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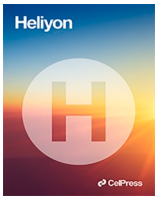

Research article

Lower serum uric acid and impairment of right cerebral hemisphere structural brain networks are related to depressive symptoms in cerebral small vessel disease: A cross-sectional study

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ABSTRACT

Cerebral small vessel disease (SVD) may be associated with an increased risk of depressive symptoms. Serum uric acid (SUA), an antioxidant, may be involved in the occurrence and development of depressive symptoms, but the mechanism remains unknown. Moreover, the relationship between structural brain networks and SUA has not been explored. This study examined the relationship between SUA and depressive symptoms in patients with SVD using graph theory analysis. We recruited 208 SVD inpatients and collected fasting blood samples upon admission. Depressive symptoms were assessed using the 24-item Hamilton Depression Rating Scale (HAMD-24). Magnetic resonance imaging was used to evaluate SVD, and diffusion tensor images were used to analyze structural brain networks using graph theory. Patients with depressive symptoms (n = 34, 25.76%) compared to those without (334.53 vs 381.28 μmol/L, $p = 0.017$) had lower SUA levels. Graph theoretical analyses showed a positive association of SUA with betweenness centrality, nodal efficiency, and clustering coefficients and a negative correlation with the shortest path length in SVD with depressive symptoms group. HAMD scores were significantly associated with nodal network metrics in the right cerebral hemisphere. Our findings suggested that lower SUA levels are significantly associated with disrupted structural brain networks in the right cerebral hemisphere of patients with SVD who have depressive symptoms.

1. Introduction

Cerebral small vessel disease (SVD) consists of a series of pathological processes affecting small arteries, arterioles, small veins, and capillaries of the brain [1]. While most SVD present with relatively mild symptoms, such as lacunar syndromes, including pure motor

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hemiparesis, pure sensory stroke, and dysarthria-clumsy hand syndrome, and may at times even manifest subtly. The overall short-term prognosis of SVD is generally more favorable than that of infarcts resulting from other stroke mechanisms. However, the long-term prognosis of small vessel diseases may differ. In addition to the corresponding brain structural changes, including lacunar infarcts (LI), white matter hyperintensities (WMH) and microbleeds (CMBs) [2,3], SVD is associated with an increased risk of depressive symptoms. Approximately 10% of patients with SVD suffer from depressive symptoms [4]. A long-term follow-up study of patients with lacunar strokes revealed that depressive symptoms persisted at high levels over the course of 3 years, and individuals exhibiting these symptoms experienced more severe cognitive decline, substantially diminishing their quality of life [5]. The primary characteristic of depressive symptoms resulting from SVD is characterized by motivational symptoms, encompassing psychomotor retardation and a loss of interest [6,7]. It has been shown that SVD may increase the risk of depression through mechanisms such as demyelination of brain tissue and white matter damage, disturbances in neural circuits involved in mood regulation and decreased levels of neurotransmitters associated with neuromodulation, such as 5-hydroxytryptamine, norepinephrine and dopamine. In addition, oxidative stress may also play an important role [8–10]. However, the pathophysiologic mechanism underlying depressive symptoms in SVD is poorly understood.

It is worth noting that oxidative reactions might be associated with an increased likelihood of experiencing depressive symptoms in SVD. Oxidative stress has been linked to an elevated risk of developing depressive symptoms. Serum uric acid (SUA), an important antioxidant, is the product of purine metabolism. Previous studies have confirmed that UA could perform neuroprotective functions by scavenging free radicals and reactive oxygen species (ROS) [11], yet its role in the mechanism of depressive symptoms in stroke patients is still under-researched. Furthermore, the involvement of the antioxidant uric acid in the occurrence and development of depression suggests a potential connection between oxidative reactions and the manifestation of depressive symptoms in patients with SVD. However, the exact underlying mechanism behind this association remains unknown and requires further investigation. Many research studies have demonstrated that lower SUA levels are closely related to depressive symptoms in patients with stroke and older individuals [12–14]. However, it is well known that hyperuricemia can cause a range of diseases that can be harmful to human health, and the effect of SUA levels on depressive symptoms remains controversial and needs to be further explored.

The highly heterogeneous clinical manifestations of SVD, sometimes without obvious clinical symptoms, are often diagnosed based on radiographic examination. Neuropsychological assessment scales are commonly used to evaluate the severity of depressive

Table 1
Clinical and demographic characteristics of SVD patients with and without depressive symptoms groups.

Variables	SVD with depressive symptoms group (n = 34)	SVD without depressive symptoms group (n = 98)	p^a
SUA (μmol/L)	334.53 (278.50, 399.25)	381.28 (311.50, 437.75)	0.017*
Demographic			
Sex (men, %)	20 (59)	55 (66)	0.431
Age (years, SD)	64.09 (11.69)	64.19 (10.87)	0.963
Education (years, SD)	9.53(3.38)	10.74 (3.40)	0.076
Vascular risk factors			
History of ischemic stroke, n (%)	16 (47)	14 (14)	<0.001***
Index ischemic stroke (years, SD)	5.11 (4.05)	5.07 (4.36)	0.976
History of coronary artery diseases, n (%)	1 (3)	12 (12)	0.117
History of hypertension, n (%)	21 (62)	66 (67)	0.554
History of diabetes, n (%)	7 (21)	32 (33)	0.184
History of hyperlipidemia, n (%)	4 (12)	16 (16)	0.523
Smoking, n (%)	11 (32)	41 (42)	0.329
Alcohol consumption, n (%)	7 (21)	25 (26)	0.564
Family history of SVD, n (%)	3 (9)	5 (5)	0.433
Serum biochemicals			
Total cholesterol (mmol/L, Median, IQR)	4.44 (3.93–5.01)	4.39 (3.60–5.00)	0.355
Triglycerides (mmol/L, Median, IQR)	1.59 (1.08–2.09)	1.77 (1.00–2.27)	0.836
LDL-C (mmol/L, Median, SD)	2.81 (0.45)	2.75 (0.82)	0.612
HDL-C (mmol/L, Median, SD)	1.11 (0.22)	1.02 (0.23)	0.066
Homocysteine (μmol/L, Median, IQR)	12.61 (9.79–15.20)	15.10 (10.29–15.57)	0.320
Creatinine (μmol/L, Median, IQR)	73.00 (60.00–84.75)	85.85 (63.00–88.25)	0.165
Urea nitrogen (mmol/L, Median, SD)	4.90 (1.16)	5.35 (1.54)	0.115
Fasting blood glucose (mmol/L, Median, IQR)	5.41 (4.60–5.68)	5.85 (4.40–6.40)	0.369
Glycated hemoglobin (%, Median, IQR)	7.76 (5.60–6.98)	6.62 (5.60–7.18)	0.670
Fibrinogen (g/L, Median, SD)	11.65 (51.13)	3.16 (0.692)	0.340
D-Dimer (mg/L, Median, IQR)	0.57 (0.22–0.50)	0.82 (0.24–0.59)	0.305
Psychological assessment			
HAMD (Median, IQR)	13.58 (9.00–15.00)	2.61 (1.00–4.00)	<0.001***
MMSE (Median, IQR)	24.09 (22.00–29.00)	25.88 (25.00–29.00)	0.088

