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Identifying and Mapping Connectivity Patterns of Brain Network Hubs in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is associated not only with regional gray matter damages, but also with abnormalities in functional integration between brain regions. Here, we employed resting-state functional magnetic resonance imaging data and voxel-based graph-theory analysis to systematically investigate intrinsic functional connectivity patterns of whole-brain networks in 32 AD patients and 38 healthy controls (HCs). We found that AD selectively targeted highly connected hub regions (in terms of nodal functional connectivity strength) of brain networks, involving the medial and lateral prefrontal and parietal cortices, insula, and thalamus. This impairment was connectivity distance-dependent (Euclidean), with the most prominent disruptions appearing in the long-range connections (e.g., 100–130 mm). Moreover, AD also disrupted functional connections within the default-mode, salience and executive-control modules, and connections between the salience and executive-control modules. These disruptions of hub connectivity and modular integrity significantly correlated with the patients' cognitive performance. Finally, the nodal connectivity strength in the posteromedial cortex exhibited a highly discriminative power in distinguishing individuals with AD from HCs. Taken together, our results emphasize AD-related degeneration of specific brain hubs, thus providing novel insights into the pathophysiological mechanisms of connectivity dysfunction in AD and suggesting the potential of using network hub connectivity as a diagnostic biomarker.

Key words: connectome, functional connectivity, graph theory, module, PCC/PCu

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by a decline of memory and cognitive functions. The prevailing β-amyloid (Aβ)-cascade hypothesis of AD pathophysiology suggests that interstitial Aβ proteins exert a toxic effect on surrounding neurons and synapses, thereby disturbing their functions (Hardy and Selkoe 2002; Selkoe 2008). Indeed, recent research suggests that, prior to neuronal death and atrophy, disruption of functional connectivity between regions may represent an early deleterious outcome of Aβ proteins in AD (Gili et al. 2011; Sheline and Raichle 2013). Even before the stage of aggregation of Aβ fragments into amyloid plaques, there is a dysfunction of synaptic transmission in many brain areas due to dimers or even monomers from the Aβ cascade (for review, see D'Amelio and Rossini 2012).

Resting-state functional MRI (R-fMRI) is a promising neuroimaging technique that can non-invasively measure spontaneous or intrinsic brain activity (Biswal et al. 1995). R-fMRI has been widely used to study inter-regional functional connectivity in healthy and diseased populations (for reviews, see Fox and Raichle 2007; Kelly et al. 2012), particularly with the capability of detecting subtle connectivity abnormalities in early AD (Jack et al. 2010; Sperling et al. 2011; Sheline and Raichle 2013). Recently, the combination of R-fMRI and graph-based network analysis allows revealing the topological organization of human whole-brain functional networks, such as small-world attributes and network modularity (for reviews, see Bullmore and Sporns 2009; He and Evans 2010; Wang et al. 2010). An important and convergent finding is that human brain functional networks contain a small number of hubs with disproportionately numerous connections (Achard et al. 2006; Buckner et al. 2009; He et al. 2009; Tomasi and Volkow 2010). These brain hubs, primarily located in the medial and lateral frontal and parietal cortices, have higher rates of cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism, and play vital roles in supporting fast communication across brain regions (Vaishnavi et al. 2010; Liang et al. 2013; Tomasi et al. 2013).

Recent research suggests that the brain hubs may be preferentially affected in AD. Buckner et al. (2009) have demonstrated that the functional hubs of healthy human brains have a striking overlap with regions showing higher Aβ deposition in patients with AD. de Haan, Mott, et al. (2012) employed a computational model to test the activity-dependent degeneration hypothesis that hub vulnerability in AD could be due to the high-level continuous baseline activity and/or associated metabolism. In mouse brains, the amount of Aβ in the interstitial fluid and the development of amyloid plaques are associated with synaptic activity (Selkoe 2006; Bero et al. 2011, 2012). These findings suggest that the brain hubs tend to have amyloid plaque deposition that leads to functional disconnections among regions. Previous R-fMRI studies reported AD-related changes in the topological architecture of whole-brain functional networks, such as the loss of small-worldness, modular disorganization, and regional dysconnectivity (Supekar et al. 2008; Sanz-Arigita et al. 2010; Liu et al. 2013; for reviews, see Xie and He 2011; Tijms et al. 2013). However, the connectivity patterns of brain hubs in R-fMRI networks in AD remain to be elucidated.

Many studies suggest that much of the brain's massive metabolic cost is attributable to the active maintenance of electrochemical gradients across neuronal membranes, which is required to support signaling and coordination of neuronal activity at anatomically separated regions (Attwell and Laughlin 2001; Niven and Laughlin 2008). The brain metabolic costs increase in proportion to the total surface area of the neuronal membrane. Thus, these costs are a function of axonal length and diameter, which are 2 key factors to determine the area of the neuronal membrane, with longer distance connections being metabolically more expensive to maintain (Karbowski 2007). Direct evidence also suggests that the metabolic costs of brain regions are closely associated with inter-regional connectivity distance: Long-range brain hubs consume more energy than short-range hubs (Sepulcre et al. 2010; Liang et al. 2013). Specifically, several recent studies have paid more attention to the topology of anatomically embedded brain networks and highlighted the importance of connectivity distances on brain network organization (Vértes et al. 2012; Alexander-Bloch et al. 2013). Relating to AD research, long-range brain hubs with increased metabolic cost may generate more Aβ deposition and lead to more serious functional disconnections. However, very few studies have directly examined whether patients with AD are mainly associated with longer distance disconnections, or AD-related disruption of brain hubs is connection-distance-dependent.

Here, we used R-fMRI and voxel-based graph analysis approaches to comprehensively investigate AD-related changes in the functional hubs of whole-brain networks. Such a voxel-wise approach avoids parcellation-dependent effects on the topological organization of brain networks (Smith et al. 2011; de Reus and van den Heuvel 2013). We sought to determine (1) whether patients with AD show disrupted hub connectivity patterns in their whole-brain functional networks and whether this disruption is connection-distance-dependent, and (2) if so, whether these topological changes in functional hubs significantly correlate with the behavioral characteristics of AD and may serve as valuable biomarkers for disease classification.

Materials and Methods

Participants

Seventy-five right-handed subjects (34 AD patients and 41 healthy controls, HCs) participated in this study. The AD patients were recruited from individuals who consulted a memory clinic at the Xuanwu Hospital with memory complaints. The HCs were recruited through advertisement from the local community. All participants were assessed clinically with the Clinical Dementia Rating (CDR) score (Morris 1993) to be categorized as HCs (CDR = 0) or as patients in the early stages of AD (18 patients with CDR = 1 and 16 patients with CDR = 0.5). The patients were given routine drug treatment (donepezil, memantine, and/or rivastigmine tartrate). All HCs had no history of neurological or psychiatric disorders, sensorimotor impairment or cognitive complaints, no abnormal anatomical findings by conventional brain MRI, and had mini-mental state examination (MMSE) scores of 28 or higher. All participants underwent a complete physical and neurological examination, standard laboratory tests, and neuropsychological assessments, which included the MMSE, Montreal Cognitive Assessment (MoCA), Extended Scale for Dementia (ESD), World Health Organization–University of California–Los Angeles Auditory Verbal Learning Test (AVLT), Clock Drawing Task (CDT), Activity of Daily Living Scale (ADL), Functional Activities Questionnaire (FAQ), Hamilton Depression Scale, and Hachinski Ischemic Score. The diagnosis of AD fulfilled the new research criteria for possible or probable AD (Dubois et al. 2007, 2010; McKhann et al. 2011).

A subset of the dataset (16 AD patients and 22 HCs) was also used to study regional brain activity in AD (Wang, Yan, et al. 2011; Dai et al. 2012). Clinical and demographic data of the remaining 70 participants are summarized in Table 1.

