BOLD fMRI correlates of intermittent sympathetic vasoconstriction and autonomic EEG arousals during sleep

PS Özbay[1], C Chang[2], D Picchioni[1], H Mandelkow[1], MG Chappel-Farley[3], P van Gelderen[1], JA de Zwart[1], and JH Duyn[1]

[1]Advanced MRI Section, LFMI, NINDS, National Institutes of Health, Bethesda, MD, United States, [2] Vanderbilt University, Nashville, TN, United States, [3]University of California, Irvine, CA, United States

Background and Purpose

The BOLD fMRI signal is well established to originate from blood flow changes in response to neuronal activity through local (intracortical) neurovascular coupling. However, potential confounding contributions of the extrinsic sympathetic innervation of central nervous system (CNS) arteries on the fMRI signal is less well known.

In our previous work[1], during rest and light sleep in healthy human subjects, we found strong correlation between whole brain fMRI signal and finger skin vascular tone (**Fig.1**), measured with photoplethysmography (PPG) from the finger-tip (**Fig. 2**), known to be regulated by sympathetic mechanisms.

To further investigate this, we analyzed concurrently acquired fMRI, EEG, and peripheral vascular tone during light sleep, to capture fluctuations in autonomic arousal associated with K-complexes, which have a strong association with phasic increases in sympathetic activity[2].

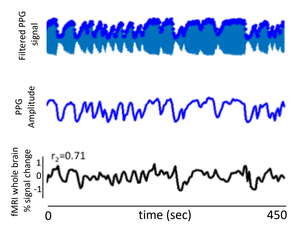

Figure 1: PPG signal, its amplitude (PPG-AMP) and fMRI signal changes during light sleep. Correlation of r_2 is between PPG-AMP and fMRI signal at 2nd lag (6 sec).

Methods

Data from healthy subjects participating in an overnight sleep study[3] were partially used in this work. Overall 9 segments from 7 subjects ranging between 100-160 TR of time were used for the analyses. Each segment included 80% to 100% of N2 sleep.

BOLD fMRI data was obtained at 3T with gradient-echo-EPI (FA = 90 , TR = 3s, TE = 36ms, in-plane resolution = 2.5mm, slice-thickness = 2mm). **Preprocessing of fMRI data** included motion coregistration, regressing out motion parameters and low-frequency signal drifts with a polynomial regression, and slice timing correction, with use of AFNI routines.

EEG and ECG were acquired concurrently during fMRI scans with a 64-channel recorder. Sleep stages were manually scored with Analyzer in 30-s epochs, after correction of MRI gradient and cardio-ballistic artifacts in the EEG[4], and filtering the EEG signals from 0.3 to 35Hz. The data from all channels were further used to detect **K-complexes** (**Fig.2**) automatically with use of a free software[5].

PPG amplitudes at each MR trigger time were extracted following band-pass filtering (0.5-2Hz) and linear interpolation of the raw signal. As its transducer is sensitive to wavelengths above 800nm, and predominantly measures total hemoglobin content in the vasculature of the skin; its amplitude reflects blood volume.

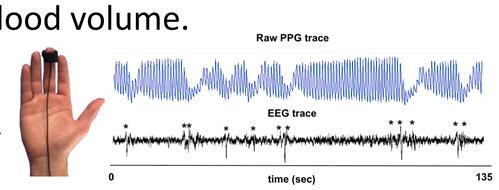

Figure 2: (left) Finger-tip PPG device, (right) sample traces of raw PPG and EEG (Fp1) during N2. Asterisk (*) signs show events of K-complexes.

We calculated low frequency **EEG power** (LF-EEG, 0.5-2Hz) per 3s fMRI volume, and performed lag dependent correlation analyses of LF-EEG and PPG amplitude (PPG-AMP) with fMRI signals.

