MENTAL DISORDERS ASSOCIATED WITH NEUROLOGICAL DISEASES

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MENTAL DISORDERS ASSOCIATED WITH NEUROLOGICAL DISEASES

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Table of Contents

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Editorial: Mental Disorders Associated With Neurological Diseases

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Keywords: mental disorders, post-stroke depression, cognitive impairment, depression, post-stroke anxiety, Parkinson's disease

Editorial on the Research Topic

Mental Disorders Associated With Neurological Diseases

Mental disorders are important comorbidities of nervous system diseases and they have a lot in common in risk factors and pathogenesis. However, mental disorders can be easily neglected by neurologists. The mechanisms underlying the association of mental disorders with neurological disease are largely unclear. This Research Topic provides a collection of research into post-stroke depression and anxiety, cognitive impairment, and depression in Creutzfeldt-Jakob and Parkinson's disease. Although the present research collection cannot cover the whole range of advancements in the field, it highlights certain key findings regarding mental disorders associated with neurological diseases and we hope that this will inspire further interest and new research efforts in this exciting area.

Depression is a global chronic medical illness that leads to low mood, loss of interest, change in appetite, insomnia, and neurocognitive dysfunction. Despite the prevalence of depression, there are still many aspects to be explored and understood. An increasing prevalence of late-life depression has been identified, the mechanisms of which remain unclear. Previous studies demonstrated that iron deposition was related to the severity of symptoms in patients with depression. Zhang et al. investigated the role of iron deposits in depression among older adults and found that iron deposits in the thalamus was an independent factor relating to depressive symptoms. This new finding may inform future studies into the underlying pathophysiological mechanisms of depression.

Cerebral autoregulation was initially considered as an intrinsic protective mechanism of the brain, which ensures relatively constant cerebral blood flow despite fluctuations in arterial blood pressure or cerebral perfusion pressure. The impairment of cerebral autoregulation has been reported to be a feature of several diseases, including cerebral stroke, and Alzheimer's disease. Luo et al. observed that cerebral autoregulation was compromised in patients with depression and negatively correlated with the depression score. Though the mechanism is still unknown, improving cerebral autoregulation could be a potential therapeutic approach to treating the neurological symptoms of depression.

Depressive disturbances are common in patients with Parkinson's disease, but the neurochemical changes that occur in these cases are still unknown. In order to address this, Lian et al. investigated clinical features and neurochemical changes in patients with Parkinson's disease. The authors report that a high proportion of patients with Parkinson's disease had depression. Motor symptoms, postural instability, gait difficulty, anxiety, and fatigue are the significant influencing factors in cases of Parkinson's disease with

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depression. Moreover, dopamine may play a more important role in Parkinson's disease with depression compared to 5-HT. In another study, Zhu et al., observed that high concentrations of dopamine may cause the high incidence of restless leg syndrome (RLS) in Parkinson's disease patients, which was accompanied by anxiety, depression, insomnia, and other mental health symptoms. This finding highlights the importance of monitoring such symptoms in the clinical management of patients with Parkinson's disease.

Post-stroke depression, the most common psychiatric implication of stroke, negatively impacts patients' rehabilitation results, cognitive function, and quality of life. In this Research Topic, Huang, Zhao et al. explore the potential interaction between depressive symptoms and cognitive impairment after stroke and found remitters of post-stroke depression had more significant cognitive improvements than non-remitters. Therefore, early recognition and intervention for potential depression after stroke is of great importance. This study also identified predictors of remission in patients with early-onset post-stroke depression, which included neurological impairment, major life events, major medical comorbidities, and frontal lobe lesion at baseline. A review in this Research Topic by Wang, Shi et al. provides a comprehensive overview of etiologies of post-stroke depression. In their article, the authors identify several factors related to the pathogenesis of post-stroke depression, including monoamine neurotransmitter change, inflammation, the hypothalamus-pituitary-adrenal axis and the hypothalamus-pituitary-thyroid axis, glial cells (astrocytes and microglia), vitamin D levels, homocysteine levels, neural network dysfunction, genetic background, and social psychological mechanisms.

Focusing on depression after intracerebral hemorrhage, Wu et al. provide a detailed review about the pathophysiology of depression after intracerebral hemorrhage, including inflammation, oxidative stress, apoptosis, and autophagy. This overview is accompanied by an in-depth exploration of the associated signaling pathways.

Recently, there has been an international focus on research into inflammation and post-stroke depression. Fang et al. produced a comprehensive review summarizing how neuroinflammation affects stroke rehabilitation and post-stroke depression, potentially offering new therapeutic targets for stroke and post-stroke depression. Contributing also to the topic of post-stroke depression, Wang, Wang et al. share their research into the association between post-stroke depression, aphasia and physical independence, in stroke patients in China at a 3-months follow-up. The authors found the incidence of post-stroke depression was independently associated with physical dependence.

Another prevalent mental disorder after a stroke is anxiety. However, studies investigating the effects of post-stroke anxiety on functional status are very limited. The article by Li et al. describes that severity of post-stroke anxiety in the acute stage was a significant indicator for daily living and stroke-specific quality of life.

In this Research Topic, Liang et al. report on a case of sporadic Creutzfeldt-Jakob disease with depression. They found that the patient's condition worsened after using antidepressants. This finding was followed by a systematic survey, which showed that survival period was associated with the type of antidepressant used (especially serotonin and noradrenaline reuptake inhibitors).

Insomnia is a highly prevalent symptom in patients with mental disorders. Exploring the common and different brain mechanisms underlying such symptoms may help refine existing treatments. Yu et al. found that the interaction of depression and insomnia was associated with decreased gray matter volume in the right orbitofrontal cortex. This finding provides new insights into the mechanisms underlying the comorbidity of insomnia and depression. The comorbidity of insomnia and anxiety disorders is also worthy of further exploration. Another study into insomnia in this Research Topic is from Huang, Zhan et al., who reveal that cortical excitability in patients with generalized anxiety disorder comorbid with insomnia is modulated by insomnia. The authors examined the recovery functions of median nerve somatosensory evoked potentials, thus shedding light on the underlying neurobiological correlates of the effects of insomnia on generalized anxiety disorder.

Cognitive impairment seems to mark a high-risk population for developing dementia and plays a crucial role in the course of mental disability. The pathophysiology of it is a field where much work is yet to be done. The contribution from Wei et al. addresses a surrogate marker (the peak width of skeletonized mean diffusivity) for cognitive impairment in cerebral white matter lesions patients, which provides new insights into the pathophysiology of cognitive impairment in these patients. A study in this Research Topic by Deng et al. found that patients with severe vertebra-basilar stenosis showed a decline in cognitive ability, and that chronic posterior circulation hypoperfusion was an independent risk factor for cognitive impairment. The cerebral venous system also plays an important part in the progress of cognitive impairment. Compression and stenosis of the draining veins have been reported to be linked with transient global amnesia (a specific kind of cognitive impairment) via magnetic resonance imaging studies. Using ultrasound examination, Han et al. further confirmed a decrease in the total flow volume of the vertebral and internal jugular veins in patients with transient global amnesia. In addition, internal jugular vein drainage was relatively compromised during the Valsalva maneuver (an activity that can trigger transient global amnesia). To clarify the mechanisms involved in dementia, Zhou et al. performed a meta-analysis of the association between cortical superficial siderosis and dementia. The authors found that pre-existing cortical superficial siderosis could be a candidate imaging indicator for Alzheimer's disease. Another interesting study in this Research Topic is from Yin et al., who found that cerebral blood flow damage in white matter is associated with global cognitive dysfunction in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Moreover, this exploratory study found cerebral blood flow was more strongly associated with global cognitive function

than mean diffusivity and that this could be a biomarker used to monitor alterations of global cognitive function in CADASIL.

Finally, the editors would like to acknowledge the authors who contributed to this Research Topic. Their honest efforts and hard work are truly admirable. The editors hope that papers comprising this Research Topic will inspire significant progress in the field of mental disorders associated with neurological diseases.

AUTHOR CONTRIBUTIONS

YY: drafted the manuscript. CW, YX, JL, and TP: revised the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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The Association Between Post-stroke Depression, Aphasia, and Physical Independence in Stroke Patients at 3-Month Follow-Up

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Objective: Few studies have examined the association between post-stroke depression (PSD), aphasia, and physical independence in Chinese patients. This study investigated the above association in stroke patients in China at 3-month follow-up.

Methods: Altogether 270 patients within 14 days after ischemic stroke were recruited and followed up at 3 months. PSD, aphasia, and physical functional status were measured using the Stroke Aphasia Depression Questionnaire (SADQ), Western Aphasia Battery (WAB), and modified Rankin Scale (mRS), respectively. Patients with mRS total score >2 were considered as having "physical dependence."

Results: Out of 248 patients at 3-month follow up, 119 (48%) were rated as having physical dependence. Multiple logistic regression analyses revealed that female ($p = 0.04$; OR = 2.2; 95% CI: 1.0–5.1), more severe stroke at admission ($p < 0.01$; OR = 1.4; 95% CI: 1.3–1.5), and more severe PSD at 3 months ($p = 0.01$; OR = 1.05; 95% CI: 1.01–1.1) were independently associated with physical dependence at 3 months.

Conclusions: Greater PSD and stroke severity were independently associated with physical dependence at 3 months after stroke. Aphasia was also associated with physical dependence but the relationship was not significant. Early and effective depression screening, treatment and stroke rehabilitation appear to be important to improve the physical outcome and reduce the burden of stroke survivors.

Keywords: aphasia, ischemic stroke, depression, PSD, physical independence

INTRODUCTION

Post-stroke depression (PSD) is one of the most common psychiatric comorbidities in stroke survivors, with a prevalence ranging from 20 to 65% (1–4). PSD is significantly associated with poor treatment adherence and increased risk of disability, mortality, stroke recurrence, and poor quality of life (5, 6). Aphasia occurs in about a third of ischemic stroke patients and is associated with impaired activity of daily life (7, 8) and higher risk of PSD (9, 10). Poor functional outcome after stroke could result in significant personal distress and family burden (11). Understanding the association between PSD, aphasia and physical independence is hence important to develop comprehensive treatment strategies for stroke survivors.

In China, the lifetime prevalence of stroke was 2.08% (95% CI, 2.02–2.13%) (12) in 2017, which translates to ∼2.9 million stroke patients. An Italy study found PSD was the only significant factor related to functional recovery from discharge to 3-month follow-up after stroke but not aphasia (13). To the best of our knowledge, there are no studies that have investigated the independent association between PSD, aphasia, and physical independence in stroke survivors in China. This study thus aimed to examine the association between PSD, aphasia, and physical independence in Chinese stroke patients at 3-month follow-up.

METHODS

Participants and Study Setting

This prospective cohort study was conducted between April 2014 and October 2015 in the Stroke Centre of Beijing Tiantan Hospital. A total of 320 patients were consecutively screened if they fulfilled the following criteria: (1) aged 18 years or older; (2) had an acute ischemic stroke within 14 days according to the WHO diagnostic criteria (14) confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); and (3) had the ability to provide informed consent and complete the assessment. Exclusion criteria included: (1) history of language impairment; (2) drug and alcohol abuse and severe psychiatric disorders; (3) other major medical conditions, such as Parkinson's disease; and (4) severe cognitive deficit defined by the Mini Mental State Examination (MMSE) total score <18 (15, 16). The first three were excluded based on the self-reported pre-stroke histories by unstructured interviews and the last was made at the start of the study. The study protocol was approved by the ethics committee of Beijing Tiantan Hospital, Capital Medical University. All participants provided written informed consent.

Measurement Instruments and Evaluation

Assessment was conducted at baseline and 3 months after index ischemic stroke. Patients' socio-demographic and clinical characteristics at baseline were recorded via a review of electronic medical records and confirmed by a clinical interview conducted by trained research neurologists. Severity and type of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) (17–19) and the Trial of Org 10172 Acute Stroke Treatment (TOAST) (20, 21).

Physical independence and degree of handicap was evaluated using the modified Ranking Scale (mRS) at 3 months, with mRS total score >2 indicating physical dependence (22, 23). As most depression scales cannot be used in stroke patients with aphasia due to their impaired communication ability, the severity of depressive symptoms at 14 ± 2 days and 3 months after index stroke was measured using the 21-item Stroke Aphasic Depression Questionnaire (SADQ) (24, 25) with total score ranges from 0 to 63, ≥19 indicating the presence of PSD, ≥ 22 indicating moderate depressive symptoms and ≥ 26 indicating major depressive symptoms. The SADQ relies on external observation of emotional behavior by nursing staff and family members in recent time. The hospital version (SADQ-H) focus on the recent week. The severity and type of aphasia was evaluated with the Aphasia Quotient (AQ) derived from the Western Aphasia Battery (WAB), with AQ < 93.8 indicating the presence of aphasia (26). The language assessment was also conducted at 3-month follow-up with much missing data on AQ score, so the data was not analyzed.

Statistical Analysis

Data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Socio-demographic and clinical variables were compared between physical independence and dependence groups using Chi-square test, independent sample *t*-test and Mann-Whitney *U*-test, as appropriate. Independent correlates of the physical dependence at 3 months were examined using multivariate logistic regression analysis with the "enter" method. The outcome at 3 months was the dependent variable, while variables that significantly differed between both groups in the univariate analyses were entered as independent variables. Significance was set at 0.05 (two-tailed).

RESULTS

Out of 320 patients with ischemic stroke who were consecutively screened, 270 fulfilled the study entry criteria and participated in the study, giving a participation rate of 84.4%. At baseline, 160 (59.3%) patients had aphasic symptom with the incidence of PSD was 47.5% compared with 29.1% in non-aphasiac patients ($p < 0.01$). At the 3-month assessment, 22 patients dropped out due to lack of interest, moving house or other unknown reasons. Of the 248 patients who completed the 3-month assessment, 119 (48.0%) had physical dependence.

Table 1 shows the socio-demographic and clinical characteristics of the whole sample and separately by outcome. Patients with physical dependence were less likely to be married, and have large-artery atherosclerosis (LAA) TOAST type and pulmonary infection, but more likely to be female, have aphasia at baseline and more severe depressive symptoms at both baseline and 3 months after stroke. In addition, they had higher NIHSS scores at baseline, and higher SADQ scores at baseline and 3 months (all *p*-values < 0.05).

The independent correlates of physical dependence are shown in **Tables 2**, **3**. Due to collinearity between SADQ-H (Hospital version using during hospitalization) and SADQ score, two multivariate logistic regression analyses were performed with

TABLE 1 | Comparison of demographic and clinical variables between physical independence and dependence groups.

	Total sample ($n = 248$)		Physical independence ($n = 129$)		Physical dependence ($n = 119$)		Statistics		
	N	**%**	***N***	**%**	***N***	**%**	χ^2	**df**	***p***
Female	72	29. 0	26	20.2	46	38.7	10.2	1	**0.001**
Higher education (high middle school or above)	88	35.5	49	38.0	39	32.8	0.7	1	0.39
Being married	229	92.3	124	96.1	105	88.2	5.4	1	**0.02**
Living with others	235	94.8	123	95.3	112	94.1	0.1	1	0.66
Diabetes	61	24.6	29	22.5	32	26.9	0.6	1	0.42
Hypertention	156	62.9	87	67.4	69	58.0	2.3	1	0.12
Hyperlipidemia	33	13.5	19	14.7	14	11.8	0.4	1	0.49
Cardiac disease	21	8.5	10	7.8	11	9.2	0.1	1	0.67
Stroke history	58	23.4	27	20.9	31	26.1	0.9	1	0.34
TOAST type (LAA)	209	84.3	115	89.1	94	79.0	4.8	1	**0.02**
Aphasia at baseline	148	59.7	66	51.2	82	68.9	8.1	1	**0.004**
Depressive symptoms at baseline	100	40.3	39	30.2	61	51.3	11.3	1	**0.001**
Moderate/Major depressive symptoms at baseline	54	21.8	15	11.6	39	32.8	16.2	1	**<0.001**
Depressive symptoms at 3 months	85	34.7	26	20.2	59	50.9	25.4	1	**<0.001**
Moderate/Major depressive symptoms at 3 months	48	19.6	8	6.2	40	34.5	31.0	1	**<0.001**
Pulmonary infection at baseline	36	14.5	13	10.1	23	9.3	4.2	1	**0.03**
Upper gastrointestinal hemorrhage at baseline	8	3.2	3	2.3	5	4.4	0.2	1	0.63
Cardiac diseases at baseline	12	4.8	5	3.9	7	5.9	0.5	1	0.46
Urinary infection at baseline	11	4.4	3	2.3	8	6.7	2.8	1	0.09
Deep venous thrombosis at baseline	20	8.1	5	3.9	15	12.6	6.3	1	**0.01**
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	**T/Z**	**df**	***p***
Age (years)	57.3	14.2	57.3	14.0	57.3	14.6	0.01	246	0.9
Stroke duration from onset to admission	6.1	6.1	6.3	6.1	5.9	6.0	−1.2	__a	0.22
NIHSS at baseline	8.3	5.3	5.1	3.7	11.8	4.5	−10.1	__a	**<0.001**
SADQ-H at baseline	14.5	7.9	12.5	7.2	16.8	8.0	−4.2	__a	**<0.001**
SADQ at 3 months	12.8	8.0	9.7	7.1	16.2	7.6	−6.3	__a	**<0.001**

Values $p < 0.05$ are bolded; a, Mann-Whitney U-test; LAA, Large-Artery Atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SADQ-H, Stroke Aphasic Depression Questionnaire (Hospital version); SADQ, Stroke Aphasic Depression Questionnaire; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

SADQ-H and SADQ separately. Finally, female, NIHSS score at admission and SADQ score at 3 months were independently associated with physical dependence at 3-month follow up (adjusted $R^2 = 0.410$ in **Table 2** and adjusted $R^2 = 0.423$ in **Table 3**).

DISCUSSION

Generally about a third of patients with ischemic stroke have poor functional outcome at different follow-up time points (27, 28). In this study, the prevalence of physical dependence was 48% using the mRS cut-off score, which is similar to the 5-year prevalence of poor functional outcome (45%) in another study with the same measure (29). However, any direct comparison should be done with caution due to the different assessment measures, follow-up time points, and demographic characteristics.

A report of the American Heart Association/American Stroke Association in 2017 and meta-analyses found that approximately a third of stroke patients develop PSD at any point after stroke (30–32). A large-scale prospective cohort study in China involving over 2,000 stroke patients found that the cumulative incidence of PSD at 1 year after the index stroke was 42% (4). Depression was found predictive of worse functional outcome in an updated meta-analysis about the impact of depression on stroke outcome (33). While up to 62–70% in aphasic patients with stroke were diagnosed as major depression according to DSM-III-R criteria at 3 months and 1 year after stroke (9, 10, 34) which was higher than our results. The reason may due to the different scales, population and time points. Aphasia have been considered for the potential association with PSD with inconsistent conclusion (35, 36). We found that the incidence of PSD in stroke patients with aphasia and non-aphasia was significantly different indicating aphasia may be a risk factor of the development of PSD.

In this study, the incidence of PSD was 34.7% at 3 months after stroke, which was independently associated with physical dependence. Similar findings were also reported previously (37–39). Depressive symptoms after stroke could result in behavioral and biological abnormalities, such as poor treatment adherence and dysregulation in autonomic system activation, which in turn, could lead to physical dependence (11, 37). However,

TABLE 2 | Independent correlates of physical dependence at 3 months[#].

Variables	Ischemic stroke patients		
	P	OR	95%CI
Feale	**0.04**	2.2	1.0,5.1
Being married	0.22	0.3	0.08,1.7
TOAST type (LAA)	0.75	1.1	0.4,3.5
Aphasia at baseline	0.32	1.4	0.6,2.9
SADQ-H score at baseline	0.72	1.08	0.9,1.05
Pulmonary infection at baseline	0.74	1.1	0.4,3.4
Deep venous thrombosis at baseline	0.27	2.4	0.5,11.5
NIHSS at admission	**<0.01**	1.4	1.3,1.5

Values p < 0.05 are bolded; a, Mann-Whitney U-test; LAA, Large-Artery Atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SADQ-H, Stroke Aphasic Depression Questionnaire (Hospital version); TOAST, Trial of Org 10172 in Acute Stroke Treatment. [#]The severity of depressive symptoms was tested by SADQ-H at baseline and SADQ at 3 months. There was collinearity between SADQ-H at baseline and SADQ at 3 months, therefore they were not entered in the analysis concurrently.

TABLE 3 | Independent correlates of physical dependence at 3 months[#].

Variables	Ischemic stroke patients		
	P	OR	95%CI
Female	0.08	2.0	0.9,4.8
Being married	0.26	0.4	0.08,1.9
TOAST type (LAA)	0.80	1.1	0.3,3.4
Aphasia at baseline	0.53	1.2	0.6,2.5
SADQ score at 3 months	**0.01**	1.05	1.01,1.1
Pulmonary infection at baseline	0.69	1.2	0.4,3.6
Deep venous thrombosis at baseline	0.30	2.2	0.4,10.3
NIHSS at admission	**<0.01**	1.4	1.2,1.5

Values p < 0.05 are bolded; a, Mann-Whitney U test; LAA, Large-Artery Atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SADQ, Stroke Aphasic Depression Questionnaire; TOAST, Trial of Org 10172 in Acute Stroke Treatment. [#]The severity of depressive symptoms was tested by SADQ-H at baseline and SADQ at 3 months. There was collinearity between SADQ-H at baseline and SADQ at 3 months, therefore they were not entered in the analysis concurrently.

since more than half of the patients suffered from aphasia in this sample, the use of the SADQ required the input of nursing staff and/or family members. Therefore, we could not exclude the possibility that nursing staff and family members were unable to distinguish between insomnia, irritability, poor appetite, anxiety, and depressive symptoms, which would cause bias in the incidence of PSD to an uncertain extent.

In this study, aphasia was measured using the AQ that covered complete aphasia, motor aphasia, sensory aphasia, transcortical mixed aphasia, transcortical motor aphasia, transcortical sensory aphasia, anomic aphasia, and conduction aphasia. Aphasia may lead to communication or comprehension difficulties, social avoidance and decreased attention, which is associated with physical dependence in stroke survivors (40). However, this finding was only confirmed in the univariate, but not in the multivariate analyses in this study. It is speculated that the association between aphasia and poor physical independence was moderated by other variables, such as depressive symptoms and severity of stroke. In addition, traditional Confucian culture favors family support and inter-dependence, particularly for family members with illness. For example, 94.8% of patients in this study were living with others. Thus, the strong family support may have offset the association between aphasia and physical dependence.

The association between demographic characteristics and physical dependence in stroke survivors have been inconsistent (41, 42). In this study, only female was independently associated with physical dependence, which is supported by previous findings (43, 44). The gender difference in physical independence in stroke survivors may be related to menstrual cycles, neuro-endocrine regulation and more frequent physical comorbidities, such as diabetes, atrial fibrillation, and coronary heart disease in women with stroke (45). As expected, stroke severity as measured by the NIHSS was positively associated with physical dependence, which is consistent with previous findings (27, 29).

There are several methodological limitations to this study. First, this was a single-center study with relatively small sample size, therefore the findings could not be generalized to all stroke patients in China. Second, depressive symptoms were measured using the SADQ based on the observation by nursing staff or family members. There may be a gap between observer-rated and self-reported measures of depression, although there are a number of self-reported measures specific for aphasia such as the Visual Analogue Mood Scales (VAMS) (46), Visual Analogue Self-Esteem Scales (VASES) (47), Disc Intensity Scale Circles (DISCS) (48), and Dynamic Visual Analogue Mood Scales (D-VAMS) (49). We chose SADQ from the perspective of relatively short items, easy operation and short time. Third, some important variables related to physical dependence, such as the use of medication, treatment adherence, the size and lesions of infarcts and the missing data about aphasia at 3-month, were not evaluated in the 3 months assessment.

In conclusion, physical dependence at 3-month follow up was common in Chinese stroke patients, which was associated with gender, greater PSD and stroke severity. Aphasia was also associated with physical dependence but the relationship was not significant. Our findings call for early and effective depression screening, treatment, and stroke rehabilitation to improve physical outcome and reduce the burden of stroke survivors in China.

AUTHOR CONTRIBUTIONS

SW and C-XW: study design. SW, NZ, YY, Y-ZS, Y-MD, M-FZ, FL, PY, and Y-TX: collection, analysis and interpretation of data. SW, C-XW, and Y-TX: drafting of the manuscript. GU, CN, and Y-TX: critical revision of the manuscript. All coauthors approval of the final version for publication.

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REFERENCES

1. Kotila M, Numminen H, Waltimo O, Kaste M. Post-stroke depression and functional recovery in a population-based stroke register. The Finnstroke study. Eur J Neurol. (1999) 6:309–12. doi: 10.1046/j.1468-1331.1999.630309.x
2. Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Mild depression in young adults with cerebral infarction at long-term follow-up: a population-based study. *Eur J Neurol.* (2005) 12:194–8. doi: 10.1111/j.1468-1331.2004.00937.x
3. Robinson RG, Jorge RE. Post-stroke depression: a review. *Am J Psychiatry* (2016) 173:221–31. doi: 10.1176/appi.ajp.2015.15030363
4. Zhang N, Wang CX, Wang AX, Bai Y, Zhou Y, Wang YL, et al. Time course of depression and one-year prognosis of patients with stroke in mainland China. *CNS Neurosci Ther.* (2012) 18:475–81. doi: 10.1111/j.1755-5949.2012.00312.x
5. House A, Knapp P, Bamford J, Vail A. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. *Stroke* (2001) 32:696–701. doi: 10.1161/01.STR.32.3.696
6. Morris PL, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year poststroke mortality. *Am J Psychiatry* (1993) 150:124–9.
7. Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke* (2006) 37:1379–84. doi: 10.1161/01.STR.0000221815.64093.8c
8. Thomas SA, Lincoln NB. Predictors of emotional distress after stroke. *Stroke* (2008) 39:1240–5. doi: 10.1161/STROKEAHA.107.498279
9. De Ryck A, Fransen E, Brouns R, Geurden M, Peij D, Mariën P, et al. Poststroke depression and its multifactorial nature: results from a prospective longitudinal study. *J Neurol Sci.* (2014) 347:159–66. doi: 10.1016/j.jns.2014.09.038
10. Shehata GA, El Mistikawi T, Al Sayed KR, Hassan HS. The effect of aphasia upon personality traits, depression and anxiety among stroke patients. *J Affect Disord.* (2015) 172:312–4. doi: 10.1016/j.jad.2014.10.027
11. Dhamoon MS, McClure LA, White CL, Lakshminarayan K, Benavente OR, Elkind MS. Long-term disability after lacunar stroke: secondary prevention of small subcortical strokes. *Neurology* (2015) 84:1002–8. doi: 10.1212/WNL.0000000000001331
12. Li Q, Wu H, Yue W, Dai Q, Liang H, Bian H, et al. Prevalence of stroke and vascular risk factors in China: a nationwide community-based Study. *Sci Rep.* (2017) 7:6402. doi: 10.1038/s41598-017-06691-1
13. Nannetti L, Paci M, Pasquini J, Lombardi B, Taiti PG. Motor and functional recovery in patients with post-stroke depression. *Disabil Rehabil.* (2005) 27:170–5. doi: 10.1080/09638280400009378
14. Kunitz SC, Gross CR, Heyman A, Kase CS, Mohr JP, Price TR, et al. The pilot stroke data bank: definition, design, and data. *Stroke* (1984) 15:740–6. doi: 10.1161/01.STR.15.4.740
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
16. Shen M, Jiamei M. Congitive scale in helathy Chinese elderly. *Chin J Gerontol.* (1991) 11:203–7.
17. Brott T, Adams HP, Olinger CP, Marle JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
18. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* (1994) 25:2220–6.
19. Sun TK, Chiu SC, Yeh SH, Chang KC. Assessing reliability and validity of the Chinese version of the stroke scale: scale development. *Int J Nurs Stud.* (2006) 43:457–63. doi: 10.1016/j.ijnurstu.2005.07.004
20. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. 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* (1993) 24:35–41.
21. Zhou Heng LJ, Wang Yong-jun J. The reliability of ischemic stroke subtype classification using the TOAST criteria. *Chin J Intern Med.* (2005) 44:825–7. doi: 10.3760/j.issn:0578-1426.2005.11.011
22. American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc.* (2009) 41:1510–30. doi: 10.1249/MSS.0b013e3181a0c95c
23. Uyttenboogaart M, Stewart RE, Vroomen, P. C, De Keyser J, Luijckx, GJ. Optimizing cutoff scores for the Barthel index and the modified Rankin scale for defining outcome in acute stroke trials. *Stroke* (2005) 36:1984–7. doi: 10.1161/01.STR.0000177872.87960.61
24. Chang Y, Jing X, Junping W. Validation of Chinese version of Stroke Aphasic Depression Questionnaire (SADQ). *Chin J Clin Psychol.* (2006) 14:230–2. doi: 10.3969/j.issn.1005-3611.2006.03.004
25. Sutcliffe LM, Lincoln NB. The assessment of depression in aphasic stroke patients: the development of the stroke aphasic depression questionnaire. *Clin Rehabil.* (1998) 12:506–13. doi: 10.1191/026921598672167702
26. Shewan CM, Kertesz A. Reliability and validity characteristics of the Western Aphasia Battery (WAB). *J Speech Hear Disord.* (1980) 45:308–24.
27. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. *Cerebrovasc Dis.* (2003) 16 (Suppl. 1):14–9. doi: 10.1159/000069936
28. Ji R, Du W, Shen H, Pan Y, Wang P, Liu G, et al. Web-based tool for dynamic functional outcome after acute ischemic stroke and comparison with existing models. *BMC Neurol.* (2014) 14:214. doi: 10.1186/s12883-014-0214-z
29. Yang Y, Shi YZ, Zhang N, Wang S, Ungvari GS, Ng CH, et al. The disability rate of 5-year post-stroke and its correlation factors: a national survey in China. *PLoS ONE* (2016) 11:e0165341. doi: 10.1371/journal.pone.0165341
30. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke* (2014) 9:1017–25. doi: 10.1111/ijs.12357
31. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. *Stroke* (2005) 36:1330–40. doi: 10.1161/01.STR.0000165928.19135.35
32. Towfighi A. Poststroke depression: a scientific statement for healthcare professionals from the american heart association/american stroke association. *Stroke* (2017) 48:e30–43. doi: 10.1161/STR.0000000000000113
33. Kutlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int J Stroke* (2014) 9:1026–36. doi: 10.1111/ijs.12356
34. Kauhanen ML, Korpelainen JT, Hiltunen P, Määttä R, Mononen H, Brusin E, et al. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovasc Dis.* (2000) 10:455–61. doi: 10.1159/000016107
35. Sienkiewicz-Jarosz H, Milewska D, Bochynska A, Chelmniak A, Dworek N, Kasprzyk K, et al. Predictors of depressive symptoms in patients with stroke - a three-month follow-up. *Neurol Neurochir Pol.* (2010) 44:13–20. doi: 10.1016/S0028-3843(14)60402-3
36. Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. *Br J Psychiatry* (1989) 154:170–82. doi: 10.1192/bjp.154.2.170
37. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. *J Neurol Neurosurg Psychiatry* (2014) 85:514–21. doi: 10.1136/jnnp-2013-306448

38. Robinson RG. *The Clinical Neuropsychiatry of Stroke*. Cambridge: Cambridge University Press (2006).
39. Shi YZ, Xiang YT, Yang Y, Zhang N, Wang S, Ungvari GS, et al. Depression after minor stroke: the association with disability and quality of life - a 1-year follow-up study. *Int J Geriatr Psychiatry* (2016) 31:421–7. doi: 10.1002/gps.4353
40. El Hachioui H, Lingsma HF, Van De Sandt-Koenderman, MW, Dippel DW, Koudstaal PJ, Visch-Brink EG. Long-term prognosis of aphasia after stroke. *J Neurol Neurosurg* Psychiatry (2013) 84:310–5. doi: 10.1136/jnnp-2012-302596
41. Fahey M, Crayton E, Wolfe C, Douiri A. Clinical prediction models for mortality and functional outcome following ischemic stroke: a systematic review and meta-analysis. *PLoS ONE* (2018) 13:e0185402. doi: 10.1371/journal.pone.0185402
42. Rempe DA. Predicting outcomes after transient ischemic attack and stroke. *Cerebrovasc Dis.* (2014) 20:412–28. doi: 10.1212/01.CON.0000446110.97667.58
43. Glader EL, Stegmayr B, Norrving B, Terént A, Hulter-Asberg K, Wester, PO, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke* (2003) 34:1970–5. doi: 10.1161/01.STR.0000083534.81284.C5
44. Liu X, Lv Y, Wang B, Zhao G, Yan Y, Xu D. Prediction of functional outcome of ischemic stroke patients in northwest China. *Clin Neurol Neurosurg.* (2007) 109:571–7. doi: 10.1016/j.clineuro.2007.05.008
45. Wang Z, Li J, Wang C, Yao X, Zhao X, Wang Y, et al. Gender differences in 1-year clinical characteristics and outcomes after stroke: results from the China National Stroke Registry. *PLoS ONE* (2013) 8:e56459. doi: 10.1371/journal.pone.0056459
46. Stern RA, Arruda JE, Hooper CR, Wolfner GD, Morey CE. Visual analogue mood scales to measure internal mood state in neurologically impaired patients: description and initial validity evidence. *Aphasiology* (1997) 11:59–71. doi: 10.1080/02687039708248455
47. Brumfitt SM, Sheeran P. The development and validation of the Visual Analogue Self-Esteem Scale (VASES). *Br J Clin Psychol.* (1999) 38 (Pt 4):387–400.
48. Turner-Stokes L. (2005). The Depression Intensity Scale Circles (DISCs): a first evaluation of a simple assessment tool for depression in the context of brain injury. *J Neurol Neurosurg Psychiatry* 76:1273–8. doi: 10.1136/jnnp.2004.050096
49. Barrows PD, Thomas SA. Assessment of mood in aphasia following stroke: validation of the Dynamic Visual Analogue Mood Scales (D-VAMS). *Clin Rehabil.* (2018) 32:94–102. doi: 10.1177/0269215517714590

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Association Between Cerebral Hypoperfusion and Cognitive Impairment in Patients With Chronic Vertebra-Basilar Stenosis

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Objective: This study aimed to investigate the association between cognitive impairment and cerebral haemodynamic changes in patients with chronic vertebra-basilar (VB) stenosis.

Methods: Patients with severe posterior circulation VB stenosis and infarction or a history of infarction for more than 2 weeks from January 2014 to January 2015 were enrolled ($n = 96$). They were divided into three groups, namely, the computed tomography perfusion (CTP) normal group, the CTP compensated group, and the CTP decompensated group. Cognitive function was assessed using a validated Chinese version of the Mini-Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Regression models were used to identify independent risk factors for cognitive impairment.

Results: The MMSE and FAB scores of patients in the CTP decompensated group were significantly lower than those of patients in the CTP normal and CTP compensated groups (all $p < 0.05$). The RBANS total and its domain scores, including immediate memory, visual acuity, and delayed memory, in the CTP compensated and CTP decompensated groups were significantly lower than those in the CTP normal group (all $p < 0.05$). Multiple regression analyses showed that CTP compensation, CTP decompensation, severe VB tandem stenosis, and multiple infarctions were independent risk factors for cognitive impairment.

Conclusions: Low perfusion caused by severe VB stenosis can lead to extensive cognitive impairments in areas such as immediate memory, visual span, and delayed memory.

Keywords: vertebra-basilar stenosis, cognitive impairment, cerebral hypoperfusion, cerebral infarction, stroke

INTRODUCTION

Neurocognitive function changes with age (1) and disease progression (2–4), which is related to pathologic mechanisms and is easily examined clinically. Carotid artery stenosis is closely related to vascular cognitive impairment (VCI) (5). Carotid artery stenosis can not only directly lead to the occurrence and rapid progression of VCI but also accelerate the development of degenerative diseases, such as Alzheimer's disease (6). Because of the collateral circulation in cerebral arteries, stenosis at the same site may cause different levels of cerebral blood flow perfusion. Studies have found that changes in cerebral flow perfusion were related to VCI in patients with carotid artery stenosis. Hypoperfusion caused by carotid artery stenosis can lead to frontal lobe damage, which in turn reduces the attention, language fluency, spatial structure, short-term memory, and executive function of patients (7). Compared with studies of VCI induced by carotid artery stenosis, few studies have examined the contribution of the posterior circulation or vertebra-basilar (VB) artery stenosis to cognitive impairment. Additionally, the correlation between cerebral blood flow perfusion and VCI in patients with VB artery stenosis remains unclear.

The stroke recurrence rate of the VB artery is reported to be relatively high (8, 9). For strokes in the posterior circulation or VB artery, transient ischaemic attack (TIA) accounts for ∼20% of ischaemic stroke cases (10). The clinical presentation of posterior circulation ischaemic strokes is unapparent and differs from those of anterior circulation or carotid artery strokes. Consequently, this type of stroke is often hidden (11). Manifestations such as vertigo, diplopia, and coughing while drinking water are generally ignored by patients. In contrast, anterior circulation symptoms, such as facial or limb paralysis, are often more likely to be noted (12).

Basilar artery stenosis may lead to poor attention, poor executive function, and long-term memory impairment in patients (13). In this study, computed tomography perfusion (CTP) was used to analyse the relationship between cognitive impairment and cerebral haemodynamic changes. We aimed to investigate the cognitive status of patients with chronic posterior circulation hypoperfusion, which, to our best knowledge, has received little systemic investigation.

MATERIALS AND METHODS

Subjects

This study was a prospective cohort study (Clinical Trial Registration URL: http://www.clinicaltrials.gov. Unique identifier: NCT01968122.). All methods were performed in accordance with the relevant guidelines and regulations. A total of 96 patients who were diagnosed with severe posterior circulation VB stenosis and had infarction or a history of infarction for more than 2 weeks from January 2014 to January 2015 were enrolled in the current study. The inclusion criteria were as follows: (1) Patients who had vertebral artery or basilar artery stenosis confirmed by CT angiography (CTA) or digital subtraction angiography (DSA) examination, with a stenosis area equal to or greater than 70% of the vascular area (14–18). In this study, 70% of patients underwent CTA examination, 50% underwent DSA examination, and 20% underwent CTA and DSA examination. (2) Cranial magnetic resonance imaging (MRI) showed that the area of nonlacunar infarction [multiple infarctions, high signal greater than or equal to two diffusion-weighted imaging (DWI) images] was $<1/3$ of the hemisphere area. The exclusion criteria were as follows: (1) patients who failed to complete the scale evaluation due to aphasia, apraxia, and dysphonia; (2) patients who had cognitive impairment caused by Alzheimer's disease and other related nervous system degeneration or nonvascular factors; (3) patients who had nervous system diseases (such as central nervous system hereditary diseases, tumors, encephalitis, demyelinating disease, Parkinson's disease, craniocerebral injury, and epilepsy) that could lead to cognitive impairment; (4) patients who had anxiety, depression, or other mental disorders; (5) patients who had severe diseases of the liver, kidney, heart, or blood; (6) patients who had hypothyroidism, chronic alcoholism, infection, or other cognitive function-related diseases; (7) patients who had a history of substance abuse, drug addiction, carbon monoxide, pesticide, and other chemical poisoning, brain parasites, etc.; and (8) patients whose first-degree relatives had dementia and psychosis, cerebral lacuna infarct, or leukodystrophy revealed by brain MRI examination. The recruitment diagram is shown in **Figure 1**. After a complete description of the study, all subjects gave their written informed consent to participate in the study. This study was approved by the Regional Committee for Ethics of Beijing Tiantan Hospital.

Baseline Data Assessment

The patients were divided into three groups: the CTP normal group, CTP compensated group, and CTP decompensated group (19). Baseline information, including gender, age, length of education, left- or right-handedness, high blood pressure, diabetes, atrial fibrillation, and smoking, was collected. Information on patient history of hypertension, diabetes, and hyperlipidaemia was recorded. Briefly, blood pressure $\geq$140/90 mm Hg (1 mm Hg = 0.133 kPa) was defined as hypertension, and fasting blood glucose $\geq$7.0 mmol/L, 2 h postprandial blood glucose $\geq$11.1 mmol/L or random blood glucose $\geq$11.1 mmol/L were defined as diabetes. Atrial fibrillation was diagnosed according to the 1979 World Health Organization (WHO) diagnostic criteria. Hyperlipidaemia was diagnosed based on the "Chinese Adult Dyslipidaemia Prevention and Control Guidelines" from 2007. Hyperlipidaemia was diagnosed when the patients met one of the following criteria: blood cholesterol concentration $>$5.17 mmol/L; blood concentration

Abbreviations: VB, Vertebra-Basilar; CTP, Computed Tomography Perfusion; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; RBANS, Repeatable Battery For The Assessment Of Neuropsychological Status; VCI, Vascular Cognitive Impairment; TIA, Transient Ischaemic Attack; CTA, Ct Angiography; DSA, Digital Subtraction Angiography; DWI, Diffusion-Weighted Imaging; MRI, Magnetic Resonance Imaging; TTP, Time To Peak; MTT, Transit Time; CBF, Cerebral Blood Flow; CBV, Cerebral Blood Volume; PCA, Posterior Cerebral Arteries; PCI, Percutaneous Coronary Intervention.

of triglycerides >1.7 mmol/L; or blood concentration of low-density lipoproteins >3.1 mmol/L.

Cognitive Function Evaluation

Cognitive function was assessed using the validated Chinese version of the Mini-Mental State Examination (C-MMSE) (20), the Frontal Assessment Battery (FAB) (21), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (22). Three researchers participated in a cognitive function training course before the study started. Repeated evaluations showed that the overall correlation coefficient of the MMSE, FAB, and RBANS for the three researchers was >0.8 after training. Finally, an RBANS total score >77.5 was defined as cognitively normal, and an RBANS total score ≤77.5 was defined as cognitively impaired (23).

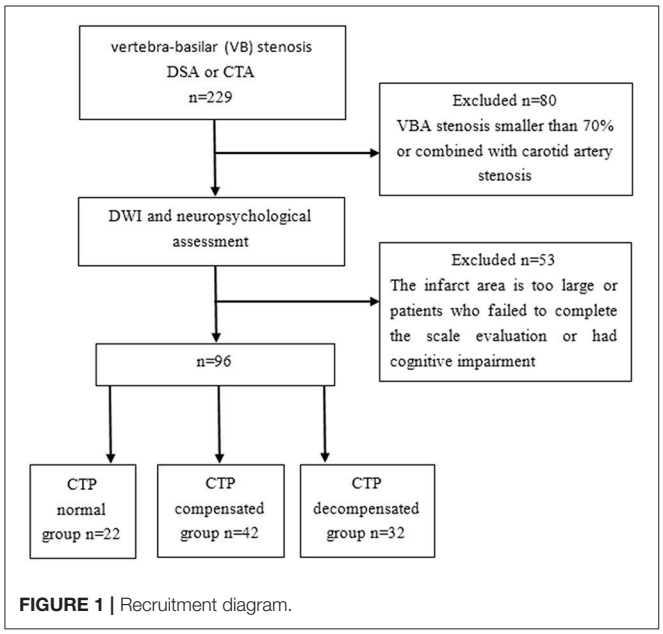

FIGURE 1 | Recruitment diagram.

Imaging Evaluation

Posterior circulation acute ischaemic infarction (including cerebral infarction) was diagnosed in patients with clinical manifestations. Additionally, such patients had high-density lesions on magnetic resonance DWI or TIA in the posterior circulation. CTP was performed using a Siemens dual-source spiral CT machine with 128 layers (Germany). Briefly, a volume of 60 mL of contrast agent (iohexol, 370 mg I/mL) was injected into the elbow middle vein at a rate of 8 mL/s using a double-tube high-pressure syringe (Ulrich Missouvi XD2501-C), and a volume shuttle scan with a scanning range of ∼110 mm was started after a delay of 4 s. Intravenous injection of iohexol was performed using an EZEM high-pressure syringe (America) at a rate of 5 mL/s. The base section plane was selected, and two layers were continuously scanned 40 times with the parameters of 80 kV, 200 mA, layer thickness 12 mm, and pitch 0.75. Forty images in each layer were scanned, and a total of 80 images were obtained. Four images of the temporal lobe and 4 images of the occipital lobe were selected from each layer image as the region of interest (ROI). The original CTP image was introduced into a dedicated postprocessing workstation (Neusoft Medical Co., Shenyang, China) and analyzed with CT perfusion software. Time to peak (TTP), transit time (MTT), cerebral blood

TABLE 1 | Sociodemographic and clinical characteristics of the subjects ($n = 96$).

Sociodemographic variables	Total cases ($n = 96$)	Group I ($n = 22$)[a]	Group II ($n = 42$)[b]	Group III ($n = 32$)[c]	*P*
SOCIODEMOGRAPHIC VARIABLES					
Age, years	62.2 ± 11.8	60.9 ± 11.5	63.1 ± 12.1	61.9 ± 11.9	0.772
Male sex (%)	74 (77.1)	16 (72.7)	34 (81.0)	24 (75.0)	0.715
Education, years	7.3 ± 2.4	7.6 ± 2.6	7.2 ± 2.4	7.3 ± 2.4	0.800
Hypertension (%)	50 (52.1)	12 (54.5)	20 (47.6)	18 (56.3)	0.737
Diabetes mellitus (%)	36 (37.5)	8 (36.4)	14 (33.3)	14 (43.8)	0.652
Atrial fibrillation (%)	6 (6.3)	0	4 (9.5)	2 (6.3)	0.327
Cigarette smoking (%)	56 (58.3)	14 (63.6)	24 (57.1)	18 (56.3)	0.845
Hyperlipidaemia (%)	46 (47.9)	8 (36.4)	18 (42.9)	20 (62.5)	0.114
LESION SITE					
Basilar artery stenosis (%)	46 (47.9)	6 (27.3)	22 (52.4)	18 (56.3)	0.083
Intracranial artery stenosis (%)	38 (39.6)	6 (27.3)	18 (42.9)	14 (43.8)	0.404
Extracranial artery stenosis (%)	32 (33.3)	16 (72.7)	6 (14.3)*	10 (31.3)	0.000
Tandem lesion (%)	20 (20.8)	6 (27.3)	4 (9.5)	10 (31.3)	0.052
INFARCT PATTERN					
No new infarct (%)	12 (12.5)	4 (18.2)	6 (14.3)	2 (6.3)	0.550
Single infarct (%)	56 (58.3)	12 (54.5)	26 (61.9)	18 (56.3)	
Multiple infarction (%)	28 (29.2)	6 (27.3)	10 (23.8)	12 (37.5)	

[a]*Group I, CTP normal group;* [b]*Group II, CTP compensated group;* [c]*Group III, CTP decompensated group. *P < 0.05, compared with group I.*

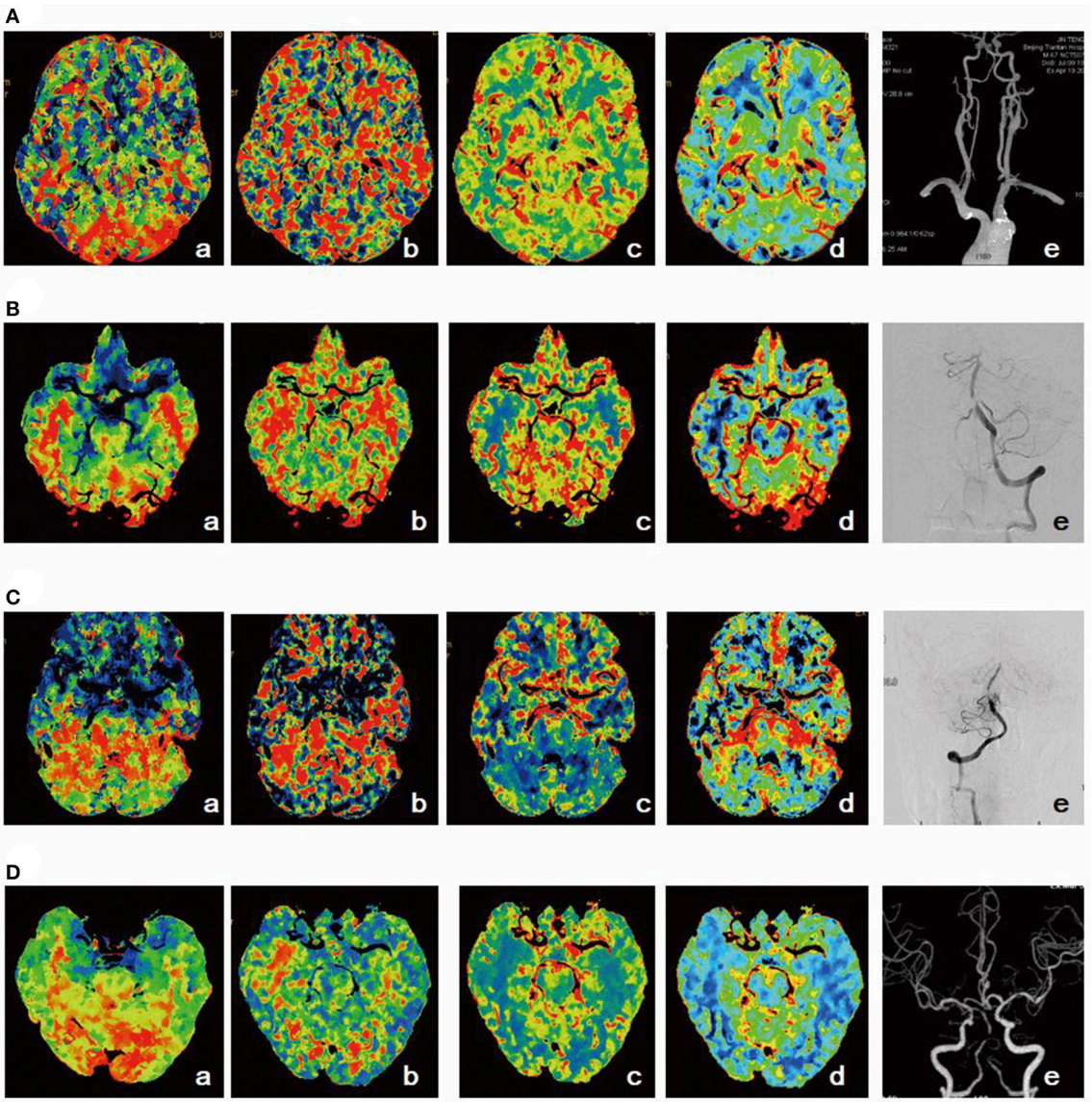

FIGURE 2 | Schematic diagram of posterior circulation perfusion. **(A)** Stage I1: TTP was prolonged (a), MTT (b), CBF (c), and CBV (d) were normal, and CTA suggested severe stenosis of the left vertebral artery opening (e). **(B)** Stage I2: TTP (a) and MTT (b) were prolonged, CBF was slightly decreased (c), CBV was elevated (d), and DSA indicated severe proximal stenosis of the basilar artery (e). **(C)** Stage I3: TTP (a) and MTT (b) were prolonged, CBF was decreased (c), CBV was slightly decreased (d), and DSA indicated severe stenosis in the middle part of the basilar artery (e). **(D)** Stage I4: TTP (a) and MTT (b) were prolonged, CBF was decreased (c), CBV was decreased (d), and CTA demonstrated occlusion in the middle part of the basilar artery (e).

flow (CBF), and cerebral blood volume (CBV) were calculated. The qualitative assessment of perfusion in the ROI, which was used in a previous study (14), was grouped as follows. The patients in the CTP normal group had complete perfusion. The patients in the CTP compensated group had hypoperfusion and preserved cerebral vascular reactivity (a lower peak, delayed TTP, increased MTT, decreased CBF, and normal or elevated CBV). In addition, the patients in the CTP decompensated group had hypoperfusion without adequate cerebral vascular reactivity.

Statistical Analysis

All statistical analyses were performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical variables of the multiple groups were compared using one-way ANOVA for continuous variables and X^2 (chi-square test) or Fisher's exact test for categorical variables. Where there was significance in the ANOVA, we used the Fisher minimum significant difference (LSD) test for *post hoc* comparisons between groups.

TABLE 2 | The association between MMSE, FAB, and RBANS scores and CT perfusion.

Cognitive evaluation	Group I[a]	Group II[b]	Group III[c]	*p*
MMSE score	25.29 ± 3.16	24.14 ± 1.73	20.37 ± 3.89*Δ	0.000
FAB score	16.25 ± 3.44	15.46 ± 4.12	13.08 ± 4.72*Δ	0.013
RBANS score	80.84 ± 14.77	70.80 ± 9.65*	58.94 ± 11.14*Δ	0.000
Immediate memory	85.54 ± 11.09	68.76 ± 18.33*	58.85 ± 14.52*Δ	0.000
Visuospatial/constructional function	83.23 ± 15.80	71.59 ± 14.68*	62.96 ± 15.00*Δ	0.000
Language	82.00 ± 9.61	81.87 ± 10.07	79.74 ± 10.64	0.614
Attention	87.97 ± 9.21	73.40 ± 14.52*	76.18 ± 12.74*	0.000
Delayed memory	87.33 ± 10.88	71.68 ± 12.32*	62.91 ± 13.9*Δ	0.000

*[a]Group I, CTP normal group; [b]Group II, CTP compensated group; [c]Group III, CTP decompensated group. *P < 0.05, compared with group I. ΔP < 0.05, compared with group II. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.*

TABLE 3 | Regression models of independent risk factors for cognitive impairment.

	Cognitive impairment	No cognitive impairment	Regression coefficient	*t*	*P*
Compensation (%)[a]	34 (50)	8 (29)	3.313	2.241	0.030
Decompensation (%)[a]	30 (44)	2 (7)	6.425	4.415	<0.001
Series or multiple stenosis (%)[b]	16 (24)	4 (14)	3.524	2.573	0.021
Multiple infarction (%)[c]	20 (30)	8 (22)	3.276	2.689	0.023

[a]Adjusted for age, sex, hypertension, diabetes, atrial fibrillation, cigarette smoking, hyperlipidaemia, lesion site, and infarct pattern; [b]Adjusted for age, sex, hypertension, diabetes, atrial fibrillation, cigarette smoking, hyperlipidaemia, perfusion type, and infarct pattern; [c]Adjusted for age, sex, hypertension, diabetes, atrial fibrillation cigarette smoking, hyperlipidaemia, perfusion type, and lesion site.

A linear regression model was used to identify risk factors for cognitive impairment in patients with VB artery stenosis. $P < 0.05$ was considered statistically significant.

RESULTS

Sociodemographic Data and Clinical Background Characteristics

A total of 96 patients were ultimately included in this study. Among them, 46 patients had severe basilar artery stenosis, 38 patients had severe intracranial artery stenosis, 32 patients had vertebral artery extracranial stenosis, 20 patients had tandem lesions, 12 patients had no new infarct (TIA), 56 patients had a single infarct, and 28 patients had multiple infarctions. The number of patients in the CTP normal group, CTP compensated group, and CTP decompensated group was 22, 42, and 32, respectively. There were no differences in the sociodemographic characteristics between the three groups (all $p > 0.05$). The rate of intracranial artery stenosis in the CTP compensated group was lower than that in the CTP normal group, ($p < 0.05$); however, the rate of intracranial artery stenosis in the CTP decompensated group was higher than that of the normal group (**Table 1**).

Association Between MMSE, FAB, and RBANS Scores and CT Perfusion

The stages of posterior circulation perfusion are summarized in **Figure 2** in the order of cognitive decline.

As presented in **Table 2**, the MMSE, FAB, and RBANS scores of the CTP decompensated group were significantly lower than those of the CTP normal and CTP compensated groups (all $p < 0.05$). The RBANS total, immediate memory, visual acuity, and delayed memory scores in the CTP compensated and CTP decompensated groups were significantly lower than those in the CTP normal group ($p < 0.05$). CTP compensated patients had reduced attention compared to that of CTP normal patients ($p < 0.05$).

Regression Models of Independent Risk Factors for Cognitive Impairment

Based on the RBANS total score, 68 patients were included in the cognitive impairment group (RBANS score ≤77.5), and 28 patients were considered to have no cognitive impairment (RBANS score >77.5 points). After adjusting for other relevant factors, CTP compensation ($p = 0.30$), CTP decompensation ($p < 0.01$), severe VB tandem stenosis ($p = 0.021$), and multiple infarctions ($p = 0.023$) were found to be independent risk factors for cognitive impairment (**Table 3**).

DISCUSSION

The primary findings of this study could be summarized as follows: (A) patients who have chronic posterior circulation hypoperfusion showed a decline in cognitive ability; (B) medial temporal lobe perfusion was associated with serious cognitive impairment; (C) in addition to language ability, there were other dimensions of cognitive impairment; and (D) in patients with chronic posterior circulation hypoperfusion, multiple stenosis and multiple infarcts were independent risk factors for cognitive impairment.

The basilar artery branches into two posterior cerebral arteries (PCA), which supply the majority of blood to the temporal lobe and thalamus. Previous studies found that cognitive impairment existed in patients with infarcts in these regions (24–26). In

our study, the cognitive ability of patients with low-perfusion percutaneous coronary intervention (PCI) generally decreased, which might be associated with chronic ischaemia and hypoxia of the brain structures mentioned above. Studies showed that the state of ischaemia and hypoxia was associated with damage to the neural network between the brainstem or cerebellar regions and the anterior circulation (25–27). Low perfusion leads to a decrease in thrombus clearance; additionally, the formation of microemboli that result from lesions caused by cerebral vascular stenosis also leads to VCI (28). In animal studies, microemboli were found to decrease the number of brain-derived neurotrophic factors in the hippocampus and lead to impaired memory in mice (29).

