SEEP contrast highlights different functional connectivity networks compared to BOLD resting state fMRI

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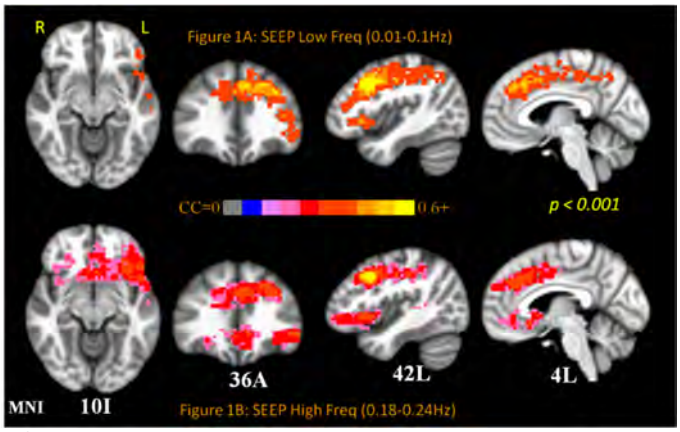
Purpose: Blood oxygen level dependent (BOLD) resting state fMRI (rsFMRI) has been the most widely employed method to explore resting-state functional connectivity (rsFC) in brain networks. A few groups[1,2] have advanced signal enhancement by extravascular protons (SEEP) as an alternate mechanism to assess brain activation in fMRI paradigms[2]. In this study we compared rsFC networks highlighted by BOLD- and SEEP-contrast rsFMRI. Further, based on recent studies[3] that show persistence of well-known BOLD rsFC networks at higher frequencies (f >0.1 Hz), we examined differences and similarities between SEEP and BOLD rsFC networks at different frequency bands.

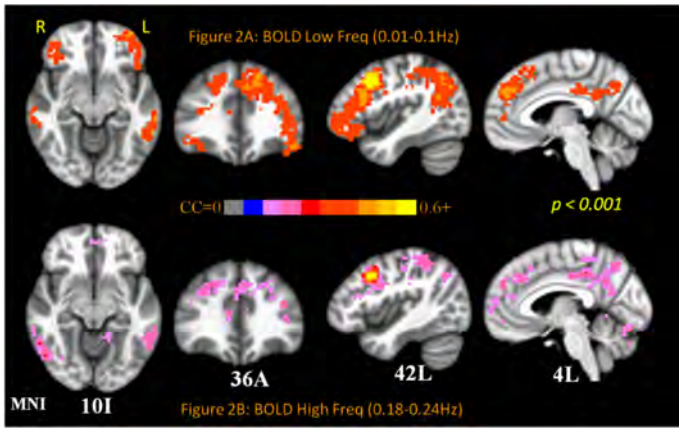
Methods: 11 right-handed normal subjects (6 male; median age ~27 years) were scanned in a Siemens 3T Tim Trio using a 32-channel array receive-only head coil. Two 9 minute long rsFMRI datasets were acquired with whole-brain (3mmX3mmX3mm resolution) multi-band slice accelerated EPI sequences[4]: 1) sensitized for *SEEP contrast*: spin-echo EPI sequence (TR/TE/FA = 2000ms/15ms/60°; 180° refocusing pulse) and 2) sensitized for *BOLD contrast*: gradient echo EPI sequence (TR/TE/FA = 2000ms/24ms/45°). The preprocessed physiological noise corrected[5] rsFMRI time-series were filtered at two different frequency bands: 1) low-pass (LF) = 0.01-0.1 Hz and 2) high-pass (HF) = 0.18-0.24Hz. Seed-based cross-correlation analysis (CCA) was performed for all four datasets: SEEP_LF, SEEP_HF, BOLD_LF and BOLD_HF. The seed reference vector was obtained from a 5 mm sphere ROI placed in left dorsolateral prefrontal cortex (around MNI co-ordinates 40, -12, 36) in middle frontal gyrus at the intersection of middle frontal sulcus and precentral sulcus for each subject. The group rsFC maps for each of the 4 datasets were obtained by 1-sample t-tests on the respective individual subject z-transformed CC maps. The resultant statistical parametric maps were clustered and significance of activation was assessed using Monte Carlo modeling to correct for multiple comparisons (3dClustSim tool in AFNI).

