Aberrant topological organization and age-related differences in the human connectome in subjective cognitive decline by using regional morphology from magnetic resonance imaging

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Abstract
Subjective cognitive decline (SCD) is characterized by self-experienced deficits in cognitive capacity with normal performance in objective cognitive tests. Previous structural covariance studies showed specific insights into understanding the structural alterations of the brain in neurodegenerative diseases. Moreover, in subjects with neurodegenerative diseases, accelerated brain degeneration with aging was shown. However, the age-related variations in coordinated topological patterns of morphological networks in individuals with SCD remain poorly understood. In this study, 77 individual morphological networks were constructed, including 42 normal controls (NCs) and 35 SCD individuals, from structural magnetic resonance imaging (sMRI). A stepwise linear regression model and partial correlation analysis were constructed to evaluate the differences in age-related alterations of the network properties in individuals with SCD compared with NCs. Compared with NC, the properties of integration and segregation in individuals with SCD were lower, and the aberrant metrics were negatively correlated with age in SCD. The rich-club connections persevered, but the paralimbic system connections were disrupted in individuals with SCD compared with NCs. In addition, age-related differences in nodal global efficiency are distributed mainly in prefrontal cortex regions. In conclusion, the age-related disruption of topological organizations in individuals with SCD may indicate that the degeneration of brain efficiency with aging was accelerated in individuals with SCD.

Keywords Aging · Structural MRI · Morphological network · Graph theory · Subjective cognitive decline

Introduction
Individuals with a subjective cognitive decline (SCD) show a self-reported persistent decline in cognitive capacity and normal performance in neuropsychological tests used to diagnose mild cognitive impairment (MCI) (Jessen et al. 2014, 2020). Compared with individuals who are unimpaired in cognitive capacity and without subjective cognitive decline, individuals with SCD are at a higher risk of cognitive decline in the future (Jessen et al. 2020; Gallassi et al. 2010; Rönnlund et al. 2015; Amariglio et al. 2018). Currently, although age is a crucial risk factor for Alzheimer’s disease (AD) (Ferreira et al. 2020; Fjell et al. 2014; Jagust 2013; Riedel et al. 2016), whether AD-related
neurodegeneration is due to aging still needs to be explored (Sivera et al. 2019; Pichet Binette et al. 2020). Previous studies based on neuroimaging revealed that gray matter (GM) atrophy (Chételat et al. 2005; Driscoll et al. 2009; Jack et al. 2008) and ventricular expansion (Jack et al. 2008; Driscoll et al. 2009) with aging accelerated in MCI patients compared with normal controls (NCs).

GM atrophy in structural magnetic resonance imaging (sMRI) characteristic of AD is one of the essential biomarkers in the A/T/N system (Besson et al. 2015; Jack et al. 2016, 2018). However, the foci of GM degeneration in individuals with SCD are distributed mainly in the medial temporal lobe, such as the hippocampus, entorhinal cortex, CA1, and subiculum (Rabin et al. 2017; Zhao et al. 2019). A voxel-based analysis revealed that the GM atrophy pattern in SCD individuals was similar to AD compared with control subjects (Peter et al. 2014). Currently, in individuals with SCD, the brain regions that showed decreased GM volumes in sMRI were mainly located in the medial temporal lobe, but studies based on other modality images observed that widely distributed regions were attacked by AD pathology (Wang et al. 2020). Exploratory research, therefore, needed to be considered to detect whether there were more GM structures in individuals with SCD that were altered. Compared with the network determined using functional MRI, the GM/morphometric networks are more similar to the networks of synchronized anatomical morphology change (Alexander-Bloch et al. 2013) and have the potential to reveal AD-related GM alterations from a system perspective. The aberrant degeneration of the GM in individuals with SCD aroused our curiosity for whether the organization of the morphological network was altered, which intended to explore the underlying neuropathological mechanism of SCD from the perspective of the human connectome.

The whole-brain GM individual network can be constructed by communities of regional morphology between brain structures, and the graph-theoretical approach can be applied to summarize complex organizations further into meaningful topological properties (He et al. 2007; Tijms et al. 2012; Alexander-Bloch et al. 2013). Furthermore, topological properties such as network efficiency, small-worldness, and modularity can reflect the working efficiency of the brain to integrate and segregate information from the perspective of the human connectome. Previous morphometric network studies have reported topological properties such as small-worldness (He et al. 2007), modularization (Chen et al. 2011), and rich-club organization (Lo et al. 2011) in the human brain. In particular, age-related changes in topological organization in healthy people have been revealed by previous GM network studies (Chen et al. 2011; Wu et al. 2012). As age is one of the most crucial risk factors in AD, examining age-related differences in network metrics may give us a better understanding of neurodegeneration and aging. Regarding neurodegenerative diseases, previous studies in AD and MCI patients revealed that neurodegeneration may disrupt the topological organization of morphometric networks (He et al. 2008; Yao et al. 2010; Li et al. 2016). In addition, amnestic MCI (aMCI) patients showed age-related alterations of the topological properties in white matter (WM) anatomical network analysis (Zhao et al. 2017). The age-related alteration of the topological organization may provide evidence for different neural mechanisms underlying aging in patients with neurodegenerative disease and may reveal whether the decline of the brain working efficiency is accelerated with aging due to cognitive issues. Regarding SCD, previous studies have focused mainly on alterations in WM anatomical networks (Yan et al. 2018; Shu et al. 2018) and functional networks (Viviano and Damoiseaux 2020; López-Sanz et al. 2017a, 2017b), but alterations in the topological organization of morphometric networks in individuals with SCD remain largely unknown. In addition, whether there are different neural mechanisms underlying aging in individuals with SCD and individuals without SCD still needs to be explored.

In this study, the probability density of GM based on sMRI was applied to construct individual morphometric networks. Graph theoretical analysis was used to survey the disruptions of topological properties of GM networks in individuals with SCD in six ways: (1) global network properties, such as global efficiency, local efficiency, shortest path length, and clustering coefficient; (2) global and local efficiency at the nodal level; (3) rich-club organization; (4) small-world properties; (5) connectivity of functional hierarchical organizations; and (6) connections classified by anatomical distance. In addition, the age-related differences in topological properties at six aspects in NC and SCD were investigated. We consider this to be exploratory research, and we hypothesized that individuals with SCD would show aberrant topological organization compared with NCs and that individuals with SCD would show a more rapid decline in network properties with aging. We expected that the abnormalities of morphometric networks in individuals with SCD might give us a better understanding of the underlying neuropathological mechanisms of SCD.

