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Hyperconnectivity of Self-Referential Network as a Predictive Biomarker of the Progression of Alzheimer's Disease

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Abstract.
Background: Self-referential processing is associated with the progression of Alzheimer's disease (AD), and cerebrospinal fluid (CSF) proteins have become accepted biomarkers of AD.
Objective: Our objective in this study was to focus on the relationships between the self-referential network (SRN) and CSF pathology in AD-spectrum patients.
Methods: A total of 80 participants, including 20 cognitively normal, 20 early mild cognitive impairment (EMCI), 20 late MCI (LMCI), and 20 AD, were recruited for this study. Independent component analysis was used to explore the topological SRN patterns, and the abnormalities of this network were identified at different stages of AD. Finally, CSF pathological characteristics (i.e., CSF Aβ, t-tau, and p-tau) that affected the abnormalities of the SRN were further determined during the progression of AD.
Results: Compared to cognitively normal subjects, AD-spectrum patients (i.e., EMCI, LMCI, and AD) showed a reversing trend toward an association between CSF pathological markers and the abnormal SRN occurring during the progression of AD. However, a certain disease state (i.e., the present LMCI) with a low concentration of CSF tau could evoke more hyperconnectivity of the SRN than other patients with progressively increasing concentrations of CSF tau (i.e., EMCI and AD), and this fluctuation of CSF tau was more sensitive to the hyperconnectivity of the SRN than the dynamic changes of CSF Aβ.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Conclusion: The integrity of the SRN was closely associated with CSF pathological characteristics, and these findings support the view that the hyperconnectivity of the SRN will play an important role in monitoring the progression of the pre-dementia state to AD.

Keywords: Alzheimer's disease spectrum patients, cerebrospinal fluid pathology, functional connectivity, hyperconnectivity, self-referential network

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by an accumulation of amyloid-β (Aβ) plaques and tau-laden neurofibrillary tangles [1]. A recently proposed AD descriptive biomarker classification scheme is associated with the "A/T/N" (Aβ, tau, and neurodegeneration/neuronal injury) system [2]. Individuals can be identified as being preclinical AD by the signs of AD pathology, such as people with mild cognitive impairment (MCI) who typically present with memory complaints [3]. An altered brain network during cognitive processing is a shared neural feature present in both AD and MCI and could be a common source of cognitive dysfunction [4]. Therefore, a better understanding of the evolution of AD pathology, the alterations of the brain networks, and the predictive biomarkers of this disease's progression are needed.

Self-referential processing is a process of relating information to the core of the self and is critical for elaborating experiential feelings of self [5]. Converging evidence points to a loss of self-reference that has been observed in AD [6, 7] and MCI subjects [8, 9]. Recent research has suggested that encoding information with respect to the self improves memory for items [10]. Furthermore, individuals characterized by functional deficits in self-reference showed greater conversion to AD than those who showed self-reference [11]. Brain networks can be noninvasively estimated via functional magnetic resonance imaging (fMRI) assessed synchronicity of the blood oxygen level-dependent (BOLD) signals. The previous neuroimaging findings suggested distinct neural underpinnings of the processes of self-reference [12]. For example, these cortical midline structures, including the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vMPFC), medial orbital prefrontal (MOPFC), and rectus gyrus, have been shown to be associated with the self-referential network (SRN) [13].

Importantly, resting-state fMRI [14–17] and task fMRI [18–19] studies have successfully revealed such an SRN exists in both the normal population and in disease states. Our previous study further revealed selective changes of the SRN at baseline in MCI compared to normal controls, such as increased functional connectivity of the vMPFC/MOPFC/rectus gyrus. These functional connections showed a greater extent of longitudinal diminishing after follow-up of the same subjects [16]. It should be noted that the default mode network (DMN) is an important network in the resting state, which is related to many regions associated with the posterior cingulate cortex, precuneus, medial prefrontal cortex, superior frontal gyrus, inferior parietal lobule, lateral temporal cortex, hippocampus, and cerebellum [20]. Although the DMN is generally considered to function as a network, the evidence suggests that the areas of the DMN are each specialized for different subfunctions [21]. Anatomically, the SRN and the DMN are at least partly formed by the same regions, and it is reasonable that the DMN is also related to self-referential processing [20] or that the SRN is as a subsystem of the DMN [22]. However, it is essential to examine the functional role of the SRN and the underlying mechanisms in the process of disease.

Brain network abnormalities may contribute to cognitive dysfunction in AD [23]. The previous studies have generally noted that brain networks are linked to AD pathology and their changes precede neurodegeneration [24]. For example, the strong interaction between the DMN and the salience network, which consists of the anterior insula and the dorsal anterior cingulate cortex, is associated with amyloid-positive individuals when neocortical tau levels are low in the ageing brain [25]. Other studies further found that the functional alterations of memory networks affected by early AD pathology (i.e., amyloid and tau pathology), providing useful information regarding their value as potential outcome measures [26, 27]. Although Aβ deposits and tau are closely related to the integrity of the networks, these AD pathologies may affect different aspects of the functional networks. In detail, tau pathology is related to a loss of the default-mode network and salience network functional connections, while Aβ pathology is related to a potential adaptive increase of these functional connections in the aging brain [28]. It has been recently suggested that there is differential vulnerability of

networks in AD [29]. However, it remains unclear whether and how the integrity of the SRN is affected by amyloid and tau pathology in the different stages of AD.

