

## Alteration pattern of gray matter and small-world networks in the human brain revealed by quantitative water diffusivity from MRI.

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**Target audience:** It is generally accepted that the diagnostic criteria for aMCI and AD focused on the use of MRIs as important supportive evidence. Therefore, it was of particular importance to explore neuroimaging diagnostic surrogate during the pathological process from aMCI to AD. Recent years, the apparent diffusion coefficient (ADC) from diffusion-weighted imaging (DWI) can quantify the variations in water diffusivity derived from microscopic structural changes. Connectivity plays a critical role in mediating cognitive function, therefore, there is already a growing literature of functional connectivity associated with the transition of aMCI to AD. Functional connectivity refers to interregional cooperation that can be represented by human cerebral cortical thickness measurements or a synchrony of low frequency fluctuations (LFFs) in signal at cerebral blood oxygen level-dependent (BOLD) functional magnetic resonance (MR) imaging. The breakdown of connectivity, both in the functional and structural system domain, plays a major role in the onset of AD symptoms. The breakdown is thought to be due to chronically progressive AD neuropathology with underlying molecular mechanisms leading downstream to neuronal and synaptic dysfunction and ultimately to neuronal loss.

**Purpose:** To investigate alteration pattern of gray matter and small-world networks in the human brain revealed by quantitative water diffusivity from MRI for aMCI and AD.

**Materials and Methods:** In total, 30 patients with AD, 30 patients with aMCI, and 30 normal controls (NCs) were recruited. DWI was performed at 3.0 T with FLAIR, and the independent ADC mapping was generated using DTIStudio software. Ninety automated anatomic labeling atlas (AAL) for regional parcellations were adopted in software Brain Search (BS), which is developed by our group. The gray scale intensities (namely ADC value for water diffusivity) of each anatomical brain region were compared among aMCI, AD and NC by BS. In order to explore the network in patients' brain, the statistical similarity in ADC value between each AAL was measured by the Pearson correlation coefficient across subjects and interregional correlation matrix. In addition, a graph theoretical analysis was performed by Brainnetviewer software to explore the small world properties.

**Results:** During the pathological process of AD, the changes of water diffusivity appeared first in the left hippocampus, then gradually progressed to the bilateral sides and eventually displayed right lateralization. The ADC values from aMCI were obviously elevated compared to the values from the NC group in the left limbic cortex. There was a negative correlation between the ADC values and the scores from MMSE, MoCA, the Digit test, Raven's IQ, and WAIS IQ. Additionally, the ADC values were positively correlated with the scores from CDR, ADL, and ADAS-Cog. The number of the correlation matrix is reduced in patients with aMCI and AD, while  $r > 0.8$ . Global and local efficiency as well as these coefficients are in consistent with the small world network property with lower cost ( $< 0.5$ ) and higher efficiency ( $> 0.5$ ) and global efficiency decreased in aMCI and AD. The brain networks included some hub nodes with many connections, including 9 regions of the limbic, 2 regions of the primary motor and sensorymotor cortex. The mean degree of human brain diffusivity networks decreased in aMCI and AD.

**Discussion:** The loss of neuron cells, axons, and dendrites in AD patients contributes to the expansion of the extracellular space, leading to a loss of restrictive barriers and acceleration of water diffusivity<sup>2</sup>. Most aMCI cases showed early AD pathologic features in the limbic cortex<sup>2, 34</sup>. In addition to hippocampus and parahippocampal gyrus, our BS software can effectively analyze other brain regions, including the insular cortex, the medial prefrontal regions, the Rolandic operculum, the thalamus and the cingulum. Recently, insula has attracted increasing attention for its role in body representation and subjective emotional experience. However, the medial prefrontal lobe seems to function in network in its role in retrospective memory. In our study, the results from water diffusivity of the limbic system correlated significantly with clinical rating scales, which measured different impairments of the cortex, including language, attention/execution, abstract reasoning and study ability. In contrast to SPM, a method based on the VBA method, BS is based on the AVOI that utilizes the AAL atlas as a template<sup>29</sup>. The advantage of using AVOI is that it parcellated each cerebral cortex into 45 anatomical brain ROIs to reduce type II statistical error. Such errors were inevitable in VBA. Furthermore, BS results are reported anatomically with AAL labeling, and it is convenient to link the ADC value changes to the affected brain regions. A limitation of this study is the lack of pathologic confirmation in all subjects. Patients who meet the clinical criteria for AD often have some degree of vascular dementia pathology. Although we excluded subjects who had a score higher than 4 on the Hachinski Ischemic Scale and those who had the presence of leukoaraiosis higher than a Fazekas' grade I, we acknowledge that some of our patients likely have mixed pathologies. We will follow-up with all cases to verify our hypothesis.

**Conclusion:** The water diffusivity for aMCI and AD displays asymmetric anatomical lateralization. Left HP connectivity dismissed in aMCI firstly, while  $r > 0.6$ . Connectivity Degree in the right HP is larger than the left. The global efficiency and the connectivity degree decreasing reflected a more regular configuration in aMCI and AD brain networks.

**Keywords:** Apparent diffusion coefficient mapping, Amnesic Mild Cognitive Impairment, Small world networks, Automated anatomic labeling atlas

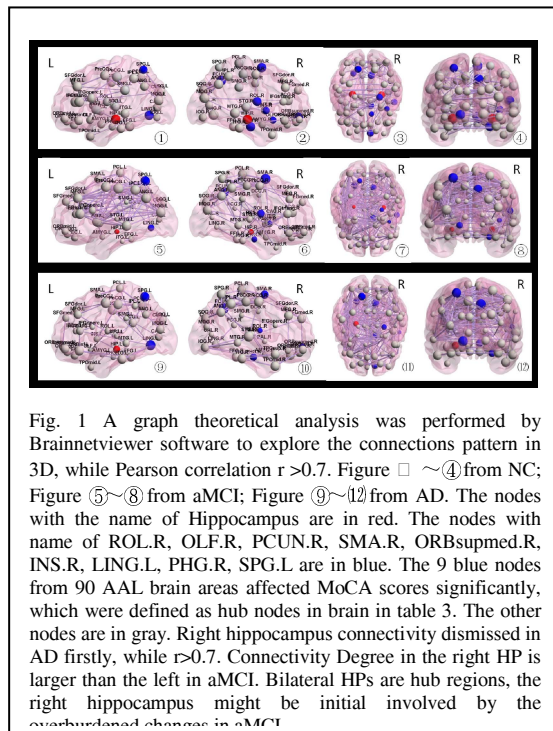


Fig. 1 A graph theoretical analysis was performed by Brainnetviewer software to explore the connections pattern in 3D, while Pearson correlation  $r > 0.7$ . Figure ①~④ from NC; Figure ⑤~⑧ from aMCI; Figure ⑨~⑫ from AD. The nodes with the name of Hippocampus are in red. The nodes with name of ROL.R, OLF.R, PCUN.R, SMA.R, ORBsupmed.R, INS.R, LING.L, PHG.R, SPG.L are in blue. The 9 blue nodes from 90 AAL brain areas affected MoCA scores significantly, which were defined as hub nodes in brain in table 3. The other nodes are in gray. Right hippocampus connectivity dismissed in AD firstly, while  $r > 0.7$ . Connectivity Degree in the right HP is larger than the left in aMCI. Bilateral HPs are hub regions, the right hippocampus might be initial involved by the overburdened changes in aMCI.