Materials and methods

Participants

In this project, 425 right-handed participants of Chinese Han nationality were recruited from May 2011 to June 2016. Regarding memory concerns, 116 patients had AD, 124 patients had MCI, 62 individuals had SCD, and 39 patients had other types of dementia. These patients were recruited from the memory clinic of the Neurology Department of
XuanWu Hospital, Capital Medical University, China. Then, 84 normal controls were enrolled from local communities in Beijing, China. This study was performed in accordance with the rule of ethics of the Medical Research Ethics Committee in XuanWu Hospital, and every subject gave their written informed consent to participate. The content of the assessment mainly includes the medical history investigation, neurologic examination, and a neuropsychological test battery. Furthermore, the volunteers received a neuropsychological evaluation from two neurologists (who worked independently and made consensus decisions), each with more than 2 years of clinical experience in neurology. Cognitive tests include the Montreal Cognitive Assessment (MoCA, Beijing version) (Lu et al. 2011), Auditory Verbal Learning Test (AVLT) (including three memory tests: AVLT-immediate recall (AVLT-I), AVLT-delayed recall (AVLT-D), and AVLT-recognition (AVLT-R)) (Zhao et al. 2017; Guo et al. 2007), Clinical Dementia Rating (CDR) (AVLT-D), and AVLT-recognition (AVLT-R) (Zhao et al. 2012; Guo et al. 2007), Clinical Dementia Rating (CDR) (Morris 1993), Hamilton Depression Rating Scale (HAMD), Activities of Daily Living (ADL) scale, Hachinski ischemic scale and the Center for Epidemiologic Studies depression scale (Dozeman et al. 2011). The tests above were in the Chinese version.

Individuals with SCD were recognized with the conceptual framework proposed by the Subjective Cognitive Decline Initiative (SCD-I) (Jessen et al. 2014) and described in our previous studies (Yan et al. 2018; Shu et al. 2018; Fu et al. 2021), including (1) self-experienced memory decline, rather than other domains of cognition and last within five years; (2) feeling of worse performance than others of the same age group; (3) the MoCA score was in the normal range; (4) only one of the two memory tests (AVLT-D and AVLT-R) was abnormal (decline one Standard Deviation (SD) compared with NC); and (5) the CDR score was 0; (6) patients diagnosed with aMCI, AD, or other types of dementia were excluded. The inclusion criteria for NC were as follows: (1) NC had no reported memory decline; (2) the MoCA, AVLT and CDR scores were in the normal range; and (3) no history of diabetes. In addition, the normal ranges of neuropsychological tests were adjusted for age and education year. The exclusion criteria for all participants in this study were: (1) HAMD scores higher than 24, and the score of Center for Epidemiologic Studies depression scale higher than 21; (2) Hachinski ischemic scale in the abnormal range (higher than 4); (3) not right-handedness; (4) the executive, visual or auditory functions impaired; (5) cognitive function decline due to no-AD neurological diseases (e.g., brain tumor, brain injury, Parkinson disease, encephalitis, normal pressure hydrocephalus, multiple sclerosis or epilepsy); (6) individuals with a history of stroke; (7) subjects with a history of alcohol or drug abuse/addiction within two years (DSM-IV(Diagnostic and Statistical Manual of Mental Disorders)); (8) large-vessel disease (e.g., cortical and/or subcortical infarcts and watershed infarcts); (9) patients with any other systemic diseases or uncertainty prevents the completion of the project; (10) subjects with frequent head motion which may influence the quality of MRI. Combined with the conceptual framework of SCD and the exclusion criteria in this study and considering the completeness of MRI data, 35 individuals with SCD and 42 demographically matched NCs were included in this study. Three neurologists in XuanWu Hospital with 8 to 28 years of experience completed this diagnostic procedure. The main demographical and neuropsychological characteristics of all subjects are summarized in Table 1.

### Image acquisition

Images were acquired from a 3.0 T Siemens system (Magnetom Trio Tim; Erlangen, Germany) by a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) 3D sequence at the Department of Radiology, XuanWu Hospital, Capital Medical University, Beijing, China. Anatomical T1 MRI was obtained with the following parameters:

| Characteristic                  | NC (n = 42)       | SCD (n = 35)       | Statistical value | p value |
|--------------------------------|-------------------|--------------------|-------------------|---------|
| Age (y)                        | 64.24 ± 6.16 (55–78) | 64.54 ± 7.29 (51–80) | 0.04              | 0.843   |
| Sex (M/F)                      | 15/27             | 15/20              | 0.410             | 0.522   |
| Education (y)                  | 11.17 ± 5.61 (0–22) | 11.83 ± 3.67 (2–18) | 0.358             | 0.551   |
| eTIV (10^3 cm³)                | 1.41 ± 0.12 (1.14–1.70) | 1.43 ± 0.14 (1.15–1.65) | 1.696             | 0.197   |
| MoCA                           | 26.02 ± 2.95 (18–30) | 25.26 ± 2.27 (19–30) | 1.583             | 0.212   |
| AVLT: immediate recall         | 9.32 ± 1.94 (6–14.7) | 8.54 ± 1.82 (5.3–13.3) | 3.219             | 0.077   |
| AVLT: delayed recall           | 10.43 ± 2.31 (6–15) | 8.86 ± 2.78 (4–15) | 7.357             | 0.008   |
| AVLT: recognition              | 12.07 ± 2.13 (8–15) | 11.37 ± 2.20 (6–15) | 1.999             | 0.162   |

NC normal controls; SCD subjective cognitive decline; eTIV estimated total intracranial volume; MoCA Montreal cognitive assessment; AVLT auditory verbal learning test; n number of subjects

*The statistical values were computed by ANOVA (F values) except for sex

bThe statistical values for sex were computed by the chi-square test (χ² score)
TR/TE/TI = 1900/2.2/900 ms; flip angle = 9°; field of view = 22.4 × 25.6 cm²; matrix size = 448 × 512; number of slices = 176; and slice thickness = 1 mm.