MRI Acquisition

All participants were scanned on a Siemens 3-T Magnetom Sonata scanner (Siemens, Erlangen, Germany). Foam pads and headphones were used to minimize head movement and scanner noise. Functional images were collected axially using an echo-planar imaging sequence: repetition time (TR)/echo time (TE) = 2000 ms/40 ms, flip angle (FA) = 90°, field of view (FOV) = 240 × 240 mm^2, matrix = 64 × 64, slices = 28, thickness = 4 mm, voxel size = 3.75 × 3.75 × 4 mm^3, gap = 1 mm, and bandwidth = 2232 Hz/pixel.7 to the scan, the subjects were instructed to keep their eyes closed but not fall asleep, elax their minds, and move as little as possible during data acquisition. The scan lasted for 478 s and thus included 239 functional volumes for each subject. A simple questionnaire indicated that all of the subjects had not fallen asleep during the scan. Three-dimensional T_1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sagittal images were also obtained using the following sequence: TR/TE = 1900 ms/2.2 ms, FA = 9°,nversion time = 900 ms, FOV = 256 × 256 mm^2, matrix = 256 × 256, slices = 176, thickness = 1 mm, and voxel size = 1 × 1 × 1 mm^3.

Image Preprocessing

$_1$-weighted images were coregistered to the mean functional image after motion correction using a linear transformation (Collignon et al. 1995) and wede then segmented into gday matter (GM), white matter, and cerebrospinalfluid tissue maps with SPM's a priori tissue maps asefedence by using a unified segmentation algorithm (Ashburner and Friston 2005). Theesultant GM, whitetter, and cerebrospinal fluid images were further nonlinearly degistered into the Montr Neurologic-altitute (MNI) space with the information estimated in uni fied segmentation and avaged acdoss all subjects toeate custom GM, white matter, and cedebrospinalfluid templates. the coregistered T_1 images were segmented again with custom tissue templates as reference images using the unified segmentation algorithm (Ashburned and Friston 2005). Such a custom template-based degistdation pdocedure allowed deducing the inaccuracy of the spatial n.3(7)-sdmalization of functional volumes due to GM atrophy in the elderly population. We then applied the transformation parameters estimated during unified segmentation to the motion-corrected functional volumes and resampled the transformational functional images to 3-mm isotropic voxels that are the minimum spatialesolution capturing cortical folding (Kiselev et al. 2003) and reflect neuronal patterns of columnar grain (Kriegeskorte et al. 2010). The data of 5 subjects (2 AD and 3 HCs) were excluded from further analysis because of the failure of imaging normalization that might be caused by severe GM atrophy 7 image artifacts. The normalized functional images further underwent spatial smoothing with a 4-mm full width at half maximum (FWHM) Gaussian kernel and removal of linear trends. Temporal band-pass filteding (0.01–0.1 Hz) was performed on the time series of each voxel using the Resting-State fMRI Data Analysisoolkit (Song et al. 2011) to reduce the effect .3(7)-sf low-frequency d6.4a.6248fts and high-frequency physiological noise (Biswal et al. 1995; Lowe et al. 1998). Finally, the nuisance signals (6 head motion paramets, global signal, cedebdospinal fluid, and white matter signals) were regressed out fd.3(7)5(m)-353.1(e)-14.9(a resting-state functional connectivity analysis.

Nodal Functional Connectivity Strength Analysis

To identify the hub degions of the whole-brain network, we performed a nodal functional connectivitytrength (FCS) analysis as follows. First, for each participant, we comd functional

Table 1 Demographic and neuropsychol data of AD patients and HCs

	AD (n = 32)	HC (n = 38)	P-value
Age (years)	52–86 (71.25 ± 8.63)	50–86 (68.39 ± 7.78)	0.15[a]
Gender (M/F)	14/18	13/25	0.41[b]
Education (years)	5–16 (9.75 ± 3.14)	5–16 (9.95 ± 3.44)	0.80[a]
CDR	0.5 (n = 14), 1 (n = 18)	0	–
MMSE	10–25 (18.56 ± 3.99)	28–30 (28.63 ± 0.67)	<0.001[a]
MoCA	8–19 (14.94 ± 3.23)	27–30 (28.63 ± 0.79)	<0.001[a]
ESD	107–200 (155.33 ± 26.48)	180–248 (227.74 ± 15.68)	<0.001[a]
AVLT	8–24 (14.81 ± 4.12)	39–52 (44.42 ± 2.74)	<0.001[a]
CDT	3–8 (6.13 ± 1.43)	8–9 (8.71 ± 0.46)	<0.001[a]
ADL	22–45 (30.41 ± 7.21)	20–22 (21.08 ± 0.78)	<0.001[a]
FAQ	4–11 (6.25 ± 1.70)	0–2 (0.55 ± 0.76)	<0.001[a]
HAMD	0–3 (1.06 ± 1.08)	0–3 (0.61 ± 1.00)	0.07[a]
HIS	0–3 (1.16 ± 0.77)	0–3 (1.13 ± 1.07)	0.91[a]

Note: Data are presented as the dange of minimum-maximum (mean ± SD).
AD, Alzheimer's HC, healthy control; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; MoCA, Montreal Ce Assessment; ESD, The

Unless otherwise stated, all functional imaging data preproces-

connectivities by estimating Pearson's correlations between the time series of any pairs of brain voxels, resulting in an individual whole-brain functional connectivity matrix. This procedure was constrained within a GM mask ($N_{voxels} = 57\,766$) generated by thresholding (cutoff = 0.2) the mean GM probability map of all 70 subjects. Then, for a given GM voxel, i, we computed its FCS using the following equation (Buckner et al. 2009; Zuo et al. 2012; Wang, Dai, et al. 2013):

$$FCS(i) = \frac{1}{N_{voxels} - 1} \sum_{j=1, j \neq i}^{N_{voxels}} z_{ij}, \quad r_{ij} > r_0 \tag{1}$$

where z_{ij} was the Fisher's Z-transformed version of correlation coefficient, r_{ij}, between voxel i and voxel j, and r_0 was a correlation threshold that was used to eliminate weak correlations possibly arising from noise (here, $r_0 = 0.2$). We also assessed the effects of different correlation thresholds on the main results, see "Validation analysis." Notably, this FCS metric is referred to as the "degree centrality" of a weighted network in graph theory (Buckner et al. 2009; Zuo et al. 2012; Wang, Dai, et al. 2013). The GM voxels with higher FCS values (>1 SD beyond the global mean) were defined as brain hubs, which are usually assumed to play central roles in the functional integrity of whole-brain networks. After the above processing, we obtained a FCS map for each subject. The spatial similarity of the FCS maps between groups was evaluated using Pearson's correlation coefficient across voxels. Given that the neighboring voxels were spatially dependent due to the physiological correlations and the smoothing preprocessing, the effective degree of freedom, df_{eff}, in the across-voxel correlation analysis was corrected to estimate the P-values (Xiong et al. 1995; Liang et al. 2013):

$$df_{eff} = \frac{N}{(FWHM_x \times FWHM_y \times FWHM_z)/v} - 2 \tag{2}$$

where v was the nominal volume of a voxel (here, $v = 3 \times 3 \times 3$ mm^3) and N was the number of voxels used in the analyses (here, $N = 57\,766$). $FWHM_x$, $FWHM_y$, and $FWHM_z$ represent the width of the Gaussian function along each of the 3 principal axes of space smoothness, respectively. Furthermore, we computed the reduced proportion of FCS, Prop(i), in the AD group relative to the HC group:

$$Prop(i) = \frac{\overline{FCS}_{AD}(i) - \overline{FCS}_{HC}(i)}{\overline{FCS}_{HC}(i)} \times 100\% \tag{3}$$

where $\overline{FCS}_{AD}(i)$ *and* $\overline{FCS}_{HC}(i)$ represent the mean FCS values of GM voxel i in the AD and HC groups, respectively. To further examine between-group differences in FCS, a general linear model (GLM) analysis was performed in a voxel-wise manner with age and gender as covariates. The statistical significance threshold was set at $P < 0.05$ and cluster size >2187 mm^3 (i.e., 81 voxels), which corresponded to a corrected $P < 0.05$ for multiple comparisons. This correction was confined within the GM mask (size: 1 559 682 mm^3) and performed by Monte Carlo simulations (Ledberg et al. 1998) using the AFNI AlphaSim program (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).

The between-group FCS difference analysis revealed regions that are disrupted in patients with AD. To further determine whether these regions showing the most significant group differences in FCS are those brain hubs with higher FCS, we generated a mean FCS map in a healthy young adult group ($n = 53$) that was

we categorized the connections showing significant group differences into intramodule (within the same functional modules) and intermodule (between different functional modules) connections.

