BMC Geriatrics

RESEARCH

Open Access

Long-term risk of late-life depression in widowed elderly: a five-year follow-up study

Yang Li[1†], Hu Xu[2†], Jiale Wu[2], Yi Ding[1], Yunqian Zhu[1], Yang Wang[3], Xingbing Chen[3*] and Hui Su[3*]

Abstract

Background Late-life depression (LLD) poses a significant health risk among the elderly, with widowhood as a prominent contributing factor. However, the mechanisms that render some widowed individuals susceptible to depression while others remain resilient remain poorly understood.

Methods In this five-year longitudinal study, we followed 203 cognitively healthy, widowed elderly individuals (mean age: 65.2 years, 100 women). The median follow-up time was 4.8 years. Brain structural networks were constructed via diffusion tensor imaging and analyzed using graph theory metrics. Logistic regression and Cox proportional hazards models were employed to assess the predictive role of structural network attributes in depression onset. Moderation models further examined the influence of psychosocial factors on depression risk.

Results During our follow-up, 22 participants developed LLD (mean age: 65.6 years, 12 women). Altered brain structural network properties, alongside key psychosocial factors, were observed in those at risk of developing depression prior to symptom emergence. Logistic and Cox regression models revealed that decreased rich-club connections, reduced nodal efficiency in the left hippocampus (HIP.L), and lower network modularity significantly predicted depression onset. Additionally, these network alterations correlated with greater depression severity at follow-up. Moderation analyses indicated that weekly exercise frequency and time spent with children notably mitigated the effects of network disruptions on depression severity.

Conclusions Among cognitively healthy widowed elders, diminished rich-club connections, modularity, and HIP.L nodal efficiency are strong predictors of future depression risk. Furthermore, low physical activity and limited family interaction may amplify susceptibility within this high-risk group, suggesting that targeted early interventions could reduce depression risk in this vulnerable population.

Clinical trial number Not applicable.

Keywords Late-life depression, Widowed, Brain network, Psychosocial factors, Depression risk

[†]Yang Li and Hu Xu contributed equally to this work.

*Correspondence:
Xingbing Chen
1000030076@ujs.edu.cn
Hui Su
koala6wjl@163.com

[1]Department of Radiology, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu, China
[2]Jiangsu University School of Medicine, Zhenjiang, Jiangsu, China
[3]Department of Radiology, Gaoyou People's Hospital, No.10, Dongyuan Road, Yangzhou 225600, Jiangsu, China

Introduction

Late-life depression (LLD) is a significant mental health issue affecting a substantial portion of the elderly population, with serious implications for overall well-being, cognitive function, and physical health [1, 2]. Characterized by its onset in individuals aged 60 and above, LLD not only diminishes quality of life but also increases risks of comorbidities and mortality [3–5]. Among the various factors contributing to depression in older adults, widowhood is one of the most influential, often triggering feelings of loss, loneliness, and social isolation [6–9]. Despite this well-established link between widowhood and depression, a crucial question remains unanswered: why do some elderly individuals develop depression after the loss of a spouse, while others remain resilient?

The brain functions as a complex network of interconnected regions, facilitating various cognitive and emotional processes [10]. Recent advancements in neuroimaging techniques have enabled researchers to investigate the concept of brain networks, elucidating how structural connectivity influences mental health outcomes [11]. Abnormalities within these networks, particularly in terms of reduced rich-club connections and altered modularity, have been implicated in the pathophysiology of depression [12]. Such alterations may impair the efficiency of information processing across brain regions, potentially leading to the manifestation of depressive symptoms [13]. A deeper understanding of the relationship between structural network changes and depression can yield valuable insights into the underlying mechanisms contributing to LLD.

Beyond structural changes, psychosocial factors significantly influence depression risk in the elderly [14]. Factors like social isolation, life stressors, and emotional regulation difficulties are key contributors to LLD [15]. Emerging evidence suggests that chronic psychosocial stress may induce neurobiological alterations, linking these stressors to structural brain changes that increase susceptibility to depression [16, 17]. This complex relationship underscores the importance of understanding how psychosocial stress interacts with neural structures to shape mental health outcomes in the elderly.

To address these gaps, we propose a five-year longitudinal study involving 203 cognitively healthy, widowed elderly individuals. Using diffusion tensor imaging (DTI) and deterministic fiber tracking, we will construct individual-level structural brain networks. Graph theory will quantify network property changes over time, enabling us to elucidate the interplay between early structural network alterations and psychosocial influences. By integrating these perspectives, our study aims to identify early indicators of LLD and inform potential preventive strategies for healthy aging populations.

Materials and methods

Demographics

A cohort of 250 cognitively healthy, widowed elderly individuals was prospectively enrolled in this study. Inclusion criteria were as follows: (1) widowed within the past year and aged over 60 years; (2) voluntary participation with signed informed consent; (3) ability to comprehend and adhere to study protocols, no significant hearing or language impairments, and capacity to complete all cognitive assessments, questionnaires, and imaging procedures; (4) absence of a depression diagnosis at baseline, as defined by DSM-IV criteria; (5) no history of major neurological conditions (e.g., epilepsy, stroke, or Parkinson's disease); and (6) intact cognitive function at baseline, as indicated by a Montreal Cognitive Assessment (MoCA) score ≥ 24. Participants were excluded if they: (1) had a prior psychiatric diagnosis (e.g., major depression, bipolar disorder, schizophrenia); (2) reported alcohol or substance abuse within six months before baseline; (3) suffered from severe physical illnesses that could impair daily functioning or participation in the study (e.g., uncontrolled cardiac or respiratory disease); (4) had contraindications to MRI scanning (e.g., metal implants, pacemakers, or severe claustrophobia); (5) experienced major head trauma, neurosurgery, or other medical events that might affect brain structure within six months before baseline; or (6) had a family history of depression or had encountered significant stressful life events (SLEs) in the preceding six months, as both genetic and environmental factors are major contributors to depression [18–20].

During the five-year follow-up, 21 participants were lost to follow-up, 8 withdrew from the study (including 5 who died in accidents), and 18 were excluded due to significant SLEs, such as the loss of another close family member or friend. None of the participants in our cohort became romantically involved over the five-year study period. Ultimately, the analysis included 203 participants, of whom 22 developed depression.

Study methods

At baseline, participants underwent MRI scanning and were monitored for up to five years, with depression onset as the primary outcome. Mental health assessments, including evaluations for SLEs, were conducted biannually via home visits or telephone interviews. Each participant underwent evaluation by two experienced psychiatrists or clinical psychologists using standardized protocols. Mental state and depression severity were assessed with the Structured Clinical Interview for DSM-IV (SCID) and the 24-item Hamilton Depression Rating Scale (HDRS) [21]. Cognitive function was measured using the MoCA [22], while the Holmes and Rahe Social Readjustment Rating Scale (SRRS) was used to

track recent SLEs [23]. Meanwhile, cardiovascular factors, weekly exercise frequency, and time spent with children, along with other demographic variables, were thoroughly assessed. Weekly exercise frequency was measured through self-reported questionnaires administered during baseline and follow-up assessments. Participants were asked to report the number of days per week they engaged in physical activity lasting at least 30 min per session [24]. In our study, time spent with children specifically referred to interactions with biological or adopted children [25]. This variable was measured based on self-reported frequency and duration of in-person interactions per week, including activities such as shared meals, conversations, and participation in social or recreational activities. Notably, virtual or phone interactions were not considered in this assessment.

MRI scanning

MRI data were acquired using a 3.0T Siemens scanner with an 8-channel phased-array head coil. T1-weighted and DTI sequences were collected. High-resolution 3D echo-planar imaging was performed with the following parameters: repetition time (TR) = 14.0 ms, echo time (TE) = 4.92 ms, flip angle = 25°, field of view (FOV) = 240 × 240 mm^2, matrix = 256 × 256, axial slice thickness = 1 mm, and 176 slices. DTI data were obtained using a diffusion-weighted single-shot spin-echo sequence (TR = 20,500 ms, TE = 103 ms, FOV = 230 × 230 mm^2, matrix = 128 × 128, b-value = 0, 1000 s/mm^2, 25 diffusion gradient directions, slice thickness = 1.2 mm, no inter-slice gap, total scan time = 20 min 12 s).

