Capacity Scores of Functional Synchrony in MCI subjects are Significantly Lower than in Age-Matched Controls Determined by ICA Analysis

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Introduction: Studies have shown that the hippocampus is an important region involved in early Alzheimer's disease (AD) onset [1]. Li, et al., demonstrated that the BOLD-based functional synchrony between voxel time courses within the region of the hippocampus was substantially decreased in AD patients [2]. It is not known, however, if the functional synchrony between the hippocampus regions and other brain regions would be significantly reduced in mildly cognitive impaired (MCI) subjects. Such a distinction in the functional synchrony between MCI and the control subjects could serve as a risk factor for marking the preclinical stage of AD. To test our hypothesis that the functional synchrony is deteriorated in MCI subjects, we examined the resting state fMRI voxel time courses for MCI and age-matched control subjects. Independent component analysis (ICA) on spontaneous low frequency fluctuations revealed a significant decrease in functional synchrony among MCI subjects when compared to the controls.

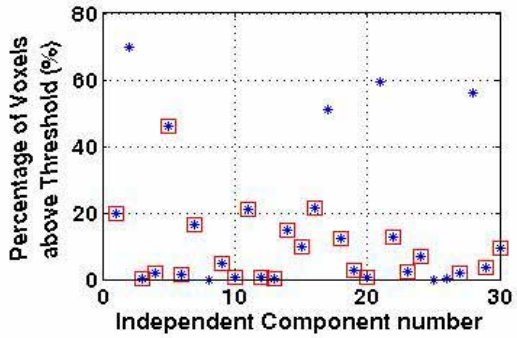
Materials and Methods: Eight MCI subjects and nine age-matched cognitively healthy control subjects were recruited and written consent forms were obtained. Resting functional MRI (fMRI) datasets of the whole brain were obtained in 6 min at a GE 3T whole body scanner with a single-shot gradient echo-echo planar imaging (EPI) pulse sequence. The imaging parameters were: TE = 25 ms, TR = 2,000 ms, flip angle = 90º, slice thickness = 4 mm, matrix size = 64×64, field of view = 24×24 cm. High resolution SPGR 3D images were acquired for anatomical reference. The resting fMRI conditions were defined, as no specific cognitive tasks were performed and subjects were instructed to think about nothing with their eyes closed during the scans while in a dim scanning room. The resting-state fMRI data was first preprocessed with registration, linear detrend, and Gaussian smoothing (4-mm kernel) 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 use of a Hamming filter to keep only low frequency fluctuations within 0.015 Hz and 0.1 Hz [2]. ICA [4] was then performed in the hippocampus to extract 30 components. Each independent component was cross correlated to the whole brain to identify voxels with a threshold of 0.25 coefficient followed by clustering. The percentage of voxels whose cross-correlation coefficients were above the threshold was calculated relative to the whole brain voxels. Those ICA components that related to motion or noise were discarded for further analysis based on the following procedures. First, any motion component was removed [5]. Second, components whose percentages of voxels were larger than 50% were removed and were considered nonrelevant components. Third, noise components and very low energy components were removed. To do this, we calculated the maximum cross correlation coefficient after a time shift between the voxel time course and the independent component time series. An ICA component with low voxel percentage (1.0%) was classified as noise or energy weak if the percentage was still low (1.5%) after such a time shift [6]. With all the remaining independent components, the corresponding percentages of voxels were averaged. The mean of the percentage of voxels was defined as the capacity score of functional synchrony for a subject.

Results: Fig. 1 shows the percentage of voxels in the whole brain that were correlated with hippocampus for each independent component obtained from a control subjects. Selected ICA components for capacity score calculation were labeled with red boxes. Fig. 2 demonstrates the capacity scores for each subject in the two groups. The means were 11±2.1% for controls and 8.0±1.8% for the MCI group. The means were significantly different with *t* test ($p = 0.005$). Using a cutoff of 9.1%, the test yielded a high sensitivity of 89% and a high specificity of 88% in differentiating MCI subjects and healthy aging subjects.

Discussion: This study examined the capacity score of functional synchrony with spontaneous low frequency fluctuations between the hippocampus and whole brain in the MCI and control subjects. The capacity scores of functional synchrony is deficient in MCI subjects and have high sensitivity and specificity. It was demonstrated that resting hippocampal activities synchronize with other brain regions stronger in control subjects than in MCI subjects. The capacity score could be served as a preclinical risk marker for AD.

References: 1. Lee, BCP., etc., *J. Neuroimaging*, 13:199, 2003. 2. Li, S-J., etc., *Radiology*, 225:253, 2002. 3. Cox, RW., *Comp. & Biomed. Research*, 29:162, 1996. 4. Hyvärinen, A., etc., *Neural Comput*. 9:1483, 1997. 5. Wu, Z., etc., *ISMRM* 2006, submitted. 6. Xu, Y., etc., *Proc. ISMRM* 13:1456, 2005.

Acknowledgement: This work was supported by NIH Grants AG20279 and RR00058.



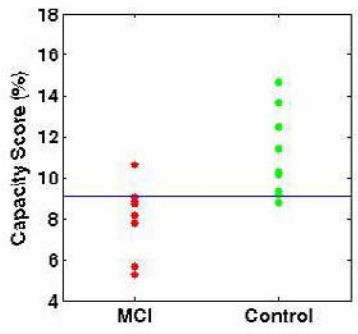


Fig. 1. Percentage of correlated voxels between hippocampus and the whole brain for each independent component. Selected components for capacity score calculation are labeled with boxes.

Fig. 2. Individual capacity scores for controls and MCI subjects. The group means were significantly different in *t* test ($p = 0.005$). The horizontal line indicates a cutoff point of 9.1%, yielding a sensitivity of 89% and a specificity of 88%.