To our knowledge, this is the first study to address whether the AD pathology contributes to an altered SRN in AD-spectrum patients. We hypothesized that the level of cerebrospinal fluid (CSF) Aβ and tau may be associated with functional abnormalities in the SRN. The aims of this study, therefore, were: 1) to determine whether altered topological patterns of the SRN are associated with CSF pathological characteristics (i.e., CSF Aβ, t-tau, and p-tau) in subjects with early-MCI (EMCI), late-MCI (LMCI), and AD patients, and 2) to identify how CSF Aβ and tau affect the abnormalities of the SRN in these patients.

MATERIAL AND METHODS

Participants

Data used in the preparation of this study were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The study was approved by each participating ADNI site's local Institutional Review Boards, as documented on the ADNI website. Written informed consent was obtained from all individuals. The present study randomly selected 80 participants and matched the groups by age, education level and gender, including 20 cognitively normal (CN), 20 early MCI (EM CI), 20 late MCI (LMCI), and 20 AD, from whom the resting-state fMRI data are available in ADNI. Full inclusion and exclusion criteria (for details, see the Supplementary Material) and detailed schedules of assessment for CN, EMCI, LMCI, and AD are available in the general procedure manual on the ADNI website (http://adni.loni.usc.edu/data-samples/access-data/).

Neuropsychological tests

All subjects underwent diagnostic evaluations in cluding a clinical interview and neuropsychological tests, which were downloaded from the ADNI database. In the present study, we focused on the performance of general cognitive ability tests using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), while Ray Auditory Verbal Learning Test (RAVLT) is used for assessing episodic memory by providing scores for evaluating different aspects of memory. In particular, the RAVLT_immediate reflects the total acquisition/learning, the RAVLT_learning reflects the learning rate, the RAVLT_forgetting reflects the long-term retention, and the RAVLT_perc_forgetting reflects forgetting rate [30].

CSF pathological markers and quantification

The levels of CSF $A\beta_{1-42}$, total tau (t-tau) and phosphorylated tau (p-tau_{181}) were obtained using the standardized ADNI protocol (http://adni.loni.usc.edu/wp-content/uploads/2010/09/CSF_Biomarker_Test_Instr.pdf). Lumbar puncture is an invasive procedure and is not obligatory in ADNI protocol, thus not all subjects in the present study had CSF samples. Finally, 63 samples for CSF analyses were obtained in this study, including 14 CN, 13 EMCI, 17 LMCI, and 19 AD patients.

Data acquisition

All subjects were scanned using a 3.0-Tesla Phi lips MRI scanner. The resting-state fMRI scans were obtained using an echo-planar imaging sequence with the following parameters: repetition time (TR) = 3000 ms; echo time (TE) = 30 ms; flip angle = 80°; acquisition matrix = 64 × 64; slice number = 48; slice thickness = 3.3 mm; spatial resolution = 3.31 × 3.31 × 3.31 mm^3.

Data preprocessing

Data analyses of four groups were conducted with SPM8 (www.fil.ion.ucl.ac.uk/spm), Resting-State fMRI Data Analysis Toolkit (REST, http://restfmri.net) and the Data Processing Assistant for resting-state fMRI (DPARSF, http://restfmri.net/forum/DPARSF). The first 10 volumes of each subject were removed for the signal equilibrium and for subject's adaptation to the scanning noise. The remaining images were corrected for timing differences and motion effects. Participants have the exclusion threshold that was set as 3 mm for the linear translation or 3 degree of any angular motion. The resulting images were spatially normalized into the Montreal

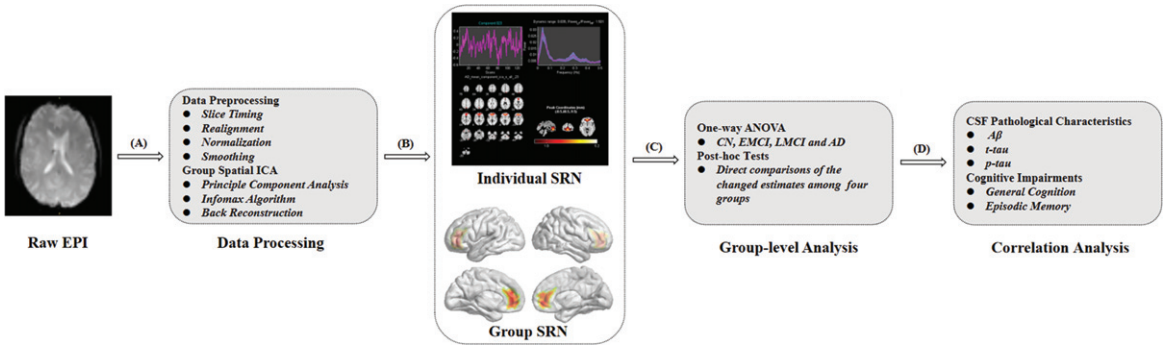

Fig. 1. A flowchart shows the whole pipeline of image processing (A), individual- and group-level analyses and statistical comparisons (B and C), and correlations with CSF biomarkers or cognitive tests (D).