Brain structural network construction

Figure 1 illustrates the flowchart of structural network construction. Whole-brain structural networks were constructed based on DTI data. Preprocessing involved geometric distortion and head motion correction, noise reduction, and anisotropic diffusion correction [26]. Deterministic fiber tracking was then employed to reconstruct white matter tracts [27]. Brain regions were parcellated into 90 nodes using the Anatomical Automatic Labeling (AAL) atlas, with edges representing the strength of white matter fiber connections between these regions, weighted by the number of fibers [28–30]. This yielded a 90 × 90 structural connectivity matrix for each participant. Network construction methods followed previously published protocols.

Structural network properties

The topological properties of brain structural networks reflect patterns of connectivity and information transfer efficiency between brain regions (For a detailed description, see Supplementary Material 1). The rich-club phenomenon describes highly interconnected hubs (rich-club nodes) that are more densely connected with each other than with other nodes, playing a central role in global network function [31]. Rich-club nodes were defined as those in the top 15% by degree (number of fiber connections), and connections were classified into rich-club (between rich-club regions), feeder (rich-club

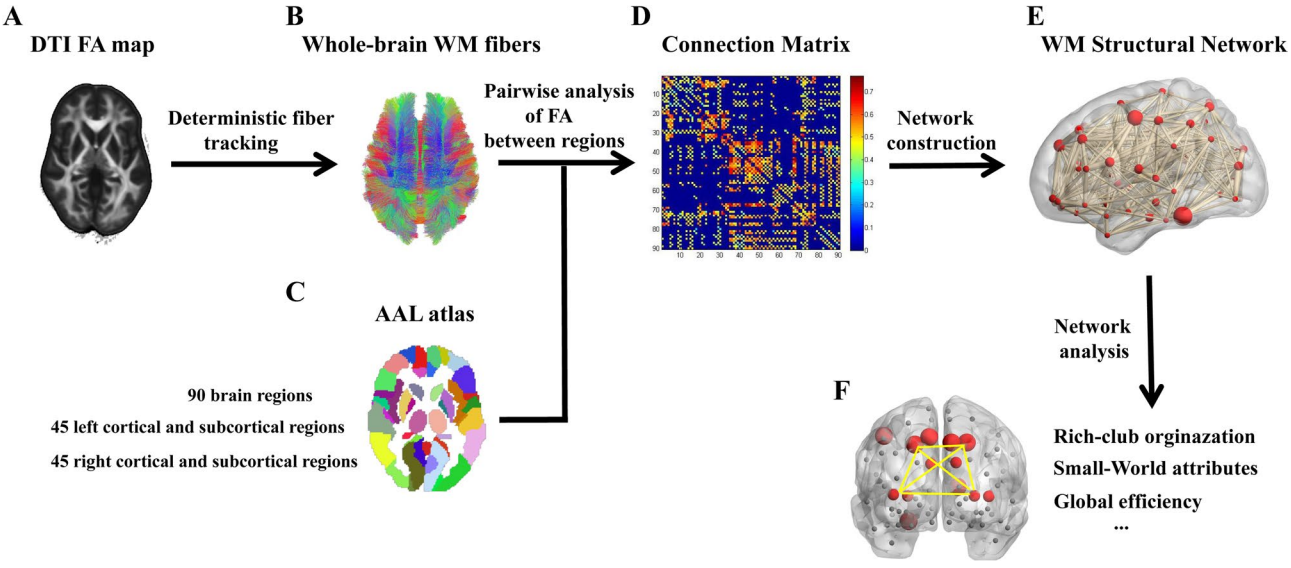

Fig. 1 Flowchart of structural network construction using diffusion MRI data. (**A**) Diffusion tensor imaging (DTI) data acquisition. (**B**) Reconstruction of white matter (WM) fiber tracts using deterministic tractography. (**C**) Whole-brain parcellation into 90 nodes according to the Anatomical Automatic Labeling (AAL) atlas. (**D**) Structural connectivity matrix construction by assigning reconstructed fibers to corresponding nodes. (E) Example of a structural network representation from a healthy subject. (**F**) Comprehensive analysis of the resulting structural network. Abbreviations: WM, white matter; FA, fractional anisotropy; AAL, Anatomical Automatic Labeling

to peripheral regions), and local (between peripheral regions) types [27, 32]. Connection strength for each type was calculated as the sum of the edge weights for that connection type [33].

Modularity captures the network's division into functional modules with dense intra-module and sparse inter-module connections, potentially reflecting specialized processing [34, 35]. Small-world properties describe networks with high local clustering and short global path lengths, supporting efficient local and global processing [36, 37]. Global efficiency measures the network's ability to transfer information via the shortest paths, reflecting the brain's functional efficiency [38]. The clustering coefficient measures the density of connections around a node, with high clustering supporting localized processing [39]. Nodal efficiency reflects the centrality of individual nodes within the network [40].

Statistical analysis

Statistical analyses were conducted using R 3.5.1 and SPSS 23.0. Normality and variance homogeneity were assessed using the Shapiro-Wilk and Levene's tests, respectively. Group comparisons were performed using independent samples t-tests or Mann-Whitney U tests, depending on the distribution of the data (adjusted for demographic factors including age, gender, cardiovascular, and social factors). To account for multiple comparisons, false discovery rate (FDR) correction was applied to adjust for comparisons between multiple brain regions. Categorical variables were analyzed using chi-square tests. Logistic regression models were used to assess associations between clinical and demographic variables and depression onset. After controlling for confounders, additional logistic regression models examined the relationship between structural network properties and depression onset. Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive performance of the models. Participants were dichotomized into high- and low-risk groups based on median structural network metrics. A multivariate Cox regression model was employed to assess the relationship between network properties and depression risk. Correlation analyses explored relationships between network properties and clinical features, adjusted for covariates. Multiple linear regression identified factors influencing HDRS scores, and moderation models tested the moderating effects of lifestyle factors on the relationship between structural network properties and depression severity.

Results

Demographic characteristics

Table 1 summarizes the demographic and clinical characteristics of all participants. A total of 203 healthy elderly widowed individuals (mean age: 65.2 years; 100 women, 103 men) completed the follow-up. The median follow-up time was 4.8 years, with a range of 0.5 to 5 years. By the study's conclusion, 22 participants were diagnosed with late-life depression (LLD group), while the remaining 181 did not develop depression (non-LLD group). The average time to depression onset in the LLD group was 3.1 years. At baseline, participants in the LLD group exhibited lower cognitive function compared to the non-LLD group, although both groups remained within the normal range ($t = 2.254$, $P = 0.025$). The LLD group also reported significantly lower weekly exercise frequency ($t = 2.306$, $P = 0.028$), spent less time with their children ($t = 2.523$, $P = 0.017$), and had a higher prevalence of death of both parents ($\chi2 = 4.532$, $P = 0.033$). No significant differences were observed between the two groups in age, gender, education level, body mass index (BMI), or HDRS scores ($P > 0.05$).