**Image preprocessing procedure**

First, nonuniformity intensity (N3) correction in FreeSurfer (version 6.0) (Fischl 2012) was performed on the sMRI data. Second, after N3 correction, the images were processed by the CAT12 (Gaser and Dahnke 2016) package embedded in Statistical Parametric Mapping software (SPM12). Through the segmentation pipeline in CAT12, T1 images were normalized to a template space and segmented into GM, WM, and cerebrospinal fluid (CSF), where the Local Adaptive Segmentation (LAS) and Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration (Ashburner 2007) were applied. Then, the GM images were normalized to the standard Montreal Neurological Institute (MNI) space. Thereafter, the voxel intensities of GM images were modulated to preserve regional volume information by Jacobian determinants derived from the normalization. Finally, the modulated GM images were isotropically smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel for further analyses.

**Construction of morphometric networks**

To construct the similarity matrix, the two fundamental elements of network nodes and edges must be determined first. In general, the nodes are defined by different anatomical atlases, and the edges are defined by the relationships between each pair of nodes.

**Node definition**

In this study, the nodes were represented by neuroanatomical structures. The automated anatomic labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002) (Table S1) was used to parcel the brain into 90 cortical and subcortical structures. In addition, the AAL atlas has been widely used in previous morphometric network analyses.

**Edge definition**

sMRI is characterized with high resolution and can accurately show the anatomical structure of the brain. Moreover, the intensity of voxels within brain regions in modulated GM images can mediate the content of brain tissue, the distribution, and the density of neuronal cells. Therefore, the distribution of intensity values of voxels within a specified brain structure from MRI images can represent the morphological features of the brain structure (Kong et al. 2015, 2014; Tijms et al. 2012). In addition, the Kullback–Leibler (KL) divergence has been widely used to estimate the similarity of two distributions; the lower the value of KL divergence, the higher the similarity of two distributions. In this study, for each pair of regions P and Q, we defined the edges (referred to as morphological similarity) between different regions by the converted symmetric KL divergence of their morphological distributions from GM images. The symmetric KL divergence can be computed by the equation:

\[
KL(P, Q) = \int_x \left( P(x) \log \left( \frac{P(x)}{Q(x)} \right) + Q(x) \log \left( \frac{Q(x)}{P(x)} \right) \right),
\]

where \( P(x) \) and \( Q(x) \) are two estimate distributions from different brain regions.

Then, the symmetric KL divergence was converted as a similarity measure using the following formula:

\[
KLS(P, Q) = e^{-KL(P, Q)}.
\]

The KLS was normalized from 0 to 1, where 0 represents the two completely different distributions, in contrast, is 1. Then, the morphological distributions were defined by estimated probability density functions (PDFs) through kernel density estimation (KDE) (Botev et al. 2010) from GM intensities of all voxels within each region. In particular, the Gaussian kernel is assumed, and the bandwidth is chosen automatically. To obtain unbiased PDFs, the number of voxels in each region was used to correct the effect of volume. In addition, the PDFs were truncated distributions, which were restricted by the range of the intensity of each region. Finally, we calculated the KLS of each pair of brain regions, and a 90 × 90 matrix was used to quantify the morphometric connection (Fig. 1).

**Network analysis**

**Threshold selection**

Because the continuous weights were able to contain more information between nodes (Barrat et al. 2004) and the structural alterations in individuals with SCD were subtle, weighted networks were used in this study to quantify the alterations of topological organization in individuals with SCD. Moreover, sparsity was defined as the ratio of the number of existing edges divided by the maximum possible number of edges in a network (Kong et al. 2015). The sparsity approach can ensure that there are the same number of nodes and edges in all individual networks. The sparsity of 15% meant that only 15% of the strongest edges remained and 85% of the weaker edges were removed. However, there is no definitive way to select a single sparsity value (He et al. 2007, 2008), and a sparsity approach with a sparsity range from 15 to 45% and an interval of 1% was used to reserve...
meaningful connections and remove redundant invalid connections in this study. The between-group differences in global topological properties at all sparsity thresholds were compared. To preserve more than 90% of the nodes in all networks and ensure that all individual networks exhibited small-world properties (He et al. 2007), the sparsity threshold was set as 30% (referred to as the median value of the sparsity range) in further analyses, including the topological properties at the nodal level, the rich-club organization, the hierarchical organization, the connections divided by anatomical distance and the age-related alterations of topological properties.

Graph theoretical characterization

The metric of integration in a network represents the capacity of the brain to integrate information from different brain regions, such as the global efficiency ($E_{\text{glob}}$) and characteristic path length ($L_p$) (Latora and Marchiori 2001; Ferrreira et al. 2019). Local efficiency ($E_{\text{loc}}$), the clustering coefficient ($C_p$), and modularity are measures of segregation, which represent biologically meaningful features of the brain to enable highly specialized processing through densely interconnected communities of regions (Ferreira et al. 2019; Watts and Strogatz 1998; Sporns 2013). In
addition, the measures of degree centrality (DC) and betweenness centrality (BC) were combined to identify the hub regions. For global, $E_{\text{glob}}$, $L_p$, $E_{\text{loc}}$, $C_p$, and small-worldness properties (sigma and gamma) were used to characterize the global topological organization of the morphometric networks (Rubinov and Sporns 2010). The clustering coefficient ($C_p$) of a node is the ratio of whether the node’s direct neighbors are neighboring each other (Watts and Strogatz 1998). $C_p$ for a network is the average $C_p$ for all nodes in the network. The characteristic path length ($L_p$) is the shortest path length between two nodes. Furthermore, the $L_p$ of a network is calculated by averaging the $L_p$ for all nodes (Watts and Strogatz 1998). The global efficiency is defined as the average reciprocal of $L_p$, which correlates with $L_p$. However, if the network is not fully connected, the value of $L_p$ will be infinite, and global efficiency can avoid this phenomenon (Rubinov and Sporns 2010; Latora and Marchiori 2001). The local efficiency is defined as the average efficiency of the local subgraphs and reveals how fault-tolerant the system; thus, it shows how efficient the communication is between the first neighbors of node $i$ when node $i$ is removed (Latora and Marchiori 2001). The nodal efficiency was defined as global and local efficiency at the nodal level. The small-world index sigma (Humphries et al. 2006) is defined as comparing the real properties of the network with respect to corresponding random networks (Lin et al. 2018), and the number of random networks in this study was 100. In addition, gamma is defined as comparing the $C_p$ of the brain network with respect to corresponding random networks, and lambda is defined as comparing the $L_p$ of the brain network with respect to corresponding random networks. The schematic representation and calculation formula of network metrics are shown in Fig. 2.