Neurological Institute (MNI) echo-planar imaging template using the default settings and resampling to $3 \times 3 \times 3\,mm^3$ voxels and smoothed with a Gaussian kernel of $6 \times 6 \times 6$ mm (full-width half-maximum FWHM) (Fig. 1A).

Independent component analysis

Group spatial independent component analysis (ICA) was used to separate the BOLD signal into spatially independent components using the Group ICA of fMRI Toolbox (GIFT) programme (http://icatb.sourceforge.net). ICA was performed separately for each group, using the minimum description length (MDL) criterion. In the present study, 16/18/22/23 ICs for the data of CN, EMCI, LMCI, and AD were obtained, respectively. In line with our previous study [16], three stages were further performed: principal component analysis (PCA) was used to reduce the data within a lower dimensionality; estimation of independent sources was performed using the Infomax algorithm; back reconstruction was conducted, consisting of computing individual subject image maps and time courses, followed by component grouping across subjects and thresholding the resulting group ICA images [31]. Then, ICs for each subject were obtained (Fig. 1A).

To display the voxels that contributed the most strongly to a particular IC, the intensity values in each spatial map were converted to Z-values, removing the average value and dividing by the standard deviation of the intensity distribution [14, 31]. Each voxel within the IC of a single subject showed a Z score that represents the degree of correlation between this voxel's time series and the mean time series of that particular IC. As implemented in the GIFT software [31], the components to be retained for further analysis among the 16/18/22/23 estimated ICs for the four groups were selected based on the largest spatial correlation with a specific SRN template. In particular, this template included the ventromedial prefrontal cortex (vMPFC), the medial orbital prefrontal cortex (MOPFC), the gyrus rectus, and the pregenual anterior cingulate gyrus. The template came from previous resting state studies [15, 16] in combination with the spatial correlation for the SRN selection criterion. It should be noted that the resulting IC based on the specific SRN template were appropriate based on our prior knowledge of this network.

Group-level analysis involving SRN

Within group (Fig. 1B): to determine the patterns of SRN in each of the four groups, the spatial maps of SRN IC in each group were submitted to a random-effect analysis using one-sample *t*-tests. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation for multiple comparisons in the whole brain (voxel-wise $p < 0.001$, FWHM = 6 mm, cluster size > 351 mm^3; see programme AlphaSim by D. Ward, and http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).

Between groups (Fig. 1C): to explore to what extent changes in the SRN are greater in AD-spectrum patients than in healthy controls, 1) one-way ANOVA was performed in the four groups. 2) *Post hoc* tests were then used to explore the details of the changes in the patterns of the SRN IC, and direct comparisons of the changed estimates among these four groups were further performed. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation for multiple comparisons in the whole brain (voxel-wise $p < 0.005$, FWHM = 6 mm, cluster size > 702 mm^3; see programme AlphaSim by D. Ward, and http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).

Statistical analysis

1) The differences among CN, EMCI, LMCI, and AD in demographic, neuropsychological, and CSF data were assessed by Kruskal-Wallis tests (i.e., a nonparametric alternative for one-way ANOVA). *Post-hoc* tests were also performed by Mann-Whiney U Tests. The thresholds were set at $p < 0.05$ using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). 2) We were particularly interested in the CSF pathological significance of intrinsic connectivity in the regions associated with the abnormal SRN (Fig. 1D). In detail, for each participant, a mean time series for each voxel of the changed SRN was computed as the reference time course. Cross-correlation analysis was then carried out between the mean time series of every voxel in the changed SRN and the CSF pathological characteristics (i.e., CSF Aβ, t-tau and p-tau). The thresholds were set at a corrected $p < 0.001$ with cluster size >351 mm^3, using REST software (http://www.restingfmri.sourceforge.net). 3) To comprehensively evaluate the relationship between CSF pathology and behavioral significance, Spearman correlation analyses between CSF pathological characteristics and cognitive performance were further performed (Fig. 1D). The thresholds were set at $p < 0.05$ using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Demographic, psychometric, and CSF pathological characteristics

The demographic and psychometric characteristics of all 80 subjects are listed in Table 1. No significant differences were observed in age, education level or sex among these four groups. General cognition (i.e., the impaired trend of MoCA and MMSE were similar in the present study) and episodic memory (i.e., RAVLT) were significantly impaired in AD compared to the CN, EMCI, and LMCI groups ($p < 0.05$). For group comparisons between CN and EMCI, RAVLT_perc_forgetting was the measure found to be significantly decreasing in EMCI relative to the CN group ($p < 0.05$). For group comparisons between EMCI and LMCI, no significant differences were detected in MMSE, MoCA or RAVLT. Overall, similar to previous findings, we observed a hierarchical, disease stage-dependent pattern of progressively worsening cognitive impairments in EMCI, LMCI, and AD patients, respectively, relative to CN.

With reference to their CSF pathological characteristics, 63 CSF samples were obtained in the present study, including 14 CN, 13 EMCI, 17 LMCI, and 19 AD patients. We observed a significant reduction of CSF Aβ levels and increased CSF t-tau and p-tau levels in the AD patients compared to the CN and LMCI groups ($p < 0.05$). Although CSF Aβ, t-tau, and p-tau levels did not differ between MCI (i.e., EMCI and LMCI) and CN, there was a tendency of pathological damage with the development of AD. For example, a progressive reduction of CSF Aβ levels was observed in AD patients compared to the CN, EMCI, and LMCI groups, respectively. However, the CSF t-tau and p-tau levels were increasing in the progression of AD, but a strange rebound (i.e., a decrease in concentration) was observed in the LMCI group.