Data represent mean ± SD, n of participants (%) or median (IQR).
HAMD, Hamilton Depression Rating Scale; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SUA, serum uric acid; SVD, cerebral small vessel disease; SD, standard deviation.
[a] *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

symptoms. However, there are no accurate biomarkers to assess the underlying mechanism. Diffusion tensor imaging (DTI), as a noninvasive and sensitive magnetic resonance imaging (MRI) technique, can detect microstructural brain damage. Fractional anisotropy (FA) is one of the commonly used parameters in DTI [15]. By computing the DTI scalar with suitable postprocessing tools, brain networks can be constructed. Graph theory can be used to quantify the topological structures of complex neural networks [16, 17]. The topological characteristics of structural brain networks have been evaluated using a variety of network metrics, including global and nodal metrics. When network connectivity in the brain is compromised, the corresponding network metrics change. Postprocessed DTI parameters can be used to evaluate microstructural changes in the brain owing to depression in patients with different diseases, such as essential tremor [18], Parkinson's disease [19], and multiple sclerosis [20]. Several findings have shown that altered levels of SUA are associated with cerebral WMH and LI in patients with SVD [21–23]. However, owing to difficulties in obtaining tissue samples to determine which genes and proteins are abnormal in SVD patients with depressive symptoms, the pathophysiological mechanism remains unclear. A difference from previous studies is that our study was conducted in patients with SVD, and few studies have examined the correlation between SUA, depressive symptoms, and structural brain networks in patients with SVD.

Hence, we aimed to explore the potential association between SUA and depressive symptoms in patients with SVD, considering the universally accepted belief among physicians that SUA contributes to the development of gout and is harmful to organs, particularly the kidneys. However, we hypothesized that SUA, due to its potential antioxidant properties, might offer some benefits to patients with SVD who experience depressive symptoms. In this study, we investigated the potential relationship between SUA and depressive symptoms in patients with SVD and explored the neuroimaging mechanisms through which SUA may potentially ameliorate depressive symptoms in patients with SVD.

2. Results

2.1. Baseline characteristics of patients with and without depressive symptoms

All participants underwent various examinations. Among the 208 participants recruited, 33 had incomplete or missing imaging data, 15 did not undergo SUA testing, 22 could not complete the neuropsychological assessment, and 6 were excluded because of severe cognitive impairment. Thus, 132 participants were included in the final study sample. The clinical and demographic characteristics of the groups with and without depressive symptoms are presented in Table 1.

The mean age was similar in the two groups (64 years). Among the 132 participants, 34 (25.76%) were diagnosed with depressive symptoms. The mean SUA level was 334.53 μmol/L in the depressive symptoms group and 381.28 μmol/L in the non-depressive symptoms group, and the difference was statistically significant ($p = 0.017$). Compared with the non-depressive symptoms group, the depressive symptoms group had higher incidence rates of ischemic stroke ($p < 0.001$) and higher 24-item Hamilton Depression Rating Scale (HAMD-24) scores ($p < 0.001$).

2.2. Global network analysis

Across all selected thresholds, both the depressive symptoms and non-depressive symptoms groups demonstrated strong small-world characteristics. In both groups, the values of γ were approximately equal to 4, σ approximately equal to 2, and γ approximately equal to 1, meeting the criteria for good small-world properties ($\gamma > 1, \lambda \approx 1, \sigma > 1$). Global efficiency and global local efficiency were not significantly lower in the depressive symptoms group compared with the non-depressive symptoms group ($p = 0.279$ and 0.216, respectively) (Table S2).

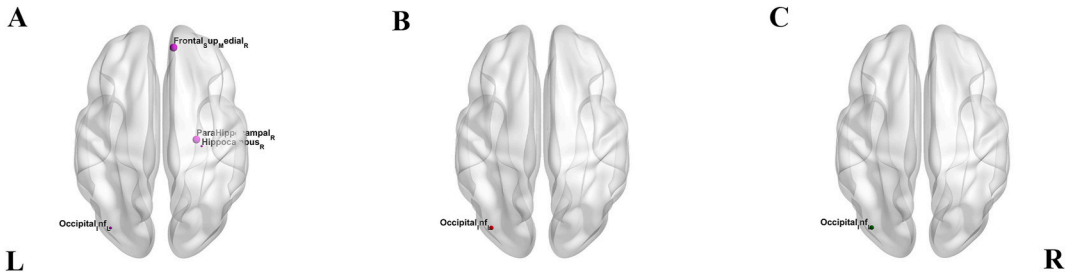

Fig. 1. Distributed brain regions with significant differences in nodal metrics between SVD patients with and without depressive symptoms groups The size of the nodes indicates the importance of between-group differences. (A) Nodes in purple showed reduced Bc in the depressed group compared with the non-depressed group. (B) Nodes in red showed impaired NCp in the depressed group compared with the non-depressed group. (C) Nodes in green showed impaired NLe in the depressed group compared with the non-depressed group. Bc, betweenness centrality; NCp, nodal clustering coefficient; NLe, nodal local efficiency. L = left; R = right. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.3. Nodal network analysis

Compared with the non-depressive symptoms group, the depressive symptoms group had lower nodal properties of betweenness centrality (Bc), nodal clustering coefficient (NCp), and nodal local efficiency (NLe). The superior frontal gyrus, middle (right supramarginal gyrus), hippocampus, and parahippocampal gyrus in the right cerebral hemisphere all demonstrated significant variations in Bc between the two groups ($p = 0.034$, 0.039, and 0.032, respectively, fasle discovery rate [FDR]-corrected). Impairments in the three nodal metrics of Bc, NCp and NLe were found in the same region within the left inferior occipital gyrus ($p = 0.039$, 0.032, and 0.041,