In our study, the executive function, immediate memory, delayed memory, and visual range of patients with PCI accompanied by hypoperfusion were impaired, which is in agreement with previous findings (30, 31). However, the language function of these patients was retained in our study, which is inconsistent with previous studies (31, 32). In these patients, the memory function, including short-term memory and delayed memory, was severely damaged, which might be related to long-term ischaemia and hypoxia of the medial temporal lobe structures. The efferent fibers and afferent fibers of the temporal lobe have a wide range of links with the frontal lobe, parietal lobe, occipital lobe, and hippocampus (33). The hippocampus plays an important role in mood, neuropsychological activities, memory, execution, language (including fluency and repetition), and other cognitive activities (34). Memory impairment may occur before stroke, which might be associated with the chronic ischaemia and hypoxia caused by the hypoperfusion of the medial temporal lobe (34). Executive function impairment may be caused by damage in part of the tissues of the VB artery, whose function is linked to the thalamus, parietal lobe, and frontal lobes (25, 26, 35, 36). Visual span impairment might be associated with chronic ischaemia and hypoxia in the occipital lobe and temporal lobe (19, 37). Further multifactor logistic regression analysis revealed that low perfusion of blood supply areas, tandem, or multiple stenosis, and multiple PCI were independent risk factors for cognitive impairment in patients with PCI. Both CTP compensated and CTP decompensated patients had cognitive impairment. The incidence of cognitive impairment in CTP decompensated patients was 6.8 times higher than that observed in the normal metabolic patients. A previous study found that the prognostic MRS score of patients with PCI was significantly higher than that of patients with anterior circulation infarction (38). Although the neurological function of patients with PCI recovers well, their cognitive function is likely to suffer sustained damage if the collateral circulation is not sufficient or chronic hypoperfusion is persistent. Tandem lesions or multiple stenosis can lead to a further decrease in perfusion in the posterior circulation area (39). The presence of chronic persistent hypoperfusion can lead to multiple infarcts in the brain, which also aggravates the cognitive impairment of patients (40). It was reported that in first-onset mild stroke patients, the occurrence of multiple infarcts and decreased hippocampal volume were positively correlated with cognitive impairment (41). Even in patients with asymptomatic stroke, multiple infarcts caused by hypoperfusion or microemboli also led to reduced hippocampal volume, resulting in decreased memory. In addition, multiple cerebral infarctions led to declines in language function, processing speed, and visual spatial competence (42).

The present study has some limitations. First, the RBANS was performed by only a single independent reviewer; therefore, there was some subjectivity in the judgement of graphic memory. Second, a small number of patients had carotid artery stenosis. As a result, these patients may be affected by cognitive effects due to anterior circulation cerebral hypoperfusion. Third, the sample size of the study is relatively small, which limits the generalizability of the results. Hence, the conclusions must be further confirmed with a larger sample size. In the future, we will design different experiments related to neurocognitive function (43, 44) and use various analytical methods to explore the pathologic mechanisms of neurocognitive deficits in patients.

AUTHOR CONTRIBUTIONS

YD and LW: analyzed and interpreted the data, wrote the paper. XS, LL, MZ, and CW: contributed to the conception or design of the work, interpreted the data. BS, MS, WG, and DM: conceived and designed the experiments, performed the experiments. NM, LS, XL, ZM, and XH: performed the experiments, drafted and revised the work. DC and FG: revised the paper, approved the final version.

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REFERENCES

1. Wang LY, Wang WH, Yan TY, Song JY, Yang WP, Wang B, et al. Beta- band functional connectivity influences audiovisual integration in older age: an EEG study. *Front Aging Neurosci.* (2017) 9:239. doi: 10.3389/fnagi.2017.00239
2. Deng YM, Chen DD, Wang LY, Gao F, Sun X, Liu L, et al. Visual field impairment predicts recurrent stroke after acute posterior circulation stroke and transient ischemic attack. *CNS Neurosci Therap.* (2018) 24:154–61. doi: 10.1111/cns.12787
3. Wang B, Niu Y, Miao LW, Cao R, Yan PF, Guo H, et al. Decreased complexity in Alzheimer's disease: resting-state fMRI evidence of brain entropy mapping. *Front Aging Neurosci.* (2017) 9:378. doi: 10.3389/fnagi.2017.00378
4. Yan TY, Wang WH, 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) 8:3237–55. doi: 10.7150/thno.23772
5. Pucite E, Krievina I, Miglane E, Erts R, Krievins D. Influence of severe carotid stenosis on cognition, depressive symptoms and quality of life. *Clin Pract Epidemiol Ment Health* (2017) 13:168–80. doi: 10.2174/1745017901713010168
6. Scherr M, Trinka E, Mc Coy M, Krenn Y, Staffen W, Kirschner M, et al. Cerebral hypoperfusion during carotid artery stenosis can lead to cognitive deficits that may be independent of white matter lesion load. *Curr Neurovasc Res.* (2012) 9:193–9. doi: 10.2174/156720212801619009
7. Duering M, Gonik M, Malik R, Zieren N, Reyes S, Jouvent E, et al. Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. *Neuroimage* (2013) 66:177–83. doi: 10.1016/j.neuroimage.2012.10.084
8. Zhu J, Wang Y, Li J, Deng J, Zhou H. Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease. *Neurology* (2014) 82:842–9. doi: 10.1212/wnl.0000000000000185
9. Gulli G, Khan S, Markus HS. Vertebrobasilar stenosis predicts high early recurrent stroke risk in posterior circulation stroke and TIA. *Stroke* (2009) 40:2732–7. doi: 10.1161/strokeaha.109.553859
10. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol.* (2007) 6:1063–72. doi: 10.1016/s1474-4422(07)70274-0
11. Emsley HCA. Posterior circulation stroke: still a Cinderella disease. *Br Med J.* (2013) 346:F3552. doi: 10.1136/bmj.f3552
12. Merwick A, Werring D. Posterior circulation ischaemic stroke. *Br Med J.* (2014) 348:g3175. doi: 10.1136/bmj.g3175
13. Floßmann E, Rothwell PM. Prognosis of vertebrobasilar transient ischaemic attack and minor stroke. *Brain* (2003) 126:1940–54. doi: 10.1093/brain/awg197
14. Campanholo KR, Conforto AB, Rimkus CM, Miotto EC. Cognitive and functional impairment in stroke survivors with basilar artery occlusive disease. *Behav Neurol.* (2015) 2015:971514. doi: 10.1155/2015/971514
15. Griffiths PD, Worthy S, Gholkar A. Incidental intracranial vascular pathology in patients investigated for carotid stenosis. *Neuroradiology* (1996) 38:25–30. doi: 10.1007/bf00593211
16. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation* (2006) 113:555–63. doi: 10.1161/CIRCULATIONAHA.105.578229
17. Miao Z, Zhang Y, Shuai J, Jiang C, Zhu Q, Chen K, et al. Thirty-day outcome of a multicenter registry study of stenting for symptomatic intracranial artery stenosis in china. *Stroke* (2015) 46:2822–9. doi: 10.1161/STROKEAHA.115.010549
18. Radak D, Babic S, Sagic D, Tanaskovic S, Kovacevic V, Otasevic P. Endovascular treatment of symptomatic high-grade vertebral artery stenosis. *J Vasc Surg.* (2014) 60:92–7. doi: 10.1016/j.jvs.2014.01.023
19. Chen YH, Lin MS, Lee JK, Chao CL, Tang SC, Chao CC, et al. Carotid stenting improves cognitive function in asymptomatic cerebral ischemia. *Int J Cardiol.* (2012) 157:104–7. doi: 10.1016/j.ijcard.2011.10.086
20. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients wit. *J Am Coll Cardiol.* (2006) 48:854. doi: 10.1161/CIRCULATIONAHA.106.177292
21. Katzman R, Zhang MY, Qu O-Y, Wang ZY, Liu WT, Yu E, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. *J Clin Epidemiol.* (1988) 41:971–8. doi: 10.1016/0895-4356(88)90034-0
22. Mok VC, Wong A, Yim P, Fu M, Lam WW, Hui AC, et al. The validity and reliability of Chinese frontal assessment battery in evaluating executive dysfunction among Chinese patients with small subcortical infarct. *Alzheimer Dis Assoc Disord.* (2004) 18:68–74. doi: 10.1097/01.wad.0000126617.54783.7
23. Wang JH, Li CB, Cheng Y, Yi ZH, Long B, Wang JJ. Reliability and validity of repeatable battery for the assessment of neuropsychological status (RBANS) in schizophrenic patients: a preliminary study. Shanghai *Arch Psychiatry* (2009) 21:265–8. doi: 10.5114/aoms.2011.25561
24. Huang CC, Chen YH, Lin MS, Lin CH, Li HY, Chiu MJ, et al. Association of the recovery of objective abnormal cerebral perfusion with neurocognitive improvement after carotid revascularization. *J Am Coll Cardiol.* (2013) 61:2503–9. doi: 10.1016/j.jacc.2013.02.059
25. Hoffmann M, Schmitt F. Cognitive impairment in isolated subtentorial stroke. *Acta Neurol Scand.* (2004) 109:14–24. doi: 10.1034/j.1600-0404.2003.00169.x
26. Hoffmann M, Cases LB. Etiology of frontal network syndromes in isolated subtentorial stroke. *Behav Neurol.* (2008) 20:101–5. doi: 10.3233/ben-2008-0220
27. Ju Y, Hussain M, Asmaro K, Zhao X, Liu L, Li J, et al. Clinical and imaging characteristics of isolated pontine infarcts: a one-year follow-up study. *Neurol Res.* (2013) 35:498–504. doi: 10.1179/1743132813y.0000000207
28. Hitchner E, Baughman BD, Soman S, Long B, Rosen A, Zhou W. Microembolization is associated with transient cognitive decline in patients undergoing carotid interventions. *J Vasc Surg.* (2016) 64:1719–25. doi: 10.1016/j.jvs.2016.06.104
29. Li W, Han T, Qin W, Zhang J, Liu H, Li Y, et al. Altered functional connectivity of cognitive-related cerebellar subregions in well-recovered stroke patients. *Neural Plast.* (2013) 2013:452439. doi: 10.1155/2013/452439
30. Himi N, Takahashi H, Okabe N, Nakamura E, Shiromoto T, Narita K, et al. Exercise in the early stage after stroke enhances hippocampal brain-derived neurotrophic factor expression and memory function recovery. *J Stroke Cerebrovasc Dis.* (2016) 25:2987–94. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.017
31. Park KC, Yoon SS, Rhee HY. Executive dysfunction associated with stroke in the posterior cerebral artery territory. *J Clin Neurosc.* (2011) 18:203–8. doi: 10.1016/j.jocn.2010.05.026
32. Martinaud O, Pouliquen D, Gérardin E, Loubeyre M, Hirsbein D, Hannequin D, et al. Visual agnosia and posterior cerebral artery infarcts: an anatomical-clinical study. *PLoS ONE* (2012) 7:e30433. doi: 10.1371/journal.pone.0030433
33. Capitani E, Laiacona M, Pagani R, Capasso R, Zampetti P, Miceli G. Posterior cerebral artery infarcts and semantic category dissociations: a study of 28 patients. *Brain* (2009) 132:965–81. doi: 10.1093/brain/awp013
34. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. *Lancet Neurol.* (2003) 2:89–98. doi: 10.1016/S1474-4422(03)00305-3
35. Graff-Radford NR, Damasio H, Yamada T, Eslinger PJ, Damasio AR. Nonhaemorrhagic thalamic infarction: clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. *Brain* (1985) 108:485–516.
36. Glickstein M, Doron K. Cerebellum: connections and functions. *Cerebellum* (2008) 7:589–94. doi: 10.1007/s12311-008-0074-4
37. Yan TY, Jin FZ, He JP, Wu JL. Development of a wide-view visual presentation system for visual retinotopic mapping during functional MRI. *J Magnet Reson Imaging* (2011) 33:441–7. doi: 10.1002/jmri.22404
38. Wang Q, Capistrant BD, Ehntholt A, Glymour MM. Long-term rate of change in memory functioning before and after stroke onset. *Stroke* (2012) 43:2561–6. doi: 10.1161/strokeaha.112.661587
39. Guppy KH, Charbel FT, Loth F, Ausman JI. Hemodynamics of in-tandem stenosis of the internal carotid artery: when is carotid endarterectomy indicated? *Surg Neurol.* (2000) 54:145–52. doi: 10.1016/s0090-3019(00)00292-5
40. Hwang J, Kim SJ, Hong JM, Bang OY, Chung CS, Lee KH, et al. Microembolic signals in acute posterior circulation cerebral ischemia sources and consequences. *Stroke* (2012) 43:747–52. doi: 10.1161/strokeaha.111.633438
41. Ng YS, Stein J, Ning M, Black-Schaffer RM. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke* (2007) 38:2309–14. doi: 10.1161/strokeaha.106.475483

42. Kliper E, Bashat DB, Bornstein NM, Shenhar-Tsarfaty S, Hallevi H, Auriel E, et al. Cognitive decline after Stroke. *Stroke* (2013) 44:1433–5. doi: 10.1161/STROKEAHA.111.000536
43. Yan TY, Feng Y, Liu TT, Wang LY, Mu N, Dong XN, et al. Theta oscillations related to orientation recognition in unattended condition: a vMMN Study. *Front Behav Neurosci.* (2017) 11:166. doi: 10.3389/fnbeh.2017.00166
44. Yan TY, Zhao S, Uono S, Bi XS, Tian A, Yoshimura S, et al. Target object moderation of attentional orienting by gazes or arrows. *Attent Percept Psychophys.* (2016) 78:2373–82. doi: 10.3758/s13414-016-1182-8

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The Orbitofrontal Cortex Gray Matter Is Associated With the Interaction Between Insomnia and Depression

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Insomnia and depression are highly comorbid symptoms in both primary insomnia (PI) and major depressive disorder (MDD). In the current study, we aimed at exploring both the homogeneous and heterogeneous brain structure alteration in PI and MDD patients. Sixty-five MDD patients and 67 matched PI patients were recruited and underwent a structural MRI scan. The subjects were sub-divided into four groups, namely MDD patients with higher or lower insomnia, and PI patients with higher or lower severe depression. A general linear model was employed to explore the changes in cortical thickness and volume as a result of depression or insomnia, and their interaction. In addition, partial correlation analysis was conducted to detect the clinical significance of the altered brain structural regions. A main effect of depression on cortical thickness was seen in the superior parietal lobe, middle cingulate cortex, and parahippocampal gyrus, while a main effect of insomnia on cortical thickness was found in the posterior cingulate cortex. Importantly, the interaction between depression and insomnia was associated with decreased gray matter volume in the right orbitofrontal cortex, i.e., patients with co-occurring depression and insomnia showed smaller brain volume in the right orbitofrontal cortex when compared to patients with lower insomnia/depression. These findings highlighted the role of the orbitofrontal cortex in the neuropathology of the comorbidity of insomnia and depression. Our findings provide new insights into the understanding of the brain mechanism underlying comorbidity of insomnia and depression.

Keywords: insomnia, depression, comorbidity, structural MRI, orbitofrontal cortex

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INTRODUCTION

Insomnia represents a common symptom seen in the world population (about 30%), with about 6–10% of the adult population reaching the diagnostic criteria for Primary insomnia (PI) (1). In contrast, major depressive disorder (MDD) is the second cause of disability worldwide, which is to become the world's most frequent and economically burdensome illness by 2030 (2, 3). Sleep complaints, especially the symptom of insomnia, are reported in up to 90% of MDD patients and can profoundly impact both the severity of depression and the course of the illness (4, 5). In addition, about 20% of patients with insomnia suffer from depression (6, 7). Furthermore,

insomnia was found to be a predictor of depression given that non-depressed people with insomnia have a 2-fold risk to develop depression according to a recent meta-analysis of longitudinal epidemiological studies (8). These findings suggest that the link between insomnia and depression is bidirectional. In addition, both antidepressants and hypnotic medication are commonly prescribed to patients with the combined condition of depression and insomnia (9, 10). Therefore, due to the heterogeneity and homogeneity between insomnia and depression, exploring the common and different brain mechanisms underlying such symptoms may help refine existing depression and insomnia treatments and develop personalized treatment for PI and MDD.

In the last decades, accumulating neuroimaging studies suggested PI and MDD to be associated with some functional and structural alterations in the brain of patients (11, 12). For example, Winkelman et al. found that patients with chronic PI reported an increased cortical volume in the rostral anterior cingulate cortex (rACC) when compared to normal sleepers, which was an indication of clinical severity (13). Other studies also reported volumetric differences in the frontal cortex, OFC, parietal cortex, precuneus and hippocampus (14, 15). In contrast, neuroimaging studies in patients with MDD described smaller volumes of the hippocampus, thalamus, insula, frontal lobe, orbitofrontal cortex and rACC (16, 17). However, due to the heterogeneity between the two diseases, such results regarding the structural brain alteration were not always consistent (11, 18). More recently, an increasing number of researchers pay attention on both the common and different brain mechanisms underlying insomnia and depression. For example, Cheng et al. conducted a study on a bit sample of healthy individuals and found an increased functional connectivity in the lateral orbitofrontal cortex (OFC), dorsolateral prefrontal cortex, anterior and posterior cingulate cortex and insula, which was associated with both sleep and depressive scores (19). Furthermore, Liu et al. reported increased amplitude of low-frequency fluctuations (ALFF) during the resting state in the right inferior frontal gyrus and anterior insula in MDD patient with insomnia when compared to MDD patients without insomnia. In addition, they suggested that the abnormal ALFF was associated with sleep disturbance scores (20). Moreover, Li et al. found that patients with PI had reduced gray matter volume in the middle cingulate cortex, which was significantly associated with self-rating for depression score (21). Yang et al. suggested that decreased gray matter volume both in the left lingual gyrus and cerebellum predicts insomnia in female MDD patients (22). Considering the high comorbidity of insomnia and depression in the two neuropsychiatric disorders, only a few study have investigated their interaction effect on brain structure in both PI and MDD patients.

In the present study, we aimed at exploring the potential brain mechanism underlying the comorbidity of insomnia and depression using structural magnetic resonance imaging (MRI). First, we detected the main and the interaction effects of insomnia and depression on brain cortical thickness and volume in four heterogeneous subgroups of patients, i.e., MDD patients with higher or lower insomnia (MDD-HI or MDD-LI), and PI patients with higher or lower depression (PI-HD or PI-LD). Second, we explored the clinical association between the influenced brain regions in each group. Based on previous neuroimaging finding on PI and MDD (21, 23, 24), we hypothesized that the prefrontal cortex, especially the OFC and the anterior cingulate cortex, would be influenced by the interaction between insomnia and depression.

METHODS AND MATERIALS

Participants

The present study is a preliminary and retrospective research, the enrollment is separately for MDD and PI group. All participants were recruited from the outpatient of department of neurology and psychiatry of the Chengdu University of Traditional Chinese Medicine (CDUTCM). We selected sixty-five MDD patients and 67 age-, gender-, and education-matched PI patients (**Table 1**). This study was approved by the Research Ethics Committee of CDUTCM and all participants gave written informed consent. The following eligibility criteria were considered for MDD patients: (1) Met the diagnostic criteria for MDD according to the Diagnostic Statistical Manual of Mental Disorder, fourth Edition (DSM-IV); (2) the Hamilton Rating Scale for Depression-17 (HAMD) score was equal or above 17; (3) Naïve to antidepressant medications or a washout period of at least five half-lives of the previously prescribed medicine was undergone (25, 26); (4) Age between 18 and 55; and (5) Age at onset was <50 years. The following inclusion criteria were considered for PI patients: (1) Met the diagnostic criteria for PI according to the DSM-IV; (2) complaints of difficulty of falling asleep, maintaining sleep or early awakening for at least 3 months; (3) Age between 18 and 55; and (4) Age at onset was <50 years. The exclusion criteria for all patients included: (1) a history of other major psychiatric disorders or a neurological illness history, except for anxiety in the current state; (2) substance abuse, including caffeine, nicotine, and alcohol (27); (3) any brain lesions found by a T2 MRI scan.

Behavior Assessment and Subgroup Division

All participants underwent both a clinical and a behavioral assessment, while a neuropsychiatric examination was performed by two experienced neurologists (SY and ZS) who reached a consensus diagnosis. The HAMD for depression severity, the Hamilton Rating Scale for Anxiety (HAMA) for anxiety evaluation, and the HAMD sleep subscale (HAMD-S) for insomnia evaluation were used for assessing MDD patients. Following, according to the HAMD-S score, the MDD group was divided into the MDD subgroup with higher insomnia (MDD-HI, HAMD-S score >3) and the MDD subgroup with lower insomnia (MDD-LD, HAMD-S score <3) (20, 28, 29). Given that 5 MDD patients reported a HAMD-S score equal to 3, they were excluded from the statistical analysis. In contrast, the Pittsburgh Sleep Quality Index (PSQI) for evaluating the insomnia severity (30), the self-rating depression scale (SDS) for depression severity, and the self-rating anxiety scale (SAS) for anxiety severity evaluation were used for assessing PI patients. Following, the PI group was also divided into two subgroups

TABLE 1 | Demographic and clinical characteristics for all participants.

Characteristic	PI-HD ($n = 29$)	PI-LD ($n = 28$)	MDD-HI ($n = 32$)	MDD-LI ($n = 28$)	$F/T/\chi^2$ value	p-Value
Age	39.24 ± 10.96	38.42 ± 11.86	39.21 ± 13.81	35.67 ± 10.37	0.592	0.622
Gender (male/female)	10/19	10/18	15/17	10/18	0.217	0.641†
Education (years)	12.96 ± 3.98	13.65 ± 3.73	12.09 ± 3.42	12.96 ± 2.83	1.93	0.129
eTIV (ml)	1,484.48 ± 126.93	1,502.34 ± 132.57	1,480.17 ± 146.82	1,485.93 ± 152.39	0.173	0.915
Duration (months)	82.17 ± 82.85	41.10 ± 33.48	78.10 ± 89.12	75.41 ± 106.28	2.78	0.007
PSQI	14.58 ± 2.13	13.52 ± 1.72	–	–	2.25	0.028
HAMD-S	–	–	4.91 ± 0.82	1.78 ± 1.20	11.91	0.000
SDS	61.00 ± 5.50	46.32 ± 3.67	–	–	11.78	0.000
HAMD	–	–	23.20 ± 4.35	16.36 ± 5.72	5.24	0.000
SAS	54.62 ± 6.09	52.65 ± 4.40	–	–	1.53	0.131
HAMA	–	–	17.40 ± 5.95	14.85 ± 5.79	1.67	0.101

† *The p-value was obtained by chi-square test; other p-values were obtained by a two-way T-test or one way analysis of variance. MDD-HI, major depressive disorder with higher insomnia; MDD-LI, major depressive disorder with lower insomnia; PI-HD, primary insomnia with higher depression; PI-LD, primary insomnia with lower depression. PSQI, Pittsburgh Sleep Quality Index; HAMD, Hamilton Rating Scale for Depression; HAMD-S, HAMD sleep subscale; SDS, self-rating depression scale; SAS, self-rating anxiety scale; HAMA, Hamilton Rating Scale for Anxiety.*

according to the SDS scores, namely the PI subgroup with higher depression (PI-HD, SDS score >55) and the PI subgroup with lower depression (PI-LD, SDS score <50). Given that 10 patients reported to have a SDS score between 50 and 55, they were not included in the statistical analysis (31).

Image Data Acquisition and Processing

All participants underwent MRI scanning on the same 3.0-Tesla magnetic resonance scanner (Discovery MR750, General Electric, Milwaukee, WI, USA) equipped with a standard head coil. All participants were instructed not to consume caffeine, alcohol, or any other psychoactive substance in the 48 h prior to the scan. Tight however comfortable foam padding was used to minimize head motion, and earplugs were employed to reduce the scanner noise. Sagittal 3D T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time (TR) = 8.16 ms, echo time (TE) = 3.18 ms, flip angle (FA) = 7°, field of view (FOV) =256 × 256 mm^2, matrix =256 × 256; slice thickness = 1 mm, no gap; and 188 sagittal slices. During the MRI examination, all subjects were instructed to relax with their eyes closed without falling asleep or thinking about something. All participants were checked for their wakening status following the scan and they all claimed to be awake during the course of the study.

The images were processed using the standard surface-based workflows in the FreeSurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/), including motion correction, non-parametric non-uniform intensity correction, intensity normalization, skull strip, automatic subcortical segmentation, white matter segmentation, tessellation, original surface smoothing, inflation, automatic topology fixer, surface registration, and cortical parcellation (32). The resulting surface reconstruction was visually inspected and manually edited in the following trouble shooting step (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingDataV6.0) by a single rater, blind to the diagnostic status. The troubleshooting included skull strip errors, segmentation errors, intensity normalization error, pial surface misplacement, and topological defect. The estimated Total Intracranial Volume (eTIV) was extracted as a covariate in a later analysis (33).

Statistical Analysis

Demographic and Behavioral Data

One-way analysis of variance (ANOVA), independent samples T-tests and chi-square tests were conducted using the Statistical Package for the Social Sciences version 20.0 (SPSS, Inc., Chicago, IL, USA) to compare the demographic and behavioral data among groups. The Pearson correlation was employed to examine the relationships between HAMD/SDS scores and HAMD-S/PSQI scores. Considering the difference in both the disease duration between the two PI subgroups and in the HAMD score between the two MDD subgroups, the Pearson Correlation analysis was also conducted to investigate the relationships between both disease duration and SDS score in the PI groups and HAMD-S scores in the MDD groups. The significance was set at $p < 0.05$.

Structural Imaging

A general linear model (GLM) analysis was employed to explore the effect of depression, insomnia, and their interaction on the reconstructed cortical surface image (mri_glmfit, FreeSurfer), regressed out the effect of gender, age, years of education, and the eTIV. The design matrices were created by a FreeSurfer Group Descriptor File (http://surfer.nmr.mgh.harvard.edu/fswiki/Fsgdf4G1V). For the main effect of depression, we set the MDD-HI, MDD-LI, and PI-HD as depressed patients, PI-LD as non-depressed patients; For the main effect of insomnia, we set the MDD-HI, PI-LD, PI-HD as insomnia patients, MDD-LI as non-insomnia patients; For the interaction of depression and insomnia effect, we set the MDD-HI, PI-HD as the interaction of depression and insomnia. The the

contrast matrix is set as the equation below:

$$Y_i = \beta_0 + \beta_1 * Gender + \beta_2 * Age + \beta_3 * Education + \beta_4 * eTIV + \beta_5 * Duration + \beta_6 * Ins + \beta_7 * Dep + \beta_8 * (Ins * Dep) + \varepsilon$$

where Y_i represents the thickness or volume of each vertex in cortex of the *i*th participant; β_0 is the intercept of the straight-line fitting in the model; β_1, β_2, β_3, β_4, *and* β_5 stand for the main effect of gender, age, education, eTIV volume, and disease duration, respectively, which were discarded as covariates of no interest in the GLM models. β_5 represents the main effect of depression, β_6 is the main effect of insomnia, β_7 describes the interaction effect of depression and insomnia. The error term ε was assumed to have a Gaussian distribution so that no correlation across participants was shown.

After the GLM analyses, a cluster-wise correction for multiple comparison was processed using the Monte Carlo Simulation (mri_glmfit-sim, FreeSurfer, the vertex-wise threshold is $p < 0.0001$, the cluster-wise $p < 0.05$, iteration is 10,000, adjust *p*-values for two hemispheres) (34).

The Relationship Between Structural Imaging Features and Behavior

To further detect whether depression and insomnia influenced the brain structural regions associated with clinical characteristics in both the MDD and PI groups, a Partial correlation analysis was conducted, after controlling for the effect of age, gender, years of education, disease duration and eTIV. The significance was set at $p < 0.05$, and the false discovery rate (FDR) correction was used for multiple comparison correction.

RESULTS

Demographic Information and Clinical Characteristics

Significant differences in age, gender, years of education and eTIV were not observed between the four groups. As **Table 1** illustrates, the disease duration in the PI-LD subgroup is shorter when compared to other groups. In addition, the PSQI score in the PI-LD subgroup is lower than the one in the PI-HD subgroup ($t = 2.25$, $p = 0.02$), while the HAMD score in the MDD-HL subgroup is higher when compared to the one in the MDD-LI subgroup ($t = 5.24$, $p < 0.001$). In contrast, a significant difference in the anxiety symptom was not found between the two PI and MDD groups. In the MDD group, the HAMD score was positively correlated with both the HAMA score ($r = 0.46$, $p < 0.001$), and the HAMD-S score ($r = 0.57$, $p < 0.001$). In concordance, the PSQI score was positively correlated with the SDS score in the PI group ($r = 0.27$, $p = 0.027$). Significant relationships between disease duration, PSQI and SAS scores were not seen in PI groups. An absence of other significant relationships between the clinical characteristics was present.

Main Effect of Depression on Brain Structure

As illustrated in **Figure 1** and **Table 2**, a main effect of depression on cortical thickness was seen in the bilateral superior parietal lobule (left SPL, 2.39 ± 0.16 vs. 2.45 ± 0.10; right SPL, 2.37 ± 0.12 vs. 2.43 ± 0.11), the right middle cingulate cortex (MCC, 2.38 ± 0.15 vs. 2.46 ± 0.12), and the right parahippocampal gyrus (2.42 ± 0.18 vs. 2.45 ± 0.16), after adjusting for the effects of gender, age, and years of education and TIV. The cortical regions affected by depression were thinner in patients with depression when compared to patients with an absence of severe depression symptom. In contrast, a significant effect of depression on cortical volume was not found.

Main Effect of Insomnia on Brain Structure

After adjusting for the effects of gender, age, and years of education, a main effect of insomnia on cortical thickness was observed in the right PCC (2.39 ± 0.16 vs. 2.43 ± 0.14). As showed in **Figure 2** and **Table 2**, the right PCC was thinner in patients with insomnia when compared to patients with an absence of severe insomnia symptom. In contrast, a significant effect of insomnia on cortical volume was not seen.

Interaction Effect of Depression and Insomnia on Brain Structure

A significant interaction effect of depression and insomnia on the right orbital frontal cortex (OFC) volume was detected, after both a flexible multiple comparison correction ($p < 0.05$) and controlling for the effects of gender, age, and years of education. As **Figure 3** displays, patients with co-occurring depression and insomnia showed smaller brain volume in the right OFC when compared to patients without severe insomnia/depression, in both the MDD and the PI groups. A significant interaction effect of depression and insomnia on cortical thickness was not present after multiple comparison correction.

Correlation Analysis

An absence of significant FDR-adjusted correlations between influenced brain regions and relative clinical traits in the MDD and PI groups was reported.

DISCUSSION

To our knowledge, the present study was the first attempt to explore the interaction of insomnia and depression on brain structure in both PI and MDD patients. Three major findings were reported. First, insomnia and depression symptoms were closely associated in both the PI and MDD patients groups. Second, depression influences the brain structure in the SPL, MCC, and parahippocampal gyrus, while insomnia mainly influences the PCC thickness. Third, depression and insomnia interaction contributes to cortical volume loss in the right OFC. These findings indicated that the OFC might be a core region for the neuropathological alteration in comorbidity of insomnia and depression. Therefore, our findings provide new insights into the understanding of the brain mechanism underlying comorbidity of insomnia and depression.

The clinical features of the four subgroups verified the close association and the comorbidity between MDD and PI. In fact, patients with insomnia in the MDD group showed more severe depression, which is consistent with a previous

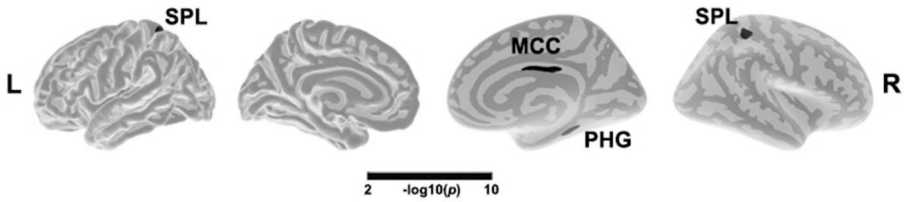

FIGURE 1 | Main effect of depression in cortical thickness across all patients. The color bar indicates the –log10(p) value after clusterwise correction for multiple comparisons using Monte Carlo simulations (vertex $p < 0.0001$, cluster $p < 0.05$). L, left; R, right; MCC, middle cingulate cortex; SPL, superior parietal lobule; PHG, parahippocampal gyrus.

TABLE 2 | The depression and insomnia and their interactive effects on cortical thickness and volume.

Clusters	Max *T* value	VtxMax	TalX	TalY	TalZ	CWP	NVtxs
MAIN EFFECT OF DEPRESSION ON CORTICAL THICKNESS							
1. Left superior parietal lobe	7.419	133,615	−16.9	−50.6	61.6	0.0058	292
2. Right superior parietal lobe	5.136	14,752	28.8	−39.5	490.0	0.0006	563
3. Right middle cingulate cortex	5.948	35,246	3.3	−7.3	29.5	0.0020	357
4. Right parahippocampal gyrus	5.825	113,996	35.8	−35.0	−13.8	0.0020	341
MAIN EFFECT OF INSOMNIA ON CORTICAL THICKNESS							
1. Right posterior cingulate cortex	6.709	24,061	5.8	−38.4	24.3	0.0026	346
INTERACTIVE EFFECT OF DEPRESSIVE AND INSOMNIA IN CORTICAL VOLUME*							
1. Right orbital frontal cortex	3.615	139,780	6.9	0.0	64.8	0.0002	3,508

**The threshold of multiple comparison correction was set as vertex p at 0.05, and cluster p at 0.05. TalX,Y,Z, the Talairach coordinate of peak vertex; VtxMax, number of peak vertex of the significant cluster; CWP, cluster-wise probability and the nominal p-value; NVtxs, number of vertices in cluster.*

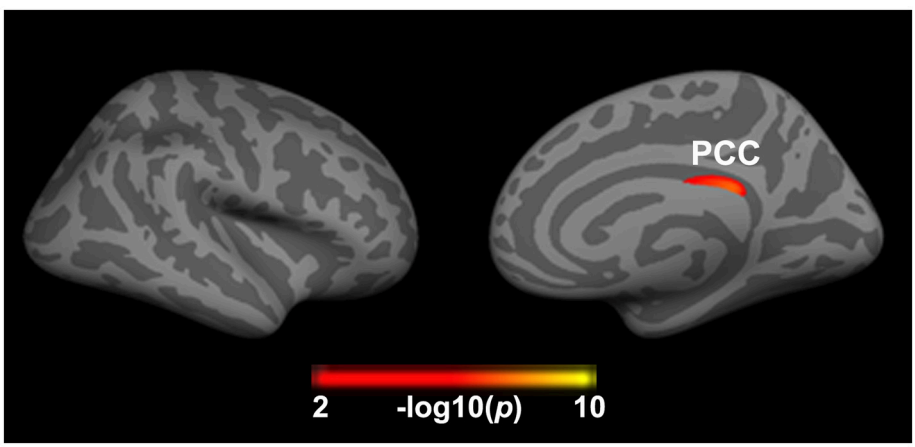

FIGURE 2 | Significant effect of insomnia on right cortical thickness across all patients. The color bar indicates the –log10(p) value after clusterwise correction for multiple comparisons using Monte Carlo simulations (vertex $p < 0.0001$, cluster $p < 0.05$). PCC, posterior cingulate cortex.

epidemiologic study (35). In concordance, PI patients with depression have a longer disease duration and more severe insomnia, which is positively associated with depression but not with the anxiety symptom. These results were proved also consistent with previous epidemiologic results on the long-term consequences of insomnia (1). The clinical results presented here support the notion that the relationship between insomnia and depression is bidirectional, and this relationship can change over time following disease progression or release (7).

In the present study, we investigated the insomnia and depression effects on brain structure in a pooled patient group. This approach enables, in fact, the detection of the insomnia/depression effect in two patient groups and might reveal the common neurobiology underlying such symptoms. Only cortical thickness was significantly influenced by insomnia and depression in the pooled population. Patients with depression showed thinning of the SPL, MCC, and parahippocampal gyrus. The SPL is involved in spatial cognition

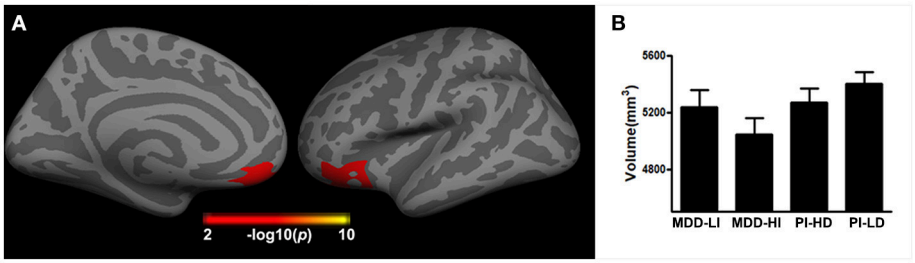

FIGURE 3 | The interactive effect of depression and insomnia on right cortical volume across all patients. **(A)** The interactive effect was found in right orbital frontal cortex; **(B)** The histogram indicated that the joint depression and insomnia showed smaller brain volume in the right orbital frontal cortex.

and sensorimotor integration (36, 37); previous studies also reported decreased gray matter volume and reduced functional connectivity in the SPL in MDD patients (38, 39). Although the alteration of the MCC is less commonly reported in depression studies, the posterior MCC is involved in attentional control during emotion regulation and showed a functional abnormality in MDD patients (40, 41). The present result provides a new insight into emotion regulation abnormality in patient with depression. Last, the parahippocampal gyrus is important for episodic memory and emotion cues processing (42); the thinning parahippocampal gyrus here found is consistent with previous structural imaging results in MDD patients (43), and indicated a common structural basis underlying both emotion and episodic memory processing in the patients with depression. Regarding patients with insomnia, the common structural alteration was seen in PCC, which is the core region of the default mode network and has been considered to be involved in emotion, memory and intrinsic control, and to be represent a neural substrate for human awareness (44, 45). The metabolism, functional connectivity abnormality and structural connectivity of the anterior default mode network was also reported in PI patients (46, 47). Generally, our findings on the main effect of insomnia and depression highlighted the morphological alteration in the thickness of the SPL, MCC, and parahippocampal gyrus in depression and of the PCC in insomnia.

Our most important finding was the localization of the insomnia/depression interaction effect on brain structure in the right OFC. The orbitofrontal area is involved in emotion, especially in reward processing, decision-making, and problem-solving abilities (48, 49). Previously, gray matter decrements in the OFC were reported in insomnia and depression patients, separately (50, 51). The decreased PFC volume may explain the insufficient decision-making and problem-solving abilities, and the attenuated recognition of environmental temperature in insomnia patients (24, 52). In addition, the reduced OFC volume may account for the distorted emotional stimuli evaluation, abnormal emotional and visceral regulation, anhedonia symptoms as well (23, 50). Interestingly, we found that co-occurrence of insomnia and depression is related to the worst volume decrease seen in the orbitofrontal cortex, especially, in MDD patients with insomnia. Baglioni and Riemann proposed a hypothesis stating that the link between persistent insomnia and depression is the alteration of the arousal system and its subsequent impact on affective and cognitive systems (53). Given that OFC receives widespread projections from arousal systems, including thalamus and amygdala (54), the decreased OFC volume may indicate an abnormal top-down control mechanism for arousal systems and dysfunctional emotional regulation and reward processing in patients with comorbidity of insomnia and depression. Overall, our results suggested that OFC is an essential area underlying the neuropathological mechanism of the comorbidity of insomnia and depression.

Two factors are likely to account for the absence in clinical significance of the alteration in cortical morphology of regions. First, considering that the behavioral assessments of depression and insomnia are not conformed between groups, we can only conduct the correlation analysis separately. Second, given that the clinical characteristics were robustly associated with demographic factors and relative stability of brain structure, some recent studies found that cortical structure feature is a relatively weak discriminant factor for current episode clinical status (55, 56). Further studies should include detailed and conformed neuropsychological tests, and a larger sample to verify this.

The limitations of the current study will now be highlighted. First, the present study is a preliminary and retrospective research, so the present study did not use the same estimating tool for depression and insomnia, we cannot explore the relationship between the influenced structural region and the clinical traits in a pooled group. In addition, the HAMD subscale of insomnia scores only has three items to estimate the insomnia, the HAMD total score is positively correlated with HAMD-S score, so it's difficult to completely remove the depression severity effect in the data analysis. These limitations regarding the clinical evaluation restricted the elaboration of our findings on brain structure. Second, not only insomnia, but also hypersomnia, is present in MDD patients (5); therefore, future studies should explore the brain mechanism underlying hypersomnia in MDD patients. Third, significant differences were found between the PI-HD and PI-LD groups in the PSQI total score, and between the MDD-HI and MDD-LI groups in the HAMD total score, which might bias the findings to uncertain extent. Fourth, the present study strictly focused on the structural change of cortical regions in depression and insomnia, whereas the subcortical and cerebellar regions were unexplored. Future studies should explore these issues further. Fifth, the present study did not include a healthy

control group, which again limits the discussion of our findings. Lastly, considering that our study had a cross-sectional design with relatively small sample sizes, future research using larger sample sizes, data pooling, and longitudinal designs is deemed necessary.

In conclusion, our present results indicated that the OFC may be a core region for the neuropathological mechanism in comorbidity of insomnia and depression. In addition, our findings provide new insights into the understanding of the brain mechanism underlying comorbidity of insomnia and depression and the development of rational treatment strategies for these patients.

AUTHOR CONTRIBUTIONS

SY, YH, and LG contributed to the conception and design of study. RL, BG, ZW, and FF contributed to the clinical estimate acquisition of imaging data. SY and LG performed imaging data analysis. SY and ZS wrote the manuscript. ZS and JY contributed revising the manuscript logically for important theoretical content. All authors contributed to the manuscript and have approved the final manuscript.

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REFERENCES

1. Morin CM, Jarrin DC. Epidemiology of insomnia. prevalence, course, risk factors, and public health burden. *Sleep Med Clin.* (2013) 8:281–97. doi: 10.1016/j.jsmc.2013.05.002
2. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med.* (2013) 10:e1001547. doi: 10.1371/journal.pmed.1001547
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* (2006) 3:e442. doi: 10.1371/journal.pmed.0030442
4. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry* (2005) 66:1254–69. doi: 10.4088/JCP.v66n1008
5. Geoffroy PA, Hoertel N, Etain B, Bellivier F, Delorme R, Limosin F, et al. Insomnia and hypersomnia in major depressive episode: prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. *J Affect Disord.* (2018) 226:132–41. doi: 10.1016/j.jad.2017.09.032
6. Soldatos CR. Insomnia in relation to depression and anxiety: epidemiologic considerations. *J Psychosom Res.* (1994) 38 (Suppl. 1):3–8.
7. Staner L. Comorbidity of insomnia and depression. *Sleep Med Rev.* (2010) 14:35–46. doi: 10.1016/j.smrv.2009.09.003
8. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* (2011) 135:10–9. doi: 10.1016/j.jad.2011.01.011
9. Jindal RD, Thase ME. Treatment of insomnia associated with clinical depression. *Sleep Med Rev.* (2004) 8:19–30. doi: 10.1016/S1087-0792(03)00025-X
10. Thase ME. Depression and sleep: pathophysiology and treatment. *Dialogues Clin Neurosci.* (2006) 8:217–26.
11. O'Byrne JN, Berman Rosa M, Gouin JP, Dang-Vu TT. Neuroimaging findings in primary insomnia. *Pathol Biol. (Paris)* (2014) 62:262–9. doi: 10.1016/j.patbio.2014.05.013
12. Jarnum H, Eskildsen SF, Steffensen EG, Lundbye-Christensen S, Simonsen CW, Thomsen IS, et al. Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *Acta Psychiatr Scand.* (2011) 124:435–46. doi: 10.1111/j.1600-0447.2011.01766.x
13. Winkelman JW, Plante DT, Schoerning L, Benson K, Buxton OM, O'Connor SP, et al. Increased rostral anterior cingulate cortex volume in chronic primary insomnia. *Sleep* (2013) 36:991–8. doi: 10.5665/sleep.2794
14. Winkelman JW, Benson KL, Buxton OM, Lyoo IK, Yoon S, O'Connor S, et al. Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. *Sleep Med.* (2010) 11:576–82. doi: 10.1016/j.sleep.2010.03.009
15. Joo EY, Noh HJ, Kim JS, Koo DL, Kim D, Hwang KJ, et al. Brain gray matter deficits in patients with chronic primary insomnia. *Sleep* (2013) 36:999–1007. doi: 10.5665/sleep.2796
16. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlosser RG. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? *Neuroimage* (2011) 54:1607–14. doi: 10.1016/j.neuroimage.2010.08.082
17. Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry* (2011) 68:675–90. doi: 10.1001/archgenpsychiatry.2011.60
18. Bora E, Fornito A, Pantelis C, Yucel M. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord.* (2012) 138:9–18. doi: 10.1016/j.jad.2011.03.049
19. Cheng W, Rolls ET, Ruan H, Feng J. Functional connectivities in the brain that mediate the association between depressive problems and sleep quality. *JAMA Psychiatry* (2018) 75:1052–61. doi: 10.1001/jamapsychiatry.2018.1941
20. Liu C-H, Guo J, Lu S-L, Tang L-R, Fan J, Wang C-Y, et al. Increased salience network activity in patients with insomnia complaints in major depressive disorder. *Front Psychiatry* (2018) 9:93. doi: 10.3389/fpsyt.2018.00093
21. Li M, Yan J, Li S, Wang T, Wen H, Yin Y, et al. Altered gray matter volume in primary insomnia patients: a DARTEL-VBM study. *Brain Imaging Behav.* (2018). doi: 10.1007/s11682-018-9844-x. [Epub ahead of print].
22. Yang X, Peng Z, Ma X, Meng Y, Li M, Zhang J, et al. Sex differences in the clinical characteristics and brain gray matter volume alterations in unmedicated patients with major depressive disorder. *Sci Rep.* (2017) 7:2515. doi: 10.1038/s41598-017-02828-4
23. Drevets WC. Orbitofrontal cortex function and structure in depression. *Ann N Y Acad Sci.* (2007) 1121:499–527. doi: 10.1196/annals.1401.029
24. Altena E, Vrenken H, Van Der Werf YD, van den Heuvel OA, Van Someren EJ. Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. *Biol Psychiatry* (2010) 67:182–5. doi: 10.1016/j.biopsych.2009.08.003
25. Korgaonkar MS, Fornito A, Williams LM, Grieve SM. Abnormal structural networks characterize major depressive disorder: a connectome analysis. *Biol Psychiatry* (2014) 76:567–74. doi: 10.1016/j.biopsych.2014.02.018
26. Williams LM, Rush AJ, Koslow SH, Wisniewski SR, Cooper NJ, Nemeroff CB, et al. International study to predict optimized treatment for depression (iSPOT-D), a randomized clinical trial: rationale and protocol. *Trials* (2011) 12:4. doi: 10.1186/1745-6215-12-4
27. Martin LM, Triscari R, Boisvert R, Hipp K, Gersten J, West RC, et al. Development and evaluation of the lifestyle history questionnaire (LHQ) for

people entering treatment for substance addictions. *Am J Occup Ther.* (2015) 69:6903250010p1-9. doi: 10.5014/ajot.2015.014050
28. Park S-C, Kim J-M, Jun T-Y, Lee M-S, Kim J-B, Jeong S-H, et al. Prevalence and clinical correlates of insomnia in depressive disorders: the CRESCEND study. *Psychiatry Investig.* (2013) 10:373–81. doi: 10.4306/pi.2013.10.4.373
29. Manber R, Blasey C, Arnow B, Markowitz JC, Thase ME, Rush AJ, et al. Assessing insomnia severity in depression: comparison of depression rating scales and sleep diaries. *J Psychiatr Res.* (2005) 39:481–8. doi: 10.1016/j.jpsychires.2004.12.003
30. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh sleep quality index in primary insomnia. *J Psychosom Res.* (2002) 53:737–40. doi: 10.1016/S0022-3999(02)00330-6
31. Su Q, Yu B, He H, Zhang Q, Meng G, Wu H, et al. Nut consumption is associated with depressive symptoms among chinese adults. *Depress Anxiety* (2016) 33:1065–72. doi: 10.1002/da.22516
32. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA*. (2000) 97:11050–5. doi: 10.1073/pnas.200033797
33. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, et al. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage* (2004) 23:724–38. doi: 10.1016/j.neuroimage.2004.06.018
34. Hagler DJ Jr., Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *Neuroimage* (2006) 33:1093–103. doi: 10.1016/j.neuroimage.2006.07.036
35. Soehner AM, Kaplan KA, Harvey AG. Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. *J Affect Disord.* (2014) 167:93–7. doi: 10.1016/j.jad.2014.05.060
36. Wolpert DM, Goodbody SJ, Husain M. Maintaining internal representations: the role of the human superior parietal lobe. *Nat Neurosci.* (1998) 1:529–33. doi: 10.1038/2245
37. Koenigs M, Barbey AK, Postle BR, Grafman J. Superior parietal cortex is critical for the manipulation of information in working memory. *J Neurosci.* (2009) 29:14980–6. doi: 10.1523/JNEUROSCI.3706-09.2009
38. Zhao Y, Chen L, Zhang W, Xiao Y, Shah C, Zhu H, et al. Gray matter abnormalities in non-comorbid medication-naive patients with major depressive disorder or social anxiety disorder. *EBio Med.* (2017) 21:228–35. doi: 10.1016/j.ebiom.2017.06.013
39. Sacchet MD, Ho TC, Connolly CG, Tymofiyeva O, Lewinn KZ, Han LK, et al. Large-scale hypoconnectivity between resting-state functional networks in unmedicated adolescent major depressive disorder. *Neuropsychopharmacology* (2016) 41:2951–60. doi: 10.1038/npp.2016.76
40. Vogt BA. Midcingulate cortex: structure, connections, homologies, functions and diseases. *J Chem Neuroanat.* (2016) 74:28–46. doi: 10.1016/j.jchemneu.2016.01.010
41. Bertocci MA, Bebko GM, Mullin BC, Langenecker SA, Ladouceur CD, Almeida JR, et al. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychol Med.* (2012) 42:1417–28. doi: 10.1017/S003329171100242X
42. Aminoff EM, Kveraga K, Bar M. The role of the parahippocampal cortex in cognition. *Trends Cogn Sci.* (2013) 17:379–90. doi: 10.1016/j.tics.2013.06.009
43. Lener MS, Kundu P, Wong E, Dewilde KE, Tang CY, Balchandani P, et al. Cortical abnormalities and association with symptom dimensions across the depressive spectrum. *J Affect Disord.* (2016) 190:529–36. doi: 10.1016/j.jad.2015.10.027
44. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain* (2014) 137:12–32. doi: 10.1093/brain/awt162
45. Vogt BA, Laureys S. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res.* (2005) 150:205–17. doi: 10.1016/S0079-6123(05)50015-3
46. Nie X, Shao Y, Liu SY, Li HJ, Wan AL, Nie S, et al. Functional connectivity of paired default mode network subregions in primary insomnia. *Neuropsychiatr Dis Treat.* (2015) 11:3085–93. doi: 10.2147/NDT.S95224
47. Kay DB, Karim HT, Soehner AM, Hasler BP, James JA, Germain A, et al. Subjective-objective sleep discrepancy is associated with alterations in regional glucose metabolism in patients with insomnia and good sleeper controls. *Sleep* (2017) 40:zsx155. doi: 10.1093/sleep/zsx155
48. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* (2000) 10:295–307. doi: 10.1093/cercor/10.3.295
49. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci.* (2005) 6:691–702. doi: 10.1038/nrn1747
50. Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, et al. Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry* (2002) 51:273–9. doi: 10.1016/S0006-3223(01)01336-1
51. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp.* (2009) 30:3719–35. doi: 10.1002/hbm.20801
52. Raymann RJ, Van Someren EJ. Diminished capability to recognize the optimal temperature for sleep initiation may contribute to poor sleep in elderly people. *Sleep* (2008) 31:1301–9.
53. Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. *Curr Psychiatry Rep.* (2012) 14:511–8. doi: 10.1007/s11920-012-0308-5
54. Rolls ET. The orbitofrontal cortex. *Philos Trans R Soc Lond B Biol Sci.* (1996) 351:1433–43. discussion: 43–4.
55. Perlman G, Bartlett E, DeLorenzo C, Weissman M, McGrath P, Ogden T, et al. Cortical thickness is not associated with current depression in a clinical treatment study. *Hum Brain Mapp.* (2017) 38:4370–85. doi: 10.1002/hbm.23664
56. Yang XH, Wang Y, Huang J, Zhu CY, Liu XQ, Cheung EF, et al. Increased prefrontal and parietal cortical thickness does not correlate with anhedonia in patients with untreated first-episode major depressive disorders. *Psychiatry Res.* (2015) 234:144–51. doi: 10.1016/j.pscychresns.2015.09.014

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REVIEW
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Mechanisms and Therapeutic Targets of Depression After Intracerebral Hemorrhage

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The relationship between depression and intracerebral hemorrhage (ICH) is complicated. One of the most common neuropsychiatric comorbidities of hemorrhagic stroke is Post-ICH depression. Depression, as a neuropsychiatric symptom, also negatively impacts the outcome of ICH by enhancing morbidity, disability, and mortality. However, the ICH outcome can be improved by antidepressants such as the frequently-used selective serotonin reuptake inhibitors. This review therefore presents the mechanisms of post-ICH depression, we grouped the mechanisms according to inflammation, oxidative stress (OS), apoptosis and autophagy, and explained them through their several associated signaling pathways. Inflammation is mainly related to Toll-like receptors (TLRs), the NF-kB mediated signal pathway, the PPAR-γ-dependent pathway, as well as other signaling pathways. OS is associated to nuclear factor erythroid-2 related factor 2 (Nrf2), the PI3K/Akt pathway and the MAPK/P38 pathway. Moreover, autophagy is associated with the mTOR signaling cascade and the NF-kB mediated signal pathway, while apoptosis is correlated with the death receptor-mediated apoptosis pathway, mitochondrial apoptosis pathway, caspase-independent pathways and others. Furthermore, we found that neuroinflammation, oxidative stress, autophagy, and apoptosis experience interactions with one another. Additionally, it may provide several potential therapeutic targets for patients that might suffer from depression after ICH.

Keywords: intracerebral hemorrhage, depression, inflammation, oxidative stress, apoptosis, review, therapeutic target, autophagy

INTRODUCTION

Each year, about 795,000 individuals suffer from a new or recurrent stroke. Nearly 610,000 among these patients experience first time attacks in their entire life; the remaining cases are reported as recurrent strokes. All stroke cases, 87% are ischemic, while intracerebral hemorrhage (ICH) strokes account for 10%, and subarachnoid hemorrhage (SAH) strokes only make up 3% of the total (1).

Post-stroke depression (PSD), the most common and frequent mental disorder after stroke, has a strong association with exacerbate deterioration of functional recovery, physical, and cognitive outcome, as well as quality of life. Moreover, PSD is even independently associated with enhanced morbidity, disability, and mortality (2–4).

Intracerebral hemorrhage (ICH) is a dangerous type of stroke, which is severer. Evidence have shown that 20% of ICH survivors existed with explicit signs of depression (5, 6). Numerous studies of PSD have been revealed, especially ischemic strokes; studies were based on medical examinations in researches. Nevertheless, the etiological factors that cause post-ICH depression are far from being elucidated. Hence, it is vital to understand the specific etiopathology of depression after ICH that can thus help people to develop effective therapeutic strategies aimed at etiological factors.

The present review will address the mechanisms, especially involved signaling pathways, and will introduce several potential therapeutic agents for the therapy of post-ICH depression. Finally, we will provide suggestions, that we hope can guide future research.

ICH TYPES

ICH is divided into primary and secondary types, depending on the response to the fundamental cause of hemorrhage (7). Primary ICH develops without any underlying vascular malformation or coagulopathy. However, some cases like tumors, trauma, as well as coagulation could lead to the formation of secondary ICH, as well as the use of thrombolytic agents (7). In any ICH case, primary brain damage will occur because of the hemorrhage. And with the development of a hematoma, secondary brain injury will gradually appear on account of a pathological and physiological reaction.

Intracerebral hemorrhage is a lethal type of stroke, in the United States, every year there are 30,000 people who die from a stroke. If the patient is lucky enough to survive, then the growth of the hematoma in the brain parenchyma could trigger multiple of reactions that lead to another insult or even more severe neurological impairments. We will discuss several aspects of secondary cerebral injury following ICH and underline the key mechanisms correlated with post ICH depression (8).

SECONDARY BRAIN INJURY-INDUCED DEPRESSION

Secondary injury is a key factor in the deterioration of the nervous system in ICH patients (9, 10). Secondary brain injury after ICH is caused by intraparenchymal hemorrhage, which then activates several signaling pathways such as inflammatory, oxidative, autophagic, and apoptotic pathways. These pathways, *in vivo*, become the bridge that links intracerebral hemorrhage and depression (8, 11–13).

Inflammation

Inflammation is a significant host defense response to cerebral damage following ICH. Once ICH occurs, components in the blood such as leukocytes, RBCs, and macrophages immediately migrate into the brain parenchyma. There is growing evidence that inflammation-induced impairment plays a crucial role in the mechanism underlying secondary brain injury after ICH (8, 14–17).

Toll-Like Receptors in Inflammation

Toll-like receptors (TLRs) are an important component of inflammatory responses and innate immunity (18, 19). TLR4 on leukocytes are important for the infiltration of both neutrophils and monocytes out of circulation (20). Recently, several clinical studies have suggested that increased levels of TLR2 and TLR4 expression in peripheral monocytes is related to a poor prognosis in patients with ICH (21). Furthermore, some studies have found an improved neurological function in TLR4-knockout ICH animal models (20, 22). Moreover, TLR4 signaling, especially those on resident microglia and on blood-derived inflammatory cells, is specific to inflammatory damage induced by ICH (20, 22, 23).