Table 1 Demographics and clinical characteristics of the participants. Data are means (standard deviation) unless otherwise noted. All of the scores are Raw values. MoCA, Montreal cognitive assessment; BMI, body mass index; WEF, weekly exercise frequency; TSC, time spend with children; HDRS, Hamilton depression rating scale

Variables	Non-LLD group ($N = 181$)	LLD group ($N = 22$)	χ2	t	*P*
Age (years)	65.2 (3.0)	65.6 (3.5)	-	−0.604	0.547
Gender (W/M)	88/93	12/10	0.276	-	0.600
Education (years)	10.8 (3.2)	10.3 (3.1)	-	0.744	0.458
MoCA scores	26.9 (2.0)	25.9 (1.9)		2.254	**0.025**
BMI	22.4 (2.6)	22.2 (3.0)	-	0.373	0.710
WEF	2.5 (1.8)	1.7 (1.5)		2.306	**0.028**
TSC	9.6 (6.0)	7.0 (4.2)	-	2.523	**0.017**
Hypertension (Y/N)	68/113	8/14	0.012		0.912
Diabetes (Y/N)	56/125	6/16	0.124		0.724
Smoking history (Y/N)	112/69	15/7	0.333		0.564
Death of both parents (N)	80	15	4.532	-	**0.033**
HDRS scores (baseline)	3.4 (2.3)	4.2 (2.5)	-	−1.567	0.119

Differences in structural network properties

At baseline, both the LLD and non-LLD groups exhibited typical rich-club organization, with similar distributions of core brain regions. However, the LLD group showed a significantly lower proportion of rich-club connections compared to the non-LLD group (5.012% vs. 5.892%, $P<0.01$, Supplementary Material 2). Further analysis revealed a marked reduction in the strength of rich-club connections in the LLD group ($t=10.823$, $P<0.001$, Fig. 2A). Both groups demonstrated small-world network properties, yet global metrics indicated that brain modularity ($t=11.754$, $P<0.001$, Fig. 2B) and clustering coefficient ($t=2.673$, $P=0.008$, Fig. 2C) were notably reduced in the LLD group. Local network analysis revealed significant reductions in nodal efficiency within the left hippocampus (HIP.L, $t=12.037$, $P<0.001$), left insula (INS.L, $t=2.463$, $P=0.015$), left precuneus (PCUN.L, $t=2.733$, $P=0.007$), and right amygdala (AMYG.R, $t=2.217$, $P=0.028$) in the LLD group (Fig. 2D). By the end of the follow-up, the LLD group exhibited further declines in rich-club connections, global efficiency, brain modularity, HIP.L nodal efficiency, right Caudate nucleus (CAU.R) and INS.L nodal efficiency, while the non-LLD group remained stable with no significant changes (Supplementary Material 3).

Structural network properties and depression risk

Logistic regression analysis was conducted with depression onset as the dependent variable and baseline clinical characteristics as independent variables (Table 2). The results indicated that weekly exercise frequency, time spent with children, and widowhood status at baseline were not significant predictors of depression onset ($p>0.05$). However, after adjusting for confounding factors, rich-club connections (OR = 0.982[95%CI:0.972–0.993], $P<0.001$), brain modularity (OR = 0.919[95%CI:0.862–0.980], $P=0.010$), and HIP.L nodal efficiency (OR = 0.946[95%CI:0.915–0.979], $P<0.001$) emerged as significant predictors of depression risk. Although the clustering coefficient demonstrated

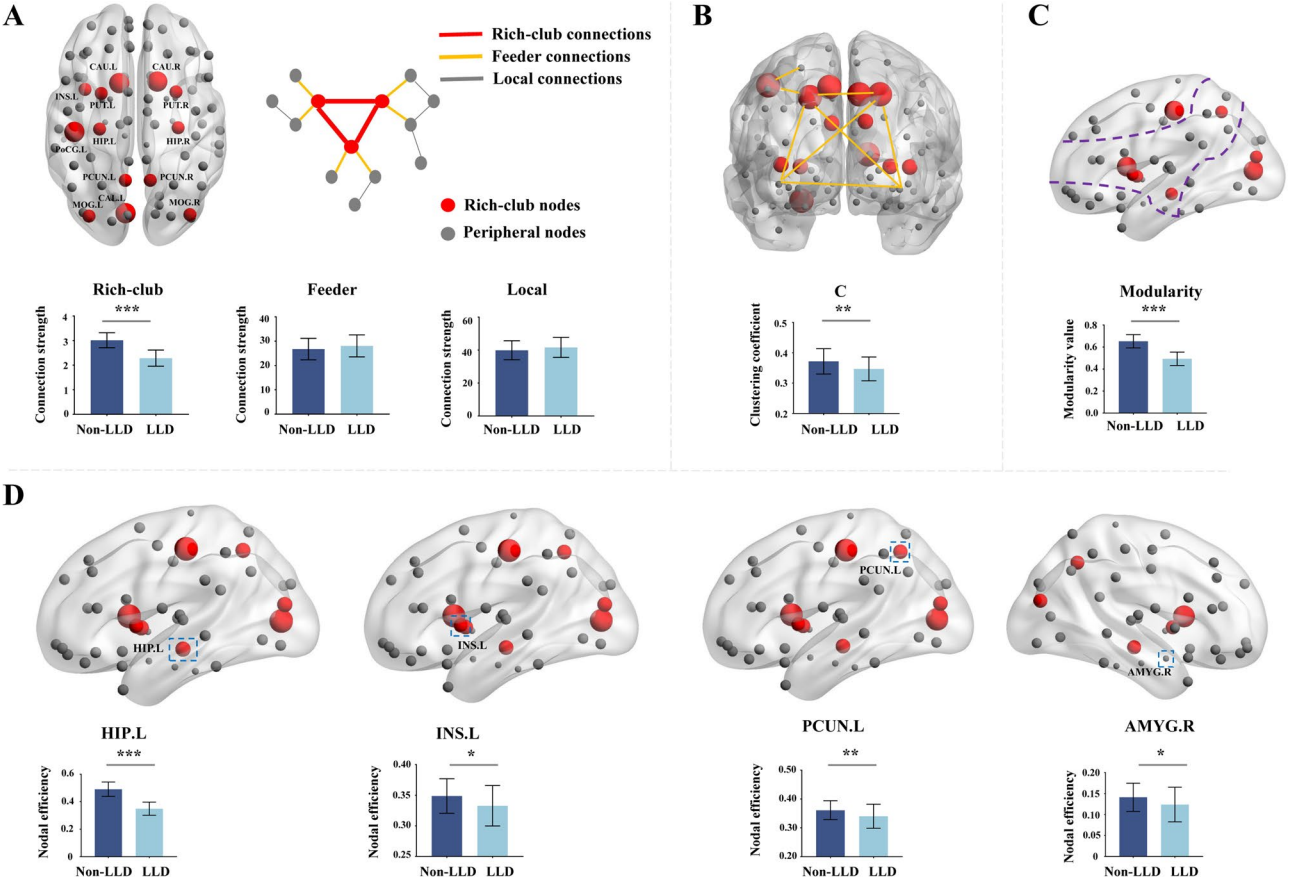

Fig. 2 Differences in structural network properties between the LLD and non-LLD groups. (**A**) Rich-club organization and connection properties in each group. Red nodes represent rich-club members identified across all subjects, with node size indicating nodal connection strength. Colors distinguish between rich-club, feeder, and local connections. Bar charts illustrate group differences in these three connection types. (**B**) Schematic of clustering coefficient and group-wise differences in clustering coefficients. (**C**) Schematic of modularity and corresponding group differences. (**D**) Group differences in nodal efficiency across the structural network. Abbreviations: C, clustering coefficients; HIP.L, left hippocampus; INS.L, left insula; PCUN.L, left precuneus; AMYG.R, right amygdala. Statistical significance: *$P<0.05$, **$P<0.01$, ***$P<0.001$

Table 2 Predicting the occurrence of depression. B, Beta statistic; SE, standard error; Wald, Wald statistic; exp, exponential; CI, confidence interval; BMI, body mass index; WEF, weekly exercise frequency; TSC, time spend with children; HDRS, Hamilton depression rating scale; HIP.L, left hippocampus; INS.L, left Insula; PCUN.L, left precuneus; AMYG.R, right amygdala; NE, nodal efficiency