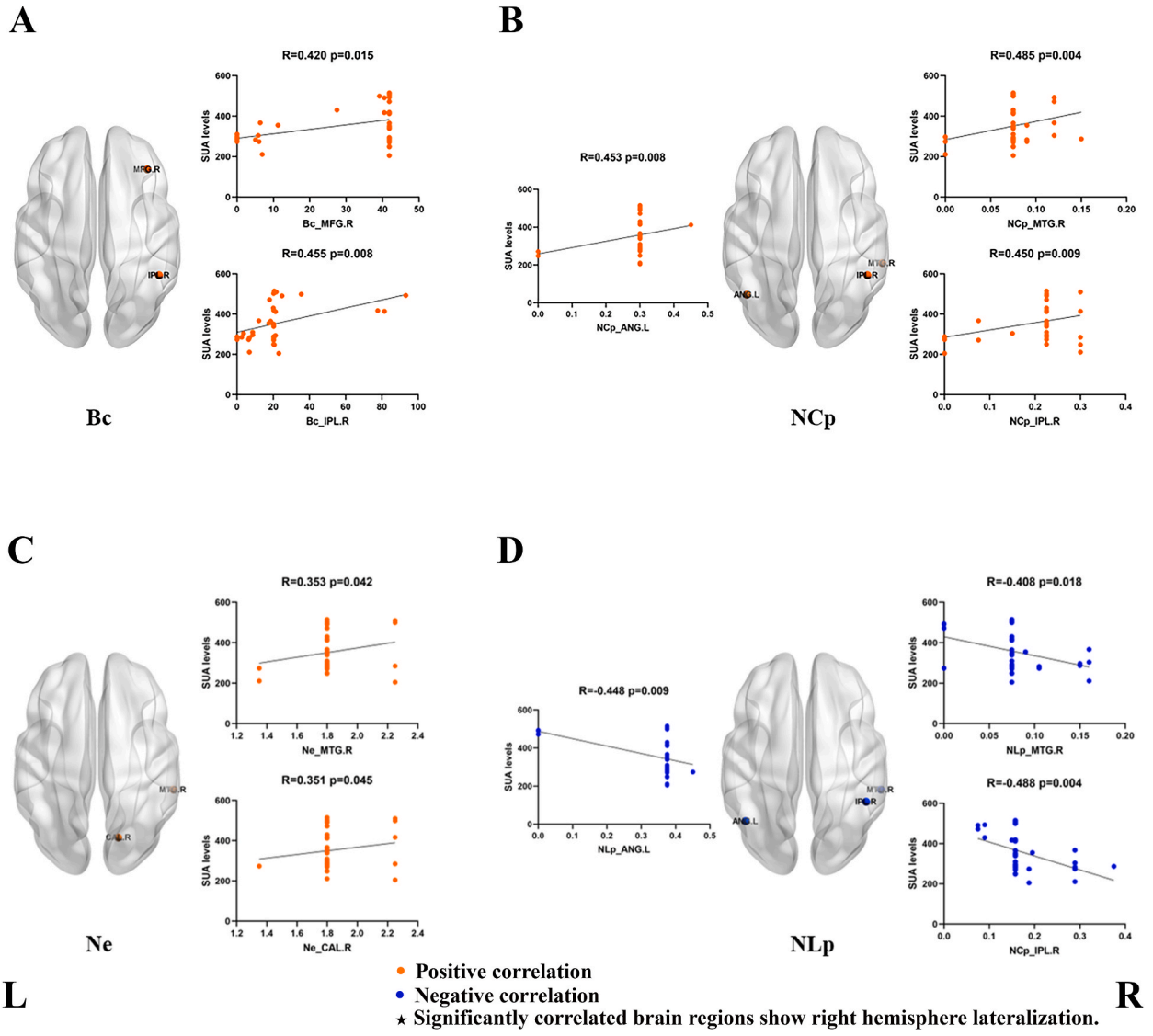

Fig. 2. Regions with significant correlations between the nodal metrics and SUA levels in SVD patients with depressive symptoms
This figure illustrated the results of the correlation analysis between node metrics and SUA levels in SVD patients with depressive symptoms. (A) Scatterplots of the correlations between Bc and SUA levels and the corresponding brain regions. (B) Scatterplots of the correlations between NCp and SUA levels and the corresponding brain regions. (C) Scatterplots of the correlations between Ne and SUA levels and the corresponding brain regions. (D) Scatterplots of the correlations between NLp and SUA levels and the corresponding brain regions. In the axial view, brain network nodes exhibiting correlations with SUA levels were overlaid onto the brain surface, predominantly localized in the right cerebral hemisphere. The node color signifies the direction of the correlation. Each scatter plot of nodal metrics corresponds to a specific brain region. The orange color indicates a positive correlation between the node metric and SUA level, while the blue color indicates a negative correlation. The correlation coefficients and p-values of the scatterplot have been labeled in the figure.ANG.L, left angular gyrus; Bc, betweenness centrality; CAL.R, calcarine fissure and surrounding cortex; IPL.R, right inferior parietal; MFG.R, right middle frontal gyrus; MTG.R, right middle temporal gyrus; NCp, nodal clustering efficiency; Ne, nodal efficiency; NLp, shortest path length; SUA, serum uric acid.L = left; R = right. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