Recently, more attention has been placed on understanding the underlying mechanisms of inflammation-induced depression. Kéri et al. found patients diagnosed as major depressive disorder (MDD) for the first time, usually had an accompanied upregulation of TLR-4 signaling. It is thought to be related to bacterial translocation or various molecular patterns that correlate with the type of injury (24). Strekalova et al. first showed that C57BL/6J mice models appeared to show depression- and anxiety-like behaviors when they were fed high amounts of cholesterol. Moreover, they reported an unexpected elevation in the level of TLR4 expression, which indicated that TLR4 may play a critical role in the central neuronal system (25). Habib and his colleagues clarified, in an experiment using diabetic/depressed rats, when dysfunctions occurred to blood vessels as well as the metabolic system, the expression of TLR-4 in the aorta increased rapidly, in addition to a rise in pro-inflammatory cytokines (26). Later, Cheng et al. found that stress-induced neuroinflammatory responses are regulated by the GSK3-dependent TLR4 pathway. This signaling pathway is involved in development of depressive-like symptoms (27). García et al. then concluded that the activation of TLR-4 in the brain and peripheral area leads to sickness symptoms, and its expression level is also a risk factor that contributes to depression (28). These results confirmed the correlation between an elevated level of the TLRs and the risk of developing depression.

An increasing body of evidence suggests that microglia are the main mediators of inflammation-related disorders, including depression. Slusarczyk et al. suggested that tianeptine, an antidepressant drug, could attenuate the level of inflammatory mediators related to TLR4 signaling and the NLRP3 inflammasome (29). In addition, chronic restraint stress (CRS)-induced depressive-like animal models were found to show inflammatory responses in the hippocampus via the toll-like receptor type 4 (TLR4)/p38 mitogen-activated protein kinase (MAPK) pathway, which could be treated by ketamine (30). Past studies demonstrated that the TLR4 signaling pathway in the CNS and the periphery are associated with activated glycogen synthase kinase-3 (GSK3), a kinase shown to be involved in depression (31, 32). GSK3 inhibition has been indicated to

reduce the production of pro-inflammatory cytokines with the stimulation of TLR4 in several different immune cells, both in clinical and basic experiments (33–35). Moreover, antidepressants like fluoxetine or the GSK3 inhibitor, TDZD-8, could improve stress-induced depressive-like behaviors via the TLR4 signaling pathway (27).

NF-kB Mediated Signal Pathway

Recently, many studies have proven the instrumental role of proinflammatory cytokines in the development of ICH. For instance, the activation of NF-kB in microglia/macrophages, which contributes to brain damage after ICH, results in the upregulation of proinflammatory cytokines (36, 37). Moreover, inhibited NF-kB activity is also related to alleviated neurological deficits (22, 38).

Furthermore, plenty of research suggests that neuroinflammation may play a significant role in the pathogenesis of depressive disorders. Koo et al. first reported that NF-κB signaling may act as a key mediator in anti-neurogenic and stress-induced behavioral actions; it may provide therapeutic targets of depression, which have never been described before (39). A few years after, evidence was provided that MDD is characterized by up-regulation of redox-sensitive transcriptional factors (Nrf2 and NF-κB), which indicated the pro-oxidative state that exists in MDD patients' peripheral blood mononuclear cells (PBMC) (40). A review concerned with adult hippocampal neurogenesis similarly supported the finding that NF-κB signaling modulates neurogenesis in adult patients, as well as expressing antidepressant actions (41). Recently, Nadeem et al. discovered that IL-17A seems to participate in comorbid depression with those who have psoriatic inflammation; this was linked to NF-κB and p38MAPK pathways that function through the up-regulated inflammatory cytokines in the brain (42). What is more, chronic stress in the basolateral amygdala (BLA) would induce the upregulation of neuropeptides and subsequently cause depressive-like behaviors. The siRNA could mediate the inhibition of NF-kB signaling in the BLA and downregulate the expression of neuropeptides, which lead to the alleviation of depressive symptoms (43). Moreover, Su et al. (44) proved that chronic unpredictable mild stress (CUMS)—induced depression-like action could be mediated through the NLRP3 inflammasome. Furthermore, the depression rat model indicated that the CUMS-induced MAPK pathway could be regulated by NLRP3 inflammasome by activating the NF-κB protein complex (44). Depression is one of the upmost psychological illness that is closely tied with inflammation. Crocin could act as a promising therapeutic target for depressive-like behaviors and neuro-inflammation caused by lipopolysaccharide (LPS). Researchers found such a phenomenon was an outcome of inhibited NLRP3 inflammasomes as well as inhibited NF-κB signaling in microglia (45). Pro-anthocyanidin, having potential anti-inflammatory and antioxidative activity efficacy, functions as an effective therapeutic candidate for depression-like behaviors induced by LPS by regulating the NF-κB signal in many cerebral regions and inhibiting the LPS-induced iNOS and the increased expression of COX-2 (46). Senegenin (SEN) is a main bioactive component of Polygala tenuifolia Willd, which has sturdy effects including anti-inflammatory actions as well as neuroprotection. At the same time, it has been used to lessen the depressive behavior in CUMS-induced rat models by inhibiting NLRP3-regulated NF-κB signaling (47). Icariin (ICA), which could be extracted from a certain traditional Chinese herb, is able to freely transverse the blood-brain barrier. It reduces neuroinflammation and OS-induced brain damage to prevent depressive-like behaviors by inhibiting the activation of NF-κB signaling in addition partially inhibition of the NLRP3-inflammasome/caspase-1/IL-1β axis, which would increase the antioxidant and anti-inflammatory ability of the cerebrum (48). With associated neuroprotection and anti-inflammatory activities, Geraniol (GE) has the potential to treat antidepressant-like behaviors in CUMS-induced depression mouse models, possibly by inhibiting the NF-κB pathway activation. Likewise, it seems that the regulation of nucleotide binding and NLRP3 inflammasome expression are both involved in this process (49). On the other hand, Chrysophanol (Chr) was also reported to function as anti-depression treatment by influencing the P2X7/NF-κB signaling pathway (50).

PPAR-γ-Dependent Pathway

CD36, belonging to the class B scavenger receptor family, is usually expressed in macrophages or microglia. It is involved in phagocytosis of many pathogens such as bacteria, apoptotic cells and oxidized low-density lipoproteins (51–53). Peroxisome proliferator-activated receptor (PPAR) -γ, which is a part of the nuclear hormone receptor superfamily, can transcriptionally regulate the expression of CD36 and participate in inflammation (54, 55). In addition, treated with PPARγ activator, the hematoma in the brain of ICH mouse model would regress quicker and neurological damage following ICH in adults would decline. Flores and his colleagues confirmed that PPARγ agonists (15d-PGJ2) raised short-term PPARγ levels, accompanied with enhanced CD36 expression and accelerated hematoma resolution. Furthermore, it improved neurological function results. Moreover, both long term ventricular dilatation after ICH and white matter loss were decreased (56).

In several clinical and basic experiments, PPAR-γ agonists have exerted anti-depressive behavioral effects. Nevertheless, no one explained these mechanisms clearly. Gold and his colleagues proposed that PPAR-γ may exhibit as a conceptually new remedial target that improves the affective, cognitive and systemic manifestations of MDD (57). Later, Agudelo et al. opened a novel therapeutic avenue for treating depression through the PGC-1α1-PPAR axis, which was usually expressed in skeletal muscles, rather than by crossing the blood-brain barrier (58). Colle et al. found that PPAR-γ agonists have antidepressant effects in 3 out of 4 RCTs and in 4 open-label studies. Consequent studies concluded that PPAR-γ agonists may have antidepressant effects (59). Recently, several studies suggested that PPAR-γ agonist exhibit their antidepressant-like effects through various pathways: Liao and his colleagues firstly revealed the regulation of the CREB/BDNF and NF-κB/IL-6/STAT3 pathways, together with the potential effects on central 5-HT neurotransmission may be implicated in depressive-like behaviors via PPAR-γ-related

effects (60). Through the upregulation of PPARγ expression, Song and his colleagues proposed that neuroinflammation could be inhibited and even play a role in its antidepressant effects (61).

Selective agonists of the nuclear transcription factor PPAR-γ are used to treat type 2 diabetes. Several studies also seem to suggest their contribution to improvement of depressive symptoms. PPAR-γ agonist pioglitazone (60, 62, 63), rosiglitazone (64–66), Troglitazone (67), atorvastatin (68), folic acid (69), Astragaloside IV (61), all of which have been reported to ameliorate depressive-like behaviors in mice via the PPAR-γ inflammasome axis.

Other Pathways

Inhibiting transient receptor potential Classic 3 (TRPC3), a member of the calcium-permeable cation channels, significantly reduced the perihematomal accumulation of reactive astrocytes, indicating that TRPC3 plays an important part in activating astrocytes following ICH. Accumulating findings indicate that neurological functions improve with reduced cerebral edema by inhibiting activated astrocytes via the TRPC3 inhibitor Pyr3.

In recent years, several studies have reported that the alterations of intracellular Ca^{2+} signaling are the basis for the pathophysiology of psychiatric disorders, including depression (70, 71). Qin and his colleagues showed a complete difference between the depression animal model group and the control group related to the expression level of TRPC3/5 and the morphology in neurons, located in the hippocampus (72). Moreover, Buran et al. found that TRPC3/6 inhibitors might play a critical part in the etiopathogenesis of depressive disorders with enhanced levels of miR-9-5p and miR-128-1-5p (73).

Oxidative Stress (OS)

Nuclear Factor Erythroid-2 Related Factor 2 (Nrf2) Pathway

Nrf2 comprises of a basic leucine zipper (bZIP) domain, which plays an important part in regulating the cellular antioxidant defense system. This includes heme oxygenase (HO) and superoxide dismutase (SOD) (74). The functions of Reactive oxygen species (ROS) are to trigger the Keap1/Nrf2/ARE pathways so as to compromise oxidative stress (OS) following ICH, which is known as an adaptive response (75–77). Keap1 is an OS sensor that negatively regulates Nrf2. Upon exposure to ROS, Nrf2 decouples from Keap1 and relocates to the nucleus before activating the antioxidant response element (ARE)-dependent cytoprotective gene that mediates cell survival (78). The neuroprotective effect of Nrf2 suggests that a greater brain damage in Nrf2 knockout mice is correlated with increased ROS and apoptosis (76, 77). Therefore, Nrf2 activation of pharmaceutical preparations is a promising target to alleviate OS-induced brain damage following ICH.

Some researchers have indicated that Nrf2 is a major redox-sensitive transcription factor, which gets involved in the process of cellular self-protection from oxidative damage and increases vulnerability to depression-like actions. As part of a review, depression was characterized by distortion in six interwoven pathways; Maes et al. proposed that inhibitors of the Nrf2 activator target the above six pathways and may produce antidepressant effects (79). Djordjevic et al. revealed the maladaptive characteristics of chronic stress at the Nrf2/Keap1 level, resulted in the production of pro-inflammatory symptoms, suggesting that these changes may take part in the pathogenesis of depression/anxiety disorders (80).

For the past few years, several drugs have been found to have an antidepressant effect by influencing the Nrf2 signaling pathway. Furthermore, their target proteins are expressed in the brain. Mendez-David and colleagues showed that the Nrf2 signaling pathway is necessary for fluoxetine-induced neuroprotection associated with SERT blockade of 5-HT transporters, rather than for enhancing BDNF expression (81). Martín-Hernández et al. confirmed that the Nrf2 pathway is involved in the oxidation/nitrosation damage detected in the prefrontal cortex (PFC); moreover, the antidepressant drug has a therapeutic effect through this route (82). By stimulating PFC, CA3, and TrkB in dentate gyrus in Nrf2-knockout animal experiments, the TrkB agonist, 7,8-dihydroxyflavone, has shown a significant antidepressant functionality (83). Mice pretreated with Nrf2 activator sulforaphane (SFN) revealed reduced depression symptoms, which resulted from frequent social defeat stress. This suggests that the Keap1-Nrf2 interaction has a critical role in the pathophysiology of depression (83). Other Nrf2-activating drugs like TBE-31 and MCE-1 have also been proven as effective for treatment of depression associated to inflammation (84). Agmatine, an endogenous neuromodulator, also promises to serve as adjuvant/monotherapy for depression. This reinforces the importance of antidepressant Nrf2 activators (85). Recently, another drug, cilostazol, manifests promising prophylactic antidepressant-like effect by activating the Nrf2 pathway as well as by recovering mitochondrial malfunction, which interrupts OS (86).

PI3K/Akt Pathway

Plenty of brain stroke studies have revealed that ROS/RNS not only directly oxidize cellular macromolecules, such as proteins, lipids, and nucleic acids, which are associated with oxidative damage, but are also involved in the cell apoptosis signaling pathways. The PI3K/Akt, MAPK/P38, and NF-κB pathways are three major OS-mediated pathway activators. Apoptosis mediated by cytochrome c is another important pathway that is mitochondria-dependent (87). In addition, there is growing evidence that the phosphatidylinositol 3-kinase (PI3K)/AKT pathway is associated with the pathophysiology of depression and the antidepressant-like effect of different compounds (88–90).

In recent years, numerous findings have been derived from both basic and clinical researches that suggest erythropoietin has the ability to fight the depressive-like symptoms. Through JAK2, erythropoietin and its receptor signaling activates plenty of downstream signaling pathways such as NF-κB, PI3K/Akt, MAPK, and STAT5, they are able to have a significant role in neuro-progression and inflammation in the CNS (91). Recently, Wu et al. concluded that following the activation and release of neuroinflammatory factor induced by stress, the probable mechanism relates to the idea that the AKT/GSK3β/CRMP-2 pathway changes the normal structure and function of the central nervous cell scaffold microtubule system, and subsequently

leads to depression (92). Moreover, Tao et al. proposed that liquiritigenin may reverse depression-like behavior in UCMS-induced animal models by modulating PI3K/Akt/mTOR mediated BDNF/TrkB signaling pathway (93). Several studies have shown that fluoxetine, creatine, atorvastatin, valproic acid as well as IGF-1 can all counteract depression-like behaviors via the PI3K/Akt Pathway (94–99).

MAPK/P38 Pathway

Earlier studies have shown that p38 MAPK, which can be stimulated by cytokine, can influence the neuroendocrine function, monoamine neurotransmission as well as other behaviorally-associated pathophysiological pathways (100). Felger et al. indicated that during chronic IFN-α treatment, depressive symptoms are highly related to the sensitivity of the p38 MAPK pathway to immune-stimuli (101). The MAO-A enzyme and p38 MAPK cascade are both involved in OS. These data and *in vitro* experiments demonstrate that the function of MAO-A is strongly inhibited by the p38 MAPK cascade. Thus, these published data indicate that the endogenous approach could be adopted to deal with OS and disorders like depression (102).

Recent research on neuroscience indicates that neurodegenerative pathways and OS pathways are both involved in depression. Bruchas et al. (103) found that the serotonin transporter can translocate to the plasma cell membrane, and that neurotransmitter-uptake is enhanced at the serotonergic nerve terminals when stress induces the activation of p38α MAPK. This finding strongly suggests that a cascade of molecular and cellular events is initiated by stress, and consequently the activation of p38α MAPK leads to a change in the hyposerotonergic state, which underlies drug-seeking and depression-like behaviors (103). MAPK and its phosphatase MKP are found to be implicated in depression and drug-addiction. Findings by Jia et al. supported the idea that there is a direct link between the phosphorylation of MAPK and depression induced by prolonged morphine withdrawal (104). In addition, Park et al. demonstrated that p38 MAPK inhibits the hypoxia response pathway (105). Moreover, Martín-Hernández et al. (106) showed that CMS increased the expression of activated MAPK p38 in addition to decreasing antioxidant transcriptional factor Nrf2. These results suggested that the translocated bacteria played a role through p38 MAPK, which aggravated oxidative injury and neuro-inflammation. This is possibly strongly linked to the pathophysiology of depression (106). These studies indicated an indirect relationship with depression, which requires further research.

Regarding drug therapy, the acute MAPK pathway was blocked, which resulted in depression-like symptoms and prevented the positive effects of ketamine. This fact suggests that the antidepressant response of ketamine is probably regulated by the MAPK pathway in some brain regions (107). Yang et al. reported that fluoxetine (FLX) is able to reduce NF-κB and p38 MAPK phosphorylation levels and may improve the anti-inflammatory consequence (108). Moreover, Moretti et al. extended the data relating to the anti-depressive-like effect of ascorbic acid, which distinctly decreased hippocampal phosphorylation of p38MAPK (109).

Autophagy

Increased autophagy has now been reported in the central nervous system after several different kinds of diseases, such as ICH. Autophagy is an essential intracellular pathway, which includes degradation and recycling of aged proteins and entire organelles (110, 111). The mTOR pathway, NF-κB pathway and PI3K pathway are major pathways involved in regulating autophagy.

The mTOR Signaling Cascade

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that belongs to the phosphoinositide kinase-related kinase family (PIKK family) and is a downstream effector of the PI3K/PKB (protein kinase B) signaling pathway. When its signaling pathway is activated, it has an important presence in regulating protein development, synthesis, proliferation and cell survival. Wang et al. conducted an experiment on mice to try to understand the negative effects of mTOR signaling (and its downstream products) on brain damage that results from ICH. It was found that if mTOR is blocked with rapamycin, PICs, scilicet, TNF-α, IL-6, IL-1β, and Caspase-3 all were upregulated indicating that apoptotic cell death could be reduced remarkably (112).

Several studies have found that ICH upregulated the expression level of miRNA-144 but decreased mTOR expression, which lead to increased inflammation and microglial autophagy. Their findings suggested that miRNA-144 was a critical regulator of autophagy by modulating mTOR (113). Later, another study published by Wang et al. indicated that miRNA-144 contributed to activated autophagy of microglia through the mTOR signaling pathway, which might be mediated by hemoglobin (114). More recently, Shi et al. suggested that IL-17A is a mediator who promoted the activation of inflammation and autophagy in microglial cells (115).

Structural and neurochemical changes in the limbic system are related to depression. The limbic structures include the hippocampus, which plays an important part in controlling emotion and mood. How the mTOR signaling pathway is relating to depression is discussed in many studies. Severe damages in mTOR signaling are revealed in postmortem studies, especially the mTOR signaling that exists in the prefrontal cortex of MDD patients (116). Feng et al. proposed that the depressive disorder is related to PLD-mTOR signaling (117). Lately, studies suggest microRNAs (miRNAs or miRs) such as miR-124-3p are implicated in certain signaling pathways, which might be associated to the pathophysiological mechanism of MDD. It was also suggested that DNA damage-inducible transcript 4 (DDIT4) is an inhibitor of the mammalian target of rapamycin (mTOR) signaling pathway and positively correlates with the expression of miR-124-3p (118).

Recent investigations found that mTOR signaling is related to several types of antidepressant drugs. Yu et al. indicated that the antidepressant effects of ketamine, in patients who have depression, could be reversed by the mTOR signaling

inhibitor rapamycin (119). Cui et al. confirmed that by improving plasticity and neurogenesis, the mammalian target of rapamycin (mTOR) signaling pathway has an important role involved in mediating the antidepressant effect of ketamine (120). Nonetheless, drugs such as imipramine are not the same as ketamine, which could inhibit the PI3K/Akt/mTOR signaling to exert its antidepressant effect (116). Moreover, Liu et al. indicated that Resveratrol expresses antidepressant effects in CUMS-induced depressive-like animal models, which was partly mediated by its up-regulation of phosphor-Akt and mTOR expressions in the PFC and hippocampus playing a part in its antioxidant effects (121). Zhang et al. presented a new insight into the role of the dopaminergic system located in mesocortical region, which revealed antidepressant actions during the l-SPD mediated antidepressant process via the D1R/PKA/mTOR signaling cascade in the mPFC (122).

NF-κB Pathway

Numerous studies have demonstrated that in several disorders, autophagy is associated with inflammation. Moreover, as a critical controller in inflammation, NF-κB is either mediated by autophagy-related proteins or regulates autophagy directly. Shen et al. indicated that autophagy is activated after ICH, which may exacerbate ICH-induced cerebral damage in animal models. Furthermore, the regulation of the NF-κB pathway maybe a key reason that results in neuro-damage via its promotion of apoptosis and inflammation (123).

As we have described in the former part of this manuscript, the NF-κB pathway is an important pathway that links ICH and ICH-induced depression. Drugs such as Crocin, Icariin, Proanthocyanidin, Senegenin, and others all have antidepressant effects via the NF-κB pathway in ICH-induced depression patients.

Apoptosis

Study findings suggest that both necrosis and apoptosis following ICH causes cell death. Some experiments revealed that apoptotic cell death existed in brain tissues from both animal models and ICH patients (124, 125). DNA fragmentation and apoptotic cell death are a consequence of activated caspases that are a part of a series of overwhelmingly complicated apoptotic mechanisms. It has been reported that cell death in ICH-induced animal models results from apoptosis mediated by caspases (126, 127). Intrinsic and extrinsic pathways are mainly responsible for apoptosis.

Apoptotic Pathways

1. Death receptor-mediated apoptosis pathway—cell death signals are likely initiated by different stimuli, such as tumors, trauma or others. Subsequently, upstream signals bind to Fas-associated proteins that have associated death domains (FADD) and receptors. Then, caspase- 8 is activated via the p53, BCL-2, FAS, NF-κB, and others, which would ultimately lead to the activation of the executioner caspase. The effector caspases then activate endonucleases, resulting in DNA fragmentation, which subsequently orchestrates the dismantling of the whole cell structure.
2. Mitochondrial apoptosis pathway—often regulated by B-cell lymphoma-2 (BCL-2) family protein. As a trigger, intrinsic signals could inhibit the pro-apoptotic BCL-2 family protein and deactivate the anti-apoptotic function of BCL-2. Consequently, the mitochondria will release cytochrome c abundantly into the cytosol, which is a significant component of the complex, apoptotic protease activating factor-1 (APAF-1) and pro-caspase-9. Downstream effector molecules activated by the Cyt-c-Apaf- 1- Procaspase- 9 complex result in apoptosis.
3. Caspase-independent pathways—Apoptosis-inducing factor (AIF), as an intermembrane protein of mitochondrial, is regulated by p53 in the absent of APAF-I, and activated by the caspase-independent pathways.

Finally, together, procaspase-8,−9, cytochrome c and other signal proteins constitute the "apoptosome," which activates the initiator caspases such as caspase 8 and−9. After that, either the extrinsic or intrinsic apoptosis pathway delivers the cell death signal to the final executioner caspase (caspase-3,−6,−7) and subsequently initiates enzymes that degrade DNA, RNA and ribose. After the process of activating procaspase to caspase, programmed cell death is initiated (128).

Depression is a condition related to abnormal brain energy metabolism that is also marked with increased apoptosis in specific cerebral areas. Bay 60-7550 (Phosphodiesterase 2 inhibitors) has been shown to be a mediator in the apoptotic process, possibly via the SOD-cGMP/PKG-anti-apoptosis signaling pathway in neuronal cells, and by inhibiting PDE2; it may be a significant novel antidepressant therapy (129). Moreover, water extracted from Panax ginseng (WEG) has been used as a treatment of several CNS disorders. Ding et al. suggested previously that WEG performed antidepressant-like effects in animal models of depression that was treated for both chronic and acute stress. Its neuroprotective effect relies on corticosterone-induced apoptosis via the downregulation of cytochrome C, ICAD, caspase-3, caspase-9 and so on (130). Moreover, both risperidone, at medium dose, and paroxetine were reported to improve modified stress re-stress (SRS)-induced depressive- like behaviors with associated down-regulated levels of cytochrome-C and caspase-9 in several regions of the brain (131). In addition, a novel antidepressant drug, Agomelatine (AG), might play an important part in the pathophysiology of depression with the amelioration of the apoptotic cells and the increase of neurogenesis in the hippocampus (132). Moreover, Apocynum venetum leaf extract (AVLE) was also reported to exert antidepressant-like activities in CUMS-induced rat models, which possibly suppressed neuronal apoptosis by regulating the Bcl-2/Bax signaling pathways, and improved the BDNF expressions in the hippocampus (133). Overload of Ca^{2+} entry as well as excessive OS in neurons are the **two** main causes of depression. Recently, Demirdaş et al. reported that with the treatment of Duloxetine (DULOX), TRPM2 and TRPV1 channels (associated with Ca^{2+} entry-induced neuronal death), were regulated to reduce apoptosis in depression-like rats models (134).

TABLE 1 | The relationship among pathophysiology of ICH-induced depression, underlying signal pathways and its potential antidepressant drugs.

Pathophysiology of ICH-induced depression	Signal pathways	Antidepressant drugs
Inflammation	Toll-like receptors (18, 19)	Tianeptine (29), Ketamine (30), Fluoxetine (27), TDZD-8 (27)
	NF-kB mediated signal pathway (36, 37)	Crocin (45), Proanthocyanidin (46), Senegenin (47), Icariin (48), Geraniol (49), Chrysophanol (50)
	PPAR-γ-dependent pathway (54, 55)	Pioglitazone (60), Astragaloside IV (61), Rosiglitazone (64), Troglitazone (67), Atorvastatin (68), Folic acid (69)
	other signaling pathways (71)	TRPC3/6 inhibitor (73)
Oxidative stress	Nrf2 pathway (74–77)	Fluoxetine (81), 7,8-dihydroxyflavone (83), Sulforaphane (83), TBE-31 (84), MCE-1 (84), Agmatine (85), Cilostazol (86)
	the PI3K/Akt pathway (88–90)	Erythropoietin (91), Liquiritigenin (93), Fluoxetine (94), Creatine (95, 96), Atorvastatin (97), valproic acid (98), IGF-1 (99)
	the MAPK/P38 pathway (100)	Ketamine (107), Fluoxetine (108), Ascorbic acid (109)
Autophagy	mTOR signaling cascade (112)	Ketamine (119, 120), Imipramine (116), Resveratrol (121)
	NF-kB mediated signal pathway (123)	Crocin (45), Proanthocyanidin (46), Senegenin (47), Icariin (48), Geraniol (49), Chrysophanol (50)
	the PI3K/Akt pathway (116)	Erythropoietin (91), Liquiritigenin (93), Fluoxetine (94), Creatine (95, 96), Atorvastatin (97), valproic acid (98), IGF-1 (99)
Apoptosis	Death receptor-mediated apoptosis pathway Mitochondrial apoptosis pathway Caspase-independent pathways	Bay 60-7550 (129), Water extracted from Panax ginseng (130), Risperidone (131), Paroxetine (131), Agomelatine (132), Apocynum venetum leaf extract (133), Duloxetine (134)
	other signaling pathways (135, 137, 139)	Mefloquine (136), lncRNA TCONS_00019174 (139)

Other Pathways

Pannexins serves a significant role in the regulation of cellular signal transduction of glial cells and extracellular neuronal regenerative currents. Nevertheless, there have been no reported findings regarding the effects of pannexins in various cerebrovascular diseases. Zhou et al. first suggested that the upregulation of Pannexin-1 (Panx1) expression may be correlated with degeneration and apoptotic cell death of neurons in the rat cerebrum after ICH. Furthermore, he speculated that this may lead to subsequent cognitive dysfunction (135). Recently, Ni et al. used a broad-spectrum Panx1 inhibitor called Mefloquine (MFQ), demonstrating that the Panx1 channel played an important role in chronic stress and MFQ-induced depression and anxiety behaviors (136).

Recently, NIX was elucidated as a novel p75 neurotrophin receptor ($p75^{NTR}$) binding protein as well as a member of the pro-apoptotic BH3-only group of proteins. When exposed to glutamate, the connection between NIX and $p75^{NTR}$, there was marked increase in the apoptosis of neurons and activation of the JNK-p53-Bax pathway (137). Fujii et al. previously offered verification for the connection between the Ser205Leu polymorphism of the p75(NTR) gene as well as MDD, which indicated that the Leu205 allele provides a protective influence to fight the development of MDD (138).

In addition, Zhou et al. suggested that the Wnt/β-catenin signaling pathway is related to the level of proliferating cell nuclear antigen (PCNA) that is present in the cerebrum of the ICH rat, in addition to the rate of cell apoptosis, it could even regulate the balance of cell proliferation and apoptosis (139). Furthermore, Ni et al. (136) found that lncRNA TCONS_00019174 exerts an antidepressant effect in rats by activating the Wnt/β-catenin pathway (139).

These new signaling pathways are proposed as potential clinical therapeutic targets for depressive disorders. This may require further research in order to explore further the relationships between ICH and depression.

CONCLUSIONS

The pathophysiology of PSD is extremely complex; A multitude of ischemia-induced neurobiological mal-function as well as psychosocial distress are involved. The symptom for alterations of monoaminergic neurotransmitter systems has been well presented due to the injury of frontal-basal ganglia brainstem pathway. It has also been proved that there is a strong relationship between neuroinflammation and acute ischemic stroke: stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and the deficit of adaptive response (140).

In this review, we addressed the mechanisms and therapeutic targets of post-ICH depression. We divided the mechanisms into inflammation, oxidative stress, autophagy, and apoptosis, and clarified them through several signaling pathways. Inflammation is mainly related to TLRs, NF-κB mediated signal pathway, the PPAR-γ-dependent pathway and other signaling pathways. OS is related to Nrf2, the PI3K/Akt pathway and the MAPK/P38 pathway. Autophagy is associated with the mTOR signaling

cascade and NF-kB mediated signal pathway. Meanwhile, apoptosis is related to the death receptor-mediated apoptosis pathway, mitochondrial apoptosis pathway, caspase-independent pathways as well as other pathways. Based on the evidence listed above, we found that neuroinflammation, OS, autophagy and apoptosis interacted with each other. OS-related brain injury is part of the pathogenic mechanism of neutrophil infiltration that follows ICH (16). Inducible NOS (iNOS) is synthesized through the induction of proinflammatory cytokines, and the molecular mechanisms for NOS activation after ICH are primarily NF-kB dependent (141, 142). If NF-κB and antioxidative defense components can be inhibited, then OS and inflammation can be reduced via PPARγ; in the meantime, the cerebral damage caused by ICH would be improved. Proinflammatory cytokines, namely TNF-α and IL-1, could induce iNOS expression in microglial cells via the KC/p38MAFP/NF-kB pathway (143). Free radicals can also induce apoptosis, and antioxidant therapy could alleviate neuronal apoptosis after ICH (144, 145). The NF-kB pathway has also been detected to mediate Hb-induced apoptosis and autophagy (146). mTOR, as a downstream effector of the PI3K/PKB signaling pathway, also plays a significant part in CNS apoptosis and autophagy. Interactions of TLRs with pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) initiate signaling through myeloid differentiation primary response-88 (MyD88) and produce cytokines through the activation of the transcription factor nuclear factor kappa beta (NF-kB) (147). Furthermore, PPARγ could stimulate hematoma regression mediated by phagocytosis, and facilitate the cleanup of the hematomas, which may reduce the generation of inflammation and toxicity. Overall, from the assessed antidepressant drugs for ICH-induced depression, we found that several drugs exerted their antidepressant-like effects via different signaling pathways and may have different pathophysiological origins (e.g., ketamine could treat depression through mTOR signaling cascade, the MAPK/P38 pathway or TLR-related signal pathways). This could provide us with evidence that some underlying correlations may exist between different signaling pathways. However, this still requires more research.

In summary, our review presents the signaling pathways relevant to post-ICH depression. Additionally, it may provide several potential therapeutic targets for the treatment of patients who show depressive behavior after ICH (**Table 1**).

Depression has a complex relevance with enhanced mortality and morbidity in ICH patients. In spite of its great clinical evidence, the underlying etiological mechanisms are still worthy to be explored. To better understand its pathophysiology and to pursue a more promising outcome of post-ICH depression, therapeutic interventions have become progressively more important for future studies.

AUTHOR CONTRIBUTIONS

All authors participated in designing the concept of this manuscript. YW, LW, CY, and KH reviewed the literature and drafted the article. YZ, SZ, and AS finalized the paper and provided suggestions to improve it.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the american heart association. *Circulation* (2018) 137:e67–492. doi: 10.1161/CIR.0000000000000558
2. Gilsanz P, Walter S, Tchetgen Tchetgen EJ, Patton KK, Moon JR, Capistrant BD, et al. Changes in depressive symptoms and incidence of first stroke among middle-aged and older US adults. *J Am Heart Assoc.* (2015) 4:e001923. doi: 10.1161/JAHA.115.001923
3. Kim YR, Kim HN, Pak ME, Ahn SM, Hong KH, Shin HK, et al. Studies on the animal model of post-stroke depression and application of antipsychotic aripiprazole. *Behav Brain Res.* (2015) 287:294–303. doi: 10.1016/j.bbr.2015.03.062
4. Lenzi GL, Altieri M, Maestrini I. Post-stroke depression. *Rev Neurol.* (2008) 164:837–40. doi: 10.1016/j.neurol.2008.07.010
5. Koivunen RJ, Harno H, Tatlisumak T, Putaala J. Depression, anxiety, and cognitive functioning after intracerebral hemorrhage. *Acta Neurol Scand.* (2015) 132:179–84. doi: 10.1111/ane.12367
6. Stern-Nezer S, Eyngorn I, Mlynash M, Snider RW, Venkatsubramanian C, Wijman CAC, et al. Depression one year after hemorrhagic stroke is associated with late worsening of outcomes. *NeuroRehabilitation* (2017) 41:179–87. doi: 10.3233/NRE-171470
7. Mayer SA, Rincon F. Treatment of intracerebral haemorrhage. *Lancet Neurol.* (2005) 4:662–72. doi: 10.1016/S1474-4422(05)70195-2
8. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. *Stroke* (2011) 42:1781–6. doi: 10.1161/STROKEAHA.110.596718
9. Babu R, Bagley JH, Di C, Friedman AH, Adamson C. Thrombin and hemin as central factors in the mechanisms of intracerebral hemorrhage-induced secondary brain injury and as potential targets for intervention. *Neurosurg Focus* (2012) 32:E8. doi: 10.3171/2012.1.FOCUS11366
10. Elliott J, Smith M. The acute management of intracerebral hemorrhage: a clinical review. *Anesth Analg.* (2010) 110:1419–27. doi: 10.1213/ANE.0b013e3181d568c8
11. Felberg RA, Grotta JC, Shirzadi AL, Strong R, Narayana P, Hill-Felberg SJ, et al. Cell death in experimental intracerebral hemorrhage: the "black hole" model of hemorrhagic damage. *Ann Neurol.* (2002) 51:517–24. doi: 10.1002/ana.10160
12. Huang FP, Xi G, Keep RF, Hua Y, Nemoianu A, Hoff JT. Brain edema after experimental intracerebral hemorrhage: role of hemoglobin degradation products. *J Neurosurg.* (2002) 96:287–93. doi: 10.3171/jns.2002.96.2.0287
13. Lee KR, Kawai N, Kim S, Sagher O, Hoff JT. Mechanisms of edema formation after intracerebral hemorrhage: effects of thrombin on cerebral blood flow, blood-brain barrier permeability, and cell survival in a rat model. *J Neurosurg.* (1997) 86:272–8. doi: 10.3171/jns.1997.86.2.0272
14. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol.* (2012) 11:720–31. doi: 10.1016/S1474-4422(12)70104-7
15. Wang J, Dore S. Inflammation after intracerebral hemorrhage. *J Cereb Blood Flow Metab.* (2007) 27:894–908. doi: 10.1038/sj.jcbfm.9600403

16. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. *Prog Neurobiol.* (2010) 92:463–77. doi: 10.1016/j.pneurobio.2010.08.001
17. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol.* (2006) 5:53–63. doi: 10.1016/S1474-4422(05)70283-0
18. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol.* (2004) 4:499–511. doi: 10.1038/nri1391
19. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest.* (2012) 122:1164–71. doi: 10.1172/JCI58644
20. Sansing LH, Harris TH, Welsh FA, Kasner SE, Hunter CA, Kariko K. Toll-like receptor 4 contributes to poor outcome after intracerebral hemorrhage. *Ann Neurol.* (2011) 70:646–56. doi: 10.1002/ana.22528
21. Rodriguez-Yanez M, Brea D, Arias S, Blanco M, Pumar JM, Castillo J, et al. Increased expression of Toll-like receptors 2 and 4 is associated with poor outcome in intracerebral hemorrhage. *J Neuroimmunol.* (2012) 247:75–80. doi: 10.1016/j.jneuroim.2012.03.019
22. Lin S, Yin Q, Zhong Q, Lv FL, Zhou Y, Li JQ, et al. Heme activates TLR4-mediated inflammatory injury via MyD88/TRIF signaling pathway in intracerebral hemorrhage. *J Neuroinflamm.* (2012) 9:46. doi: 10.1186/1742-2094-9-46
23. Fang H, Wang PF, Zhou Y, Wang YC, Yang QW. Toll-like receptor 4 signaling in intracerebral hemorrhage-induced inflammation and injury. *J Neuroinflamm.* (2013) 10:27. doi: 10.1186/1742-2094-10-27
24. Keri S, Szabo C, Kelemen O. Expression of toll-like receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder. *Brain Behav Immun.* (2014) 40:235–43. doi: 10.1016/j.bbi.2014.03.020
25. Strekalova T, Evans M, Costa-Nunes J, Bachurin S, Yeritsyan N, Couch Y, et al. Tlr4 upregulation in the brain accompanies depression- and anxiety-like behaviors induced by a high-cholesterol diet. *Brain Behav Immun.* (2015) 48:42–7. doi: 10.1016/j.bbi.2015.02.015
26. Habib M, Shaker S, El-Gayar N, Aboul-Fotouh S. The effects of antidepressants "fluoxetine and imipramine" on vascular abnormalities and Toll like receptor-4 expression in diabetic and non-diabetic rats exposed to chronic stress. *PLoS ONE* (2015) 10:e0120559. doi: 10.1371/journal.pone.0120559
27. Cheng Y, Pardo M, Armini RS, Martinez A, Mouhsine H, Zagury JF, et al. Stress-induced neuroinflammation is mediated by GSK3-dependent TLR4 signaling that promotes susceptibility to depression-like behavior. *Brain Behav Immun.* (2016) 53:207–222. doi: 10.1016/j.bbi.2015.12.012
28. Garcia Bueno B, Caso JR, Madrigal JL, Leza JC. Innate immune receptor Toll-like receptor 4 signalling in neuropsychiatric diseases. *Neurosci Biobehav Rev.* (2016) 64:134–47. doi: 10.1016/j.neubiorev.2016.02.013
29. Slusarczyk J, Trojan E, Glombik K, Piotrowska A, Budziszewska B, Kubera M, et al. Targeting the NLRP3 inflammasome-related pathways via tianeptine treatment-suppressed microglia polarization to the M1 phenotype in lipopolysaccharide-stimulated cultures. *Int J Mol Sci.* (2018) 19:E1965. doi: 10.3390/ijms19071965
30. Tan S, Wang Y, Chen K, Long Z, Zou J. Ketamine alleviates depressive-like behaviors via down-regulating inflammatory cytokines induced by chronic restraint stress in mice. *Biol Pharm Bull.* (2017) 40:1260–7. doi: 10.1248/bpb.b17-00131
31. Beurel E. Regulation by glycogen synthase kinase-3 of inflammation and T cells in CNS diseases. *Front Mol Neurosci.* (2011) 4:18. doi: 10.3389/fnmol.2011.00018
32. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther.* (2015) 148:114–31. doi: 10.1016/j.pharmthera.2014.11.016
33. Martin M, Rehani K, Jope RS, Michalek SM. Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat Immunol.* (2005) 6:777–84. doi: 10.1038/ni1221
34. Yuskaitis CJ, Jope RS. Glycogen synthase kinase-3 regulates microglial migration, inflammation, and inflammation-induced neurotoxicity. *Cell Signal* (2009) 21:264–73. doi: 10.1016/j.cellsig.2008.10.014
35. Beurel E, Jope RS. Lipopolysaccharide-induced interleukin-6 production is controlled by glycogen synthase kinase-3 and STAT3 in the brain. *J Neuroinflamm.* (2009) 6:9. doi: 10.1186/1742-2094-6-9
36. Aronowski J, Hall CE. New horizons for primary intracerebral hemorrhage treatment: experience from preclinical studies. *Neurol Res.* (2005) 27:268–79. doi: 10.1179/016164105X25225
37. Wagner KR. Modeling intracerebral hemorrhage: glutamate, nuclear factor-kappa B signaling and cytokines. *Stroke* (2007) 38 (Suppl. 2):753–8. doi: 10.1161/01.STR.0000255033.02904.db
38. Su X, Wang H, Zhu L, Zhao J, Pan H, Ji X. Ethyl pyruvate ameliorates intracerebral hemorrhage-induced brain injury through anti-cell death and anti-inflammatory mechanisms. *Neuroscience* (2013) 245:99–108. doi: 10.1016/j.neuroscience.2013.04.032
39. Koo JW, Russo SJ, Ferguson D, Nestler EJ, Duman RS. Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proc Natl Acad Sci USA.* (2010) 107:2669–74. doi: 10.1073/pnas.0910658107
40. Lukic I, Mitic M, Djordjevic J, Tatalovic N, Bozovic N, Soldatovic I, et al. Lymphocyte levels of redox-sensitive transcription factors and antioxidative enzymes as indicators of pro-oxidative state in depressive patients. *Neuropsychobiology* (2014) 70:1–9. doi: 10.1159/000362841
41. Bortolotto V, Cuccurazzu B, Canonico PL, Grilli M. NF-kappaB mediated regulation of adult hippocampal neurogenesis: relevance to mood disorders and antidepressant activity. *Biomed Res Int.* (2014) 2014:612798. doi: 10.1155/2014/612798
42. Nadeem A, Ahmad SF, Al-Harbi NO, Fardan AS, El-Sherbeeny AM, Ibrahim KE, et al. IL-17A causes depression-like symptoms via NFkappaB and p38MAPK signaling pathways in mice: implications for psoriasis associated depression. *Cytokine* (2017) 97:14–24. doi: 10.1016/j.cyto.2017.05.018
43. Kim TK, Kim JE, Choi J, Park JY, Lee JE, Lee EH, et al. Local interleukin-18 system in the basolateral amygdala regulates susceptibility to chronic stress. *Mol Neurobiol.* (2017) 54:5347–58. doi: 10.1007/s12035-016-0052-7
44. Su WJ, Zhang Y, Chen Y, Gong H, Lian YJ, Peng W, et al. NLRP3 gene knockout blocks NF-kappaB and MAPK signaling pathway in CUMS-induced depression mouse model. *Behav Brain Res.* (2017) 322 (Pt A):1–8. doi: 10.1016/j.bbr.2017.01.018
45. Zhang L, Previn R, Lu L, Liao RF, Jin Y, Wang RK. Crocin, a natural product attenuates lipopolysaccharide-induced anxiety and depressive-like behaviors through suppressing NF-kB and NLRP3 signaling pathway. *Brain Res Bull.* (2018) 142:352–9. doi: 10.1016/j.brainresbull.2018.08.021
46. Jiang X, Liu J, Lin Q, Mao K, Tian F, Jing C, et al. Proanthocyanidin prevents lipopolysaccharide-induced depressive-like behavior in mice via neuroinflammatory pathway. *Brain Res Bull.* (2017) 135:40–46. doi: 10.1016/j.brainresbull.2017.09.010
47. Li H, Lin S, Qin T, Li H, Ma Z, Ma S. Senegenin exerts anti-depression effect in mice induced by chronic un-predictable mild stress via inhibition of NF-kappaB regulating NLRP3 signal pathway. *Int Immunopharmacol.* (2017) 53:24–32. doi: 10.1016/j.intimp.2017.10.001
48. Liu B, Xu C, Wu X, Liu F, Du Y, Sun J, et al. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. *Neuroscience* (2015) 294:193–205. doi: 10.1016/j.neuroscience.2015.02.053
49. Deng XY, Xue JS, Li HY, Ma ZQ, Fu Q, Qu R, et al. Geraniol produces antidepressant-like effects in a chronic unpredictable mild stress mice model. *Physiol Behav.* (2015) 152 (Pt A):264–71. doi: 10.1016/j.physbeh.2015.10.008
50. Zhang K, Liu J, You X, Kong P, Song Y, Cao L, et al. P2X7 as a new target for chrysophanol to treat lipopolysaccharide-induced depression in mice. *Neurosci Lett,* (2016) 613:60–5. doi: 10.1016/j.neulet.2015.12.043
51. Baranova IN, Kurlander R, Bocharov AV, Vishnyakova TG, Chen Z, Remaley AT, et al. Role of human CD36 in bacterial recognition, phagocytosis, and pathogen-induced JNK-mediated signaling. *J Immunol.* (2008) 181:7147–56. doi: 10.4049/jimmunol.181.10.7147
52. Fadok VA, Warner ML, Bratton DL, Henson PM. CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (alpha v beta 3). *J Immunol.* (1998) 161:6250–7.

53. Zeng Y, Tao N, Chung KN, Heuser JE, Lublin DM. Endocytosis of oxidized low density lipoprotein through scavenger receptor CD36 utilizes a lipid raft pathway that does not require caveolin-1. *J Biol Chem.* (2003) 278:45931–6. doi: 10.1074/jbc.M307722200
54. Sundararajan S, Gamboa JL, Victor NA, Wanderi EW, Lust WD, Landreth GE. Peroxisome proliferator-activated receptor-gamma ligands reduce inflammation and infarction size in transient focal ischemia. *Neuroscience* (2005) 130:685–96. doi: 10.1016/j.neuroscience.2004.10.021
55. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell* (1998) 93:241–52. doi: 10.1016/S0092-8674(00)81575-5
56. Flores JJ, Klebe D, Rolland WB, Lekic T, Krafft PR, Zhang JH. PPARgamma-induced upregulation of CD36 enhances hematoma resolution and attenuates long-term neurological deficits after germinal matrix hemorrhage in neonatal rats. *Neurobiol Dis.* (2016) 87:124–33. doi: 10.1016/j.nbd.2015.12.015
57. Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-gamma systems. *Mol Psychiatry* (2013) 18:154–65. doi: 10.1038/mp.2012.167
58. Agudelo LZ, Femenia T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V, et al. Skeletal muscle PGC-1alpha1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell* (2014) 159:33–45. doi: 10.1016/j.cell.2014.07.051
59. Colle R, de Larminat D, Rotenberg S, Hozer F, Hardy P, Verstuyft C, et al. PPAR-gamma agonists for the treatment of major depression: a review. *Pharmacopsychiatry* (2017) 50:49–55. doi: 10.1055/s-0042-120120
60. Liao L, Zhang XD, Li J, Zhang ZW, Yang CC, Rao CL, Zhou CJ, et al. Pioglitazone attenuates lipopolysaccharide-induced depression-like behaviors, modulates NF-kappaB/IL-6/STAT3, CREB/BDNF pathways and central serotonergic neurotransmission in mice. *Int Immunopharmacol.* (2017) 49:178–86. doi: 10.1016/j.intimp.2017.05.036
61. Song MT, Ruan J, Zhang RY, Deng J, Ma ZQ, Ma SP. Astragaloside IV ameliorates neuroinflammation-induced depressive-like behaviors in mice via the PPARgamma/NF-kappaB/NLRP3 inflammasome axis. *Acta Pharmacol Sin.* (2018) 39:1559–70. doi: 10.1038/aps.2017.208
62. Zeinoddini A, Sorayani M, Hassanzadeh E, Arbabi M, Farokhnia M, Salimi S, et al. Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. *Depress Anxiety* (2015) 32:167–73. doi: 10.1002/da.22340
63. Bonato JM, Bassani TB, Milani H, Vital M, de Oliveira RMW. Pioglitazone reduces mortality, prevents depressive-like behavior, and impacts hippocampal neurogenesis in the 6-OHDA model of Parkinson's disease in rats. *Exp Neurol.* (2018) 300:188–200. doi: 10.1016/j.expneurol.2017.11.009
64. Eissa Ahmed AA, Al-Rasheed NM, Al-Rasheed NM. Antidepressant-like effects of rosiglitazone, a PPARgamma agonist, in the rat forced swim and mouse tail suspension tests. *Behav Pharmacol.* (2009) 20:635–42. doi: 10.1097/FBP.0b013e328331b9bf
65. Zong J, Liao X, Ren B, Wang Z. The antidepressant effects of rosiglitazone on rats with depression induced by neuropathic pain. *Life Sci.* (2018) 203:315–22. doi: 10.1016/j.lfs.2018.04.057
66. Zhao Z, Zhang L, Guo XD, Cao LL, Xue TF, Zhao XJ, et al. Rosiglitazone exerts an anti-depressive effect in unpredictable chronic mild-stress-induced depressive mice by maintaining essential neuron autophagy and inhibiting excessive astrocytic apoptosis. *Front Mol Neurosci.* (2017) 10:293. doi: 10.3389/fnmol.2017.00293
67. d'Abramo C, Ricciarelli R, Pronzato MA, Davies P. Troglitazone, a peroxisome proliferator-activated receptor-gamma agonist, decreases tau phosphorylation in CHOtau4R cells. *J Neurochem.* (2006) 98:1068–77. doi: 10.1111/j.1471-4159.2006.03931.x
68. Shahsavarian A, Javadi S, Jahanabadi S, Khoshnoodi M, Shamsaee J, Shafaroodi H, et al. Antidepressant-like effect of atorvastatin in the forced swimming test in mice: the role of PPAR-gamma receptor and nitric oxide pathway. *Eur J Pharmacol.* (2014) 745:52–8. doi: 10.1016/j.ejphar.2014.10.004
69. Budni J, Lobato KR, Binfare RW, Freitas AE, Costa AP, Martin-de-Saavedra MD, et al. Involvement of PI3K, GSK-3beta and PPARgamma in the antidepressant-like effect of folic acid in the forced swimming test in mice. *J Psychopharmacol.* (2012) 26:714–23. doi: 10.1177/0269881111424456
70. Naziroglu M, Demirdas A. Psychiatric disorders and TRP channels: focus on psychotropic drugs. *Curr Neuropharmacol.* (2015) 13:248–57. doi: 10.2174/1570159X13666150304001606
71. Mizoguchi Y, Monji A. TRPC channels and brain inflammation. *Adv Exp Med Biol.* (2017) 976:111–121. doi: 10.1007/978-94-024-1088-4_10
72. Qin X, Liu Y, Zhu M, Yang Z. The possible relationship between expressions of TRPC3/5 channels and cognitive changes in rat model of chronic unpredictable stress. *Behav Brain Res.* (2015) 290:180–6. doi: 10.1016/j.bbr.2015.04.054
73. Buran I, Etem EO, Tektemur A, Elyas H. Treatment with TREK1 and TRPC3/6 ion channel inhibitors upregulates microRNA expression in a mouse model of chronic mild stress. *Neurosci Lett.* (2017) 656:51–7. doi: 10.1016/j.neulet.2017.07.017
74. Zhao X, Aronowski J. Nrf2 to pre-condition the brain against injury caused by products of hemolysis after ICH. *Transl Stroke Res.* (2013) 4:71–5. doi: 10.1007/s12975-012-0245-y
75. Shang H, Yang D, Zhang W, Li T, Ren X, Wang X, et al. Time course of Keap1-Nrf2 pathway expression after experimental intracerebral haemorrhage: correlation with brain oedema and neurological deficit. *Free Radic Res.* (2013) 47:368–75. doi: 10.3109/10715762.2013.778403
76. Wang J, Fields J, Zhao C, Langer J, Thimmulappa RK, Kensler TW, et al. Role of Nrf2 in protection against intracerebral hemorrhage injury in mice. *Free Radic Biol Med.* (2007) 43:408–14. doi: 10.1016/j.freeradbiomed.2007.04.020
77. Zhao X, Sun G, Zhang J, Strong R, Dash PK, Kan YW, et al. Transcription factor Nrf2 protects the brain from damage produced by intracerebral hemorrhage. *Stroke* (2007) 38:3280–6. doi: 10.1161/STROKEAHA.107.486506
78. Qaisiya M, Coda Zabetta CD, Bellarosa C, Tiribelli C. Bilirubin mediated oxidative stress involves antioxidant response activation via Nrf2 pathway. *Cell Signal* (2014) 26:512–20. doi: 10.1016/j.cellsig.2013.11.029
79. Maes M, Fisar Z, Medina M, Scapagnini G, Nowak G, Berk M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates–Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology* (2012) 20:127–50. doi: 10.1007/s10787-011-0111-7
80. Djordjevic J, Djordjevic A, Adzic M, Mitic M, Lukic I, Radojcic MB. Alterations in the Nrf2-Keap1 signaling pathway and its downstream target genes in rat brain under stress. *Brain Res.* (2015) 1602:20–31. doi: 10.1016/j.brainres.2015.01.010
81. Mendez-David I, Tritschler L, Ali ZE, Damiens MH, Pallardy M, David DJ, et al. Nrf2-signaling and BDNF: a new target for the antidepressant-like activity of chronic fluoxetine treatment in a mouse model of anxiety/depression. *Neurosci Lett.* (2015) 597:121–6. doi: 10.1016/j.neulet.2015.04.036
82. Martin-Hernandez D, Bris AG, MacDowell KS, Garcia-Bueno B, Madrigal JL, Leza JC, et al. Modulation of the antioxidant nuclear factor (erythroid 2-derived)-like 2 pathway by antidepressants in rats. *Neuropharmacology* (2016) 103:79–91. doi: 10.1016/j.neuropharm.2015.11.029
83. Yao W, Zhang JC, Ishima T, Dong C, Yang C, Ren Q, et al. Role of Keap1-Nrf2 signaling in depression and dietary intake of glucoraphanin confers stress resilience in mice. *Sci Rep.* (2016) 6:30659. doi: 10.1038/srep30659
84. Yao W, Zhang JC, Ishima T, Ren Q, Yang C, Dong C, et al. Antidepressant effects of TBE-31 and MCE-1, the novel Nrf2 activators, in an inflammation model of depression. *Eur J Pharmacol.* (2016) 793:21–7. doi: 10.1016/j.ejphar.2016.10.037
85. Freitas AE, Egea J, Buendia I, Gomez-Rangel V, Parada E, Navarro E, et al. Agmatine, by improving neuroplasticity markers and inducing Nrf2, prevents corticosterone-induced depressive-like behavior in mice. *Mol Neurobiol.* (2016) 53:3030–45. doi: 10.1007/s12035-015-9182-6
86. Abuelezz SA, Hendawy N. Insights into the potential antidepressant mechanisms of cilostazol in chronically restraint rats: impact on the Nrf2 pathway. *Behav Pharmacol.* (2018) 29:28–40. doi: 10.1097/FBP.0000000000000335
87. Chan PH. Mitochondria and neuronal death/survival signaling pathways in cerebral ischemia. *Neurochem Res.* (2004) 29:1943–9. doi: 10.1007/s11064-004-6869-x