Associations of CSF pathological characteristics with abnormal SRN in AD-spectrum patients

In line with our previous study [16] and other studies [14, 15], the SRN was associated with the vMPFC, MOPFC, gyrus rectus, and pregenual anterior cingulate gyrus among the four groups (Fig. 2). Compared to CN, one-way ANOVA showed increased functional connectivity between vMPFC/MOPFC/rectus (i.e., peak MNI coordinate: –9, 36, –18, peak intensity: 69.0001, BA:11/25/47) and the mean time series of the SRN in AD-spectrum patients, while no significantly decreased functional connectivity was observed in the present study (Fig. 3A). After *post hoc* analysis, we found an undulant SRN-connectivity curve that was similar to the "inverse U-shaped curve" in the progression of AD (Fig. 3B). In detail, EMCI patients showed increased hyperconnectivity of the vMPFC/MOPFC/rectus in the SRN when compared to CN, and the peak connectivity was observed in LMCI and the AD patients showed a gradually decreasing connectivity.

The CSF pathological biomarkers were closely related to the integrity of the SRN. In the CN group, higher intrinsic connectivity of the SRN was associated with a higher CSF Aβ concentration and lower CSF t-tau and p-tau concentrations (Fig. 4). However, a reversing toward of an association between CSF markers and SRN connectivity occurred in the progression of AD. In the patient groups (from EMCI to LMCI to AD), a gradually negative association between CSF Aβ level and SRN connectivity combined with a gradually positive association between CSF tau level and SRN connectivity were seen in the progression of AD (Fig. 4). Considering that a sudden

Table 1
Demographic and neuropsychological and cerebrospinal fluid data

Items	CN ($n=20$)	EMCI ($n=20$)	LMCI ($n=20$)	AD ($n=20$)	P	*Post hoc* analyses					
						CN versus EMCI	CN versus LMCI	CN versus AD	EMCI versus LMCI	EMCI versus AD	LMCI versus AD
Demographics											
Age (y)	75.3 ± 5.4	73.0 ± 7.1	72.5 ± 8.6	72.2 ± 7.0	0.774	0.301	0.461	0.211	0.862	0.883	0.862
Education (y)	15.9 ± 2.1	15.3 ± 2.9	15.4 ± 2.3	15.5 ± 2.6	0.536	0.565	0.529	0.429	0.289	0.841	0.201
Gender (male/female)	9/11	9/11	9/11	7/13	0.895	1.000	1.000	0.524	1.000	0.524	0.524
General cognition											
MMSE	28.5 ± 1.6	28.0 ± 1.8	27.7 ± 1.7	23.0 ± 2.5	<0.001*	0.314	0.127	<0.001*	0.445	<0.001*	<0.001*
MoCA	25.1 ± 2.3	24.1 ± 3.6	21.9 ± 4.1	15.5 ± 4.9	<0.001*	0.495	0.005*	<0.001*	0.086	<0.001*	<0.001*
Episodic Memory											
RAVLT_immediate	42.9 ± 9.2	37.3 ± 11.1	31.7 ± 7.2	21.9 ± 7.6	<0.001*	0.072	<0.001*	<0.001*	0.091	<0.001*	<0.001*
RAVLT_learning	5.5 ± 2.6	4.8 ± 3.0	3.1 ± 2.0	0.8 ± 1.6	<0.001*	0.277	0.004*	<0.001*	0.121	<0.001*	<0.001*
RAVLT_forgetting	4.3 ± 2.8	5.3 ± 2.3	4.2 ± 2.3	4.1 ± 1.9	0.2	0.127	0.862	0.779	0.127	0.052	0.565
RAVLT_perc_forgetting	40.2 ± 25.4	62.4 ± 28.2	59.3 ± 31.8	96.9 ± 9.6	<0.001*	0.023*	0.020*	<0.001*	0.968	<0.001*	<0.001*
Cerebrospinal fluid	**($n=14$)**	**($n=13$)**	**($n=17$)**	**($n=19$)**							
Aβ (pg/ml)	1175.6 ± 490.8	1016.8 ± 463.1	861.8 ± 330.0	684.4 ± 279.0	0.030*	0.65	0.597	0.017*	0.934	<0.001*	0.016*
t-tau (pg/ml)	262.9 ± 96.7	341.1 ± 203.2	260.5 ± 100.7	365.6 ± 134.8	0.024*	0.458	0.769	0.003*	0.65	0.071	0.023*
p-tau (pg/ml)	25.2 ± 12.1	33.90 ± 24.1	25.7 ± 10.9	35.1 ± 13.3	0.025*	0.402	0.597	0.005*	0.621	0.099	0.015*

Values were presented as the mean ± standard error (SE); the p value of one-way ANOVA is obtained by Kruskal-Wallis test, and the p value of *Post-hoc* test is obtained by Mann-Whiney U Test, which were used here due to the fact that the data were not normally distributed; * indicates a statistical difference between groups, $p < 0.05$. CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; Aβ, amyloid-β; t-tau, total tau; p-tau, phosphorylated tau.