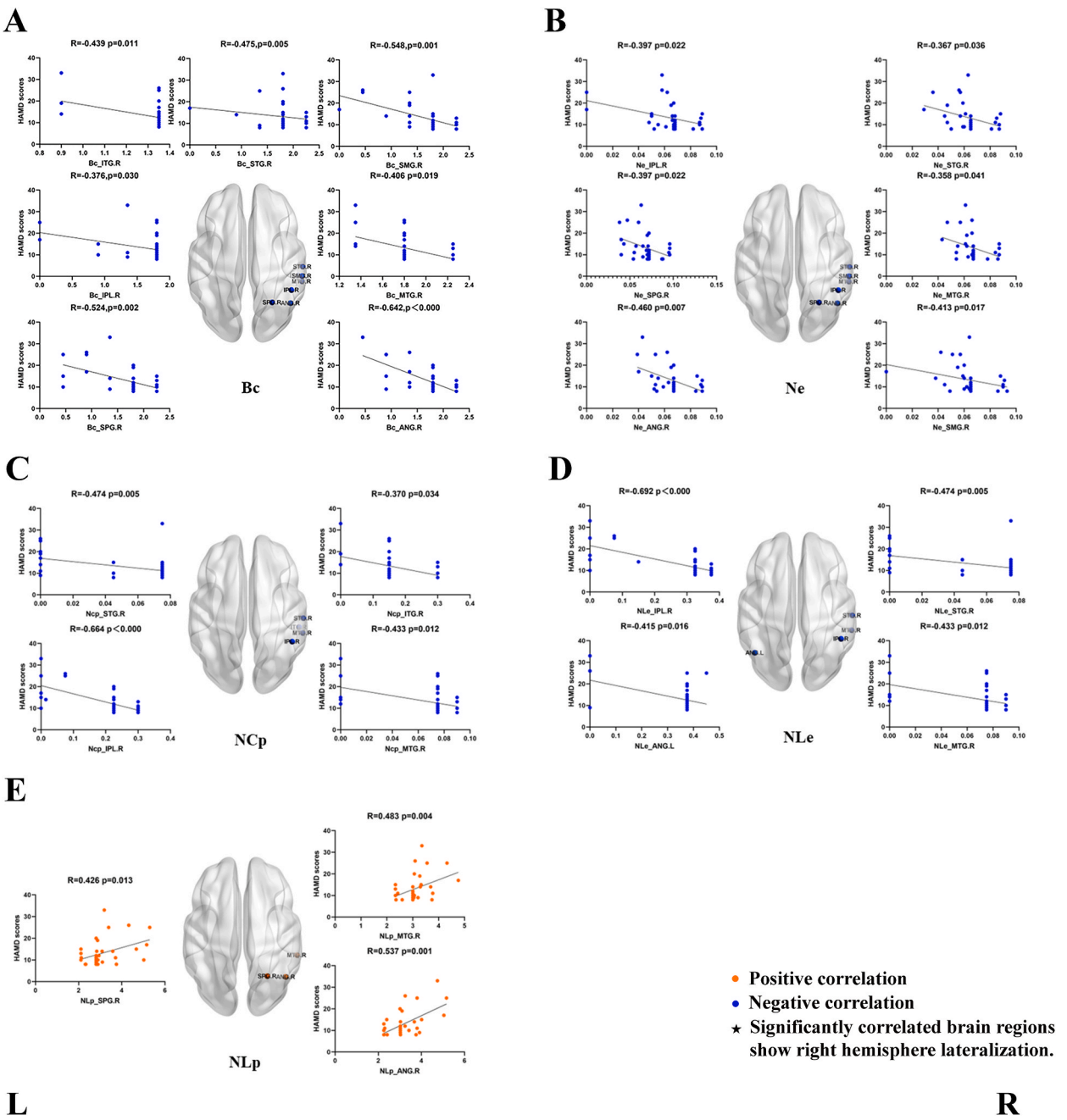

Fig. 3. Regions with significant correlations between the nodal metrics and HAMD scores in SVD patients with depressive symptoms
This figure illustrated the results of the correlation analysis between node metrics and HAMD scores in SVD patients with depressive symptoms. (A) Scatterplots of the correlations between Bc and HAMD scores and the corresponding brain regions. (B) Scatterplots of the correlations between Ne and HAMD scores and the corresponding brain regions. (C) Scatterplots of the correlations between NCp and HAMD scores and the corresponding brain regions. (D) Scatterplots of the correlations between NLe and HAMD scores and the corresponding brain regions. (E) Scatterplots of the correlations between NLp and HAMD scores and the corresponding brain regions. In the axial view, brain network nodes exhibiting correlations with HAMD scores were overlaid onto the brain surface, predominantly localized in the right cerebral hemisphere. The node color indicates direction of correlation. Each scatter plot of nodal metrics corresponds to a specific brain region. The orange color indicates a positive correlation between the node metric and HAMD scores, while the blue color indicates a negative correlation. The correlation coefficients and p-values of the scatterplot have been labeled in the figure. ANG.L, left angular gyrus; Bc, betweenness centrality; HAMD, Hamilton Depression Rating Scale; IPL.R, right inferior parietal; ITG.R, right inferior temporal gyrus; MTG.R, right middle temporal gyrus; NCp, nodal clustering efficiency; Ne, nodal efficiency; NLe, nodal local efficiency; NLp, shortest path length; SMG.R, right supramarginal gyrus; SPG.R, right superior parietal gyrus; STG.R, right superior temporal gyrus. L = left; R = right. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

FDR-corrected) (Fig. 1 (A-C), Table S3).

2.4. Correlations between nodal network metrics and SUA levels

In patients with SVD with depressive symptoms, SUA was positively associated with Bc, NCp, and nodal efficiency (Ne) and was negatively correlated with nodal path length (NLp). The relevant brain regions for Bc were the right inferior parietal lobule (IPL) ($R = 0.46$, $p < 0.01$) and right middle frontal gyrus ($R = 0.42$, $p < 0.05$). Two nodes of Ne were distributed around the right temporal lobe ($p < 0.05$). The altered nodes of NCp and NLp had the same distribution but had opposite correlation trends with SUA. These brain regions were the right IPL, left angular gyrus (ANG), and right middle temporal gyrus (MTG). The results were statistically significant (Fig. 2 (A-D), Table S4).

2.5. Correlations between nodal network metrics and HAMD scores

In SVD patients with depressive symptoms group, several nodal metrics were significantly associated with HAMD scores, including Bc, NCp, Ne, NLe, and NLp, adjusted for age and sex (Fig. 3 (A-E), Table S5). The relevant brain regions that exhibited disrupted nodal metrics included the right superior temporal gyrus, supramarginal gyrus, MTG, inferior temporal gyrus, IPL, superior parietal gyrus, right ANG, and left ANG, mainly distributed in the right parietal and temporal lobes.

3. Discussion

This study investigated the association between SUA and depressive symptoms in patients with SVD and alterations in structural brain networks (Fig. 4). We concluded through network analysis that elevated SUA levels may be associated with neuroprotective effects against depressive symptoms. Our findings illustrated that lower SUA levels were strongly correlated with more severe depressive symptoms in patients with SVD. In addition, SUA was correlated with altered nodal metrics (Bc, NCp, Ne, NLe, and NLp) in the parietal and temporal lobes of the right cerebral hemisphere in the depressive symptoms group. Furthermore, compared with those of patients in the non-depressive symptoms group, topological structural networks (measured by Bc, NCp, and NLp) in SVD patients with depressive symptoms were disrupted and were correlated with the severity of depressive symptoms. The small-world characteristics of the structural brain networks were well maintained in all participants.

In this study, SVD patients with depressive symptoms had lower SUA levels on admission, which is consistent with findings from earlier studies [9,11]. However, unlike previous studies, our study focused on patients with SVD. Owing to its highly heterogeneous clinical symptoms and less severe morbidity, the complications of SVD are often underappreciated. The pathogenesis of depression involves inflammatory responses and oxidative stress [24–26]. The findings of our investigation that elevated SUA is likely to exert neuroprotective effects against depressive symptoms can be explained by its antioxidant function in oxidative stress [27,28]. Uric acid is an oxidizable substrate for hemoglobin/hydrogen peroxide systems and can be used as an electron donor to prevent oxidative damage. An experimental study in older rats was conducted to show that infusion of uric acid 24 h before middle cerebral artery occlusion or 1 h after reperfusion dramatically reduced ischemic damage to the cerebral cortex and striatum and improved behavioral outcomes [29]. The specific mechanism of protection may involve the attenuation of the deleterious effects of ROS and the suppression of lipid peroxidation. Optimal function of neuronal cells relies on adequate antioxidants, such as SUA, to remove ROS and prevent oxidative damage to nerve cells. This is due to the fact that neuronal cell membranes have a large surface area, and their main component is polyunsaturated fatty acids, while ROS often reacts with lipids. Therefore, patients with SVD with lower SUA levels have

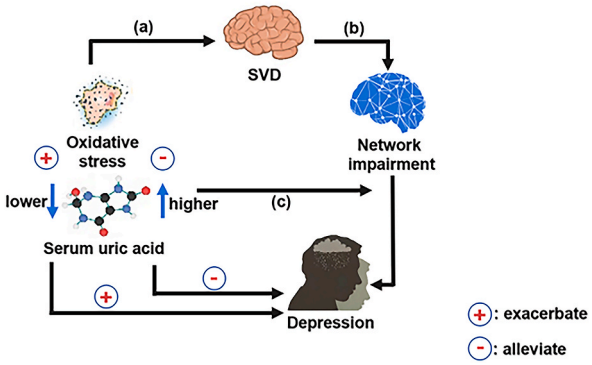

Fig. 4. Diagram showing the association between cerebral small vessel disease, depression, uric acid, and structural brain network damage
Depression is a major clinical complication of cerebral small vessel disease (SVD). (a) Oxidative stress is one of the main pathogenic mechanisms of cerebral small vessel disease and is also involved in the development of depression. As an antioxidant, serum uric acid (SUA) may exert neuroprotective effects against depression. SVD patients with lower SUA levels have a higher risk of depression. (b) The disruption of structural brain networks in patients with SVD can lead to depression. (c) Decreased SUA levels can further deteriorate the damage to the structural brain networks and increase the risk of depression.

a higher risk of depressive symptoms as their brains are more susceptible to damage from oxidative stress. Earlier studies have illustrated the neuroprotective effects of SUA in a multitude of diseases, for example, Alzheimer's disease and Parkinson's disease [30], providing supporting evidence for our results.

