# Resting-State Functional Connectivity Mapping in Humans using Spin-echo EPI BOLD

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**Target audience:** Researchers in fMRI-based resting-state functional connectivity and fMRI contrast mechanisms

**Purpose:** First demonstrated in 1995 [1], functional MRI (fMRI) recordings of the brain in the resting-state exhibit correlations within consistent brain networks [2] such as the default-mode network (DMN). Without the need for the subject to perform a task, resting-state fMRI has the vast potential to facilitate the study of functional connectivity and the detection of abnormalities resulting from neurological disorders. The vast majority of resting-state fMRI scans use gradient-echo EPI (GE-EPI) acquisition, due to its sensitivity to fluctuations in the blood oxygen level dependent (BOLD) signal, though they can include strong intravascular effects from large veins. Conversely, spin echo EPI (SE-EPI) sequences are relatively more sensitive to the extravascular effects surrounding microvasculature, and hence may provide better spatial specificity for detecting neuronal activity [3], with the added benefit of minimizing signal loss/artifacts caused by susceptibility gradients. While it has been shown that SE-EPI can generate functional connectivity maps in rats similar to those generated by GE-EPI [4], this study is the first to demonstrate this in human subjects, and specifically targets high-susceptibility brain areas.

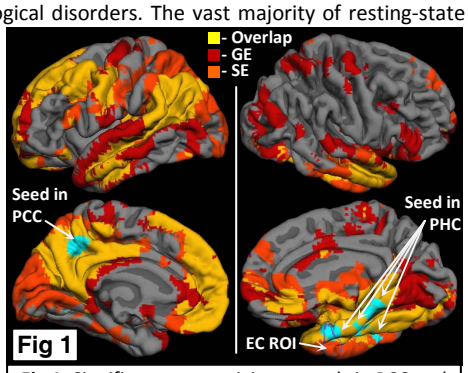


**Fig 1:** Significant connectivity to seeds in PCC and in PHC: SE (orange), GE (red), overlap (yellow). Top: lateral cortex: bottom: medial surface.

**Methods:** 4 subjects were scanned on a 3T Tim Trio scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. Two 8 min resting-state scans, one a 26 slice GE-EPI scan (TE = 30ms, Echo Spacing = 0.55ms, readout train = 35.2 ms) and the other a 24 slice SE-EPI scan (TE = 40ms, Echo Spacing = 0.47ms, readout train = 30.1 ms), were acquired for each subject (both with TR = 2000ms, 64x64 matrix, 3.44mm in-plane resolution, 4.6mm slice thickness, flip angle = 90°) as well as a T1 weighted anatomical scan (3D-MPRAGE, TR/TE/TI = 2400/2.43/1000ms, 256x256x192 matrix, 1x1x1mm$^3$ resolution, flip angle = 8°). The initial non-steady-state frames were removed from all fMRI scans before running slice timing and motion correction, co-registering to the anatomical, spatially normalizing to MNI305 space and the native anatomical scan, and spatially smoothing (8mm FWHM). All functional data was band-pass filtered (0.008-0.09Hz) and white matter, cerebrospinal fluid, and motion correction signals were included as confound regressors. Then, using the CONN toolbox [5], voxel to seed correlation maps were calculated as a measure of connectivity to seeds placed in the in the *posterior cingulate cortex (PCC)*, *parahippocampal cortex (PHC)*, and *caudate head (CH)*. Also, sensitivity and specificity of functional connectivity maps (statistically significant voxels only) generated using SE and GE BOLD data were computed based on predefined ROI masks demarcating the default-mode network.

