Exploring dynamic functional connectivity alterations in the preclinical stage of Alzheimer's disease: an exploratory study from SICOLDE

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Abstract

Introduction

Exploring functional connectivity (FC) alterations is important for the understanding of underlying neuronal network alterations in subjective cognitive decline (SCD). The objective of this study was to discover stable and subtle dynamic functional connectivity (FC) changes in the preclinical stage of Alzheimer's disease (AD), and to explore the associations between dynamic FCs and amyloid accumulation.

Methods

Ninety-seven normal control (NC) subjects, 101 subjective cognitive decline (SCD) subjects, and 55 cognitive impairment (CI) subjects with neuropsychological assessments and resting-state functional magnetic resonance images constituted the whole cohort. Of these, 29 NCs and 52 SCDs with amyloid images were selected as the sub-cohort. First, independent components (ICs) identified by group independent component analysis (ICA) were used to define static and dynamic brain networks. Static and sliding-window dynamic FCs were then calculated. Second, the connection between each pair of ICs was compared between groups in the two cohorts. Hubs were obtained and considered as seeds in the subsequent seed-based dynamic FC analysis. One-way analysis of variance (ANOVA) was used to compare the seed-based dynamic FC maps between groups in the whole cohort, while a 2×2 ANOVA model was used to measure the group or amyloid effects in the sub-cohort. Post-hoc analysis was applied, and differences were considered significant if the cluster-level FWE-corrected p-value was less than 0.001. Finally, correlation analysis was conducted between the altered dynamic FCs, neuropsychological assessments, and amyloid burden.

Results

The results showed that 42 ICs were revealed. Compared with the static FCs, the dynamic FCs were found to be more stable and sensitive between groups. The effective dynamic FCs included those between the salience/ventral attention network, the default mode network, and the visual network. Specifically, the dynamic FC of the thalamus/caudate (IC 25) drove the hub role in the group differences between the NC and SCD groups. In the seed-based dynamic FC analysis, the dynamic FC between the thalamus/caudate and the middle temporal/frontal gyrus was observed to be higher in the SCD and CI groups in the whole cohort. Moreover, a higher dynamic FC between the thalamus/caudate and visual cortex was observed in the amyloid positive group. Finally, the altered dynamic FC was associated with the amyloid global level standardized uptake value ratio.

Conclusion

Our findings indicate that dynamic FCs can reflect subtle changes in the preclinical stage of AD.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease with latent onset and progressive development. The irreversible damage and ineffective treatment of AD led us to focus on its early stage (1). There has been renewed interest in subjective cognitive decline (SCD), which is considered to be the first symptomatic manifestation of AD (2). The characteristics of SCD individuals include persistent concerns about cognitive decline, but normal performance on standardized cognitive tests (3). Previous research has found a higher risk of converting to mild cognitive impairment (MCI) and dementia in participants with SCD when compared with individuals without SCD (2, 4–6). Therefore, SCD has been proposed as a possible preclinical stage of AD (2).

Resting-state functional magnetic resonance imaging (rs-fMRI) plays a key role in reflecting cognizance of brain functions, especially in exploring the abnormal connectivity patterns of brain regions in patients with AD (7–9). More specifically, previous research on functional connectivity (FC) has explored the abnormal changes that occur in functional networks in the brains of SCD individuals (10, 11). For instance, research shows that the global functional network is significantly increased in SCD (12), and that altered FC is primarily located in the posterior brain regions (13). Likewise, studies have also revealed that the significant FC reduction has been reported between the precuneus and occipital regions, including superior occipital gyrus and the bilateral cuneus (14–17).

Given the different employed technologies and patient samples, further research on FC in SCD patients is necessary. One additional reason for differing findings between previous studies could be the minor and atypical FC changes in the SCD stage, which are difficult to detect by conventional FC methods. To date, research has tended to focus on static FC, assuming that FC remains stationary over the duration of a scan of several minutes. However, extensive evidence suggests that FC, even at rest, should be understood as a dynamic measure. In recent years, dynamic FCs obtained from rs-fMRI time series has proven highly informative regarding the underlying brain connectivity patterns, as it enables slight changes over a short period of time to be explored (18–20). For example, research based on sliding-window analysis found that the occurrence frequency of a default mode network (DMN)-dominated dynamic FC state was significantly different in SCD patients (20). However, there have been few attempts to directly compare static and dynamic FCs or to determine whether dynamic FCs could undergo stable and subtle changes in subjects with SCD. In addition, the molecular mechanism resulting in these subtle changes remains unknown.