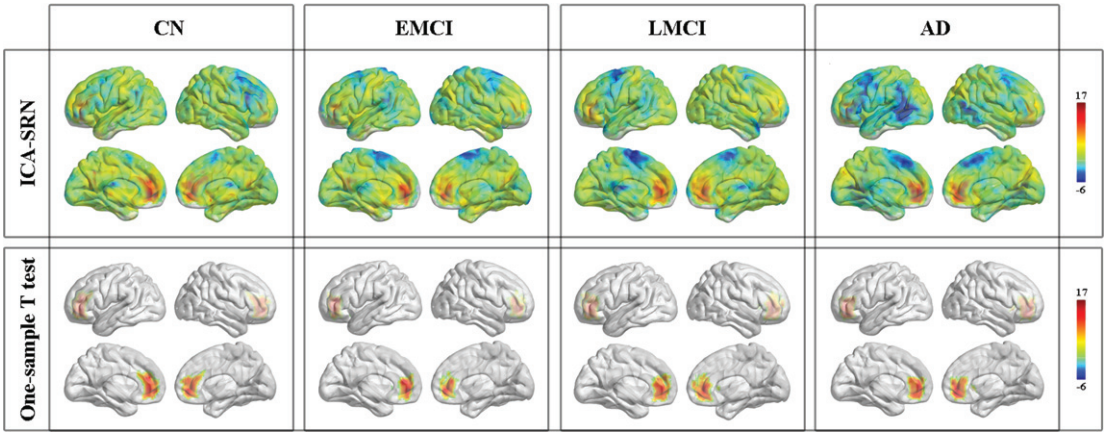

Fig. 2. The topological SRN pattern was observed in the CN, EMCI, LMCI, and AD groups, respectively. The SRN is demonstrated across the majority of clusters including the vMPFC, MOPFC, gyrus rectus, and pregenual anterior cingulate gyrus among these four groups. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation.

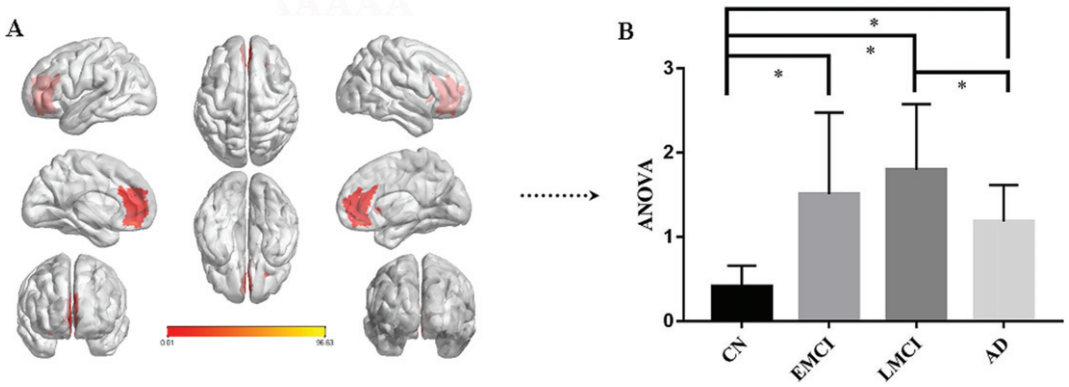

Fig. 3. A) Compared to CN, one-way ANOVA showed the hyperconnectivity of the vMPFC/MOPFC/rectus in the SRN in AD-spectrum patients. B) After *post hoc* analysis, an undulant SRN-connectivity curve was found to be similar to the "inverse U-shaped curve" in the progression of AD. In detail, the EMCI patients showed hyperconnectivity of the vMPFC/MOPFC/rectus in SRN when compared to CN, and the peak connectivity was observed in LMCI and the following AD patients showed a gradually decreasing connectivity. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation.

fluctuation after the progressively increasing concentration of CSF tau levels evoked the highest peak hyperconnectivity of the SRN in the LMCI group when compared to other groups, this indicated that the fluctuation of the CSF tau concentration was more sensitively tracking the hyperconnectivity of the SRN than the dynamic changes of CSF Aβ.

Associations of CSF pathological characteristics with cognitive impairments in AD-spectrum patients

As shown in Fig. 5, relationships among the clinical and cognitive test variables and CSF pathological biomarkers were found in AD-spectrum patients. No significant correlations were found between CSF pathological biomarkers and any cognitive impairment in the four groups, but it must be kept in mind that the number of samples with CSF in each group is small, and all of the patients belong to the AD spectrum. The correlation analysis was then performed in the whole AD-spectrum patients, including the EMCI, LMCI, and AD groups. We observed a significant positive correlation between CSF Aβ concentration and the MMSE scores (rho = 0.390, p = 0.002), and it was negatively related to RAVLT_perc_forgetting scores (rho = –0.400, p = 0.001) in AD-spectrum patients. Conversely, the MMSE scores displayed a significantly negative correlation with the CSF t-tau (rho = –0.347, p = 0.005) and p-tau (rho = –0.352, p = 0.005) concentration, while the RAVLT_perc_forgetting scores was significantly positively