To the best of our knowledge, there are few studies exploring the correlation between SUA and structural brain networks. Additional studies are required to investigate whether antioxidant substances can influence the effects of SVD on structural brain networks. We used DTI and graph theory analysis to examine the association between SUA and structural brain networks in SVD patients with depressive symptoms. DTI is a highly sensitive MRI tool that allows the detection of microstructural damage to the brain. A previous study indicated that apathy was related to white matter tract dysconnectivity in SVD as measured using whole-brain network analysis [31]. Our study found that the structural brain networks of patients with depressive symptoms were disrupted compared to patients without these symptoms. The nodal metrics found to be impaired included Bc, NCp, and NLp, and the relevant brain regions were distributed in the right superior frontal gyrus, hippocampus and parahippocampal gyrus, and left inferior occipital gyrus. This indicates that the impairment was associated with the depressive symptoms, aligning with the findings of a previous study [32]. These nodes are distributed in the parietal and temporal lobes of the non-dominant cerebral hemisphere. Some of the regions are involved in emotional regulation circuits. The amygdala and hippocampus are important structures for emotion regulation, constituting the anatomical foundation for depression [33,34]. Dörfel et al. reported a specific activation in the right supramarginal gyrus for emotion regulation [35]. We hypothesized that decreased nodal metrics in the structural networks of many brain regions in patients with depressive symptoms might impact connectivity and lead to network alterations and resulting reductions in neuronal signal transmission, culminating in emotional dysfunction. This was especially the case in regions of the brain that have close relationships with emotion regulation. Reduced connection within the frontoparietal control system may be associated with deficiencies in mood regulation, according to a systematic review of resting-state functional connectivity investigations examining network dysfunction in individuals with major depressive disorder [36]. Differences in research metrics and network analysis methods might clarify the disparities between our and their findings. Disruption of structural brain networks may aid in demonstrating the probable pathophysiology of depressive symptoms in SVD. However, we found no differences in brain network properties in the frontal lobes between the two groups. A potential reason is that patients with SVD had a comparable level of prefrontal impairment, and the significance was minimized by comparison. Another possible reason is that in our study, we explored structural changes in subcortical white matter fiber bundles. Since subcortical white matter fiber bundles are close to the cortex, relatively incoherent and more difficult to identify on a microscopic scale, it may fail to follow the true fiber tract trajectory. Thus, the FA values may have errors, affecting the results.

In addition, we explored the correlation between nodal metrics, SUA, and HAMD scores in SVD patients with depressive symptoms. Bc, NCp, and Ne were positively correlated with SUA levels, unlike NLp. The results showed that elevated SUA levels might shorten the path length and improve information transmission efficiency in the brain structural connectome. Similar results were found for HAMD scores, suggesting that the less efficient the information transfer, the more severe the depressive symptoms. In addition, we noticed that these altered nodes were mainly distributed in the right cerebral hemisphere, which can be explained by the fact that the non-dominant cerebral hemisphere is primarily associated with emotion regulation [37]. Therefore, these findings provide credence to the idea that higher SUA levels could reduce damage to brain microstructures and increase information transmission efficiency, thus reducing depressive symptoms. However, statistically significant differences were not found in global properties for all participants, indicating that long-range connections between segregated brain structures may function well.

Our study indicates that SUA levels should not be excessively lowered in SVD patients with depressive symptoms to prevent further aggravation of depressive symptoms, which representing a novel approach to patient management. Our findings may also contribute to explaining the pathophysiological mechanisms observed in neuroimaging and provide supportive evidence for utilizing peripheral blood markers in SVD, another consideration to be integrated into clinical consultations and management. This study was innovative and has the potential to be further adopted by guidelines in the future. Our research had some limitations. Firstly, SUA levels can be affected by various confounding factors, such as gender, diet, obesity, diabetes, and medications, which were not explicitly excluded in this study. Secondly, the relationship between stroke and depressive symptoms has been confirmed in previous studies [38–40]. The effects of stroke history on depressive symptoms in SVD patients were not excluded in our study, although there was no statistically significant difference in years of previous strokes between the two groups. Thirdly, the effect of dynamic variations in SUA on depressive symptoms should be assessed. Fourthly, there are no studies providing a Minimal Clinically Important Difference (MCID) for SUA levels in the SVD population, which may limit the clinical application of our findings. Fifthly, the sample size was small, and a healthy control group was not included. Sixthly, due to the limitations of the scanning technique, there may be the non-uniformity of magnetic field gradients for DTI [41], which may affect the results.

In conclusion, our findings suggest that elevated SUA levels may be associated with neuroprotective effects, potentially reducing the prevalence of depressive symptoms, as indicated by graph theoretical analysis. However, it is important to note that whether the relationships are causal is uncertain and needs to be explored in more studies.

4. Materials and methods

4.1. Participants

We prospectively recruited 208 inpatients diagnosed with SVD. The First Affiliated Hospital of Sun Yat-sen University's Department of Neurology served as the recruitment site for all study participants. The inclusion criteria were as follows: 1) age between 18 and 70 years; 2) patients with ischemic stroke in the presence or absence of clinical symptoms of acute lacunar stroke syndrome combined with at least one of the neuroimaging features of SVD, including recent small subcortical infarct, WMH, CMBs, or EPVS [1,42]; and 3)

agreement to sign a consent document with full knowledge. The exclusion criteria were as follows: 1) any cause of stroke other than SVD, including intracranial or extracranial large artery stenosis >50%, cardioembolic source of stroke according to the Trial of Org 10172 in Acute Stroke Treatment criteria [43], and large subcortical infarcts (>15 mm maximum diameter) on conventional MRI scans; 2) white matter hyperintensities caused by other diseases such as multiple sclerosis or leukodystrophy; 3) history of cerebral hemorrhage or major central nervous system disease; 4) history of psychiatric disorders, including depression and anxiety, and dementia per DSM-V criteria; 5) history of antidepressant or cognitive enhancer usage prior to study enrollment; 6) inability to complete relative scale evaluation; and, 7) contraindications for undergoing MRI.

All participants signed written informed consent forms. The First Affiliated Hospital of Sun Yat-sen University Research Ethics Committee accepted and approved the study protocols.

4.2. Data collection

Demographic data included age, sex, years of education, and vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol consumption, history of stroke, history of heart disease, and family history of SVD.

Fasting blood samples were collected at admission and analyzed in the clinical laboratory of The First Affiliated Hospital of Sun Yat-sen University, including SUA, triacylglycerols, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, creatinine, and fasting blood glucose. The level of SUA was measured using the uricase peroxidase method.

4.3. Neuropsychological assessments

The evaluations above were performed by three professional neurologists. Depressive symptoms were assessed using the HAMD-24 because of its reliability, validity, and ease of operation, with a cutoff score of 7 [44]. Higher scores indicate more severe depressive symptoms. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [45] because the accuracy of emotion assessment can be affected by cognitive impairment. The cutoff values of MMSE are based on the highest level of education. Patients with dementia were excluded.

Participants were assigned to one of two groups based on established HAMD-24 cut-off scores [44]. The depressed group was defined as the participants with a total HAMD score $\geq$8, and the non-depressed group was defined as the participants with a total HAMD score <8.

4.4. MRI acquisition parameters

All participants were scanned using a 3.0-T MRI scanner (Siemens Healthineers, Erlangen, Germany). The protocol included a T1-weighted 3-dimensional magnetization-prepared rapid gradient echo imaging sequence (slice thickness = 1 mm, repetition time = 8.7 ms, echo time = 3.2 ms, and flip angle = 12°), axial T2-fluid-attenuated inversion recovery sequence, and DTI (slice thickness = 2 mm, repetition time = 10 000 ms, echo time = 122.2 ms, and flip angle = 90°). The details of the MRI protocol were listed in Table S1.

4.5. Image preprocessing

Preprocessing of DTI data was carried out using the Pipeline for Analyzing Brain Diffusion Images toolkit [46], a MATLAB (The Mathworks, Natick, NA, USA) toolbox that utilizes FMRIB Software Library [47], Pipeline System for Octave and MATLAB, Diffusion Toolkit, and MRIcron. DTI images and T1 images of all subjects were used in the preprocessing procedure. The preprocessing process requires the use of a range of software and self-contained toolkits, as shown in the text. The preprocessing is done in the following steps: 1) Converting DICOM files into NIfTI images. 2) Estimating the brain mask. 3) Cropping the raw images. 4) Correcting for the eddy-current effect. 5) Averaging multiple acquisitions. 6) Calculating diffusion tensor (DT) metrics. After the final step, we will obtain the data of DTI metrics, including FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Due to the limitations of the scanning equipment and methodology, the non-uniformity of magnetic field gradients for DTI is difficult to be corrected for [41]. FA may reflect the microstructural integrity of the white matter. We selected FA as the DTI metric for subsequent brain network analysis.

