ARCHIVAL REPORT

Disrupted Functional Brain Connectome in Individuals at Risk for Alzheimer's Disease

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Background: Alzheimer's disease disrupts the topological architecture of whole-brain connectivity (i.e., the connectome); however, whether this disruption is present in amnestic mild cognitive impairment (aMCI), the prodromal stage of Alzheimer's disease, remains largely unknown.

Methods: We employed resting-state functional magnetic resonance imaging and graph theory approaches to systematically investigate the topological organization of the functional connectome of 37 patients with aMCI and 47 healthy control subjects. Frequency-dependent brain networks were derived from wavelet-based correlations of both high- and low-resolution parcellation units.

Results: In the frequency interval .031–.063 Hz, the aMCI patients showed an overall decreased functional connectivity of their brain connectome compared with control subjects. Further graph theory analyses of this frequency band revealed an increased path length of the connectome in the aMCI group. Moreover, the disease targeted several key nodes predominantly in the default-mode regions and key links primarily in the intramodule connections within the default-mode network and the intermodule connections among different functional systems. Intriguingly, the topological aberrations correlated with the patients' memory performance and differentiated individuals with aMCI from healthy elderly individuals with a sensitivity of 86.5% and a specificity of 85.1%. Finally, we demonstrated a high reproducibility of our findings across different large-scale parcellation schemes and validated the test-retest reliability of our network-based approaches.

Conclusions: This study demonstrates a disruption of whole-brain topological organization of the functional connectome in aMCI. Our finding provides novel insights into the pathophysiological mechanism of aMCI and highlights the potential for using connectome-based metrics as a disease biomarker.

Key Words: Connectivity, connectomics, default-mode, MCI, modularity, small-world

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by a decline in cognitive and memory functions likely caused by aberrant neuronal circuitry (1–3). Amnestic mild cognitive impairment (aMCI), a transition state between normal aging and AD, has a high risk of progressing to AD (4). Numerous studies have reported that the brains of patients with aMCI have impaired structural integrity (5,6) and functional connectivity (7–10). However, whether aMCI patients also exhibit a disrupted topological organization in their whole-brain networks remains largely unknown.

Recent studies have suggested that human whole-brain structural and functional networks (i.e., the connectome [11,12]) can be constructed using multimodal neuroimaging data and that their topological organization can be characterized quantitatively using various graph theory metrics (13–15). With these metrics, many nontrivial organizational principles, including small-worldness, modularity, and highly connected hubs, have been observed in the human brain connectome. Moreover, these network properties are disrupted in many neuropsychiatric disorders (13,16–18). These studies have accelerated the process of mapping the human connectome in healthy and diseased states. Specifically, in patients with AD, several research groups have reported topological alterations in the whole-brain connectome, including a loss of small-worldness and a redistribution of hubs (19–23). With respect to aMCI, only two studies have explored the topological organization of the whole-brain connectome. Using structural magnetic resonance imaging, Yao *et al.* (24) found no differences in the topology of cortical-thickness networks between patients with aMCI and healthy control subjects. However, using magnetoencephalography data, Buldu *et al.* (25) reported reorganization of the functional connectome in aMCI patients during a memory task.

Here, we employed resting-state functional magnetic resonance imaging (R-fMRI) to investigate the topological changes in the functional connectome in patients with aMCI. R-fMRI measures intrinsic or spontaneous neuronal activity of the brain (26,27) and has been applied to reveal aMCI-related breakdowns in functional brain synchronization (7,9,28). The current study focuses exclusively on the topological architecture of the intrinsic functional brain connectome in aMCI. Specifically, we sought to determine whether aMCI disrupts the topological organization of the whole-brain functional network and, if so, whether those topological abnormalities are associated with individual clinical or behavioral variables. Furthermore, we examined whether these abnormalities differentiated patients with aMCI from healthy elderly individuals.

Methods and Materials

Participants

Eighty-four right-handed participants, comprising 37 patients with aMCI (17 men and 20 women) and 47 sex-, age-, and education-matched healthy control subjects (HC: 20 men and 27 women), participated in this study. The patients were recruited from the memory clinic of the neurology department of Xuanwu Hospital, Capital Medical University, Beijing, China. The control subjects were recruited from the local community using advertisements. At the time of the study, none of the patients had ever been treated with

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Received Jan 12, 2012; revised Mar 15, 2012; accepted Mar 26, 2012.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.03.026

Table 1. Demographics and Clinical Characteristics of the Participants

	HC ($n = 47$)	aMCI ($n = 37$)	p Value
Gender (Male/ Female)	20/27	17/20	.756[a]
Age (Years)	50–79 (63.4 ± 7.7)	41–79 (66.8 ± 9.4)	.184[b]
Education (Years)	0–22 (11.4 ± 5.0)	0–20 (9.8 ± 4.2)	.136[b]
MMSE	20–30 (28.5 ± 2.0)	16–30 (24.7 ± 3.5)	$<10^{-7}$[b]
CDT	1–3 (2.8 ± .6)	1–3 (2.1 ± .8)	$<10^{-4}$[b]
CDR	0	.5	—
AVLT-Immediate Recall	6–14.7 (8.8 ± 2.0)	2.7–10.7 (5.7 ± 1.9)	$<10^{-9}$[b]
AVLT-Delayed Recall	4–15 (9.8 ± 2.8)	0–14 (5.1 ± 3.3)	$<10^{-9}$[b]
AVLT-Recognition	3–15 (11.6 ± 2.7)	1–14 (8.8 ± 3.3)	$<10^{-4}$[b]

Data are presented as the range of minimum–maximum (mean ± SD). Notably, there were no outliers for any characteristics of both of the groups using the criterion of 2.5 interquartile ranges from lower/upper quartile values of the samples.

aMCI, amnestic mild cognitive impairment; AVLT, Auditory Verbal Learning Test; CDR, Clinical Dementia Rating Scale; CDT, Clock Drawing Test; HC, healthy control subjects; MMSE, Mini-Mental State Examination.