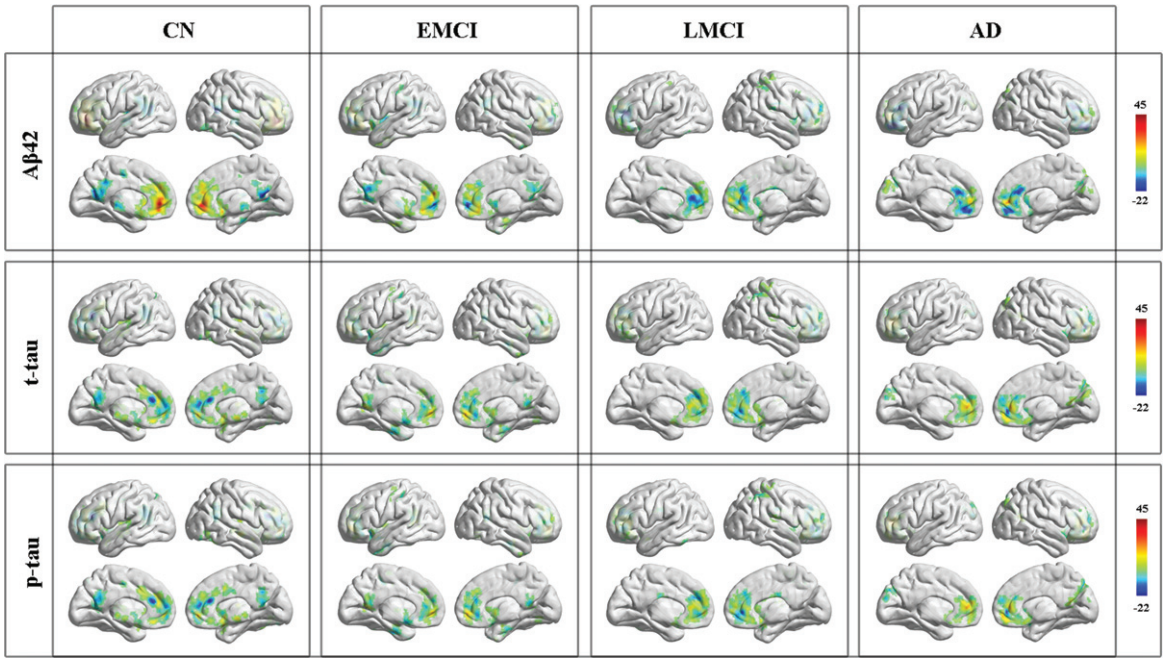

Fig. 4. In the CN group, higher intrinsic connectivity of the SRN is associated with a higher CSF Aβ concentration (yellow) and a lower CSF tau (i.e., t-tau and p-tau) concentration (blue). In the patient groups (from EMCI to LMCI to AD), a gradually negative association (blue) between CSF Aβ level and SRN connectivity combined with a gradually positive association (yellow) between CSF tau level and SRN connectivity were seen in the progression of AD. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation.

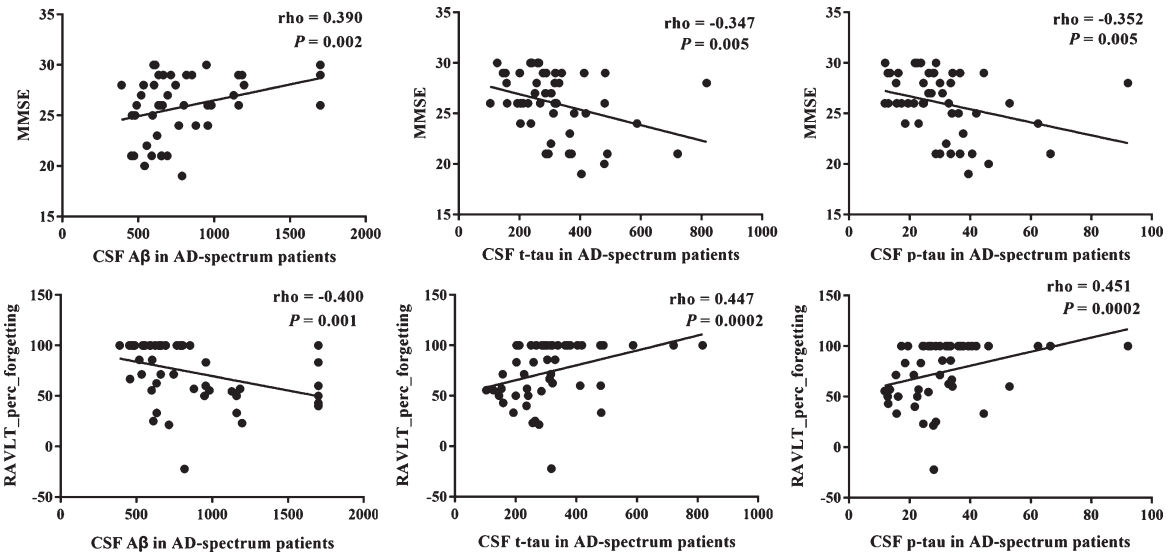

Fig. 5. In the AD-spectrum patients, a significant positive correlation between CSF Aβ concentration and the MMSE scores (rho = 0.390, $p = 0.002$), and they were negatively related to RAVLT_perc_forgetting scores (rho = –0.400, $p = 0.001$). Conversely, the MMSE scores displayed a significantly negative correlation with the CSF t-tau (rho = –0.347, $p = 0.005$) and p-tau (rho = –0.352, $p = 0.005$) concentration, while the RAVLT_perc_forgetting scores was significantly positively correlated with the CSF t-tau (rho = 0.447, $p = 0.0002$) and p-tau (rho = 0.451, $p = 0.0002$) level in the same subjects. It should be noted that one subject had a negative score in RAVLT_perc_forgetting. The RAVLT procedure was repeated for 5 consecutive trials (Trials 1 to 5). However, this existence is reasonable when the score of Trial 5 is less than the score of the delayed recall. In detail, RAVLT_perc_forgetting (RAVLT Forgetting divided by the score of Trial 5) and RAVLT_forgetting (the score of Trial 5 minus the score of the delayed recall) are calculated according to the defined scoring method.