4.6. Network construction

We constructed the network using deterministic beam characterization. The entire brain was divided into 45 regions for each hemisphere using the automated anatomical labeling (AAL) template [48], with each region representing a network node. Cerebellar regions were excluded as the study did not involve the cerebellum. Specifically, each participant's b0 image was co-registered to T1-weighted image using a linear affine transformation. Simultaneously, a symmetric diffeomorphic nonlinear transformation was used to register the T1-weighted images to Montreal Neurological Institute space [49]. Ultimately, these transformations facilitated the registration of the AAL image to each subject's diffusion image space. The 90 regions of the AAL atlas were used as network nodes, forming the basis of participant-specific structural connectivity matrices. The brain network analysis in this study did not involve connecting edges.

4.7. Network analysis

The global and nodal topological properties were calculated using the graph theoretical network analysis (GRETNA) toolbox [50]. Previous research has determined that the sparsity threshold range is 0.1–0.3 with an interval of 0.01. The global network metrics were calculated based on the thresholds of the clustering coefficient (Cp), characteristic path length (Lp), normalized Cp (γ), normalized Lp (λ), small-worldness (σ), global efficiency (Eg), and local efficiency (Eloc). The following nodal network metrics, including NCp, NLp, nodal efficiency (Ne), NLe, nodal degree centrality (Dc), and nodal Bc were estimated. NCp reflects the degree of aggregation of individual nodes with their surroundings. Ne measures the segregation and specialization within a network. NLp indicates the shortest path of a node to transmit information. Bc reflects the network traffic carried by nodes in the network [50]. Statistical testing of global and nodal network measures was also performed using the GRETNA toolbox.

4.8. Visualization of brain network

After performing statistical analysis, we utilized BrainNet Viewer to visualize these nodes [51]. Initially, we uploaded both the brain surface file (BrainMesh_ICBM152_smoothed.nv) and the node file into the software. Following that, we adjusted the figure configuration parameters within the options panel, including output layout, background color, surface transparency, node color and size, edge color and size, and image resolution. Subsequently, BrainNet Viewer systematically rendered the brain surface and nodes and edges, displaying the brain network from various perspectives based on the loaded files. Lastly, the generated figures were exported to common image file formats for further use (Figs. 1–3).

4.9. Statistical analysis

The demographic data and neuropsychological scores were analyzed using SPSS 25.0 (IBM SPSS Statistics, Armonk, NY, USA). Normality of data distribution was tested by Kolmogorov–Smirnov test. Box plots were used for the calculation of outliers. When outliers were found, we determined whether the outliers existed or not based on domain knowledge and experience. In this study, we removed 5 outliers (1 in MMSE scores of the SVD with depressive symptoms group and 4 in MMSE scores of the SVD without depressive symptoms group) to increase the accuracy and reliability of the data. Depending on whether the data were regularly or non-normally distributed, data results are given as percentages for categorical variables and medians (interquartile range) or means (standard deviation) for continuous variables. The Chi-squared and Student's t-tests were used to compare proportions. For normally distributed variables, analysis of variance was utilized, whereas for asymmetrically distributed variables, the Mann-Whitney *U* test was used. Network analysis was performed using the GRETNA toolbox. A two-sample *t*-test was used to analyze global and nodal properties between the groups with and without depressive symptoms, followed by multiple comparison correction procedures with FDR, Bonferroni, or network-based statistic methods [52]. Sex and age were added to the statistical analysis as covariates of no interest. All tests were two-tailed and the threshold for statistical significance was set at $p < 0.05$. Correlation analysis was used to explore the association of brain network metrics with SUA levels and HAMD scores, which was also performed using the GRETNA toolbox.

Ethics approval

The study was approved by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University (Approval No: 2018109). Written informed consent was obtained from all the participants.

Data availability statement

The data supporting the findings of this study will be available on request to the corresponding author. Please be advised that sharing the neuroimaging data is not permitted in accordance with the requirements of the institutional review board (IRB).

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CRediT authorship contribution statement

Lei Yu: Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ming Yi:** Resources, Investigation, Data curation. **Jiayu Guo:** Resources, Data curation. **Jinbiao Li:** Resources, Data curation. **Huixing Zeng:** Resources, Data curation. **Liqian Cui:** Validation, Project administration. **Xiangming Xu:** Resources, Data curation. **Gang Liu:** Validation, Software. **Yuhua Fan:** Supervision, Project administration. **Jinsheng Zeng:** Supervision, Project administration, Funding acquisition. **Shihui Xing:** Supervision. **Yicong Chen:** Validation, Investigation. **Meng Wang:** Software, Resources. **Shuangquan Tan:** Formal analysis, Writing – review & editing. **Leow Yi Jin:** Validation, Formal analysis. **Dilip Kumar:** Validation, Formal analysis. **Ashwati Vipin:** Visualization, Software. **Soo See Ann:** Visualization, Software. **Fatin Zahra Binte Zailan:** Validation, Investigation. **Gurveen Kaur Sandhu:** Visualization, Validation. **Nagaendran Kandiah:** Writing – review & editing, Supervision, Methodology. **Chao Dang:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Abbreviations

SVD	small vessel disease
SUA	serum uric acid
HAMD	Hamilton Depression Rating Scale
MMSE	Mini-Mental State Examination