88. Kitagishi Y, Kobayashi M, Kikuta K, Matsuda S. Roles of PI3K/AKT/GSK3/mTOR pathway in cell signaling of mental illnesses. *Depress Res Treat.* (2012) 2012:752563. doi: 10.1155/2012/752563
89. Shi HS, Zhu WL, Liu JF, Luo YX, Si JJ, Wang SJ, et al. PI3K/Akt signaling pathway in the basolateral amygdala mediates the rapid antidepressant-like effects of trefoil factor 3. *Neuropsychopharmacology* (2012) 37:2671–83. doi: 10.1038/npp.2012.131
90. Numakawa T, Adachi N, Richards M, Chiba S, Kunugi H. Brain-derived neurotrophic factor and glucocorticoids: reciprocal influence on the central nervous system. *Neuroscience* (2013) 239:157–72. doi: 10.1016/j.neuroscience.2012.09.073
91. Ma C, Cheng F, Wang X, Zhai C, Yue W, Lian Y, et al. Erythropoietin pathway: a potential target for the treatment of depression. *Int J Mol Sci.* (2016) 17:E677. doi: 10.3390/ijms17050677
92. Wu Z, Wang G, Wei Y, Xiao L, Wang H. PI3K/AKT/GSK3beta/CRMP-2-mediated neuroplasticity in depression induced by stress. *Neuroreport* (2018) 29:1256–63. doi: 10.1097/WNR.0000000000001096
93. Tao W, Dong Y, Su Q, Wang H, Chen Y, Xue W, et al. Liquiritigenin reverses depression-like behavior in unpredictable chronic mild stress-induced mice by regulating PI3K/Akt/mTOR mediated BDNF/TrkB pathway. *Behav Brain Res.* (2016) 308:177–86. doi: 10.1016/j.bbr.2016.04.039
94. Zeng B, Li Y, Niu B, Wang X, Cheng Y, Zhou Z, et al. Involvement of PI3K/Akt/FoxO3a and PKA/CREB signaling pathways in the protective effect of fluoxetine against corticosterone-induced cytotoxicity in PC12 cells. *J Mol Neurosci.* (2016) 59:567–78. doi: 10.1007/s12031-016-0779-7
95. Pazini FL, Cunha MP, Rosa JM, Colla AR, Lieberknecht V, Oliveira A, et al. Creatine, similar to ketamine, counteracts depressive-like behavior induced by corticosterone via PI3K/Akt/mTOR pathway. *Mol Neurobiol.* (2016) 53:6818–34. doi: 10.1007/s12035-015-9580-9
96. Cunha MP, Budni J, Ludka FK, Pazini FL, Rosa JM, Oliveira A, et al. Involvement of PI3K/Akt signaling pathway and its downstream intracellular targets in the antidepressant-like effect of creatine. *Mol Neurobiol.* (2016) 53:2954–68. doi: 10.1007/s12035-015-9192-4
97. Ludka FK, Constantino LC, Dal-Cim T, Binder LB, Zomkowski A, Rodrigues AL, et al. Involvement of PI3K/Akt/GSK-3beta and mTOR in the antidepressant-like effect of atorvastatin in mice. *J Psychiatr Res.* (2016) 82:50–7. doi: 10.1016/j.jpsychires.2016.07.004
98. Lima IVA, Almeida-Santos AF, Ferreira-Vieira TH, Aguiar DC, Ribeiro FM, Campos AC, et al. Antidepressant-like effect of valproic acid-Possible involvement of PI3K/Akt/mTOR pathway. *Behav Brain Res.* (2017) 329:166–71. doi: 10.1016/j.bbr.2017.04.015
99. Kuang WH, Dong ZQ, Tian LT, Li J. IGF-1 defends against chronic-stress induced depression in rat models of chronic unpredictable mild stress through the PI3K/Akt/FoxO3a pathway. *Kaohsiung J Med Sci.* (2018) 34:370–6. doi: 10.1016/j.kjms.2018.02.004
100. Hu X, Tao C, Gan Q, Zheng J, Li H, You C. Oxidative stress in intracerebral hemorrhage: sources, mechanisms, and therapeutic targets. *Oxid Med Cell Longev.* (2016) 2016:3215391. doi: 10.1155/2016/3215391
101. Felger JC, Alagbe O, Pace TW, Woolwine BJ, Hu F, Raison CL, et al. Early activation of p38 mitogen activated protein kinase is associated with interferon-alpha-induced depression and fatigue. *Brain Behav Immun.* (2011) 25:1094–8. doi: 10.1016/j.bbi.2011.02.015
102. Cao X, Rui L, Pennington PR, Chlan-Fourney J, Jiang Z, Wei Z, et al. Serine 209 resides within a putative p38(MAPK) consensus motif and regulates monoamine oxidase-A activity. *J Neurochem.* (2009) 111:101–10. doi: 10.1111/j.1471-4159.2009.06300.x
103. Bruchas MR, Schindler AG, Shankar H, Messinger DI, Miyatake M, Land BB, et al. Selective p38alpha MAPK deletion in serotonergic neurons produces stress resilience in models of depression and addiction. *Neuron* (2011) 71:498–511. doi: 10.1016/j.neuron.2011.06.011
104. Jia W, Liu R, Shi J, Wu B, Dang W, Du Y, et al. Differential regulation of MAPK phosphorylation in the dorsal hippocampus in response to prolonged morphine withdrawal-induced depressive-like symptoms in mice. *PLoS ONE* (2013) 8:e66111. doi: 10.1371/journal.pone.0066111
105. Park EC, Rongo C. The p38 MAP kinase pathway modulates the hypoxia response and glutamate receptor trafficking in aging neurons. *Elife* (2016) 5:e12010. doi: 10.7554/eLife.12010
106. Martin-Hernandez D, Caso JR, Bris AG, Maus SR, Madrigal JL, Garcia-Bueno B, et al. Bacterial translocation affects intracellular neuroinflammatory pathways in a depression-like model in rats. *Neuropharmacology* (2016) 103:122–33. doi: 10.1016/j.neuropharm.2015.12.003
107. Reus GZ, Vieira FG, Abelaira HM, Michels M, Tomaz DB, dos Santos MA, et al. MAPK signaling correlates with the antidepressant effects of ketamine. *J Psychiatr Res.* (2014) 55:15–21. doi: 10.1016/j.jpsychires.2014.04.010
108. Yang JM, Rui BB, Chen C, Chen H, Xu TJ, Xu WP, et al. Acetylsalicylic acid enhances the anti-inflammatory effect of fluoxetine through inhibition of NF-kappaB, p38-MAPK and ERK1/2 activation in lipopolysaccharide-induced BV-2 microglia cells. *Neuroscience* (2014) 275:296–304. doi: 10.1016/j.neuroscience.2014.06.016
109. Moretti M, Budni J, Ribeiro CM, Rieger DK, Leal RB, Rodrigues ALS. Subchronic administration of ascorbic acid elicits antidepressant-like effect and modulates cell survival signaling pathways in mice. *J Nutr Biochem.* (2016) 38:50–6. doi: 10.1016/j.jnutbio.2016.09.004
110. Klionsky DJ, Emr SD. Autophagy as a regulated pathway of cellular degradation. *Science* (2000) 290:1717–21. doi: 10.1126/science.290.5497.1717
111. De Duve C, Pressman BC, Gianetto R, Wattiaux R, Appelmans F. Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. *Biochem J.* (1955) 60:604–17.
112. Wang JP, Zhang MY. Role for target of rapamycin (mTOR) signal pathway in regulating neuronal injury after intracerebral hemorrhage. *Cell Physiol Biochem.* (2017) 41:145–53. doi: 10.1159/000455983
113. Yu A, Zhang T, Zhong W, Duan H, Wang S, Ye P, et al. miRNA-144 induces microglial autophagy and inflammation following intracerebral hemorrhage. *Immunol Lett.* (2017) 182:18–23. doi: 10.1016/j.imlet.2017.01.002
114. Wang Z, Yuan B, Fu F, Huang S, Yang Z. Hemoglobin enhances miRNA-144 expression and autophagic activation mediated inflammation of microglia via mTOR pathway. *Sci Rep.* (2017) 7:11861. doi: 10.1038/s41598-017-12067-2
115. Shi H, Wang J, Wang J, Huang Z, Yang Z. IL-17A induces autophagy and promotes microglial neuroinflammation through ATG5 and ATG7 in intracerebral hemorrhage. *J Neuroimmunol.* (2018) 323:143–51. doi: 10.1016/j.jneuroim.2017.07.015
116. Abelaira HM, Reus GZ, Neotti MV, Quevedo J. The role of mTOR in depression and antidepressant responses. *Life Sci.* (2014) 101:10–4. doi: 10.1016/j.lfs.2014.02.014
117. Feng P, Huang C. Phospholipase D-mTOR signaling is compromised in a rat model of depression. *J Psychiatr Res.* (2013) 47:579–85. doi: 10.1016/j.jpsychires.2013.01.006
118. Wang Q, Zhao G, Yang Z, Liu X, Xie P. Downregulation of microRNA1243p suppresses the mTOR signaling pathway by targeting DDIT4 in males with major depressive disorder. *Int J Mol Med.* (2018) 41:493–500. doi: 10.3892/ijmm.2017.3235
119. Yu JJ, Zhang Y, Wang Y, Wen ZY, Liu XH, Qin J, et al. Inhibition of calcineurin in the prefrontal cortex induced depressive-like behavior through mTOR signaling pathway. *Psychopharmacology* (2013) 225:361–72. doi: 10.1007/s00213-012-2823-9
120. Cui W, Ning Y, Hong W, Wang J, Liu Z, Li MD. Crosstalk between inflammation and glutamate system in depression: signaling pathway and molecular biomarkers for ketamine's antidepressant effect. *Mol Neurobiol.* (2018). doi: 10.1007/s12035-018-1306-3. [Epub ahead of print].
121. liu S, Li T, Liu H, Wang X, Bo S, Xie Y, et al. Resveratrol exerts antidepressant properties in the chronic unpredictable mild stress model through the regulation of oxidative stress and mTOR pathway in the rat hippocampus and prefrontal cortex. *Behav Brain Res.* (2016) 302:191–9. doi: 10.1016/j.bbr.2016.01.037
122. Zhang B, Guo F, Ma Y, Song Y, Lin R, Shen FY, et al. Activation of D1R/PKA/mTOR signaling cascade in medial prefrontal cortex underlying the antidepressant effects of l-SPD. *Sci Rep.* (2017) 7:3809. doi: 10.1038/s41598-017-03680-2

123. Shen X, Ma L, Dong W, Wu Q, Gao Y, Luo C, et al. Autophagy regulates intracerebral hemorrhage induced neural damage via apoptosis and NF-kappaB pathway. *Neurochem Int.* (2016) 96:100–12. doi: 10.1016/j.neuint.2016.03.004
124. Qureshi AI, Suri MF, Ostrow PT, Kim SH, Ali Z, Shatla AA, et al. Apoptosis as a form of cell death in intracerebral hemorrhage. *Neurosurgery* (2003) 52:1041–7. doi: 10.1227/01.NEU.0000057694.96978.BC
125. Wang YX, Yan A, Ma ZH, Wang Z, Zhang B, Ping JL, et al. Nuclear factor-kappaB and apoptosis in patients with intracerebral hemorrhage. *J Clin Neurosci.* (2011) 18:1392–5. doi: 10.1016/j.jocn.2010.11.039
126. Matsushita K, Meng W, Wang X, Asahi M, Asahi K, Moskowitz MA, et al. Evidence for apoptosis after intercerebral hemorrhage in rat striatum. *J Cereb Blood Flow Metab.* (2000) 20:396–404. doi: 10.1097/00004647-200002000-00022
127. Sun H, Li L, Zhou F, Zhu L, Ke K, Tan X, et al. The member of high temperature requirement family HtrA2 participates in neuronal apoptosis after intracerebral hemorrhage in adult rats. *J Mol Histol.* (2013) 44:369–79. doi: 10.1007/s10735-013-9489-4
128. Wu Z, Zou X, Zhu W, Mao Y, Chen L, Zhao F. Minocycline is effective in intracerebral hemorrhage by inhibition of apoptosis and autophagy. *J Neurol Sci.* (2016) 371:88–95. doi: 10.1016/j.jns.2016.10.025
129. Ding L, Zhang C, Masood A, Li J, Sun J, Nadeem A, et al. Protective effects of phosphodiesterase 2 inhibitor on depression- and anxiety-like behaviors: involvement of antioxidant and anti-apoptotic mechanisms. *Behav Brain Res.* (2014) 268:150–8. doi: 10.1016/j.bbr.2014.03.042
130. Jiang Y, Li Z, Liu Y, Liu X, Chang Q, Liao Y, et al. Neuroprotective effect of water extract of Panax ginseng on corticosterone-induced apoptosis in PC12 cells and its underlying molecule mechanisms. *J Ethnopharmacol.* (2015) 159:102–12. doi: 10.1016/j.jep.2014.10.062
131. Garabadu D, Ahmad A, Krishnamurthy S. Risperidone attenuates modified stress-re-stress paradigm-induced mitochondrial dysfunction and apoptosis in rats exhibiting post-traumatic stress disorder-like symptoms. *J Mol Neurosci.* (2015) 56:299–312. doi: 10.1007/s12031-015-0532-7
132. Yucel A, Yucel N, Ozkanlar S, Polat E, Kara A, Ozcan H, et al. Effect of agomelatine on adult hippocampus apoptosis and neurogenesis using the stress model of rats. *Acta Histochem.* (2016) 118:299–304. doi: 10.1016/j.acthis.2016.02.007
133. Li X, Wu T, Yu Z, Li T, Zhang J, Zhang Z, et al. Apocynum venetum leaf extract reverses depressive-like behaviors in chronically stressed rats by inhibiting oxidative stress and apoptosis. *Biomed Pharmacother.* (2018) 100:394–406. doi: 10.1016/j.biopha.2018.01.137
134. Demirdas A, Naziroglu M, Ovey IS. Duloxetine reduces oxidative stress, apoptosis, and Ca(2+) entry through modulation of TRPM2 and TRPV1 channels in the hippocampus and dorsal root ganglion of rats. *Mol Neurobiol.* (2017) 54:4683–95. doi: 10.1007/s12035-016-9992-1
135. Zhou L, Liu C, Wang Z, Shen H, Wen Z, Chen D, et al. Pannexin-1 is involved in neuronal apoptosis and degeneration in experimental intracerebral hemorrhage in rats. *Mol Med Rep.* (2018) 17:5684–91. doi: 10.3892/mmr.2018.8624
136. Ni M, He JG, Zhou HY, Lu XJ, Hu YL, Mao L, et al. Pannexin-1 channel dysfunction in the medial prefrontal cortex mediates depressive-like behaviors induced by chronic social defeat stress and administration of mefloquine in mice. *Neuropharmacology* (2018) 137:256–67. doi: 10.1016/j.neuropharm.2017.12.004
137. Shen J, Chen X, Li H, Wang Y, Huo K, Ke K. p75 neurotrophin receptor and its novel interaction partner, NIX, are involved in neuronal apoptosis after intracerebral hemorrhage. *Cell Tissue Res.* (2017) 368:13–27. doi: 10.1007/s00441-016-2510-y
138. Fujii T, Yamamoto N, Hori H, Hattori K, Sasayama D, Teraishi T, et al. Support for association between the Ser205Leu polymorphism of p75(NTR) and major depressive disorder. *J Hum Genet.* (2011) 56:806–9. doi: 10.1038/jhg.2011.107
139. Zhou L, Deng L, Chang NB, Dou L, Yang CX. Cell apoptosis and proliferation in rat brains after intracerebral hemorrhage: role of Wnt/beta-catenin signaling pathway. *Turk J Med Sci.* (2014) 44:920–7. doi: 10.3906/sag-1308-100
140. Villa RF, Ferrari F, Moretti A. Post-stroke depression: mechanisms and pharmacological treatment. *Pharmacol Ther.* (2018) 184:131–44. doi: 10.1016/j.pharmthera.2017.11.005
141. Li N, Worthmann H, Deb M, Chen S, Weissenborn K. Nitric oxide (NO) and asymmetric dimethylarginine (ADMA): their pathophysiological role and involvement in intracerebral hemorrhage. *Neurol Res.* (2011) 33:541–8. doi: 10.1179/016164111X13007856084403
142. Zhao X, Zhang Y, Strong R, Zhang J, Grotta JC, Aronowski J. Distinct patterns of intracerebral hemorrhage-induced alterations in NF-kappaB subunit, iNOS, and COX-2 expression. *J Neurochem.* (2007) 101:652–63. doi: 10.1111/j.1471-4159.2006.04414.x
143. Ryu J, Pyo H, Jou I, Joe E. Thrombin induces NO release from cultured rat microglia via protein kinase C, mitogen-activated protein kinase, and NF-kappa B. *J Biol Chem.* (2000) 275:29955–9. doi: 10.1074/jbc.M001220200
144. Lu H, Shen J, Song X, Ge J, Cai R, Dai A, et al. Protective effect of Pyrroloquinoline Quinone (PQQ) in rat model of intracerebral hemorrhage. *Cell Mol Neurobiol.* (2015) 35:921–30. doi: 10.1007/s10571-015-0187-5
145. Chang CF, Cho S, Wang J. (-)-Epicatechin protects hemorrhagic brain via synergistic Nrf2 pathways. *Ann Clin Transl Neurol.* (2014) 1:258–271. doi: 10.1002/acn3.54
146. Benvenisti-Zarom L, Chen-Roetling J, Regan RF. Inhibition of the ERK/MAP kinase pathway attenuates heme oxygenase-1 expression and heme-mediated neuronal injury. *Neurosci Lett.* (2006) 398:230–4. doi: 10.1016/j.neulet.2006.01.003
147. Pandey GN, Rizavi HS, Bhaumik R, Ren X. Innate immunity in the postmortem brain of depressed and suicide subjects: role of Toll-like receptors. *Brain Behav Immun.* (2018). doi: 10.1016/j.bbi.2018.09.024. [Epub ahead of print].

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Predictors of Remission of Early-Onset Poststroke Depression and the Interaction Between Depression and Cognition During Follow-Up

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Objectives: This study aimed to examine the rate of remission in individuals experiencing early-onset poststroke depression (PSD) in China and to identify predictors of remission during a 3-month follow-up. This study also explored the interaction between cognitive impairment and depression.

Methods: A total of 820 patients with PSD from a massive multicenter prospective cohort project in China (PRIOD) were included in the present study. Depressive symptoms were measured with the Hamilton Depression Rating Scale (17 Items, HDRS-17) at 2 weeks and the endpoint of the 3-month follow-up. The cut-off score of HDRS-17 (<8) was used to define remission of depression at the endpoint. The Mini-Mental State Exam (MMSE) was used to evaluate the cognitive impairment of the patients (at the 2-week follow-up and 3-month endpoint). The National Institutes of Health Stroke Scale (NIHSS) was used to measure the severity of stroke.

Results: (1) Six hundred and forty-two patients completed the 3-month follow-up, and 332 (51.7%) patients remitted by the end of the study. Univariate analyses indicated that there was a higher proportion of patients who had hypertension, frontal lobe lesion, basal ganglia lesion, poor outcome at 2 weeks, high scores on the NIHSS at 2 weeks, major life events within 3 months, and major medical diseases within 3 months in the nonremission group. In stepwise multiple logistic regression analyses, remission was significantly predicted by lower NIHSS scores at 2 weeks ($p = 0.001$, $OR = 1.086$, 95% CI 1.035–1.139), fewer major life events ($p = 0.036$, $OR = 5.195$, 95% CI 1.111–27.283), fewer major medical comorbidities ($p = 0.015$, $OR = 2.434$, 95% CI 1.190–4.979), and fewer frontal lobe lesions ($p = 0.042$, $OR = 1.717$, 95% CI 1.019–2.891). (2) After controlling for confounding variables, repeated measures analysis of variance revealed

a significant interaction between time (2 weeks vs. 3 months) and group (remitters vs. nonremitters) on MMSE scores [$F_{(1,532)} = 20.2$, $p < 0.001$].

Conclusions: Early-onset PSD patients with milder neurological impairment, fewer major life events, fewer major medical comorbidities and no frontal lobe lesion at baseline were more likely to achieve remission 3 months after stroke. Only remitters of PSD improved significantly in cognitive impairment after stroke.

The PRIOD trial is registered at http://www.isrctn.com/, number ISRCTN62169508.

Keywords: early-onset, poststroke depression, predictors of remission, cognitive impairment, follow-up

INTRODUCTION

Stroke is still the third leading cause of death, and the incidence rate of stroke has been increasing by 8.7% every year in China (1). However, a progressive decrease in stroke mortality and the subsequent increase of survivors with residual impairments and disabilities have been observed in recent years (2). Stroke can cause physical disability as well as essential emotional and cognitive complications, which can be seriously debilitating. Poststroke depression (PSD) is the most common psychiatric implication of stroke. The prevalence rate is estimated to be 41.8% in the first year following stroke (3), although the rate varies across studies due to methodological discrepancies. It is important to note that depression can result from physical disability (4), and vice versa. Emotional distress can also have a negative influence on the mortality, recovery, physical and cognitive functioning, and quality of life of stroke survivors (5–7).

The mechanisms of PSD are complex and likely to involve multifactorial interactions (8). Previous studies have identified robust predictors of PSD, such as level of functional impairment (4) and stroke severity (9). Sociodemographic factors, such as young/old age, female sex, low education, living alone, a neurotic personality, and unemployment, were often found to be associated with PSD (10–12). Some studies have revealed that patients were more likely to develop PSD if their lesions were on the left side, on the frontal lobe or in the basal ganglia (13–15), but inconsistent findings were also reported (16–18).

To better understand PSD, a few studies have focused on the natural progression and explored trajectories of depressive symptoms following stroke, but the results were far from conclusive (19). PSD cases present in the initial poststroke period may differ from those who develop PSD later, in terms of mechanism and symptomatology. It has been reported that neuroanatomical factors, such as left hemisphere lesions involving the basal ganglia, are responsible for the initial poststroke period depression (20), whereas psychological factors could contribute to both the initial period and later PSD (21). The term "early-onset PSD" is often used to describe the depressive symptoms that appear in the acute phase (within 1–2 weeks after the stroke attack) of stroke (22). Limited attention has been paid to the predictive factors of the remission of early-onset depressive symptoms over time. Therefore, knowledge about the predictors of remission of early-onset PSD is warranted to facilitate clinicians to make an optimal treatment plan, given that administration of antidepressants and nonpharmacological interventions remains controversial (23, 24).

Cognitive impairment after stroke has often been reported with various prevalence rates, possibly due to methodological differences such as the tools and timing of the cognitive evaluation (25, 26). Notably, cognitive impairment after stroke has been associated with reduced functional recovery, increased risk of mortality, and the possibility of evolving to degenerative diseases (27–30). There seems to be a complicated interaction between depressive symptoms and cognitive functioning in poststroke patients over time (31). Cognitive impairments partly overlap with depressive symptoms, and the two syndromes may coexist in patients suffering from stroke (32, 33). In some cases, cognitive impairment caused by stroke may increase the risk of PSD (34, 35); whereas in other cases, cognitive impairment may also result from the depressive symptoms (36). The relationship between PSD and cognitive impairment after stroke has not been sufficiently elucidated in previous studies.

To date, there have been some studies investigating the natural course of PSD, but very few of them specifically focused on early-onset PSD and its interaction with cognitive function over time. This is an important topic that is essential for improving both the long-term physical and psychological outcomes after stroke. The primary aim of this study was to describe the trajectory and outcome of early-onset PSD over a 3-month follow-up, with a focus on remission of depressive symptoms as well as its interaction with cognition. The hypothesis was that patients who remained depressed at the 3-month endpoint would be more likely to have had more severe functional impairments and more risk factors for developing PSD than patients who remitted from their depressive symptoms. The second hypothesis was that the remitters would have more significant cognitive improvements than nonremitters.

METHODS

Study Participants

The present study was part of a larger project: Incidence and Outcome of patients with poststroke Depression in China (PRIOD) (Project No. ISRCTN62169508, April 2008 to April

2010). PRIOD is a multicenter prospective cohort study with the participation of 56 hospitals (3). The project aimed to investigate the prevalence of PSD in China during a one-year follow-up period after first stroke onset and related risk factors for PSD.

The inclusion criteria of PRIOD were described in detail in a previous publication (3). In brief, patients who fulfilled the following criteria were enrolled in PRIOD: (1) a diagnosis of stroke according to the WHO diagnostic criteria, which was confirmed with CT or MR imaging; (2) onset of stroke within 14 days prior to recruitment; and (3) aged over 18 years old. The exclusion criteria of PRIOD were (1) patients with dementia or other neurological diseases that could affect cognitive functions; (2) patients with a history of or current major psychiatric disorders or alcohol or drug abuse; and (3) patients who did not appropriately communicate.

Data Collection and Scale Assessment

Eligible patients were consecutively enrolled in the present study. Patients' demographic information, medical history, personal history, family history, diagnostic information, and intervening measures were collected with a case report form at baseline. Major medical comorbidities were defined as cancer, severe cardiovascular disease (acute myocardial infarction, congestive heart failure, angina pectoris), severe kidney disease, and stroke relapse. Major life events were assessed using a self-designed form, and most of the items were adapted from "the list of threatening experiences," including the death of parents, spouses, or children, as well as serious family conflicts, family members suffering from serious illness, and divorce (37). All these events were commonly reported to cause moderate or marked long-term threat (37).

The stroke patients were screened for depression at 2 weeks after stroke, as was usually done in other studies in early-onset PSD (22, 38). The follow-up assessments were scheduled at 3 months after stroke, because this time point seemed to be a watershed for patients with PSD. Previous studies demonstrated that some biological features of early-onset PSD disappeared at or beyond 3 months after stroke (17, 39).

Experienced neurologists who implemented the scale assessment were blinded to the patients' clinical information. They all received standardized training for the assessments, and interrater reliability reached an acceptable level. Major or minor depression was determined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). DSM-IV suggests that a person should be considered to have mild depressive symptoms if he/she experienced at least 2, but less than 5, of the depressive symptoms listed as the diagnostic criteria for at least 2 weeks, and at least one of the symptoms must be either depressed mood or loss of pleasure/interest (40). The Hamilton Rating Scale for Depression-17 (41) was applied to monitor the degree of depression at the 2-week and 3-month follow-up points. The validity and reliability of the Chinese version HRSD-17 had been proven in previous studies (42). In the present study, early-onset depression was defined as the presence of a depressive episode at 2 weeks after stroke. Remission of depression was defined by the cut-off score on the HRSD-17 (<8) at the endpoint.

The National Institutes of Health Stroke Scale (NIHSS) was used to measure the severity of Stroke (43). The modified RANKIN scale (mRS) was used to assess the neural functional recovery after stroke at the baseline and at the 3-month follow-up point. In the present study, mRS < 2 represented a favorable prognosis (benign outcome), while mRS ≥ 2 indicated an unfavorable prognosis (poor outcome), as in previous studies (44, 45). Cognitive impairment was evaluated with the Mini-Mental State Examination (MMSE) (46). The score for the MMSE scale ranged from 1-30 points. The higher the score, the better the cognitive function.

In the present study, hemorrhagic stroke and ischemic stroke were determined by MRI or CT scan results. The images of MRI (T1 and T2 weighted, fluid-attenuated inversion-recovery sequence, diffusion weighted imaging) or CT scans were retrieved from clinical routine exams. The lesions responsible for the stroke event were identified and reported by radiologists from each site who were blinded to the patients' psychiatric diagnoses. All the research radiologists among various sites have received standard training regarding image interpretation. When the stroke lesions were located in more than one brain region, every affected region was identified, recorded and used in the statistical analyses.

Telephone or face-to-face interviews were conducted at the follow-up point of 2 weeks and 3 months after the stroke attack. Information about the death, stroke relapse, medication regimen, life events, mRS scores, MMSE, and HRSD-17 scores was collected. Antidepressants were prescribed by the treating physicians according to the patients' clinical needs and clinical practice guidelines for depression. Participants were also allowed to take psychotherapy of various types, durations and number of sessions. The use of antidepressants was recorded at 3 months after stroke, which was discussed in detail in our previous article (47).

Statistical Analysis

Data were analyzed with SPSS 23.0 (SPSS, Inc., IBM Company, USA). Comparisons between remitters and nonremitters with regard to sociodemographic characteristics, scores on the NIHSS and MMSE, functional outcomes as measured by the mRS, lesion locations, medical and personal history with respect to smoking, drinking, taking antidepressants, and receiving psychotherapy were performed using independent sample *t*-tests, Mann–Whitney *U* tests, Fisher's exact test, and chi-square tests, where appropriate. Multivariate logistic regression analyses with the backward Wald method were used to identify predictors of remission at the 3-month follow-up point. In the regression analyses, remission was entered as the dependent variable, and all variables that showed significant differences between the two groups in the aforementioned univariate analyses were entered as independent variables. Receiver operating characteristic (ROC) curves with the area under the curve values were calculated for remission, showing the predicted probabilities from the final model of logistic regression analysis.

Repeated measures analysis of variance (ANOVA) was performed for the Mini-Mental State Examination (MMSE)

scores with group (remitters vs. nonremitters) as the between-group factor, time (2 weeks vs. 3 months) as the within-group factor, and variables that showed significant differences between the two groups in the aforementioned univariate analyses as covariates. The effects of time, group, and the interaction between time and group were examined. A two-tailed probability value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Among 2828 patients who participated in PRIOD, 1992 patients were exclude because their HDRS scores were missing or they did not have depression (HDRS-17 total score = <7) 2 weeks after stroke. Among the remaining 836 patients with depression, 16 patients had a past history of mental disorders. Eight hundred and twenty PRIOD participants met the PSD criteria within 2 weeks after stroke and entered the present study for assessment. Therefore, the prevalence rate of PSD was 29.37% (820/2828). During the follow-up period from the beginning of the 2nd week to the end of the 3rd month, 10 patients died, 153 patients lost contact, and 15 patients lacked HRSD-17 scores. In the end, a total of 642 patients were included in the final analysis. They were divided into the nonremission group (HRSD-17 score $\geq$ 8, $n = 310$) and the remission group (HRSD-17 score $<$ 8, $n = 332$) according to the HRSD-17 score at the 3-month follow-up (**Figure 1**).

Comparison Between Patients Included and Those Excluded From the Analyses

Among 820 patients who entered the study, 178 patients were excluded from the analyses. The excluded patients ($n = 178$) did not differ significantly from the included patients ($n = 642$) with regard to gender (male: 64.04% vs. 59.66%, $p = 0.289$), marital status (married: 89.89% vs. 93.45%, $p = 0.107$), education status ($\geq$12 years of education: 42.24% vs. 35.78%, $p = 0.183$), stroke type (ischemic stroke: 77.97 vs. 77.88%, $p = 0.795$), first episode stroke (68.98 vs. 75.04%, $p = 0.059$), diabetes (28.32 vs. 22.84%, $p = 0.135$), hypertension (68.39 vs. 71.18%, $p = 0.475$), hyperlipidemia (23.57 vs. 19.44% $p = 0.255$), smoking (29.57 vs. 19.44%, $p = 0.255$), drinking (11.24 vs. 12.62%, $p = 0.620$), positive family history of stroke (24.56 vs. 18.50%, $p = 0.078$), stroke relapse (8.33 vs. 2.50%, $p = 0.134$), major life events (0.00 vs. 2.18%, $p = 1.000$), and basal ganglia lesion (47.75 vs. 51.25%, $p = 0.409$). However, there were significant differences in age (64.51 $\pm$ 11.67 vs. 61.80 $\pm$ 11.54, $p = 0.006$), NIHSS score at 2 weeks (5.25 $\pm$ 3.95 vs. 4.08 $\pm$ 3.46, $p < 0.001$), MMSE at 2 weeks (23.06 $\pm$ 6.36 vs. 24.66 $\pm$ 5.26, $p = 0.006$), HDRS-17 at 2 weeks (13.37 $\pm$ 4.60 vs. 12.24 $\pm$ 3.90, $p = 0.003$), major medical comorbidities (20.83 vs. 6.54%, $p = 0.022$), poor outcome at 2 weeks (67.80 vs. 56.23%, $p = 0.006$), taking antidepressants (62.22 vs. 18.07%, $p < 0.001$), receiving psychotherapy (32.26 vs. 9.03%, $p < 0.001$), and frontal lobe lesion (20.22% vs. 11.06%, $p < 0.001$) compared to the patients included in the analysis. The two groups of patients were compared in order to determine whether the patients included in the following analyses were representative of the whole sample, and whether the conclusion could be generalized to other populations.

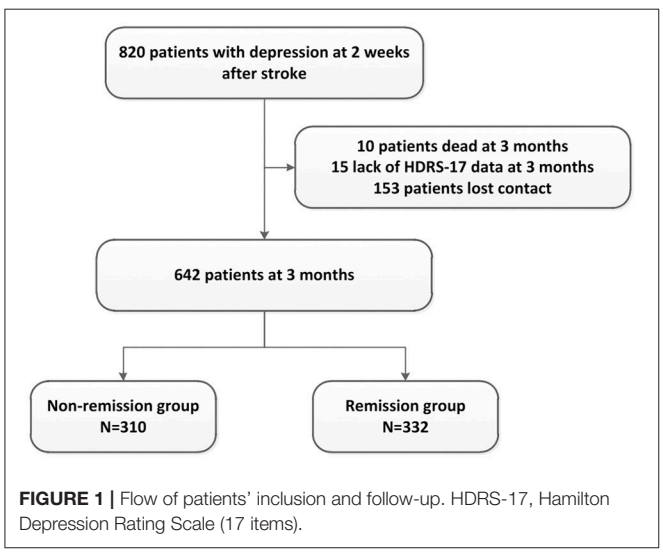

FIGURE 1 | Flow of patients' inclusion and follow-up. HDRS-17, Hamilton Depression Rating Scale (17 items).

Comparison of Demographic and Clinical Characteristics Between Remitters and Non-remitters at 3 Months After Stroke

At the end of the 3-month follow-up, there were 332 (51.7%) remitters and 310 (48.3%) nonremitters determined by the cut-off point of the HDRS-17 total score. The average total score on the HDRS-17 was 13.33 $\pm$ 4.63 in nonremitters and 3.89 $\pm$ 2.14 in the remitters. The baseline demographic and clinical characteristics of remitters and nonremitters at the 3-month follow-up are presented in **Table 1**. Univariate analyses indicated that there was a higher proportion of patients with hypertension (74.92 vs. 67.69%, $p = 0.046$), frontal lobe lesion (13.87 vs. 8.44%, $p = 0.028$), basal ganglia lesion (55.48 vs. 47.29%, $p = 0.038$), poor outcome at 2 weeks (61.29 vs. 51.51%, $p = 0.013$), high scores on NIHSS at 2 weeks (4.61 $\pm$ 3.67 vs. 3.59 $\pm$ 3.18, $p < 0.001$), major life events within 3 months (3.87 vs. 0.60%, $p = 0.005$), and major medical comorbidities at 3 months (9.68 vs. 3.61%, $p = 0.002$) in the nonremission group. On the other hand, remitters had a low HDRS-17 total score (11.42 $\pm$ 3.32 vs. 13.11 $\pm$ 4.27, $p < 0.001$) at 2 weeks.

Exploring the Independent Predictors of Remission at 3 Months After Stroke

Stepwise multivariate logistic regression analyses were used to identify predictors of remission of PSD at 3 months. In the regression analyses, remission was entered as the dependent variable, and all variables that showed significant differences between two groups in the aforementioned univariate analyses were entered as independent variables. The results are shown in **Table 2**. Remission was significantly predicted by lower NIHSS scores at 2 weeks ($p = 0.001$, $OR = 1.086$, 95% CI 1.035–1.139), fewer major life events ($p = 0.036$, $OR = 5.195$, 95% CI 1.111–27.283), fewer major medical comorbidities ($p = 0.015$, $OR = 2.434$, 95% CI 1.190–4.979), and not having frontal lobe lesions ($p = 0.042$, $OR = 1.717$, 95% CI 1.019–2.891). **Figure 2**

TABLE 1 | Comparison of demographic and clinical characteristics between remitters and nonremitters at 3 months.

Variables	Remitters ($n = 332$)	Nonremitters ($n = 310$)	X^2	p-value
DEMOGRAPHIC CHARACTERISTICS				
Age (mean ± SD)	61.67 ± 11.64	61.93 ± 11.45	–	0.734
Male (%)	61.45	57.74	0.914	0.339
Married (%)	93.05	93.87	0.176	0.675
Education ≥ 12 years (%)	36.56	34.95	0.179	0.672
VASCULAR RISK FACTORS				
Family history of stroke (%)	19.69	17.26	0.610	0.435
Smoking (%)	32.65	30.49	0.335	0.563
Drinking (%)	13.86	11.29	0.957	0.328
Diabetes (%)	20.68	25.17	1.785	0.182
Hypertension (%)	67.69	74.92	3.990	0.046*
Hyperlipidemia (%)	20.47	18.32	0.422	0.516
NEUROIMAGING CHARACTERISTICS				
Frontal lobe (%)	8.44	13.87	4.818	0.028*
Temporal lobe (%)	12.05	9.35	1.212	0.271
Parietal-occipital lobe (%)	15.96	14.52	0.260	0.610
Basal ganglia (%)	47.29	55.48	4.309	0.038*
Infratentorial region (%)	24.40	19.35	2.379	0.123
Left side lesion	34.91	36.21	0.115	0.734
CLINICAL VARIABLES				
Ischemic stroke (%)	79.82	75.80	1.499	0.221
First episode of stroke (%)	77.34	72.58	1.937	0.164
Poor outcome at 2 weeks (%)	51.51	61.29	6.236	0.013*
Taking antidepressants (%)	16.27	20.00	1.511	0.219
Receiving psychotherapy (%)	7.23	10.97	2.727	0.099*
Major life events (%)	0.60	3.87	8.029	0.005*
Major medical diseases (%)	3.61	9.68	9.638	0.002*
Stroke relapse (%)	2.11	2.90	0.409	0.523
NIHSS at 2 weeks (mean ± SD)	3.59 ± 3.18	4.61 ± 3.67	–	<0.001*
MMSE at 2 weeks (mean ± SD)	24.95 ± 4.89	24.31 ± 5.67	–	0.334
HDRS at 2 weeks (mean ± SD)	11.42 ± 3.32	13.11 ± 4.27	–	<0.001*
MMSE at 3 months (mean ± SD)	26.63 ± 3.65	24.72 ± 5.31	–	<0.001*
HDRS at 3 months (mean ± SD)	3.89 ± 2.14	13.33 ± 4.63	–	–

*SD, Standard Deviations; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental Exam; HRSD-17, Hamilton Depression Rating Scale (17 items); *P < 0.05.*

presents the ROC curve for the predicted probabilities from the final model of the multiple logistic regression analysis. The area under the ROC curve was estimated to be 0.637 ($p < 0.001$, 95% CI 0.593–0.680), indicating that the overall accuracy of the final model to predict patients' remission (with a predicted probability of 0.5 or greater) was acceptable.

Comparison Between Remitters and Nonremitters Regarding Longitudinal Changes in MMSE

At 2 weeks after stroke, there was no significant difference in MMSE between the two groups. However, nonremitters performed significantly poorer on MMSE than remitters at 3 months after stroke (**Table 1**). After controlling for NIHSS, hypertension, major life events, major medical comorbidities, frontal lobe lesion and basal ganglia lesion, the results of a repeated measures ANOVA revealed significant time (2 weeks vs. 3 months) *group (remitters vs. nonremitters) interaction on MMSE [$F_{(1, 532)} = 20.2$, $p < 0.001$]. In the remitter group, MMSE scores changed toward better performance from 2 weeks (24.95 ± 4.89) to 3 months (26.63 ± 3.65). In the non-remitter group, MMSE scores did not change from 2 weeks (24.31 ± 5.67) to 3 months (24.72 ± 5.31) (**Figure 3**).

DISCUSSION

This study systematically examined predictors of clinical remission of early-onset PSD and explored the potential interaction between depressive symptoms and cognitive impairment after stroke. The two hypotheses were both

TABLE 2 | Predictors of nonremission at 3 months (multivariate stepwise logistic regression model) ($n = 642$).

	B	S.E.	Wald	Sig.	OR	95% C.I.	
						Lower	Upper
NIHSS at 2 weeks	0.082	0.025	14.298	0.001	1.086	1.035	1.139
Major life events	1.648	0.787	4.368	0.036	5.195	1.111	24.283
Major medical comorbidities	0.890	0.365	5.938	0.015	2.434	1.190	4.979
Frontal lobe lesion	0.540	0.266	4.128	0.042	1.717	1.019	2.891
Basal ganglia lesion	0.283	0.168	2.829	0.093	1.328	0.954	1.847
Hypertension	0.313	0.184	2.902	0.088	1.367	0.954	1.960

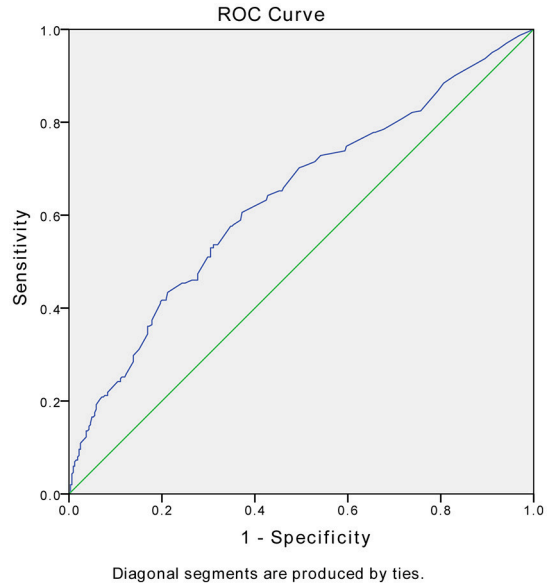

FIGURE 2 | Receiver operating characteristic (ROC) curves for the model of remission vs. nonremission**.** The area under the ROC curve was estimated to be 0.637 ($p < 0.001$, 95% CI 0.593–0.680).

confirmed by the results. Milder neurological impairment as indicated by NIHSS at 2 weeks, fewer major life events, fewer medical comorbidities and no frontal lobe lesion were significant predictors of the remission of PSD 3 months after stroke. These factors have been reported in previous studies as risk factors for the development of PSD (15, 48). For early-onset PSD patients, only remitters gained significant improvement in cognition over 3 months of follow-up.

Among the patients from PRIOD, 29.37% had depressive symptoms. This prevalence rate of PSD is close to most of the rates reported in previous studies, in which PSD was generally observed in approximately one-third of stroke cases, despite a large variety of criteria used to diagnose PSD (49–52). Among depressed patients who completed the 3-month follow-up, the remission rate was 51.7%. Some authors believe that the symptoms of PSD are self-limiting, and a longitudinal study reported that most patients diagnosed with acute PSD recovered (53). Previous studies demonstrated that approximately 50% of PSD patients would have symptom remission after 6 months, and the rate would increase to 89% at 12 months after stroke (54). Remission of PSD over the first a few months after stroke is vital, and symptom remission has been associated with higher recovery in the activity of daily living function for these patients (55).

The logistic regression analysis in the present study clearly confirmed that the course of PSD was a result of multifactorial interactions involving both biological and psychosocial determinants. Stroke severity and lesion locations served as the main biological factors in this study. Stroke severity, as indicated by NIHSS scores, has been one of the most consistent risk factors for PSD. A growing body of evidence has shown that the more severe the stroke is, the more likely a patient would develop PSD (26, 56). Higher NIHSS scores were associated with more severe depression after stroke. The results from Ilut et al.'s study suggested that the NIHSS score can predict the long-term prognosis of stroke, and a score over 11 could even bring a 9.4-fold higher probability of experiencing severe depression (15). This association may represent the biological mechanism of the pathophysiology of PSD. Severe stroke could lead to a series of biological changes in the brain and body, as well as psychological and functional alterations, all of which could contribute to the development of depression. Serious brain lesions may damage the function of some brain regions that are responsible for mood (57, 58). Much attention has been paid to the relationship between the onset of PSD and lesion locations, although this issue remains inconclusive (59, 60). Frontal lobe lesions were identified as a predictor of nonremission, which is in line with previous clinical and laboratory studies. Researchers have been trying to establish a connection between neuroimaging markers and the occurrence and development of depressive symptoms after stroke. Some neural circuits have been implicated in the development of both major depressive disorder and PSD (61–65), often involving frontal areas (51, 66, 67). On the one hand, the frontal lobe plays a critical role in regulating emotion and cognitive functions (68). On the other hand, metabolic changes were discovered in the frontal lobe in PSD patients through MRI spectroscopy (69). Experimental rats with middle cerebral artery occlusion (MCAO) were found to be 14 times more likely to exhibit depressive-like behaviors than sham-operated control rats, and BDNF levels were downregulated in certain brain regions in the frontal and other cortical regions (70). The prefrontal cortex has also been implicated in the bilateral internal carotid artery occlusion (BICAO) model as one of the several vulnerable brain areas associated with depressive-like

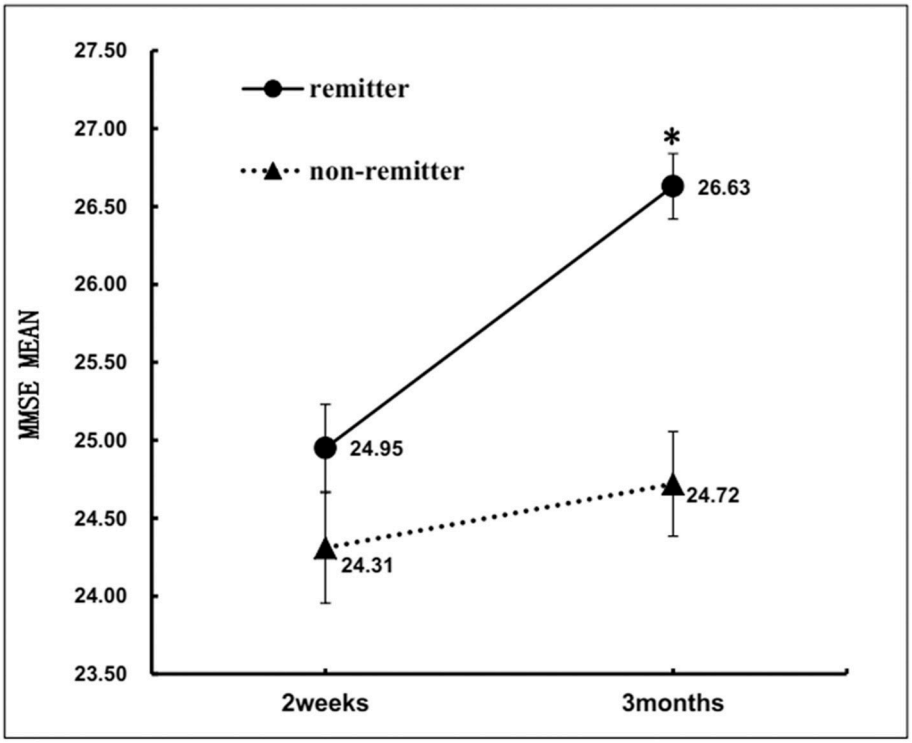

FIGURE 3 | Changes in MMSE scores over follow-up time in remitters and nonremitters. *$p < 0.001$.

behaviors after ischemia (71). PSD patients with frontal lobe lesions exhibited more persistent or recurrent symptoms than those without frontal lobe lesions in the first year after stroke onset (72).

Moreover, the stroke attack may also result in a decreased socioeconomic status, quality of life and general self-efficacy (GSE) (73), which contributed to a vicious circle between functional deficits and onset of PSD (74, 75). Other psychosocial factors include suffering from major medical comorbidity and exposure to major life events, which were also independent predictors of nonremission. Patients who underwent severe major medical diseases (including stroke relapse) after stroke attack may have an increased risk of depression onset or deterioration. Comorbid medical conditions may result in a patient's increased psychological burden, including a decline in the quality of life and rehabilitation faith, which may further cause depressed mood (76). Then, the depressed mood may in turn negatively affect the existing medical conditions, thus creating a vicious circle (77). Even in depressive patients who had no previous stroke, somatic symptoms have been reported to potentially worsen the outcome of depressive disorder. A study in patients with major depressive disorder indicated that remission rates in patients with more severe somatic symptoms were significantly lower than those in patients without somatic symptoms (78). Another 2-year follow-up study showed that "somatic symptoms" was an independent predictor of a worse prognosis of MDD (79). Therefore, major medical comorbidities and their companying somatic symptoms may have a tremendous negative impact on the probability of remission of depression. In the general population, exposure to major life events is a risk factor for the subsequent development of the depressive disorder (80). Likewise, studies demonstrated that patients with PSD had more major life events than nondepressed stroke patients before and after 6 months of stroke onset (48, 81, 82). The present study found that major life events not only served as a risk factor for developing depression but also prevented PSD patients from achieving remission. Therefore, more medical attention should be paid to PSD patients experiencing major life events.

Hypertension and poor outcomes at week 2 showed statistical significance in the univariate analysis, but they were eventually removed in the multivariate logistic regression. Concerning hypertension, the present result suggested that it did not contribute to the symptom resolution of depression, which is consistent with previous literature (83). The chi-square test indicated that mRS scores were significantly lower in the remission group than in the nonremission group. Many studies have shown that functional impairments might play a key role in the pathogenesis and development of PSD (16, 54). In a review in 2014, the researchers revealed that depression was negatively associated with functional outcome in stroke survivors and that the severity of stroke was the most significant contributor to PSD (84). However, a poor functional outcome may also be due to stroke severity and major medical comorbidities, and these are

more robust independent predictors of remission in the present study.

The beneficial effects of antidepressant treatment in patients with PSD have been proved in a number of previous studies. These studies suggested noradrenaline reuptake inhibitors (NRIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs) all brought a considerable higher HAMD score reduction than the control treatments (85). There has also been a body of evidence indicating positive effects of cognitive behavioral psychotherapy in patients with PSD (86). However, neither antidepressants nor psychotherapy was associated with higher remission rate in the present study. PRIOD is a non-interventional study. Antidepressants and psychotherapies were used according patient's clinical needs with various doses, regimens, durations and number of sessions. These confounding factors could partly explain the inconsistent results with previous studies.

The present study also found a significant group (remitters vs. nonremitters) by time (from 2 weeks to 3 months) interaction with respect to MMSE scores, and only remitters had a significant improvement on the MMSE. Cognitive impairment and its relationship with depression in stroke survivors have long been of interest to the research community. Ischemic brain injury can cause both dementia (87) and depression (56). However, the causal relationship between cognitive impairment and depression after stroke remains debatable. In some studies, significant improvement had been achieved with regard to poststroke depressive symptoms during treatment with antidepressants, while cognitive function remained impaired (88–90). Therefore, some authors claimed that depressive symptoms might be secondary to cognitive impairment, which was caused by stroke and would follow its own course of recovery (88). However, cognitive functioning did not improve significantly in the aforementioned studies may be attributed partly to the inclusion of mixed cohorts of patients with various severities of depression. Patients with mild depressive disorder would not be expected to show cognitive improvement (32, 91). In Murata et al.'s study, only patients with major depressive disorder were enrolled, and patients with a significant reduction in depression severity also showed significant cognitive improvement over time (32). Although the present research also included both major and mild depression, as described in the method section, the outcome measure is symptom remission rather than reduction of depression severity. In addition, the sample size of the present study is much larger than that of previous studies. Therefore, the discrepancies with some previous studies could possibly be due to these methodological differences. The interaction between cognitive function and depressive symptoms in patients with PSD warrants further exploration.

The strengths of the present study include a large sample size, a wide range of sociodemographic and clinical variables, and the exclusion of patients with a history of mental disorders. However, the results should be explained with caution due to the following methodological limitations. First, 21.7% patients were excluded from the analyses because of incomplete follow-up information, and they were significantly different from the included patients in some factors. For this reason, the conclusion could not be simply applied to all studied populations. Second, patients with dementia and severe aphasia were excluded from the present study, and the subjects enrolled had relatively moderate deficits in neurological function and lower mortality. The exclusion of patients with severe cognitive and neurological deficits may potentially prevent generalization of findings to all stroke patients. Third, the MMSE has been found to overestimate impairments in persons over age 60 and in persons with less than 9 years of education (92); thus, it may not be sensitive to the cognitive changes in the present sample. A more sensitive and detailed neuropsychological battery is needed to monitor the longitudinal changes in cognitive function in patients with early-onset PSD. Fourth, psychological determinants, such as personality and coping styles, also play an important role in the course of PSD, but they were not collected in the present study.

CONCLUSION

In conclusion, this study showed that approximately half of early-onset PSD patients remitted 3 months after stroke. Patients with less severe stroke, fewer major life events, fewer major medical comorbidities and frontal lobe lesions were more likely to have a favorable outcome regarding depression 3 months after stroke. Moreover, only remitters of PSD improved significantly in cognitive impairment after stroke. These results highlight the importance of early identification and intervention for patients with potentially persistent depression after stroke.

DATA AVAILABILITY STATEMENT

The datasets analyzed for this study can be found in the website: http://www.tt.zhinanmed.com/.

ETHICS STATEMENT

The PRIOD protocol was approved by the Medical Ethics Committee of Beijing TianTan Hospital, Capital Medical University. The project was carried out in accordance with the Declaration of Helsinki Guidelines, and all participants offered written consent form for the study.