Functional organization and anatomical distance

Structural covariance and fMRI functional connectivity showed a significant statistical relationship (Alexander-Bloch et al. 2013). To prove that the individual GM networks we built are biologically meaningful, we investigated the connectivity strength of the networks at a functional organization level. To further characterize alterations in the global and local functional organization of brain networks in SCD individuals, a parcellation scheme including five key functional modules (primary sensory, subcortical, limbic, paralimbic, and association areas.) was applied in this study (Supekar et al. 2009). In a previous study, MCI targeted more middle- and long-distance functional connections, and the connections were defined by the anatomical distance (Wang et al. 2013). In this study, we computed the anatomical distance (Euclidean distance between stereotaxic coordinates of the centroids for two regions) of brain structures parceled by the AAL atlas. The connections were classified into short-range (lower than 45 mm), middle-range (higher than 45 mm and lower than 80 mm) and long-range (higher than 80 mm) (Wang et al. 2013) connections to investigate whether the GM networks are influenced by anatomical distance. Then, the interconnectivity and intraconnectivity of the five modules and the connections in each distance range were calculated.

All network analyses were performed on the GRETNA toolbox (Wang et al. 2015), and the results were visualized by the BrainNet Viewer toolbox (Xia et al. 2013).

Statistical analysis

Between-group differences

Group differences in age, years of education, estimated total intracranial volume (eTIV), and neuropsychological test scores (Moca and AVLT) were evaluated by analyses of variance (ANOVA) ($p < 0.05$). Then, the chi-square test was used to assess the differences in sex distribution ($p < 0.05$). A general linear model was used to determine between-group differences of global and nodal network properties as well as the differences of connections classified by function organization, anatomical distance, and hub regions, where the group factor was used as the fixed effect and the factors of age, sex and years of education were covariates ($p < 0.05$). Moreover, the between-group differences in nodal network properties were determined using Bonferroni corrections for multiple comparisons, which means $p < 0.05/90$. Finally, we have used a network-based statistic (NBS) approach based on the principles underpinning traditional cluster-based thresholding of statistical parametric maps (Zalesky et al. 2010) to identify a disconnected subnetwork in the SCD.
group compared with the NC group (age, sex, and years of education were covariates, and the strength of the connectivity for each edge in the brain network at sparsity of 30% was an independent variable), with the p values of edge and component being 0.01 and 0.001, respectively. The number of nonparametric permutations is 1000. For a detailed description of NBS, see Zalesky et al. (2010).

Age-related differences

A two-step procedure was applied to determine the correlation between age and the network metrics in each group. First, a stepwise regression model ($p < 0.05$) began with age, group, age $\times$ group interaction, sex, years of education as independent variables and network metrics as the dependent variable, and returned the subset of terms producing the most accurate model (Zhao et al. 2017; Brown et al. 2011). The stepwise regression is an exploratory approach (Kupper et al. 1976) to determine which variables should be included in a final model, which can determine the greatest extent whether the network metrics have a significant correlation with the age $\times$ group interaction. Similar to the previous study (Toledo et al. 2015), considering exploratory, no multiple comparison correction was performed in this step. The interpretability of the selected model was confirmed by performing a partial correlation analysis ($p < 0.05$) (sex and years of education are covariances) between significant interaction effect network metrics and age separately for the NC group and SCD group. This step can evaluate the significant network metrics which showed an interactive effect.

Fig. 2 Between-group differences in global network metrics as a function of sparsity. (1) The middle column is the schematic representation and calculation formula of network metrics. From top to bottom, they are clustering coefficient, shortest path length or characteristic path length, local efficiency, global efficiency, and the schematic representation of the small-world network and random network. (2) The left and right columns are the between-group differences of the network metrics. The arrows point from the representation of the network parameters to the results of the between-group differences. The error bars represent the standard deviation. One asterisk indicates $p < 0.05$, and two asterisks indicate $p < 0.01$, and three asterisks indicate $p < 0.001$.

\[
E_{cc} = \frac{1}{N} \sum_{i \neq j} \frac{1}{N_i} \sum_{j,k \in E} L_{j,k}
\]

\[
E_{loc} = \frac{1}{N \sum_{i \neq j} \left( \frac{1}{N_i} \sum_{j,k \in E} L_{j,k} \right)}
\]
of group and age in the first step and may help reduce the possibility of false-positive errors in this research.

**Associations between network metrics and cognitive scores**

We used partial Pearson’s correlations ($p < 0.05$) controlled for age, sex, and years of education to evaluate how clinical
Between-group differences of network metrics

Global network properties

Small-world networks are characterized by higher clustering coefficients and similar characteristic path lengths compared with random networks. In this study, all individual morphometric networks exhibited small-world properties, where the $L_p$ values were similar to those of the matched random networks ($\lambda \approx 1$), and the $C_p$ values were higher than those of the matched random networks ($\sigma > 1$) at all sparsity thresholds. In addition, sigmas higher than 1 in all networks demonstrate that small-world organizations were shown in each network. The sigma was lower in the SCD group than in the NC group ($p < 0.05$), and the sparsity was 17% to 33% ($F = 6.516, p = 0.013, \text{Cohen's } d = 0.5842$, at a sparsity of 30%). In addition, another small-world parameter, gamma (at sparsity of 15% to 32% except for 16%), was lower in individuals with SCD than in NCs ($p < 0.05$) ($F = 5.69, p = 0.019, \text{Cohen's } d = 0.5459$, at sparsity of 30%). Compared with the NC group, the changes in $E_{\text{glob}}$ (lower in SCD) ($F = 7.591, p = 0.0074, \text{Cohen's } d = 0.6293$, at a sparsity of 30%) and $L_p$ (higher in SCD) ($F = 7.543, p = 0.0076, \text{Cohen's } d = 0.6286$, at a sparsity of 30%) were significant in the SCD group at sparsities from 22 to 45%. Significant decreases in $C_p$ (except the sparsity of 17% and 37%) ($F = 12.4396, p = 0.00074, \text{Cohen's } d = 0.8072$, at the sparsity of 30%) and $E_{\text{loc}}$ (except the sparsity of 21%) ($F = 14.0116, p = 0.00036, \text{Cohen's } d = 0.8564$, at the sparsity of 30%) were detected in the SCD group compared with the NC group (Fig. 2). In addition, all the network properties at a sparsity of 30% in individuals with SCD deteriorated compared with NC.