Connectivity Distance-Related FCS Analysis

covariates. Statistical significance was set at $P < 0.05$ and cluster size >12 663 mm^3, which corresponded to a corrected $P < 0.05$. Compared with the HC group, the AD group showed significant GM loss in many brain regions, especially in the medial and lateral frontal and parietal cortices and insula that exhibited AD-related disruption in FCS (see Results), indicating the necessity of correcting the GM atrophy in the R-fMRI study. We thus performed a voxel-by-voxel GLM analysis again to compare between-group differences in FCS by adding individual GM density values as an additional covariate.

The Effects of Different Preprocessing/Analysis Strategies

(1) Correlation types. Given the controversies in the treatment of negative correlations in R-fMRI network studies (Fox et al. 2009; Murphy et al. 2009; Wang, Zuo, et al. 2011), we also performed an FCS analysis including both positive and negative connections (absolute values) to assess the stability of our findings. (2) Correlation and connectivity density thresholds. While computing FCS, we used a single correlation threshold of 0.2 to eliminate potentially spurious correlations. To determine whether our main results depended on the choice of correlation threshold, we recomputed FCS maps using 5 different correlation thresholds (0, 0.1, 0.3, 0.4, and 0.5). Additionally, we also recomputed the FCS maps and performed corresponding statistical analyses under various network densities or sparsities (1%, 5%, 10%, and 20%), ensuring the same number of connections across subjects. (3) Head motion. Recent literature has suggested that head motion has a confounding effect on functional connectivity analysis (Power et al. 2012a, 2012b; Van Dijk et al. 2012; Satterthwaite et al. 2013; Yan et al. 2013). In this study, we did not find significant differences in head motion between the 2 groups [two-tailed two-sample *t*-test: $P = 0.33$ for translational, $P = 0.11$ for rotational, $P = 0.66$ for mean framewise displacement of Jenkinson (Jenkinson et al. 2002)]. Nonetheless, to exclude any possible effects of head motion, 2 analysis strategies were performed: (a) We re-analyzed FCS by including mean framewise displacement as an additional covariate (Yan et al. 2013). (b) We re-performed a 'scrubbing' procedure on the preprocessed images (Power et al. 2012a; Yan et al. 2013). For each subject, R-fMRI volumes were first censored based on a criterion of framewise displacement >0.2 mm, and the FCS analysis was then re-analyzed using these censored R-fMRI data. (4) Spatial smoothing. Given that spatial smoothing in the preprocessing steps might introduce artificial local correlations between voxels that were unrelated to their functional connections, we validated our major results without this smoothing preprocessing. (5) Global signal removal. Currently, whether global signal should be removed during R-fMRI preprocessing is controversial. Several previous studies have suggested that global signal is associated with non-neuronal activity such as respiration and should be removed (Fransson 2005; Birn et al. 2006; Chang and Glover 2009; Fox et al. 2009). However, this processing introduces widespread negative functional connectivities and thus may alter the intrinsic correlation structure of brain networks (Murphy et al. 2009; Weissenbacher et al. 2009). To explore the effects of global signal removal on our results, we re-analyzed our data without regressing out the global signal.

Test–Retest Reliability

To validate the test–retest reliability of the nodal FCS metric, we repeated the principle analyses with a public test–retest dataset (http://fcon_1000.projects.nitrc.org/indi/CoRR/html/bnu_1.html). Briefly, the dataset consists of two approximately 6.5 min R-fMRI scans that were acquired from 53 healthy young adults (male/female: 28/25; age: 19–30 years) who completed 2 MRI scan sessions within an interval of approximately 6 weeks (40.94 ± 4..

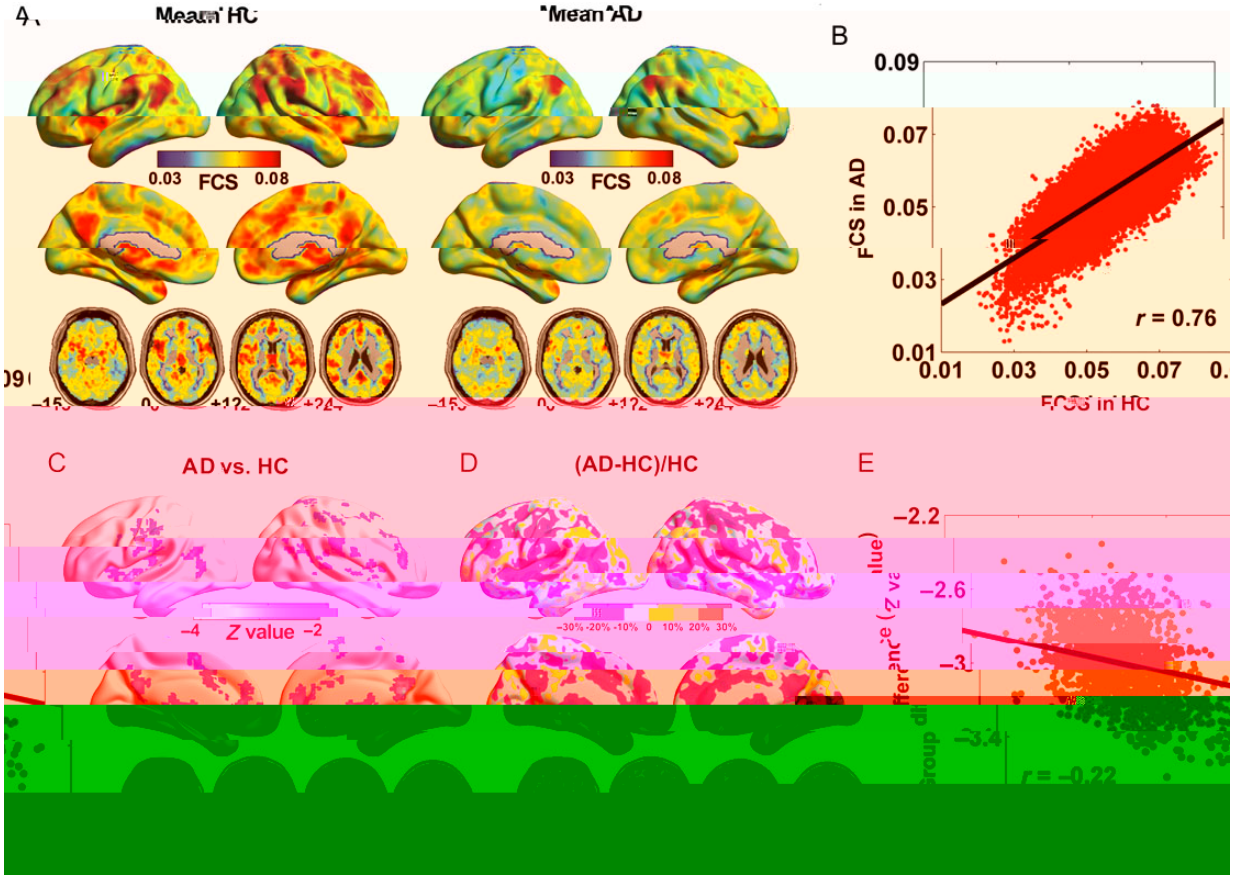

Figure 1. Within- and between-group FCS maps. (*A*) Mean FCS maps within HC and AD groups. (*B*) Scatter plot showing the across-voxel relationship between the mean FCS maps of the 2 groups. (*C*) Z-statistical difference maps between the 2 groups. (*D*) The reduced proportion of FCS in the AD group relative to the HC group. Notably, most of the regions showing AD-related changes in FCS were up to 20% lower in AD than in the control group. (*E*) Scatter plot showing the across-voxel relationship between the FCS values of hub regions in a healthy young adult group and the Z-statistical difference map. Notably, the correlation analysis was performed within a set of GM voxels that were considered hubs in the healthy young group and simultaneously showed significant differences between the AD and control groups. We resampled the FCS and Z-values into a Gaussian distribution, respectively: a mean of 0.05 and a standard deviation of 0.01 dimensionless units for FCS values, a mean of −3 and a standard deviation of 0.2 dimensionless units for Z-values. The FCS values were mapped on the cortical surface by using in-house BrainNet Viewer (Xia et al., 2013). FCS, functional connectivity strength; HC, healthy control; AD, Alzheimer's disease.

correlation matrix with 47 rows and 47 columns for each group (Fig. 3A) and further decomposed them into 3 major modules (HC: $Q_{max} = 0.471$, Z-score = 5.587; AD: $Q_{max} = 0.540$, Z-score = 1.365): the DMN, the salience network (SN), and the executive-control network (ECN; Fig. 3B and Supplementary Fig. 2). Notably, the modular structure of the HC group was highly similar to that of the AD group (Supplementary Fig. 2). Furthermore, we found that 60 ROI–ROI functional connectivities exhibited AD-related decreases ($q < 0.05$, false discovery rate correction), categorized as intramodule (53/60, 88.3%) and intermodule connections (7/60, 11.7%; Fig. 3C). These intramodule disconnections primarily belonged to the ECN (22/60, 36.6%), followed by the SN (19/60, 31.7%) and the DMN (12/60, 20%). Intermodule disconnections were located between the SN and ECN. Only one connection—between the left middle occipital gyrus and the left calcarine fissure and surrounding cortex—exhibited a significant increase in the AD group relative to the HC group.