correlated with the CSF t-tau (rho = 0.447, p = 0.0002) and p-tau (rho = 0.451, p = 0.0002) levels in AD-spectrum patients.

DISCUSSION

This is the first study to investigate the relationships among CSF pathological characteristics, cognition, and SRN abnormalities, in a cohort of individuals across the clinical AD spectrum. The main findings were as follows: 1) CSF AD pathological characteristics were closely related to the integrity of SRN. Among AD-spectrum patients, a higher intrinsic connectivity of the SRN was associated with a lower CSF Aβ level and a higher CSF tau level, while a reverse association between CSF markers and SRN connectivity occurred in cognitively normal subjects. 2) A certain disease state (i.e., the present LMCI) with a low concentration of CSF tau could evoke more hyperconnectivity of SRN than other patients, with a progressively increasing concentration of CSF tau (i.e., EMCI and AD), and this fluctuation of CSF tau was more sensitive to the hyperconnectivity of the SRN than the dynamic change of CSF Aβ. These findings support the view that the hyperconnectivity of the SRN will play an important role in monitoring the progression from the pre-dementia state to AD.

CSF Aβ and tau level are distinctively associated with SRN connectivity in AD-spectrum patients

In this study, the undulant curve of the SRN-connectivity was similar to the "inverse U-shaped curve" in the progression of AD. In detail, AD-spectrum patients (i.e., EMCI, LMCI, and AD) showed increased functional connectivity of the SRN when compared to cognitively normal individuals, and the peak connectivity was observed in LMCI. During the progression of AD, a gradually decreasing connectivity was observed. It has been shown that the greater the magnitude of hyperactivation in the early stages of illness, the faster the rate and magnitude of the subsequent cognitive decline [32]. This hyperconnectivity of the SRN is in line with different proposed models of brain aging (i.e., HERA, HAROLD, PASA, CRUNCH, STAC, GOLDEN Ageing) that postulate that the increased engagement of brain regions are trying to compensate for the cognitive and functional decline [33]. This probably works by engaging more diverse nonspecific processing resources. It is only when this response mechanism can no longer sustain the impairment that the connectivity deficit will appear. Therefore, the hyperconnectivity of the SRN may be reduced further in late AD and eventually becomes lower than in the controls.

In line with a previous study [28], we found higher intrinsic connectivity within the SRN is associated with a higher CSF Aβ concentration and a lower CSF tau concentration in cognitively normal individuals. However, our study further observed that a gradually negative association between CSF Aβ level and the SRN connectivity combined with a gradually positive association between the CSF tau level and the SRN connectivity developed during the progression of AD. A decreasing concentration of CSF Aβ and an increasing concentration of CSF tau are associated with the disease progression of AD.

Therefore, the present findings may indicate that the early stage of this disease could evoke hyperconnectivity of the SRN until this AD pathology is overwhelmed, which would then lead to hypoconnectivity. These observations were also in line with a recent PET study, where a lower level of brain tau deposition was associated with higher intrinsic connectivity within resting-state networks in healthy controls, while there was a shift toward a more positive association in patients with AD, i.e., higher connectivity, higher levels of brain tau deposition [34].

According to the brain network degeneration hypothesis, AD pathology will stereotypically propagate with disease progression [35]. The overlap between spatial AD pathology and resting-state networks has a fair-to-moderate level [36–38], and these functional hub regions are in particular susceptible to the accumulation of AD pathology [39]. Although the detailed mechanisms are still unknown, they may be associated with higher metabolic activity and have differential gene expression leading to the most prominent Aβ or tau retention among these resting-state networks [35].

Therefore, the SRN is one of the most valuable resting state networks. We hypothesized that the SRN breakdown is driven by Aβ or tau accumulation. However, the relationships between AD pathology and functional connectivity of brain networks are more tenuous in AD, where the consensus in terms of the location, size, and direction of the fMRI effects has been more difficult to establish [25]. Previous studies have reported regions of both increased and decreased connectivity with an elevated brain Aβ burden [40–43].

One reason for these discrepant reports is that both hyperconnectivity and hypoconnectivity effects may be different at different stages of the disease.

For example, a longitudinal amyloid-PET imaging study reported increased connectivity among low Aβ individuals who developed a high Aβ burden at follow-up, whereas AD patients had reduced connectivity [44]. The hyperconnectivity may be an important component of a pathological feedback mechanism that is both being driven by and driving the production of AD pathology [45]. In addition, there are alternative accounts for the inverse pattern by Schultz et al. (2017) [25]: first, it is possible that the effect is due to a survival bias such that high-amyloid individuals are associated with a low tau burden; second, increased connectivity may be compensatory and could represent a systems-level response to neuronal injury from pathological insult; third, it may be underdeveloped relative to the dynamic reality of brain connectivity.