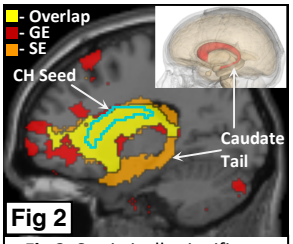


**Fig 2:** Statistically significant connectivity to seed in the head of the caudate using SE and GE

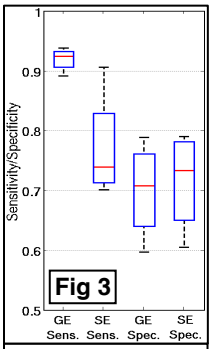


**Fig 3:** Sensitivity and specificity across all subjects of GE and SE sequences to DMN

**Results**: The group-average GE and SE-BOLD based connectivity maps are shown on the cortical surface in Fig. 1, for both the PCC and the PHC seeds. The subcortical connectivity maps (SE and GE) for the caudate seed are shown in Fig. 2, along with an inset anatomical diagram of the full caudate in red. Compared to GE, SE maps included more connectivity between PHC and the entorhinal cortex (EC) (a region known to be functionally connected to the PHC [6]). Interestingly, SE-BOLD connectivity maps also showed caudate connectivity extending from its head to its tail, which GE-BOLD failed to show. The sensitivity and specificity of both techniques for detecting the default-mode network is shown in Fig. 3, across all subjects. SE-EPI provided a lower sensitivity than GE-EPI (but still accurately produced the default-mode network at statistically significant levels in all subjects) and slightly higher specificity. Finally, a raw GE-EPI scan is overlaid on a SE-EPI scan of the same subject in Fig. 4; note the GE-EPI's loss of signal in areas affected by susceptibility (e.g. medial orbitofrontal cortex (MOFC), inferior temporal lobe (ITL)).

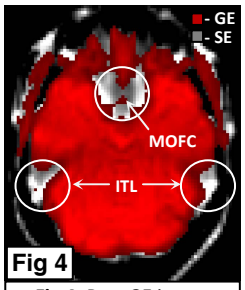


**Fig 4:** Raw GE image over raw SE image

**Discussion**: These results demonstrate that not only is SE-EPI sensitive to resting-state BOLD fluctuations in the human brain and able to produce default-mode connectivity maps, but that in certain ROIs, such as the entorhinal cortex and subcortical regions such as the caudate, it is actually more sensitive than GE-EPI. This can most likely be attributed to SE-EPI's lower sensitivity to susceptibility effects, making it more robust than GE-EPI to BOLD fluctuations in ROIs normally affected by these issues, such as the medial orbitofrontal cortex, inferior temporal lobe, parahippocampal gyrus (which contains the entorhinal cortex), and tail of the caudate (close to the amygdala) [7]. The lower sensitivity of SE-EPI compared to GE-EPI in the default-mode network is a result of the higher sensitivity of GE-EPI to the $T_2$* changes caused by intravascular effects. The increase in specificity seen with SE-EPI may be an indication of sensitivity to localized microvasculature rather than large veins, but it may again be a result of SE-EPI's reduced sensitivity to the BOLD signal. Note that to maximally benefit from the advantages of SE-EPI BOLD, the EPI readout echo train length should be made as short as is feasible.

**Conclusion:** SE-EPI can be used confidently to generate resting-state functional connectivity maps. In the case of the default-mode network, it shows lower sensitivity but marginally higher specificity than GE-EPI. The unique advantage of SE-EPI over GE-EPI is particularly evident when studying ROIs affected by signal loss/artifacts due to susceptibility effects, such as those related to MR field inhomogeneities, metal implants or lung-volume changes.

**References:** **[1]** Biswal, B et al. Magn Res Med 1995; 34:537-41 **[2]** Damoiseaux, J et al. Proc Natl Acad Sci USA 2006; 103:13848-53 **[3]** Yacoub, E et al. Magn Res Med 2003; 49:655-64 **[4]** Majeed, W et al. Proc Intl Soc Mag Res Med 2009; 17:1666 **[5]** Whitfield-Gabrieli, S et al. Brain Connect 2012; 2:125-41 **[6]** Lacy, J et al. Hippocampus 2012; Jun 27 **[7]** Merboldt, K-D et al. Neuroimage 2001; 14:253-257