Distance-Dependent FCS Patterns and AD-Related Abnormalities

To understand the distance-dependent FCS results, we considered the above-mentioned FCS as a full-range FCS metric. Figure 4A shows the within- and between-group FCS maps for every connectivity distance studied. We noted that the FCS maps (both the within- or between-group FCS results) showed similar patterns at the neighboring distance bins, but were very different between very short and long distances. For example, both groups exhibited higher FCS in the visual cortex and lower FCS in the IPL at the 30–40 mm distance, but the pattern was inversed at the 120–130 mm distance; the between-group differences results showed decreased FCS in AD were primarily located in the thalamus at the 30–40 mm distance, but in the PCC/PCu and MPFC at the 120–130 mm distance. Notably, the most significant AD-related FCS decreases appeared in the 100–130 mm range (Fig. 4B), suggesting that AD was mainly associated with longer distance disconnections. Additionally, we observed that several regions exhibited higher FCS in the AD group, for example, in the left fusiform gyrus at the 0–20 mm range and in the left intraparietal cortex at the 30–50 mm range (Fig. 4A,B).

We further explored the spatial similarity of the mean FCS patterns at different distances. Using a hierarchical clustering analysis, we classified the 18 FCS bins into 2 bins: 0–90 mm (short-range FCS) and 90–180 mm (long-range FCS; Fig. 4C). The clustering results were identical for the HC and AD groups. For each group, the short-range hubs (0–90 mm) were mainly located

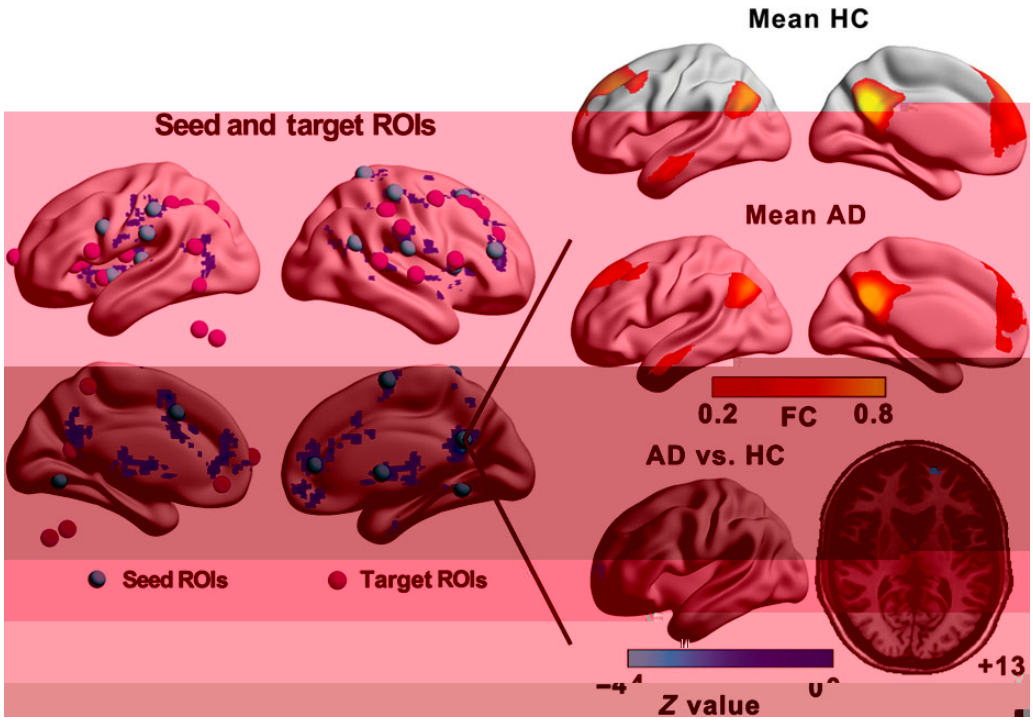

Figure 2. Definitions of seed and target ROIs. The left panel indicates the locations of the seed (cyan spheres) and target ROIs (magenta spheres). The magenta nodes outside of the brain are the regions of cerebellum. As an example, the right panel shows the mean functional connectivity maps of the PCC seed ROI (a 4-mm radius sphere centered on the maximal peak voxel: x, y, z = [0, −54, 27] mm) within the HC and AD groups and the Z-statistical differences between the 2 groups. Notably, the PCC showed significant group differences in the MPFC, which was considered a target ROI. The details of the 20 seed and 27 target ROIs are presented in Table 3. PCC, posterior cingulate cortex; MPFC, medial prefrontal cortex; HC, healthy control; AD, Alzheimer's disease.

well as the test–retest reliability of the nodal FCS metric. (1) The effects of GM loss. We observed that the AD patients showed widespread GM atrophy, with the most significant loss occurring bilaterally in the PCC/PCu, MPFC, IPL, medial temporal lobe, and insula (Fig. 8A). After taking the GM atrophy into account, we still observed the AD-related FCS decreases in the PCC/PCu, MPFC, and IPL (Fig. 8A), which was largely consistent with the main results without the GM correction (Fig. 1C). (2) The effects of correlation type. We re-generated the FCS maps using absolute correlation values including both positive and negative connections, and found that the main results preserved. For each group, the correlation analysis across voxels also confirmed a high spatial similarity between the FCS maps using the positive correlation and the FCS maps using the absolute correlation ($rs > 0.99$). The disrupted regions were mostly similar (spatial correlation, $r = 0.94$), except for the left insula and thalamus (Supplementary Fig. 3A). (3) The effects of correlation thresholds ($r_0 = 0, 0.1, 0.3, 0.4$, and 0.5) and connectivity density (density = 1%, 5%, 10%, and 20%). We found that the FCS maps of each group and the between-group difference maps under different thresholds (Supplementary Figs 3 and 4) were similar to our main results (Fig. 1). Notably, decreased FCS values in patients with AD were found in the PCC/PCu and MPFC regardless of different threshold values and thresholding approaches. (4) The effects of head motion. Using both the statistical analysis accounting for mean framewise displacement at the group-level (Yan et al. 2013; Fig. 8B) and the 'scrubbing' procedure in preprocessed images (Power et al. 2012a; Yan et al. 2013), we found that the main results in the PCC/PCu, MPFC, and IPL were not affected (Fig. 8B). Note that in this scrubbing analysis, to have sufficient time points for stable results, subjects with ≤5 min of data remaining after censoring were excluded from the analysis (8 AD patients and 11 HCs were excluded by this criterion; 51 of 70 subjects remained). (5) The effects of spatial smoothing in image preprocessing. Without spatial smoothing in image preprocessing, we observed significant group differences in the PCC and thalamus (Supplementary Fig. 5A). The between-group FCS differences in the MPFC and insula also survived the height threshold but not the extent threshold (1323 mm^3). Given that the spatial smoothing might impact distance-related FCS results, we also examined the distance-related FCS pattern without smoothing in the preprocessing. The between-group FCS differences at distance between 0 and 10 mm (Supplementary Fig. 5B) were similar to those in the main analyses at this distance range (Fig. 4A), indicating that the smoothing procedure did not influence our main findings at the short distance. Notably, the significant between-group FCS differences were also observed in longer distances (e.g., 90–130 mm), but the number of voxels showing group differences decreased without the smoothing (Supplementary Fig. 5B). (6) The effects of global signal removal. Without global signal removal, we observed that the AD group showed significantly decreased FCS in the PCC/PCu, MPFC, insula, and thalamus (Fig. 8C), which was largely consistent with our results with global signal removal. However, the lateral parietal cortices exhibited non-significant results without global signal removal. (7) Test–retest reliability. Visually, the spatial patterns of nodal FCS maps were highly similar between the 2 sessions. Pearson's correlation analysis revealed high correlation coefficient between the FCS maps in the 2 sessions ($r = 0.97$, $df_{eff} = 28\,098$, Supplementary Fig. 6). The test–retest reliability map showed spatially non-homogeneous pattern across the brain: A large amount of hub regions, including the medial and lateral frontal and parietal cortex, showed fair-to-good test–retest reliability (intraclass correlation coefficient above 0.4).