AUTHOR CONTRIBUTIONS

JH and F-CZ wrote the draft of the manuscript. JH, F-CZ, BG, PY, and LZ organized the database. AW and F-CZ performed the statistical analysis. C-YW and CW contributed the revision of the final version. CW contributed conception and design of the study. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

1. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence, and Mortality of Stroke in China: results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation* (2017) 135:759–71. doi: 10.1161/CIRCULATIONAHA.116.025250
2. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Global Health* (2013) 1:e259–e81. doi: 10.1016/S2214-109X(13)70089-5
3. Zhang N, Wang CX, Wang AX, Bai Y, Zhou Y, Wang YL, et al. Time Course of Depression and One-Year Prognosis of Patients with Stroke in Mainland China. *CNS Neurosci Therapeut.* (2012) 18:475–81. doi: 10.1111/j.1755-5949.2012.00312.x
4. Ayerbe L, Ayis SA, Crichton S, Rudd AG, Wolfe CD. Explanatory factors for the association between depression and long-term physical disability after stroke. *Age Ageing* (2015) 44:1054–8. doi: 10.1093/ageing/afv132
5. Karaahmet OZ, Gurcay E, Avluk OC, Umay EK, Gundogdu I, Ecerkale O, et al. Poststroke depression: risk factors and potential effects on functional recovery. *Int J Rehabil Res.* (2017) 40:71–5. doi: 10.1097/MRR.0000000000000210
6. Shi YZ, Xiang YT, Yang Y, Zhang N, Wang S, Ungvari GS, et al. Depression after minor stroke: the association with disability and quality of life–a 1-year follow-up study. *Int J Geriat Psychiatry* (2016) 31:421–7. doi: 10.1002/gps.4353
7. Guajardo VD, Terroni L, Sobreiro Mde F, Zerbini MI, Tinone G, Scaff M, et al. The influence of depressive symptoms on quality of life after stroke: a prospective study. *J Stroke Cerebrovasc Dis.* (2015) 24:201–9. doi: 10.1016/j.jstrokecerebrovasdis.2014.08.020
8. Villa RF, Ferrari F, Moretti A. Post-stroke depression: Mechanisms and pharmacological treatment. Pharmacology & therapeutics (2018) 184:131–44. doi: 10.1016/j.pharmthera.2017.11.005
9. Wang Z, Zhu M, Su Z, Guan B, Wang A, Wang Y, et al. Post-stroke depression: different characteristics based on follow-up stage and gender-a cohort perspective study from Mainland China. *Neurol Res.* (2017) 39:996–1005. doi: 10.1080/01616412.2017.1364514
10. Eriksen S, Gay CL, Lerdal A. Acute phase factors associated with the course of depression during the first 18 months after first-ever stroke. *Disab Rehabilit.* (2016) 38:30–5. doi: 10.3109/09638288.2015.1009181
11. Kouwenhoven SE, Kirkevold M, Engedal K, Kim HS. Depression in acute stroke: prevalence, dominant symptoms and associated factors. A systematic literature review. *Disab Rehabilit.* (2011) 33:539–56. doi: 10.3109/09638288.2010.505997
12. Ouimet M, Primeau F, Cole M. Psychosocial risk factors in poststroke depression: a systematic review. *Can J Psychiatry* (2001) 46:819–28. doi: 10.1177/070674370104600905
13. Hama S, Yamashita H, Yamawaki S, Kurisu K. Post-stroke depression and apathy: Interactions between functional recovery, lesion location, and emotional response. *Psychogeriatrics* (2011) 11:68–76. doi: 10.1111/j.1479-8301.2011.00358.x
14. Rajashekaran P, Pai K, Thunga R, Unnikrishnan B. Post-stroke depression and lesion location: a hospital based cross-sectional study. *Indian J Psychiatry* (2013) 55:343. doi: 10.4103/0019-5545.120546
15. Ilut S, Stan A, Blesneag A, Vacaras V, Vesa S, Fodoreanu L. Factors that influence the severity of post-stroke depression. *J Med Life* (2017) 10:167.
16. Nys G, Van Zandvoort M, Van der Worp H, De Haan E, De Kort P, Kappelle L. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. *J Neurol Sci.* (2005) 228:27–33. doi: 10.1016/j.jns.2004.09.031
17. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. *Stroke* (2004) 35:794–802. doi: 10.1161/01.STR.0000117237.98749.26
18. Nickel A, Thomalla G. Post-stroke depression: impact of lesion location and methodological limitations—a topical review. *Front Neurol.* (2017) 8:498. doi: 10.3389/fneur.2017.00498
19. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. *Stroke* (2013) 44:1105–10. doi: 10.1161/STROKEAHA.111.679340
20. Herrmann M, Bartels C, Schumacher M, Wallesch C-W. Poststroke depression. Is there a pathoanatomic correlate for depression in the postacute stage of stroke? *Stroke* (1995) 26:850–6.
21. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical–clinical correlates of major post-stroke depression. *Br J Psychiatry* (1999) 175:163–7. doi: 10.1192/bjp.175.2.163
22. Geng LY, Qian FY, Qian JF, Zhang ZJ. The combination of plasma glutamate and physical impairment after acute stroke as a potential indicator for the early-onset post-stroke depression. *J Psychosomat Res.* (2017) 96:35–41. doi: 10.1016/j.jpsychores.2017.01.006
23. Ayerbe L, Ayis S, Crichton SL, Rudd AG, Wolfe CD. Explanatory factors for the increased mortality of stroke patients with depression. *Neurology* (2014) 83:2007–12. doi: 10.1212/WNL.0000000000001029
24. Sun Y, Liang Y, Jiao Y, Lin J, Qu H, Xu J, et al. Comparative efficacy and acceptability of antidepressant treatment in poststroke depression: a multiple-treatments meta-analysis. *BMJ open* (2017) 7:e016499. doi: 10.1136/bmjopen-2017-016499
25. Hoffmann M, Schmitt F, Bromley E. Vascular cognitive syndromes: relation to stroke etiology and topography. *Acta Neurol Scand.* (2009) 120:161–9. doi: 10.1111/j.1600-0404.2008.01145.x
26. Sun N, Li Q-J, Lv D-M, Man J, Liu X-S, Sun M-L. A survey on 465 patients with post-stroke depression in China. *Arch Psychiatric Nurs.* (2014) 28:368–71. doi: 10.1016/j.apnu.2014.08.007
27. Barker-Collo S, Feigin V. The impact of neuropsychological deficits on functional stroke outcomes. *Neuropsychol Rev.* (2006) 16:53–64. doi: 10.1007/s11065-006-9007-5
28. Farner L, Wagle J, Engedal K, Flekkøy KM, Wyller TB, Fure B. Depressive symptoms in stroke patients: a 13month follow-up study of patients referred to a rehabilitation unit. *J Affect Disord.* (2010) 127:211–8. doi: 10.1016/j.jad.2010.05.025
29. Hobson P, Meara J. Cognitive function and mortality in a community-based elderly cohort of first-ever stroke survivors and control subjects. *J Stroke Cerebrovasc Dis.* (2010) 19:382–7. doi: 10.1016/j.jstrokecerebrovasdis.2009.07.006
30. T O'Brien J, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. *Lancet Neurol.* (2003) 2:89–98. doi: 10.1016/S1474-4422(03)00305-3
31. Terroni L, Sobreiro MF, Conforto AB, Adda CC, Guajardo VD, Lucia MCSd, et al. Association among depression, cognitive impairment and executive dysfunction after stroke. *Dement Neuropsychol.* (2012) 6:152–7. doi: 10.1590/S1980-57642012DN06030007

32. Murata Y, Kimura M, Robinson RG. Does cognitive impairment cause poststroke depression? *Am J Geriat Psychiatry* (2000) 8:310–7. doi: 10.1097/00019442-200011000-00007
33. Rose E, Ebmeier K. Pattern of impaired working memory during major depression. *J Affect Disord* (2006) 90:149–61. doi: 10.1016/j.jad.2005.11.003
34. Elbaz A, Vicente-Vytopilova P, Tavernier B, Sabia S, Dumurgier J, Mazoyer B, et al. Motor function in the elderly Evidence for the reserve hypothesis. *Neurology* (2013) 81:417–26. doi: 10.1212/WNL.0b013e31829d8761
35. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* (2009) 8:1006–18. doi: 10.1016/S1474-4422(09)70236-4
36. Kauhanen M-L, Korpelainen J, Hiltunen P, Brusin E, Mononen H, Määttä R, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke* (1999) 30:1875–80. doi: 10.1161/01.STR.30.9.1875
37. Brugha T, Bebbington P, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med.* (1985) 15:189–94. doi: 10.1017/S003329170002105X
38. Wongwandee M, Tangwongchai S, Phanthumchinda K. Relationship between poststroke depression and ischemic lesion location. *J Med Assoc Thail Chotmaihet Thangphaet* (2012) 95:330–6. Available online at: http://www.thaiscience.info/journals/Article/JMAT/10971416.pdf
39. Hosking SG, Marsh NV, Friedman PJ. Depression at 3 months poststroke in the elderly: predictors and indicators of prevalence. *Aging Neuropsychol Cogn.* (2000) 7:205–16. doi: 10.1076/anec.7.4.205.798
40. American PAA. Diagnostic and statistical manual of mental disorders. Psychiatry Research (1994) 189:158–9.
41. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry (*1960) 23:56. doi: 10.1136/jnnp.23.1.56
42. Zheng Y, Zhao J, Phillips M, Liu J, Cai M, Sun S, et al. Validity and reliability of the Chinese Hamilton depression rating scale. *Br J Psychiatry* (1988) 152:660–4. doi: 10.1192/bjp.152.5.660
43. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
44. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke* (1999) 30:1538–41. doi: 10.1161/01.STR.30.8.1538
45. Uyttenboogaart M, Stewart RE, Vroomen PC, De Keyser J, Luijckx G-J. Optimizing cutoff scores for the Barthel index and the modified Rankin scale for defining outcome in acute stroke trials. *Stroke* (2005) 36:1984–7. doi: 10.1161/01.STR.0000177872.87960.61
46. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Research* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
47. Yuan HW, Wang CX, Zhang N, Bai Y, Shi YZ, Zhou Y, et al. Poststroke depression and risk of recurrent stroke at 1 year in a Chinese cohort study. *PLoS ONE* (2012) 7:e46906. doi: 10.1371/journal.pone.0046906
48. Bush BA. Major life events as risk factors for post-stroke depression. *Brain Injury* (1999) 13:131–7. doi: 10.1080/026990599121791
49. Gandolfo C, Provinciali L, Torta R, Toso V, Group tDS. The Italian multicenter observational study on post–stroke depression (DESTRO). *J Neurol.* (2006) 253:556–62. doi: 10.1007/s00415-006-0058-6
50. Townend B, Whyte S, Desborough T, Crimmins D, Markus R, Levi C, et al. Longitudinal prevalence and determinants of early mood disorder post-stroke. *J Clin Neurosci.* (2007) 14:429–34. doi: 10.1016/j.jocn.2006.01.025
51. Vataja R, Leppävuori A, Pohjasvaara T, Mäntylä R, Aronen HJ, Salonen O, et al. Poststroke depression and lesion location revisited. *J Neuropsychiatry Clin. Neurosci.* (2004) 16:156–62. doi: 10.1176/jnp.16.2.156
52. Verdelho A, Henon H, Lebert F, Pasquier F, Leys D. Depressive symptoms after stroke and relationship with dementia A three-year follow-up study. *Neurology* (2004) 62:905–11. doi: 10.1212/01.WNL.0000115107.66957.8C
53. Bour A, Rasquin S, Aben I, Boreas A, Limburg M, Verhey F. A one-year follow-up study into the course of depression after stroke. *J Nutr Health Aging* (2010) 14:488–93. doi: 10.1007/s12603-010-0033-x
54. Robinson RG, Spalletta G. Poststroke depression: a review. *Can J Psychiatry* (2010) 55:341–9. doi: 10.1177/070674371005500602
55. Chemerinski E, Robinson RG, Kosier JT. Improved recovery in activities of daily living associated with remission of poststroke depression. *Stroke* (2001) 32:113–7. doi: 10.1161/01.STR.32.1.113
56. Alajbegovic A, Djelilovic-Vranic J, Alajbegovic S, Nakicevic A, Todorovic L, Tiric-Campara M. Post stroke depression. *Med Arch.* (2014) 68:47–50. doi: 10.5455/medarh.2014.68.47-50
57. Wei C, Zhang F, Chen L, Ma X, Zhang N, Hao J. Factors associated with post-stroke depression and fatigue: lesion location and coping styles. *J Neurol.* (2016) 263:269–76. doi: 10.1007/s00415-015-7958-2
58. Zhang Y, Zhao H, Fang Y, Wang S, Zhou H. The association between lesion location, sex and poststroke depression: meta-analysis. *Brain Behav.* (2017). doi: 10.1002/brb3.788
59. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. *Lancet* (2000) 356:122–6. doi: 10.1016/S0140-6736(00)02448-X
60. Santos M, Kövari E, Gold G, Bozikas VP, Hof PR, Bouras C, et al. The neuroanatomical model of post-stroke depression: towards a change of focus? *J Neurol Sci.* (2009) 283(1–2):158–62. doi: 10.1016/j.jns.2009.02.334
61. Meyer J. Neuroimaging markers of cellular function in major depressive disorder: implications for therapeutics, personalized medicine, and prevention. *Clin Pharmacol Therapeut.* (2012) 91:201–14. doi: 10.1038/clpt.2011.285
62. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* (2008) 213:93–118. doi: 10.1007/s00429-008-0189-x
63. Terroni L, Amaro Jr E, Iosifescu DV, Tinone G, Sato JR, Leite CC, et al. Stroke lesion in cortical neural circuits and post-stroke incidence of major depressive episode: a 4-month prospective study. *World J Biol Psychiatry* (2011) 12:539–48. doi: 10.3109/15622975.2011.562242
64. Lorenzetti V, Allen NB, Fornito A, Yücel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J Affect Disord.* (2009) 117:1–17. doi: 10.1016/j.jad.2008.11.021
65. Eker C, Gonul AS. Volumetric MRI studies of the hippocampus in major depressive disorder: meanings of inconsistency and directions for future research. *World J Biol Psychiatry* (2010) 11:19–35. doi: 10.1080/15622970902737998
66. Vataja R, Pohjasvaara T, Leppävuori A, Mäntylä R, Aronen HJ, Salonen O, et al. Magnetic resonance imaging correlates of depression after ischemic stroke. *Arch Gen Psychiatry* (2001) 58:925–31. doi: 10.1001/archpsyc.58.10.925
67. Tang WK, Lu JY, Chen YK, Chu WC, Mok V, Ungvari GS, et al. Association of frontal subcortical circuits infarcts in poststroke depression: a magnetic resonance imaging study of 591 Chinese patients with ischemic stroke. *J Geriat Psychiatry Neurol.* (2011) 24:44–9. doi: 10.1177/0891988710392375
68. Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Res Neuroimaging* (2009) 174:81–8. doi: 10.1016/j.pscychresns.2009.03.012
69. Glodzik-Sobanska L, Slowik A, McHugh P, Sobiecka B, Kozub J, Rich KE, et al. Single voxel proton magnetic resonance spectroscopy in post-stroke depression. *Psychiatry Res Neuroimaging* (2006) 148:111–20. doi: 10.1016/j.pscychresns.2006.08.004
70. Ifergane G, Boyko M, Frank D, Shiyntum HN, Grinshpun J, Kuts R, et al. Biological and behavioral patterns of post-stroke depression in rats. *Can J Neurol Sci.* (2018):1–11. doi: 10.1017/cjn.2017.302
71. Liu S, Han S, Dai Q, Li S, Li J. BICAO-induced ischaemia caused depressive-like behaviours and caspase-8/-9-dependent brain regional neural cell apoptosis in mice. *Stroke Vasc Neurol.* (2018) 3:1–8. doi: 10.1136/svn-2017-000109
72. Shi Y-Z, Xiang Y-T, Wu S-L, Zhang N, Zhou J, Bai Y, et al. The relationship between frontal lobe lesions, course of post-stroke depression, and 1-year prognosis in patients with first-ever ischemic stroke. *PLoS ONE* (2014) 9:e100456. doi: 10.1371/journal.pone.0100456
73. Dabrowska-Bender M, Milewska M, Gołabek A, Duda-Zalewska A, Staniszewska A. The impact of ischemic cerebral stroke on the quality of life of patients based on clinical, social, and psychoemotional factors. *J Stroke Cerebrovasc Dis.* (2017) 26:101–7. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.036

74. Volz M, Möbus J, Letsch C, Werheid K. The influence of early depressive symptoms, social support and decreasing self-efficacy on depression 6 months post-stroke. *J Affect Disord.* (2016) 206:252–5. doi: 10.1016/j.jad.2016.07.041
75. Wottrich AW, Åström K, Löfgren M. On parallel tracks: newly home from hospital—people with stroke describe their expectations. *Disab Rehabilit.* (2012) 34:1218–24. doi: 10.3109/09638288.2011.640381
76. Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. *Psychosom Med.* (2004) 66:845–51. doi: 10.1097/01.psy.0000145823.85658.0c
77. Rief W, Broadbent E. Explaining medically unexplained symptoms-models and mechanisms. *Clin Psychol Rev.* (2007) 27:821–41. doi: 10.1016/j.cpr.2007.07.005
78. Novick D, Montgomery W, Aguado J, Kadziola Z, Peng X, Brugnoli R, et al. Which somatic symptoms are associated with an unfavorable course in Asian patients with major depressive disorder? *J Affect Disord.* (2013) 149:182–8. doi: 10.1016/j.jad.2013.01.020
79. Bekhuis E, Boschloo L, Rosmalen JG, de Boer MK, Schoevers RA. The impact of somatic symptoms on the course of major depressive disorder. *J Affect Disord.* (2016) 205:112–8. doi: 10.1016/j.jad.2016.06.030
80. Sun X-j, Niu G-f, You Z-q, Zhou Z-k, Tang Y. Gender, negative life events and coping on different stages of depression severity: a cross-sectional study among Chinese university students. *J Affect Disord.* (2017) 209:177–81. doi: 10.1016/j.jad.2016.11.025
81. Guiraud V, Gallarda T, Calvet D, Turc G, Oppenheim C, Rouillon F, et al. Depression predictors within six months of ischemic stroke: the DEPRESS Study. *Int J Stroke* (2016) 11:519–25. doi: 10.1177/1747493016632257
82. Morris PL, Robinson RG, Raphael B, Samuels J, Molloy P. The relationship between risk factors for affective disorder and poststroke depression in hospitalised stroke patients. Australian and New Zealand *J Psychiatry* (1992) 26:208–17. doi: 10.1177/000486749202600204
83. Virtanen M, Ferrie JE, Akbaraly T, Tabak A, Jokela M, Ebmeier KP, et al. Metabolic syndrome and symptom resolution in depression: a 5-year follow-up of older adults. *J Clin Psychiatry* (2017) 78:e1–e7. doi: 10.4088/JCP.15m10399
84. Kutlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int J Stroke* (2014) 9:1026–36. doi: 10.1111/ijs.12356
85. Deng L, Sun X, Qiu S, Xiong Y, Li Y, Wang L, et al. Interventions for management of post-stroke depression: a Bayesian network meta-analysis of 23 randomized controlled trials. *Sci Reports* (2017) 7:16466. doi: 10.1038/s41598-017-16663-0
86. Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, et al. Cognitive behavioral therapy for post-stroke depression: a meta-analysis. *J Affect Disord.* (2018) 235:589–96. doi: 10.1016/j.jad.2018.04.011
87. Kase C, Wolf P, Kelly-Hayes M, Kannel W, Beiser A, D'Agostino R. Intellectual decline after stroke. *Stroke* (1998) 29:805–12. doi: 10.1161/01.STR.29.4.805
88. Andersen G, Vestergaard K, Riis J, Ingeman-Nielsen M. Dementia of depression or depression of dementia in stroke? *Acta Psych Scand* (1996) 94:272–8. doi: 10.1111/j.1600-0447.1996.tb09860.x
89. Lipsey J, Pearlson G, Robinson R, Rao K, Price T. Nortriptyline treatment of post-stroke depression: a double-blind study. *Lancet* (1984) 323:297–300. doi: 10.1016/S0140-6736(84)90356-8
90. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *Am J Psychiatry* (2000) 157:351–9. doi: 10.1176/appi.ajp.157.3.351
91. Robinson RG, Bolla-Wilson K, Kaplan E, Lipsey JR, Price TR. Depression influences intellectual impairment in stroke patients. *Br J Psychiatry* (1986) 148:541–7. doi: 10.1192/bjp.148.5.541
92. Naugle RI, Kawczak K. Limitations of the mini-mental state examination. *Cleveland Clin J Med.* (1989) 56:277–81. doi: 10.3949/ccjm.56.3.277

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The Effect of Insomnia on Cortical Excitability in Patients With Generalized Anxiety Disorder

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The high rate of comorbidity between insomnia and anxiety disorders have been confirmed by previous studies. However, the underlying neurobiological correlates of the relationship between insomnia and anxiety disorders are largely unknown. The aim of the present study was to investigate the effect of insomnia on cortical excitability in patients with generalized anxiety disorder (GAD) by examining the recovery functions of median nerve somatosensory evoked potentials (SEPs) in patients with GAD without insomnia and patients with GAD comorbid with insomnia. We studied the recovery functions of median nerve SEPs in 12 medication-naive patients with GAD without insomnia, 15 medication-naive patients with GAD comorbid with insomnia, and 15 age and sex matched healthy controls. SEPs in response to single stimulus and paired stimuli at interstimulus intervals (ISIs) of 20, 60, 100, and 150 ms were recorded. The recovery function of the P25 component showed significantly reduced suppression in patients with GAD without insomnia as compared to patients with GAD comorbid with insomnia and healthy controls. There were no significant differences in the recovery functions of median nerve SEPs between patients with GAD comorbid with insomnia and healthy controls. The present study suggested that the cortical excitability of right parietal cortex increased in patients with GAD without insomnia, and cortical excitability in patients with GAD comorbid with insomnia was modulated by insomnia. Our findings provide new insights into the underlying neurobiological correlates of the effects of insomnia on GAD, which could ultimately be used to inform clinical intervention.

Keywords: insomnia, generalized anxiety disorder, somatosensory evoked potential, recovery function, right parietal cortex

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INTRODUCTION

Epidemiological studies have shown a high rate of comorbidity between insomnia and anxiety disorders. A number of longitudinal studies indicated that the relationship between insomnia and anxiety disorders is bidirectional. Insomnia contributes to the development of anxiety disorders, and anxiety disorders result in insomnia (1, 2). Treating chronic insomnia can often reduce the severity of anxiety symptoms, and similarly, treating anxiety can often improve insomnia (3). Generalized anxiety disorder (GAD) is the most common anxiety disorder, which is characterized by pervasive worry, difficulty concentrating, feeling restless, easily fatigued, muscle tension, and

sleep disturbances (4). About 75% of patients with GAD have insomnia (5, 6). Sleep difficulties are included in the diagnostic criteria for GAD (4). Previous studies showed that GAD independently predicted insomnia, and higher levels of insomnia significantly predicted higher levels of GAD (7). Despite the well-documented association between insomnia and anxiety, the underlying neurobiological correlates remain unclear.

Patients with anxiety disorders characteristically show physical and psychological arousal (8). It is believed that anxiety is associated with alterations in brain excitability (9). Previous studies found that patients with anxiety disorders had significant high right parietal activity (10–13). These results suggested that the cortical excitability of right parietal lobe might be abnormal in patients with anxiety disorders. Previous studies also found that the functions of right parietal lobe in patients with GAD are abnormal. Etkin et al. (14) found an altered functional connectivity between bilateral posterior parietal cortex and the amygdala in patients with GAD using fMRI. Wu et al. (15) noted that patients with GAD had more activity in their right parietal lobes during vigilant tasks. Brambilla et al. (16) found that white-matter connectivity is impaired in the right parietal lobe in patients with GAD. These findings indicated that the cortical excitability of right parietal lobe might be abnormal in patients with GAD.

Several previous studies have revealed abnormal cortical excitability in anxiety disorders, including obsessive-compulsive disorder (17), social anxiety disorder (18), post-traumatic stress disorder (19), and generalized anxiety disorder (20). So far, there have been only one published study investigating cortical excitability in patients with GAD. Li CT et al. measured motor cortical excitability of patients with GAD using paired-pulse transcranial magnetic stimulation (20). They found that GAD patients had significantly lower intracortical facilitation (ICF). They concluded that GAD was associated with impaired intracortical facilitation, and such ICF deficits predicted the severity of anxiety. However, they did not consider the impact of insomnia on cortical excitability in patients with GAD.

Previous studies demonstrated that insomnia have a significant impact on GAD. Insomnia and sleep deprivation can significantly increase anxiety (21), and GAD patients with higher levels of insomnia have higher levels of anxiety symptoms (7). Thus, we assumed that insomnia could lead to changes in cortical excitability of patients with GAD, and cortical excitability might be different between patients with GAD without insomnia and patients with GAD comorbid with insomnia.

Paired-pulse stimulation techniques are used as common tools to investigate cortical excitability and cortical plastic changes. The recovery function of cortical somatosensory evoked potential (SEPs) component in the paired-pulse paradigm, which has been used in our previous study (22), has been applied to study the cortical excitability in patients with various psychiatric and neurological disorders (23, 24). When paired stimuli are delivered at different inter-stimulus intervals (ISIs), the amplitude of the SEP evoked by the second stimulus is suppressed depending on the interstimulus interval. The longer is the ISI, the higher is the amplitude of the SEP evoked by the second stimulus, until a complete amplitude recovery is observed (25–27). To improve the understanding of the neurophysiological effects of insomnia on GAD, the present study investigated alterations of cortical excitability of right parietal cortex in patients with GAD without insomnia and patients with GAD comorbid with insomnia by examining the recovery functions of median nerve SEPs. We hypothesized that the cortical excitability of right parietal cortex might be abnormal in patients with GAD without insomnia, and the cortical excitability of right parietal cortex in patients with GAD comorbid with insomnia might be modulated by insomnia.

METHODS

Participants

We studied the recovery functions of median nerve SEPs in 12 medication-naive patients with GAD without insomnia, 15 medication-naive patients with GAD comorbid with insomnia, and 15 age and sex matched healthy controls. All participants were recruited from neurology outpatient clinics of Xuanwu Hospital. All procedures of this study were approved by the Institutional Review Board of Xuanwu Hospital and written informed consent was obtained from each participant.

All participants were interviewed and examined by two experienced neurologists. The interview included the administration of the Pittsburgh Sleep Quality Index (PSQI) (28), the Hamilton Anxiety Rating Scale (HAMA) (29) and the Hamilton Depression Rating Scale (HAMD, 24-item version) (30).

All participants aged from 18 to 60 years old. All patients met diagnostic criteria for GAD according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV). Patients with GAD comorbid with insomnia also met diagnostic criteria for insomnia based on criteria for insomnia related to another mental disorder from the DSM-IV with duration of insomnia $\geq$ 3 months. Patients with GAD without insomnia were required to have the HAMA score of $\geq$ 14, the PSQI score of $<$ 7, and the HAMD-24 score of $<$ 20. Patients with GAD comorbid with insomnia were required to have the HAMA score of $\geq$ 14, the PSQI score of $\geq$ 7, and the HAMD-24 score of $<$ 20. All patients were required to have no prior history of other psychiatric diseases, including all types of anxiety disorders other than GAD, depression, substance or alcohol abuse or dependence, and other sleep disorders.

Healthy controls were required to have no history of psychiatric diseases and sleep disorders, and have the PSQI score of $<$ 7, the HAMA score of $<$ 7, the HAMD-24 score of $<$ 8.

Exclusion criteria for both groups were as follows: evidence of neurological or other physical diseases such as respiratory, cardiac, renal, hepatic, and endocrinal diseases as assessed by clinical history, physical examination or routine laboratory tests; any medication that might affect central nervous system within 14 days; irregular sleep patterns associated with shift work, frequent travel or personal preference (as indicated by a weekly variation $>$ 3 h in bedtime or wake time, or time in bed duration $<$ 5.5 or $>$ 10 h per night); concurrent psychotherapy or counseling; pregnancy or breastfeeding women.

SEPs Recording Procedure

For SEPs recording, we used the same method and parameters as in our earlier study (22). Left median nerve was stimulated at the wrist at an intensity fixed at about 1.2 times the motor threshold (stimulus duration: 0.2 ms, stimulus rate: 1 Hz). SEPs were recorded (the Neuropack M1 MEB-9200 EP/EMG measuring system, Nihon Kohden Corporation, Japan) with the recording electrodes placed over the ipsilateral Erb point, the spinous process of the sixth cervical vertebra (Cv6), and the contralateral parietal area (C4', 2 cm posterior to the C4 placement of the international 10–20 system). All recording electrodes were referred to the right earlobe.

We recorded the N9 potential from the ipsilateral Erb's point, the N13 potential from Cv6, and the P14, N20, and P25 potentials from the parietal region contralateral to the stimulation side.

SEPs Recovery Functions

Recovery functions of SEPs were studied using the same method and parameters as in our earlier study (22). Paired stimuli of equal intensity were given at ISIs of 20, 60, 100, and 150 ms. Single trial SEPs were taken as control. The sequences of these trials were randomized among the subjects. At least three hundred sweeps were averaged for each condition. To ascertain reproducibility of results, SEPs of each condition (single stimulus, and paired stimuli at ISIs of 20, 60, 100, and 150 ms) were recorded at least twice, one trial after another trial. Then we obtained the average SEPs time series of each condition used for subtraction. To obtain SEPs evoked by the test stimulus (T-SEPs), we subtracted SEPs evoked by single stimulus alone (S-SEPs) from those elicited with paired stimuli.

We measured amplitudes of SEPs from the preceding peak (peak-to-peak) to prevent the impact of baseline shift on the results. For SEPs recovery functions, the amplitudes of each component in the subtracted SEPs waveform were measured. Then we calculated the relative amplitude ratios of T-SEPs to those of the corresponding S-SEPs at different ISIs. Finally, we obtained SEP recovery curves (SEP-Rs) by plotting the amplitude ratios of T-SEP/S-SEP against the interstimulus intervals. The value of ratio ≥ 1 means that there is no suppression.

Statistical Analysis

All statistical analysis was carried out with SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL). The demographic and clinical characteristics at baseline were compared among the three groups using Pearson's chi-square test and One-way Analysis of Variance (ANOVA) followed by the LSD *post-hoc* test. For the amplitudes of SEPs obtained by single stimulus, we used one-way ANOVA test. For recovery functions obtained by paired stimuli, we employed a repeated measures ANOVA with ISI as the within-subjects factor and group as the between-subjects factor. A $p \leq 0.05$ was considered statistically significant results.

TABLE 1 | Demographic and clinical characteristics of the participants.

Variable	Controls	GAD without insomnia	GAD comorbid with insomnia
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Cases	15	12	15
Male/Female	6/9	4/8	6/9
Age	43.27 (10.31)	40.08 (10.92)	39.87 (8.65)
PSQI	2.20 (1.08)	3.33 (1.07)	14.47 (3.54)[b,c]
HAMA	3.60 (2.44)	16.75 (2.30)[a]	20.13 (3.89)[b,d]
HAMD	5.00 (1.31)	9.50 (2.39)[a]	13.67 (2.50)[b,c]

PSQI, Pittsburgh Sleep Quality Index; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.

[a] *Indicates significant differences between patients with GAD without insomnia and the controls ($p < 0.01$).*

[b] *Indicates significant differences between patients with GAD comorbid with insomnia and the controls ($p < 0.01$).*

[c] *Indicates significant differences between patients with GAD comorbid with insomnia and patients with GAD without insomnia ($p < 0.01$).*

[d] *Indicates significant differences between patients with GAD comorbid with insomnia and patients with GAD without insomnia ($p < 0.05$).*

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the participants, including age, sex, and the scores of PSQI, HAMA, and HAMD, are summarized in **Table 1**.

There were no significant differences among the three groups with respect to age ($F = 0.54$, $p = 0.59$) and sex ($\chi^2 = 0.16$, $p = 0.92$). The PSQI score was significantly higher in patients with GAD comorbid with insomnia than the other two groups ($p < 0.01$). There were no significant differences in PSQI scores between patients with GAD without insomnia and the controls ($p > 0.05$). The HAMA scores were significantly higher in patients with GAD comorbid with insomnia ($p < 0.01$) and patients with GAD without insomnia ($p < 0.01$) than the controls. The HAMA scores were significantly higher in patients with GAD comorbid with insomnia than patients with GAD without insomnia ($p < 0.05$). Similarly, the HAMD scores were significantly higher in patients with GAD comorbid with insomnia ($p < 0.01$) and patients with GAD without insomnia ($p < 0.01$) than the controls. The HAMD scores were significantly higher in patients with GAD comorbid with insomnia than patients with GAD without insomnia ($p < 0.01$).

Single-Pulse SEPs

Mean values and standard deviations of the amplitudes of SEPs components in the single-pulse condition are shown in **Table 2**.

In the single stimulus condition, there were no significant differences in the amplitudes of SEPs components among the three groups ($p > 0.05$).

TABLE 2 | Mean amplitudes (μV) of SEPs components in the single stimulus condition.

Components	Controls	GAD without insomnia	GAD comorbid with insomnia	*p*-value
N9	6.88 (3.03)	6.06 (1.76)	6.95 (2.40)	0.14
N13	3.47 (0.77)	3.19 (0.57)	3.42 (0.77)	0.10
N20	2.99 (0.94)	3.29 (1.34)	3.08 (0.98)	0.36
P25	4.78 (2.28)	5.58 (2.95)	5.10 (2.79)	0.30

Each value is expressed as mean (standard deviation).

SEPs Recovery Functions

Mean values and standard deviations of the amplitude ratios of T-SEP/S-SEP at different ISIs are shown in **Table 3**.

The N9 component evoked by the test stimulus in healthy controls were suppressed (the amplitude ratios of T-SEP/S-SEP ratios < 1.0) at ISI of 20 ms, and recovered at ISI of 60 ms. In patients with GAD without insomnia and patients with GAD comorbid with insomnia, the N9 component behaved similarly to the normal controls. The repeated measures ANOVA showed that there were no significant differences among the three groups ($F = 0.80$, $p = 0.46$).

The N13 component evoked by the test stimulus in healthy controls were suppressed at all ISIs of 20, 60, 100, and 150 ms. In patients with GAD without insomnia and patients with GAD comorbid with insomnia, the N13 component behaved similarly to the normal controls. The repeated measures ANOVA showed that there were no significant differences among the three groups ($F = 2.35$, $p = 0.11$).

The N20 component evoked by the test stimulus in healthy controls were suppressed at all ISIs of 20, 60, 100, and 150 ms. In patients with GAD without insomnia, the N20 component evoked by the test stimulus recovered at ISI of 150 ms. In patients with GAD comorbid with insomnia, the N20 component behaved similarly to the controls. The repeated measures ANOVA showed that there were no significant differences among the three groups ($F = 0.31$, $p = 0.74$).

The P25 component evoked by the test stimulus in healthy controls were suppressed at all ISIs of 20, 60, 100, and 150 ms. In patients with GAD without insomnia, the P25 component evoked by the test stimulus were not suppressed at ISI of 20 ms, and suppressed at ISIs of 60, 100, and 150 ms. In patients with GAD comorbid with insomnia, the P25 component evoked by the test stimulus were suppressed at all ISIs. The repeated measures ANOVA showed that the recovery functions of the P25 component were significantly different among the three groups ($F = 10.96$, $p < 0.01$). *Post-hoc* tests showed significant differences between the patients with GAD without insomnia and the controls ($p < 0.01$), the patients with GAD without insomnia and the patients with GAD comorbid with insomnia ($p < 0.01$), but no significant differences between the patients with GAD comorbid with insomnia and the controls ($p = 0.89$).

Figure 1 shows mean (± SD) recovery curves of the P25 component in the three groups.

DISCUSSION

In the present study, we investigated changes in cortical excitability in patients with GAD without insomnia and patients with GAD comorbid with insomnia by examining the recovery functions of median nerve SEPs. Our findings demonstrated that patients with GAD without insomnia exhibited reduced suppression of the cortical P25 component, but patients with GAD comorbid with insomnia showed no significant differences in the recovery functions of median nerve SEPs compared with the other two groups.

Previous studies suggested that the N20 component originates mainly in Brodmann's area 3b, and the P25 potential is generated by neurons in the Brodmann Areas 1and 2 of the parietal cortex (31, 32). It has been proposed that the N20 component reflects thalamocortical input to the primary somatosensory cortex, whereas the P25 component represents intracortical processing (33). The SEP recovery function of the cortical components is believed to reflect cortical excitability (24). Therefore, the normal recovery pattern of the N20 component and the disinhibited recovery pattern of the P25 component in patients with GAD without insomnia suggested an increased excitability of the parietal cortex.

The gamma-aminobutyric acid (GABA) system is believed to play a key role in the pathophysiology of GAD (34–36). Benzodiazepines, which act by enhancing inhibitory activity in the GABAergic receptor complex, are considered to be one of the most effective agents for GAD (37). Previous findings suggested that a GABA receptor-mediated mechanism in cerebral cortex might play a crucial role in the mechanism of paired-pulse inhibition (38–40). Therefore, these findings suggested that the dysfunction of inhibitory GABAergic interneurons in cerebral cortex might contribute to the disinhibited pattern of the cortical P25 component in patients with GAD without insomnia.

The level of excitability of cortical neurons depends on the balance between the GABA-related inhibitory and glutamate-related excitatory systems (41). Glutamate neurotransmitter system has also been identified to be involved in anxiety disorders (42). Pregabalin has been shown to be effective in the treatment of GAD. It works in part by reducing the release of glutamate (43). Riluzole, a drug that reduces glutamate release and consequently increase the expression of glutamate receptors, may also be effective in the treatment of mood and anxiety disorders. Other compounds, which act on the glutamate system, have also been demonstrated to have the potential to treat GAD (44, 45). Thus, these findings suggested that the glutamate neurotransmitter system might also contribute to the disinhibited pattern of

TABLE 3 | The amplitude ratios of T-SEP/S-SEP at different ISIs in the three groups.

ISIs		N9	N13	N20	P25
20 ms	Controls	0.92 (0.25)	0.84 (0.24)	0.88 (0.29)	0.72 (0.34)
	GAD without insomnia	0.94 (0.27)	0.88 (0.14)	0.78 (0.31)	1.23 (0.33)
	GAD comorbid with insomnia	1.04 (0.30)	0.78 (0.18)	0.79 (0.19)	0.47 (0.29)
60 ms	Controls	1.03 (0.30)	0.84 (0.21)	0.84 (0.28)	0.55 (0.21)
	GAD without insomnia	1.07 (0.55)	0.91 (0.27)	0.93 (0.36)	0.80 (0.29)
	GAD comorbid with insomnia	0.87 (0.15)	0.82 (0.23)	0.85 (0.21)	0.64 (0.26)
100 ms	Controls	1.04 (0.27)	0.96 (0.19)	0.89 (0.35)	0.73 (0.16)
	GAD without insomnia	1.10 (0.15)	0.98 (0.24)	0.86 (0.26)	0.88 (0.12)
	GAD comorbid with insomnia	1.09 (0.31)	0.96 (0.18)	0.92 (0.11)	0.86 (0.28)
150 ms	Controls	1.07 (0.32)	0.96 (0.13)	0.93 (0.17)	0.82 (0.19)
	GAD without insomnia	1.11 (0.35)	1.05 (0.28)	1.11 (0.24)	0.79 (0.24)
	GAD comorbid with insomnia	0.96 (0.12)	0.95 (0.12)	0.94 (0.18)	0.81 (0.13)

ISIs, Interstimulus intervals. Each value is expressed as mean (standard deviation).

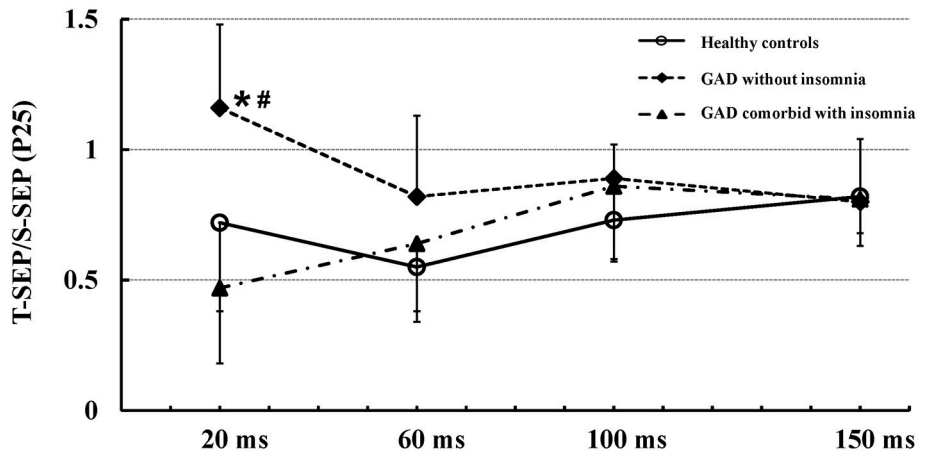

FIGURE 1 | Mean (± SD) recovery curves of the P25 component in the three groups. The recovery function of the P25 component showed significantly reduced suppression in patients with GAD without insomnia (solid diamonds, dashed line) as compared to patients with GAD comorbid with insomnia (solid triangles, dash-dotted line) and healthy controls (open circles, solid line). There were no significant differences in the recovery function of the P25 component between patients with GAD comorbid with insomnia and healthy controls. *Indicates significant difference between patients with GAD without insomnia and healthy controls ($p < 0.01$). #Indicates significant difference between patients with GAD without insomnia and patients with GAD comorbid with insomnia ($p < 0.01$).

the cortical P25 component in patients with GAD without insomnia.

Interestingly, the present study showed that recovery pattern of the P25 components in patients with GAD comorbid with insomnia was not significantly different from the other two groups. We proposed that the most possible mechanism is the effects of insomnia on GAD. Previous studies suggested that insomnia and sleep deprivation can significantly increase anxiety (21), and higher levels of insomnia significantly predicted higher levels of GAD (7). In the present study, the HAMA scores were significantly higher in patients with GAD comorbid with insomnia than patients with GAD without insomnia. These results suggested that insomnia aggravates the severity of the disease. Thus, the cortical excitability in patients with GAD comorbid with insomnia might be modulated by insomnia. The present study found an increased excitability of the parietal cortex in patients with GAD without insomnia. Our previous study also found that the cortical excitability of the parietal cortex increased in patients with primary insomnia (22). Previous findings suggested that a decrease in GABA and a compensatory increase in glutamate might be involved in the mechanisms of the increased excitability of the parietal cortex in both patients with GAD without insomnia and patients with primary insomnia (46, 47). We proposed that because of the impact of insomnia, there might be not enough glutamate being released, that might result in decompensation of the GABA-related inhibitory and glutamate-related excitatory systems in patients with GAD comorbid with insomnia.

Our study has several limitations. First, the present study used the recovery function of median nerve SEPs to investigate cortical excitability. This method can only reflect the regional

cortical excitability of parietal lobe. Future studies could use task-related fMRI to explore differences in brain activation patterns between patients with GAD without insomnia and patients with GAD comorbid with insomnia. Then we can better understand the underlying neurobiological correlates of the relationship between insomnia and GAD. Second, we did not investigate the GABA and glutamate systems directly. Future studies could use magnetic resonance spectroscopy (MRS) to investigate differences in cortical GABAergic and glutamatergic neurotransmission between patients with GAD without insomnia and patients with GAD comorbid with insomnia. Third, the relatively small sample size is another limitation of the present study. Future studies with larger sample sizes could be conducted to confirm our conclusion.

In conclusion, the present study demonstrated that the cortical excitability of right parietal cortex increased in patients with GAD without insomnia. The cortical excitability in patients with GAD comorbid with insomnia was modulated by insomnia. The cortical GABA-related inhibitory and glutamate-related excitatory systems might play key roles in the mechanisms of the effects of insomnia on GAD. Our findings provide new insights into the underlying neurobiological correlates of the effects of insomnia on GAD, which could ultimately be used to inform clinical intervention.

AUTHOR CONTRIBUTIONS

YW designed the research, supervised the project and revised the article. ZH and CC performed the research, drafted the article and analyzed data. YH, NL, YD, and LW collected data and interpreted the data. SZ interpreted data and revised the draft. All authors reviewed the paper and approved it to submit.

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REFERENCES

1. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev.* (2002) 6:97–111. doi: 10.1053/smrv.2002.0186
2. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* (2013) 36:1059–68. doi: 10.5665/sleep.2810
3. Belleville G, Ivers H, Belanger L, Blais FC, Morin CM. Sequential treatment of comorbid insomnia and generalized anxiety disorder. *J Clin Psychol.* (2016) 72:880–96. doi: 10.1002/jclp.22300
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision, DSM-IV-TR. Washington, DC: American Psychiatric Association (2000).
5. Anderson DJ, Noyes RJ, Crowe RR. A comparison of panic disorder and generalized anxiety disorder. *Am J Psychiatry* (1984) 141:572–5. doi: 10.1176/ajp.141.4.572
6. Belanger L, Morin CM, Langlois F, Ladouceur R. Insomnia and generalized anxiety disorder: effects of cognitive behavior therapy for gad on insomnia symptoms. *J Anxiety Disord.* (2004) 18:561–71. doi: 10.1016/S0887-6185(03)00031-8
7. Alvaro PK, Roberts RM, Harris JK. The independent relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence. *Sleep Med.* (2014) 15:934–41. doi: 10.1016/j.sleep.2014.03.019
8. McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. *Depress Anxiety* (2012) 29:264–81. doi: 10.1002/da.21891
9. Jeans RF, Toman JE. Anxiety and cerebral excitability; prolongation of seizure latency by anxiety and other factors in patients undergoing electroshock therapy. *AMA Arch Neurol Psychiatry* (1956) 75:534–47. doi: 10.1001/archneurpsyc.1956.02330230084011
10. Bruder GE, Fong R, Tenke CE, Leite P, Towey JP, Stewart JE, et al. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. *Biol Psychiatry* (1997) 41:939–48. doi: 10.1016/S0006-3223(96)00260-0
11. Metzger LJ, Paige SR, Carson MA, Lasko NB, Paulus LA, Pitman RK, et al. PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *J Abnorm Psychol.* (2004) 113:324–9. doi: 10.1037/0021-843X.113.2.324
12. Coan JA, Allen JJ. Frontal EEG asymmetry as a moderator and mediator of emotion. *Biol Psychol.* (2004) 67:7–49. doi: 10.1016/j.biopsycho.2004.03.002
13. Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. *J Abnorm Psychol.* (2006) 115:715–29. doi: 10.1037/0021-843X.115.4.715
14. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Arch Gen Psychiatry* (2009) 66:1361–72. doi: 10.1001/archgenpsychiatry.2009.104
15. Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. *Biol Psychiatry* (1991) 29:1181–99. doi: 10.1016/0006-3223(91)90326-H
16. Brambilla P, Como G, Isola M, Taboga F, Zuliani R, Goljevscek S, et al. White-matter abnormalities in the right posterior hemisphere in generalized anxiety disorder: a diffusion imaging study. *Psychol Med.* (2012) 42:427–34. doi: 10.1017/S0033291711001255
17. Wassermann EM, Greenberg BD, Nguyen MB, Murphy DL. Motor cortex excitability correlates with an anxiety-related personality trait. *Biol Psychiatry* (2001) 50:377–82. doi: 10.1016/S0006-3223(01)01210-0
18. Pallanti S, Borgheresi A, Pampaloni I, Giovannelli F, Bernardi S, Cantisani A, et al. Motor cortex excitability correlates with novelty seeking in social anxiety: a transcranial magnetic stimulation investigation. *J Neurol.* (2010) 257:1362–8. doi: 10.1007/s00415-010-5533-4
19. Centonze D, Palmieri MG, Boffa L, Pierantozzi M, Stanzione P, Brusa L, et al. Cortical hyperexcitability in post-traumatic stress disorder secondary to minor accidental head trauma: a neurophysiologic study. *J Psychiatry Neurosci.* (2005) 30:127–32.
20. Li CT, Lu CF, Lin HC, Huang YZ, Juan CH, Su TP, et al. Cortical inhibitory and excitatory function in drug-naive generalized anxiety disorder. *Brain Stimul.* (2017) 10:604–8. doi: 10.1016/j.brs.2016.12.007
21. Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med.* (2016) 24:109–18. doi: 10.1016/j.sleep.2016.07.019
22. Huang Z, Zhan S, Li N, Ding Y, Wang Y. Abnormal recovery function of somatosensory evoked potentials in patients with primary insomnia. *Psychiatry Res.* (2012) 198:463–7. doi: 10.1016/j.psychres.2011.11.024

23. Shibasaki H, Yamashita Y, Neshige R, Tobimatsu S, Fukui R. Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. *Brain* (1985) 108:225–40. doi: 10.1093/brain/108.1.225
24. Ugawa Y, Genba-Shimizu K, Kanazawa I. Somatosensory evoked potential recovery (SEP-R) in various neurological disorders. *Electroencephalogr Clin Neurophysiol.* (1996) 100:62–7. doi: 10.1016/0168-5597(95)00195-6
25. Shagass C, Schwartz M. Cerebral responsiveness in psychiatric patients. Intensity-response gradients and recovery cycles of somatosensory evoked potentials. *Arch Gen Psychiatry* (1963) 8:177–89. doi: 10.1001/archpsyc.1963.01720080067010
26. Shagass C, Schwartz M. Recovery functions of somatosensory peripheral nerve and cerebral evoked responses in man. *Electroencephalogr Clin Neurophysiol.* (1964) 17:126–35. doi: 10.1016/0013-4694(64)90144-0
27. Visani E, Canafoglia L, Rossi Sebastiano D, Agazzi P, Panzica F, Scaioli V, et al. Giant SEPs and SEP-recovery function in Unverricht-Lundborg disease. *Clin Neurophysiol.* (2013) 124:1013–8. doi: 10.1016/j.clinph.2012.11.011
28. Buysse DJ, Reynolds CR, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193-213. doi: 10.1016/0165-1781(89)90047-4
29. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x
30. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
31. Allison T, McCarthy G, Wood CC, Jones SJ. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. a review of scalp and intracranial recordings. *Brain* (1991) 114:2465–503. doi: 10.1093/brain/114.6.2465
32. Valeriani M, Restuccia D, Di Lazzaro V, Le Pera D, Barba C, Tonali P, et al. Dipolar sources of the early scalp somatosensory evoked potentials to upper limb stimulation. effect of increasing stimulus rates. *Exp Brain Res.* (1998) 120:306–15. doi: 10.1007/s002210050404
33. Wolters A, Schmidt A, Schramm A, Zeller D, Naumann M, Kunesch E, et al. Timing-dependent plasticity in human primary somatosensory cortex. *J Physiol.* (2005) 565:1039–52. doi: 10.1113/jphysiol.2005.084954
34. Millan MJ. The neurobiology and control of anxious states. *Prog Neurobiol.* (2003) 70:83–244. doi: 10.1016/s0301-0082(03)00087-x
35. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. *Psychopharmacol Bull.* (2003) 37:133–46.
36. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry* (2011) 16:383–406. doi: 10.1038/mp.2010.120
37. Reinhold JA, Rickels K. Pharmacological treatment for generalized anxiety disorder in adults: an update. *Expert Opin Pharmacother.* (2015) 16:1669–81. doi: 10.1517/14656566.2015.1059424
38. Deisz RA, Prince DA. Frequency-dependent depression of inhibition in guinea-pig neocortex *in vitro* by GABAB receptor feed-back on GABA release. *J Physiol.* (1989) 412:513–41.
39. Mennerick S, Zorumski CF. Paired-pulse modulation of fast excitatory synaptic currents in microcultures of rat hippocampal neurons. *J Physiol.* (1995) 488:85–101. doi: 10.1113/jphysiol.1995.sp020948
40. Stude P, Lenz M, Hoffken O, Tegenthoff M, Dinse H. A single dose of lorazepam reduces paired-pulse suppression of median nerve evoked somatosensory evoked potentials. *Eur J Neurosci.* (2016) 43:1156–60. doi: 10.1111/ejn.13224
41. Isaacson JS, Scanziani M. How inhibition shapes cortical activity. *Neuron* (2011) 72:231–43. doi: 10.1016/j.neuron.2011.09.027
42. Krystal JH, Mathew SJ, D'Souza DC, Garakani A, Gunduz-Bruce H, Charney DS. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. *CNS Drugs* (2010) 24:669–93. doi: 10.2165/11533230-000000000-00000
43. Baldwin DS, Ajel K, Masdrakis VG, Nowak M, Rafiq R. Pregabalin for the treatment of generalized anxiety disorder: an update. *Neuropsychiatr Dis Treat* (2013) 9:883–92. doi: 10.2147/NDT.S36453
44. Dunayevich E, Erickson J, Levine L, Landbloom R, Schoepp DD, Tollefson GD. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. *Neuropsychopharmacology* (2008) 33:1603–10. doi: 10.1038/sj.npp.1301531
45. Mathew SJ, Amiel JM, Coplan JD, Fitterling HA, Sackeim HA, Gorman JM. Open-label trial of riluzole in generalized anxiety disorder. *Am J Psychiatry* (2005) 162:2379–81. doi: 10.1176/appi.ajp.162.12.2379
46. Winkelman JW, Buxton OM, Jensen JE, Benson KL, O'Connor SP, Wang W, et al. Reduced brain GABA in primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). *Sleep* (2008) 31:1499–506. doi: 10.1093/sleep/31.11.1499
47. Riaza BC, Perez-Rodriguez MM, Vaquero-Lorenzo C, Baca-Garcia E. New perspectives in glutamate and anxiety. *Pharmacol Biochem Behav.* (2012) 100:752–74. doi: 10.1016/j.pbb.2011.04.010

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Effects of Cerebral Blood Flow and White Matter Integrity on Cognition in CADASIL Patients

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Background: It remains unclear whether the degree of white matter tract damage or cerebral hypoperfusion can better predict global cognitive impairment in CADASIL. We sought to determine the independent effects of cerebral perfusion status and white matter integrity on the cognition.

Methods: We reviewed prospectively collected clinical and imaging data from genetically-confirmed CADASIL patients who underwent both arterial spin labeling (ASL) perfusion MRI and diffusion tensor imaging (DTI). We analyzed the cerebral blood flow (CBF), mean diffusion (MD), and fractional anisotropy (FA) by dividing the brain tissue into white matter hyperintensity (WMH) and normal-appearing white matter (NAWM). Global cognitive function was evaluated by using Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

Results: Of the included 29 CADASIL patients, the mean age was 48.4 ± 7.9 years, and 17 (58.6%) were women. MD was significantly correlated with CBF in both WMH ($r = -0.407$, $P = 0.035$) and NAWM ($r = -0.437$, $P = 0.023$) after adjusting for age and WMH volume. A MoCA score was obtained in 13 patients and was significantly correlated with CBF in both WMH ($r = 0.742$, $P = 0.004$) and NAWM ($r = 0.659$, $P = 0.014$). Both CBF in WMH (area under the curve, 0.767; 95% CI, 0.586-0.947, $P = 0.015$) and MD in WMH (area under the curve, 0.740; 95% CI, 0.557–0.924, $P = 0.028$) were good predictors for cognitive impairment (MMSE score < 27). However, multiple linear regression analysis revealed that global cognitive function was independently associated with CBF in WMH only (standardized $\beta = 0.485$, $P = 0.015$), after adjusting for age, gender, WMH volume, the presence of subcortical infarcts and DTI metrics.

Conclusions: Our findings suggested that cerebral hypoperfusion was more strongly associated with global cognitive dysfunction than the severity of brain microstructural damage, supporting that CBF assessed by ASL could serve as a candidate imaging indicator for monitoring alterations of global cognitive function in CADASIL.

Keywords: *NOTCH3*, CADASIL, diffusion tensor imaging, cognitive impairment, cerebral blood flow, arterial spin labeling

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INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an early-onset monogenic variant of cerebral small vessel disease (CSVD) caused by mutations in the *NOTCH3* gene (1), whose prevalence is at least 4.6 per 100,000 adults (2). Pathologically, there is deposition of granular osmiophilic material in the basal membrane of small arteries and capillaries in close association with progressive degeneration of smooth muscle cells (3, 4). Cognitive impairment is the second most frequent clinical manifestation of CADASIL, principally affecting processing speed, executive function, and attention from an early stage (5–7).

The mechanism of cognitive dysfunction in CADASIL remains uncertain. No strong correlation has been found between cognitive function and T2 lesion load on conventional MRI (8), since T2 high signal can be caused by severe neuronal loss or subtle damage to vascular tissues that leaves neural fibers intact. Therefore, diffusion tensor imaging (DTI), which is sensitive to the microstructural integrity of white matter, is used in the CADASIL population. Previous studies have shown that the degree of white matter tract damage may relate to global cognitive function (9, 10). On the other hand, cerebral hypoperfusion was also found to be correlated with cognitive impairment or dementia in CADASIL (11, 12). However, interaction may exist between cerebral hypoperfusion and disruption of brain microstructure. It's unclear whether white matter integrity or cerebral perfusion condition could better predict the global cognitive outcome.

To our knowledge, few previous studies have investigated the relationship between cerebral perfusion status and white matter integrity or their correlations with cognitive function in CADASIL. We thus performed both 3D arterial spin labeling (ASL) perfusion MRI, which provides measures of cerebral blood flow (CBF), and DTI in genetically-confirmed CADASIL patients, in order to determine the independent effects of CBF and DTI metrics on cognition.

MATERIALS AND METHODS

Study Subjects

This was an investigator-initiated prospective single-center study. During the years 2007–2017, we performed *NOTCH3* gene testing in patients with probable CADASIL. CADASIL suspicion arose when typical clinical features (migraine, stroke, cognitive deficits, or psychiatric symptoms), positive family history, or neuroimaging were suggestive of an inherited CSVD. Affected family members of index patients were not included in the current study. We then enrolled patients who (i) had a deleterious mutation of *NOTCH3*; (ii) underwent both ASL and DTI at the same time; and (iii) received a cognitive function assessment based on the Mini-Mental State Examination (MMSE) and/or the Montreal Cognitive Assessment (MoCA). We excluded patients whose image quality was poor due to motion artifacts. This study has been approved by our local human ethics committee. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained for all patients.

We retrieved demographic, clinical, and radiological data including age (disease onset and first visit) and gender; the vascular risk factors such as history of hypertension, diabetes mellitus, hyperlipidemia, and smoking; clinical features including ischemic events, migraine, family history, MMSE and MoCA score; and conventional neuroimaging findings such as intracranial arterial stenosis, the severity of white matter hyperintensities (WMHs), temporal poles hyperintensity, external capsule involvement, and subcortical infarcts (single and multiple) were recorded. Family history was collected by means of a structured interview that focused on the typical CADASIL disturbances referred to by all the proband's relatives. The family history was considered positive when at least one typical disturbance was present in at least one of the proband's first-degree relatives.

MRI Parameters

MRI was performed on a 3.0T system (MR750, GE Healthcare, United States) equipped with an 8-channel phased array head coil. MR sequences contained high-resolution 3D sagittal T1-weighted imaging (T1-WI), fluid attenuated inversion recovery (FLAIR), DTI and 3D ASL. A single shot, diffusion-weighted spin echo echo-planar imaging sequence was performed for DTI. Maximum b-value was 1,000 s/mm^2 in 30 non-collinear directions; one volume was acquired without diffusion weighting (b-value = 0 s/mm^2). Other parameters of DTI were as follows: TR = 8,000 ms; TE = 80.8 ms; flip angle = 90°; FOV = 25.6 × 25.6 cm^2; matrix size = 128 × 128; slice thickness = 2.0 mm without interslice gap. 3D ASL was acquired using spin-echo pulse sequence with TR/TE = 4611/10.5 ms, TI = 1,525 ms, flip angle = 111°, slice thickness = 4 mm, matrix = 128 × 128, FOV = 24 × 24 cm^2. High-resolution 3D sagittal T1WI was acquired using spoiled gradient echo sequence with TR/TE = 7.3/3.0 ms, TI = 450 ms, flip angle = 8°, slice thickness = 1 mm, matrix = 250 × 250, FOV = 25 × 25 cm^2. Time-of-flight magnetic resonance angiography (TOF-MRA) consisted of 3 slabs with TR = 20 ms; TE = 3.2 ms; flip angle = 15°; FOV = 24 × 24 cm^2; matrix size = 320 × 224; slice thickness = 1.4 mm. FLAIR parameters were TR = 9,000 ms; TE = 150 ms; TI = 2,250 ms; FOV = 24 × 24 cm^2; matrix size = 256 × 192; slice thickness = 5.0 mm. Axial FLAIR sequence was used to measure the lesion volume of WMHs with the following parameters: TR = 8,400 ms; TE = 152 ms; FOV = 24 × 24 cm^2 matrix size = 256 × 256; flip angle = 90°; TI = 2,100 ms; slice thickness = 4.0 mm without interslice gap. The whole brain was imaged.

NOTCH3 Gene Analysis

We used the diagnostic strategy established by Joutel et al. (13). We initially screened exons 3 and 4 for mutations, and if no mutations were present, we then analyzed the remaining exons, i.e., 2 and 5–23. Co-segregation was analyzed if any variant was found, and the presence of all identified, novel, disease-associated variants was examined in 100 controls by direct DNA sequencing.

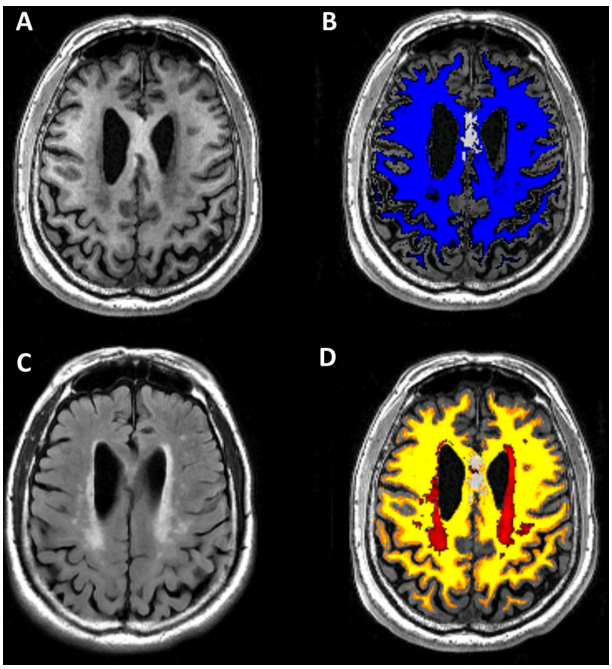

FIGURE 1 | Flowchart demonstrating our imaging process for each subject. The 3DT1 image **(A)** was segmented to white mater mapping **(B)** automatically on Statistical Parametric Mapping (SPM). Then the T2-FLAIR image **(C)** was co-registered to 3DT1 image. White matter hyperintensity (WMH) lesion segmentation was based on co-registered T2FLAIR image **(C)** on Lesion Segmentation Tool in SPM. Normal-appearing white mater mapping **(D)** was obtained by image subtraction of white mater mapping and WMH lesion.

TABLE 1 | Main characteristics of CADASIL patients.

Variable	*N* = 29 (mean ± SD) or *n* (%)
Age at disease onset (year)	42.0 ± 9.4
Age at first neurological examination (year)	48.4 ± 7.9
Female	17 (58.6%)
Clinical features	
Ischemic TIA/stroke	17 (58.6%)
MMSE score	23.8 ± 6.9
Migraine with aura	10 (34.5%)
Family history	25 (86.2%)
Vascular risk factors	
Hypertension	4 (13.8%)
Diabetes	1 (3.4%)
Hyperlipidemia	6 (20.7%)
Smoking	6 (20.7%)
Neuroimaging findings	
Lesion load of WMH (ml)	64.1 ± 31.7
Temporal poles hyperintensity	18 (62.1%)
External capsule involvement	21 (72.4%)
Subcortical infarcts	20 (69.0%)
Single	3 (15.0%)
Multiple	17 (85.0%)

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; SD, standard deviation; TIA, transient ischemic attack; MMSE, Mini-mental state examination; WMH, white matter hyperintensity.

Imaging Analysis

DTI images were post-processed using FSL (www.fmrib.ox.ac.uk/fsl) to extract brain, remove bulk motion, and eddy current induced distortions. Then we calculated the parametric maps of mean diffusivity (MD) (a measure of the apparent diffusion coefficient averaged in all spatial directions), and fractional anisotropy (FA) (a measure of the directionality of diffusion) with DTIfit command in FSL. The raw data of ASL were transferred to a separate workstation (ADW, GE), where the quantitative CBF maps were generated by a custom-built program. The segmentation of normal-appearing white matter (NAWM) and WMH tissue masks was automatically processed in the native space using 3D T1WI and FLAIR images by the lesion segmentation tool (LST) toolbox in Statistical Parametric Mapping Version 8 (SPM8) (**Figure 1**) (14). The processed WMH and NAWM masks were further manually corrected by using ITK-SANP software (www.itksnap.org). The steps of manual correction included (i) removal of non-brain tissue, deep gray matter, brain stem, and cerebellum; and (ii) correction of false segmentation (positives or negatives). After co-registration, the masks of WMH and NAWM were used to obtain averaged MD, FA, and CBF of corresponding tissues in each subject.

Statistical Analysis

All numeric variables were expressed as mean ± SD. The difference between FA, MD, and CBF in WMH and their counterparts in NAWM were compared using paired *t*-tests. Pearson's correlation analysis was used for the continuous variables. In addition, we performed partial Pearson's correlation analysis to determine the correlation between CBF and the metrics of DTI (FA and MD) by adjusting for age and WMH volume. The association of CBF, MD, FA, age, gender, WMH volume, and the presence of subcortical infarcts was tested using the univariate linear regression model. The association of the variables, whose $P < 0.1$, with MMSE score was estimated using the multiple linear regression model. Receiver operating characteristic curve analysis was used to determine predictive value. All analyses were performed blinded to participant identifying information. Statistical significance was set at a $P < 0.05$. All statistical analyses were performed with SPSS package.