Results and Discussion: The DLPFC SEEP_HF rsFC was best visualized in terms of sensitivity and specificity at average (across group) CC = 0.2 (corresponding to map sparsity = 0.08). In order to best illustrate the similarities and differences between the four contrasts, we adjusted the average CC threshold for SEEP_LF, BOLD_LF, BOLD_HF DLPFC rsFC maps to obtain the same sparsity (0.08) as SEEP_HF. Further the results reported for SEEP_LF, SEEP_HF and BOLD_LF survive a multiple comparison p <0.001 threshold (p < 0.01 for BOLD_HF) based on the group rsFC t-test maps. The SEEP_HF rsFC map (Figure 1B; Table) shows that LDLPFC exhibited distinct (highlighted in bold in Table) and strong connections with ventral striatum, caudal putamen, claustrum, subgenual cingulate (SgC) and ventral anterior cingulate cortex (VACC) that were not seen at the same sparsity thresholds in the BOLD_LF and BOLD_HF (Figure 2) as well as the SEEP_LF (Figure 1A) rsFC maps. Thus coherent high frequency (f > 0.18 Hz) resting state fluctuations in SEEP fMRI time-series are better able to trace well known[6,7] anatomic fronto-striatal connections than the BOLD contrast. Further, both SEEP_LF and SEEP_HF rsFC maps exhibited a strong and inverse dependence of connectivity strength with distance from the seed. The BOLD_HF dataset exhibited connectivity with similar regions as the BOLD_LF but with decreased strength and extent. Both BOLD and SEEP contrasts at the two frequency bands exhibited connectivity with fronto-parietal attention network (with BOLD_LF rsFC >> SEEP rsFC) in the parietal cortex, as well as premotor cortex and the frontal pole. In addition LDLPFC's BOLD rsFC maps exhibited connectivity to the default mode network regions: posterior cingulate cortex (PCC) and temporoparietal junction (TPJ) likely due to the placement of the DLPFC seed in Brodmann area 9 close to superior frontal gyrus (SFG) which is connected to DMN[8].

Conclusion: The results of this study show that rsFMRI obtained with SEEP contrast (especially at higher frequencies) exhibits differential sensitivity to functional connectivity networks compared to BOLD rsFMRI. While BOLD rsFC networks exhibit higher sensitivity to state-dependent brain networks (e.g. DMN), the SEEP contrast (especially at higher frequencies) exhibits higher sensitivity to anatomic connections. Further work is needed to better characterize structure-function relationships and state dependence of SEEP fMRI rsFC networks over wider range of frequencies.

SEEP-HF (p < 0.001)	Ventromedial prefrontal cortex (VMPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC), **ventral VACC, SgC**, dorsal anterior cingulate (DACC), **ventral striatum, caudal putamen, claustrum**, anterior insula, insula, inferior frontal gyrus (IFG), cingulate gyrus, supplementary motor area (SMA), superior frontal gyrus (SFG), premotor cortex, frontal eye fields (FEF), superior temporal gyrus (STG), primary motor cortex (M1), primary somatosensory cortex (S1), inferior parietal lobule (IPL).
SEEP-LF (p < 0.001)	VLPFC, DACC, IFG, cingulate gyrus, SMA, SFG, premotor cortex, FEF, STG, M1, S1, paracentral lobule (PCL), IPL, superior parietal lobule (SPL), precuneus
BOLD-LF (p < 0.001)	VLPFC, DACC, IFG, SFG, premotor cortex, FEF, posterior middle temporal gyrus (MTG), IPL, SPL, temporoparietal junction (TPJ), supramarginal gyrus, angular gyrus, posterior cingulate cortex (PCC)
BOLD-HF (p < 0.01)	VMPFC, SFG, premotor cortex, FEF, posterior MTG, M1, S1, IPL, SPL, TPJ, supramarginal gyrus, angular gyrus, PCC.





References [1] Stroman P. et al., Magn Reson Imag 19:827-31, 2001; [2] Figley et al., Magn Reson Imag 28:1234-43, 2010; [3] Gohel et al., Brain Connect, 2014; [4] Moeller et al., Mag. Res. Med. 63:1144-1153., 2010.; [5] Bianciardi M., et al., Magn. Reson. Imag. 27:1019-1029, 2009; [6]; Haber S., et al., Brain Res. Bull. 78: 69–74, 2009; [7] Johansen-Berg H., et al., Cereb Cortex 18:1374-1383, 2008; [8] van Den Heuvel M., et al., J. Neurosci., 28:10844 –1085, 2008.