Table 3 Forty-seven ROIs

ROIs	MNI coordinates (mm)		
	x	y	z
PCC	**0**	**−54**	**27**
Left PreCG	**−51**	**6**	**31**
Left IPL	**−57**	**−26**	**46**
Left SMG	**−66**	**−27**	**21**
Right IPL	**51**	**−31**	**56**
Right SPG	**18**	**−45**	**63**
Right SMA	**3**	**−5**	**65**
Right ACC	**1**	**19**	**26**
Right MPFC	**3**	**54**	**3**
Right MFG	**27**	**18**	**54**
Right ALC	**18**	**−54**	**−15**
Right STG	**56**	**−56**	**21**
Right SMG	**57**	**−17**	**20**
Right INS	**39**	**12**	**6**
Left INS	**−39**	**0**	**−3**
Right MFG	**39**	**39**	**18**
Left ALC	**−12**	**−65**	**−11**
Right THA	**3**	**0**	**3**
Left HES	**−36**	**−24**	**6**
Left MTG	**−54**	**−57**	**18**
Left SFG	−15	60	9
Left ITG	−54	−63	−12
Left MOG	−30	−75	30
Left ANG	−33	−51	36
Left IPL	−51	−42	54
Left IFGtriang	−36	30	12
Left SPG	−24	−72	48
Right IPL	57	−30	51
Right PoCG	42	−30	42
Left PUT	−30	−9	12
Left PCu	−12	−48	57
Left ORBsup	−12	45	−12
Left PCL	−36	−72	−45
Left PCL	−30	−60	−39
Left CAL	−15	−60	15
Left INS	−42	6	−3
Left INS	−33	21	9
Right MTG	66	−39	9
Right IFGoperc	54	12	12
Left IFGoperc	−57	12	15
Right SMG	69	−21	36
Right MFG	42	0	51
Right MFG	27	36	27
Right MFG	30	30	42
Right MFG	33	18	48
Right MFG	27	27	48
Right STG	60	−12	3

Note: Bold text indicates the 20 seed ROIs derived from group FCS analysis and others indicate 27 target ROIs showing AD-related functional connectivity differences with seed ROIs.

x, y, z, coordinates of primary peak locations in the MNI space; PCC, posterior cingulate cortex; PreCG, precental gyrus; IPL, inferior parietal lobule; SMG, supramarginal gyrus; SPG, superior parietal gyrus; SMA, supplementary motor area; ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex; MFG, middle frontal gyrus; ALC, anterior lobe of cerebellum; STG, superior temporal gyrus; SMG, supramarginal gyrus; INS, insula; THA, thalamus; HES, heschl gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; ANG, angular gyrus; IFGtriang, inferior frontal gyrus, triangular part; PoCG, postcentral gyrus; PUT, putamen; PCu, precuneus; ORBsup, superior frontal gyrus, orbital part; PCL, posterior lobe of cerebellum; CAL, calcarine fissure and surrounding cortex; IFGoperc, inferior frontal gyrus, opercular part.

Discussion

Using R-fMRI and graph-based network analysis, we showed disrupted functional connectivity patterns in AD. Our main findings are as follows: (1) AD selectively disrupted network hub regions with higher FCS, involving the PCC/PCu, MPFC, IPL, insula, and thalamus. Importantly, this disruption was connectivity distance-dependent; (2) AD mainly disrupted within-module connections in the DMN, SN, and ECN and inter-module connections between the SN and ECN; and (3) disrupted network hub connectivity significantly correlated with patients' cognitive performance and distinguished individuals with AD from the HCs with high sensitivity and specificity.

Disrupted Brain Network Hubs in AD

An emerging feature of the connectional architecture of the human brain is that certain areas, known as hubs, act as way stations for information processing by connecting distinct, functional specialized systems (Achard et al. 2006; Sporns et al. 2007). In this study, we found that the functional hubs in the HC group were located primarily in the DMN regions, dlPFC, thalamus, and insula, consistent with previous functional network studies (Buckner et al. 2009; Tomasi and Volkow 2010; Zuo et al. 2012; Liang et al. 2013; Wang, Dai, et al. 2013). We noted that a similar hub distribution existed in the AD group, suggesting a relative preservation of the crucial roles played by these hubs. However, the patients showed the most significant FCS decreases in many hub regions, suggesting that specific brain hubs might be preferentially targeted by AD pathology. This was further evidenced by the high negative correlation between the FCS maps in the healthy young adults and group difference maps. Based on meta-analyses of published structural MRI data, Crossley et al. (2014) found that the GM lesions in AD were mainly concentrated in highly connected brain hubs such as the medial temporal and parietal regions, providing further support for our findings. The DMN regions, the core components of functional hubs, are involved in a variety of function processing, including episodic memory (Cabeza et al. 2002; Buckner 2004), a major cognitive domain impaired in early AD. A number of previous R-fMRI studies have reported abnormal spontaneous activity in the DMN in AD (Greicius et al. 2004; Wang, Zang, et al. 2006; Jones et al. 2011; Brier et al. 2012) and in the prodromal stage of AD—mild cognitive impairment (Sorg et al. 2007; Hedden et al. 2009). Beyond the DMN regions, the AD patients also exhibited decreased FCS in the dlPFC, insula, and thalamus. The dlPFC plays crucial roles in many cognitive tasks including episodic memory (Murray and Ranganath 2007), working memory, and executive function (Curtis and D'Esposito 2003); abnormal dlPFC functional connectivity has been observed in individuals at risk for AD (Liang et al. 2011). The insula is involved in somatosensation, interoception, motivation, and the maintenance of homeostasis (Deen et al. 2011). Previous studies have shown that the insula exhibits GM atrophy (Karas et al. 2003; Honea et al. 2009) and functional disconnection (Wang et al. 2007) in AD. The thalamus is a key region for integrating neural activity from widespread neocortical inputs and outputs (Postuma and Dagher 2006), and abnormal thalamic functional connectivity has been demonstrated in AD (Sanz-Arigita et al. 2010). Thus, these AD-related FCS decreases in specific brain hubs provide further support for network dysfunction in this disease.