RESULTS

A total of 29 genetically-confirmed CADASIL patients were included for the final analysis. The demographic, clinical and imaging characteristics were demonstrated in **Table 1**. The age at disease onset was 42.0 ± 9.4 years (ranged from 21 to 57 years), and the age at first neurological examination was 48.4 ± 7.9 years (ranged from 31 to 63 years), and 17 (58.6%) were women. The MMSE score was 23.8 ± 6.9 (ranged from 7 to 30). Seventeen (58.6%) of them suffered at least one transient ischemic attack or completed stroke, 10 (34.5%) had a migraine

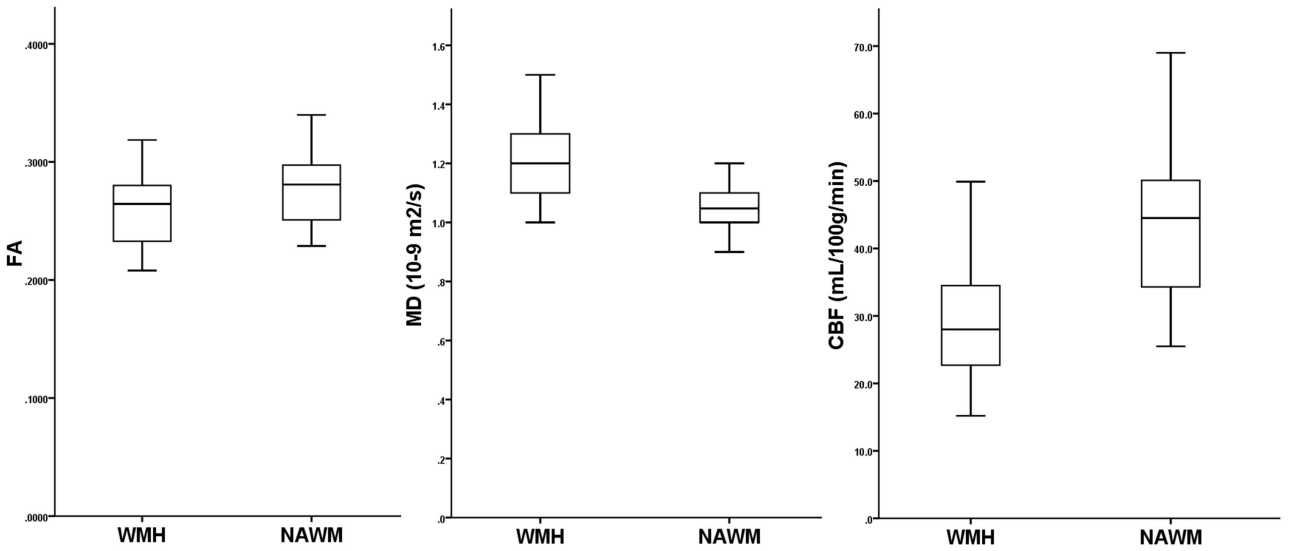

FIGURE 2 | Comparisons of fractional anisotropy (FA), mean diffusion (MD) and cerebral blood flow (CBF) in white matter hyperintensities (WMH) and their corresponding normal-appearing white matter (NAWM).

with aura, and 25 (86.2%) had a positive family history. Only one patient had severe arterial stenosis (right middle cerebral artery), with a MMSE score of 27 and MoCA score of 15. No obvious intracranial arterial stenosis was shown in the other patients.

MD, FA, and CBF in WMH and NAWM were not associated with age (all $P > 0.05$). There existed a significant association between the WMH volume and FA in WMH (Pearson $r = -0.543$, $P = 0.002$), and in NAWM (Pearson $r = -0.757$, $P < 0.001$), while a tendency was detected with MD in WMH (Pearson $r = 0.322$, $P = 0.088$) and in NAWM (Pearson $r = 0.363$, $P = 0.053$). As illustrated in **Figure 2**, FA and CBF were significantly decreased in WMH compared to NAWM, while MD was significantly increased. After adjusting for age and WMH volume, MD was significantly correlated with CBF in both WMH ($r = -0.407$, $P = 0.035$) and NAWM ($r = -0.437$, $P = 0.023$), while there lacked of an association between FA and CBF in both WMH ($r = 0.196$, $P = 0.328$) and NAWM ($r = 0.159$, $P = 0.427$) (**Table 2**).

Univariate linear regression analysis demonstrated that MMSE score was significantly associated with CBF in both WMH and NAWM, and mean FA and MD in WMH, but not in NAWM (**Table 3**). Nevertheless, MMSE score was not significantly associated with WMH volume (standardized $\beta = -0.189$, $P = 0.325$). The cut-off point of CBF in WMH was 27 mL/100 g/min (area under the curve, 0.767; 95% CI, 0.586–0.947, $P = 0.015$), and this yielded a sensitivity of 73.3% and a specificity of 78.6% for prediction of cognitive impairment (MMSE score < 27), while CBF in NAWM was not a good predictor (area under the curve, 0.676; 95% CI, 0.480–0.872, $P = 0.106$). The cut-off point of MD in WMH was 1.250 10^{-9} m^2/s (area under the curve, 0.740; 95% CI, 0.557–0.924, $P = 0.028$), and this yielded a sensitivity of 71.4% and a specificity of 60.0% for prediction of cognitive impairment, while FA in WMH was not a good predictor (area under the curve, 0.629; 95% CI, 0.419–0.838, $P = 0.239$). MoCA score was obtained in 13 patients. After adjusting for age and WMH volume, MoCA score was significantly correlated with CBF in both WMH ($r = 0.742$, $P = 0.004$) and NAWM ($r = 0.659$, $P = 0.014$), while there was a trend toward significance between MoCA and MD in WMH ($r = -0.519$, $P = 0.069$). Multiple linear regression analysis revealed that global cognitive function was independently associated with CBF in WMH only (standardized $\beta = 0.485$, $P = 0.015$), after adjusting for age, gender, WMH volume, the presence of subcortical infarcts, and DTI metrics (**Table 3**).

TABLE 2 | Partial correlation between cerebral blood flow and DTI-derived indices after adjusting for age and lesion load of WMH.

	CBF-WMH		CBF-NAWM	
	r	*P* value	*r*	*P* value
FA-WMH	0.196	0.328	0.288	0.146
FA-NAWM	0.146	0.469	0.159	0.427
MD-WMH	**−0.407**	**0.035**	−0.380	0.051
MD-NAWM	−0.235	0.238	**−0.437**	**0.023**

DTI, diffusion-tensor imaging; WMH, white matter hyperintensity; CBF, cerebral blood flow; NAWM, normal-appearing white matter; FA, fractional anisotropy; MD, mean diffusivity. Bold indicates p < 0.05.

DISCUSSION

In the current study, we investigated the effects of both cerebral perfusion status and white matter integrity on cognitive

TABLE 3 | Univariate and multivariate linear regression analyses of imaging variables with MMSE score.

	Univariate		Multivariate	
	Standardized β	***P* value**	**Standardized β**	***P* value**
FA-WMH	**0.378**	**0.043**	0.262	0.386
FA-NAWM	0.337	0.074	–	**–**
MD-WMH (10^{-9} m^2/s)	**−0.409**	**0.028**	−0.133	0.602
MD-NAWM (10^{-9} m^2/s)	−0.285	0.134	–	–
CBF-WMH (mL/100g/min)	**0.452**	**0.014**	**0.485**	**0.015**
CBF-NAWM (mL/100g/min)	**0.439**	**0.017**	0.205	0.565

MMSE, Mini-mental state examination; FA, fractional anisotropy; WMH, white matter hyperintensity; NAWM, normal-appearing white matter; MD, mean diffusivity; CBF, cerebral blood flow. Age, gender, lesion load of WMH, and the presence of subcortical infarcts were adjusted in the multiple linear regression models. Bold indicates $p < 0.05$.

function in CADASIL patients. Our findings suggested that cerebral hypoperfusion was more strongly associated with global cognitive dysfunction than the severity of brain microstructural damage, which might differ from that in sporadic CSVD.

Although almost all demented CADASIL patients appeared to have confluent and diffuse WMH, some asymptomatic or mildly affected subjects had similar lesions (15). Therefore, the extent of WMH on T2-weighted images or FLAIR did not account for the phenotypic severity in CADASIL. Chabriat et al. first used DTI to detect the microstructural tissular alterations underlying T2 signal abnormalities and found that water diffusivity measured within WMH correlated with both MMSE and Rankin scale scores (9). Another DTI study also showed that the diffusion abnormalities of the thalamus correlated with cognitive function in CADASIL without dementia, especially for executive dysfunction (10). In addition, attentional network connectivity was proven to be associated with cognitive performance in CADASIL based on functional MRI (16), while the increased rapid-onset cortical plasticity might contribute to largely preserved cognitive function despite extensive ischemic changes (17).

Increased *Notch3* activity mediates reduction in maximal dilator capacity of cerebral arteries in CADASIL and may contribute to reductions in CBF (18). Previous studies also reported the relationship between cerebral hypoperfusion and cognitive dysfunction. A SPECT study of a German CADASIL family showed that cognitive impairment was linked to hypoperfusion in the basal ganglia, and demented patients had a pattern of frontal, temporal, and basal ganglial hypoperfusion (19). A significant reduction in absolute and relative CBF was found within areas of WMH, and this reduction was more severe in demented than in non-demented CADASIL patients (12). Another perfusion metric of cerebral blood volume was also proved to be correlated with disability and cognitive impairment in CADASIL (11).

In the current study, we found that both CBF and MD in WMH were good predictors for cognitive impairment according to receiver operating characteristic curve analysis, while multiple linear regression analysis revealed that CBF in WMH was more strongly associated with global cognitive function. There is no doubt that both cerebral hypoperfusion and brain microstructural damage contribute to cognitive decline. However, brain microstructural changes appear secondary to cerebral perfusion changes, considering both the association between regional MD and CBF, and the results of multiple linear regression analysis. Cerebral hypoperfusion in *NOTCH3* mutation carriers was supposed to precede the development of brain microstructural damage. CADASIL patients had both impaired cerebral and peripheral vasoreactivity at an early stage (20), and hemodynamic parameters were found to be abnormal in the superficial nerve fiber layer of the optic nerve head and retinal capillaries (21, 22). Chronic cerebral hypoperfusion reduced the activity of extracellular signal-regulated kinases, leading to neuronal adaptive responses, and impaired the function of microglial cells, which were implicated in amyloid-β elimination (23). Interestingly, both cognitive decline and cerebral hypoperfusion improved in a CADASIL patient during 2-year administration of lomerizine (24). Our findings suggested that CBF assessed by ASL could serve as a candidate imaging indicator for monitoring alterations of global cognitive function in CADASIL.

Our study had several limitations. First, although we prospectively collected data using a CADASIL registry and MRI protocol, our study design was cross-sectional. Longitudinal studies are needed to explore the causality between cerebral hypoperfusion, white matter integrity and cognitive outcome. Second, the number of CADASIL patients included in the current study was small, which reduced the power to detect significant effects and precluded comprehensive statistical analysis. Third, the MMSE is a crude measure of cognitive functioning that is insensitive to executive dysfunction and is not sensitive enough to detect mild cognitive impairment. Since only part of the enrolled subjects had a MoCA score, the multivariate analysis for MoCA was inapplicable due to the small sample size. More specific tests of executive function and neuropsychological assessment are required in future studies. Fourth, we did not focus on the CBF in subcortical gray matter nuclei, which might also contribute to the cognitive function. Moreover, the emerging technique of diffusion kurtosis imaging allows the measurement of mean kurtosis, which does not require tissue's directionality and hence it could provide more detailed information of microstructural integrity than DTI. The relationship between mean kurtosis and cognitive function should be further investigated in CADASIL.

In conclusion, our study demonstrated a significant association between cerebral hypoperfusion and the severity of brain microstructural damage, while the cerebral perfusion status was more strongly associated with global cognitive function than with white matter integrity.

AUTHOR CONTRIBUTIONS

XY drafted and revised the manuscript, participated in study concept and design, conducted the statistical analyses,

analyzed and interpreted the data. SY participated in study concept and design, data interpretation and made a major contribution in revising the manuscript. ML participated in the study design and made contribution in revising the manuscript. YZ assisted in designing the MRI sequences and imaging analysis, and assessed the cognitive function of the participants.

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REFERENCES

1. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* (1996) 383:707–10. doi: 10.1038/383707a0
2. Moreton FC, Razvi SS, Davidson R, Muir KW. Changing clinical patterns and increasing prevalence in CADASIL. *Acta Neurol Scand.* (2014) 130:197–203. doi: 10.1111/ane.12266
3. Tournier-Lasserve E, Joutel A, Melki J, Weissenbach J, Lathrop GM, Chabriat H, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nat Genet.* (1993) 3:256–9. doi: 10.1038/ng0393-256
4. Ruchoux MM, Guerouaou D, Vandenhaute B, Pruvo JP, Vermersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Acta Neuropathol.* (1995) 89:500–12. doi: 10.1007/BF00571504
5. Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, et al. Cognitive profile in CADASIL. *J Neurol Neurosurg Psychiatry* (2006) 77:175–80. doi: 10.1136/jnnp.2005.068726
6. Dichgans M. Cognition in CADASIL. *Stroke* (2009) 40 (Suppl. 3):S45–7. doi: 10.1161/STROKEAHA.108.534412
7. Peters N, Opherk C, Danek A, Ballard C, Herzog J, Dichgans M. The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. *Am J Psychiatry* (2005) 162:2078–85. doi: 10.1176/appi.ajp.162.11.2078
8. Dichgans M, Filippi M, Bruning R, Iannucci G, Berchtenbreiter C, Minicucci L, et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. *Neurology* (1999) 52:1361–7. doi: 10.1212/WNL.52.7.1361
9. Chabriat H, Pappata S, Poupon C, Clark CA, Vahedi K, Poupon F, et al. Clinical severity in CADASIL related to ultrastructural damage in white matter: *in vivo* study with diffusion tensor MRI. *Stroke* (1999) 30:2637–43. doi: 10.1161/01.STR.30.12.2637
10. O'Sullivan M, Singhal S, Charlton R, Markus HS. Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. *Neurology* (2004) 62:702–7. doi: 10.1212/01.WNL.0000113760.72706.D2
11. Bruening R, Dichgans M, Berchtenbreiter C, Yousry T, Seelos KC, Wu RH, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: decrease in regional cerebral blood volume in hyperintense subcortical lesions inversely correlates with disability and cognitive performance. *AJNR Am J Neuroradiol.* (2001) 22:1268–74. doi: 10.1016/S0925-4927(01)00096-8
12. Chabriat H, Pappata S, Ostergaard L, Clark CA, Pachot-Clouard M, Vahedi K, et al. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. *Stroke* (2000) 31:1904–12. doi: 10.1161/01.STR.31.8.1904
13. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssiere C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *Lancet* (1997) 350:1511–5. doi: 10.1016/S0140-6736(97)08083-5
14. Park JH, Jeon BH, Lee JS, Newhouse PA, Taylor WD, Boyd BD, et al. CADASIL as a useful medical model and genetic form of vascular depression. *Am J Geriatr Psychiatry* (2017) 25:719–27. doi: 10.1016/j.jagp.2017.03.013
15. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, et al. Patterns of MRI lesions in CADASIL. *Neurology* (1998) 51:452–7. doi: 10.1212/WNL.51.2.452
16. Cullen B, Moreton FC, Stringer MS, Krishnadas R, Kalladka D, Lopez-Gonzalez MR, et al. Resting state connectivity and cognitive performance in adults with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Cereb Blood Flow Metab.* (2016) 36:981–91. doi: 10.1177/0271678X16636395
17. List J, Duning T, Meinzer M, Kurten J, Schirmacher A, Deppe M, et al. Enhanced rapid-onset cortical plasticity in CADASIL as a possible mechanism of preserved cognition. *Cereb Cortex* (2011) 21:2774–87. doi: 10.1093/cercor/bhr071
18. Baron-Menguy C, Domenga-Denier V, Ghezali L, Faraci FM, Joutel A. Increased notch3 activity mediates pathological changes in structure of cerebral arteries. *Hypertension* (2017) 69:60–70. doi: 10.1161/HYPERTENSIONAHA.116.08015
19. Mellies JK, Baumer T, Muller JA, Tournier-Lasserve E, Chabriat H, Knobloch O, et al. SPECT study of a German CADASIL family: a phenotype with migraine and progressive dementia only. *Neurology* (1998) 50:1715–21. doi: 10.1212/WNL.50.6.1715
20. Moreton FC, Cullen B, Delles C, Santosh C, Gonzalez RL, Dani K, et al. Vasoreactivity in CADASIL: comparison to structural MRI and neuropsychology. *J Cereb Blood Flow Metab*. (2018) 38:1085–95. doi: 10.1177/0271678X17710375
21. Rufa A, Dotti MT, Frezzotti P, De Stefano N, Caporossi A, Federico A. Hemodynamic evaluation of the optic nerve head in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Arch Neurol.* (2004) 61:1230–3. doi: 10.1001/archneur.61.8.1230
22. Harju M, Tuominen S, Summanen P, Viitanen M, Poyhonen M, Nikoskelainen E, et al. Scanning laser Doppler flowmetry shows reduced retinal capillary blood flow in CADASIL. *Stroke* (2004) 35:2449–52. doi: 10.1161/01.STR.0000145048.94499.b9
23. Bordeleau M, ElAli A, Rivest S. Severe chronic cerebral hypoperfusion induces microglial dysfunction leading to memory loss in APPswe/PS1 mice. *Oncotarget* (2016) 7:11864–80. doi: 10.18632/oncotarget.7689
24. Mizuno T, Kondo M, Ishigami N, Tamura A, Itsukage M, Koizumi H, et al. Cognitive impairment and cerebral hypoperfusion in a CADASIL patient improved during administration of lomerizine. *Clin Neuropharmacol.* (2009) 32:113–6. doi: 10.1097/WNF.0b013e31816c82a6

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An Investigation on the Clinical Features and Neurochemical Changes in Parkinson's Disease With Depression

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Objective: To investigate the clinical features and neurochemical changes in Parkinson's disease with depression (PD-D).

Methods: A total of 478 PD patients were divided into PD-D and PD patients without depression (PD-ND) groups according to the 24-item Hamilton Depression Rating Scale (HAMD) score. Demographic variables, motor and non-motor symptoms and activities of daily living were evaluated. The independent influencing factors of PD-D were investigated via binary logistic regression analysis. The levels of neurotransmitters in cerebrospinal fluid (CSF) were measured and their correlations with HAMD score were analyzed.

Results: The proportion of PD-D was 59.0%, of which 76.95, 20.92, and 2.13% had mild, moderate, and severe depression, respectively. Anxiety/somatization was the most prevalent sub-factor of HAMD in PD-D. The scores of UPDRS III, postural instability/gait difficulty (PIGD) type and the scores of 14-item Hamilton Anxiety Scale (HAMA) and 14-item Chalder Fatigue Scale (FS) were independently associated with PD-D. The levels of dopamine (DA) and 5-hydroxytryptamine (5-HT) were all significantly reduced in PD-D group compared with those in PD-ND group. HAMD scores were negatively correlated with the DA levels in CSF.

Conclusions : PD patients have a high proportion of depression, mainly of mild and moderate levels. The profile of depression in PD population is subtly different from that of the general population. Motor symptoms, PIGD type, anxiety and fatigue are the significant influencing factors of PD-D. Compared to 5-HT, DA may play a more important role in PD-D.

Keywords: depression, Parkinson's disease, risk factor, dopamine, serotonin

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder with both the characteristic motor symptoms and a variety of non-motor symptoms. Depression, one of the most common non-motor symptoms of PD (1), used to be regarded as a psychological reaction to PD, and thus frequently be underestimated and undertreated. The failure to detect PD with depression (PD-D) and offer timely treatment would lead to worse outcomes for patients and caregivers (2).

Clinically, studies on PD-D have yielded conflicting results. In terms of demographic information, for example, some investigators showed that the frequency of PD-D increased with age (3), while others claimed that younger patients were more susceptible to PD-D (4). Some studies identified that being female and having a longer disease duration were the risk factors for PD-D (5), but some did not (6). From the aspect of symptoms, worse motor symptoms might be associated with PD-D (7). However, there were few studies that investigated the relationship between clinical type of PD and PD-D. For non-motor symptoms, most studies agreed that anxiety was the independent influencing factor (8), but other non-motor symptoms, for instance, fatigue, cognitive decline and sleep disturbances, had considerably varied reports (4, 9). Therefore, there is a lack of consensus on the influencing factors of PD-D. Studies consisting of large samples are necessary to explore both general and specific factors related to PD-D. In addition, there are few studies investigating the sub-factors of the 24-item Hamilton Depression Scale (HAMD) in PD-D.

The underlying mechanisms of PD-D have not been adequately clarified. Currently, PD-D is known to be of biological cause, and may be affected by multiple factors including genetic predisposition, biochemical disturbances, and psychological events (7, 10). The altered levels of neurotransmitters may serve as the biochemical basis of depression. 5-hydroxytryptamine (5-HT), dopamine (DA), and norepinephrine (NE), which were altered in the pathological process of PD, were known to play important roles in primary depression (11). Therefore, the pathophysiology of PD-D might also be related to the changes in the serotonergic, dopaminergic and noradrenergic systems (12). However, the changes in the above neurotransmitters for PD-D patients may not be the same as those in patients with idiopathic depression, which major biochemical compromise is the serotonergic system. To our best knowledge, there are limited studies on the neurotransmitters levels in cerebrospinal fluid (CSF) from PD-D patients.

In this study, PD-D was assessed using HAMD (13); motor symptoms and other non-motor symptoms were evaluated by a series of rating scales; the levels of 5-HT, DA, and NE in the CSF were measured by high performance liquid chromatography (HPLC), and their correlations with HAMD scores were analyzed. The objectives of this study were to investigate the clinical features, influencing factors and neurochemical mechanisms of PD-D.

METHODS

Ethics Statement

This study met the guidelines of Helsinki Declaration on ethical principles for medical research involving human subjects, and the protocol was approved by the ethical review board of Beijing Tiantan Hospital. All participants signed written informed consents before they were recruited in the study.

Participants

Total 500 PD patients were consecutively recruited from the Department of Neurology and Geriatrics of the Beijing Tiantan Hospital from November 2014 to November 2017. Patients were diagnosed with idiopathic PD based on the criteria of the Parkinson's UK Brain Bank (14).

Exclusion criteria included severe systemic diseases, such as heart failure, pulmonary disease, gastrointestinal disorders, anemia, infectious disease and chronic inflammatory disease, deep brain stimulation, and conditions that might interfere with the reliable completion of clinical assessments.

Demographic variables including sex, age, age of onset, disease duration, side of onset, education level and anti-parkinson therapy, including the types of drugs, levodopa equivalent daily dose (LEDD) and the durantion of taking medicines, etc. LEDD was calculated as previously proposed (15).

Clinical Assessment For PD Patients

Depression

PD-D was diagnosed according to the diagnostic criteria for depression in PD (16). Patients with depression resulted from systemic diseases, organic mental disorders, psychoactive substances or non-addictive substances and patients on anti-depressants were excluded from analyses.

Twenty-two patients were excluded due to ineligibility. A final total of 478 PD patients were included in the research. Patients with HAMD score of $\geq$8 points and fulfilled the above diagnostic criteria were assigned to the PD-D group. Within the PD-D group, patients with HAMD scores of 8–19 points, 20–34 points and $\geq$35 points were categorized as having mild, moderate and severe depression, respectively. PD patients with HAMD scores of $<$8 points were assigned to the group of PD patients without depression (PD-ND).

The 24 items of HAMD can be grouped into the following 7 factors (5): (1) anxiety/somatization (6 items: psychic anxiety, somatic anxiety, gastrointestinal symptoms, hypochondriasis, insight, and general symptoms); (2) weight loss (1 item); (3) cognitive disturbances (6 items: self-guilt, suicide, agitation, depersonalization and derealization, paranoid, and obsessive-compulsive symptom); (4) circadian fluctuations (1 item); (5) retardation symptoms (4 items: depression, work and interests, retardation, and sexual symptoms); (6) sleep disturbances (3 items: difficulty falling asleep, superficial sleep and early awakening); (7) hopelessness symptoms (3 items: helplessness, hopelessness and worthlessness).

Motor Function, Non-motor Symptoms, and Activities of Daily Living

The severity of PD was evaluated according to the Hoehn and Yahr (H-Y) stage. The motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) III. PD patients were divided into three phenotypes according to the clinical phenotype classification by Jankovic (17): tremor-dominant (TD) subtype, postural instability and gait difficulty (PIGD) subtype and mixed subtype. Items 16, 20, and 21 of the UPDRS were for tremor symptoms; items 13, 14, 15, 29, and 30 of UPDRS were for PIGD symptoms. The phenotype was defined by the ratio of the mean tremor score to PIGD score. TD subtype was defined as the ratio $\geq$1.5, PIGD subtype as the ratio $\leq$1.0 and mixed subtype as the ratio between 1.0 and 1.5.

A variety of non-motor symptoms were assessed using the following scales: the Montreal Cognitive Assessment Scale (MoCA) (18) for cognitive impairment, the 14-item Hamilton Anxiety Scale (HAMA) (19) for anxiety, the 14-item Chalder Fatigue Scale (FS) (20) for fatigue, the Rapid Eye Movement Sleep Behavior Disorder (RBD) Screening Questionnaire (RBDSQ) (21) for RBD, the Scale for Outcomes in PD for Autonomic Symptoms (SCOPA-AUT) (22) for autonomic dysfunction, and the Restless Legs Syndrome (RLS) Severity Rating Scale (RLSRS) (23) for RLS.

Activities of daily living (ADL) were evaluated by ADL Scale.

Measurements of Neurotransmitters in CSF From PD Patients

Anti-parkinsonian drugs were withdrawn for 12–14 h if the patients' condition allowed and longer time was considered unethical by our ethical committee. For medical washout period should be three times of the t1/2 of the medicine, the subjects taking drugs with long t1/2, including controlled release Sinemet (Sinement CR), Pramipexole and controlled release Piribedil (Piribedil CR) were excluded in the analysis of neurotransmitters. Under fasting condition, 5 ml CSF was taken in a polypropylene tube through lumbar puncture, between 7 and 9 a.m. CSF samples were centrifuged immediately at 3,000 rpm at 4°C. Then, approximately 0.5 ml volume of CSF was aliquoted into separate Nunc cryotubes and kept frozen at −80°C until usage in the assays.

The levels of neurotransmitters, including DA, 5-HT, and NE in CSF from PD patients were measured by HPLC (24). LC-MS-MS 6410 chromatograph and Phenomenex 150*2 mm and 150*3 mm chromatographic columns were from the Agilent Company (California, USA), and the standard sample was from Sigma Company (California, USA). In total PD patients, 89 patients agreed lumbar puncture and after excluding patients used drugs with long T1/2, 76 patients' neurotransmitters in CSF were analyzed.

Statistical Analyses

Statistical analyses were performed using SPSS Statistics 20.0 (IBM Corporation, 220 New York, USA). *P*-value of less than an alpha level of 0.05 was defined as statistically significant.

Demographic information, motor and non-motor symptoms and ADL scores between PD-D and PD-ND group were compared. Continuous variables, if normally distributed, were presented as means ± SDs and the 2 groups were compared using 2-tailed *t*-test; if not normally distributed, the data were presented as median (quartile) and compared using non-parametric test. Discrete variables were compared using Chi-square test.

Binary logistic regression analysis was used to investigate the independent influencing factors of PD-D. The covariates with statistical differences in single-factor analysis were divided into a multivariate model; Backward elimination was applied to remove non-significant variables. Influencing factors were presented as odd ratios (OR) with 95% confidence intervals (CI).

Three kinds of neurotransmitters levels of CSF between PD-D and PD-ND groups were compared. Bonferroni correction was made and P was reduced to 0.017 ($0.05/n = 0.05/3 \approx 0.017$). Pearson correlation analyses were conducted between HAMD scores and neurotransmitters levels in CSF in the PD group. Binary logistic regression analysis was used. The covariates contained the neurotransmitters which had statistical differences in single-factor analysis and the independent influencing factors of PD-D in the above mentioned binary logistic regression analysis; Backward elimination was applied to remove non-significant variables.

RESULTS

Frequency of Depression of PD

Among 478 PD patients, 282 (59.00%) were diagnosed with PD-D: of which, 76.95% (217/282 cases) had mild depression, 20.92% (59/282 cases) had moderate depression, and 2.13% (6/282 cases) had severe depression. The remaining 196 cases (41.00%) were in the PD-ND group.

Assessment of Each Sub-factor of HAMD for PD-D and PD-ND Groups

The assessment of each sub-factor of HAMD was shown in **Table 1**. Anxiety/somatization was the most common sub-factor reported in PD-D group at 99.30%, followed by retardation symptoms (97.51%) and hopelessness symptoms (89.71%). Anxiety/somatization also occurred in the largest frequency of PD-ND patients, but compared with those of PD-D, the frequency of each sub-factor of HAMD was much lower.

Demographic Variables, Motor Function, Non-motor Symptoms, and ADL of PD-D and PD-ND Groups

Demographic variables, motor function, non-motor symptoms and ADL scores were compared between PD-D and PD-ND groups in **Table 2**.

Compared with the PD-ND group, the PD-D group showed a significantly earlier age of onset, remarkably longer disease duration, and significantly lower education level. There was no significant difference in the other demographic variables,

TABLE 1 | Assessment of each sub-factor of HAMD for PD-D and PD-ND groups.

	Frequency (*n*, %)		Score (mean ± *SD*)		Range of the score (min–max)	
	PD-ND	PD-D	PD-ND	PD-D	PD-ND	PD-D
Anxiety/somatization	107 (54.60%)	280 (99.30%)	1.08 ± 1.21	4.64 ± 2.48	0–5	0–13
Retardation symptoms	93 (47.40%)	275 (97.51%)	0.69 ± 0.88	3.53 ± 1.86	0–4	0–12
Hopelessness symptoms	89 (45.40%)	253 (89.71%)	0.69 ± 0.90	2.76 ± 1.89	0–4	0–10
Sleep disturbances	60 (30.60%)	211 (74.82%)	0.51 ± 0.96	2.30 ± 1.84	0–5	0–6
Cognitive disturbances	28 (14.30%)	200 (70.92%)	0.14 ± 0.35	1.79 ± 1.95	0–1	0–10
Weight loss	28 (9.20%)	100 (35.46%)	0.12 ± 0.41	0.49 ± 0.73	0–3	0–3
Circadian fluctuations	12 (6.10%)	97(34.40%)	0.10 ± 0.41	0.63 ± 0.97	0–4	0–4

including sex, age, side of onset and the condition usage of the anti-Parkinson drugs between the two groups.

The PD-D group had a significantly advanced H-Y stage, significantly increased UPDRS III score and higher proportion of the PIGD subtype.

The PD-D group scored significantly lower MoCA score and higher scores of HAMA, FS, RBDSQ, SCOPA-AUT, and RLSRS scales when compared with the PD-ND group, demonstrating that the PD-D group had more severe cognitive impairment, anxiety, fatigue, RBD, autonomic dysfunction, and RLS.

Compared with the PD-ND group, the score of ADL scale in the PD-D group was significantly decreased, suggesting that the PD-D group had significantly poor ADL.

Factors Associated With PD-D

Binary logistic regression analysis was performed using the above variables that found statistical differences between PD-D and PD-ND groups. The results showed that the scores of UPDRS III, PIGD type, and the scores of HAMA and FS were independently associated with PD-D (**Table 3**).

Levels of Neurotransmitters in CSF From PD-D and PD-ND Groups

The levels of DA, 5-HT, and NE in CSF from the PD-ND and PD-D groups were compared (**Table 4**). In the PD-D group, the levels of DA and 5-HT were all reduced compared with those in the PD-ND group. However, only DA level showed a significant difference after Bonferroni correction.

The correlational analyses between HAMD scores and neurotransmitters levels in CSF from PD patients were further conducted (**Table 5**). It was found that the HAMD scores had a negative correlation with DA level in CSF ($r = -0.278$, $P < 0.05$). However, no significant relationship between HAMD scores and the levels of 5-HT and NE in CSF was detected.

Binary logistic regression analysis was performed to investigate the relationship of PD-D and DA levels in CSF. The covariates contained the levels of DA in CSF and the scores of UPDRS III, PIGD type and the scores of HAMA and FS (**Table 6**). The results showed that the DA levels significantly negatively correlated with PD-D.

DISCUSSION

Though PD was previously characterized by the classical motor symptoms, recent studies have suggested that non-motor symptoms play significant roles in the deterioration of the quality of life for PD patients (25, 26). As one of the mood disorders, depression is often covered by motor symptoms and fails to present as the chief complaint. It is important to diagnose PD-D, because it is one of the main determinants of quality of life for PD patients and lack of PD-D diagnosis results in heavy burden to the families of patients (27, 28).

The prevalence of PD-D differs greatly across studies, ranging from 2.7 to 90%, and around 35% of PD patients presented significant depressive symptoms clinically (29), which was much higher than that in general population (30). The variation might be resulted from different diagnostic criteria, rating scales, sample sizes, and study population (31). In the current study, a large sample containing 478 Chinese PD patients was established, of which, 59% of the population suffered from depression. Analysis of the severity of depression in PD patients indicated that mild, moderate, and severe depression accounted for 76.95, 20.92, and 2.13%, respectively, implying that PD-D was featured by the mild and moderate depression (9). Clinical trials have shown that mild depressive symptoms are a variable process and may result in remission or take a turn for more severe and persistent symptoms over time (32).

Previous studies rarely investigated the 7 sub-factors of HAMD-24 items in detail. In this investigation, the results showed that PD-D patients had the highest frequency of anxiety/somatization, which was followed by the symptoms of retardation and hopelessness. The cognitive disturbances, which contains suicide, had the fifth frequency. This suggested that the profile of depression in PD population was subtly different from that of the general population which showed a high rate of suicide (33).

In this study, the binary logistic regression analysis showed that the UPDRS III score, PIGD type, the scores of HAMA and FS were the significant influencing factors of PD-D. Motor symptoms were significantly evidently different between PD-D and PD-ND groups. Some earlier studies failed to find a significant relationship between motor symptoms and PD-D (9, 34); the inconsistency may be caused by patients' stronger perception of depression than actual disability in "on" phase.

TABLE 2 | Demographic variables, motor function, non-motor symptoms, and ADL of PD-D and PD-ND groups.

	PD-ND group (196 cases)	PD-D group (282 cases)	*P*
DEMOGRAPHIC INFORMATION			
Female (*n*, %)	87 (44.39%)	150 (53.19%)	0.058
Age (year, $\overline{X} \pm s$)	63.00 (56.00–70.00)	61.50 (55.75–69.00)	0.278
Age of onset (year, $\overline{X} \pm s$)	59.87 ± 11.16	57.51 ± 10.89	0.024*
Disease duration [year, Median (Q1-Q3)]	2.00 (1.00–4.00)	3.00 (1.00–5.00)	<0.001**
Low education level (<9 years) (*n*, %)	93 (47.45%)	176 (62.41%)	<0.001**
Left side of onset (n, %)	82 (41.84%)	132 (46.81%)	0.282
ANTI-PARKINSON DRUG			
LEDD [mg, M (Q1-Q3)]	0.75 (0, 6.90)	1.16 (0, 3.00)	0.341
Kinds of Anti-parkinson drug			
Madopar (*n*, %)	85 (43.37%)	144 (51.06%)	0.098
Sinemet CR (*n*, %)	12 (6.12%)	20 (7.09%)	0.677
Entacapone (*n*, %)	7 (3.57%)	19 (6.74%)	0.133
Pramipexole (*n*, %)	45 (22.96%)	48 (17.02%)	0.107
Piribedil CR (*n*, %)	36 (18.37%)	49 (17.38%)	0.780
Selegiline (*n*, %)	4 (2.04%)	4 (1.42%)	0.722
Antane (*n*, %)	9 (4.59%)	23 (8.16%)	0.125
Duration of anti-PD therapy			
≤1 year	61 (31.12%)	82 (29.08%)	0.059
>1–≤3years	84 (42.86%)	96 (34.04%)	
>3–≤7years	35 (17.86%)	64 (22.70%)	
>7years	16 (8.16%)	40 (14.18%)	
MOTOR FUNCTION			
H-Y stage (*n*, %)			
Early stage (stage 1–2.5)	179 (91.33%)	224 (79.43%)	<0.001**
Advanced score (stage 3–5)	17 (8.67%)	58 (20.57%)	
Total UPDRS III [point, Median (Q1-Q3)]	18.00 (12.00–27.00)	28.00 (19.00–40.00)	<0.001**
Tremor	3.00 (2.00–6.00)	5.00 (2.00–8.00)	
Rigidity	3.00 (1.00–5.00)	5.00 (2.00–9.00)	
Bradykinesia	7.00 (5.00–11.00)	11.00 (7.00–16.00)	
Postural instability/gait difficulty	3.00 (2.00–4.00)	4.00 (3.00–6.00)	
CLINICAL TYPE (*n*, %)			
TD subtype	67 (35.40)	6 (2.70)	<0.001**
PIGD subtype	106 (52.40)	276 (97.30)	
Mixed subtype	25 (12.20)	0 (0.00)	
NON-MOTOR SYMPTOMS			
MoCA [point, Median (Q1-Q3)]	23.00 (19.00–27.00)	21.00 (16.00–25.00)	<0.001**
HAMA [point, Median (Q1-Q3)]	3.00 (1.00–5.00)	12.00 (8.00–17.75)	<0.001**
FS [point, Median (Q1-Q3)]	7.00 (4.00–10.00)	10.00 (8.00–12.00)	<0.001**
RBDSQ [points, Median (Q1-Q3)]	1.00 (0.00–4.00)	3.00 (1.00–7.00)	<0.001**
SCOPA-AUT [points, Median (Q1-Q3)]	33.00 (29.00–37.00)	36.00 (32.00–43.00)	<0.001**
RLSRS [point, Median (Q1-Q3)]	0.00 (0.00–6.00)	0.00 (0.00–18.00)	<0.001**
ADL			
ADL [point, Median (Q1-Q3)]	22.00 (20.00–30.00)	32.50 (23.00–42.25)	<0.001**

**P < 0.05; **P < 0.01. LEDD, levodopa equivalent daily dose; Sinemet CR, controlled release Sinemet; Piribedil C, controlled release Piribedil; UPDRS III, Unified Parkinson's Disease Rating Scale III; TD, tremor-dominant; PIGD, postural instability/gait difficulty; MoCA, Montreal Cognitive Assessment Scale; HAMA, the 14-item Hamilton Anxiety Scale; FS, the 14-item Chalder Fatigue Scale; RBDSQ, the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT, the Scale for Outcomes in PD for Autonomic Symptoms; RLSRS, Restless Legs Syndrome Severity Rating Scale.*

Worse motor symptoms may aggravate patients' psychological and physical burden, which would increase the sense of guilt and despair. Besides, our study found that PIGD type was independently associated with PD-D. Accordingly, good management of motor symptoms is important for PD-D.

In our previous study (35), PIGD patients had more severe or faster neurodegeneration than TD group. In addition, PIGD severity might be related to the depletion of homovanillic acid, one of the metabolites of DA, in CSF (35). Moreover, in the current study, the decrease of DA might correlate with PD-D.

TABLE 3 | Logistic regression analysis of factors associated with PD-D.

	B	OR	95% CI	*P*
Age of onset	−0.033	0.967	0.935–1.000	0.052
UPDRS III score	0.049	1.050	1.020–1.082	0.001*
PIGD type	−3.611	0.027	0.007–0.106	<0.001**
HAMA score	0.285	1.330	1.216–1.454	<0.001**
FS score	0.111	1.117	1.005–1.241	0.040*
RBDSQ score	0.078	1.081	0.988–1.241	0.090
Constant number	−1.611	0.200		0.152

*$P < 0.05$, **$P < 0.01$. UPDRS III, Unified Parkinson's Disease Rating Scale III; PIGD, postural instability/gait difficulty; HAMA, the 14-item Hamilton Anxiety Scale; FS, the 14-item Chalder Fatigue Scale; RBDSQ, the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; B, regression coefficient or intercept; OR, odds ratio; CI, confidence interval.*

TABLE 4 | Levels of neurotransmitters in CSF from PD-D and PD-ND groups.

	PD-ND group (24 cases)	PD-D group(52 cases)	*P*
DA (fg/mL, $\overline{X} \pm s$)	8.042 ± 2.423	6.025 ± 2.214	0.001*
5-HT (fg/mL, $\overline{X} \pm s$)	19.221 ± 7.358	14.796 ± 8.365	0.029
NE (fg/mL, $\overline{X} \pm s$)	483.004 ± 140.534	496.229 ± 125.904	0.683

$P < 0.017$. DA, dopamine; 5-HT,5-hydroxytryptamine; NE, norepinephrine.

TABLE 5 | Correlation of HAMD scores with the levels of neurotransmitters in CSF from PD patients.

	R	*P*
DA (fg/ml)	−0.278	0.015*
5-HT (fg/ml)	−0.22	0.056
NE (fg/ml)	0.056	0.63

$P < 0.017$. DA, dopamine; 5-HT, 5-hydroxytryptamine; NE, norepinephrine.

Therefore, the PIGD group might be vulnerable to PD-D. Much effort should be paid to PD patients with PIGD type to mitigate depression.

The comorbidity of depression and anxiety in PD patients was as high as 14–50% (36, 37). In this study, the logistic regression analysis demonstrated that anxiety was one of the risk factors of PD-D. Anxiety and depression in PD patients often exist together, suggesting that they may have a common biochemical basis. They may both be related to the extensive serotonergic alteration and a more limited dopaminergic breakdown (38). Moreover, increased levels of inflammatory markers in CSF were strongly associated with depression, anxiety and other non-motor symptoms of PD (39). Nonetheless, research suggests that the comorbidity of depression and anxiety might be resulted from the superposition of different pathophysiological mechanisms of anxiety and depression rather than the common mechanism (37).

Fatigue was previously considered as a manifestation of PD-D, but in recent years, it has been recognized as a non-motor symptom independent of depression. A previous study showed that fatigue was correlated with depression (40). We further demonstrated that fatigue was one of the significant influencing factors of depression in PD patients. Our previous studies found that the decrease of serotonin dysfunction might be correlated with fatigue in PD patients (24). There was much interest in whether PD-D and fatigue shared the similar pathophysiologic mechanisms, for example, serotonergic dysfunction (41, 42). The underlying mechanism needs further investigation.

TABLE 6 | Logistic regression analysis of the relationship of DA in CSF and PD-D.

	B	OR	95% CI	*P*
UPDRS III score	0.03	1.031	0.949–1.112	0.460
PIGD type	−2.628	0.072	0.007–1.124	0.042*
HAMA score	0.822	2.275	1.211–3.846	0.008*
DA	−1.012	0.364	0.172–0.816	0.014*
Constant number	3.679	39.587		0.154

$P < 0.05$. UPDRS III, Unified Parkinson's Disease Rating Scale III; PIGD, postural instability/gait difficulty; HAMA, the 14-item Hamilton Anxiety Scale; DA, dopamine; B, Regression coefficient or intercept; OR, odds ratio; CI, confidence interval.

The research on the mechanisms of PD-D has not reached consensus. Studies showed that other chronic diseases, which also resulted in movement disorders, had lower incidences of depression than PD (28). What's more, depressive symptoms could appear before motor symptoms in PD patients (43). Therefore, as endogenous depression, PD-D is likely related to the characteristic pathology of PD. Theoretically, according to Braak stage of PD pathology (44), Lewy bodies deposit in the raphe nuclei, locus caeruleus, substantia nigra, and ventral tegmental area, and cause progressive loss of neurons and subsequent depletion of several neurotransmitters, including 5-HT, NE, and DA, etc.

At Braak stage II, the serotonergic neurons are affected. A study reported that PD-D patients had reduced levels of 5-hydroxyindole acetic acid (5-HIAA, a metabolite of 5-HT) in CSF than PD-ND patients (45, 46). However, Olivola and investigators failed to find the changes of 5-HT in the CSF of PD-D patients (47). These studies, including our study, showed the lack of correlation between depression and 5-HT or 5-HIAA in CSF. However, a positron emission tomography (PET) imaging study indicated a close correlation between PD-D and 5-HT transporter (48), although other similar studies failed to display consistent results (49, 50). Although there are many plausible theories explaining that deficits of the monoaminergic neurotransmitters are related to depression (51), the roles of serotonergic system on PD-D are less certain in human studies.

The level of DA is increasingly recognized as an important indicator for serious problems in PD-D; this is supported by pathological, experimental, and neuroimaging studies (52). The DA transporter availability was also proven to be reduced in PD-D in several PET studies (12, 53, 54). As a DA receptor agonist, pramipexole (0.125–1.0 mg three times per day) could improve the depressive symptoms in PD patients, and 80% of the improvements was caused by a direct effect of treatment on depressive symptoms while 20% worked through the alleviation of motor symptoms (55). Pramipexole could upregulate the

expression of dopamine receptor D3 (56). The same effect was found in Ropinirole (57) and a prospective multicenter study showed that Ropinirole (a median dose of 10 mg) could improve both anxious and depressive symptoms in PD patients (58). The anti-depressant effect also was obtained in Rasagiline with higher doses than those used for the control of motor symptoms (1 mg/day) (59) and it might be related with its role for dopamine-enhancing (60). Unfortunately, none of these studies reported an association between the levels of neurotransmitters in CSF and PD-D. The results of our study supported the model that PD-D arised as a result of the dysfunction in dopaminergic pathways (61). On the other hand, DA helped to improve the motor symptoms, which was an independent influencing factor for PD-D. In this study, it showed that in PD-D patients, both the DA and 5-HT levels in CSF were decreased, however, only the level of DA in CSF was correlated with HAMD score. These results suggested that DA played a more significant role on PD-D. Therefore, it is plausible to speculate that dopaminergic-centered therapy may be much helpful for PD-D.

Most of NE neurons are distributed in the locus caeruleus. Previous investigations on the association between NE and PD-D were rather limited with relatively small sample sizes. Additionally, these studies chiefly focused on the damages of NE neurons and related innervations, and their correlation with PD-D. For example, a study observed that neuronal loss in locus caeruleus was different between PD-D and PD-ND groups (62). Another PET study using ^{11}C-RTI-32 as an *in vivo* marker for both DA and NE transporter binding, revealed that PD-D might be associated with the loss of NE innervations in the limbic system (12). Although the above studies showed clues implying the potential involvement of NE in PD-D, there was no direct evidence linking NE reduction in CSF to PD-D. In this study, the NE levels in CSF did not differ significantly between PD-D and PD-ND groups, and PD-D did not correlate with NE level in CSF. Therefore, NE might not be a critical neurotransmitter for PD-D.

This study has the following limitations. CSF samples were not obtained from all PD patients enrolled in this study due to difficulties including old age, hyperosteogeny, and intolerance of holding position for lumbar puncture, etc. CSF samples from PD patients with moderate and severe depression were also relatively limited. Thus, further investigations with more CSF samples, especially from moderate and severe PD-D patients and prolonged follow-up time are much needed to support the results from the current study. What's more, as a retrospective and observational study, our study provided limited grounds for drawing definite conclusions. Longitudinal studies are required to elucidate how the depression in PD patients affects the progression and prognosis of these patients.

In summary, PD patients have a high frequency of mild and moderate depression. Motor symptoms, PIGD type, anxiety and fatigue are the significant influencing factors of PD-D. DA plays a more important role on PD-D. Results from this study provide new insights for the management of the above risk factors of PD-D and possible route for reduction of PD-D by targeting dopaminergic system.

AUTHOR CONTRIBUTIONS

T-HL drafting the manuscript, study design, analysis of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis. PG study design, accepts responsibility for the conduct of research and will give final approval, acquisition of data. L-JZ, YH, S-YY, LL, ZJ, Q-JY, R-DW, L-XL, and Y-SP accepts responsibility for the conduct of research and will give final approval, acquisition of data. WZ study design, analysis of data, accepts responsibility for the conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision.

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REFERENCES

1. Cosentino C, Nunez Y, Torres L. Frequency of non-motor symptoms in Peruvian patients with Parkinson's disease. *Arq Neuropsiquiatr.* (2013) 71:216–9. doi: 10.1590/0004-282X20130005
2. Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J. Detecting depression in Parkinson disease: a systematic review and meta-analysis. *Neurology* (2016) 87:426–37. doi: 10.1212/wnl.0000000000002898
3. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Risk of incident depression in patients with Parkinson disease in the UK. *Eur J Neurol.* (2011) 18:448–53. doi: 10.1111/j.1468-1331.2010.03176.x
4. Ziropadja L, Stefanova E, Petrovic M, Stojkovic T, Kostic VS. Apathy and depression in Parkinson's disease: the Belgrade PD study report. *Parkinsonism Relat Disord.* (2012) 18:339–42. doi: 10.1016/j.parkreldis.2011.11.020
5. Zhu J, Lu L, Pan Y, Shen B, Xu S, Hou Y, et al. Depression and associated factors in nondemented Chinese patients with Parkinson's disease. *Clin Neurol Neurosurg.* (2017) 163:142–8. doi: 10.1016/j.clineuro.2017.10.031
6. Quelhas R, Costa M. Anxiety, depression, and quality of life in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* (2009) 21:413–9. doi: 10.1176/appi.neuropsych.21.4.413
7. Leentjens AF, Moonen AJ, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, et al. Modeling depression in Parkinson disease: disease-specific and nonspecific risk factors. *Neurology* (2013) 81:1036–43. doi: 10.1212/WNL.0b013e3182a4a503
8. Ou R, Wei Q, Hou Y, Yuan X, Song W, Cao B, et al. Vascular risk factors and depression in Parkinson's disease. *Eur J Neurol.* (2018) 25:637–43. doi: 10.1111/ene.13551
9. Cui SS, Du JJ, Fu R, Lin YQ, Huang P, He YC, et al. Prevalence and risk factors for depression and anxiety in Chinese patients with Parkinson disease. *BMC Geriatr.* (2017) 17:270. doi: 10.1186/s12877-017-0666-2
10. Shin MS, Kim TW, Lee JM, Sung YH, Lim BV. Treadmill exercise alleviates depressive symptoms in rotenone-induced Parkinson disease rats. *J Exerc Rehabil.* (2017) 13:124–9. doi: 10.12965/jer.1734966.483
11. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. *Neurobiol Dis.* (2012) 46:581–9. doi: 10.1016/j.nbd.2011.12.041
12. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* (2005) 128(Pt 6):1314–22. doi: 10.1093/brain/awh445
13. Williams JB. Standardizing the Hamilton Depression Rating Scale: past, present, and future. *Eur Arch Psychiatry Clin Neurosci.* (2001) 251(Suppl. 2):Ii6–12. doi: 10.1007/BF03035120
14. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* (1992) 55:181–4.
15. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord.* (2010) 25:2649–53. doi: 10.1002/mds.23429
16. Starkstein S, Dragovic M, Jorge R, Brockman S, Merello M, Robinson RG, et al. Diagnostic criteria for depression in Parkinson's disease: a study of symptom patterns using latent class analysis. *Mov Disord.* (2011) 26:2239–45. doi: 10.1002/mds.23836
17. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. *Parkinson Study Group Neurol.* (1990) 40:1529–34.
18. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology* (2009) 73:1738–45. doi: 10.1212/WNL.0b013e3181c34b47
19. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* (1959) 32:50–5.
20. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. *J Psychosom Res.* (1993) 37:147–53.
21. Zea-Sevilla MA, Martinez-Martin P. Rating scales and questionnaires for assessment of sleep disorders in Parkinson's disease: what they inform about? *J Neural Transm.* (2014) 121(Suppl. 1):S33–40. doi: 10.1007/s00702-014-1217-z
22. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord.* (2004) 19:1306–12. doi: 10.1002/mds.20153
23. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. *Sleep Med.* (2003) 4:121–32. doi: 10.1016/S1389-9457(02)00258-7
24. Zuo LJ, Yu SY, Hu Y, Wang F, Piao YS, Lian TH, et al. Serotonergic dysfunctions and abnormal iron metabolism: relevant to mental fatigue of Parkinson disease. *Sci Rep.* (2016) 6:19. doi: 10.1038/s41598-016-0018-z
25. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord.* (2010) 25:2493–500. doi: 10.1002/mds.23394
26. Muller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord.* (2013) 19:1027–32. doi: 10.1016/j.parkreldis.2013.07.010
27. Carod-Artal FJ, Ziomkowski S, Mourao Mesquita H, Martinez-Martin P. Anxiety and depression: main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. *Parkinsonism Relat Disord.* (2008) 14:102–8. doi: 10.1016/j.parkreldis.2007.06.011
28. Sagna A, Gallo JJ, Pontone GM. Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. *Parkinsonism Relat Disord.* (2014) 20:708–15. doi: 10.1016/j.parkreldis.2014.03.020
29. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord.* (2008) 23:183–9; quiz: 313. doi: 10.1002/mds.21803
30. Baxter AJ, Charlson FJ, Cheng HG, Shidhaye R, Ferrari AJ, Whiteford HA. Prevalence of mental, neurological, and substance use disorders in China and India: a systematic analysis. *Lancet Psychiatry* (2016) 3:832–41. doi: 10.1016/s2215-0366(16)30139-0
31. Aarsland D, Pahlhagen S, Ballard CG, Ehrt U, Svenningsson P. Depression in Parkinson disease–epidemiology, mechanisms and management. *Nat Rev Neurol.* (2011) 8:35–47. doi: 10.1038/nrneurol.2011.189
32. Ravina B, Elm J, Camicioli R, Como PG, Marsh L, Jankovic J, et al. The course of depressive symptoms in early Parkinson's disease. *Mov Disord.* (2009) 24:1306–11. doi: 10.1002/mds.22572
33. Even C, Weintraub D. Is depression in Parkinson's disease (PD) a specific entity? *J Affect Disord.* (2012) 139:103–12. doi: 10.1016/j.jad.2011.07.002
34. Schrag A, Jahanshahi M, Quinn NP. What contributes to depression in Parkinson's disease? *Psychol Med.* (2001) 31:65–73. doi: 10.1017/s0033291799003141
35. Zuo LJ, Piao YS, Li LX, Yu SY, Guo P, Hu Y, et al. Phenotype of postural instability/gait difficulty in Parkinson disease: relevance to cognitive impairment and mechanism relating pathological proteins and neurotransmitters. *Sci Rep.* (2017) 7:44872. doi: 10.1038/srep44872
36. Dissanayaka NN, Sellbach A, Matheson S, O'Sullivan JD, Silburn PA, Byrne GJ, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord.* (2010) 25:838–45. doi: 10.1002/mds.22833
37. Negre-Pages L, Grandjean H, Lapeyre-Mestre M, Montastruc JL, Fourrier A, Lepine JP, et al. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectionnal DoPaMiP study. *Mov Disord.* (2010) 25:157–66. doi: 10.1002/mds.22760
38. Maillet A, Krack P, Lhommee E, Metereau E, Klinger H, Favre E, et al. The prominent role of serotonergic degeneration in apathy, anxiety and depression in *de novo* Parkinson's disease. *Brain* (2016) 139(Pt 9):2486–502. doi: 10.1093/brain/aww162
39. Lindqvist D, Hall S, Surova Y, Nielsen HM, Janelidze S, Brundin L, et al. Cerebrospinal fluid inflammatory markers in Parkinson's disease–associations with depression, fatigue, and cognitive impairment. *Brain Behav Immun.* (2013) 33:183–9. doi: 10.1016/j.bbi.2013.07.007
40. Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, D'Amelio M, De Pandis MF, et al. Prevalence of fatigue in Parkinson disease and its clinical correlates. *Neurology* (2014) 83:215–20. doi: 10.1212/wnl.0000000000000587
41. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* (2010) 133:3434–43. doi: 10.1093/brain/awq268
42. Politis M, Niccolini F. Serotonin in Parkinson's disease. *Behav Brain Res.* (2015) 277:136–45. doi: 10.1016/j.bbr.2014.07.037

43. Fang F, Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, et al. Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. *Mov Disord.* (2010) 25:1157–62. doi: 10.1002/mds.23092
44. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* (2009) 373:2055–66. doi: 10.1016/s0140-6736(09)60492-x
45. Kostic VS, Djuricic BM, Covickovic-Sternic N, Bumbasirevic L, Nikolic M, Mrsulja BB. Depression and Parkinson's disease: possible role of serotonergic mechanisms. *J Neurol.* (1987) 234:94–6.
46. Mayeux R, Stern Y, Cote L, Williams JB. Altered serotonin metabolism in depressed patients with parkinson's disease. *Neurology* (1984) 34:642–6.
47. Olivola E, Pierantozzi M, Imbriani P, Liguori C, Stampanoni Bassi M, Conti M, et al. Serotonin impairment in CSF of PD patients, without an apparent clinical counterpart. *PLoS ONE* (2014) 9:e101763. doi: 10.1371/journal.pone.0101763
48. Boileau I, Warsh JJ, Guttman M, Saint-Cyr JA, McCluskey T, Rusjan P, et al. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. *Mov Disord.* (2008) 23:1776–80. doi: 10.1002/mds.22212
49. Politis M, Wu K, Loane C, Turkheimer FE, Molloy S, Brooks DJ, et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology* (2010) 75:1920–7. doi: 10.1212/WNL.0b013e3181feb2ab
50. Strecker K, Wegner F, Hesse S, Becker GA, Patt M, Meyer PM, et al. Preserved serotonin transporter binding in *de novo* Parkinson's disease: negative correlation with the dopamine transporter. *J Neurol.* (2011) 258:19–26. doi: 10.1007/s00415-010-5666-5
51. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. *J Neuropsychiatry Clin Neurosci.* (1995) 7:524–33; discussion 523–4. doi: 10.1176/jnp.7.4.524
52. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci.* (2017) 18:435–50. doi: 10.1038/nrn.2017.62
53. Vriend C, Raijmakers P, Veltman DJ, van Dijk KD, van der Werf YD, Foncke EM, et al. Depressive symptoms in Parkinson's disease are related to reduced [123I]FP-CIT binding in the caudate nucleus. *J Neurol Neurosurg Psychiatry* (2014) 85:159–64. doi: 10.1136/jnnp-2012-304811
54. Vuckovic MG, Wood RI, Holschneider DP, Abernathy A, Togasaki DM, Smith A, et al. Memory, mood, dopamine, and serotonin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *Neurobiol Dis.* (2008) 32:319–27. doi: 10.1016/j.nbd.2008.07.015
55. Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* (2010) 9:573–80. doi: 10.1016/s1474-4422(10)70106-x
56. Tokunaga N, Choudhury ME, Nishikawa N, Nagai M, Tujii T, Iwaki H, et al. Pramipexole upregulates dopamine receptor D(2) and D(3) expression in rat striatum. *J Pharmacol Sci.* (2012) 120:133–7. doi: 10.1254/jphs.12096SC
57. Kang SY, Ryu HS, Sunwoo MK, Kim SJ, Baik JS, Park MY, et al. Sleepiness and depression in Parkinson's Disease patients treated with ropinirole and levodopa. *J Mov Disord.* (2017) 10:123–9. doi: 10.14802/jmd.17048
58. Rektorova I, Balaz M, Svatova J, Zarubova K, Honig I, Dostal V, et al. Effects of ropinirole on nonmotor symptoms of Parkinson disease: a prospective multicenter study. *Clin Neuropharmacol.* (2008) 31:261–6. doi: 10.1097/WNF.0b013e31815d25ce
59. Korchounov A, Winter Y, Rossy W. Combined beneficial effect of rasagiline on motor function and depression in *de novo* PD. *Clin Neuropharmacol.* (2012) 35:121–4. doi: 10.1097/WNF.0b013e31823b1da8
60. Smith KM, Eyal E, Weintraub D. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol.* (2015) 72:88–95. doi: 10.1001/jamaneurol.2014.2472
61. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry* (2007) 64:327–37. doi: 10.1001/archpsyc.64.3.327
62. Frisina PG, Haroutunian V, Libow LS. The neuropathological basis for depression in Parkinson's disease. *Parkinson Relat Disord.* (2009) 15:144–8. doi: 10.1016/j.parkreldis.2008.04.038

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Diversiform Etiologies for Post-stroke Depression

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After the onset of stroke, many patients suffer from emotional behavior changes. Approximately, one-third of stroke survivors are affected by post-stroke depression (PSD), making it a serious social and public health problem. Post-stroke depression (PSD) has an important impact on the course, recovery, and prognosis of stroke. The pathogenesis of PSD is very complex, involving many factors such as biological mechanism and social psychological mechanisms. This article provides a brief review of the hot issues related to etiologies of PSD.