Nodal network properties and rich-club organization

Compared with the NC group, the nodal local and global efficiency were significantly decreased in the SCD group only in the left paracentral lobule ($p < 0.05$, Bonferroni corrected). Similar hub distributions were observed in the two groups, located mainly in the left thalamus, prefrontal lobe, occipital lobe, and parietal lobe, of which 17 regions were in NC and 16 regions were in SCD (Fig. 3A and Table S4). In addition, 13 hub regions in the two groups overlapped. For different categories of connections classified by hub regions (Fig. 3B), the feeder connections showed a lower strength in SCD subjects than in NCs ($F = 11.515, p = 0.001$), which is consistent with previous WM network studies (Shu et al. 2018; Yan et al. 2018). All comparisons in this section were performed at a sparsity of 30%.

Results

Background characteristics of the participants

The differences were not significant in age, sex, years of education, eTIV, MoCA scores, ALVT-immediate recall scores, or AVLT-recognition scores between the NC and SCD groups. In particular, the SCD group performed worse than the NC group in delayed recall of the AVLT ($p < 0.05$). The results of this section are summarized in Table 1.

Reproducibility analysis

Herein, we computed the global network metrics within a wide range of sparsities (15–45%), and the between-group differences were assessed in all sparsity thresholds. In addition, we employed different parcellation schemes to define network nodes. The AAL atlas contains 12 subcortical structures, and we removed the subcortical structures to construct a 78 × 78 network to quantify the cortical network connections and repeated the above analysis. Moreover, to test the reproducibility of the results, we repeated the above analysis using the Neuromorphometric atlas (Gaser and Dahnke 2016) (Table S2) and Brainnetome atlas (Fan et al. 2016) (Table S3).
**Functional organization and anatomical distance**

For intraconnections within the five functional organizations, lower connectivity strength of the paralimbic system was observed in individuals with SCD ($F = 5.216, p = 0.025$) (Fig. 3E). The intermodule connections between the paralimbic and association areas ($F = 4.375, p = 0.04$) and the interconnections between the paralimbic and subcortical areas ($F = 4.291, p = 0.042$) were significantly lower in SCD subjects than in NC subjects. In addition, the strength of long connectivity (anatomical distance larger than 80 mm) was significantly decreased in individuals with SCD compared with NCs ($F = 4.22, p = 0.044$) (Fig. 3B).

Analysis of the network-based statistic resulted in one subnetwork with 24 nodes and 24 connections (edge-$p < 0.01$ and component-$p = 0.002$) (Fig. 3C). The NBS connectivity strength was the total strength within the disconnected network. Receiver operating characteristic curve (ROC) analysis revealed the connectivity strength of the subnetwork identified by NBS, showing a high area under the curve (AUC) value of 0.959 for classifying the two groups (Fig. 3D). In addition, the network connectivity strength in the SCD group was lower than that in the NC group ($F = 4.538, p = 0.037$) (Fig. 3B). The results in this section were based on networks with a sparsity of 30%.

**Age-related effects on topological properties of network**

This section summarizes all the network metrics that showed significant relationships with age × group interaction in the stepwise regression model and the partial correlation analyses for the selected network metrics.

Regarding the global network metrics, the age × group interaction effects exhibited significance in characteristic path length ($r = 3.387, p = 0.001, \beta = 0.359$) (Fig. 4A), global efficiency ($r = −3.395, p = 0.001, \beta = −0.359$) (Fig. 4A), clustering coefficient ($r = −3.603, p = 0.001, \beta = −0.384$) (Fig. 5A) and local efficiency ($r = −3.991, p < 0.001, \beta = −0.419$) (Fig. 5A) (Table 2). The following partial correlation analyses showed significant relationships between characteristic path length ($r = 0.416, p = 0.008$), global efficiency ($r = −0.421, p = 0.007$), clustering coefficient ($r = −0.291, p = 0.0499$), local efficiency ($r = −0.402, p = 0.01$) and age within the SCD group, while those network metrics exhibited nonsignificant correlations within the NC group.

Regarding the nodal global efficiency, the regression model revealed significant age × group interaction effects in 7 regions (Table 2) (all $p < 0.05$), including the left superior frontal dorsolateral gyrus, bilateral inferior frontal opercular gyrus, right superior frontal medial orbital gyrus, left anterior cingulate and paracingulate gyri, right parahippocampal gyrus and temporal pole of the middle temporal gyrus (Fig. 4B). Partial correlation analyses demonstrated that nodal global efficiency of the bilateral inferior frontal opercular gyrus (left: $r = −0.331, p = 0.03$; right: $r = −0.289, p = 0.05$), right superior frontal medial orbital gyrus ($r = −0.396, p = 0.011$), left anterior cingulate and paracingulate gyri ($r = −0.300, p = 0.045$) showed significant negative correlations with age within the SCD group, while nonsignificant correlations were found in the NC group (Fig. 4B). In addition, the nodal global efficiency of the right parahippocampal gyrus ($r = −0.347, p = 0.014$) showed a significant negative correlation with age in the NC group but not in the SCD group (Fig. 4B). Regarding the nodal local efficiency, 7 regions demonstrated significant age × group interaction effects in the stepwise regression model (Table 2) (all $p < 0.05$), including the right middle frontal orbital gyrus, right superior frontal medial orbital gyrus, right insula, right inferior occipital gyrus, right paracentral lobule and left putamen (Fig. 5B). Partial correlation analyses revealed that nodal local efficiency of the right insula ($r = −0.486, p = 0.002$), right inferior occipital gyrus ($r = −0.292, p = 0.05$), and left putamen ($r = −0.379, p = 0.014$) showed significant negative age-related within the SCD group, while nonsignificant correlations were found in the NC group (Fig. 5B). In addition, the right paracentral lobule ($r = −0.302, p = 0.029$) showed a significant decrease with age in nodal local efficiency in the NC group but not within the SCD group (Fig. 5B). The final models of the stepwise regression have been summarized in Table S5 in Supplementary Materials.