Additionally, we also observed decreased FCS in several sensorimotor regions (PreCG, PoCG, and SMA). A structural MRI study has demonstrated a gradual loss of GM in primary sensorimotor

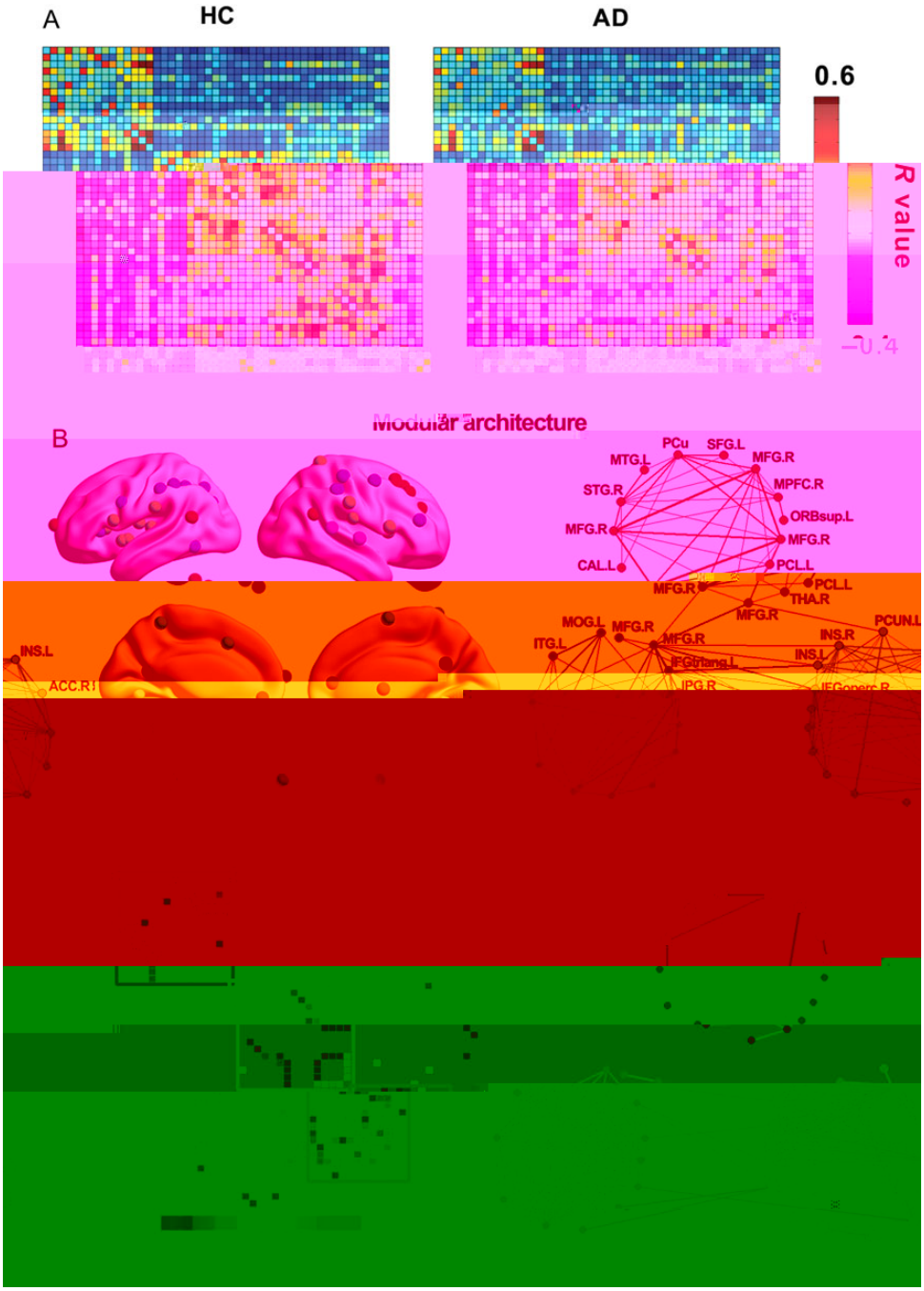

Figure 3. Modular analysis of the brain functional network. (A) Correlation matrices among 47 ROIs are shown for the HC (left panel) and AD (right panel) groups. (B) Surface (left panel) and topological (right panel) representations of the modular architecture of the brain networks in the HC group. Three modules were identified, the DMN (red colors), SN (green colors) and ECN (blue colors). The red nodes outside the brain are the regions of cerebellum. The within-module nodes and edges are marked in the same color. The intermodule connections are marked with black lines. Notably, 4 nodes (2 in magenta and 2 in yellow) on the surfaces did not belong to the DMN, SN, or ECN in the modular detection and therefore were not shown in the right panel. (C) Matrix (left panel) and topological (right panel) representations of AD-related functional connectivity decreases. Blue and cyan lines represent AD-related decreases in inter- and intramodule connections, respectively. Notably, between-group statistical comparisons were restricted to positive correlations of either the HC or AD group. DMN, default-mode network; SN, salience network; ECN, executive-control network; HC, healthy control; AD, Alzheimer's disease.

cortex that mirrors the progression of AD severity (Frisoni, Prestia, et al. 2009). Several R-fMRI studies found that the sensorimotor regions were functionally affected in early AD (Brier et al. 2012; Wang, Xia, et al. 2013; Xia et al. 2014). However, AD patients included in this study did not report any clinically evident motor deficits. The discrepancy between functional disconnection in the sensorimotor system and normal motor behaviors in the patients could be explained as brain reserve: The brain has a buffer or reserve capacity to withstand a degree of change brought about by aging and disease (Staff 2012). The biomarker model that relates disease stage to AD suggests that the synaptic dysfunction and brain structural loss are earlier than the decline of clinical performances (Jack et al. 2010; Sperling et al. 2011), providing further support for our findings.

Figure 4. Distance-dependent within- and between-group FCS maps. (*A*) Within-group mean FCS maps and between-group *Z*-statistical difference maps in different distance bins. (*B*) The number of voxels showing significant group differences in FCS in different distance bins. (*C*) Hierarchical clustering analysis based on the spatial correlation map of FCS under different distance bins for the HC group. (*D*) Within-group mean FCS maps and between-group *Z*-statistical difference maps for short- and long-range FCS. FCS, functional connectivity strength; HC, healthy control; AD, Alzheimer's disease.

Many brain hubs are preferentially affected in AD, which could be explained by 2 lines of views. First, previous studies have found that the spatial pattern of typical hub regions in young healthy subjects strongly overlaps with high Aβ deposition in AD (Buckner et al. 2009) and cortical hubs are disconnected in non-demented subjects with elevated Aβ burden (Drzezga et al.

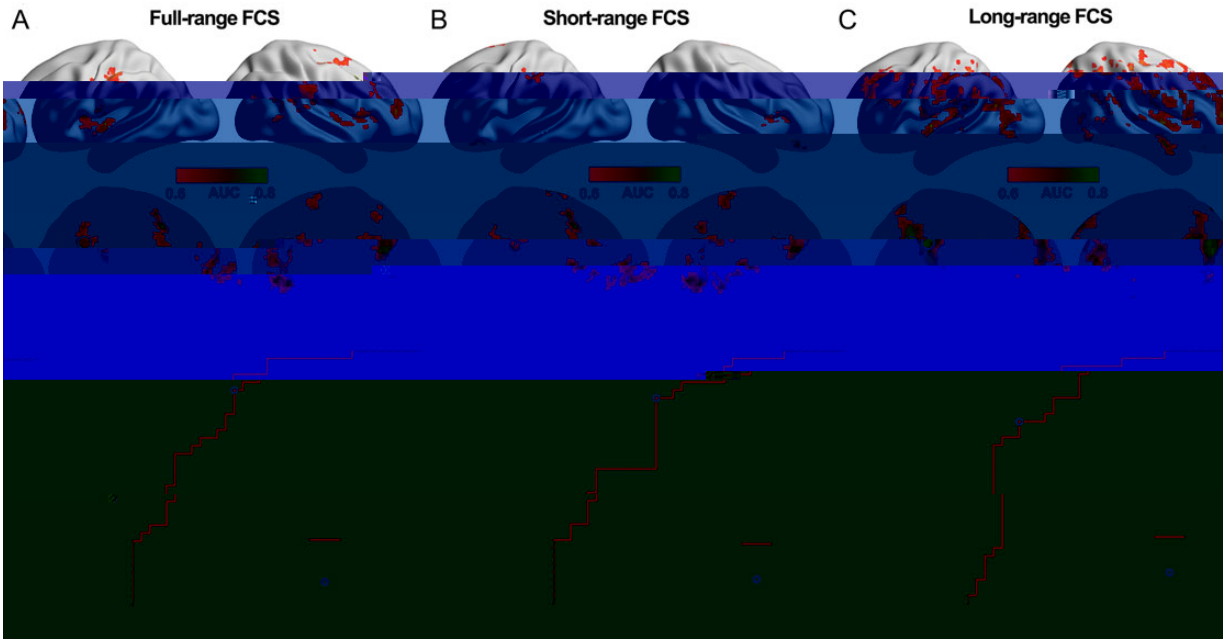

Figure 5. VDA-ROC analysis results based on the full-, short- and long-range FCS maps. The upper panel shows VDA-ROC analysis of full-range (*A*), short-range (*B*), and long-range (*C*) maps. The lower panel plots the ROC curves at the highest classification power location (i.e., PCC/PCu). FCS, functional connectivity strength; VDA-ROC, voxel-wise discriminant analysis based on the receer operating characteristics curve approach.