Keywords: post-stroke depression, depression, stroke, biological mechanism, social psychological mechanisms, default mood network

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INTRODUCTION

Post-stroke depression (PSD) refers to persistent depression after a stroke. Expressed as loss of interest, decreased energy, decreased appetite, sleep disorders, low self-evaluation, self-blame, and even repeated self-injury, suicidal thoughts or behaviors. It is the most common emotional disorder after stroke. As early as 1977, Folstein et al. reported PSD for the first time, and its incidence rate was as high as 45% (1). Patients with major depression after stroke account for 10–25% of stroke patients, and those with mild depression account for 10–40% of stroke patients. Symptoms were most common in the third month after stroke, and the prevalence did not decrease in the following year (2). The clinical manifestations of patients with post-stroke depression (PSD) are more complicated. Clinically, the patient's performance is often divided into core symptoms and non-core symptoms. The main symptoms are: (1) most of the time patients feel unhappy, even painful; (2) lose interest and pleasure, and cannot get happiness from the things they usually love; (3) energy decline, easy to feel tired, even lose the belief of living, suicidal tendencies. Non-core symptoms are mainly: (1) weight loss, difficulty sleeping, insomnia and dreams, unexplained loss of appetite, pain, general malaise; (2) nervousness, anxiety; (3) self-evaluation decline, self-blame, worthless, hesitant, attention decreased, etc. The diagnosis of typical cases of PSD is not difficult. Patients with a history of stroke, low mood, lack of interest or loss of fun, plus some psychological, or physical symptoms can make a diagnosis. A considerable number of patients do not show obvious sadness and despair, but mainly a variety of physical symptoms, such as fatigue, anxiety, tension headache, loss of appetite, sleep disorders. Post-stroke depression affects the patient's cognitive function and quality of life, increases the patient's mortality and self-killing rate, and imposes a heavy burden on society and the family. However, there are still many ambiguities about the risk factors, etiologies of PSD. Therefore, early accurate etiologies of PSD is very important and should be taken seriously by clinicians. The research progress in the incidence, etiologies is summarized as follows.

INCIDENCE AND PREVALENCE OF PSD

There are significant differences in the incidence of PSD, due to differences in study selection, time to assessment after stroke, assessment methods and diagnostic criteria (3). A systematic review of 14 studies involving the prevalence of PSD found that the peak of depression was 3–6 months after stroke, and the prevalence was 9–34%. The prevalence of depression remained at a high level until 1–3 years after stroke; the prevalence of mild depression after stroke was ∼8–22% (4). Hackett analyzed 51 studies: Using the Hamilton Depression Scale (HDRS), the lowest PSD rate was 26%. The highest incidence of PSD was 41% with the Montgomery-Asberg Depression Rating Scale and the Zung Depression Scale (5). Schöttke believes that the incidence of PSD was 31.1%, post-stroke anxiety prevalence was 20.4% (6). Chemerinski et al. analyzed 24 studies and classified patients with strokes from different sources. The results showed that the incidence of major depression in acute hospitalized stroke patients was 22%, mild depression was 17%; Out-patient stroke with severe depression was 23%, mild depression was 35%; community patients had severe depression of 13% and mild depression was 10% (7).

ETIOLOGIES OF PSD

The pathogenesis of PSD is complex, involving many factors such as biological mechanism and social psychological mechanisms.

Biological Mechanism

Monoamine Neurotransmitter Change

Numerous studies on depression have confirmed that noradrenergic and serotonergic neurons involved in emotional regulation in the brain are located in the brainstem. Its axons pass through the hypothalamus, basal ganglia, corpus callosum, and radial crown, and finally reach the frontal cortex. 5-HT and NE are both monoamine neurotransmitters, mainly involved in depression, anxiety, self-injury suicidal behavior, and sleep disorders. When stroke destroys the above related structures, it can cause a decrease in NE and 5-HT levels, and patients are more prone to depression (4). Some scholars have found that the concentration of serotonin metabolites in cerebrospinal fluid of patients with PSD is reduced (8). Combined with clinical application of antidepressants such as selective serotonin reuptake inhibitors (SSRIs), it is effective in the treatment of PSD. It was further confirmed that the occurrence of PSD is associated with a decrease in monoamine neurotransmitters (9).

Studies have found that the occurrence of PSD is related to neurotransmitters such as glutamate (Glu) and gamma-aminobutyric acid (GABA). Hypoxia-induced hypoxia causes a decrease in ATP and changes in membrane permeability leading to K+ efflux and Ca2+ influx, leading to an increase in excitatory amino acids such as glutamate, while re-uptake is blocked, excitatory amino acids accumulate outside the cell, leading to post-synaptic Excessive excitation, degeneration, and necrosis of neurons. Increased Glu leads to post-synaptic neurons, excessive excitability, ulceration, and necrosis. Patients with PSD are often accompanied by changes in the level of glutamate in the frontal lobe. PSD patients have a significantly elevated glutamate/creatinine ratio in the frontal lobes and anterior cingulate gyrus. This change is associated with the Hamilton Depression Scale (HDRS) is associated with patients with high scores (10). Wang et al. used MRI spectroscopy studies to show that patients with PSD have higher glutamate levels than stroke patients without PSD (11). The mechanism of PSD is related to the imbalance of GABA expression, and a decrease in GABA can lead to a low level of NE (12).

Inflammation Mechanism

Inflammation refers to the defense response of living tissue to the stimulation of biological, physical, chemical, and other damage factors. Various inflammatory factors refer to cytokines involved in the inflammatory response, and are hydrophilic specific polypeptides or small molecular proteins secreted by activated immune cells. When inflammation occurs in the body, inflammatory factors inactivate the phosphorylation of the inhibitor of nuclear factor kappa B (IκB) resulting in a decrease in the inhibition of nuclear factor kappa B (NF-κB) by IκB, which causes NF-κB to enter the nucleus and bind to specific NF-κB. Inducing the transcription of related genes and promoting the expression of genes, causing an increase in anxiety and other depressive behaviors. IL-1, IL-2, IL-6, and TNF-α are mainly produced by mononuclear macrophages, which are involved in the inflammatory response and promote the immune response. Both IL-10 and IL-13 are important inhibitory cytokines, mainly produced by Th2 cells, which inhibit the production of pro-inflammatory cytokines, suppress immune responses, and protect nerves. Inflammation plays a protective role in maintaining the homeostasis of the body. However, if it is overreacted, it can damage normal tissues and organs. Studies have found that inflammation under certain conditions can damage the internal balance of the body, causing metabolic disorders, leading to abnormal secretion of neurotransmitters, resulting in depression (13). Spalletta et al. believe that the occurrence of PSD may be related to immune activation, leading to increased secretion of cytokines, and proposed a "cytokine hypothesis." After stroke, astrocytes and microglia in the central nervous system produce cytokines and their receptors, including IL-1, IL-6, TNF-α, and IFN-γ. The phenomenon of immune activation and increased cytokines (14).

Studies have suggested that inflammatory factors may cause depression through neurodegeneration, decreased regeneration, decreased ω-3 fatty acids, decreased levels of tryptophan, and elevated levels of metabolites. Inflammatory factors interact with each other to form a network system that regulates immune responses (15, 16). Inflammatory factors can increase the activity of indoleamine-2,3-dioxygenase (IDO), increase the metabolism of tryptophan, and increase the concentration of quinolinic acid and kynurenine. The level of serotonin precursors synthesized by tryptophan is reduced, causing a decrease in serotonin concentration and accelerating depressive symptoms in patients (17, 18).

Yang et al. studies found that IL-18, IL-1, IL-6 play an important role in the occurrence, development and prognosis

of PSD (19). Kim et al. performed polymorphisms of pro-inflammatory cytokine genes such as IL-1β, IL-6, IL-8, TNF-α, and polymorphisms of anti-inflammatory cytokines such as IL-4 and IL-10 in patients with PSD. The results showed that the IL-10-1082A/A genotype was closely related to PSD, and the IL-4 + 33C/C genotype was only associated with heavy PSD (20). After a year of follow-up of PSD patients, Su et al. found that IL-10 levels in the depression group were significantly lower than those in the non-depressed group, and IL-10 levels were negatively correlated with depression. IL-10 may have antidepressant effects (21). Spalletta et al. believe that stroke promotes the release of inflammatory factors such as C-reactive protein (CRP), interleukin-1(IL-1), tumor necrosis factor-α (TNF-α), IL-6. These factors stimulate and produce a toxic effect on the monoamine neurotransmitter system. As a result, its function declines, causing depression to occur (22). Increased expression of TNF-α, IL-1β, and cortisol releasing factor was found in the hippocampus of PSD rats, and interaction between cortisol releasing factor and TNF-α signaling pathway was found in PSD (23). Studies by Reichenberg et al. have shown that induction of TNF-α production by experimental stimulation can induce depression and cognitive function changes in humans (24).

Hypothalamus-Pituitary-Adrenal Axis and Hypothalamus-Pituitary-Thyroid Axis

Studies have shown that inflammation can affect the function of the hypothalamic-pituitary-adrenal axis (HPA), promote the metabolism of monoamine transmitters, and induce depression (14). Pro-inflammatory factors activate HPA and promote excessive secretion of cortisol, and excess cortisol damages nerve cells through cytotoxicity. Abnormal activity of the HPA and hypothalamus-pituitary-thyroid axis (PHT), leading to elevated plasma cortisol. Elevated plasma cortisol induces the production of tryptophan pyrrolase and aminotransferase in the liver, which both degrade blood tryptophan (5-HT precursor) and tyrosine (NE precursor), resulting in 5-HT and NE synthesis are reduced, promoting, or aggravating the occurrence and development of PSD (25–27). Persistent and excessive secretion of cortisol can inhibit hippocampal neuronal regeneration and reduce neural plasticity in the pre-frontal cortex, leading to PSD.

Glial Cells

Astrocytes

Glial cells are widely distributed in the central and peripheral nervous systems and are mainly divided into three types: astrocytes, oligodendrocytes, and microglia. Astrocytes are the most important glial cells, which secrete a variety of neurotrophic factors, and play an important role in energy metabolism regulation, neurotrophic factor release, neuronal synaptic remodeling and nerve formation. A large body of evidence indicates that astrocyte dysfunction is an important factor in the onset of depression. Studies have reported that astrocyte hyperplasia is a characteristic response to central nervous system inflammation or injury. Astrocytes and microglia work together to regulate the release of pro-inflammatory cytokines and anti-inflammatory cytokines, maintaining the normal physiological functions of the brain. Astrocytes can release a variety of neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF 2) etc. Such neurotrophic factors regulate nerve function, promote nerve growth, and increase synaptic plasticity and delivery efficiency (28). Neurotrophic factor is a molecule that promotes the development and survival of neurons. It can prevent the pathological changes of ischemic brain injury, and can reduce the apoptosis of neurons and effectively improve the neurological function of patients after stroke. Previous experimental studies have found that neurotrophic factors are closely related to the condition and prognosis of PSD (29). A number of studies have found that levels of neurotrophic factors are significantly reduced in patients with PSD (30). A meta-analysis study showed a decrease in the expression of GDNF in the brain of patients with depression. Studies have shown that the reduction of GDNF and BDNF levels in the brain of patients with depression is associated with decreased hippocampal nerve regeneration. Antidepressants can increase the production of BDNF and GDNF in rat hippocampus (31–33). Selective serotonin reuptake inhibitors (SSRIs) significantly increased the expression of BDNF mRNA in astrocytes, suggesting that antidepressants can exert antidepressant effects by increasing astrocyte BDNF synthesis. Fluoxetine can increase the synthesis of GDNF and BDNF in astrocytes; amitriptyline can promote the synthesis and release of astrocytes FGF-2, BDNF, and GDNF (34, 35). Other studies have shown that astrocytes can synthesize antibodies and anti-inflammatory factors and inhibit the synthesis of pro-inflammatory factors. Astrocyte dysfunction can aggravate the inflammatory response and aggravate central nervous system damage (36).

Microglia

Microglia are immune cells of the central nervous system. When tissue damage or brain infection occurs, microglia are first activated to perform functions such as antigen recognition, phagocytosis, and antigen presentation (37). When activated, microglia can produce a large number of pro-inflammatory factors, causing degeneration and necrosis of neurons. Under normal circumstances, microglia are in a resting state, receive synaptic signals by sensing changes in the extracellular environment, thereby participating in intersynaptic interactions; and can also express neurotransmitters such as dopamine and serotonin. When the extracellular environment changes, microglia can be activated and undergo morphological changes, releasing inflammatory factors (38). Activated microglia are divided into two polarization states, M1 and M2. Polarized M1 microglia produce pro-inflammatory cytokines and neurotoxicity participate in the development of neural network dysfunction and promote inflammation. Polarized M2 microglia secrete anti-inflammatory mediators and neurotrophic factors involved in restoring homeostasis (39). Previous studies have shown that autopsy after suicide in patients with major depression found activation of microglia in the pre-frontal cortex and lateral anterior cingulate gyrus. Moreover, activation of microglia in the anterior cingulate cortex, hippocampus,

and thalamus is associated with suicide caused by depression (40). The cause of depression is related to the secretion of pro-inflammatory factors by M1 microglia. A variety of antidepressants have anti-inflammatory effects and can reverse the M1 type polarization of microglia. Fluoxetine and citalopram, widely used clinically, regulate the immune system by inhibiting M1 polarization and improving M2 polarization of microglia, mediating the therapeutic effects of drugs (41).

Vitamin D

Vitamin D is a neurosteroid hormone, 25-hydroxyvitamin D is its main form in the blood circulation (42). Vitamin D is derived from food, especially from fish oil, which is synthesized on the skin and is affected by light. Vitamin D receptor (VDR) is located in an important area of the brain associated with depression and emotional behavior, such as cingulate gyrus, hippocampus, thalamus, hypothalamus, and substantia nigra (43). VDR is also present in immune cells and has an immunomodulatory effect (44). Vitamin D can regulate neurotransmitters such as serotonin in the brain through tryptophan-hydroxylase 2, vitamin D deficiency may lead to central morphological changes and decreased synthesis of neurotransmitters such as norepinephrine and dopamine (45). Studies by Puchacz et al. showed that vitamin D is involved in the regulation of the expression of the tyrosine hydroxylase gene, which catalyzes the production of levodopa by tyrosine in dopamine biosynthesis (46). Studies have found that vitamin D levels are negatively correlated with inflammatory markers, and the relationship between depression and inflammatory response can be regulated by the immune system (47). In the central nervous system, vitamin D acts as a neuroprotective factor through its antioxidant activity to increase the efficiency of neuronal projection and regulate the synthesis of neurotransmitters. A meta-analysis found that low vitamin D levels are associated with depression levels and are the biological basis for depression susceptibility (48). Studies have shown that supplemental reduced vitamin D levels contribute to the improvement of depressive symptoms in patients with depression, but different studies have also been reported (49). Han et al. also believe that vitamin D levels are positively correlated with PSD within 24 h after stroke onset (50). A prospective randomized controlled clinical trial by Shaffer et al. found that vitamin D supplementation helps prevent PSD. High serum vitamin D levels protect patients from PSD, and recent randomized controlled trials have shown that vitamin D supplementation can improve depressive symptoms in patients (51, 52).

Homocysteine

Some studies have concluded that high homocysteine levels are significantly associated with PSD. Stroke patients with high levels of homocysteine are relatively more prone to PSD (53). High homocysteine (Hhcy) has a direct toxic effect on blood vessels, causing further damage to the cerebral blood vessels, leading to the occurrence of depression (54). Hhcy affects the production and metabolism of monoamine neurotransmitters such as DA, 5-HT, NE, etc. These neurotransmitters play an important role in the pathogenesis of depression (55). Liu et al. studied 18 patients with ischemic stroke and selected three core regions of DMN (left parietal cortex, pre-frontal cortex, posterior cingulate ganglion/wedge anterior cortex). Then, the difference between the patient and the normal person ReHo was compared, and the ReHo of the posterior cingulate cortex of all stroke patients was found to be reduced. The functional connectivity (FC) analysis was performed using the posterior cingulate cortex for the region of interest, and the FC values of posterior cingulate cortex and anterior cingulate were found to be reduced (56).

Neural Network Dysfunction

Resting-state functional magnetic resonance imaging (rs-fMRI) indirectly reflects the functions of brain local and neural networks through signal changes, which have the advantages of non-invasiveness and reproducibility. Since the early 1990s, it has had an important impact on the development of neuroscience and psychology. In recent years, it has also begun to be used in the research of diseases such as PSD, and has gradually become one of the important means for studying the physiological and pathological activities of brain function. At present, the commonly used analytical methods for rs-fMRI are as follows: Regional homogeneity (ReHo), Amplitude of low-frequency fluctuation (ALFF), Functional connectivity (FC) (57). The most widely studied is the default mood network (DMN), which mainly involves the medial pre-frontal cortex, posterior cingulate gyrus/pre-wedge lobes, bilateral apical lobes (including angular gyrus), bilateral lateral temporal lobe, hippocampus, etc. Studies have shown that the default network is closely related to the monitoring of internal and external environments, the processing of emotions, introspection, the maintenance of thinking cognition, and the extraction of thought memories. A large number of studies have shown that there is an abnormality in the brain network under the resting state of depression, and DMN is an important neuropathological mechanism of depression (58, 59). Zhang et al. performed FC analysis on patients with cerebral infarction, and found that compared with non-PSD and normal people, PSD patients had changes in the right frontal gyrus and the left gyrus and the anterior cingulate gyrus. In addition, the FC values of the left temporal and anterior cingulate gyrus were significantly associated with the severity of depression (60). Liu et al. (56) studied 18 patients with ischemic stroke, and selected 3 core regions of DMN (left parietal cortex, pre-frontal cortex, posterior cingulate gyrus/anterior cranial cortex), and then compared patients and normal Human differences. The ReHo of the posterior cingulate cortex was found to decrease in all stroke patients, and the posterior cingulate gyrus was used as a functional area for FC analysis, and the FC value of the posterior cingulate gyrus and the anterior cingulate gyrus was found to be reduced (56). Zhang et al. studied 26 patients with PSD, and the results showed that the default emotional network, cognitive control network, and emotional network FC of PSD patients changed. The left lower parietal lobe, the left eyelid portion of the inferior temporal gyrus and the left anterior gyrus were significantly associated with the Hamilton Depression Rating Scale for PSD patients. Changes in the three neural networks may be associated with the development of PSD in the subacute phase of stroke (61).

At present, there are many studies on the relationship between PSD and stroke sites, but the conclusions are not the same. Current brain imaging studies of depression have shown that subcortical white matter damage leads to a susceptibility to depression by destroying certain neural circuits associated with emotions. Depression brain function changes mainly in the pre-frontal cortex, anterior cingulate gyrus, amygdala, ventral striatum, hippocampus, insula, thalamus, and basal ganglia. The pre-frontal cortex is thought to play a key role in cognitive and emotional activities, and functional abnormalities in these brain regions may present with affective and cognitive impairments. Current studies have shown that left hemisphere stroke is more prone to depression than right hemisphere stroke. The lesions near the frontal pole have a specific correlation with the degree of PSD. The lesions associated with PSD were: frontal lobe, left basal ganglia, and temporal lobe, and the incidence of lesions near the extreme was high (62). Carson et al. found that the occurrence of PSD was not related to stroke lesions after evaluation of related studies (63). PSD has nothing to do with the stroke site. The reasons for the difference between the two may be different sample sizes, differences in diagnostic criteria, ethnic differences, geographical differences, and so on (64). Vataja et al. found that the lesions of acute stroke were located in the left hemisphere, especially in the left anterior hemisphere, and their chance of developing depression was higher than in the right hemisphere. It is believed that the damage of the globus pallidus and the volume of injury are related to the diagnosis of depression within 3 months after stroke (65). Angeleri et al. observed the observation of the 3 years after the stroke, 3 years or more after stroke, the incidence of depression is not related to the lesion in the left or right hemisphere (66). Shimoda et al. observed the relationship between lesions and PSD at different time points after stroke. In the acute phase of stroke, PSD was associated with left anterior hemisphere lesions; at 3–6 months, PSD was related to the distance from the lesion to the frontal pole and lesion volume; and 1–2 years later, PSD was related to the distance from the right hemisphere lesion to the occipital pole and lesion volume (67).

Cognitive dysfunction is one of the common complications in stroke patients. Most studies have concluded that depression has a significant relationship with cognitive dysfunction. However, the specific relationship between the two is still controversial. Many studies have identified the most relevant factors for PSD and cognitive impairment: low education, speech impairment, stroke severity, and previous diabetes history (68). Murata et al. found that cognitive function improved with the improvement of PSD symptoms (69).

Genetic Background

Regarding the gene hypothesis, there is clear evidence that the shortening of the promoter region associated with the serotonin gene is associated with severe PSD. Studies have shown that individuals and families with a history of depression may be one of the risk factors for major depression after stroke (70, 71). The expression of some genes is considered to be a risk factor for PSD. Brain-derived neurotrophic factor (BDNF) plays an important role in the pathophysiology of PSD. It has been suggested that the single nucleotide polymorphisms rs1778929 and rs1187323 in the tyrosine receptor kinase B (TrkB) gene of BDNF are significantly associated with PSD (72). Kim et al. evaluated 222 stroke patients and followed up for 1 year. The increase in methylation status of 5-HTTLPR (The serotonin transporter-linked polymorphic region, 5-HTTLPR) SS genotype was associated with PSD. Higher levels of BDNF gene methylation were associated with PSD occurring at follow-up (73). The serotonin transporter gene (SLC6A4) has also been shown to play an important role in the pathophysiology of PSD. Studies have found that 2 weeks after stroke, higher SLC6A4 promoter methylation status is independently associated with PSD and is more pronounced 1 year after stroke, and is significantly associated with worsening depressive symptoms within 1 year (74). Studies have shown that apolipoprotein E (APOE) polymorphism is associated with PSD, APOE rs429358 polymorphism increases the probability of PSD, APOE rs429358-C allele may be post-stroke nerve Functional recovery is harmful (75).

Social Psychological Mechanisms

After cerebrovascular disease, most patients have different degrees of physical dysfunction, resulting in loss of work and life. The combined effects of family, society, and physiology lead to physiological and psychological imbalance in stroke patients. Psychosocial factors such as poor living ability, negative life events, family burden, social family support may all contribute to PSD. Acute stroke is a stressful event that increases the secretion of glucocorticoids, causing elevated blood glucose and abnormal neurotransmitters, leading to depression (76). The onset of PSD is not a single mechanism. Whyte et al. proposed that PSD, like other psychiatric diseases, is under the bio-psycho-social medical model, and that biological factors and psychological factors may contribute to the onset of PSD (4).

Studies have shown that the degree of education is negatively correlated with the occurrence of PSD, probably because patients with low levels of education have limited cognitive levels (77). Studies by Backhouse et al. showed that lower education levels were associated with an increased risk of PSD symptoms, but confidence intervals and heterogeneity were greater (78).

The relationship between age and PSD has been controversial. Previous studies have found that the younger patients with acute stroke, the higher the risk of PSD. This may be due to young people taking on greater family and social responsibility. After the stroke, the social roles and economic status of young patients are more prominent and the psychological acceptance is poor (79). Some studies have shown that age is positively correlated with the occurrence of depression. With the increase of age, the body's various functions are declining, frustration and attention to the body become more and more prominent. There are also many studies that do not have a clear correlation between age and PSD (80).

Studies have shown varying incidence rates for patients of different genders. Most studies have found that women are more likely to develop PSD earlier than men. This may be related to women's poor psychological quality, sensitivity, psychological

and physiological imbalance. Another possible explanation is that women live longer than men, so women have an average age greater than men when they encounter a stroke (81). However, another study found that the prevalence of male PSD is higher than that of females. It may be that men have more family and social responsibility for men. Therefore, changes in work ability and social status caused by stroke will produce greater psychological stress in men (82). However, another part of the study concluded that there is no difference between the two (83).

In the study of pre-existing personality characteristics of patients with PSD, it is found that patients with neuroticism, introversion, emotional instability, and strong dependence are more likely to develop PSD (84). Pessimism, negative coping, introversion, acceptability, etc. are independent risk factors for PSD.

Regarding the marital status of patients, studies have shown that widowhood, divorce, and solitary living are closely related to depression. It may be related to the patient's loneliness, social isolation, long-term physical illness, and decreased stress ability.

The severity of stroke directly affects the quality of life of patients and has a great impact on the occurrence of PSD. Many studies have shown that the ability of daily living is related to the occurrence of PSD in the early stage of stroke. The more severe the neurological damage, the lower the ability of daily living, the greater the risk of PSD. There was a significant correlation between the activities of daily living (ADL) and the incidence of depression after stroke. Low ADL is an important factor leading to PSD. The severe physical dysfunction, low self-care ability and loss of working ability make patients have great psychological pressure (85).

Studies on chronic diseases and depression have shown that chronic diseases such as hypertension, diabetes, dyslipidemia, and respiratory diseases are also in the category of psychosomatic diseases. Due to the long course of chronic diseases and the difficulty of treatment, patients are often in a state of anxiety and depression. Most patients have low ability to recognize these mental illnesses. Current research shows that among vascular risk factors, only hypertension can predict PSD. Diabetes, hyperlipidemia, obesity, and smoking were not independent predictors of PSD (86).

Social support can be divided into two categories, one is objective, visible or practical support; the other is subjective and empirical emotional support. Good social support will force the patient's psychological endurance, indirectly promote the recovery of stroke patients and improve their quality of life, while stroke patients who lack social support are more likely to develop PSD (87). Kotila et al. found that patients who lived in community-active areas after stroke had fewer PSD than those without community activity, suggesting that appropriate rehabilitation activities can reduce PSD (88).

CONCLUSION

PSD seriously affects the quality of life of patients, which is a burden on individuals, families, and society. It is necessary to explore the pathogenesis and related influencing factors, establish appropriate diagnostic criteria and scales, and determine the best preventive and therapeutic measures. The pathogenesis of PSD is extremely complex and may be the result of multiple factors and multiple pathways. There are still many uncertainties in the neurobiological mechanisms of PSD. It is believed that with the improvement of science and technology, people will gradually uncover the mystery of the biological mechanism of PSD and provide a more accurate theoretical basis for the diagnosis and treatment of PSD.

AUTHOR CONTRIBUTIONS

YS and ZW wrote the main manuscript text, contributed equally to this work and should be regarded as co-first author. FD contributed substantially to the conception and design of this work, drafting of the work, and revised it critically for important intellectual content. FL, NJ, JG, and XP collected the data etc.

REFERENCES

1. Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. *J Neurol Neurosurg Psychiatry* (1977) 40:1018–20. doi: 10.1136/jnnp.40.10.1018
2. Chemerinski E, Robinson RG, Kosier JT. Improved recovery in activities of daily living associated with remission of poststroke depression. *Stroke* (2001) 32:113–7. doi: 10.1161/01.STR.32.1.113
3. Linden T, Blomstrand C, Skoog I. Depressive disorders after 20 months in elderly stroke patients: a case-control study. *Stroke* (2007) 38:1860–3. doi: 10.1161/STROKEAHA.106.471805
4. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol Psychiatry* (2002) 52:253–64. doi: 10.1016/S0006-3223(02)01424-5
5. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. *Stroke* (2005) 36:1330–40. doi: 10.1161/01.STR.0000165928.19135.35
6. Schottke H, Giabbiconi CM. Post-stroke depression and post-stroke anxiety: prevalence and predictors. *Int Psychogeriatr.* (2015) 27:1805–12. doi: 10.1017/S1041610215000988
7. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. *Psychosomatics* (2000) 41:5–14. doi: 10.1016/S0033-3182(00)71168-6
8. Bryer JB, Starkstein SE, Votypka V, Parikh RM, Price TR, Robinson RG. Reduction of CSF monoamine metabolites in poststroke depression: a preliminary report. *J Neuropsychiatry Clin Neurosci.* (1992) 4:440–2. doi: 10.1176/jnp.4.4.440
9. Karaiskos D, Tzavellas E, Spengos K, Vassilopoulou S, Paparrigopoulos T. Duloxetine versus citalopram and sertraline in the treatment of poststroke depression, anxiety, and fatigue. *J Neuropsychiatry Clin Neurosci.* (2012) 24:349–53. doi: 10.1176/appi.neuropsych.11110325
10. Valentine GW, Sanacora G. Targeting glial physiology and glutamate cycling in the treatment of depression. *Biochem Pharmacol.* (2009) 78:431–9. doi: 10.1016/j.bcp.2009.04.008

11. Wang X, Li YH, Li MH, Lu J, Zhao JG, Sun XJ, et al. Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. *Eur Arch Psychiatry Clin Neurosci.* (2012) 262:33–8. doi: 10.1007/s00406-011-0209-3
12. Sanacora G, Mason GF, Krystal JH. Impairment of GABAergic transmission in depression: new insights from neuroimaging studies. *Crit Rev Neurobiol.* (2000) 14:23–45. doi: 10.1615/CritRevNeurobiol.v14.i1.20
13. Joyce PR, Hawes CR, Mulder RT, Sellman JD, Wilson DA, Boswell DR. Elevated levels of acute phase plasma proteins in major depression. *Biol Psychiatry* (1992) 32:1035–41. doi: 10.1016/0006-3223(92)90065-8
14. Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. *Mol Psychiatry* (2006) 11:984–91. doi: 10.1038/sj.mp.4001879
15. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. *J Affect Disord.* (2010) 125:287–94. doi: 10.1016/j.jad.2009.12.014
16. Song C, Wang H. Cytokines mediated inflammation and decreased neurogenesis in animal models of depression. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) 35:760–8. doi: 10.1016/j.pnpbp.2010.06.020
17. Pascoe MC, Crewther SG, Carey LM, Crewther DP. Inflammation and depression: why poststroke depression may be the norm and not the exception. *Int J Stroke* (2011) 6:128–35. doi: 10.1111/j.1747-4949.2010.00565.x
18. Connor TJ, Starr N, O'Sullivan JB, Harkin A. Induction of indolamine 2,3-dioxygenase and kynurenine 3-monooxygenase in rat brain following a systemic inflammatory challenge: a role for IFN-gamma? *Neurosci Lett.* (2008) 441:29–34. doi: 10.1016/j.neulet.2008.06.007
19. Yang L, Zhang Z, Sun D, Xu Z, Zhang X, Li L. The serum interleukin-18 is a potential marker for development of post-stroke depression. *Neurol Res.* (2010) 32:340–6. doi: 10.1179/016164110X12656393665080
20. Kim JM, Stewart R, Kim SW, Shin IS, Kim JT, Park MS, et al. Associations of cytokine gene polymorphisms with post-stroke depression. *World J Biol Psychiatry* (2012) 13:579–87. doi: 10.3109/15622975.2011.588247
21. Su JA, Chou SY, Tsai CS, Hung TH. Cytokine changes in the pathophysiology of poststroke depression. *Gen Hosp Psychiatry* (2012) 34:35–9. doi: 10.1016/j.genhosppsych.2011.09.020
22. Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci.* (1998) 62:583–606. doi: 10.1016/S0024-3205(97)00990-9
23. Wang SS, Chen HY, Sun H, Wang T, Guan JQ. Activation of TNF-alpha and signaling pathway in the hypothalamus of the rats subjected to chronic unpredictable mild stressors after middle cerebral artery occlusion. *Sheng Li Xue Bao* (2014) 66:463–8. doi: 10.13294/j.aps.2014.0054
24. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* (2001) 58:445–52. doi: 10.1001/archpsyc.58.5.445
25. Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, et al. Post-stroke depression, antidepressant treatment and rehabilitation results. A case-control study. *Cerebrovasc Dis.* (2001) 12:264–71. doi: 10.1159/000047714
26. Tateno A, Kimura M, Robinson RG. Phenomenological characteristics of poststroke depression: early- versus late-onset. *Am J Geriatr Psychiatry* (2002) 10:575–82. doi: 10.1097/00019442-200209000-00011
27. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am.* (1998) 21:293–307. doi: 10.1016/S0193-953X(05)70006-X
28. Lindsay RM, Wiegand SJ, Altar CA, DiStefano PS. Neurotrophic factors: from molecule to man. *Trends Neurosci.* (1994) 17:182–90. doi: 10.1016/0166-2236(94)90099-X
29. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Zhang H, Pavuluri MN. Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) 34:645–51. doi: 10.1016/j.pnpbp.2010.03.003
30. Lee HY, Kim YK. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. *Neuropsychobiology* (2008) 57:194–9. doi: 10.1159/000149817
31. Lin PY, Tseng PT. Decreased glial cell line-derived neurotrophic factor levels in patients with depression: a meta-analytic study. *J Psychiatr Res.* (2015) 63:20–7. doi: 10.1016/j.jpsychires.2015.02.004
32. Martinez-Turrillas R, Del Rio J, Frechilla D. Sequential changes in BDNF mRNA expression and synaptic levels of AMPA receptor subunits in rat hippocampus after chronic antidepressant treatment. *Neuropharmacology* (2005) 49:1178–88. doi: 10.1016/j.neuropharm.2005.07.006
33. Liu Q, Zhu HY, Li B, Wang YQ, Yu J, Wu GC. Chronic clomipramine treatment restores hippocampal expression of glial cell line-derived neurotrophic factor in a rat model of depression. *J Affect Disord.* (2012) 141:367–72. doi: 10.1016/j.jad.2012.03.018
34. Mercier G, Lennon AM, Renouf B, Dessouroux A, Ramauge M, Courtin F, et al. MAP kinase activation by fluoxetine and its relation to gene expression in cultured rat astrocytes. *J Mol Neurosci.* (2004) 24:207–16. doi: 10.1385/JMN:24:2:207
35. Kajitani N, Hisaoka-Nakashima K, Morioka N, Okada-Tsuchioka M, Kaneko M, Kasai M, et al. Antidepressant acts on astrocytes leading to an increase in the expression of neurotrophic/growth factors: differential regulation of FGF-2 by noradrenaline. *PLoS ONE* (2012) 7:e51197. doi: 10.1371/journal.pone.0051197
36. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. *CNS Spectr.* (2008) 13:501–10. doi: 10.1017/S1092852900016734
37. Liu Y, Li M, Zhang Z, Ye Y, Zhou J. Role of microglia-neuron interactions in diabetic encephalopathy. *Ageing Res Rev.* (2018) 42:28–39. doi: 10.1016/j.arr.2017.12.005
38. Dwyer JB, Ross DA. Modern microglia: novel targets in psychiatric neuroscience. *Biol Psychiatry* (2016) 80:e47–9. doi: 10.1016/j.biopsych.2016.08.006
39. Plastira I, Bernhart E, Goeritzer M, DeVaney T, Reicher H, Hammer A, et al. Lysophosphatidic acid via LPA-receptor 5/protein kinase D-dependent pathways induces a motile and pro-inflammatory microglial phenotype. *J Neuroinflamm.* (2017) 14:253. doi: 10.1186/s12974-017-1024-1
40. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain Behav Immun.* (2014) 42:50–9. doi: 10.1016/j.bbi.2014.05.007
41. Chakraborty S, Kaushik DK, Gupta M, Basu A. Inflammasome signaling at the heart of central nervous system pathology. *J Neurosci Res.* (2010) 88:1615–31. doi: 10.1002/jnr.22343
42. Patrick RP, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB J.* (2014) 28:2398–413. doi: 10.1096/fj.13-246546
43. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat.* (2005) 29:21–30. doi: 10.1016/j.jchemneu.2004.08.006
44. Borges MC, Martini LA, Rogero MM. Current perspectives on vitamin D, immune system, and chronic diseases. *Nutrition* (2011) 27:399–404. doi: 10.1016/j.nut.2010.07.022
45. Ganji V, Milone C, Cody MM, McCarty F, Wang YT. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. *Int Arch Med.* (2010) 3:29. doi: 10.1186/1755-7682-3-29
46. Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK. Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. *Brain Res Mol Brain Res.* (1996) 36:193–6. doi: 10.1016/0169-328X(95)00314-I
47. Nicholas C, Davis J, Fisher T, Segal T, Petti M, Sun Y, et al. Maternal vitamin D deficiency programs reproductive dysfunction in female mice offspring through adverse effects on the neuroendocrine axis. *Endocrinology* (2016) 157:1535–45. doi: 10.1210/en.2015-1638
48. Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, et al. The association between low vitamin D and depressive disorders. *Mol Psychiatry* (2014) 19:444–51. doi: 10.1038/mp.2013.36
49. Gowda U, Mutowo MP, Smith BJ, Wluka AE, Renzaho AM. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. *Nutrition* (2015) 31:421–9. doi: 10.1016/j.nut.2014.06.017

50. Han B, Lyu Y, Sun H, Wei Y, He J. Low serum levels of vitamin D are associated with post-stroke depression. *Eur J Neurol.* (2016) 23:e27. doi: 10.1111/ene.12938
51. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med.* (2014) 76:190–6. doi: 10.1097/PSY.0000000000000044
52. May HT, Bair TL, Lappe DL, Anderson JL, Horne BD, Carlquist JF, et al. Association of vitamin D levels with incident depression among a general cardiovascular population. *Am Heart J.* (2010) 159:1037–43. doi: 10.1016/j.ahj.2010.03.017
53. Pascoe MC, Crewther SG, Carey LM, Noonan K, Crewther DP, Linden T. Homocysteine as a potential biochemical marker for depression in elderly stroke survivors. *Food Nutr Res.* (2012) 56:14973. doi: 10.3402/fnr.v56i0.14973
54. Folstein M, Liu T, Peter I, Buell J, Arsenault L, Scott T, et al. The homocysteine hypothesis of depression. *Am J Psychiatry* (2007) 164:861–7. doi: 10.1176/ajp.2007.164.6.861
55. Dufouil C, Alperovitch A, Ducros V, Tzourio C. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. *Ann Neurol.* (2003) 53:214–21. doi: 10.1002/ana.10440
56. Liu J, Qin W, Wang H, Zhang J, Xue R, Zhang X, et al. Altered spontaneous activity in the default-mode network and cognitive decline in chronic subcortical stroke. *J Neurol Sci.* (2014) 347:193–8. doi: 10.1016/j.jns.2014.08.049
57. Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.* (2007) 29:83–91. doi: 10.1016/j.braindev.2006.07.002
58. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA.* (2003) 100:253–8. doi: 10.1073/pnas.0135058100
59. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci USA.* (2001) 98:676–82. doi: 10.1073/pnas.98.2.676
60. Zhang P, Xu Q. Dysfunction of affective network in post ischemic stroke depression: a resting-state functional magnetic resonance imaging study. *J Biomed Biotech.* (2014) 2014:846830. doi: 10.1155/2014/846830
61. Zhang P, Wang J, Xu Q, Song Z, Dai J, Wang J. Altered functional connectivity in post-ischemic stroke depression: a resting-state functional magnetic resonance imaging study. *Eur J Radiol.* (2018) 100:156–65. doi: 10.1016/j.ejrad.2018.01.003
62. Robinson R. Neuropsychiatric consequences of stroke. *Annu Rev Med.* (1997) 48:217–29. doi: 10.1146/annurev.med.48.1.217
63. Carson A, MacHale S, Allen K, Lawrie S, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. *Lancet* (2000) 356:122–6. doi: 10.1016/S0140-6736(00)02448-X
64. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. *Stroke* (2004) 35:794–802. doi: 10.1161/01.STR.0000117237.98749.26
65. Vataja R, Leppavuori A, Pohjasvaara T, Mantyla R, Aronen HJ, Salonen O, et al. Poststroke depression and lesion location revisited. *J Neuropsychiatry Clin Neurosci.* (2004) 16:156–62. doi: 10.1176/jnp.16.2.156
66. Angeleri F, Angeleri VA, Foschi N, Giaquinto S, Nolfe G, Saginario A, et al. Depression after stroke: an investigation through catamnesis. *J Clin Psychiatry* (1997) 58:261–5. doi: 10.4088/JCP.v58n0605
67. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. *Biol Psychiatry* (1999) 45:187–92. doi: 10.1016/S0006-3223(98)00178-4
68. Pustokhanova L, Morozova E. Cognitive impairment and hypothymia in post stroke patients. *J Neurol Sci.* (2013) 325:43–5. doi: 10.1016/j.jns.2012.11.013
69. Murata Y, Kimura M, Robinson RG. Does cognitive impairment cause post-stroke depression? *Am J Geriatr Psychiatry* (2000) 8:310–7. doi: 10.1097/00019442-200011000-00007
70. Andersen G, Vestergaard K, Ingemann-Nielsen M, Lauritzen L. Risk factors for post-stroke depression. *Acta Psychiatr Scand.* (1995) 92:193–8. doi: 10.1111/j.1600-0447.1995.tb09567.x
71. Morris PL, Robinson RG, Raphael B, Samuels J, Molloy P. The relationship between risk factors for affective disorder and poststroke depression in hospitalised stroke patients. *Aust N Z J Psychiatry* (1992) 26:208–17. doi: 10.1177/000486749202600204
72. Zhou Z, Ding X, Yang Q, Hu J, Shang X, Huang X, et al. Association between single-nucleotide polymorphisms of the tyrosine kinase receptor B (TrkB) and post-stroke depression in China. *PLoS ONE* (2015) 10:e0144301. doi: 10.1371/journal.pone.0144301
73. Kim JM, Stewart R, Kang HJ, Kim SY, Kim SW, Shin IS, et al. A longitudinal study of BDNF promoter methylation and genotype with poststroke depression. *J Affect Disord.* (2013) 149:93–9. doi: 10.1016/j.jad.2013.01.008
74. Kim JM, Stewart R, Kang HJ, Kim SW, Shin IS, Kim HR, et al. A longitudinal study of SLC6A4 DNA promoter methylation and poststroke depression. *J Psychiatr Res.* (2013) 47:1222–7. doi: 10.1016/j.jpsychires.2013.04.010
75. Li XB, Wang J, Xu AD. Apolipoprotein E polymorphisms increase the risk of post-stroke depression. *Neural Regen Res.* (2016) 11:1790–6. doi: 10.4103/1673-5374.194748
76. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* (2005) 64:1348–53. doi: 10.1212/01.WNL.0000158442.08857.FC
77. De Ryck A, Brouns R, Fransen E, Geurden M, Van Gestel G, Wilssens I, et al. A prospective study on the prevalence and risk factors of poststroke depression. *Cerebrovasc Dis Extra* (2013) 3:1–13. doi: 10.1159/000345557
78. Backhouse EV, McHutchison CA, Cvoro V, Shenkin SD, Wardlaw JM. Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression in later life: a systematic review and meta-analysis. *PLoS ONE* (2018) 13:e0200525. doi: 10.1371/journal.pone.0200525
79. Desmond DW, Remien RH, Moroney JT, Stern Y, Sano M, Williams JB. Ischemic stroke and depression. *J Int Neuropsychol Soc.* (2003) 9:429–39. doi: 10.1017/S1355617703930086
80. Hadidi N. Interventions for preventing falls in acute and chronic care hospitals: a systematic review and meta-analysis. *J Am Geriatr Soc.* (2008) 56:1776–7. doi: 10.1111/j.1532-5415.2008.01783.x
81. Taylor-Piliae RE, Hepworth JT, Coull BM. Predictors of depressive symptoms among community-dwelling stroke survivors. *J Cardiovasc Nurs.* (2013) 28:460–7. doi: 10.1097/JCN.0b013e318258ad57
82. Kulkantrakorn K, Jirapramukpitak T. A prospective study in one year cumulative incidence of depression after ischemic stroke and Parkinson's disease: a preliminary study. *J Neurol Sci.* (2007) 263:165–8. doi: 10.1016/j.jns.2007.07.014
83. Berg A, Palomaki H, Lehtihalmes M, Lonnqvist J, Kaste M. Poststroke depression: an 18-month follow-up. *Stroke* (2003) 34:138–43. doi: 10.1161/01.STR.0000048149.84268.07
84. Storor DL, Byrne GJ. Pre-morbid personality and depression following stroke. *Int Psychogeriatr.* (2006) 18:457–69. doi: 10.1017/S1041610206003188
85. Kauhanen M, Korpelainen JT, Hiltunen P, Brusin E, Mononen H, Maatta R, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke* (1999) 30:1875–80. doi: 10.1161/01.STR.30.9.1875
86. Tennen G, Herrmann N, Black SE, Levy KS, Cappell J, Li A, et al. Are vascular risk factors associated with post-stroke depressive symptoms? *J Geriatr Psychiatry Neurol.* (2011) 24:215–21. doi: 10.1177/0891988711422526
87. Jaracz K, Kozubski W. [The role of social support in the quality of life after stroke. A review of selected experimental research]. *Neurol Neurochir Pol.* (2006) 40:140–50.
88. Kotila M, Numminen H, Waltimo O, Kaste M. Depression after stroke: results of the FINNSTROKE study. *Stroke* (1998) 29:368–72. doi: 10.1161/01.STR.29.2.368

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Association Between Cortical Superficial Siderosis and Dementia in Patients With Cognitive Impairment: A Meta-Analysis

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Background: It remains unclear whether cortical superficial siderosis (cSS) is associated with dementia and its subtypes. We thus performed a meta-analysis to evaluate the relationship between dementia and cSS.

Methods: We searched EMBASE, PubMed, and Web of Science for relevant studies assessing risk of dementia and prevalence of cSS in patients with cognitive impairment. Fixed-effects and random-effects models were performed.

Results: Seven eligible studies including 3,218 patients with definite cognitive impairment were pooled in meta-analysis. The prevalence of cSS was 3.4%. The pooled analysis demonstrates odds ratio for cSS and dementia to be 1.60 (95% CI 1.04–2.44; $p = 0.031$). Subgroup analysis further indicated a significant association between cSS and Alzheimer's disease (AD) (OR = 2.01, 95% CI 1.34–3.02; $p < 0.001$), but not non-AD dementia (OR = 0.700, 95% CI 0.435–1.128; $p = 0.143$).

Conclusions: Our meta-analysis of available published data demonstrates an increased prevalence of dementia in the subjects with pre-existing cSS, especially for AD. These findings suggest cSS to be a candidate imaging indicator for AD. Further longitudinal research is needed to investigate the clinical relevance.

Keywords: dementia, Alzheimer's disease, superficial siderosis, cognitive impairment, meta-analysis

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INTRODUCTION

Dementia is a major public health concern associated with the aging population, and currently affects millions of individuals worldwide, while Alzheimer's disease (AD) is the most common cause of dementia in the elderly (1). The pathogenesis of AD consists of two parts, of which one is the amyloid cascade hypothesis, linked to cerebral amyloid angiopathy (CAA), and the other is the vascular hypothesis, linked to cerebral small vessel disease (CSVD) (2).

Cortical superficial siderosis (cSS) is characterized by linear hypointensities over the cortical surface of the supratentorial cerebral convexities on gradient recalled echo (GRE) or susceptibility weighted imaging (SWI) (3). The underlying pathological mechanism of cSS remains elusive, and generally assumed to reflect recurrent blood leaking episodes in the subarachnoid space (4).

Patients with probable CAA manifested a much higher prevalence of cSS (34%) (5), compared with those from the general population (0.7%) (6). Moreover, Shams et al.'s study showed a link between cSS and the neuroimaging markers of CSVD (7). We therefore hypothesized that cSS itself might be a significant predictor for dementia, especially AD.

However, few studies investigated the relationship between cSS and dementia, and the results are controversial. Zonneveld et al. found a higher prevalence of cSS in patients with AD than those with mild cognitive impairment (MCI) (8), whereas a recent study failed to demonstrate the diagnostic significance of cSS for AD (9). We thus performed a meta-analysis to determine whether associations between cSS and dementia or AD exist in patients with cognitive impairment.

MATERIALS AND METHODS

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (10, 11).

Search Strategy and Eligibility Criteria

We searched appropriate articles by systematic queries of NCBI (PubMed), ISI Web of Science, and EMBASE databases on the 10th of September 2018, using the following search terms: "superficial siderosis" in association with "dementia" or "Alzheimer" or "cognition" or "cognitive." Articles not published in English were translated and case reports were excluded. The references of all identified publications were reviewed for any additional studies not indexed. Two authors identified potentially relevant studies, resolving any uncertainties with a third author.

Both retrospective and prospective studies were eligible for inclusion if they (1) assessed the cognitive status for each subject in the cohort, and (2) provided the detailed data of cSS in each group according to the cognitive status.

Study Selection and Data Extraction

Two authors considered all titles and abstracts for eligibility in a systematic manner, went through all articles selected as relevant and extracted data independently. We extracted information on study design, MRI parameters for cSS detection, definition of cSS, criteria of neuropsychological assessment, number, and demographics of participants (including age and sex), mini mental state examination (MMSE) score of participants, number of participants with cSS, number of participants of different cognitive status, and the severity of cSS (focal or disseminated) by using a unified data form. Discrepancies were resolved by consensus.

Data Analysis

We used a fixed effects model (Mantel and Haenszel method) to calculate the pooled ORs and corresponding 95% confidence intervals (CIs), with weights calculated using the inverse variance method, because of the relatively small number of the outcome events. Subgroup analysis was performed to isolate patients with AD only. Statistical heterogeneity was assessed using I-squared statistics with inspection of the forest plot. Publication bias was evaluated with Egger's test, Begg's test, and the funnel plot. We repeated all analyses using random-effects models. All statistical analysis was performed with Stata 11.2 (StataCorp LP, Texas, USA).

RESULTS

We identified 79 articles from PubMed, 159 from EMBASE, and 76 from Web of Science in our initial search. Fourteen studies (all published) met our predetermined criteria, however, five of these were from a same cohort, and other three were from cohorts of intracerebral hemorrhage (ICH) population. Finally, seven studies were pooled in a meta-analysis (**Figure 1**) (7–9, 12–15). Characteristics of the included studies are summarized in **Table 1**. The definition of cSS was almost the same across all included studies: hypointense linear structures within the subarachnoid space or in the superficial layers of the cerebral cortex on GRE or SWI.

Study demographics are summarized in **Table 2**. These studies were composed of 4,005 patients with cSS evaluation (study sample size range: 212–1,504), 110 (2.7%) of which had cSS on initial GRE or SWI, while 4.9% of AD patients had cSS. The severity of cSS was classified as focal (restricted to $\leq$3 sulci) or disseminated ($\geq$4 sulci) in six studies (7–9, 13–15), and with detailed data in three (7, 8, 14). The cognitive statuses were classified as AD, vascular dementia, other dementia or undetermined, MCI, subjective cognitive complains, or cognitively normal (**Table 2**).

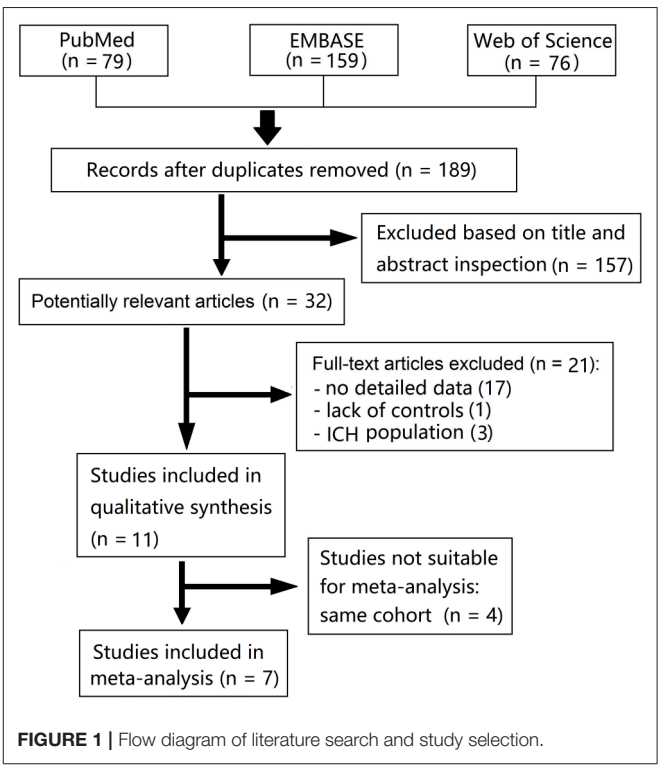

FIGURE 1 | Flow diagram of literature search and study selection.

TABLE 1 | Characteristics of included studies.

Study reference	Design	Inclusion criteria	MRI parameters		Neuropsychological assessment
			Sequence	Field strength	
Kantarci et al. (12); Western cohort	Prospective*, the ADNI study	(1) Aged 55 and above; (2) elderly controls; (3) MCI subjects; (4) AD patients; (5) with T2* GRE images	T2*-GRE	3.0 T	Clinical dementia rating core
Wollenweber et al. (13); Western cohort	Prospective, memory clinic patients	(1) Aged 50 and above; (2) with standardized MRI	T2*-GRE	3.0 T	MCI: Petersen criteria; dementia: ICD-10 criteria
Zonneveld et al. (8); Western cohort	Prospective, the Amsterdam Dementia Cohort	(1) Underwent standardized dementia screening; (2) with SWI sequence	SWI	3.0 T	MCI: Petersen criteria; AD: NINCDS-ADRDA criteria; VaD: NINDS-AIREN criteria
Na et al. (14); Asian cohort	Prospective, from Samsung Medical Center	(1) Diagnosed with cognitive impairment; (2) with PiB-PET and standardized MRI	T2*-GRE	3.0 T	MCI: Petersen criteria; AD: NINCDS-ADRDA criteria; VaD: DSM-IV
Charidimou et al. (15); Western cohort	Prospective, from out-patient memory clinic	(1) Suspected cognitive impairment; (2) with standardized MRI	T2*-GRE	3.0 T	Clinical Dementia Rating core
Inoue et al. (9); Asian cohort	Prospective, from the dementia clinic	(1) Suspected cognitive impairment; (2) with standardized MRI	SWI	3.0 T	MCI: IWG-MCI criteria; AD: NINCDS-ADRDA criteria; VaD: NINDS-AIREN criteria
Shams et al. (7); Western cohort	Prospective, the Karolinska Imaging Dementia Study	(1) Underwent dementia investigation; (2) underwent MRI with hemosiderin sensitive sequences	SWI or T2*-GRE	3.0 or 1.5 T	ICD-10 criteria

cSS, cortical superficial siderosis; the ADNI study, the Alzheimer's Disease Neuroimaging Initiative study; MCI, mild cognitive impairment; AD, Alzheimer's disease; GRE, gradient-recalled echo; ICD, international classification of diseases; SWI, susceptibility-weighted imaging; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PiB-PET, pittsburg compound B-positron emission tomography; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; IWG-MCI, International Working Group on Mild Cognitive Impairment.

**ANDI is a longitudinal multicenter natural history study for AD, while the data of cSS and cognition was cross-sectional.*

TABLE 2 | Study demographics and outcomes.