In the present study, the static and dynamic FCs calculated from rs-fMRI and the amyloid accumulation acquired by positron emission tomography (PET) images were investigated in two cohorts. It was assumed that the abnormal switching of individual brain function networks may be very subtle in the SCD stage. The purpose of this study is thus to explore dynamic FC alterations in subjects with SCD, and that the altered dynamic FCs may be associated with the global amyloid burden.

Materials And Methods

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Figure 1 shows the flowchart of this study, which includes a) subjects selection, b) imaging preprocessing, c) data analysis and d) statistical analysis. More details on the methods and materials were described in the following sections.

Participants

All applied research datasets were obtained from the Sino Longitudinal Study on Cognitive Decline (SILCODE, ClinicalTrials.gov identifier: NCT03370744) project (21). SILCODE is a project aimed at the diagnosis of SCD and MCI in the early stage of AD using multimodal data, including basic clinical information, neuropsychological assessment, biological markers, and neuroimaging. The study was approved by the Medical Ethics Committee of Xuanwu Hospital of Capital Medical University and was carried out in accordance with the Declaration of Helsinki. All subjects gave written informed consents and written consent to permit publication of clinical details.

The whole cohort was made up of 97 individuals with SCD and 101 age- and gender-matched normal control (NC) subjects (45 males and 56 females). In addition, 55 patients with cognitive impairment (40 MCI and 15 AD subjects together) from the SILCODE project were selected as a reference group to verify the abnormality across the dementia disease spectrum.

Of these, 52 SCD and 29 NC subjects with amyloid-PET (Florbetapir F-18 [AV45]) scanning were selected as our sub-cohort. Eighteen of the SCD subjects (34.6%) and 12 of the NC subjects (41.4%) were classified as the amyloid positivity group according to an a priori established cutoff value of 1.18 (22) for the cortical standardized uptake value ratio (SUVR) (further details given in data preprocessing section).

It is notable that only SCD subjects meeting the SCD-plus criteria were included in the study. The inclusion criteria for SCD-plus are as follows: (a) self-reported experience of persistent decline in memory compared with a previous state (within the past 5 years); (b) scores within the normal range (adjusted for age, sex, and education) on both the Mini-Mental State Examination and the Montreal Cognitive Assessment; (c) a Clinical Dementia Rating score of 0; (d) aged 60 years or older; and (e) concern (worry) about cognitive decline. The NC subjects were volunteers without cognitive decline concerns and whose neuropsychological tests scores were in the normal range. The following exclusion criteria were applied: (a) history of stroke; (b) depression; (c) cognitive decline from another cause (e.g., brain tumor, Parkinson's disease, encephalitis, or epilepsy); (d) other diseases that cause cognitive decline (e.g., thyroid dysfunction, severe anemia, syphilis, or HIV); (e) history of psychosis or congenital mental growth retardation; or (f) traumatic brain injury. The final diagnosis was confirmed by experienced neurologists.

Neuropsychological Assessment

A standardized clinical evaluation protocol was used according to the SILCODE project (21), including a medical history interview, neurologic examination, and a battery of neuropsychological tests for all subjects. The neuropsychological tests include the Chinese version of the Mini-Mental State Examination (MMSE), the Beijing version of the Montreal Cognitive Assessment Basic (MoCA-B), Subjective Cognitive

Decline Questionnaire 9 (SCD-Q9), Clinical Dementia Rating (CDR), Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), and Geriatric Depression Scale (GDS).

Imaging Acquisition

All subjects were imaged with an integrated simultaneous 3.0 T TOF PET/MR (SIGNA PET/MR, GE Healthcare, Milwaukee, Wisconsin, USA) at the Xuanwu Hospital of Capital Medical University. The parameters for the T1-weighted 3D brain structural images were as follows: spoiled gradient-recalled echo sequence (SPGR) sequence, field of vision (FOV) = $256 \times 256 \text{ mm}^2$, matrix = 256×256 , slice thickness = 1 mm, no gap, slice number = 192, repetition time (TR) = 6.9 ms, echo time (TE) = 2.98 ms, inversion time (TI) = 450 ms, flip angle = 12° , voxel size = $1 \times 1 \times 1 \text{ mm}^3$.