	B	SE	Wald	*P*	Exp (B)	95% CI
Age	0.291	0.131	3.266	0.071	1.338	1.035–1.729
Gender	−0.070	0.132	0.285	0.594	0.932	0.720–1.207
Education	−0.030	0.245	0.015	0.901	0.970	0.600–1.569
MoCA scores	0.055	0.289	0.036	0.849	1.056	0.600–1.862
BMI	−0.168	0.232	0.524	0.469	0.846	0.536–1.332
WEF	−0.183	0.375	0.237	0.626	0.833	0.399–1.737
TSC	−0.191	0.177	1.173	0.279	0.826	0.584–1.169
Death of both parents	0.097	0.107	0.832	0.362	1.102	0.893–1.359
HDRS scores	0.288	0.299	0.924	0.337	1.333	0.742–2.397
Rich-club connections	−0.018	0.005	12.866	**< 0.001**	0.982	0.972–0.993
Clustering coefficient	0.006	0.010	0.359	0.549	1.006	0.987–1.026
Modularity	−0.084	0.033	6.657	**0.010**	0.919	0.862–0.980
HIP.L NE	−0.055	0.017	10.447	**0.001**	0.946	0.915–0.979
INS.L NE	−1.030	1.065	0.935	0.334	0.357	0.044–2.883
PCUN.L NE	−0.159	0.084	3.567	0.059	0.853	0.724–1.005
AMYG.R NE	−0.495	0.373	1.755	0.185	0.610	0.293–1.266

some predictive value, its significance diminished after adjusting for weekly exercise frequency and death of both parents status ($P > 0.05$). ROC curve analysis indicated that rich-club connections, brain modularity, and HIP.L nodal efficiency had strong predictive power for depression onset, with area under the curve values of 0.822, 0.804, and 0.840, respectively (Fig. 3B). A combined analysis of these factors yielded an even greater predictive effect (AUC = 0.924, $P < 0.001$, Fig. 3B).

A multivariate Cox regression model further validated the predictive role of rich-club connections, right hippocampal nodal efficiency, and brain modularity for depression risk (Fig. 3A). Participants were stratified into two groups based on the median values of these indicators, and time-to-depression risk models were constructed over the 5-year follow-up period. Participants with lower rich-club connections (HR = 2.126[95%CI:1.279–3.534], $P = 0.004$), brain modularity (HR = 2.692[95%CI:1.622–4.469], $P < 0.001$), and HIP.L nodal efficiency (HR = 2.055[95%CI:1.296–3.259], $P = 0.002$) were at higher risk of developing depression (Fig. 3C). Additionally, the death of both parents was identified as a contributing factor to increased depression risk (HR = 0.586[95%CI:0.370–0.929], $P = 0.023$; Fig. 3A).

Changes in structural network properties and clinical characteristics

Table 3 presents the correlation analysis between changes in structural network properties and clinical characteristics. After adjusting for covariates, no significant correlations were observed between baseline structural network indicators and baseline HDRS scores ($P > 0.05$). However, by the end of the follow-up, significant correlations were observed between baseline rich-club connections (β=-0.471, $P = 0.027$), brain modularity (β=-0.524, $P = 0.012$), and HIP.L nodal efficiency (β=-0.481, $P = 0.023$) with depression severity in the LLD group, but not in the non-LLD group ($P > 0.05$). Additionally, rich-club connections were significantly associated with cognitive scores in both the LLD (baseline: β = 0.590, $P = 0.004$; endpoint: β = 0.555, $P = 0.007$) and non-LLD groups (baseline: β = 0.466, $P = 0.038$; endpoint: β = 0.618, $P = 0.003$) at both baseline and endpoint.

Moderating effects of weekly exercise frequency and time spent with children

To explore potential moderators of the relationship between structural network properties and depression severity, we first identified predictors of HDRS scores. Multivariate linear regression analysis revealed that death of both parents (β=-0.450, $P = 0.035$), lower weekly exercise frequency (β=-0.516, $P = 0.014$), and shorter time spent with children (β=-0.478, $P = 0.025$) were associated with greater depression severity at onset (Supplementary Material 4). Further moderation analysis showed that weekly exercise frequency significantly moderated the relationship between rich-club connections ($\beta_{\text{rich-club connections-weekly exercise frequency}} = -0.271,\ P = 0.029$; Fig. 4A) and brain modularity ($\beta_{\text{brain modularity-weekly exercise frequency}}$=-0.333, $P = 0.011$; Fig. 4B) with depression severity in man participants, suggesting that higher exercise frequency may attenuate the depressive effects associated with lower structural network properties. Additionally, time spent with children moderated the

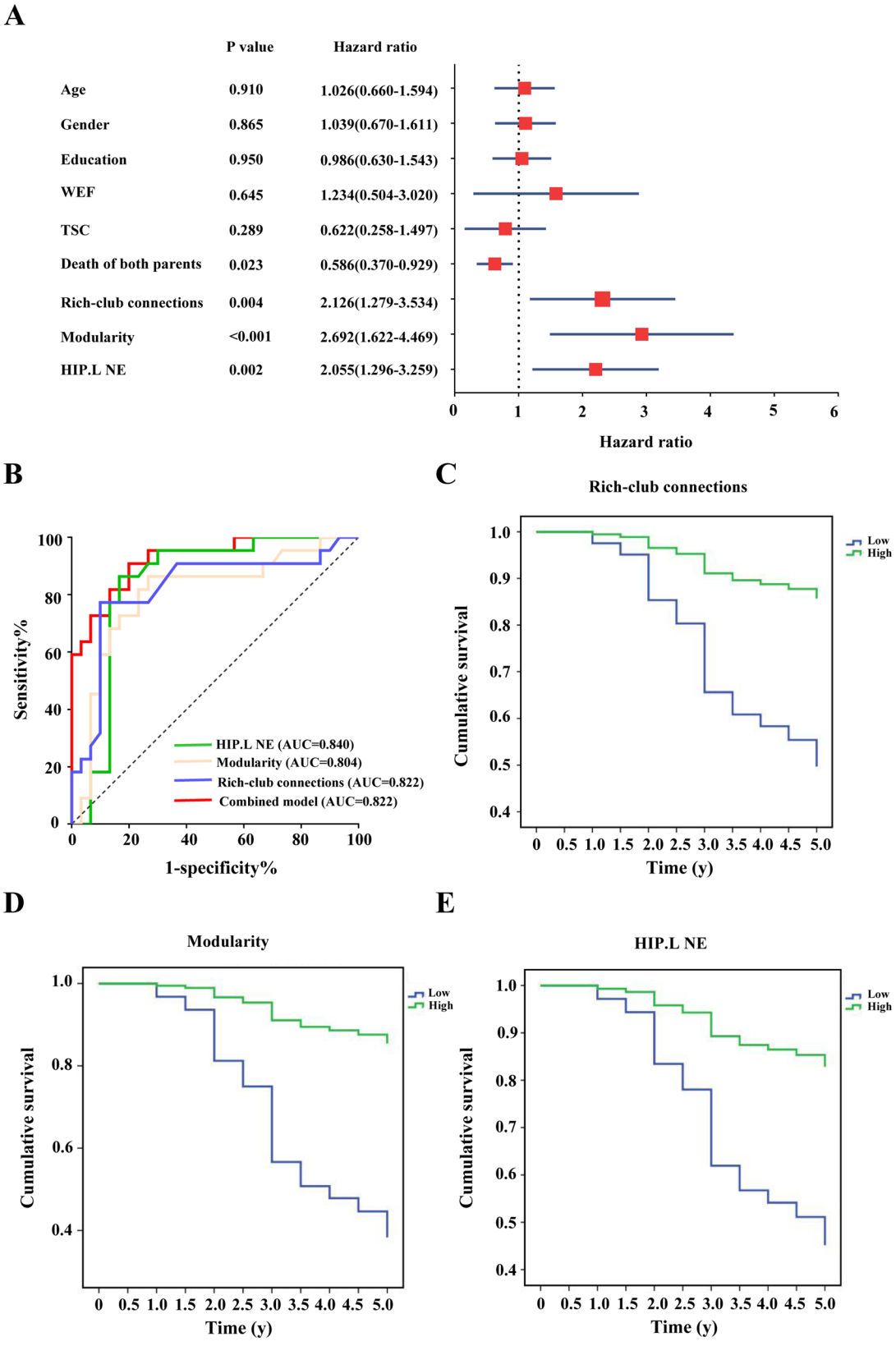

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Structural network properties and risk of depression onset. (**A**) Hazard ratios for variables associated with depression onset, displayed with 95% confidence intervals, based on Cox proportional hazards models. Significant predictors include death of both parents, rich-club connections, modularity, and left hippocampal nodal efficiency (HIP.L NE). (**B**) Receiver operating characteristic (ROC) curves for the predictive accuracy of modularity, rich-club connectivity, and HIP.L NE on depression onset, with AUC values provided for each predictor; the combined model exhibits the highest accuracy (AUC = 0.842). (**C**- **E**) Kaplan-Meier survival curves showing cumulative probability of depression-free survival over time, stratified by high and low values of (**C**) rich-club connections, (**D**) modularity, and (**E**) HIP.L NE. Patients with lower values in these metrics are at higher risk for depression onset, underscoring the prognostic value of structural network properties. Abbreviations: WEF, weekly exercise frequency; TSC, time spent with children; NE, nodal efficiency

