Biphasic Changes of Functional Hippocampal Connectivity Identifies AD Risks

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Introduction: The functional brain networks have been shown to be organized as anticorrelated networks [1] with biphasic characteristics. As one of the initial loci of Alzheimer's disease (AD), the hippocampus plays an important role in brain memory networks. Disruption of the hippocampal connectivity represents a risk factor in early AD progression [2, 3]. However, it is not clear if the functional hippocampal connectivity also presents the biphasic characteristics and if the change of these characteristics can identify AD risks. In this study, we examined the functional hippocampal connectivity at resting-state using functional MRI (fMRI) to test our hypothesis that the anticorrelated networks exist in hippocampal connectivity and the changes of the biphasic characteristics within the networks identify amnestic mild cognitive impaired (aMCI) and AD subjects from age-matched cognitively normal (CN) subjects.

Materials and Methods: Sixteen aMCI subjects, 14 AD subjects, and 20 CN subjects were recruited and written consent forms were obtained. Resting 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, field of view of 24 cm. High-resolution SPGR 3D images were obtained for anatomical reference. The resting-state fMRI data was first preprocessed with registration by AFNI software [4]. Based on the motion parameters achieved from registration, one aMCI subject, two AD subjects, and one CN subject were excluded from further analysis due to more than 1 mm or 1º motion. 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 detrend and removal of the average signals from white matter and CSF, as well as the six motion vectors from volume registration to reduce confounding factors. Next, the Hamming filter was applied to keep only low frequency fluctuations within 0.015 Hz and 0.1 Hz [5]. The functional hippocampal connectivity map was obtained with two steps: 1) Cross-correlate the seed voxel time course in the hippocampus to all voxel time courses within regions defined by Tzourio-Mazoyera [6] for individual subjects, followed by Fisher's transformation. 2) Conduct a group *t*-test against zero for each group of CN, aMCI, and AD subjects to identify voxels with significant functional hippocampal connectivity and the *t* score is converted to *z* score. Cluster analysis (Alphasim, AFNI) is then performed to identify brain regions of significant functional hippocampal connectivity with individual voxel significant level of $p < 0.05$ and cluster size > 4048 mm^3. To further explore the hippocampal connectivity in differentiating the CN, aMCI, and AD groups, the hippocampal connectivity index (HCI) is calculated for each individual subject as the average *z* score obtained from cross correlation coefficient within left inferior parietal cortex (IPC) negatively correlated to hippocampus.

Results: The functional hippocampal connectivity maps for the CN, aMCI, and AD groups are shown in Figure 1. Network positively correlated to the hippocampus is indicated with warm color and the network negatively correlated to hippocampus is indicated with cold color. In the CN group, significant positive hippocampal connectivity is found in the bilateral posterior cingulated cortex (PCC) extended to cuneus and precuneus, anterior cingulated cortex, and the hippocampus itself. Reduced hippocampal connectivity is observed in the PCC and hippocampus in the AD group, but not clearly seen in the aMCI group. The network with significant negative correlation to the hippocampus is found in the bilateral superior frontal cortex (SFC) and the IPC in the CN group. In the negatively correlated network, the bilateral IPC is diminished for both aMCI and AD groups and the left SFC is diminished in the AD group. The HCIs within the left IPC (circled in the left three columns in Fig. 1) were -2.91±0.93, -2.40±0.41, and -2.13 ±0.24 for the groups of CN, aMCI, and AD, respectively. A significant difference in the HCI was found between the groups of CN and MCI (p = 0.04), CN and AD (p = 0.002), and MCI and AD (p = 0.04).

Discussion: We examined the functional hippocampal connectivity at resting-state using fMRI. The hippocampal connectivity in the CN group consists of significant anticorrelated networks, which are similar to the default mode network [7]. The AD group suffers a disrupted network in both positive and negative correlation to the hippocampus, while the aMCI group mainly suffers the disrupted network in negative correlation to hippocampus. Regions with reduced biphasic characteristics in aMCI and AD groups are consistent with findings in other AD studies [8]. Furthermore, the HCI within the network can differentiate the three groups. These results suggest that the biphasic characteristics of the resting-state brain network are important in healthy CN subjects and are deteriorated along with AD progression. The HCI may serve as a potential biomarker for early AD.

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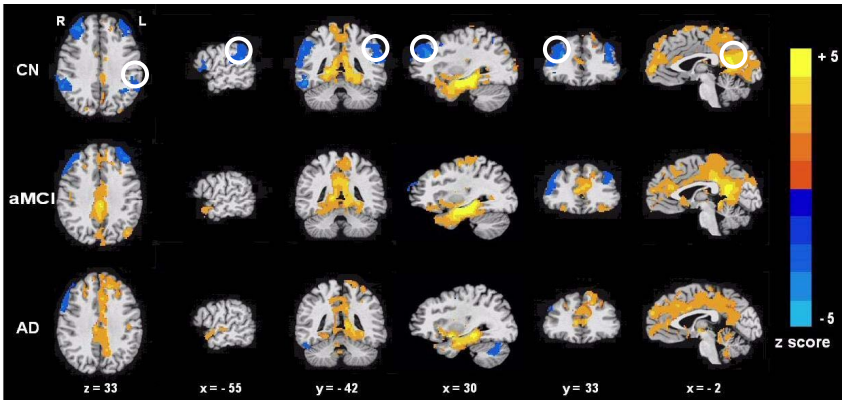

Figure 1. Functional hippocampal connectivity maps for CN, aMCI, and AD groups. Network positively correlated to hippocampus is indicated with warm color and the network negatively correlated to hippocampus is indicated with cold color. In the CN group, regions positively correlated to the hippocampus include bilateral PCC extended to cuneus and precuneus, anterior cingulated cortex. Regions negatively correlated to hippocampus include SFC and IPC. The aMCI group suffers disruption of the negative connection in bilateral IPC. The AD group suffers reduced positive connection in bilateral PCC and disruption of the negative connection in bilateral IPC and left SFC. The white circles represent the regions of interests.