A single-shot gradient-echo EPI sequence was used for rs-fMRI with the following parameters: 8 mins with eye closed scanning, FOV = $224 \times 224 \text{ mm}^2$, matrix = 64×64 , slice thickness = 4.0 mm, gap = 1.0 mm, slice number = 28, interleaved scanning, TR = 2000 ms, TE = 30 ms, flip angle = 90° , voxel size = $3.5 \times 3.5 \times 4 \text{ mm}^3$, volume number = 240.

PET images were acquired by [^{18}F] florbetapir (AV-45) PET in three-dimensional acquisition mode. For A β PET, a 35-min dynamic scan was acquired approximately 40 min after an intravenous injection of 7–10 mCi [^{18}F] florbetapir. The PET data were acquired using a time of flight ordered subset expectation maximization (TOF-OSEM) algorithm with the following parameters: eight iterations, 32 subsets, matrix = 192×192 , FOV = 350×350 , half-width height = 3.

Imaging Preprocessing

All functional imaging data and T1 image preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) (23). The first 10 volumes were discarded to allow for stabilization of the initial signal. The remaining volumes were corrected for slicing time and realigned to the first volume for head motion (subjects who had more than 3.0 mm of translation and 1.0° of rotation were excluded). Functional images were co-registered to T1 images and spatially normalized into the standard Montreal Neurological Institute (MNI) brain space with 3-mm isotropic resolution using the deformation field from the segmentation of T1 images. The fMRI images that had any linear drift were removed and corrected for 24 head movement parameters, white matter, and cerebrospinal fluid signals. Temporal band-pass filtering (0.01–0.1 Hz) was performed and images were smoothed using an isotropic Gaussian with a full-width at half-maximum of 6 mm.

The PET images were preprocessed using the PETPVE12 toolbox based on SPM12 (24). Each participant's AV45 PET image was co-registered to the corresponding T1-weighted image and normalized to MNI space with Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DALTEL) (25). A voxel-based partial volume effects (PVE) correction was applied on the normalized images using the Müller-Gärtner method (26). The PVE-corrected image was smoothed to reduce noise and improve image quality using an isotropic Gaussian smoothing kernel with a full-width at a half-maximum setting

of 6 mm^3 . For each subject, the global SUVR for the corrected PET image was calculated using the mean uptake value of cortical regions divided by the mean uptake value of all the cerebellar regions.

Functional Brain Network Construction

A functional brain network between independent components (ICs) was constructed by group independent component analysis (Group-ICA) using the GIFT toolbox in MATLAB (27). First, subject-specific data were reduced and 66 components were retained based on principal component analysis (PCA). At the global level (101 NC subjects in our study), 42 components were retained and the Infomax ICA algorithm in ICASSO was repeated 100 times to improve the stability of the final decomposition.

A static brain network was constructed for each subject by computing the pairwise Pearson's correlation values among all 42 ICs. Averaged time signals were obtained for each IC, and Pearson's correlation coefficient was computed for every IC pair using the whole time series (remaining 230 timepoints). This resulted in a 42×42 matrix representing the static FC. The correlation values were then converted to Fisher's z-scores to ensure a Gaussian-like distribution.

A dynamic brain network was constructed for every subject using a sliding-window approach (28, 29). The pairwise correlation coefficient between the 42 ICs was calculated based on Ham50, a Hamming window of 50 TRs (100 s) and a sliding-window over 1 TR (2 s), resulting in a total of 181 windows (depending on the length of the functional scan) (30, 31). For each subject, a 42×42 correlation coefficient matrix was obtained for each window, and the standard deviation of the correlation matrices across all windows was calculated to give the temporal variability, which represents the dynamic FC.

Hub IC and Seed-based FC Analysis

In this study, the FCs in both static and dynamic brain networks (42×42) were compared between the NC and CI groups and between the NC and SCD groups in the whole cohort, and between the NC2 and SCD2 groups in the sub-cohort. After each comparison, a different T-value matrix (42×42) and its corresponding P-value matrix (42×42) were obtained. The T-value matrix was thresholded to produce a binary matrix. Then, the hub IC was defined when the degree of an IC fell more than three standard deviations from the averaged degree of all ICs in the T-value matrix (32, 33).

Every hub was treated as a seed, and seed-based dynamic FC analyses at the voxel level were subsequently performed in the two cohorts using the DynamicBC toolbox (34). Correlation maps between voxels in the hub (seed) and other voxels from the entire brain were calculated based on a window length of 50 TR and a step size of 1 TR. Standard deviation maps were calculated from the correlation maps and then converted to z-maps using the Fisher Z-transformation.