2011), suggesting that increasing Aβ burden leads to functional disconnection of brain hubs. These observations conform with the Aβ-cascade hypothesis of AD that neurotoxic Aβ aggregation may lead to synaptic dysfunction and eventually synaptic loss (Hardy and Selkoe 2002; Selkoe 2008). Alternatively, a growing number of studies suggest that continuously high levels of spontaneous activity that are associated with high metabolism might lead to amyloid deposition (Bero et al. 2011; Walker and Jucker 2011). Therefore, the hub regions with higher connectivity and metabolism level might have a greater chance to have amyloid deposition. In suppo6le of this theory, de Haan, Mott, et al. (2012) used a computational modeling approach to demonstrate that hubs are more vulnerable to activity-dependent degeneration. In summary, there may be a bidirectional relationship between functional connectivity and Aβ deposition in AD; such a relationship has been demonstrated in mouse brain models (Bero et al. 2012). This bidirectional relationship might underlie why hub regions are preferentially affected by AD pathology.

We used R-fMRI to show AD-related network dysfunction. Notably, functional disruption in AD was also demonstrated using other neurophysiological techniques such as electroencephalograph or magnetoencephalograph (Stam et al. 2007, 2009; de Haan, van der Flier, et al. 2012). Specifically, using magnetoencephalograph data, Stam et al. (2009) examined functional connectivity changes in the resting-state brain networks in patients with AD, and found that highly connected network hubs tend to be disrupted in the patients. Also using magnetoencephalograph data, de Haan, van der Flier, et al. (2012) observed that the eigenvector centrality of the brain functional networks was the highest in the parietal regions and was disrupted in patients with AD. Convergent to the current study, these neurophysiological evidences also pointed out the notion that specific brain hubs are preferentially targeted by AD. Given the different temporal and spatial resolutions and neuronal mechanisms among electroencephalograph, magnetoencephalograph, and R-fMRI, the combination of these different techniques would be important to map a comprehense picture of the underlying loss of network connections in AD.

Disrupted Hub-Related Connectivity and Modular Integrity in AD

We further identified AD-associated changes in the hub-relevant connectivity network. This network contains 3 main components: the DMN, the SN, and the ECN. The connections attacked by AD are involved in both intramodule connectivity within each component and intermodule connectivity between the SN and ECN. This finding is comparable with previous reports of disrupted connectivity within the DMN (Greicius et al. 2004; Brier et al. 2012), SN (Brier et al. 2012; Chen et al. 2013), and ECN (Brier et al. 2012; Li et al. 2012) in AD. Of note, 2 previous studies also reported increased connectivity within the SN (Zhou et al. 2010; Agosta et al. 2012). This discrepancy could be attributed to the different functional connectivity approaches: the 2 previous studies used independent component analysis, which identifies sets of brain regions that are separable on the basis of statistical patterns in their dynamic time series, whereas our directly identified intrinsic modules of brain networks and further examined functional connectivity patterns within modules. We also observed decreased connections between the SN and ECN. The SN is thought to play a role in recruiting relevant brain regions for the processing of sensory information (Seeley et al. 2007; Palaniyappan and Liddle 2012), and the ECN is related to the maintenance and manipulation of information and decision making in the context of goal-directed behavior (Bunge et al. 2001; Koechlin and Summerfield 2007). Therefore, we speculate that SN–ECN disconnection might lead to decreased sensory information integration, which could further accounted for the cognile de ficits in AD such as impaired judgment and disorientation.

Network Hubs, Connectivity Distance, and Diagnostic Biomarkers

Disparate spatial patterns of short- versus long-range functional connections have been reported previously (Sepulcre et al. 2010; Liang et al. 2013). In the present study, long-range functional hubs were mainly located in the PCC/PCu, MPFC, IPL, and lateral frontal and temporal cortices, and these hubs exhibited significant decreases in long-range FCS in AD. These regions are involved in high-level cognitive functions such as episodic memory, executive controls, integrity of sensory information,

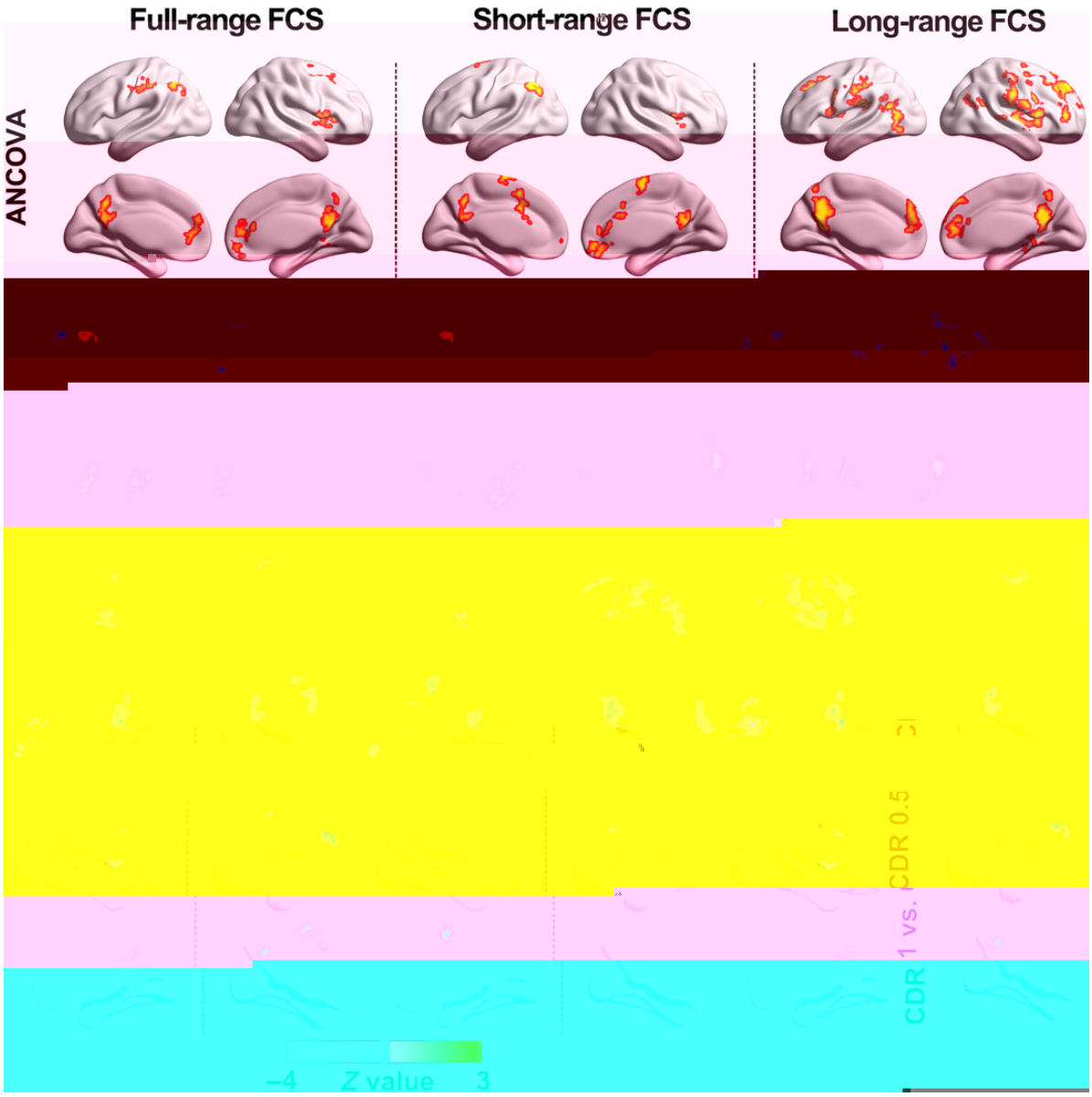

Figure 7. Disrupted FCS patterns in the very mild (CDR = 0.5) and mild (CDR = 1) AD groups when compared with the HC group. These group-based analysis results based on full-, short-, and long-range FCS maps were separately obtained by using a voxel-based, one-way analysis of covariance (ANCOVA) with age and gender as covariates, followed by post hoc two-sample *t*-tests. Notably, there were no significant differences in age, gender, and education level among the 3 groups. ANCOVA, one-way analysis of covariance; CDR, Clinical Dementia Rating; FCS, functional connectivity strength; HC, healthy control.

findings. Of note, in this study, we obtained a cutoff point (i.e., 90 mm) between short- and long-range hubs using FCS-based hierarchical clustering analysis, which captured connectivity related information and could be better than the previously employed arbitrary cutoff point of 75 mm (Achard et al. 2006; He, Chen, et al. 2007).