relationship between rich-club connections and depression risk across all participants (woman: $\beta_{\text{rich-club connections-time spent with children}}$=-0.325, P = 0.013; man: $\beta_{\text{rich-club connections-time spent with children}}$=-0.326, P = 0.036; Fig. 4C and D), underscoring the protective role of familial interactions in depression prevention.

Discussion

This study presents a five-year longitudinal investigation into the relationship between brain structural network properties and the future onset of LLD in a healthy elderly cohort. Our findings reveal that individuals who later developed depression had exhibited significant alterations in brain structural networks prior to symptom onset. Specifically, reductions in rich-club connections, brain modularity, and HIP.L nodal efficiency emerged as key predictors of future depression. Additionally, our moderation analyses indicated that weekly exercise frequency and time spent with children significantly influenced the relationship between these structural network changes and depression risk, underscoring the role of lifestyle factors in modulating depressive outcomes. These results offer novel insights into the early neural markers of LLD and suggest potential targets for preventive interventions.

At baseline, reduced rich-club connections was significantly associated with the future development of LLD, highlighting its potential as an early biomarker. Rich-club connections represent core brain regions that are highly interconnected, supporting efficient communication across the brain network [41, 42]. Previous studies have implicated diminished rich-club connections in various neuropsychiatric disorders, including depression [43], Alzheimer's disease [44], and schizophrenia [45]. In the context of depression, reduced rich-club connections may signal impaired brain network efficiency, leading to cognitive dysfunction and emotional dysregulation [46, 47]. Our findings extend prior research by demonstrating that reductions in rich-club connections can be detected prior to LLD onset, suggesting that it may not only reflect a phenotypic feature of depression but also serve as an early indicator of vulnerability to the disorder. Monitoring changes in this network feature could facilitate early identification of individuals at elevated risk for LLD.

Furthermore, lower brain modularity and HIP.L nodal efficiency were predictive of future LLD. Brain modularity reflects the extent to which brain regions are organized into specialized modules that coordinate efficiently [48, 49]. Reduced modularity indicates a breakdown in this organization, potentially leading to deficits in cognitive and emotional processing [50]. Similarly, the HIP.L, critical for memory and emotional regulation, may lose its capacity to effectively process emotional stimuli when nodal efficiency is reduced, heightening the risk of depression [51–53]. These findings align with previous research and underscore the significance of these network changes as early markers of depression risk [17, 54].

Our moderation analysis revealed that weekly exercise frequency and time spent with children significantly moderated the impact of structural network changes on depression onset. Physical activity is well-established as a protective factor against depression, promoting neuroplasticity, enhancing cerebral blood flow, and improving the function of neural circuits involved in emotional regulation [55–57]. Our results suggest that exercise mitigates the negative impact of reduced rich-club connections and brain modularity on depression risk. Additionally, time spent with children provided a protective effect, which may be linked to the emotional support and psychological benefits derived from family interactions [58, 59]. This is particularly relevant for widowed individuals, for whom companionship from children may counteract the heightened risk of depression.

Our results show that weekly exercise frequency significantly moderated the relationship between rich-club connections, brain modularity, and depression severity in men, but not in women. This stronger effect in men may be due to several factors. Research suggests older men engage in more structured physical activity with greater neuroprotective effects, while women may participate in less intense activities [60]. Additionally, sex-specific differences in brain plasticity and hormonal regulation (e.g., testosterone vs. estrogen) may make men more responsive to exercise's neuroprotective effects [61]. Lastly, cultural differences in coping styles may explain why men use exercise more as a stress coping mechanism, while women may rely more on social support [62].

We acknowledge the connection between LLD and early signs of dementia [63]. Although our study focused on the neurobiological mechanisms of LLD, we included MoCA scores as a covariate to control for baseline cognitive function, ensuring participants were cognitively healthy (MoCA ≥ 24) at enrollment. To explore cognitive status and depression risk further, we conducted a

Table 3 Association of changes in structural network properties with clinical characteristics

Structural network properties		HDRS (baseline)		MoCA (baseline)		HDRS (endpoint)		MoCA (endpoint)	
		r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Non-LLD group (*N* = 181)									
Rich-club connections	baseline	−0.122	0.608	**0.466**	**0.038**	−0.429	0.059	−0.101	0.670
	endpoint	0.057	0.810	−0.437	0.054	0.113	0.634	**0.618**	**0.003**
Clustering coefficient	baseline	−0.223	0.343	0.188	0.427	−0.288	0.217	0.048	0.839
	endpoint	−0.247	0.293	0.039	0.871	−0.084	0.726	0.375	0.103
Modularity	baseline	0.245	0.299	0.125	0.600	−0.393	0.087	0.091	0.703
	endpoint	−0.384	0.095	0.062	0.796	0.091	0.702	0.268	0.254
HIP.L NE	baseline	−0.227	0.336	−0.266	0.257	−0.117	0.624	0.061	0.800
	endpoint	−0.070	0.769	0.232	0.326	−0.056	0.813	0.120	0.614
INS.L NE	baseline	−0.203	0.392	0.081	0.733	−0.293	0.210	0.019	0.937
	endpoint	−0.249	0.291	0.171	0.470	−0.029	0.902	0.423	0.063
PCUN.L NE	baseline	−0.0217	0.359	0.075	0.753	−0.311	0.182	−0.096	0.686
	endpoint	−0.009	0.970	−0.023	0.923	−0.328	0.158	−0.153	0.519
AMYG.R NE	baseline	−0.130	0.586	0.325	0.163	−0.025	0.916	0.024	0.919
	endpoint	−0.269	0.252	0.045	0.852	−0.294	0.209	0.266	0.057
LLD group (*N* = 22)									
Rich-club connections	baseline	−0.037	0.869	**0.590**	**0.004**	**−0.471**	**0.027**	0.085	0.707
	endpoint	−0.201	0.371	0.253	0.255	−0.244	0.274	**0.555**	**0.007**
Clustering coefficient	baseline	−0.117	0.603	0.042	0.854	−0.089	0.694	0.084	0.712
	endpoint	0.023	0.919	−0.009	0.967	0.144	0.523	0.278	0.211
Modularity	baseline	−0.084	0.711	0.057	0.800	**−0.524**	**0.012**	0.356	0.104
	endpoint	−0.212	0.344	0.311	0.159	−0.413	0.056	−0.066	0.771
HIP.L NE	baseline	−0.221	0.324	0.130	0.564	**−0.481**	**0.023**	−0.034	0.881
	endpoint	−0.261	0.240	0.020	0.928	−0.386	0.076	0.364	0.095
INS.L NE	baseline	−0.194	0.387	−0.026	0.910	−0.354	0.105	0.033	0.885
	endpoint	−0.129	0.568	0.221	0.322	−0.404	0.062	0.283	0.202
PCUN.L NE	baseline	0.034	0.882	−0.009	0.967	−0.351	0.109	0.119	0.699
	endpoint	−0.254	0.255	0.227	0.311	0.089	0.692	0.403	0.063
AMYG.R NE	baseline	−0.046	0.887	0.009	0.968	−0.217	0.331	0.190	0.400
	endpoint	−0.156	0.489	0.200	0.381	−0.118	0.600	0.300	0.180