Results

Low-frequency EEG power (LF-EEG) and PPG amplitude (PPG-AMP) correlations

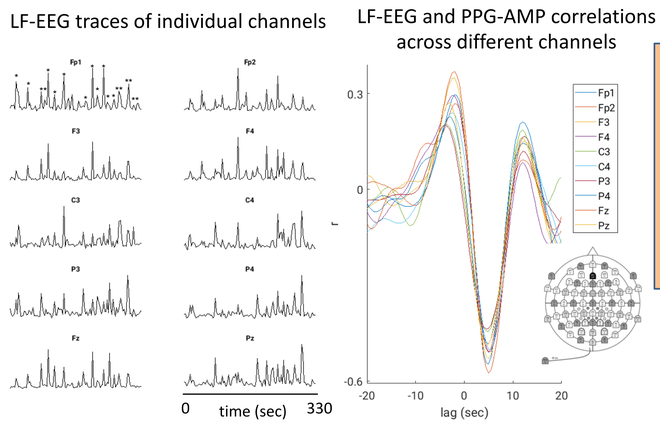

Figure 3: Exemplary result from a segment of N2 sleep. **(left)** LF-EEG traces from different channels for comparison, with Asterisk (*) signs denoting K-complexes detected with use of all channels. **(right)** Lag-dependent correlations of LF-EEG and PPG-AMP. **Channel Fp1 has been used for further correlation analyses.**

LF-EEG & fMRI correlation maps showed a negative correlation in grey matter (i.e. **increased low frequency EEG power, decreased fMRI signal**), with a further delayed negative response in white matter and ventricular regions.

The patterns of LF-EEG & fMRI correlation maps (e.g. at lag of 6 sec) resembled the PPG-AMP & fMRI correlation maps (e.g. at lag of 0 sec), suggesting a common origin.

During time segments of N2 sleep, we observed a high co-occurrence (>80%) of K-complexes with PPG-AMP drops, followed by decrease in the fMRI signal.

We found substantial (negative) correlation between LF-EEG and peripheral vascular tone, consistent with previous studies that linked it to sympathetic activation[2,6]. **Positive lag indicates LF-EEG precedes PPG-AMP.**

References:

[1] Özbay et al., NeuroImage, 2018. [2] Ackner and Pampiglione, J. Neurol. Neurosurg. Psychiatry, 1957. [3] Moehlman et al., J Neurosci Methods, 2018. [4] Iber et al., American Academy of Sleep Medicine, 2007. [5] Combrisson et al., Front Neuroinform, 2017. [6] Catcheside et al., Sleep, 2002.

Lag dependent voxel-by-voxel based spatial correlations with fMRI

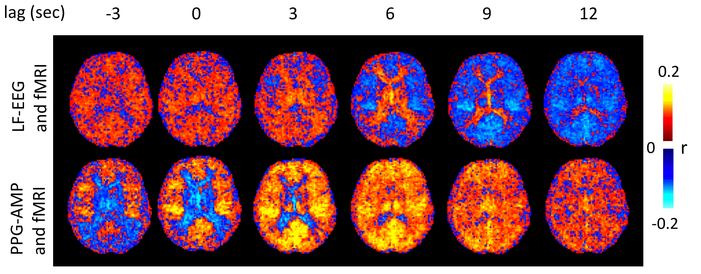

Figure 4: Mean voxel wise correlation maps of LF-EEG (top) and PPG-AMP (bottom) with fMRI (n=7). Each row represents corresponding maps with various lags in seconds (1-lag = 3sec (1 TR)). Positive lag means LF-EEG/PPG-AMP precedes fMRI signal.

Conclusion

Intermittent PPG-AMP drops are interpreted as systemic vasoconstrictive events, related to EEG measures of arousal, as previously observed during sleep[2].

Spatio-temporal patterns of correlation maps (**Fig.4**) are consistent with the known vascular delay between the deep (medullary) and superficial vascular territories in periventricular white and cortical gray matter[1].

The co-occurrence of EEG and peripheral measures of sympathetic activity and their temporal relationship with fMRI suggest a mechanism other than local vasodilation contributes to fMRI. Since sympathetic activity is known to play a role with a wide variety of conditions and arousal states, it likely affects most fMRI studies during both task and rest conditions.

Contact: pinar.ozbay@nih.gov