Functional Hippocampal Connectivity Identifies AD Risks in Mild Cognitive Impairment Subjects

Z. Wu[1], G. Xu[1], P. Antuono[2], and S-J. Li[1]

[1]Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States, [2]Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Introduction: The hippocampus in medial temporal lobe (MTL) is one of the initial loci of the Alzheimer's Disease (AD). Functional synchrony within the hippocampus [1] and the functional connectivity within the default-mode network were found to be deteriorated in AD subjects [2]. We hypothesized that the hippocampal connectivity is significantly reduced in amnestic mild-cognitive impaired (aMCI) subjects. Moreover, the regional hippocampal connectivity can serve as a risk factor for marking the preclinical stage of AD. In the present study, cross-correlation analysis on spontaneous low-frequency fluctuations in the resting-state voxel time courses revealed a significant reduction in the hippocampal connectivity that could differentiate aMCI from age-matched cognitively normal (CN) subjects.

Materials and Methods: Sixteen aMCI subjects and 21 CN subjects were recruited and written consent forms were obtained. Resting functional MRI (fMRI) datasets were obtained from the whole brain in 6 min at a GE 3T whole-body scanner with a single-shot gradient echo-echo planar imaging (EPI) pulse sequence. The imaging parameters were: TE = 25 ms, TR = 2,000 ms, flip angle = 90º, slice thickness of 4 mm, matrix size of 64×64, filed of view of 24 cm. High resolution SPGR 3D images were acquired for anatomical reference. The resting fMRI conditions were defined, as no specific cognitive tasks were performed. The lights were dimmed and subjects were instructed to close their eyes and think about nothing during scans. The resting-state fMRI data was first preprocessed with registration by AFNI software [3]. Out of the 180 points for each voxel time series, 173 points were kept, while the first 5 and the last 2 points were discarded to preserve steady-state data only, followed by Hamming filter to keep only low-frequency fluctuations within 0.015 Hz and 0.1 Hz [4]. The regional hippocampal connectivity map was obtained with two steps: 1) Cross-correlate each voxel time course in the hippocampus to all voxel time courses of the whole brain for individual subjects. In order to reduce the contamination of noise and motion artifacts, only voxels with absolute values of the cross-correlation coefficients within the range of 0.15 and 0.60 were included in the functional connectivity analysis. 2) Conduct group *t*-tests between the aMCI and CN groups with a program (Alphasim, AFNI) to identify brain regions (or ROIs) of significant difference between the two groups, thereby creating the regional hippocampal connectivity map (rHCM). The regional hippocampal connectivity index (rHCI) was then obtained by averaging the absolute value of cross-correlation coefficients within the rHCM.

Results: The voxelwise group comparison between the MCI and control groups revealed a reduction in the rHCM, which included the bilateral medial frontal gyrus, cunes, precunes, anterior and posterior cingulate gyrus, superior temporal gyrus, parahippocampal gyrus, fusiform gyrus, and right inferior parietal lobe (Figure 1). The rHCI for the CN (0.395 ± 0.013) was significantly lower than that of the aMCI (0.358 ± 0.010) using *t*-test ($p < 10^{-10}$), as shown in Figure 2. With a cutoff value of 0.377, the test yielded a sensitivity of 90.5% and a specificity of 93.8% in distinguishing aMCI from CN subjects. Figure 3 shows that the rHCI was significantly correlated with the RAVLT ($R^2 = 0.37$, $p = 0.0001$) neuropsychological test scores.

Discussion: We examined the functional connectivity between the hippocampus and the whole brain and found significantly lower connectivity in the regions of cuneus, precuneus, and posterior cingulate, etc, in aMCI subjects. The rHCI between these regions and the hippocampus provides the differentiation of aMCI from normal aging with high sensitivity and specificity. The rHCI is highly correlated to neuropsychological test scores, which implies that the mild-cognitive memory impairment is related to the hippocampal connectivity loss occurring in the MTL network. Our results suggest that the rHCI could potentially serve as a noninvasive quantitative marker for the preclinical stage of early AD.

References: 1. Li, S-J, et al., *Radiology*, 225:253, 2002. 2. Greicius, MD, et al, *PNAS*, 101(13): 4637, 2004. 3. Cox, RW, *Comput Biomed Res*, 29(3):162, 1996. 4. Orfanidis, SJ, *Introduction to signal processing*. Englewood Cliffs, NJ: Prentice Hall, 1996.

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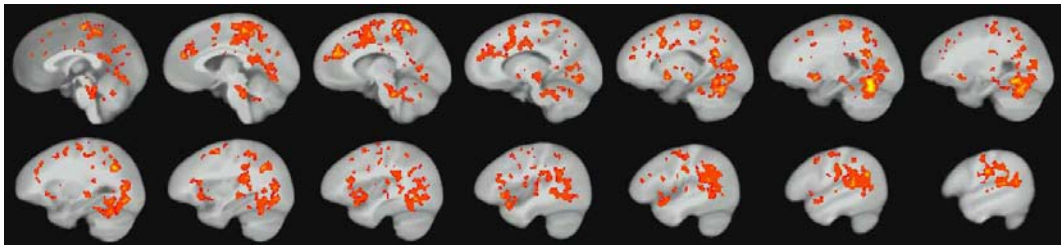

Figure 1. Disruption of the hippocampus connectivity is region-specific between amnestic MCI and CN groups. These regions include 1. bilateral medial frontal gyrus; 2. bilateral precunes; 3. anterior cingulate gyrus, 4. posterior cingulate gyrus; 5. bilateral superior temporal gyrus; 6. bilateral parahippocampal gyrus; 7. posterior lateral cortex, 8. fusiform gyrus, etc.

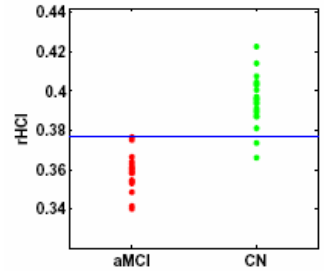

Figure 2

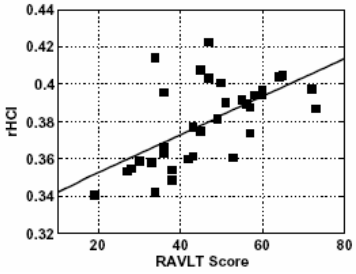

Figure 3

Figure 2. Regional hippocampal connectivity index (rHCI) within the hippocampal connectivity map can significantly separate the MCI group from CN group with a sensitivity of 90.5% and a specificity of 93.8%.

Figure 3. Linear regression between rHCI and RAVLT scores. The regional hippocampal connectivity index is significantly correlated to the scores of RAVLT ($R^2 = 0.37$, $p = 0.0001$), which implies that the mild-cognitive memory impairment is related to the hippocampal connectivity loss.