References

[1] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (7) (2010) 689–701, https://doi.org/10.1016/S1474-4422(10)70104-6.
[2] C.L. White, L.A. Mcclure, P.M. Wallace, J. Braimah, A. Liskay, A. Roldan, O.R. Benavente, The correlates and course of depression in patients with lacunar stroke: results from the Secondary Prevention of Small Subcortical Strokes (SPS3) study, Cerebrovasc. Dis. 32 (4) (2011) 354–360, https://doi.org/10.1159/000330350.
[3] Y. Chen, X. Chen, V. Mok, W. Lam, K. Wong, W. Tang, Poststroke depression in patients with small subcortical infarcts, Clin. Neurol. Neurosurg. 111 (3) (2009) 256–260, https://doi.org/10.1016/j.clineuro.2008.10.008.
[4] T.T. Van Sloten, S. Sigurdsson, M.A. Van Buchem, C.L. Phillips, P.V. Jonsson, J. Ding, M.T. Schram, T.B. Harris, V. Gudnason, L.J. Launer, Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: the AGES-reykjavik study, Am. J. Psychiatr. 172 (6) (2015) 570–578, https://doi.org/10.1176/appi.ajp.2014.14050578.
[5] A. Grool, L. Gerritsen, N. Zuithoff, W. Mali, Y.G. Van Der Graaf, Mi, Lacunar infarcts in deep white matter are associated with higher and more fluctuating depressive symptoms during three years follow-up, Biol. Psychiatr. 73 (2) (2013) 169–176, https://doi.org/10.1016/j.biopsych.2012.08.024.
[6] A. Grool, Y.G. Van Der Graaf, Mi, W. Mali, T. Witkamp, K. Vincken, M. Geerlings, S.S. Group, Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the Second Manifestations of ARTerial disease (SMART)-Medea study, Psychol. Med. 42 (2) (2012) 359–370, https://doi.org/10.1017/S0033291711001383.
[7] R.L. Brookes, V. Herbert, S. Paul, K. Hannesdottir, H.S. Markus, R.G. Morris, Executive dysfunction, awareness deficits and quality of life in patients with cerebral small vessel disease: a structural equation model, Neuropsychology 28 (2) (2014) 247–253, https://doi.org/10.1037/neu0000015.
[8] I.K. Loubinoux, G. Endres, M, P.F. Schumann-Bard, T, R.K. Filipkowski, L, A. Popa-Wagner, Post-stroke depression: mechanisms, translation and therapy, J. Cell Mol. Med. 16 (9) (2012) 1961–1969, https://doi.org/10.1111/j.1582-4934.2012.01555.x.
[9] M.H. Van Agtmaal, Ajhm, F. Pouwer, C.S. Stehouwer, Mt, Association of microvascular dysfunction with late-life depression: a systematic review and meta-analysis, JAMA Psychiatr. 74 (7) (2017) 729–739, https://doi.org/10.1001/jamapsychiatry.2017.0984.
[10] R. Wang, K. Liu, X. Ye, S. Yan, Association between cerebral microbleeds and depression in the general elderly population: a meta-analysis, Front. Psychiatr. 9 (2018) 94, https://doi.org/10.3389/fpsyt.2018.00094.
[11] B. Ames, R. Cathcart, E. Schwiers, P. Hochstein, Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis, Proc. Natl. Acad. Sci. U. S. A. 78 (11) (1981) 6858–6862, https://doi.org/10.1073/pnas.78.11.6858.
[12] Y. Gu, B. Han, L. Wang, Y. Chang, L. Zhu, W. Ren, M. Yan, X. Zhang, J. He, Low serum levels of uric acid are associated with development of poststroke depression, Medicine (Baltim.) 94 (45) (2015) e1897, https://doi.org/10.1097/MD.0000000000001897.
[13] Y. Li, L. Zhao, D. Yu, G. Ding, Associations between serum uric acid and depression among middle-aged and elderly participants in China, Psychol. Health Med. 24 (10) (2019) 1277–1286, https://doi.org/10.1080/13548506.2019.1622748.
[14] G. Li, J. Miao, W. Sun, X. Song, Y. Lan, X. Zhao, X. Qiu, C. Zhang, Z. Zhu, S. Zhu, Lower serum uric acid is associated with post-stroke depression at discharge, Front. Psychiatr. 11 (2020) 52, https://doi.org/10.3389/fpsyt.2020.00052.