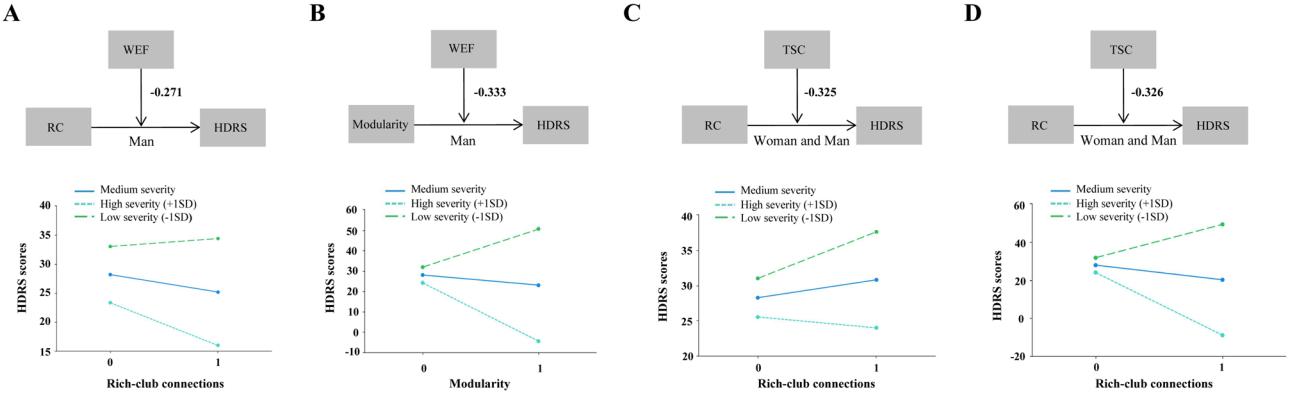

Fig. 4 Moderating effects of psychosocial factors on the relationship between structural network properties and depression severity. (**A**-**D**) Moderation analysis of the associations between structural network properties and HDRS scores, stratified by varying levels of moderator variables. Abbreviations: RC, rich-club connections; WEF, weekly exercise frequency; TSC, time spent with children; HDRS, Hamilton Depression Rating Scale

sensitivity analysis stratified by MoCA scores. The results showed consistent associations between brain network alterations (e.g., reduced rich-club connections, HIP.L nodal efficiency) and depression onset across both high and low cognitive status groups, suggesting these changes are independent of baseline cognitive differences. Future studies with larger samples and longer follow-ups should explore longitudinal cognitive changes and their relationship with depression.

The use of structural network analysis enabled us to detect early alterations in white matter connectivity, offering a more nuanced view of brain changes than traditional imaging techniques, which often capture only macroscopic anatomical differences [47, 64]. Structural network analysis reveals the efficiency and coordination of communication between brain regions, allowing for the identification of potential pathological changes before clinical symptoms manifest [65, 66]. Our longitudinal design provided a unique opportunity to observe how changes in brain network properties over time predict depression risk, offering important insights for early intervention strategies. By focusing on a healthy elderly population, we were able to identify individuals at elevated risk for depression, providing a foundation for personalized preventive approaches aimed at improving mental health outcomes in this vulnerable group.

While our study focused on the overall relationship between structural brain network alterations, psychosocial factors, and LLD risk, we acknowledge the importance of sex differences. Research suggests that neurobiological and psychosocial factors contribute to sex-specific depression susceptibility [67, 68]. Our moderation analysis showed that weekly exercise frequency moderated the relationship between structural network properties and depression severity in men but not women, highlighting potential sex differences. However, given our sample size (203 participants, 22 with LLD), full sex-stratified analyses would lack statistical power. Future studies with larger cohorts are needed to explore sex-specific brain network alterations and their role in LLD risk, which may inform personalized interventions.

Our study has several limitations. The relatively small sample size, particularly in the LLD group, limited our ability to explore sex differences and may affect the generalizability of our findings. Expanding the cohort in future research would strengthen the robustness of these results. Additionally, while we adjusted for a range of confounding factors, unmeasured variables such as socioeconomic status and lifestyle habits may have influenced the observed relationships. Future research could also benefit from incorporating multimodal imaging techniques, such as functional connectivity and molecular imaging, to provide a more comprehensive understanding of the pathophysiology of LLD.

In conclusion, our findings highlight the clinical and public health relevance of identifying structural brain network alterations as early biomarkers for LLD, enabling early detection and timely interventions. Incorporating regular physical activity and social connections into preventive mental health programs, especially for widowed elderly individuals, could reduce the burden of depression. Given the aging population and rising prevalence of LLD, integrating brain network screening and psychosocial support into routine geriatric care, particularly in community-based healthcare settings, could improve mental health outcomes and quality of life for older adults at risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-06028-y.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Yang Li, Hu Xu, Xingbing Chen, and Hui Su made a substantial contribution to the concept and design, analysis and interpretation of data; Yang Li wrote the manuscript and provided figures; Xingbing Chen, and Hui Su revised the article critically with substantial modification; Jiale Wu, Yi Ding, Yunqian Zhu, and Yang Wang organized the study and supported the data analysis. All authors were involved in the theoretical discussion and performing of the experiments. All authors read and approved the final version of the manuscript.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was supported by National Natural Science Foundation of China (81871343); Jiangsu Provincial Key Research and Development Program (BE2017698, BE2021693); Natural Science Foundation of Jiangsu Province (BK20181226, BK20171311); Key Projects of the Gaoyou Municipal Health Commission (GY20221201); Key Projects of the Yangzhou Municipal Health Commission (2023-1-03).

Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by the Gaoyou People's Hospital Ethics Committee (GYYY2018025) and conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants were thoroughly informed about the study's objectives and procedures, and written informed consent was obtained from each participant.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 19 November 2024 / Accepted: 7 May 2025
Published online: 19 May 2025