Regarding connectivity at the divisional level (association, limbic, paralimbic, primary sensory, and subcortical), the stepwise regression model revealed that intracnectivity of the paralimbic system, interconnectivity between the association area and paralimbic system, and interconnectivity between the paralimbic system and subcortical system showed significant age × group interaction effects across all participants ($p < 0.05$). For partial correlation analyses, the interconnectivity between the association area and paralimbic system ($r = −0.321, p = 0.034$) showed a significant correlation with age within the SCD group, while a nonsignificant correlation was found in the NC group. Additionally, the intracnectivity of the paralimbic system in the NC group showed a significant correlation with age but not in the SCD group. The connectivity strength of the subnetwork identified by NBS exhibited significant age × group interaction effects in the regression model ($r = −11.514, p < 0.001, \beta = −0.799$), and the following partial correlation analyses revealed a significant correlation between age and the calculated connectivity strength in the SCD group ($r = −0.412, p = 0.009$), while a nonsignificant correlation was found in the NC group (Fig. 3F). All comparisons in this section were performed at a sparsity of 30%.
Associations between altered network metrics and clinical performance

Regarding the small-world properties, the sigma in the SCD group showed a negative correlation with the delayed recall score of AVLT ($r = -0.329$, $p = 0.033$) and recognition score of AVLT ($r = -0.297$, $p = 0.049$). In addition, gamma showed a negative correlation with the recognition score of AVLT ($r = -0.308$, $p = 0.043$) in individuals with SCD. Within the SCD group, the nodal global efficiency of the left superior frontal dorsolateral gyrus ($r = 0.473$, $p = 0.003$) and right inferior frontal opercular gyrus ($r = -0.305$, $p = 0.045$) showed a significant correlation with the delayed recall score of the AVLT. Then, lower nodal efficiency of the bilateral inferior frontal opercular gyrus (left: $r = -0.331$, $p = 0.032$; right: $r = -0.362$, $p = 0.021$) was correlated with higher recognition scores of AVLT in the SCD group. The nodal local efficiency of the right insula exhibited a positive correlation with the delayed recall score of AVLT ($r = 0.321$, $p = 0.036$). In addition, the nodal local efficiency in the right superior frontal medial orbital gyrus ($r = 0.321$, $p = 0.037$) showed a significant correlation with MoCA scores. Regarding connectivity strength, the strength of feeder ($r = -0.302$, $p = 0.046$) connectivity showed a significant negative correlation with MoCA scores. Details of the results were summarized in Table S6 in Supplementary Materials.

Fig. 4 Age-related differences in global efficiency and characteristic path length (A), and the distribution of regions with significant age-related differences in nodal global efficiency (B). The anatomical structures were visualized by the BrainNet Viewer toolbox.
Reproducibility findings

To evaluate the reproducibility of the findings, we performed the following analyses to evaluate the potential effects of subcortical structures and parcellation schemes on the between-group differences and age-related differences in network topological properties in the NC and SCD groups. Most of the findings of global network metrics reported above were reproducible across different parcellation schemes. The $E_{\text{glob}}, E_{\text{local}}, C_p$ reduced, and the $L_p$ increased in individuals with SCD compared with NCs (Fig. S1–3). The small-world properties (e.g., sigma, gamma, and lambda) in NCs were stronger than those in individuals with SCD across different parcellation schemes. In the small-world networks, the higher the values of sigma and gamma, and the lower value of lambda, the stronger the small-world properties. Due to different parcellation protocols, the brain structures defined in different atlases cannot correspond completely; therefore, the results of the nodal network metrics cannot be compared directly across different parcellation schemes. Regarding the nodal global and local efficiency, the brain regions that showed significant age correlations were partially reproducible across different parcellation schemes. However, the distributions of the hub regions were similar across various parcellation schemes, such as the structures were mainly located in the Frontal lobe and Occipital lobe (Fig. S4). As shown in the Supplementary Materials (Table S4 and Table S–11, Fig. S1–4), the effects of subcortical structures and parcellation scheme are slight in global network metrics, but the local network metrics were changed due to different parcellation schemes. The details of the reproducibility findings are listed in the Supplementary Materials.
Table 2 Global and nodal network metrics with significant age × group interaction effects through regression model and partial correlation analysis

| Network metrics | p value (T value) of interaction | Partial correlation within each group |
|-----------------|---------------------------------|-------------------------------------|
|                 |                                 | NC                                   | SCD                                  |
| \(L_p\)         | 0.001 (3.387)                   | \(r = 0.162; p = 0.159\)             | \(r = 0.416; p = 0.008\)             |
| \(C_p\)         | 0.001 (−3.603)                  | \(r = −0.01; p = 0.477\)            | \(r = −0.291; p = 0.0499\)          |
| \(E_{\text{glob}}\) | 0.001 (−3.395)                 | \(r = −0.172; p = 0.144\)          | \(r = −0.421; p = 0.007\)           |
| \(E_{\text{loc}}\) | <0.001 (−3.991)               | \(r = 0.026; p = 0.437\)            | \(r = −0.402; p = 0.010\)          |

Regions for nodal \(E_{\text{glob}}\):
- Left superior frontal dorsolateral gyrus: \(0.049 (−2.002)\)
- Left inferior frontal opercular gyrus: \(0.019 (−2.407)\)
- Right inferior frontal opercular gyrus: \(0.009 (−2.694)\)
- Right superior frontal medial orbital gyrus: \(0.017 (−2.438)\)
- Left anterior cingulate: \(0.018 (−2.411)\)
- Right parahippocampal gyrus: \(0.014 (−2.512)\)
- Left temporal pole: middle temporal gyrus: \(0.004 (−2.976)\)

Regions for nodal \(E_{\text{loc}}\):
- Right middle frontal orbital gyrus: \(0.018 (t = −2.416)\)
- Right superior frontal medial orbital gyrus: \(0.007 (t = −2.774)\)
- Right gyrus rectus: \(0.032 (t = −2.186)\)
- Right insula: \(0.014 (t = −2.505)\)
- Right inferior occipital gyrus: \(0.006 (t = −2.808)\)
- Right paracentral lobule: \(<0.001 (t = −4.199)\)
- Left putamen: \(0.008 (t = −2.747)\)

