Resting-State Functional Hubs at Multiple Frequencies Revealed by MR-Encephalography

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Introduction Resting-state fMRI is performed in the absence of specific cognitive tasks and it records spontaneous BOLD signal fluctuations [1], which reflect the baseline human brain activity. Common resting-state studies analyze signal fluctuations below 0.1 Hz acquired by conventional echo-planar imaging with TR around two seconds. However it has been reported that resting-state functional connectivity can still be observed at higher frequencies [2-4]. High-temporal resolution imaging provides the possibility to observe the brain networks in the temporal and spectral dimensions in addition to the common spatial perspective. MR-Encephalography (MREG, [5]) is one of the fast-imaging techniques that are able to obtain a whole-brain volume image in less than one second. In this study we used MREG with a highly under-sampled single-shot stack of spirals trajectory [6] to record resting-state fMRI signal with 100-msec temporal resolution. Independent component analysis (ICA) and partial correlation analysis were used to analyze the network characteristics and determined the hub locations at different frequencies, which is important for understanding the functional coordination of the brain.

Methods Resting-state fMRI data from ten healthy volunteers were collected on a 3.0 T Siemens Trio scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Subjects were instructed to close their eyes and relax during the scan session. The single-shot stack of spirals acquisition has a TR of 100 msec. In each session 4096 time frames were acquired (total scan time 6 min 50 sec), and the first 15 sec were discarded for signal stability consideration. Imaging volume has a 192 × 192 × 192 mm^3 FOV, and was later reconstructed into a 64 × 64 × 64 matrix using the forward operator estimated from a non-uniform FFT (nuFFT) algorithm based on coil sensitivity weightings and measured gradient trajectory. All post-processing was done in MATLAB (The Mathworks, Inc., Natick, MA).

Reconstructed images were corrected for rigid-body motion in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and filtered into three frequency bands (0.01~0.1 Hz, 0.5~0.8 Hz and 1.5~5 Hz). ICA based on Infomax algorithm was performed with target component number set to 80 for the optimized number of reliable components determined by Icasso result. The partial correlation between each pair of reliable components' time courses was calculated and used to construct a weighted connectivity matrix. From the connectivity matrix we calculated the modified connection strength ([7], eq.3, $\alpha = 0.5$) of each spatial component. Clustering coefficients, shortest path lengths of the networks were also estimated.

Results The connection strength maps at different frequencies are shown in Figure 1. The highly-connected hubs at 0.01~0.1 Hz include medial prefrontal cortex, pre- and post-central cortices, posterior cingulate cortex (PCC), precuneus and visual regions. In the two higher frequency bands the hub areas are the medial prefrontal cortex, pre- and post-central cortices, precuneus and visual cortices. Other network characteristic measures are listed in Table 1. In the three frequency bands the ratio of the average clustering coefficients over random networks with the same set of nodes are 1.39, 1.42, and 1.25, respectively. Networks in all three bands also exhibit comparable characteristic path lengths as random networks, with the length ratios being 0.97, 0.98, and 0.97, respectively.

Discussion The high connection strength areas at 0.01~0.1Hz are consistent with the functional hubs reported in literature. The most significant difference between signals below 0.1 Hz and above 0.5 Hz is the drop in connectivity in PCC, which is a major part of the default mode network. Similar connectivity decrease in PCC region could already be observed at 0.2 ~ 0.3 Hz in previous degree centrality study [8]. All three average clustering coefficient ratio values over randomized network of the same vertex set are greater than one, only at 1.5~5 Hz the value dropped about 10% compared to the lower two bands. The average shortest path lengths are very close to those in random networks. Big clustering coefficient ratio and shortest path length ratio around one together display hints of a small-world organization in the resting-state brain functional structure across a broad range of frequencies.

Conclusion This study used high temporal resolution MREG technique to assess resting-state functional connectivity at different frequencies. From the preliminary data we identified hub regions at 0.01~0.1 Hz, 0.5~0.8 Hz and 1.5~5 Hz. In these small-world-like networks similar hub regions were found across multiple frequency bands but difference was also observed in parts of the default mode network. Further study of this frequency-dependent network structure could provide extra information about the baseline organization of human brains.

References [1] Biswal *et al.*, MRM 34: 537–541 (1995); [2] Wu *et al.*, NeuroImage 42:1047-1055 (2008); [3] Niazy *et al.*, Prog. Brain Res. 193:259–276 (2011); [4] Lee *et al.*, Neuroimage 65:216–222 (2012); [5] Hennig *et al.*, NeuroImage, 34:212-219; [6] Assländer *et al.*, NeuroImage 73:59-70 (2013); [7] Opsahl *et al.*, Soc. Networks 32:245-251 (2010); [8] Liao *et al.*, NeuroImage, *in press.*
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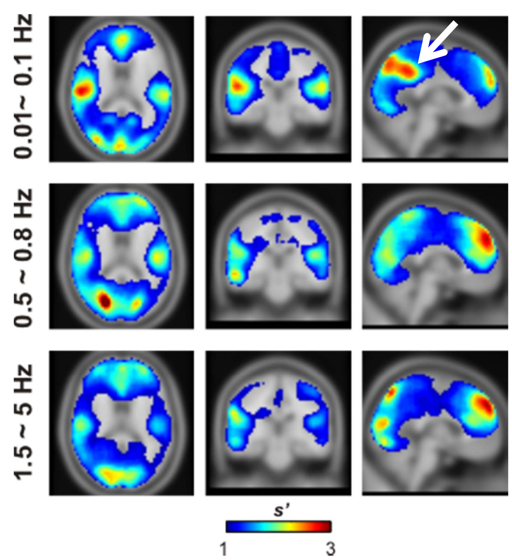

Figure 1 The spatial distribution of connectivity strength at different frequencies. The strongly connected areas include medial prefrontal cortex, pre- and post-central cortices, precuneus and visual cortices. The connecting strength in PCC (white arrow) is strong only at the lowest frequency.

Frequency (Hz)	Clustering Coefficient	Characteristic Path Length
0.01 ~ 0.1	1.39	0.97
0.5 ~ 0.8	1.42	0.98
1.5 ~ 5.0	1.25	0.97

Table 1 The network characteristic measures at different frequencies. The Clustering Coefficient and Characteristic Path Length are normalized to the average of 100 randomized networks of the same set of vertices.