References

1. Goke K, McClintock SM, Mah L, Rajji TK, Lee HH, Nestor SM, Downar J, Noda Y, Daskalakis ZJ, Mulsant BH, et al. Cognitive profiles in treatment-Resistant Late-Life depression and their impact on treatment outcomes. Biol Psychiatry Cogn Neurosci Neuroimaging. 2024;9(11):1199–210.
2. Liu W, Li H, Lin X, Li P, Zhu X, Su S, Shi J, Lu L, Deng J, Sun X. Blunted superior Temporal gyrus activity to negative emotional expression after mindfulness-based cognitive therapy for late-life depression. Front Aging Neurosci. 2022;14:1001447.
3. Farioli Vecchioli S, Sacchetti S, Nicolis di Robilant V, Cutuli D. The role of physical exercise and Omega-3 fatty acids in depressive illness in the elderly. Curr Neuropharmacol. 2018;16(3):308–26.
4. Szanto K, Galfalvy H, Vanyukov PM, Keilp JG, Dombrovski AY. Pathways to Late-Life suicidal behavior: cluster analysis and predictive validation of suicidal behavior in a sample of older adults with major depression. J Clin Psychiatry 2018; 79(2).
5. Zhong Y, Pham S, Porta G, Douaihy A, Marsland A, Brent D, Melhem NM. Increased burden of cardiovascular risk among youth suicide attempters. Psychol Med. 2022;52(10):1901–9.
6. Zhang AZ, Wang QC, Huang KM, Huang JG, Zhou CH, Sun FQ, Wang SW, Wu FT. Prevalence of depression and anxiety in patients with chronic digestive system diseases: A multicenter epidemiological study. World J Gastroenterol. 2016;22(42):9437–44.
7. Xue S, Lu A, Chen W, Li J, Ke X, An Y. A latent profile analysis and network analysis of anxiety and depression symptoms in Chinese widowed elderly. J Affect Disord. 2024;366:172–80.
8. de Sousa ILM, Silveira R, Takito MY, Pereira AL, Lucianelli-Junior D, Carmona GS, Viegas A, Teixeira FB, Santos OS, Valentin FN. The impact of the social isolation in elderly Brazilian mental health (anxiety and depression) during the COVID-19 pandemic. Front Psychiatry. 2022;13:888234.
9. Li X, Ge T, Dong Q, Jiang Q. Social participation, psychological resilience and depression among widowed older adults in China. BMC Geriatr. 2023;23(1):454.
10. Zhang X, Niu P, Su M, Zhou L, Huang Y, Chen J, Liu S. Topological differences of striato-thalamo-cortical circuit in functional brain network between premature ejaculation patients with and without depression. Brain Behav. 2024;14(6):e3585.
11. Cross NE, Pomares FB, Nguyen A, Perrault AA, Jegou A, Uji M, Lee K, Razavipour F, Ali OBK, Aydin U, et al. An altered balance of integrated and segregated brain activity is a marker of cognitive deficits following sleep deprivation. PLoS Biol. 2021;19(11):e3001232.
12. Xu X, Tang R, Zhang L, Cao Z. Altered topology of the structural brain network in patients with Post-stroke depression. Front Neurosci. 2019;13:776.
13. Fang F, Godlewska B, Cho RY, Savitz SI, Selvaraj S, Zhang Y. Personalizing repetitive transcranial magnetic stimulation for precision depression treatment based on functional brain network controllability and optimal control analysis. NeuroImage. 2022;260:119465.
14. Xing L, Guo Z, Long Z. Energy landscape analysis of brain network dynamics in Alzheimer's disease. Front Aging Neurosci. 2024;16:1375091.
15. Liu X, Yang H, Becker B, Huang X, Luo C, Meng C, Biswal B. Disentangling age- and disease-related alterations in schizophrenia brain network using structural equation modeling: A graph theoretical study based on minimum spanning tree. Hum Brain Mapp. 2021;42(10):3023–41.
16. Mai N, Zhong X, Chen B, Peng Q, Wu Z, Zhang W, Ouyang C, Ning Y. Weight Rich-Club analysis in the white matter network of Late-Life depression with memory deficits. Front Aging Neurosci. 2017;9:279.
17. Peng D, Shi F, Shen T, Peng Z, Zhang C, Liu X, Qiu M, Liu J, Jiang K, Fang Y, et al. Altered brain network modules induce helplessness in major depressive disorder. J Affect Disord. 2014;168:21–9.
18. Li Y, Xie Y, Xu Y, Xian X, Wang R, Cai L, Li G, Li Y. Interleukin-6-white matter network differences explained the susceptibility to depression after stressful life events. J Affect Disord. 2022;305:122–32.
19. Ye J, Wen Y, Chu X, Li P, Cheng B, Cheng S, Liu L, Zhang L, Ma M, Qi X, et al. Association between herpes simplex virus 1 exposure and the risk of depression in UK biobank. Clin Transl Med. 2020;10(2):e108.
20. Zeng Y, Navarro P, Xia C, Amador C, Fernandez-Pujals AM, Thomson PA, Campbell A, Nagy R, Clarke TK, Hafferty JD, et al. Shared genetics and Couple-Associated environment are major contributors to the risk of both clinical and Self-Declared depression. EBioMedicine. 2016;14:161–7.
21. Liu P, Li Q, Zhang A, Liu Z, Sun N, Yang C, Wang Y, Zhang K. Similar and different regional homogeneity changes between bipolar disorder and unipolar depression: A Resting-State fMRI study. Neuropsychiatr Dis Treat. 2020;16:1087–93.
22. Fan SP, Chen YF, Li CH, Kuo YC, Lee NC, Chien YH, Hwu WL, Tseng TC, Su TH, Hsu CT, et al. Topographical metal burden correlates with brain atrophy and clinical severity in Wilson's disease. NeuroImage. 2024;299:120829.
23. Ortega L, Montalvo I, Monseny R, Burjales-Marti MD, Martorell L, Sanchez-Gistau V, Vilella E, Labad J. Perceived stress, social functioning and quality of life in first-episode psychosis: A 1-year follow-up study. Early Interv Psychiatry. 2021;15(6):1542–50.
24. Wang X, Li W, Song F, Wang L, Fu Q, Cao S, Gan Y, Zhang W, Yue W, Yan F et al. Carotid atherosclerosis detected by ultrasonography: A National Cross-Sectional study. J Am Heart Assoc 2018;7(8).
25. Kang HW, Park M, Wallace Hernandez JP. The impact of perceived social support, loneliness, and physical activity on quality of life in South Korean older adults. J Sport Health Sci. 2018;7(2):237–44.
26. Del Re EC, Bouix S, Fitzsimmons J, Blokland GAM, Mesholam-Gately R, Wojcik J, Kikinis Z, Kubicki M, Petryshen T, Pasternak O, et al. Diffusion abnormalities in the corpus callosum in first episode schizophrenia: associated with enlarged lateral ventricles and symptomatology. Psychiatry Res. 2019;277:45–51.
27. Liu X, He C, Fan D, Zang F, Zhu Y, Zhang H, Zhang Z, Zhang H, Xie C. Alterations of core structural network connectome associated with suicidal ideation in major depressive disorder patients. Transl Psychiatry. 2021;11(1):243.
28. Ohashi K, Anderson CM, Bolger EA, Khan A, McGreenery CE, Teicher MH. Susceptibility or resilience to maltreatment can be explained by specific differences in brain network architecture. Biol Psychiatry. 2019;85(8):690–702.
29. Joel D, Berman Z, Tavor I, Wexler N, Gaber O, Stein Y, Shefi N, Pool J, Urchs S, Margulies DS, et al. Sex beyond the genitalia: the human brain mosaic. Proc Natl Acad Sci U S A. 2015;112(50):15468–73.
30. Liu J, Ma S, Mu J, Chen T, Xu Q, Dun W, Tian J, Zhang M. Integration of white matter network is associated with interindividual differences in psychologically mediated placebo response in migraine patients. Hum Brain Mapp. 2017;38(10):5250–9.
31. Mishra VR, Sreenivasan KR, Yang Z, Zhuang X, Cordes D, Mari Z, Litvan I, Fernandez HH, Eidelberg D, Ritter A, et al. Unique white matter structural connectivity in early-stage drug-naive Parkinson disease. Neurology. 2020;94(8):e774–84.
32. Peng L, Feng J, Ma D, Xu X, Gao X. Rich-Club organization disturbances of the individual morphological network in subjective cognitive decline. Front Aging Neurosci. 2022;14:834145.
33. Tuladhar AM, Lawrence A, Norris DG, Barrick TR, Markus HS, de Leeuw FE. Disruption of rich club organisation in cerebral small vessel disease. Hum Brain Mapp. 2017;38(4):1751–66.
34. Fleischer V, Koirala N, Droby A, Gracien RM, Deichmann R, Ziemann U, Meuth SG, Muthuraman M, Zipp F, Groppa S. Longitudinal cortical network reorganization in early relapsing-remitting multiple sclerosis. Ther Adv Neurol Disord. 2019;12:1756286419838673.
35. Li X, Li H, Jiang X, Li J, Cao L, Liu J, Xing H, Huang X, Gong Q. Characterizing multiscale modular structures in medication-free obsessive-compulsive disorder patients with no comorbidity. Hum Brain Mapp. 2022;43(7):2391–9.
36. Zhang T, Zhao Z, Zhang C, Zhang J, Jin Z, Li L. Classification of early and late mild cognitive impairment using functional brain network of Resting-State fMRI. Front Psychiatry. 2019;10:572.
37. Fang S, Wang Y, Jiang T. Epilepsy enhance global efficiency of Language networks in right Temporal lobe gliomas. CNS Neurosci Ther. 2021;27(3):363–71.
38. Garcia-Ramos C, Dabbs K, Lin JJ, Jones JE, Stafstrom CE, Hsu DA, Meyerand ME, Prabhakaran V, Hermann BP. Progressive dissociation of cortical and subcortical network development in children with new-onset juvenile myoclonic epilepsy. Epilepsia. 2018;59(11):2086–95.
39. Abazid M, Houmani N, Dorizzi B, Boudy J, Mariani J, Kinugawa K. Weighted brain network analysis on different stages of clinical cognitive decline. Bioeng (Basel) 2022;9(2).
40. Lei D, Li W, Tallman MJ, Patino LR, McNamara RK, Strawn JR, Klein CC, Nery FG, Fleck DE, Qin K, et al. Changes in the brain structural connectome after a prospective randomized clinical trial of lithium and quetiapine treatment in youth with bipolar disorder. Neuropsychopharmacology. 2021;46(7):1315–23.
41. Zhao X, Tian L, Yan J, Yue W, Yan H, Zhang D. Abnormal Rich-Club organization associated with compromised cognitive function in patients with schizophrenia and their unaffected parents. Neurosci Bull. 2017;33(4):445–54.
42. Ma Z, Perez P, Ma Z, Liu Y, Hamilton C, Liang Z, Zhang N. Functional atlas of the awake rat brain: A neuroimaging study of rat brain specialization and integration. NeuroImage. 2018;170:95–112.