Statistical Analysis

Demographic and Clinical Data. One-way analysis of variance (ANOVA) models and post-hoc analysis were used to assess the group differences of age, education level, and neuropsychological

whole cohort. For the sub-cohort, two-sample t-tests were used

to measure the group effect of age, education level, and neuropsychological measurements. A chi-squared test was used to assess gender differences and APOE ϵ 4 carrier distributions in the two cohorts. A p-value of less than 0.05 was considered significant.

Group Differences in Static and Dynamic FCs. As described above, the connection of each pair of ICs in both the static and dynamic FC matrices (42×42) was compared using two-sample t-tests. A p-value of less than 0.05 was considered significant.

Group Differences in Seed-based Dynamic FC Analysis. In the whole cohort, voxel-level two-sample t-tests were used to compare group differences in the seed-based dynamic FC z-maps between the NC and SCD groups and between the NC and CI groups. A cluster-level FWE-corrected p-value of less than 0.001 was considered significant.

In the sub-cohort with PET images, instead of t-tests, a voxel-level 2×2 ANOVA model was used to explore whether group and amyloid effects exist in the dynamic FC z-maps. Post-hoc analysis was then applied, and group or amyloid effects with a cluster-level FWE-corrected p-value of less than 0.001 were considered significant.

Correlation Analysis. In the whole cohort, correlation analysis was further used to examine the relationship between the altered dynamic FCs and neuropsychological assessments within the SCD group and the CI group. A p-value of less than 0.05 was considered significant.

For the group or amyloid effects in the sub-cohort, correlation analysis was conducted between the altered dynamic FCs and global AV-45 SUVR, and neuropsychological assessments of the SCD group (SCD-negative and SCD-positive group). A p-value of less than 0.05 was considered significant.

Results

Demographic and Clinical Characterization

Table 1 shows the demographic and clinical details of the two cohorts. As shown in Table 1, there were no age and gender differences among the three groups, but lower education years in the CI group ($T = 2.98, p = 0.003$) when compared with the NC group. Significantly higher SCD-9, HAMD, HAMA, and GDS values were observed in the SCD and CI groups when compared with the NC group (all $p < 0.001$).

Table1. Demographic and clinical characteristics

Whole-cohort (n = 253)

Sub-cohort (n = 81)

	NC (101)	SCD plus (97)	CI (55)	NC2 (29)	SCD2 (52)
Age	65.89 ± 5.41	66.01 ± 4.95	67.07 ± 8.06	67.72 ± 4.75	66.24 ± 4.82
Gender (M/F)	45/56	23/74	29/26	12/17	13/39
Education	12.3 ± 3.08	12.56 ± 2.8	10.62 ± 3.78 ^{b*}	13.34 ± 3.04	12.57 ± 2.72
MMSE	29.02 ± 0.99	29.04 ± 0.92	25.67 ± 3.17 ^{b**}	29.14 ± 0.9	29.14 ± 0.88
MoCA-B	26.18 ± 2.21	26.07 ± 2.15	20.47 ± 3.76 ^{b**}	26.14 ± 2.21	26.27 ± 2.17
SCD-9	3.18 ± 2.09	5.4 ± 1.47 ^{a**}	4.79 ± 2.05 ^{b**}	2.91 ± 2.17	5.52 ± 1.64 ^{a*}
HAMD	1.88 ± 2.06	4.32 ± 3.61 ^{a**}	5.57 ± 6.22 ^{b**}	2.17 ± 2.26	3.92 ± 3.71 ^{a*}
HAMA	2.44 ± 2.41	5.2 ± 3.38 ^{a**}	4.79 ± 4.67 ^{b*}	3.07 ± 2.36	4.71 ± 3.4 ^{a*}
GDS	1.69 ± 1.38	2.3 ± 1.76 ^{a**}	3.07 ± 2.49 ^{b*}	1.55 ± 1.54	2.43 ± 2.12 ^{a*}
A (%)	/	/	/	12 (41.4%)	18 (34.6%)
APOE 4 (%)	21 (20.8%)	27 (27.8%)	21 (38.2%)	8 (27.6%)	15 (28.8%)

Data are presented as mean ± SD (min-max). NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment; M, male; F, female; MMSE, Mini-Mental State Examination; MoCA-B, Montreal Cognitive Assessment-Basic; SCD-9, subjective cognitive decline questionnaire including nine reliable items; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; GDS, Geriatric Depression Scale; Aβ+, amyloid positive;

* represents $p < 0.05$; ** represents $p < 0.001$;

^a represents the significant difference between NC and SCD group;

^b represents the significant difference between NC and CI group.