Significant effects (\(p < 0.05\)) are indicated by bold text

NC normal controls; SCD subjective cognitive decline; \(E_{\text{glob}}\) global efficiency; \(E_{\text{loc}}\) local efficiency; \(L_p\) characteristic path length; \(C_p\) clustering coefficient

Discussion

This study used individual morphometric networks and graph theory analysis to investigate the altered topological properties in individuals with SCD compared with NCs and age-related differences in the two groups. The main findings were as follows: (1) global network metrics such as global/local efficiency, clustering coefficients, and small-world properties decreased in individuals with SCD compared with NCs; (2) altered nodal network metrics in individuals with SCD were located mainly in the prefrontal lobe, parietal lobe and subcortical system; (3) compared with NCs, significant decreases in global/local efficiency with increasing age were found in SCD subjects; (4) significant age-related differences in nodal network metrics between the two groups were located mainly in the prefrontal lobe; and (5) disrupted strength of the paralimbic system and feeder connectivity were found in the SCD group. Finally, the robustness of the results was validated using different sparsity thresholds and applying various parcellation schemes.

Aberrant topological organization in individuals with SCD

Compared with NC, we observed lower global/local efficiency, clustering coefficients, sigma, and gamma, as well as higher shortest path length in the SCD group. The results of global/local efficiency, clustering coefficients, shortest path length and gamma were consistent with previous WM structural network studies of SCD (Shu et al. 2018; Yan et al. 2018). In addition, the strength of network connectivity in the SCD group was lower than the strength of network connectivity in the NC group. Several previous morphometric network analyses of MCI and AD have revealed that significantly increased shortest path length and decreased global efficiency were exhibited in AD-related patients (Li et al. 2016, 2018; He et al. 2008; Yao et al. 2010). In contrast with our results, the clustering coefficients in AD-related patients based on GM networks exhibited a significant increase (He et al. 2008; Li et al. 2016; Yao et al. 2010). In our opinion, the main factor is that those studies were based on group networks, while our study was based on individual networks. Specifically, the group network means “one group, one network”, while the individual network means the networks are
constructed separately for all participants. Thus, the group network may reduce individual differences and require numerous participants. With studies based on functional MRI, decreased strength of functional connectivity in individuals with SCD, AD and MCI patients were found (Wang et al. 2013; Bai et al. 2011; Li et al. 2019; Viviano et al. 2019). Regarding WM structural network studies based on diffusion MRI, increased shortest path length and decreased efficiency were exhibited in AD and MCI patients (Shu et al. 2012; Zhao et al. 2017; Lo et al. 2010; Daianu et al. 2015; Cao et al. 2020). In summary, the trends of topological organization alterations in individuals with SCD were similar to those in AD-related patients, indicating a higher risk of cognitive decline in the future.

The functional network based on fMRI-coordinated brain activity correlations of the fluctuating magnetic properties of oxygenated blood between regions can reflect the synchronized activity between brain regions (Alexander-Bloch et al. 2013). Disrupted topological organization of the functional network in AD-related patients meant that functional integration and segregation of brain activity deteriorated. WM fiber bundles across the entire brain traced in diffusion MRI were labeled the ‘WM anatomical network’, reflecting the WM fiber connections between brain regions. Altered topological organization of the WM structure network in AD-related patients meant that WM fiber connections were impaired. Then, the GM network coordinates the morphological features between GM regions of the brain, reflecting the synchronized anatomical changes of the GM in the brain (Alexander-Bloch et al. 2013). Altered topological organization of the GM network in AD-related patients may suggest GM loss in correlated regions or localized degeneration in one structure. The similarities in “Results” across different imaging modalities meant that the synchronized anatomical change indeed results from brain connectivity of some kind, such as synchronized brain activity change and WM fiber connections. Our results are partially consistent with previous studies across imaging modalities above, which mean that the GM networks of individuals could independently and accurately explore the structural alterations of the brain at the network level in individuals with SCD.

Regarding rich-club organization, the distributions of hub regions were similar in the two groups, and decreased strength of feeder connectivity was shown in the SCD group, for which our results are consistent with previous network studies based on diffusion MRI (Shu et al. 2018; Yan et al. 2018). Previous studies demonstrated that rich-club organization persisted in AD and MCI patients, and connections, including peripheral regions, were attacked (Cao et al. 2020; Daianu et al. 2015). Although hub regions characterized by high activity and metabolism may accelerate the pathology of AD (Buckner et al. 2009), whether attacks begin within hub regions or non-hub regions remains unclear. Our results showed that the connections, including peripheral regions, were vulnerable in individuals with SCD compared with NCs.

Regarding functional organization, the intra- and interconnections, including the paralimbic system, decreased in the SCD group compared with the NC group. The paralimbic system is one of the transmodal areas with the highest synaptic levels of sensory-fugal processing (Mesulam 1998), which plays a causal role in activating attentional and memory systems within association areas to facilitate controlled processing of stimuli during cognitively demanding tasks (Supekar et al. 2009; Sridharan et al. 2008). In our results, the weakened integration of the paralimbic system and association areas in individuals with SCD may induce a decline in cognitive ability. In addition, the altered intraconnections in the paralimbic system and weakened interconnections between the paralimbic system and subcortical in the SCD group may indicate that individuals with SCD are at higher risk of cognitive decline in the future compared with NC.

GM degeneration in individuals with SCD has been detected in previous studies (Zhao et al. 2019; Rabin et al. 2017). However, the underlying neuropathological mechanism of GM degeneration in SCD remains barely known. We have revealed GM degeneration in individuals with SCD at a large system level, and researchers should consider studies combined with multimodal imaging techniques in the future.

**Age-related differences of network metrics**

Regarding global network metrics, the global efficiency and local efficiency in SCD showed significant age × group interaction effects, consistent with previous MCI studies results (Zhao et al. 2017). Then, partial correlation analyses revealed that global efficiency and local efficiency were significantly correlated with age in individuals with SCD, while nonsignificant correlations were found in NC subjects. Moreover, similar to global/local efficiency, the shortest path length and clustering coefficients showed significant age × group interaction effects, and there were significant relationships between those properties and age in individuals with SCD. Age is the main risk factor for AD, and the accelerated decrease in global network metrics with age in SCD indicates that SCD subjects have a future risk of cognitive decline.

