalamus and cerebellum. Nearly identical results were obtained when using the binary eye signal, suggesting that the open/close transitions (rather than pupil dilation or variation in eyelid height while the eyes are open) primarily account for this correlation pattern.

2. Temporal relationship between eye and fMRI signals. ROIs were defined in 2 areas of negative correlation (V4, IPS) and 2 areas of positive correlation (thalamus, cerebellum); **Fig. 2**. Lagged cross-correlation of the fMRI time series from these regions with respect to the eye signal revealed that increases in the thalamus/cerebellar regions preceded decreases in the negative, cortical regions. Whole-brain maps of the optimal time lag between eye and fMRI signals confirmed that regions of positive correlation had an earlier onset than those of negative correlation (**Fig. 3**). Negative time lags indicate regions in which the maximum fMRI signal change preceded the behavioral (eye) change.

3. *Correlation between electrophysiology and spontaneous eye open/closure.* LFP data from all 4 cortical sites demonstrated a significant relationship with the eye signal. Decreases in LFP power within a high-frequency band (>40 Hz) and a lower-frequency band (<10 Hz in V1, V4; <15 Hz in frontal, parietal) accompanied increases in the eye signal ($p<0.01$ all sites; permutation test). The respective time lags between the (un-convolved) eye signal and the high-frequency LFP in each of the 4 electrodes were -2.6s, -2.6s, -2.6s, 0s (V1, V4, Frontal, Parietal) and -2.6s, -5.2s, -5.2s, -5.2s for low-frequency LFP, indicating the electrophysiological changes coincided with (or preceded) the eyelid signal.



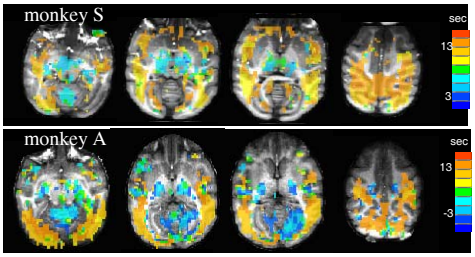


Fig. 1 (Left): Voxel-wise correlations with the HRF-convolved eye signal, showing widespread negative correlation with cortex and focal positive correlations.
Fig. 2 (Bottom left): Lagged cross-correlation between the unconvolved eye signal and the fMRI time series from selected positively (red) and negatively (blue) correlated ROIs. ROIs are shown in Fig. 1.
Fig. 3 (Below): Maps showing the time-lag of optimal cross-correlation between the unconvolved eye signal and each voxel's fMRI time series.

Discussion & conclusions: We observe a robust relationship between resting-state electrophysiological and fMRI signals and a behavioral index of vigilance state based on eye open/closure. Temporal analysis indicates that thalamic and cerebellar regions have arousal-related signal increases that preceded the signal decreases in cortex (and earlier than the behavioral event), suggesting that their activity may index changes in state that precede or drive the behavioral (eye open/closing) event. The significant relationship with LFP data further supports the neural basis of this phenomenon. The presence of strong, widespread spatial correlations with the eye signal also suggests that a considerable fraction of fluctuations in human resting-state fMRI could be linked with endogenous variations in arousal/vigilance state.

References: [1] Fukunaga M et al, Neuroimage (2006) [2] Wong CW et al, Neuroimage (2013) [3] Schölvinck ML et al, PNAS(2010) [4] SPM (www.fil.ion.ucl.ac.uk/spm/)