[a]The p value was obtained using a two-tail Pearson chi-square test.

[b]The p value was obtained using a two-sample two-tail t test.

specific medications, such as anti-acetylcholinesterase drugs. Diagnoses of aMCI were made by experienced neurologists using Petersen's criteria (4,29). The detailed inclusion and exclusion criteria are described in Supplement 1. Each participant was assessed using a standardized clinical evaluation protocol that included the Mini-Mental State Examination (MMSE) (30), the Clock Drawing Test (CDT), the Auditory Verbal Learning Test (AVLT) (31), and the Clinical Dementia Rating Scale (32). In Table 1, we present the detailed demographics and clinical characteristics of the participants. Datasets from a subset of the general population have been used to study local brain activity in patients with aMCI (33). This study was approved by the Medical Research Ethics Committee and Institutional Review Board of Xuanwu Hospital, and informed consent was obtained from each participant.

Data Acquisition

All participants were scanned using a 3.0 T Siemens Trio scanner (Erlangen, Germany) at Xuanwu Hospital, Capital Medical University, within a single session (Supplement 1). During the data acquisition, participants were asked to lie quietly in the scanner with their eyes closed. The scan lasted for 478 seconds in total and included 239 volumes for each participant.

Data Preprocessing

Data preprocessing was performed using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/software/SPM8/; Wellcome Trust Center for Neuroimaging, University College London, United Kingdom; Supplement 1) and included the removal of the first five volumes, correction for time offsets between slices and head motion, spatial normalization to the Montreal Neurological Institute space, temporal high-pass filtering (cutoff frequency = .01 Hz), and regression of nuisance signals of six head-motion profiles. Given the controversy of removing the global signal in the preprocessing of R-fMRI data (34,35), we did not regress the global signal out (22,36,37). Notably, the head-motion profiles were matched between the aMCI and HC groups ($p > .248$ in any direction).

Network Construction

In this study, brain networks were constructed at the macroscale where nodes represented brain regions and edges represented interregional resting-state functional connectivity (RSFC). To define network nodes, we divided the brain into 1024 regions of interest (ROIs) according to a high-resolution, randomly generated brain atlas (H-1024) (38). To measure interregional RSFC, we calculated the Pearson correlation between any pair of ROIs in the wavelet coefficients that were obtained by the maximal overlap discrete wavelet transform method (39). Here, we estimated RSFC in four wavelet scales (scale 1, .125–.250 Hz; scale 2, .063–.125 Hz; scale 3, .031–.063 Hz; and scale 4, .016–.031 Hz). To further de-noise spurious interregional correlations, only those correlations whose corresponding p values passed through a statistical threshold ($p < .05$, Bonferroni-corrected) were retained (40). Details on the network construction can be found in Supplement 1.

Network Analysis

For the constructed brain networks, we calculated both global and regional network metrics to characterize their overall architecture and regional nodal centrality, respectively. The global network metrics included small-world attributes (clustering coefficient, C^W and characteristic path length, L^W) (41) and modularity ($Q_{\max}$) (42) and their normalized versions using random networks ($\tilde{C}^W$, $\tilde{L}^W$, and $\tilde{Q}_{\max}$). Typically, a small-world network shows $\tilde{C}^W > 1$ and $\tilde{L}^W \approx 1$ (41) and a modular network shows $\tilde{Q}_{\max} > 1$. For regional network measures, we employed nodal strength (i.e., weighted degree centrality) among numerous nodal metrics (43) because of its high test-retest reliability (44). See Supplement 1 for the formulas and Rubinov and Sporns (45) for a recent review on the uses and interpretations of these network measures.

Statistical Analysis

Between-Group Differences. Between-group differences in topological attributes (both global and regional measures) were inferred by nonparametric permutation tests (21,46). Briefly, for each network metric, we initially calculated the between-group difference of the mean values. An empirical distribution of the difference was then obtained by randomly reallocating all of the values into two groups and recomputing the mean differences between the two randomized groups (10,000 permutations). The 95th percentile points of the empirical distribution were used as critical values in a one-tailed test of whether the observed group differences could occur by chance. To localize the specific pairs of regions in which the functional connectivity was altered in the aMCI patients, we used a network-based statistic (NBS) approach (47). In brief, a primary cluster-defining threshold was first used to identify suprathreshold connections, within which the size (i.e., number of edges) of any connected components was then determined. A corrected p value was calculated for each component using the null distribution of maximal connected component size, which was derived empirically using a nonparametric permutation approach (10,000 permutations). Notably, before the permutation tests, multiple linear regressions were applied to remove the effects of age and gender, the age-gender interaction, and education level (43,48–53). The details of the statistical analyses can be found in Supplement 1.

Relationships Between Network Measures and Clinical Variables. Multiple linear regressions were used to assess the relationships between network metrics and clinical variables (AVLT-immediate recall, AVLT-delayed recall, AVLT-recognition, and MMSE score) in the aMCI group. Age, gender, the age-gender interaction, and education level were also controlled.

Network Classification

We plotted the receiver operating characteristic curves to determine whether graph-based network metrics might serve as biomarkers for diagnosing aMCI. This analysis was performed using the