In the sub-cohort, consistently higher SCD-9, HAMD, HAMA, and GDS values were observed in the SCD2 group when compared with the NC2 group (all $p < 0.05$).

Group Differences in Static and Dynamic FCs

Table 2 and Fig. 2 show between-group comparisons of paired IC connections (NC group differs from SCD group and NC group differs from CI group) with uncorrected p-thresholds ($p < 0.05$). Forty-two ICs from the Group-ICA were classified into eight networks (Yeo-7-networks and a cerebellar network, CN). The Loading [MathJax]/jax/output/CommonHTML/jax.js N), somatomotor network (SMA), dorsal attention network

(DAN), ventral attention network (VAN) (also described as salience network (SN)), limbic network (LN), frontoparietal network (FPN), and default mode network (DMN). The spatial location and classification of the eight networks are shown in Supplementary Figure S1 and Table S1.

Table 2

Group differences between NC and CI, and between NC and SCD in static FC and dynamic FC

		NC and CI in the whole-cohort	NC and SCD in the whole-cohort	NC2 and SCD2 in the sub-cohort
Static FC	Number of FC (ICs)	72 connections (30 ICs)	10 connections (13 ICs)	3 connections (5 ICs)
	IC connected networks	VN, SMN, DAN, SN/VAN, LN, FPN, DMN, CN	VN, SMN, SN/VAN, LN, CN	VN, DAN, LN, CN
	Hub IC	IC-26 (SN/VAN)	IC-28 (CN)	IC-28 (CN)
Dynamic FC (Ham50)	Number of FC (ICs)	37 connections (27 ICs)	17 connections (23 ICs)	30 connections (21 ICs)
	IC connected networks	VN, SMN, DAN, SN/VAN, LN, FPN, DMN, CN	VN, SMN, DAN, SN/VAN, LN, FPN, DMN, CN	VN, SMN, DAN, SN/VAN, LN, DMN, CN
	Hub IC	IC-8 (SN/VAN)	IC-25 (SN/VAN)	IC-25 (SN/VAN)
NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment; FC, functional connectivity; ICs, independent components; VN, visual network; SMN, sensorimotor network; DAN, dorsal attention network; SN/VAN, salience and ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN, default mode network; CN, cerebellar network; Ham50, hamming window with window length of 50 TRs.				

Table 3

Post hoc showed group differences of dynamic FC in the whole-cohort and amyloid effect of dynamic FC in sub-cohort (FWE corrected $p < 0.001$)

	Cluster size	MNI coordinate [mm]			T- value	Side	Anatomical regions
		x	y	z			
Group difference in Whole-cohort	1341	-48	-42	9	3.85	L	MTG
		-3	-78	45	3.64	L	PCUN
		-15	-72	0	3.51	L	LING
	744	-6	39	48	4.13	L	MFG
		-21	54	39	4.00	L	SFG
		-27	27	51	3.58	L	MFG
Group effect in sub-cohort	335	51	-15	-6	4.33	R	MTG
		54	36	-12	3.80	R	IFG
		48	6	-24	3.75	R	MTG
Amyloid effect in sub-cohort	469	3	-90	-6	3.62	R	CAL
		12	-93	15	3.55	R	CUN
		12	-96	-9	3.39	R	LING
L, Left hemisphere; R, Right hemisphere; MTG, Middle temporal gyrus; PCUN, Precuneus; ITG, Inferior temporal gyrus; MFG, Middle frontal gyrus; SFG, Superior frontal gyrus; TFG, Inferior frontal gyrus; CAL, Calcarine; CUN, Cuneus, LING, Lingual.							

As shown in Table 2, the static FCs significantly differed between the NC and CI groups for all eight networks (72 FCs of 30 ICs, Table 2 and Fig. 2A). For the group differences between the NC and SCD groups, 10 FCs of the 13 ICs covering VN, SMN, SN/VAN, LN, and CN were significantly found in the whole cohort (Table 2 and Fig. 2B) and three FCs of the five ICs covering VN, DAN, LN, and CN (Table 2 and Fig. 2C) were significantly found in the sub-cohort.

