Regional Hippocampal Connectivity Index: Evaluation of an fMRI Marker for Alzheimer's Disease

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Introduction: Alzheimer's Disease (AD) is a chronic disorder with an insidious onset. In order to facilitate the prevention and treatment of AD, researchers and clinicians must be able to mark its preclinical stage before the brain damage becomes irreversible. Conventional fMRI studies found increased BOLD activation [1,2] and decreased BOLD responses [3,4] in amnestic mild-cognitive impairment (aMCI) and AD groups. Such a discrepancy could significantly impair the potential for the fMRI-BOLD method to serve as a biomarker for AD, since the relationship between the compensatory responses and the disease progression is nonmonotonic. In addition, the fMRI-BOLD method has a well-known drawback in its high inter- and intra-subject variability. In a longitudinal study, the repeatability and reliability measurements are vitally important, especially when the longitudinal measurement is for studying the changes in individuals, rather than evaluating group differences. In this study, we propose a regional hippocampal connectivity index (rHCI) as a risk biomarker for early AD. The relationship between the rHCI and age was tested using cognitively healthy and aMCI subjects and the repeatability was tested in cognitively normal (CN) subjects.

Materials and Methods: Four groups of subjects, as shown in the table, were recruited and written consent forms were obtained. Group I consisted of healthy young subjects; Group II was comprised of age-matched CN subjects; Group III represented the aMCI subjects; Group IV consisted of age-matched CN subjects who were scanned twice in 2005 and 2006 with at least a one-year interval. 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, sagittal slice thickness = 4 mm, number of slices = 36, matrix size = 64×64, field of view = 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 in the scan room were dimmed and subjects were instructed to close their eyes and think about nothing during the scans. The rHCI was calculated as the cross-correlation of voxel time courses between the hippocampus and the disrupted hippocampal connectivity map [5]. Linear regression analysis was performed for the rHCI in Groups I and II to evaluate the index change with age among healthy people. Nonlinear regression analysis was performed for the rHCI in Groups I and III to demonstrate the index decline evident in MCI and younger subjects. For Group IV, the rHCIs were compared using the two scans from each subject in order to provide test-retest repeatability over a one-year period.

Group	Category	Age	# of Subjects
I	Young	30 ≤ Age ≤ 58	13
II	Healthy Aging	Age ≥ 65	21
III	aMCI	Age ≥ 65	16
IV	Healthy Aging	Age ≥ 65	9

Results: The linear regression analysis showed that there is no significant correlation between the rHCI and the age of cognitively normal subjects (Figure 1). On the other hand, in diseased aging, as evidenced by aMCI subjects, the rHCI showed accelerated decay (F-test, $P<1.1\times10^{-6}$) (Figure 2). The averaged changes measured in 2006 decreased (-1.1%) with a standard deviation of ±3.6%. All individual subjects showed less than 5% change in comparison with the measured connectivity in 2005.

Discussion: The results suggest that the rHCI is preserved in the cognitively healthy population with age, while subjects with early AD risk have a significant decline. This monotonic characteristic between the rHCI and diseased aging is essential in establishing a risk marker for AD. In comparison, the task-driven fMRI methods, that induce the U-shaped nonmonotonic BOLD responses due to compensatory mechanisms, would be limited as potential markers. The changes of the rHCI observed in a one-year period are not significant. The -1.1% decline may reflect the rate of the normal aging processes. The test-retest results demonstrate that the hippocampal connectivity measurement in the medial temporal lobe network is a reliable measure for longitudinal study. In conclusion, the proposed rHCI provides a monotonic marker with age and a reliable test-retest index that allows robust measurement for a longitudinal AD study.

References: 1. Dickerson, BC, et al. *Ann Neurol* 2004;56(1):27-35. 2. Grady, CL, et al. *J Neurosci* 2003;23(3):986-993 3. Machulda, MM, et al. *Neurology* 2003;61(4):500-506. 4. Petrella, JR, et al. *Radiology* 2006;240(1):177-186. 5. Wu, Z., et al., *ISMRM* 2007, submitted.

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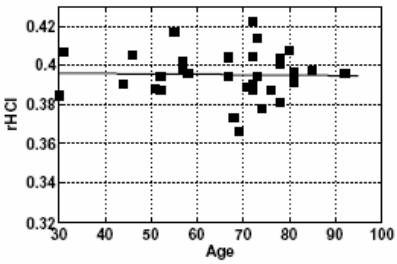

Figure 1

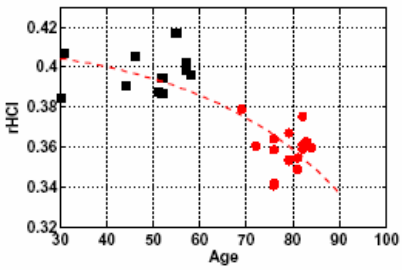

Figure 2

Figure 1. Linear regression analysis showed no significant correlation between the rHCI and the age of cognitively normal subjects.

Figure 2. Accelerated rHCI decay in aMCI (filled red dots) compared to young subjects (filled black squares).