Regarding nodal efficiency metrics, some brain regions showed a negative correlation with age in individuals with SCD, including the bilateral inferior frontal opercular gyrus, right superior frontal medial orbital gyrus, left anterior cingulate and paracingulate gyri, right insula, right inferior occipital gyrus, and left putamen. Moreover, these regions were located mainly in the prefrontal lobe and subcortical system. The lateral prefrontal cortex plays a critical role in the working memory-executive function network (Mesulam
to be explored. 

In addition, the prefrontal regions and DMN are vulnerable to AD pathology (Zhou et al. 2015; McKenna et al. 2016; Simic et al. 2014).

Moreover, the nodal efficiency of the parahippocampal gyrus showed a significant correlation with age in the NC group but not in the SCD group. The parahippocampal gyrus plays a vital role in episodic memory, preferentially involved in AD pathology (Jack et al. 2016; Yin et al. 2015). However, the cortical thickness of the parahippocampal gyrus showed no differences between individuals with and without SCD (Schultze et al. 2015). The results of the nodal efficiency of the parahippocampal gyrus indicate that the parahippocampal gyrus may play a compensatory role in individuals with SCD. In addition, the efficiency of the parahippocampal gyrus may decrease with aging in healthy people. SCD may be the first symptom of incipient neurodegenerative disease, which has received increasing attention because of evidence of its association with an increased risk of future objective cognitive decline (Jessen et al. 2020). However, the progressive of neurodegenerative due to normal aging and AD pathology may be different. Collectively, the underlying mechanism of the age-related changes, AD-related pathologies changes, and their co-pathologies in the brain still needs to be explored.

**Correlation between network metrics and clinical scores**

Clinical neuropsychological testing is a conventional method for memory examinations and disease-assisted diagnoses. This study used two test scores for correlation analysis, including AVLT and MoCA. We observed that the delayed recall score of AVLT exhibited a negative correlation with sigma and gamma in individuals with SCD. Moreover, a negative correlation between sigma and the recognition score of AVLT was found in individuals with SCD. The values of sigma, gamma, lambda and path length can represent the small-world property of a network. The results indicate that the weaker the small-world properties of the GM network in individuals with SCD, the worse the performance of the cognitive tests. A longitudinal study based on morphometric networks for individuals with SCD revealed that lower gamma, lambda and path length values were significantly associated with a steeper decline in global cognition, including memory decline (Verfaillie et al. 2018). In addition, the small-world index sigma is defined as comparing the gamma with lambda. It meant that if there were no differences of lambda between groups, the higher the value of gamma and the higher the sigma values. A more randomly organized GM network in individuals with SCD may be the main reason, similar to Verfaillie’s study (Verfaillie et al. 2018). For instance, a-synchronized patterns of aberrations may lead to more "spurious" correlations between two brain regions that previously did not show similarity before and potentially resulted in a more randomly organized GM network than before (Verfaillie et al. 2018). Regarding nodal efficiency, lower nodal local efficiency is associated with lower clinical behavioral scores. The nodal global efficiency of the left superior frontal dorsolateral gyrus negatively correlated with clinical behavioral scores, but the nodal global efficiency of the bilateral inferior frontal opercular gyrus showed a positive correlation with clinical behavioral scores. The opposite results of the nodal global efficiency may be due to the compensation mechanism; if some regions were attacked by AD pathological early, the working efficiency of other regions might be enhanced for compensation. For example, in individuals with SCD, increased functional connectivity was shown in DMN regions, reflecting an “effort” of the brain to compensate for subclinical losses of cognitive function (Hafkemeijer et al. 2013). Nevertheless, more research is required to investigate the relationships between potential pathophysiological mechanisms and the alterations of the GM networks in individuals with SCD.

**Effects of different brain parcellation atlases**

Considering the different definitions of the nodes may affect the organization of the networks; therefore, we have used three parcellation schemes (AAL Cortical, Neuromorphometric and Brainnetome) for reproducibility analysis to evaluate the robustness of this study. In this study, global network metrics (\(C_p, L_p, \sigma_{loc}\) and \(E_g\)) reported above were reproducible across different parcellation schemes; however, the results of the nodal network metrics (hub regions and age-related regions) were partially reproducible. Two potential factors may account for the observed differences. First, previous studies have shown that differences in network size may affect the topological organization of GM brain networks (Li et al. 2021; Zhao et al. 2021). In this study, the number of brain regions defined by the three atlases was different (AAL(90), AAL Cortical(78), Neuromorphometric(112) and Brainnetome(246)), which resulted in the size of networks being different. Second, the parcellation protocols of the three atlases were independent and different (Fan et al. 2016; Li et al. 2021; Tzourio-Mazoyer et al. 2002). Specifically, the anatomical structures in the AAL atlas were manually parcellated from one brain, while the Neuromorphometric atlas is based on the 35 parcellated brains and is a probabilistic atlas. Regarding the Brainnetome atlas, the parcellation protocol was based on connectional architecture and the atlas contains information on both anatomical and functional connections. All these factors may partially interpret the observed differences due to brain parcellation schemes.
Limitations

Methodological issues in our research should be addressed. First, the sample size is small. Although we constructed the individual network in this study, large sample size will be better. Second, cross-sectional samples were used in this study. A longitudinal study may be more appropriate to investigate GM degeneration in individuals with SCD over time. Third, only the distribution of GM density was used to construct the networks, and more morphological indices will be used to define the network connections in the future. Fourth, the very limited neuropsychological battery adopted was always a limitation. As the modified research framework for SCD was published (Jessen et al. 2020), more comprehensive neuropsychological tests should be addressed.

Conclusions

In summary, this study revealed that aberrant topological organization was shown in individuals with SCD, including decreased local/global efficiency, clustering coefficients, sigma, gamma, and increased shortest path length. Compared with the NC group, the rich-club connections in individuals with SCD persevered, but the strength of feeder connectivity decreased. Moreover, the connectivity of the paralimbic system was disrupted in individuals with SCD compared with NC subjects. In addition, the age-related decreases in nodal global efficiency in individuals with SCD are distributed mainly in the prefrontal lobe. The findings in this study may enhance the understanding of the underlying pathological mechanisms in individuals with SCD.

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Data availability The data, material and code that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All authors declare that they have no competing interests.

Ethical approval This study was approved by the Medical Research Ethics Committee in XuanWu Hospital, China, and all individuals gave written informed consent to participate.

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