[15] P. Hagmann, L. Jonasson, P. Maeder, J. Thiran, V. Wedeen, R. Meuli, Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond, Radiographics 26 (2006) S205–S223, https://doi.org/10.1148/rg.26si065510.
[16] A.G. Van Norden, K.F. De Laat, E.J. Van Dijk, I.W. Van Uden, L.J. Van Oudheusden, R.A. Gons, D.G. Norris, M.P. Zwiers, F.E. De Leeuw, Diffusion tensor imaging and cognition in cerebral small vessel disease: the RUN DMC study, Biochim. Biophys. Acta 1822 (3) (2012) 401–407, https://doi.org/10.1016/j.bbadis.2011.04.008.
[17] E. Bullmore, O. Sporns, Complex brain networks: graph theoretical analysis of structural and functional systems, Nat. Rev. Neurosci. 10 (3) (2009) 186–198, https://doi.org/10.1038/nrn2575.
[18] Y. Sengul, H. Otcu, I. Ustun, H.S. Sengul, T. Cersonsky, A. Alkan, E.D. Louis, Neuroimaging depression and anxiety in essential tremor: a diffusion tensor imaging study, Clin. Imag. 58 (2019) 96–104, https://doi.org/10.1016/j.clinimag.2019.06.016.
[19] Z. Li, W. Liu, C. Xiao, X. Wang, X. Zhang, M. Yu, X. Hu, L. Qian, Abnormal white matter microstructures in Parkinson's disease and comorbid depression: a whole-brain diffusion tensor imaging study, Neurosci. Lett. 735 (2020) 135238, https://doi.org/10.1016/j.neulet.2020.135238.
[20] A. Feinstein, P. O'connor, N. Akbar, L. Moradzadeh, C.J. Scott, N.J. Lobaugh, Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients, Mult. Scler. 16 (2) (2010) 189–196, https://doi.org/10.1177/1352458509355461.
[21] F. Crosta, U. Occhiuzzi, G. Passalacqua, E. Occhiuzzi, A. Cimini, D. Grassi, C. Ferri, C. Marini, C. Borghi, G. Desideri, Association between the serum uric acid levels and lacunar infarcts in the elderly, J. Mol. Neurosci. 65 (3) (2018) 385–390, https://doi.org/10.1007/s12031-018-1096-0.
[22] M.J. Sun, B.H. Li, C.Y. Long, Y.Q. Wang, Y. Zhou, Y. Liu, S.Q. Liao, Y. Pi, L. Guo, L.L. Zhang, J.C. Li, Association between serum uric acid levels and cerebral white matter lesions in Chinese individuals, Int. J. Neurosci. 126 (12) (2016) 1103–1111, https://doi.org/10.3109/00207454.2015.1128903.
[23] S.W. Han, T.J. Song, C.D. Bushnell, S.S. Lee, S.H. Kim, J.H. Lee, G.S. Kim, O.J. Kim, I.S. Koh, J.Y. Lee, S.H. Suk, S.I. Lee, H.S. Nam, K.Y. Lee, J.H. Park, Serum uric acid is associated with cerebral white matter hyperintensities in patients with acute lacunar infarction, J. Neuroimaging 26 (3) (2016) 351–354, https://doi.org/10.1111/jon.12308.
[24] R.F. Villa, F. Ferrari, A. Moretti, Post-stroke depression: mechanisms and pharmacological treatment, Pharmacol. Ther. 184 (2018) 131–144, https://doi.org/10.1016/j.pharmthera.2017.11.005.
[25] R.G. Robinson, R.E. Jorge, Post-stroke depression: a review, Am. J. Psychiatr. 173 (3) (2016) 221–231, https://doi.org/10.1176/appi.ajp.2015.15030363.
[26] C.N. Black, M. Bot, P.G. Scheffer, P. Cuijpers, B.W. Penninx, Is depression associated with increased oxidative stress? A systematic review and meta-analysis, Psychoneuroendocrinology 51 (2015) 164–175, https://doi.org/10.1016/j.psyneuen.2014.09.025.
[27] A. Cherubini, C. Ruggiero, M.C. Polidori, P. Mecocci, Potential markers of oxidative stress in stroke, Free Radic. Biol. Med. 39 (7) (2005) 841–852, https://doi.org/10.1016/j.freeradbiomed.2005.06.025.
[28] G.T. Glantzounis, Ec. Kappas, Am. and D. Galaris, Uric acid and oxidative stress, Curr. Pharmaceut. Des. 11 (32) (2005) 4145–4151, https://doi.org/10.2174/138161205774913255.
[29] Z.F. Yu, Bruce-Keller, J. Annadora, Y. Goodman, M.P. Mattson, Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo, J. Neurosci. Res. 53 (5) (1998) 613–625, https://doi.org/10.1002/(sici)1097-4547(19980901)53:5<613::Aid-jnr11>3.0.Co;2-1.
[30] C. Tana, A. Ticinesi, B. Prati, A. Nouvenne, T. Meschi, Uric acid and cognitive function in older individuals, Nutrients 10 (2018), https://doi.org/10.3390/nu10080975.
[31] J. Tay, A.M. Tuladhar, M.J. Hollocks, R.L. Brookes, D.J. Tozer, T.R. Barrick, M. Husain, F.E. De Leeuw, H.S. Markus, Apathy is associated with large-scale white matter network disruption in small vessel disease, Neurology 92 (11) (2019) e1157–e1167, https://doi.org/10.1212/WNL.0000000000007095.
[32] X. Xie, Y. Shi, J. Zhang, Structural network connectivity impairment and depressive symptoms in cerebral small vessel disease, J. Affect. Disord. 220 (2017) 8–14, https://doi.org/10.1016/j.jad.2017.05.039.
[33] W. Li, B.D. Ward, C. Xie, J.L. Jones, P.G. Antuono, S.J. Li, J.S. Goveas, Amygdala network dysfunction in late-life depression phenotypes: relationships with symptom dimensions, J. Psychiatr. Res. 70 (2015) 121–129, https://doi.org/10.1016/j.jpsychires.2015.09.002.
[34] W. Taylor, Y. Deng, B. Boyd, M. Donahue, K. Albert, M. Mchugo, J. Gandelman, B. Landman, Medial temporal lobe volumes in late-life depression: effects of age and vascular risk factors, Brain Imaging Behav 14 (1) (2020) 19–29, https://doi.org/10.1007/s11682-018-9969-y.
[35] D. Dorfel, J.P. Lamke, F. Hummel, U. Wagner, S. Erk, H. Walter, Common and differential neural networks of emotion regulation by Detachment, Reinterpretation, Distraction, and Expressive Suppression: a comparative fMRI investigation, Neuroimage 101 (2014) 298–309, https://doi.org/10.1016/j.neuroimage.2014.06.051.
[36] R.H. Kaiser, J.R. Andrews-Hanna, T.D. Wager, D.A. Pizzagalli, Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity, JAMA Psychiatr. 72 (6) (2015) 603–611, https://doi.org/10.1001/jamapsychiatry.2015.0071.
[37] J. Borod, Interhemispheric and intrahemispheric control of emotion: a focus on unilateral brain damage, J. Consult. Clin. Psychol. 60 (3) (1992) 339–348, https://doi.org/10.1037//0022-006x.60.3.339.
[38] I. Aben, J. Denollet, R. Lousberg, F.W. Verhey, A. F. Honig, Personality and vulnerability to depression in stroke patients: a 1-year prospective follow-up study, Stroke 33 (10) (2002) 2391–2395, https://doi.org/10.1161/01.str.0000029826.41672.2e.
[39] T. Jørgensen, I. Wium-Andersen, M. Wium-Andersen, M. Jørgensen, E. Prescott, S. Maartensson, P. Kragh-Andersen, M. Osler, Incidence of depression after stroke, and associated risk factors and mortality outcomes, in a large cohort of Danish patients, JAMA Psychiatr. 73 (10) (2016) 1032–1040, https://doi.org/10.1001/jamapsychiatry.2016.1932.
[40] C. Tsai, C. Wu, T. Hung, S. Chou, J. Su, Incidence and risk factors of poststroke depression in patients with acute ischemic stroke: a 1-year prospective study in Taiwan, Biomed. J. 39 (3) (2016) 195–200, https://doi.org/10.1016/j.bj.2015.10.004.
[41] R. Bammer, B. Acar, M.E. Moseley, In vivo MR tractography using diffusion imaging, Eur. J. Radiol. 45 (3) (2003) 223–234, https://doi.org/10.1016/s0720-048x(02)00311-x.
[42] M. Duering, G. Biessels, A. Brodtmann, C. Chen, C. Cordonnier, F.D. De Leeuw, S, R. Frayne, E. Jouvent, N. Rost, A. Ter Telgte, R.B. Al-Shahi Salman, Wh, H. Bae, R. Brown, H. Chabriat, A. De Luca, C. Decarli, A. Dewenter, F. Doubal, M. Ewers, T. Field, A. Ganesh, S. Greenberg, K. Helmer, S. Hilal, A.J. Jochems, H, H. Kuijf, B. Lam, J.M. Lebenberg, Bj Maillard, P, V. Mok, L. Pantoni, S.S. Rudilosso, Cl Schirmer, Md Schmidt, R, C. Smith, J. Staals, M. Thrippleton, S. Van Veluw, P. Vemuri, Y. Wang, D. Werring, M. Zedde, R. Akinyemi, O.M. Del Brutto, Hs, Y. Zhu, E. Smith, M. Dichgans, J. Wardlaw, Neuroimaging standards for research into small vessel disease-advances since 2013, Lancet Neurol. 22 (7) (2023) 602–618, https://doi.org/10.1016/S1474-4422(23)00131-X.
[43] H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, E.E. Marsh, Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment, Stroke 24 (1) (1993) 35–41, https://doi.org/10.1161/01.str.24.1.35, 3rd.
[44] M. Hamilton, A rating scale for depression, J. Neurol. Neurosurg. Psychiatry 23 (1) (1960) 56–62, https://doi.org/10.1136/jnnp.23.1.56.
[45] M. Naudin, K. Mondon, W. El-Hage, E. Perriot, M. Boudjarane, T. Desmidt, A. Lorette, C. Belzung, C. Hommet, B. Atanasova, Taste identification used as a potential discriminative test among depression and Alzheimers disease in elderly: a pilot study, Psychiatr. Res. 228 (2) (2015) 228–232, https://doi.org/10.1016/j.psychres.2015.03.021.
[46] Z. Cui, S. Zhong, P. Xu, Y. He, G. Gong, PANDA: a pipeline toolbox for analyzing brain diffusion images, Front. Hum. Neurosci. 7 (2013) 42, https://doi.org/10.3389/fnhum.2013.00042.
[47] T.E. Behrens, M.W. Woolrich, M. Jenkinson, H. Johansen-Berg, R.G. Nunes, S. Clare, P.M. Matthews, J.M. Brady, S.M. Smith, Characterization and propagation of uncertainty in diffusion-weighted MR imaging, Magn. Reson. Med. 50 (5) (2003) 1077–1088, https://doi.org/10.1002/mrm.10609.
[48] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer, M. Joliot, Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain, Neuroimage 15 (1) (2002) 273–289, https://doi.org/10.1006/nimg.2001.0978.
[49] G. Gong, Y. He, L. Concha, C. Lebel, D.W. Gross, A.C. Evans, C. Beaulieu, Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography, Cerebr. Cortex 19 (3) (2009) 524–536, https://doi.org/10.1093/cercor/bhn102.

[50] J. Wang, X. Wang, M. Xia, X. Liao, A. Evans, Y. He, GRETNA: a graph theoretical network analysis toolbox for imaging connectomics, Front. Hum. Neurosci. 9 (2015) 386, https://doi.org/10.3389/fnhum.2015.00386.
[51] M. Xia, J. Wang, Y. He, BrainNet viewer: a network visualization tool for human brain connectomics, PLoS One 8 (7) (2013) e68910, https://doi.org/10.1371/journal.pone.0068910.
[52] A. Zalesky, A. Fornito, E.T. Bullmore, Network-based statistic: identifying differences in brain networks, Neuroimage 53 (4) (2010) 1197–1207, https://doi.org/10.1016/j.neuroimage.2010.06.041.