Based on the dynamic FC (Ham50), all eight networks contributed to revealing the significant group differences between the NC and CI groups (37 FCs of the 27 ICs, Table 2 and Fig. 2D), between the NC and SCD groups in the whole cohort (17 differing FCs of the 23 ICs, Table 2 and Fig. 2E), and between the NC2 and SCD2 groups in the sub-cohort (30 differing FCs of the 21 ICs, Table 2 and Fig. 2F). Moreover, the significant group differences revealed by other dynamic parameters (Ham30, Gau30 and Gau50) were provided in Supplementary Figure S1 and Table S1.

The hubs of static and dynamic brain networks in the two cohorts are listed in Table 2. IC 25, located at the bilateral thalamus/caudate, was the only hub-IC that was stably defined in all dynamic FCs (Table 2

and Table S2). Hence, the spatial voxels of IC 25 were extracted and averaged as the seed in the following seed-based dynamic FC analysis.

In addition, to explore the influence of the window parameters on dynamic FC networks, two window types (Hamming and Gauss) and two window lengths (30 TR and 50 TR) were calculated (35, 36). When compared with Ham30, similar group difference pattern between the NC and CI groups and NC and SCD groups in both cohorts were revealed by Gau50, whereas sparser connections between the NC and SCD groups were revealed by Ham30 and Gau30. The results were listed in Supplementary Figure S2 and Table S2.

Seed-based Dynamic FC Analysis

In the whole cohort, both the CI and SCD groups showed significantly increased dynamic FC between IC 25 and the left middle temporal gyrus, the left precuneus, the left lingual gyrus, and the left middle and superior frontal gyrus when compared with the NC group (Tables and Fig. 3A, 3B).

In the sub-cohort, the group and amyloid effects were revealed simultaneously in a 2×2 (group × amyloid status) ANOVA model. No interaction effects were found in the model. Group effects showing increased dynamic FC between IC 25 and the middle temporal gyrus were found in the SCD group (Tables and Fig. 4A, 4B) when compared with the NC group. Apart from the group effects, amyloid effects with higher dynamic FC between IC 25 and the right calcarine were observed in the amyloid positive group when compared with the amyloid negative group (Tables and Fig. 4A, 4B).

Correlation Analysis

In the whole cohort, there was no significant correlation between the altered dynamic FCs and clinical variables in either the CI group or the SCD group.

In the sub-cohort, significant negative association was only found between dynamic FC (IC 25 and the middle temporal gyrus) and global AV-45 SUVR in the SCD-negative group ($r = -0.483$, $p = 0.004$, Fig. 4C). Significant positive correlations were found between dynamic FC (IC 25 and the calcarine gyrus) and global AV-45 SUVR ($r = 0.474$, $p = 0.04$, Fig. 4D) and clinical HAMD scores ($r = 0.490$, $p = 0.03$, Fig. 4E) in the SCD-positive group.

Discussion

In the present study, static and dynamic brain networks were evaluated to explore changes in FC in SCD. The SCD-related variations were sensitively and stably detected by the dynamic FC, whereas no variations were observed in static FC. The alterations in the dynamic FC were abundantly discovered and repeated in the two cohorts. Moreover, the group and amyloid effects on dynamic FC found in the SCD sub-cohort were associated with global AV-45 SUVR. Our study suggests that the role of dynamic FC in detecting subtle but vital evidence in the SCD group is coming to the fore.

Altered FC, as determined by either static or dynamic FCs in our CI group, is consistent with previous studies in the CI group or across the AD spectrum (37–39). However, in the SCD stage, when compared with dynamic FC, only slight differences in static FC were found between the SCD and NC groups, and no differences were repeatedly detected in our sub-cohort. The reason may be that the alterations in brain connectivity for SCD could be subtle and undiscoverable by conventional static FC approaches. Hence, sliding-window dynamic FC was employed for its sensitivity in reflecting the moment-to-moment resting-state activity (40). The results show that higher dynamic FC is associated with more frequent changes in FC strength over a short time between regions. The alteration in the SCD stage could be subtle or fleeting, and may only be captured by this dynamic measure. Moreover, the sensitivity of tracking the altered patterns in the SCD group was identified in different types of dynamic FC, regardless of the dynamic window parameters.