CSF Aβ and tau level differentially correspond to the hyperconnectivity of SRN in the different stages of AD

As expected, the present study found that CSF Aβ was progressively decreasing during AD development. However, CSF tau was generally increasing and then there was a sudden decline (i.e., LMCI stage) during progression. It should be noted that considerable variation in the CSF tau biomarker levels exists among individuals with AD, with some showing long-term stability [46], others increasing at follow-up [47] and some exhibiting a decreased annual change [48].

Although the pathological mechanism remains unknown, a possible reason is that CSF Aβ and tau progress independently and they independently predict cognitive decline in symptomatic AD/MCI [49]. CSF tau reflects the extent of the cortical neurofibrillary tangle pathology and lower CSF Aβ levels are associated with greater Aβ neuritic plaques [50]. A brain Aβ and tau pathological distribution have been observed in relation to the resting state functional brain networks from the previous fMRI studies [51–53]. We further confirmed this result from the perspective of CSF pathological characteristics. In line with the previous studies, we were also able to stratify our sample regarding the relationship between CSF AD pathology and cognition. For example, CSF tau level is directly related to memory performance [54] and the general notion is that the CSF Aβ level is also strongly associated with cognitive decline [55].

This present study observed a hierarchical, disease stage-dependent pattern of progressively impaired episodic memory in AD-spectrum patients (from EMCI to LMCI to AD). The prefrontal cortex (i.e., the ventromedial and medial orbital) is the key hub of the SRN [13]. Accumulating evidence has shown the contribution of the prefrontal cortex (i.e., the ventromedial and medial orbital) to episodic memory processes, as top-down regulation from this region onto the hippocampus [56, 57]. Therefore, these findings indicated that impaired episodic memory is associated with the integrity of the SRN in the development of AD.

Interestingly, this study observed significant associations of CSF AD pathology, cognitive changes, and abnormalities of the SRN in LMCI patients. It is noteworthy that an interesting phenomenon for a tendency of a strange rebound (i.e., a decrease in CSF tau concentration) occurred in the LMCI group. Recent investigations of cognitively unimpaired individuals found a significant relationship where higher CSF tau levels were associated with increased hippocampal activity [54], and brain tau accumulation in inferior temporal brain regions was associated with increased hippocampal activity [58].

The reason for this may be that these cognitively unimpaired individuals can be expected to have very limited regional spread of tau pathology, and in sufficient quantities in a successful attempt to compensate for other degraded brain regions. Interestingly, this observation has also been extended to the clinical AD-spectrum patients. In line with our previous study, we found increased functional connectivity of brain regions regarding the selective changes of the vMPFC/MOPFC/rectus gyrus in the SRN [16]. We propose that the hyperconnectivity of the SRN in the present LMCI patients is a result of brain plasticity after damage to the neural system and it is only when this mechanism becomes overextended that the underlying deficits will begin to surface. One could argue that the more effective this mechanism is, the longer it disguises the effects of increasing levels of brain dysfunction [59]. We further hypothesize that brain functional compensation could be most prominently evoked in these individuals with a sudden fluctuation after dynamic changes of CSF tau (i.e., LMCI), while the smoothly increasing concentration of CSF tau (i.e., EMCI and AD) cannot cause the maximum functional activity. In other words, there is a changing relationship between the concentration of CSF tau and brain activation in the progression of AD. The detected dynamic state suggests that there may be

different pathological processes taking place at specific moments during AD progression [60], albeit the underlying mechanism is still unclear. However, these findings mark the important risk stage (i.e., a sudden fluctuation after a dynamic change of CSF tau is involved in the bottleneck of compensation) for these patients with cognitive impairments that will soon develop into AD, and this observation may prove to be valuable in future secondary prevention trials.

There were several technical and biological limitations in this study. First, the total number of participants and CSF samples available for analysis was relatively small, which may limit its statistical power. We look forward to additional studies with pre-study power calculations and larger sample sizes to expand upon these preliminary findings. Second, it is easy to ignore the importance of the loss of self-reference in clinical AD spectrum patients. Recent the viewpoints of clinic and neuroimaging were becoming increasingly evidence on the phenomenon of the impaired function of self-reference in AD spectrum patients [7, 9, 15, 16, 18, 61, 62]. The lack of a score of self-reference is a key weakness of this approach, and additional correlation analysis of brain and discrepancy scores could reinforce the significance of the present findings. Third, it cannot be assumed that these datasets in all groups have the same number of ICs, and it would be better to apply MDL separately on the present four datasets. The "breakdown" of functional connectivity in resting-state networks was associated with the patients, and it is thought to be a reduction in connectivity, while changing the topology of the resting-state networks. Therefore, these data should be interpreted with caution.

In conclusion, we identified that the integrity of the SRN was closely associated with CSF pathological characteristics in the progression of AD. These findings may have important clinical implications, as this investigative approach may lead to a better understanding of the hyperconnectivity of SRN and a possible means to monitor the development of the pre-dementia state to AD.

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SUPPLEMENTARY MATERIAL

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