To further address the extent to which FCS metrics could serve as a biomarker to differentiate individuals with AD from HCs, we proposed the VDA-ROC analysis approach and found a high sensitivity and specificity in the PCC/PCu, especially for long-range FCS. The PCC/PCu is a core region of human brain structural (Hagmann et al. 2008; Gong et al. 2009) and functional (Tomasi and Volkow 2010; Liang et al. 2013) networks. Neuroimaging studies have consistently reported AD-related abnormalities in this region, such as hypometabolism (Minoshima et al. 1997), hypoperfusion (Hirao et al. 2005), amyloid deposition (Frisoni, Lorenzi, et al. 2009), cortical thinning (He et al. 2008), and functional disconnectivity (Greicius et al. 2004; Wang et al. 2007; Xia et al. 2014). These studies provide crucial evidence that the PCC/PCu FCS could be a biomarker for the early diagnosis of AD, and could also be used to evaluate the progression of the disease. Recently, many pattern recognition techniques have been widely investigated to automatically classify patients with AD or prodromal AD from healthy elders (Wang, Jiang, et al. 2006; Fan et al. 2008; Dai et al. 2012; Wee et al. 2012; Wang, Zuo, et al. 2013; Falahati et al. 2014). These approaches can be roughly grouped into 2 different categories—node-based or connectivity-based—depending on the type of features extracted from the neuroimaging data. In the first category, the features are defined as the measures of the brain nodes, such as GM volume

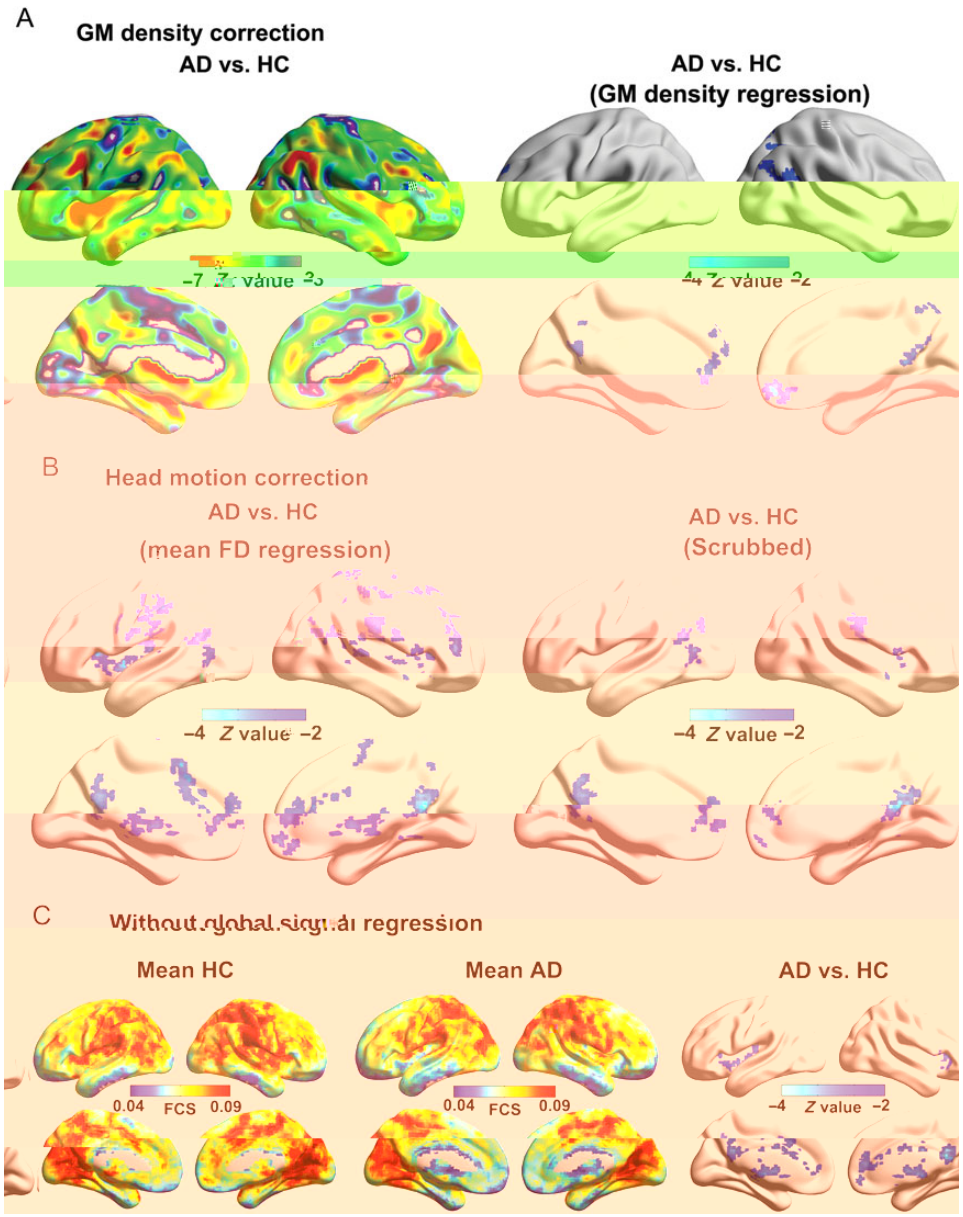

Figure 8. Validation analyses of between-group FCS differences. (A) The effect of GM density correction. The left panel shows Z-statistical differences in GM density between 2 groups. The right panel shows Z-statistical differences in FCS after considering GM density as additional covariates. (B) The effect of head motion correction. Between-group Z-statistical differences in FCS after considering the mean framewise displacement as an additional covariate (left panel) or after a 'scrubbing' procedure during preprocessing (right panel). (C) The effect of global signal regression. Within-group mean FCS maps and between-group Z-statistical FCS difference maps without global signal regression. GM, gray matter; FCS, functional connectivity strength; HC, healthy control; AD, Alzheimer's disease.

(Fan et al. 2008; Dai et al. 2012; Falahati et al. 2014), amplitude of low-frequency fluctuations (Dai et al. 2012), and FCS (the current study). In the second category, the features are the measures of the connectivity, such as functional correlations (Wang, Jiang, et al. 2006; Wee et al. 2012; Wang, Zuo, et al. 2013) and fiber connectivity (Wee et al. 2012) between regions. Future studies would be valuable to explore which type of features, or their combinations, are more sensitive for classifying patients with AD.

Overall, our results support the hypotheses that: (1) brain hubs with increased metabolic cost could result in amyloid plaque deposition and further lead to their functional disconnections, and (2) the disrupted brain hubs patterns in AD are connection-distance-dependent, being characterized by the disruptions of longer distance connections, which tend to consume more energy.

Further Considerations

Several issues need to be further considered. First, to address the recent concern about the spurious findings caused by head motion (Power et al. 2012a, 2012b; Van Dijk et al. 2012; Satterthwaite et al. 2013), we used both regression and scrubbing methods to validate our results, and our main findings were preserved. Nonetheless, it is worth noting that the effects of residual motion might still exist, which needs to be further validated using the optimal head motion correction methods. Second, the current

dataset is cross-sectional, therefore not allowing us to examine FCS-related dynamic changes with AD progression. Future follow-up studies are warranted to examine AD-related longitudinal changes in the network hub connectivity. Third, new criteria to diagnose AD emphasized the biomarker evidence from positron emission tomography amyloid imaging and cerebrospinal fluid. In the future, effective combination of these biomarkers (Koch et al. 2014; Myers et al. 2014) would be important to clinically diagnose AD and explore the pathophysiological mechanisms underlying these disruptions of brain hubs in AD.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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