The salience/ventral attention network was observed to show group differences between the NC and CI groups in both static and dynamic brain networks. However, its contribution in differentiating the NC and SCD groups was only strongly involved in the dynamic measures, especially when connecting to the DMN and VN. The abnormal connectivity patterns between SN and DMN in the AD spectrum have frequently been reported (39, 41–43). The findings relating to dynamic FC in our SCD group may indicate that typical abnormal SN-DMN patterns exist in the preclinical AD stage. SN, together with its connected brain networks, contributes to a variety of complex brain cognitive functions, including sensory, emotional, behavioral, and self-awareness effects (42, 44, 45). The altered connectivity between SN and CN found in our SCD cohort using dynamic FC has seldom been reported in individuals with AD, CI, or SCD. Although visual deficits and measurements of such changes in the visual cortex of AD patients have been reported (46), the connectivity between SN and the visual cortex may improve our understanding of how the visual system and cognitive system are affected by each other, which may also provide new insights into the early stages of AD.

More specifically, the SCD-related abnormality in SN revealed by the dynamic brain network was mainly projected to the bilateral thalamus and caudate (regions of IC 25 in our study). Volume reduction of the thalamus/caudate had been reported in previous SCD or CI studies (47–49), and atrophy is considered a risk factor for motor, language, executive, and visual spatial control (50–52). In our SCD group, dynamic FC was found to be significantly increased in the thalamus/caudate when connecting to the left middle temporal gyrus, the precuneus, and the middle frontal gyrus, which exactly constitute the DMN. Increased static connectivity of the thalamus/caudate connected with regions in the DMN has already been observed in individuals with SCD relative to controls, and may represent a crucial step in characterizing SCD to the AD stage (53). Hence, our dynamic measure complements the evidence that altered dynamic FC of the thalamus/caudate could serve as an important neuroimaging feature for the preclinical stages of AD.

Interestingly, amyloid effects were observed to produce higher dynamic FCs between the thalamus/caudate and the visual cortex in the amyloid positive group when compared with the amyloid negative group. This finding is consistent with the hypothesis that the relationship between amyloid deposition and FC alterations in the AD spectrum has been

systematically explored in a recent review, and the association is thought to vary at different stages of the disease (54). In our study, the association between dynamic FC and global AV-45 SUVR interestingly had a negative correlation in the SCD-negative group and a positive correlation in the positive group. First, the SCD-negative group is not considered to be involved in the AD disease continuum according to the latest criteria (55). Hence, the negative correlation fits well with early works on clinical normal elderly patients who described a hypoconnectivity accompanying amyloid deposition pattern (14, 56). Focusing on the preclinical and clinical stages, the pattern that hyperconnectivity may be associated with amyloid deposition has been challenged (57–59). The positive correspondence in our SCD-positive group suggests amyloid accumulation to progress along with dynamic FC, and the correspondence to start already in the preclinical stage. Collectively, our results provide additional evidence of amyloid overload related compensatory mechanisms, even at specific stages of the preclinical AD continuum. Nevertheless, further studies investigating amyloid deposition and dynamic FC simultaneously and especially longitudinally are required.

Limitations

Several limitations to this study should also be acknowledged. First, the sample size in our sub-cohort was relatively small, which could limit the statistical power and reproducibility of the results. Second, in the connectivity construction, we only used sliding-window analysis with four combinations of window type (Hamming or Gauss) and window size (50 TR and 30 TR), and did not examine other parameters such as step size, and did not consider the methodological validation of other analytical strategies (60). Finally, this is cross-sectional research that lacks longitudinal evidence for the development of dynamic FC. There is a lack of validation of the association between dynamic FC and amyloid accumulation in the late stages of AD in the current work because of the absence of amyloid PET images for the CI group.

Conclusion

In conclusion, SCD-related FC changes can be sensitively and stably detected by the dynamic brain network, but are very difficult to identify using the static brain network. Altered dynamic FC patterns mainly occur when the salience/ventral attention network connects with the default mode network and visual network in individuals with SCD, and the alterations are associated with global SUVR. Our findings indicate that dynamic FCs can reflect subtle changes in the preclinical stage of AD.