43. Long Z, Chen D, Lei X. Enhanced rich club connectivity in mild or moderate depression after nonpharmacological treatment: A preliminary study. Brain Behav. 2023;13(10):e3198.
44. Markett S, Boeken OJ, Wudarczyk OA, Alzheimer's Disease Neuroimaging I. Multimodal imaging investigation of structural rich club alterations in Alzheimer's disease and mild cognitive impairment: amyloid deposition, structural atrophy, and functional activation differences. Eur J Neurosci. 2024;60(3):4169–81.
45. Hua JPY, Cummings J, Roach BJ, Fryer SL, Loewy RL, Stuart BK, Ford JM, Vinogradov S, Mathalon DH. Rich-club connectivity and structural connectome organization in youth at clinical high-risk for psychosis and individuals with early illness schizophrenia. Schizophr Res. 2023;255:110–21.
46. Deng X, Liu L, Luo J, Liu L, Hui X, Feng H. Research on the mechanism of cognitive decline in patients with acoustic neuroma. Front Neurosci. 2022;16:933825.
47. Yan T, Wang W, Yang L, Chen K, Chen R, Han Y. Rich club disturbances of the human connectome from subjective cognitive decline to Alzheimer's disease. Theranostics. 2018;8(12):3237–55.
48. Yang Z, Telesford QK, Franco AR, Lim R, Gu S, Xu T, Ai L, Castellanos FX, Yan CG, Colcombe S, et al. Measurement reliability for individual differences in multilayer network dynamics: cautions and considerations. NeuroImage. 2021;225:117489.
49. Cai L, Dong Q, Niu H. The development of functional network organization in early childhood and early adolescence: A resting-state fNIRS study. Dev Cogn Neurosci. 2018;30:223–35.
50. Betzel RF, Byrge L, Esfahlani FZ, Kennedy DP. Temporal fluctuations in the brain's modular architecture during movie-watching. NeuroImage. 2020;213:116687.
51. Miranda AM, Bravo FV, Chan RB, Sousa N, Di Paolo G, Oliveira TG. Differential lipid composition and regulation along the hippocampal longitudinal axis. Transl Psychiatry. 2019;9(1):144.
52. Huerta PT, Robbiati S, Huerta TS, Sabharwal A, Berlin RA, Frankfurt M, Volpe BT. Preclinical models of overwhelming sepsis implicate the neural system that encodes contextual fear memory. Mol Med. 2016;22:789–99.
53. Roberts G, Perry A, Lord A, Frankland A, Leung V, Holmes-Preston E, Levy F, Lenroot RK, Mitchell PB, Breakspear M. Structural dysconnectivity of key cognitive and emotional hubs in young people at high genetic risk for bipolar disorder. Mol Psychiatry. 2018;23(2):413–21.
54. Kandilarova S, Stoyanov D, Kostianev S, Specht K. Altered resting state effective connectivity of anterior Insula in depression. Front Psychiatry. 2018;9:83.
55. Haucke M, Heinz A, Liu S, Heinzel S. The impact of COVID-19 lockdown on daily activities, cognitions, and stress in a lonely and distressed population: Temporal dynamic network analysis. J Med Internet Res. 2022;24(3):e32598.
56. Mannes ZL, Waxenberg LB, Cottler LB, Perlstein WM, Burrell LE 2nd, Ferguson EG, Edwards ME, Ennis N. Prevalence and correlates of psychological distress among retired elite athletes: A systematic review. Int Rev Sport Exerc Psychol. 2019;12(1):265–94.
57. Yang HW, Bae JB, Oh DJ, Moon DG, Lim E, Shin J, Kim BJ, Lee DW, Kim JL, Jhoo JH, et al. Exploration of cognitive outcomes and risk factors for cognitive decline shared by couples. JAMA Netw Open. 2021;4(12):e2139765.
58. Chatters LM, Taylor RJ, Woodward AT, Nicklett EJ. Social support from church and family members and depressive symptoms among older African Americans. Am J Geriatr Psychiatry. 2015;23(6):559–67.
59. Mitchell UA, Gutierrez-Kapheim M, Nguyen AW, Al-Amin N. Hopelessness among Middle-Aged and older Blacks: the negative impact of discrimination and protecting power of social and religious resources. Innov Aging. 2020;4(5):igaa044.
60. Rancourt D, Barker DH, Jelalian E. Sex as a moderator of adolescents' weight loss treatment outcomes. J Adolesc Health. 2018;62(5):591–7.
61. Liu G, Wang Y, Zheng W, Cheng H, Zhou R. P11 Loss-of-Function is associated with decreased cell proliferation and neurobehavioral disorders in mice. Int J Biol Sci. 2019;15(7):1383–95.
62. Canal-Rivero M, Montes-Garcia C, Garrido-Torres N, Moreno-Mellado A, Reguera-Pozuelo P, Ruiz-Veguilla M, Crespo-Facorro B. The impact of COVID-19 pandemic on the psychological well-being among health care workers: A 6-month cohort longitudinal survey study. Rev Psiquiatr Salud Ment. 2023;16:25–37.
63. Bae JB, Han JW, Kwak KP, Kim BJ, Kim SG, Kim JL, Kim TH, Ryu SH, Moon SW, Park JH, et al. Is dementia more fatal than previously estimated?? A Population-based prospective cohort study. Aging Dis. 2019;10(1):1–11.
64. Koirala N, Anwar AR, Ciolac D, Glaser M, Pintea B, Deuschl G, Muthuraman M, Groppa S. Alterations in white matter network and microstructural integrity differentiate Parkinson's disease patients and healthy subjects. Front Aging Neurosci. 2019;11:191.
65. Shu N, Wang X, Bi Q, Zhao T, Han Y. Disrupted topologic efficiency of white matter structural connectome in individuals with subjective cognitive decline. Radiology. 2018;286(1):229–38.
66. Wang B, Zhan Q, Yan T, Imtiaz S, Xiang J, Niu Y, Liu M, Wang G, Cao R, Li D. Hemisphere and gender differences in the Rich-Club organization of structural networks. Cereb Cortex. 2019;29(11):4889–901.
67. Wang W, Liang W, Sun C, Liu S. Sex differences in depression: insights from multimodal Gray matter morphology and peripheral inflammatory factors. Int J Mol Sci 2024;25(24).
68. Huang GP, Mai LP, Zheng ZJ, Wang XP, He GD. Sex differences in the association between the muscle quality index and the incidence of depression: A cross-sectional study. World J Psychiatry. 2024;14(9):1335–45.

Publisher's note