Abbreviations

FC, functional connectivity; NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment; NC+, normal controls positive; NC-, normal controls negative; SCD+, subjective cognitive decline positive; rs-fMRI, resting-state functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; IC, independent component; ICA, independent component analysis; SD, standard deviation; SFC, static functional connectivity; DFC, dynamic functional connectivity; MMSE, Mini-Mental State Examination; MoCA-B, Montreal Cognitive Assessment-B; APOE, apolipoprotein E; AD, Alzheimer's disease; SCD, subjective cognitive decline; CI, cognitive impairment; NC, normal controls; NC+, normal controls positive; NC-, normal controls negative; SCD+, subjective cognitive decline positive; rs-fMRI, resting-state functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; IC, independent component; ICA, independent component analysis; SD, standard deviation; SFC, static functional connectivity; DFC, dynamic functional connectivity; MMSE, Mini-Mental State Examination; MoCA-B, Montreal Cognitive Assessment-B; APOE, apolipoprotein E; AD, Alzheimer's disease.

Assessment-Basic; SCD-9, subjective cognitive decline questionnaire including nine reliable items; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; GDS, Geriatric Depression Scale; A β +, amyloid positive; VN, visual network; SMN, sensorimotor network; DAN, dorsal attention network; SN/VAN, salience and ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN, default mode network; CN, cerebellar network; L, Left hemisphere; R, Right hemisphere; MTG, Middle temporal gyrus; PCUN, Precuneus; ITG, Inferior temporal gyrus; MFG, Middle frontal gyrus; SFG, Superior frontal gyrus; TFG, Inferior frontal gyrus; CAL, Calcarine; CUN, Cuneus, LING, Lingual.

Declarations

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Authors' contributions

Fan Yang: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization. Xueyan Jiang: Conceptualization, Methodology, Formal analysis, Validation, Writing - Original Draft, Visualization. Feng Yue: Validation, Writing - Review & Editing, Supervision. Luyao Wang: Validation, Writing - Review & Editing. Henning Boecker: Conceptualization, Writing - Review & Editing, Supervision. Ying Han: Conceptualization, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. Jiehui Jiang: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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Availability of data and materials

The dataset generated and analyzed in the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Xuanwu Hospital of Capital Medical University and was carried out in accordance with the Declaration of Helsinki. The Journal's position on issues involved in ethical publication were read and affirm that this report is consistent with those guidelines.

Consent for publication

Not applicable.

Competing interest

On behalf of all authors, the corresponding author confirms no conflict of interest.

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Figures

A flowchart of the proposed method in this study. (A) Subjects from SILCODE projects were selected for the whole-cohort and sub-cohort; (B) resting-state functional MRI T1-weighted structural MRI and amyloid-PET (Florbetapir F-18 [AV45]) images were preprocessing to reduce machine noise and artifacts; (C) static and dynamic functional connectivity was constructed to compare group differences in both cohorts and hubs was defined for the following seed-based dynamic FC analyses; (D) statistical analysis was applied including group differences analysis and correlation analysis. NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment; NC+, normal controls positive; NC-, normal controls negative; SCD+, subjective cognitive decline positive; SCD-, subjective cognitive decline negative; rs-fMRI, resting-state functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; ICA, independent component analysis; SD, standard deviation; SFC, static functional connectivity; DFC, dynamic functional connectivity.

Figure 2

Circular plot of group differences in static and dynamic functional connectivity. FC, functional connectivity; IC, independent component; NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment; VN, visual network; SMN, sensorimotor network; DAN, dorsal attention network;

SN/VAN, salience and ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN, default mode network; CN, cerebellar network; Ham50, hamming window with window length of 50 TRs.

Figure 3

Group differences in seed-based dynamic functional connectivity analysis.(A) Bar plot of dynamic FC between the thalamus/caudate and the middle temporal gyrus and the middle frontal gyrus; (B) The MTG and MFG brain regions in the atlas. Multiple comparisons correction was performed using FWE corrected $p < 0.001$. FC, functional connectivity; IC, independent component; NC, normal controls; SCD, subjective cognitive decline; CI, cognitive impairment.

Figure 4

Group and amyloid effect of altered dynamic functional connectivity. (A) bar plot of dynamic FC between the thalamus/caudate and the middle temporal gyrus and the calcarine; (B) The MTG and CAL brain regions in the atlas; (C) the linear plot of the significant correlation coefficients between dynamic FC with global AV-45 SUVR of SCD-negative group; (D) significant correlation coefficients between dynamic FC with global AV-45 SUVR of SCD-positive group; (E) significant correlation coefficients between dynamic FC with HAMD score of SCD-positive group.

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