Study reference	Kantarci et al. (12)	Wollenweber et al. (13)	Zonneveld et al. (8)	Na et al. (14)	Charidimou et al. (15)	Inoue et al. (9)	Shams et al. (7)	Total
Population size	562	212	809	232	339	347	1,504	4,005
Age, y	–	74 (mean)	66 (mean)	72 (mean)	73 (mean)	74 (mean)	63 (mean)	67 (mean)
Male	295 (52.5%)	89 (42.0%)	450 (55.6%)	97 (41.8%)	148 (43.7%)	130 (37.4%)	709 (47.1%)	1,918 (47.9%)
MMSE score	–	26 (median)	24 (mean)	22 (mean)	–	21 (mean)	25 (mean)	24 (mean)
COGNITIVE STATUS								
AD	40 (7.1%)	Any dementia	249 (30.8%)	62 (26.7%)	86 (25.4%)	162 (46.7%)	423 (28.1%)	26.9%
VaD	–	84 (39.6%)	12 (1.5%)	74 (31.9%)	18 (5.3%)	28 (8.1%)	54 (3.6%)	5.8%
Other dementia or undetermined	–		237 (29.3%)	–	42 (12.4%)	74 (21.3%)	224 (14.9%)	19.2%
MCI	351 (62.5%)	128 (60.4%)	143 (17.7%)	96 (41.4%)	162 (47.8%)	51 (14.7%)	418 (27.8%)	33.7%
SCC or CN	171 (30.4%)	–	168 (20.8%)	–	31 (9.1%)	32 (9.2%)	385 (25.6%)	22.1%
cSS prevalence	6 (1.1%)	13 (6.1%)	17 (2.1%)	12 (5.2%)	10 (2.9%)	12 (3.5%)	40 (2.7%)	2.7%
Focal cSS	–	7	11	6	7	7	33	–
Disseminated cSS	–	6	6	6	3	5	7	–
CMB prevalence	90 (16%)	25 (12%)	214 (29%)*	108 (47%)	74 (22%)[&]	160 (46%)	288 (19%)[&]	24%
cSS prevalence in AD	1 (2.5)	–	12 (4.8%)	3 (4.8%)	5 (5.8%)	8 (4.9%)	21 (5.0%)	4.9%

MMSE, mini mental state examination; AD, Alzheimer's disease; VaD, vascular dementia; MCI, mild cognitive impairment; SCC, subjective cognitive complains; CN, cognitively normal; cSS, cortical superficial siderosis; CMB, cerebral microbleed.

** 749 of 809 subjects had available data of CMB.*

[&] Only the number of lobar CMB was given.

The cognitively normal patients ($n = 171$) and those with subjective cognitive complains ($n = 616$) were excluded, thus only patients with definite cognitive impairment were included in the meta-analysis. Among patients with dementia, 76 of 1,869 (4.1%) had cSS compared with 33 of 1,349 patients (2.4%) without dementia. Pooled analysis demonstrated OR for the presence of cSS and dementia to be 1.60 (95% CI 1.04–2.44; $p = 0.031$) with no evidence of statistical heterogeneity ($I^2 = 0.0\%$, $p = 0.621$) (**Figure 2**). There was no evidence of a publication bias either from the result of Egger's test ($p = 0.604$) or Begg's test ($p = 0.881$), and the shape of the funnel plot seemed symmetrical (**Figure 3**). After excluding the AD Neuroimaging Initiative study (12), which only enrolled AD patients, the association of cSS with dementia remained significant (OR = 1.156, 95% CI 1.028–1.301; $p = 0.016$).

After excluding one study without data of dementia subtype (13), pooled analysis of the remaining six studies (7–9, 12, 14, 15), including 3,006 patients (96 with cSS), demonstrated OR for the presence of cSS and AD to be 2.01 (95% CI 1.34–3.02; $p < 0.001$) with no evidence of statistical heterogeneity ($I^2 = 0.0\%$, $p = 0.592$) (**Figure 4**), while no significant association was found between cSS and non-AD dementia (OR = 0.700, 95% CI 0.435–1.128; $p = 0.143$) (7–9, 14, 15). However, in the three studies with detailed data of cSS severity (7, 8, 14), the presence of disseminated cSS was not associated with dementia (OR = 0.873, 95% CI 0.337–2.260; $p = 0.523$), or AD (OR = 1.379, 95% CI 0.554–3.431; $p = 0.976$). All analyses were consistent when using a random-effects model.

DISCUSSION

Our meta-analysis in more than 3,000 subjects with cognitive impairment reported the existence of a positive relationship between cSS and AD, but not for non-AD dementia. These findings suggest cSS to be a candidate imaging indicator for AD.

Patients with cSS usually had lower cognitive scores (13). The Rotterdam Scan Study revealed a very low prevalence of cSS (0.7%) in a general population (6), while cSS was found in ∼3% of patients in a memory clinic population, and with a prevalence of 5% in patients with AD (7–9, 13–15). Only one (0.001%, 1/787) subject with normal cognitive function was reported to have cSS in the studies considered (7–9, 12, 15). The abnormally low prevalence would reduce the efficacy of detecting significant effects, therefore, we only enrolled cognitive impairment patients in the current meta-analysis. Lummel et al. included in their study 113 subjects with non-traumatic and non-aneurysmal cSS, the most common etiologies was CAA, followed by reversible cerebral vasoconstriction syndrome,

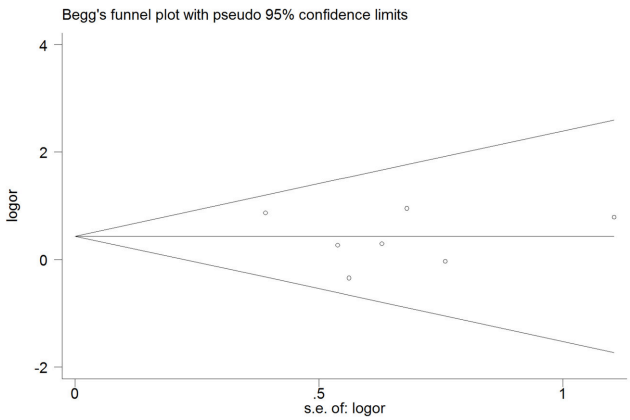

FIGURE 3 | Publication bias from studies about the association between dementia and the presence of cortical superficial siderosis.

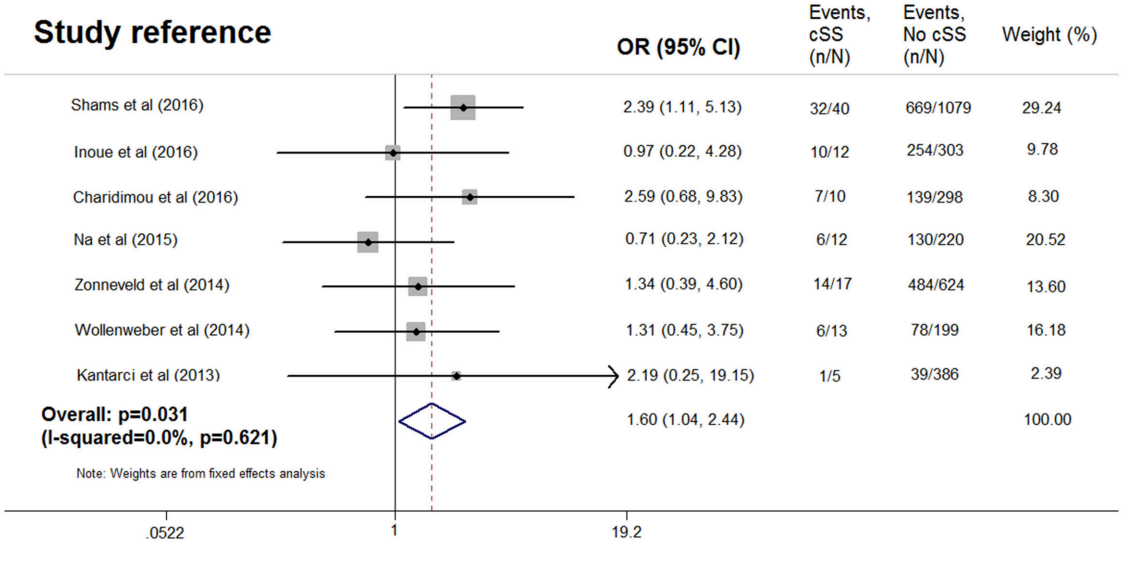

FIGURE 2 | Meta-analysis of the association between dementia and cortical superficial siderosis in the subjects with cognitive impairment.

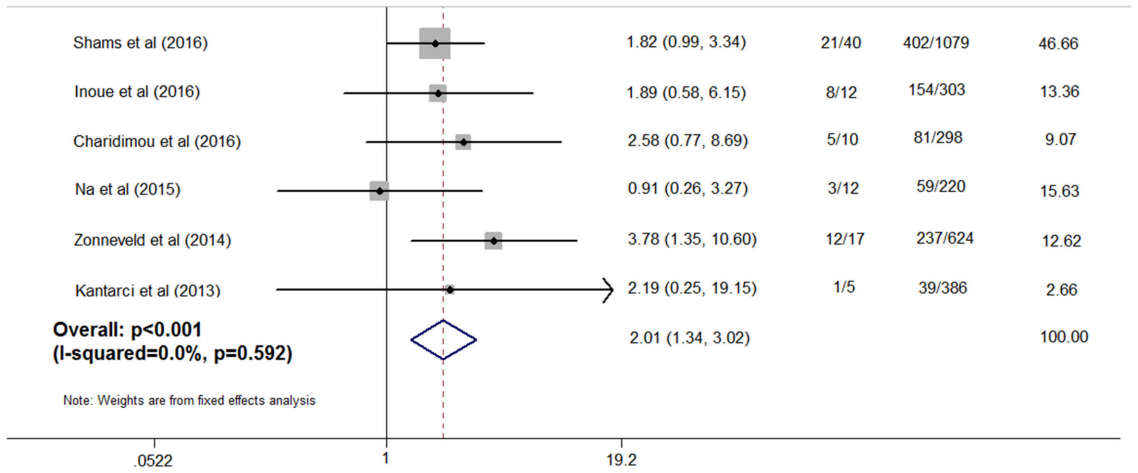

FIGURE 4 | Meta-analysis of the association between Alzheimer's disease and cortical superficial siderosis in the subjects with cognitive impairment.

central nervous system vasculitis, and hyperperfusion syndrome (3). The clinical manifestations for cSS were: acute ICH: 49%; transient focal neurological episodes: 34%; cognitive impairment: 12%; generalized seizure: 4%; and headache: 2% (3).

The underlying mechanism of the pathological association between cSS and AD is not clear. The close relation between cSS and CAA might support the amyloid pathology. All of the individuals who presented with cSS in the Rotterdam Scan Study had cerebral microbleeds in lobar locations (6). The presence of cSS was also associated with lobar microbleeds in the memory clinic populations (7, 9, 15). In addition, the APOE genotype was more common in cases with cSS compared to those without (7, 14, 15). Immunohistochemistry staining showed severe CAA with A-β in the leptomeningeal and cortical vessels of a patient with both AD and cSS (16). Renard et al. evaluated cerebrospinal fluid amyloid-β 1–40 (Aβ40), amyloid-β 1–42 (Aβ42), total and phosphorylated-tau (t-tau and p-tau) in patients with symptomatic isolated cSS, and found that the patients with cSS showed higher t-tau and lower Aβ42 compared to the controls, and lower t-tau, p-tau, and Aβ40 compared to the AD patients (17). Moreover, *in vivo* amyloid imaging using [^{11}C] Pittsburg compound B (PiB)-PET was performed in a cognitively impaired population, and cSS was found to be associated with higher global PiB retention ratio, and not present in any of the patients with a negative PiB scan (14), further supporting the hypothesis that cSS reflects an amyloid rather than the ischemic etiology.

Cognitive impairment was more frequent in patients with disseminated cSS, while transient focal neurological episodes were more often found in those with focal cSS (3). In the patients with spontaneous ICH, disseminated cSS was a key risk factor of new-onset dementia and recurrent symptomatic ICH (18, 19). However, the presence of disseminated cSS was not associated with dementia incidence in a recent longitudinal study of patients with probable CAA (OR = 1.268, 95% CI 0.702–2.292; $p = 0.431$) (20). Similarly, the severity of cSS could not predict dementia or AD in our meta-analysis. To sum up, the presence of disseminated cSS could predict dementia in patients with ICH, while it was not associated with dementia incidence in memory clinic populations. Disseminated cSS seems more important in the subjects with ICH, thus the characteristics of cohorts might be the key point. Considering the small sample size of patients with disseminated cSS, future studies are needed to investigate the clinical relevance of cSS severity.

Our study had several limitations. First, our analysis had inherent biases associated with the use of observational studies, and most of them were cross-sectional studies. All studies were subject to selection bias because not every individual underwent GRE or SWI. Moreover, the causality between cSS and dementia is still unclear, and future longitudinal studies are needed to clarify this association. Second, the use of unadjusted data rendered our analysis vulnerable to confounding variables, such as the neuroimaging markers of CSVD. Third, the clinical diagnostic criteria for dementia and its subtype might be not quite similar in each cohort.

In conclusion, our analysis shows that the presence of cSS is associated with AD. Future large multicenter studies and individual patient data meta-analyses are needed to investigate the importance of cSS in the pathogenesis and longitudinal progression of AD in the subjects with cognitive impairment.

AUTHOR CONTRIBUTIONS

YJ: design of the study, interpretation of data for the study, revision of the study for important intellectual content, and final approval of this version of the manuscript; CZ and KL:

acquisition of data for the study, drafting of the study, revising the study for important intellectual content, and interpretation of data for the study; SY: acquisition of data for the study, drafting of the study, and revising the study for important intellectual content.

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REFERENCES

1. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology* (2013) 80:1778–83. doi: 10.1212/WNL.0b013e31828726f5
2. Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? *Brain* (2011) 134(Pt. 2):335–44. doi: 10.1093/brain/awq321
3. Lummel N, Wollenweber FA, Demaerel P, Bochmann K, Malik R, Opherk C, et al. Clinical spectrum, underlying etiologies and radiological characteristics of cortical superficial siderosis. *J Neurol.* (2015) 262:1455–62. doi: 10.1007/s00415-015-7736-1
4. Charidimou A, Jager RH, Fox Z, Peeters A, Vandermeeren Y, Laloux P, et al. Prevalence and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy. *Neurology* (2013) 81:626–32. doi: 10.1212/WNL.0b013e3182a08f2c
5. Boulouis G, Charidimou A, Jessel MJ, Xiong L, Roongpiboonsopit D, Fotiadis P, et al. Small vessel disease burden in cerebral amyloid angiopathy without symptomatic hemorrhage. *Neurology* (2017) 88:878–84. doi: 10.1212/WNL.0000000000003655
6. Vernooij MW, Ikram MA, Hofman A, Krestin GP, Breteler MM, van der Lugt A. Superficial siderosis in the general population. *Neurology* (2009) 73:202–5. doi: 10.1212/WNL.0b013e3181ae7c5e
7. Shams S, Martola J, Charidimou A, Cavallin L, Granberg T, Shams M, et al. Cortical superficial siderosis: prevalence and biomarker profile in a memory clinic population. *Neurology* (2016) 87:1110–7. doi: 10.1212/WNL.0000000000003088
8. Zonneveld HI, Goos JD, Wattjes MP, Prins ND, Scheltens P, van der Flier WM, et al. Prevalence of cortical superficial siderosis in a memory clinic population. *Neurology* (2014) 82:698–704. doi: 10.1212/WNL.0000000000000150
9. Inoue Y, Nakajima M, Uetani H, Hirai T, Ueda M, Kitajima M, et al. Diagnostic significance of cortical superficial siderosis for Alzheimer disease in patients with cognitive impairment. *AJNR Am J Neuroradiol.* (2016) 37:223–7. doi: 10.3174/ajnr.A4496
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339:b2535. doi: 10.1136/bmj.b2535
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis OF Observational Studies in Epidemiology (MOOSE) group. *JAMA* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
12. Kantarci K, Gunter JL, Tosakulwong N, Weigand SD, Senjem MS, Petersen RC, et al. Focal hemosiderin deposits and beta-amyloid load in the ADNI cohort. *Alzheimers Dement.* (2013) 9(Suppl. 5):S116–23. doi: 10.1016/j.jalz.2012.10.011
13. Wollenweber FA, Buerger K, Mueller C, Ertl-Wagner B, Malik R, Dichgans M, et al. Prevalence of cortical superficial siderosis in patients with cognitive impairment. *J Neurol.* (2014) 261:277–82. doi: 10.1007/s00415-013-7181-y
14. Na HK, Park JH, Kim JH, Kim HJ, Kim ST, Werring DJ, et al. Cortical superficial siderosis: a marker of vascular amyloid in patients with cognitive impairment. *Neurology* (2015) 84:849–55. doi: 10.1212/WNL.0000000000001288
15. Charidimou A, Ni J, Martinez-Ramirez S, Vashkevich A, Ayres A, Rosand J, et al. Cortical superficial siderosis in memory clinic patients: further evidence for underlying cerebral amyloid angiopathy. *Cerebrovasc Dis.* (2016) 41:156–62. doi: 10.1159/000442299
16. Feldman HH, Maia LF, Mackenzie IR, Forster BB, Martzke J, Woolfenden A. Superficial siderosis: a potential diagnostic marker of cerebral amyloid angiopathy in Alzheimer disease. *Stroke* (2008) 39:2894–7. doi: 10.1161/STROKEAHA.107.510826
17. Renard D, Gabelle A, Hirtz C, Demattei C, Thouvenot E, Lehmann S. Cerebrospinal fluid Alzheimer's disease biomarkers in isolated supratentorial cortical superficial siderosis. *J Alzheimers Dis.* (2016) 54:1291–5. doi: 10.3233/JAD-160400
18. Moulin S, Labreuche J, Bombois S, Rossi C, Boulouis G, Henon H, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurol.* (2016) 15:820–9. doi: 10.1016/S1474-4422(16)00130-7
19. Moulin S, Casolla B, Kuchcinski G, Boulouis G, Rossi C, Henon H, et al. Cortical superficial siderosis: a prospective observational cohort study. *Neurology* (2018) 91:e132–8. doi: 10.1212/WNL.0000000000005778
20. Xiong L, Boulouis G, Charidimou A, Roongpiboonsopit D, Jessel MJ, Pasi M, et al. Dementia incidence and predictors in cerebral amyloid angiopathy patients without intracerebral hemorrhage. *J Cereb Blood Flow Metab.* (2018) 38:241–9. doi: 10.1177/0271678X17700435

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Transient Global Amnesia Linked to Impairment of Brain Venous Drainage: An Ultrasound Investigation

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Background: Previous neuroimaging and ultrasound studies suggested that compression and stenosis of the internal jugular vein (IJV) in patients with transient global amnesia (TGA) may impair IJV drainage, while a patent IJV releases intracranial pressure caused by the Valsalva maneuver (VM).

Methods: Seventy-nine TGA patients with complete ultrasound examination data during admission were recruited prospectively to evaluate IJV drainage, which included the time-averaged mean velocity, and the cross-sectional lumen area of the IJV at the vein's middle (J2) and distal (J3) segments and the cross-sectional area during a 10-s VM to test for any retrograde or anti-grade flow. Forty-five TGA patients and 45 age- and sex-matched control subjects underwent complete contrast-enhanced magnetic resonance (MR) venous studies, which included time-resolved imaging of contrast kinetics, contrast-enhanced axial T1-weighted MR imaging, and phase-contrast-based non-contrast enhanced magnetic resonance venography (MRV).

Results: In those subjects with complete MRV studies, the flow volumes exhibited at both the J2 and J3 segments of the left IJV and left vertebral vein (VV) were significantly lower in the TGA patients than in the control subjects. Although there was no significant difference in the flow volume of right IJV, the total of bilateral IJV, and VV flow volumes was still significantly lower in the TGA patients. As compared with the control subjects, the TGA patients exhibited significantly higher prevalence of completely blocked right IJV drainage at the J3 segment during the VM, but non-significantly higher for the left IJV at the J3 segment and for the right IJV at the J2 segment.

Conclusion: Our results confirmed that the total venous flow decreases in the IJVs and VVs of the patients with TGA. This is consistent with the findings of previous MR imaging studies that have reported about compression and stenosis of the draining veins. We also found that IJV drainage is relatively compromised during the VM in the patients with TGA.

Keywords: internal jugular vein (IJV), magnetic resonance venography (MRV), transient global amnesia (TGA), ultrasound, Valsalva maneuver (VM), vertebral vein (VV), hemodynamics

INTRODUCTION

Transient global amnesia (TGA) is defined as a sudden and transient inability to acquire new information (1). It can be triggered by certain events including Valsalva maneuver (VM)–like activities (1–3). Cerebral venous congestion/hypertension is one of the conditions that has been linked to TGA, which results from venous reflux while performing a VM in the subjects with internal jugular vein valve incompetence (IJVVI) (4–6). However, previous ultrasound and non-contrast venous magnetic resonance (MR) angiography studies have not supported a causal relationship between IJVVI and TGA (7–9). Previous studies have also reported that VM-induced pressure in the chest and abdomen is mainly transmitted to the intracranium via the epidural venous plexus (10, 11). Theoretically, bilateral IJV patency is needed for the brain venous drainage, which is regarded as a protective mechanism against intracranial venous hypertension. Stenosis or obstruction of the IJV hinders the brain venous drainage. This can directly cause intracranial hypertension (12, 13) and impair the protective function of IJV during the VM, which worsens the increased intracranial pressure further (11, 14). Consistent with this hypothesis of the venous outflow obstruction, we have previously showed that many patients with TGA exhibit stenosis or obstruction of the left brachiocephalic vein (BCV) (15). Using MR imaging, we have also demonstrated that the patients with TGA manifest a higher prevalence of compression/stenosis of the bilateral IJVs and left BCV, and transverse sinus (TS) hypoplasia, which supports the hypothesized role of abnormal brain venous drainage in the pathogenesis of TGA (16). Hence, we hypothesized that the compression/stenosis of the bilateral IJVs and left BCV would impede the brain venous drainage, which would result in reduced IJV flow volumes exhibited in the patients with TGA. We further hypothesized that in the patients with TGA, the IJV drainage would be particularly blocked during the VM, resulting in a phenomenon known as "IJV non-patency." This would impair the role of IJV drainage in releasing the intracranial pressure. We tested these hypotheses with ultrasound evaluations of the morphology and hemodynamics of the extracranial IJVs and vertebral veins (VVs) at rest and during the VM.

METHODS

Study Design and Participants

The main study design and the participants have been described elsewhere (16). In brief, from January 2008 to December 2012, 79 patients with TGA were admitted to the Taipei Veterans General Hospital Neurology Department. All were examined by a neurologist, and TGA was diagnosed according to the criteria as modified and validated by Hodge and Warlow (1). All the TGA patients underwent complete ultrasound examination including analyses of the IJV responses during the VM; but of those, 34 patients had already underwent an emergency MRI at the emergency department to exclude the possibility of acute ischemic stroke, and hence did not undergo the complete MR venous study. The remaining 45 patients underwent complete ultrasound examinations and complete contrast-enhanced magnetic resonance (MR) venous studies, which included magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and magnetic resonance venography (MRV) assessments of the IJV drainage. We prospectively recruited 45 age- and sex-matched control subjects from the individuals who underwent physical check-ups and presented no history of neurologic signs or symptoms. However, we did not recruit any controls for the subgroup of those 34 patients who did not undergo complete venous MR imaging studies.

Those 45 control subjects also underwent complete MRI, MRA, and MRV studies and ultrasound assessments. In accordance with the regulations of our government and the regulations of the Ethics Committee of Taipei Veterans General Hospital and in compliance with the Declaration of Helsinki, all the participants provided informed written consent with their signatures. The study protocol was approved by the Taipei Veterans General Hospital's institutional review board, and the study was conducted according to the institutional guidelines. All the participants gave the written informed consent.

Ultrasound Acquisition

All the participants underwent color-coded duplex sonography with a 7-MHz iU22 linear transducer (Philips Medical Systems, Andover, MA), performed within 7 days after their TGA attacks, by a technician who had more than 10 years of experience in venous ultrasound studies and was blinded to the subjects' characteristics. The method for ultrasound examinations of the extracranial venous system has been reported elsewhere (17–20). In brief, the IJV's time-averaged mean velocity (TAMV, cm/s) and the cross-sectional lumen area (CSA, cm^2) were recorded at its middle (J2) and distal (J3) segments (19, 20). The location of J2 and J3 is the point where the common facial vein drains into the IJV (19, 20). The IJV segment above this point is J3, and below is J2. We acquired the TAMVs by directing the Doppler

cursor parallel to the vein with the gate adjusted to comprise the entire lumen. We measured the TAMVs with the iU22's built-in software, and included at least three cardiac cycles on the Doppler spectrum. The probe was then turned by 90° at the same IJV segments to measure the CSAs, which were measured thrice as B-mode images. These images were averaged for later analysis. Both the CSAs and TAMVs were recorded at a brief apnea after the three respiratory states (20). The recordings made during the brief apnea after the three respiratory states are shown in the figures as follows: (1) normal respiration (resting or baseline) (**Figures 1A,D**), (2) deep inspiration (**Figures 1B,E**), and (3) expiration (**Figures 1C,F**). During the latter two respiratory states, the subjects were instructed to avoid strain-inducing breath-holding, because it could increase intra-thoracic pressure. We recorded the CSAs of the IJVs during a 10-s VM to test the incidence of reflow or no flow (**Figure 2**). The flow volume (FV) equals the TAMV multiplied by the CSA. Since it was difficult to obtain the CSAs of the VVs, we estimated the diameters of the VVs while modeling the VVs as having perfectly circular cross-sections. We measured the diameters of the VVs adjacent to the V2 segment of the vertebral artery. We also determined the jugular venous reflux (JVR) at the baseline and during the VM. Our methods for performing the VM and detecting the JVR have been described elsewhere (17, 21).

All the ultrasound data and color imaging records were collected prospectively. Two trained neurologists, who were also blinded to the subjects' clinical characteristics, reviewed the collected data for the CSAs, TAMVs, and FVs for the IJVs, and the diameters and TAMVs for the VVs. A consensus meeting was conducted to discuss any problems or disagreements.

MR Imaging Study

Our methods for MRI and grading of TS hypoplasia and stenosis/compression of the IJV and BCV have been described elsewhere (16, 20). In brief, we performed contrast-enhanced MRI of all the participants using a 1.5-T Excite II MRI device (GE Medical Systems, Waukesha, WI), which included time-resolved imaging of contrast kinetics (TRICKS), contrast-enhanced axial T1-weighted MRI (Contrast T1), and phase-contrast based non-contrast enhanced MRV. All the patients were examined within 10 days after their TGA attacks.

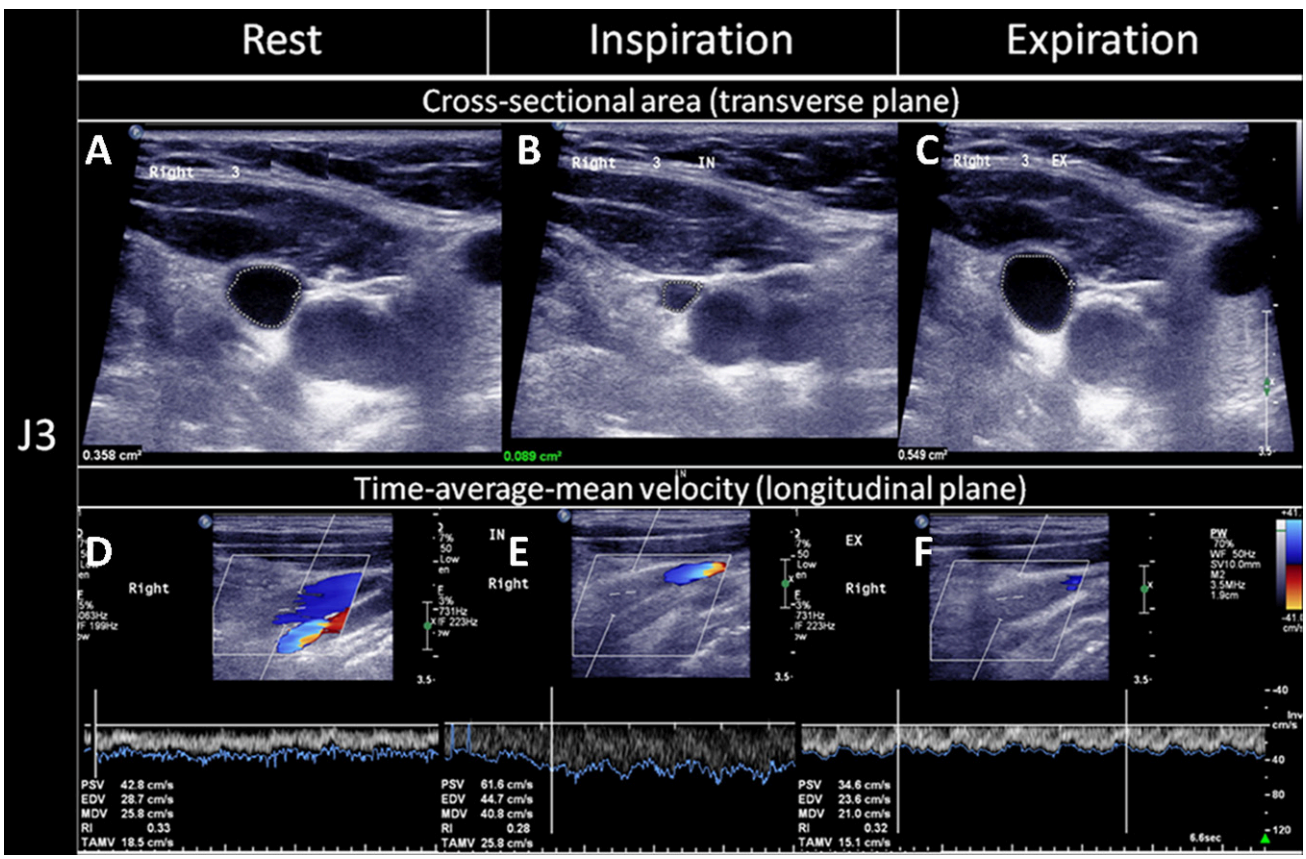

FIGURE 1 | Quantitative evaluation of the CSAs and TAMVs of the IJVs during the three respiratory states. The cross-sectional lumen areas (CSAs) and time-average-mean velocities (TAMVs) of the upper segment of the internal jugular vein (IJV, J3) were recorded during a brief apnea after the three respiratory statuses, namely: **(A,D)** at rest (normal respiratory status, **(B,E)**; deep inspiration; and **(C,F)** expiration. As compared to that at rest, the CSA decreased **(B)** while the TAMV increased **(E)** during the deep inspiration, and the CSA increased **(C)** while the TAMV decreased **(F)** during the expiration. The figure was reproduced with the permission of Chao et al. (20).

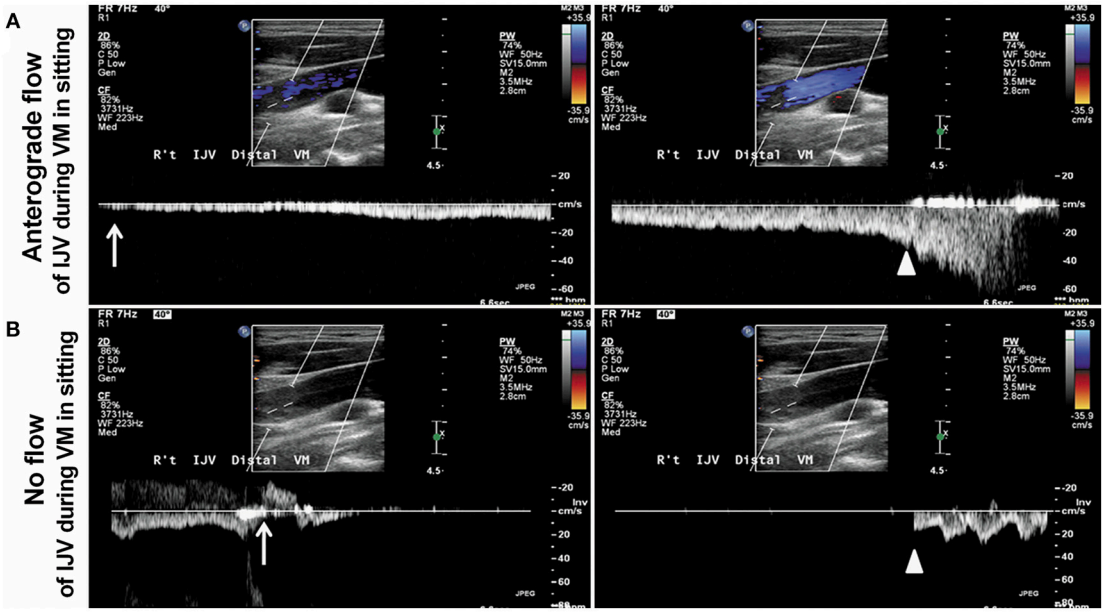

FIGURE 2 | Display of Doppler spectra of the IJV (internal jugular vein) during the VM (Valsalva maneuver) in the sitting position. **(A)** Patient 1. An anterograde flow in the right IJV during the VM in the sitting position (upper **A**) suggests that the pressure can be released by reopening the IJV in a 42-year-old healthy female with patent IJV. **(B)** Patient 2. No flow in the right IJV during the VM in the sitting position (lower **B**) with a transient venous reflux (arrow, **B)** indicates that the intracranial venous pressure cannot be relieved effectively by the reopening the IJV in a 53-year-old TGA patient with significant IJV stenosis/obstruction. The arrows indicate the beginning of the VM, and the arrowheads indicate the end of the VM. The figure was reproduced with the permission of Han et al. (16).

The IJV morphologies were assessed at the level of upper IJV (C1–2 level) and middle IJV (C3–5 level) using Contrast T1. The IJV compression/stenosis was graded according to the following criteria (16, 22): grade 0 = normal round or ovoid appearance; grade 1 = mild flattening; grade 2 = moderate flattening; grade 3 = severe flattening or non-visualized appearance (**Figure 1A**).

Based on the filling defect shown on TRICKS, the left BCV obstruction was graded as follows: grade 0 = normal or compression ≤20%; grade 1 = compression >20% and ≤80%; grade 2 = compression >80%; grade 3 = grade 2 + presence of different types of venous collaterals (23).

Based on MRV and Contrast T1 studies, TS morphology was graded based on the criteria modified from that given by Han et al. (16) and Cheng et al. (24). All the asymmetrical percentages were calculated relative to the contralateral TS, as follows: grade 0 = symmetry or asymmetry ≤10%; grade 1 = asymmetry >10% and ≤50%; grade 2 = asymmetry >50%; grade 3 = aplasia or TS signal absent. Hypoplasia was defined as an asymmetry <50%. We have illustrated the locations for performing MRV and Contrast T1 examinations in our previous paper (16). However, in this study, only the findings of Contrast T1 were used for the analysis of hypoplasia.

All the MR imaging scans were examined by a neuroradiologist and a neurologist. The intra-class correlation coefficient for grading indicated an inter-rater reliability of 0.91. If inconsistencies resulted between the reports given by the two MRI readers, they discussed and reached a "consensus."

Statistical Analysis

Since this study was the first ultrasound study to evaluate the mechanism of jugular venous outflow impairment in the TGA patients, the sample size could not be pre-determined. The ultrasound data, such as the time-averaged mean velocity (TAMV), flow velocity (FV), and cross-sectional lumen (CSA) were skewed and were observed to be not normally distributed for the jugular venous flow. Thus, the expression of medians and inter-quartile ranges was used, and Wilcoxon rank sum analysis was performed. The chi-square test was performed for the categorical data. The same applies to the CSAs data for the TS, IJV, and VV. We compared the ultrasound data from the patients and control subjects using the Wilcoxon rank sum test. We used the chi-square tests to compare the prevalence of IJVVI or IJV patency during the VM. We defined the statistical significance as a 2-sided $p < 0.05$. All the analyses were performed with a SAS, 9.2 (SAS Institute, Cary, NC).

RESULTS

The demographic and clinical characteristics of all the 79 TGA patients, and the subset of 45 patients and 45 age- and sex-matched controls who underwent complete MRI, MRA, and MRV examinations are shown in **Table 1**. The patients and controls did not differ significantly in terms of their vascular risk factors. The TAMVs, FVs, and CSAs of the bilateral IJVs in the age- and sex-matched 45 patients and 45 controls are

TABLE 1 | Demographic data and clinical features of TGA patients and controls.

	TGA (total number of patients)	TGA patients with complete MRV study	Control subjects with complete MRV study
	n = 79	*n* = 45	*n* = 45
DEMOGRAPHIC			
Age	61.4 ± 8.7 (32–85)	61.5 ± 8.7 (35–85)	61.5 ± 8.7 (35–85)
Gender (M/F)	57/24	19/26	19/26
Coronary artery disease	2 (2.5%)	1 (2.2%)	0 (0%)
Hyperlipidemia	5 (6.3%)	3 (6.7%)	2 (4.4%)
Hypertension	8 (10.1%)	4 (8.9%)	5 (11.1%)
Diabetes mellitus (DM)	4 (5.0%)	2 (4.4%)	1 (2.2%)
Headache with cough	7 (8.8%)	4 (8.9%)	0 (0%)
Mitral valve prolapse (MVP)	6 (7.6%)	3 (6.7%)	2 (4.4%)
Sleep apnea syndrome (SAS)	2 (2.2%)	1 (2.2%)	0 (0%)
Syncope	5 (6.3%)	3 (6.7%)	0 (0%)
Insomnia	3 (3.8%)	1 (2.7%)	0 (0%)
Glaucoma	5 (6.3%)	2 (4.4%)	0 (0%)
Carotid stenosis	1 (1.3%)	0 (0%)	0 (0%)
MCA stenosis	5 (6.3%)	3 (6.7%)	0 (0%)
Previous stroke	3 (3.8%)	1 (2.2%)	0 (0%)
CLINICAL PROFILES OF TGA			
Recurrent	35 (44.3%)	21 (46.7%)	
Duration of amnesia (hours)	7.9 ± 8.3 (0.2–14)	7.5 ± 7.9 (0.2–11)	
VM–like activities or precipitating factors, *n* (%)	26 (32.9%)	16 (35.6%)	

TGA, Transient Global Amnesia.

shown in **Table 2**. As compared to the controls, the TGA patients exhibited significantly lower TAMVS at the J2 and J3 segments of the bilateral IJVs. They also exhibited significantly lower FVs in the left IJV at the J2 and J3 segments and in the left VV. The FVs were not significantly lower in the right IJV; however, the patients still exhibited significantly lower total flow volumes in the bilateral IJVs and VVs. In both the patients and controls, the CSAs of the bilateral IJVs were not significantly different either at the J2 or J3 segment. The TGA patients exhibited a significantly higher prevalence of IJVVI (patients vs. controls: 82 vs. 44%); however, the side-specific prevalence was significantly greater on the left side (patients vs. controls: 53 vs. 20%), while the right-sided prevalence being comparable between the patients and controls (patients vs. controls: 29 vs. 24%). Furthermore, we detected a significant difference in the prevalence of left-sided IJVVI between the subjects with and without the presence of left BCV compression/stenosis [19 (61%) vs. 14 (24%), $p = 0.0044$].

We have often observed that the IJV drainage flow usually appears ∼4–8 s after initiating the VM, so we simply defined the complete absence of IJV drainage flow at the J2 or J3 segment within 10 s of initiating the VM as IJV "non-patency." **Table 3** displays the relationship between the ultrasound findings of IJV non-patency during the VM, and the MRI findings of venous compression/obstruction or TS hypoplasia in those 90 study subjects (45 patients and 45 controls). For the left IJV, the prevalence of ultrasound-detected IJV non-patency during the VM was significantly greater at the J2 segment in the study subjects with an upstream TS hypoplasia than that in the patients without such hypoplasia (56.9 vs. 44.3%, respectively; $p = 0.0425$). For the right IJV, the prevalence of IJV non-patency at the J2 segment was significantly higher in the patients with IJV compression at C1 or C4 than in the patients without such compression (62.07 vs. 28.57%, respectively; $p = 0.0111$). We found no significant difference in the prevalence of bilateral IJV non-patency during the VM between those age- and sex-matched patients and controls who underwent complete MRI examinations. However, since there are no statistical differences in all the flow profiles between two groups of TGA patients with and without venous MR imaging as shown in **Table S1**, thus we included the 34 patients who underwent complete ultrasound examinations but incomplete MRI examinations for analysis, we found a significant difference in the prevalence of IJV non-patency during the VM between the patients and controls (**Table 4**). Specifically, we found that the patients exhibited significantly higher IJV non-patency at the right J3 segment (patients: 32.1%; controls: 11.6%; $p = 0.0128$), but not significantly higher in the left J3 segment (patients: 49.35%; controls: 37.21%), and the right J2 segment (patients: 44.00%; controls: 32.56%).

DISCUSSION

Our results confirmed our first hypothesis that the patients with TGA having IJV stenosis/compression at various segments would exhibit significantly lower total FVs in the bilateral IJVs and VVs resulting in important consequences than that exhibited by the control subjects. More importantly, our findings are consistent with our second hypothesis that the prevalence of right IJV non-patency at various segments during the VM would be significantly higher in the study subjects with IJV stenosis/compression at various segments; and therefore, would be higher in the TGA patients than that in the controls, which supports our novel hypothesis of venous pathogenesis involved in the TGA attacks (16). Specifically, an insufficient IJV patency prevents the release of increased intracranial pressure and venous congestion/hypertension in the basilar plexus and cavernous sinus caused by VM-like maneuvers. Moreover, venous stasis and occlusion may cause constriction of cerebral arterioles (16), which further compromises cerebral hemodynamics.

Venous Flow Velocity and FV in IJVs

This study, our previous study (20), and other studies (22, 23) all revealed that the IJV or BCV compression and stenosis significantly reduce the IJV FVs. These result in the venous drainage being routed through less efficient alternative routes, such as the tortuous path through the spinovertebral venous plexus. This obstruction of the venous drainage may also induce changes in the arterial blood flow, such as arterial constriction, through the venoarterial reflex (25). Such changes may explain the observation in our previous studies (21, 24)

TABLE 2 | Comparisons of the TAMVs, FVs, and CSAs of the IJVs between the age- and sex-matched TGA patients and control subjects.

Segment	Parameter	Patients with TGA $n = 45$		Control subjects $n = 45$	
		Left	Right	Left	Right
J2	TAMV (mm/s)	72.4** (45.6–109.0)	143.0* (103.0–206.0)	98.9 (61.2–158.0)	152.0 (91.0–231.0)
	CSA (mm^2)	60 (34–75)	73 (47–101)	45 (35–76)	75 (47–105)
	FV (mL/min)	3.53* (2.54–6.38)	12.14 (6.81–15.86)	4.35 (3.30–8.72)	15.95 (11.43–22.34)
J3	TAMV (mm/s)	79.6* (41.9–134.0)	147.0* (97.0–203.0)	101.0 (67.4–164.0)	189.0 (141.0–208.0)
	CSA (mm^2)	22 (17–30)	39 (24–66)	29 (15–37)	34 (23–43)
	FV (mL/min)	1.35* (0.59–3.32)	5.68 (2.89–10.53)	3.09 (1.67–4.52)	6.61 (4.02–7.51)
IJV	Reflux (number of cases)	24 (53%)**	13 (29%)	9 (20%)	11 (24%)
VV	FV (mL/min)	2.03** (0.76–4.33)	8.40 (3.40–14.04)	5.80 (1.65–23.27)	13.13 (3.87–16.70)
J2	Total FV (mL/min)	15.71 (12.31–20.59)		16.29 (13.55–22.98)	
J3	Total FV (mL/min)	9.68 (5.08–12.22)		9.40 (6.40–12.18)	
Bilateral J2 FVs + Bilateral VV FVs	Total FV(mL/min)	29.43* (19.17–39.10)		36.17 (29.44–52.54)	

*CSA, Cross-Section Lumen Area; FV, Flow Volume; IJV, Internal Jugular Vein; TAMV, Time-Averaged Mean Velocity; TGA, Transient Global Amnesia; VV, Vertebral Vein; *$p < 0.05$: when comparing the TGA patients and controls (ipsilateral IJV); **$p < 0.01$: when comparing the TGA patients and controls (ipsilateral IJV).*

TABLE 3 | The prevalence of no-reflow in the IJVs with and without venous compression/stenosis during the VM in the study subjects with complete MR venous examination.

Venous compression/stenosis	Segment	No-reflow in the IJVs during the VM
TS hypoplasia in contrast T1 ($n = 20$)	J3	50/48%
	J2	56.9/44.3%*
Left C1 or C4 compression (Yes/No) (Yes = 42; No = 48)	J3	54.2/45.5%
	J2	75.0/72.7%
Right C1 or C4 compression (Yes/No) (Yes = 40; No = 50)	J3	36.7/10.7%**
	J2	62.1/28.6%$^{\#}$
BCV compression (Yes/No) (Yes = 31; No = 59)	J3	51.7/46.4%
	J2	44.8/46.4%

*MR, Magnetic Resonance; BCV, Brachiocephalic Vein; IJV, Internal Jugular Vein; TS, Transverse Sinus; VM, Valsalva Maneuver; *$p = 0.0425$; **$p = 0.021$; $^{\#}p = 0.0111$.*

TABLE 4 | The prevalence of no-reflow in the IJVs during the VM in all the 79 TGA patients and 45 controls among the study subjects with complete MR venous examination.

Side	Segment	Patients with TGA $n = 79$	Controls $n = 45$
Left	J3	49.35% ($n = 77$)	37.21% ($n = 43$)
Left	J2	70.89% ($n = 79$)	67.44% ($n = 43$)
Right	J3	32.05%* ($n = 78$)	11.63%* ($n = 43$)
Right	J2	44.00% ($n = 75$)	32.56% ($n = 43$)

*IJV, Internal Jugular Vein; TGA, Transient Global Amnesia; VM, Valsalva Maneuver; MR, Magnetic Resonance; *$p = 0.0128$.*

that, the patients with transient monocular blindness without carotid stenosis exhibited increased downstream resistance of the retrobulbar arteries (i.e., ophthalmic artery, posterior ciliary artery, and central artery) in association with significantly increased prevalence of compression/stenosis in the bilateral IJVs (26). In this study, we did not measure the venous FV in the spinovertebral venous plexus, because it is undetectable by the ultrasound; therefore, we do not know the changes in the total venous drainage from the bilateral TSs, though the patients exhibited significantly lower total FV in the bilateral IJVs and VVs.

Prevalence of IJV Non-patency During the VM

Our results supported our second hypothesis that the prevalence of IJV non-patency during the VM would be higher in the TGA patients than that in the controls. We observed a significant difference in the prevalence of right IJV non-patency (patients: 32.1%; controls: 11.6%; $p = 0.0128$) as compared to that for the left IJV non- patency (patients: 49.4%; controls: 37.2%). An abundance of evidence indicates that VM-induced pressure from the chest and abdomen is mainly transmitted to the intracranial compartment via the epidural venous plexus or vertebral venous plexus. Orthograde IJV outflows emerging shortly after the beginning of the VM, thus, serve as a mechanism for regulating the intracranial pressure and equalizing the pressure within the venous system (10, 11, 14, 16). Our findings indicate that the patients with TGA may experience defective intracranial pressure regulation during the VM-like movements. As described earlier, we restricted our definition of IJV non-patency to complete absence of the IJV drainage at the J3 or J2 segment during the first 10 s of the VM; but, this consideration regarding the IJV drainage might be unexhaustive. Several patients with partial or limited IJV drainage were excluded from this definition, which may explain why we observed a lower prevalence of IJV non-patency during the VM. Further research is needed to develop a more sensitive and specific definition of IJV non-patency during the VM.

Incompetence of Jugular Venous Valves

Cerebral venous congestion/hypertension, which results from the venous reflux during the VM consequent to the IJVVI, is linked to TGA (4–6). However, previous ultrasound studies using

either retrograde flow (27) or air bubbles (28) during the VM explained the involvement of only the proximal region of the IJV in the IJVVI, ignoring the rest of the IJV and the entire BCV, and possibly missing other important IJV/BCV abnormalities. Unsurprisingly, previous ultrasound and non-contrast MRA results have not supported a causal relationship between the IJVVI and TGA (7–9). Other than the IJVVI, we have previously described three ultrasound patterns of IJV abnormalities in the patients with TGA: (i) an isolated reverse flow in the left jugular vein branch (JB), (ii) a segmental reverse flow in the left distal IJV, and (iii) a continuous reverse flow in the left IJV and JB (29). All the three of these IJV patterns are suggestive of the venous outflow obstruction or compression/stenosis of the left BCV (29). Similar to other studies (4–6), even in this study, the overall prevalence of IJVVI was higher in the TGA patients than that in the controls (**Table 2**); but, the prevalence was higher in the left IJV only, and not in the right IJV. Furthermore, we found that the prevalence of IJVVI was significantly higher in the individuals with left BCV compression/stenosis. This suggests that the IJVVI might occur secondary to the BCV compression/stenosis on the left side. The fact that the IJVVI was more frequently observed on the right side, as reported in other studies (28), raises the question of whether the jugular venous valves are vulnerable in cases of IJV compression/stenosis due to pressure imbalances across the valves or whether the previous air bubble methodology overestimated the IJVVI prevalence (30). Further research is needed to address this question.

Assessments of IJV Compression With Different Imaging Modalities

It is worth mentioning that despite the patients exhibiting reduced flow velocities and FVs in each of the segments of the bilateral IJVs, the diameters of their IJV segments were comparable to that of the controls (**Table 2**). Moreover, the patients' right IJVs were slightly wider than that of the controls. This may be partially explained by the Bernoulli's equation, which states that the pressure in the venous lumen is inversely proportional to the flow rate, so that the lumen diameter may be enlarged with flow stasis resulting from the venous stenosis/compression. As described earlier, the FV of the IJV decreases in cases of IJV or BCV stenosis/compression (20, 22, 23). However, discrepancies in the diagnosis of IJV compression/stenosis may be observed due to different types of venous examination (31). Catheter venography has been traditionally regarded as the gold standard for diagnosing venous disorders involving compression/stenosis, but it does not measure the flow velocity or FV; hence, it cannot prove or disprove the MRI or ultrasound findings that indicate decreased IJV FV resulting from compression/stenosis.

Study Limitations

This study has several limitations, particularly regarding the use of ultrasound to study the IJV. First, there are no ideal, fixed locations for measuring the CSA and TAMV in the J2 and J3 segments; and these measurements may vary if the IJVs are non-uniform in diameter, which may occur in the cases where the IJV is affected by segmental dilatation, narrowing, or compression. However, the FV was calculated by multiplying the TAMV by the CSA, and it was theoretically correct according to the Bernoulli's equation. We measured the CSA and TAMV at the widest available lumen of the J2 and J3 segments to minimize the bias. This allowed us to detect the differences in both the FVs and TAMVs between the patients and controls. Second, it is unexhaustive to consider complete absence of IJV drainage during the VM while explaining IJV non-patency. Several of our subjects exhibited limited or intermittent flow, which suggests partial IJV blockage. However, we excluded these subjects from our definition of IJV non-patency, which may have caused us to underestimate the prevalence of IJV non-patency during the VM. Third, left BCV blockage may disappear during deep inspiration (15), which usually precedes the VM; hence, paradoxical reopening of the left BCV and left IJV occurs during the VM. This causes further underestimation of the prevalence of non-patency.

CONCLUSION

Our results further confirmed that decrease in the total flow of the IJVs and VVs reflect impaired venous drainage in the patients with TGA, which is consistent with the findings of previous MRI studies that reported about the compression/stenosis of the bilateral IJVs and the left BCV. Second, our findings support the hypothesis that the compression/stenosis of the bilateral IJVs and left BCV may block the IJV drainage during the VM, which may prevent the release of intracranial hypertension caused by the VM. Further study is needed to obtain a more sensitive and specific definition of IJV non-patency during the VM.

AUTHOR CONTRIBUTIONS

H-HH and JW conceived and designed the experiments. KH, A-CC, F-CC, C-PC, and H-YH performed the experiments. KH, W-YS, and H-HH analyzed the data. A-CC, F-CC, C-PC, and H-YH contributed materials/analysis tools. KH and H-HH wrote the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00067/full#supplementary-material

REFERENCES

1. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153cases. *J Neurol Neurosurg Psychiatry* (1990) 53:834–43. doi: 10.1136/jnnp.53.10.834
2. Velasco R, Al-Hussayni S, Bermejo PE. Sexual intercourse as a trigger of transient global amnesia. *Rev Neurol.* (2008) 47:301–3.
3. Quinette P, Guillery-Girard B, Dayan J, de la Sayette V, Marquis S, Viader F, et al. What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases. *Brain* (2006) 129:1640–58. doi: 10.1093/brain/awl105
4. Lewis SL. A etiology of transient global amnesia. *Lancet* (1998) 352:397–9. doi: 10.1016/S0140-6736(98)01442-1
5. Cejas C, Cisneros LF, Lagos R, Zuk C, Ameriso SF. Internal jugular vein valve incompetence is highly prevalent in transient global amnesia. *Stroke* (2010) 41:67–71. doi: 10.1161/STROKEAHA.109.566315
6. Modabbernia A, Taslimi S, Ashrafi M, Modabbernia MJ, Hu HH. Internal jugular vein reflux in patients with transient global amnesia: a meta-analysis of case-control studies. *Acta Neurol Belg.* (2012) 112:237–44. doi: 10.1007/s13760-012-0072-7
7. Baracchini C, Tonello S, Farina F, Viaro F, Atzori M, Ballotta E, et al. Jugular veins in transient global amnesia: innocent bystanders. *Stroke* (2012) 43:2289–92. doi: 10.1161/STROKEAHA.112.654087
8. Lochner P, Nedelmann M, Kaps M, Stolz E. Jugular valve incompetence in transient global amnesia. A problem revisited. *J Neuroimaging* (2014) 24:479–83. doi: 10.1111/jon.12042
9. Schreiber SJ, Doepp F, Klingebiel R, Valdueza JM. Internal jugular vein valve incompetence and intracranial venous anatomy in transient global amnesia. *J Neurol Neurosurg Psychiatry* (2005) 76:509–13. doi: 10.1136/jnnp.2004.043844
10. Epstein HM, Linde HW, Crampton AR, Ciric IS, Eckenhoff JE. The vertebral venous plexus as a major cerebral venous outflow tract. *Anesthesiology* (1970) 32:332–7. doi: 10.1097/00000542-197004000-00007
11. Guerci AD, Shi AY, Levin H, Tsitlik J, Weisfeldt ML, Chandra N. Transmission of intrathoracic pressure to the intracranial space during cardiopulmonary resuscitation in dogs. *Circ Res* (1985) 56:20–30. doi: 10.1161/01.RES.56.1.20
12. Gooding CA, Stimac GK. Jugular vein obstruction caused by turning of the head. *Am J Roentgenol.* (1984) 142:403–6. doi: 10.2214/ajr.142.2.403
13. Weiss KL, Wax MK, Haydon RC III, Kaufman HH, Hurst MK. Intracranial pressure changes during bilateral radical neck dissections. *Head Neck* (1993) 15:546–52. doi: 10.1002/hed.2880150612
14. Gisolf J, van Lieshout JJ, van Heusden K, Pott F, Stok WJ, Karemaker JM. Human cerebral venous outflow pathway depends on posture and central venous pressure. *J Physiol.* (2004) 560:317–27. doi: 10.1113/jphysiol.2004.070409
15. Chung CP, Hsu HY, Chao AC, Chang FC, Sheng WY, Hu HH. Detection of intracranial venous reflux in patients of transient global amnesia. *Neurology* (2006) 66:1873–7. doi: 10.1212/01.wnl.0000219620.69618.9d
16. Han K, Chao AC, Chang FC, Chung CP, Hsu HY, Sheng WY, et al. Obstruction of venous drainage linked to transient global amnesia. *PLoS ONE* (2015) 10:e0132893. doi: 10.1371/journal.pone.0132893
17. Chung CP, Hsu HY, Chao AC, Sheng WY, Hu HH. Jugular venous hemodynamic changes with aging. *Ultrasound Med Biol.* (2010) 36:1776–82. doi: 10.1016/j.ultrasmedbio.2010.07.006
18. Chi HY, Lin CS, Hsu MH, Chan PC, Hu HH. Chronic influences of obstructive sleep apnea on cerebral venous flow. *J Ultrasound Med.* (2015) 34:2043–8. doi: 10.7863/ultra.14.12065
19. Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound–recommendations for a protocol. *Int Angiol.* (2011) 30:571–97.
20. Chao AC, Han K, Chang FC, Hsu HY, Chung CP, Sheng WY, et al. Ultrasound diagnosis of transverse sinus hypoplasia using flow profiles of the internal jugular vein. *PLoS ONE* (2017) 12:e0181119. doi: 10.1371/journal.pone.0181119
21. Hsu HY, Chao AC, Chen YY, Yang FY, Chung CP, Sheng WY, et al. Reflux of jugular and retrobulbar venous flow in transient monocular blindness. *Ann Neurol.* (2008) 63:247–53. doi: 10.1002/ana.21299
22. Sethi SK, Utriainen DT, Daugherty AM, Feng W, Hewett JJ, Raz N, et al. Jugular venous flow abnormalities in multiple sclerosis patients compared to normal controls. *J Neuroimaging* (2015) 25:600–7. doi: 10.1111/jon.12183
23. Feng W, Utriainen D, Trifan G, Elias S, Sethi S, Hewett J, et al. Characteristics of flow through the internal jugular veins at cervical C2/C3 and C5/C6 levels for multiple sclerosis patients using MR phase contrast imaging. *Neurol Res.* (2012) 34:802–9. doi: 10.1179/1743132812Y.0000000079
24. Cheng CY, Chang FC, Chao AC, Chung CP, Hu HH. Internal jugular venous abnormalities in transient monocular blindness. *BMC Neurol.* (2013) 13:94. doi: 10.1186/1471-2377-13-94
25. Mchedlishvili GI. Vascular mechanisms pertaining to the intrinsic regulation of the cerebral circulation. *Circulation* (1964) 30:597–610. doi: 10.1161/01.CIR.30.4.597
26. Chao AC, Hsu HY, Chung CP, Chen YY, Yen MY, Wong WJ, et al. Altered retrobulbar hemodynamics in patients who have transient monocular blindness without carotid stenosis. *Stroke* (2007) 38:1377–9. doi: 10.1161/01.STR.0000260188.51784.6e
27. Sander D, Winbeck K, Etgen T, Knapp R, Klingelhofer J, Conrad B. Disturbance of venous flow patterns in patients with transient global amnesia. *Lancet* (2000) 356:1982–4. doi: 10.1016/S0140-6736(00)03313-4
28. Maalikjy Akkawi N, Agosti C, Anzola GP, Borroni B, Magoni M, Pezzini A, et al. Transient global amnesia: a clinical and sonographic study. *Eur Neurol.* (2003) 49:67–71. doi: 10.1159/000068501
29. Chung CP, Hsu HY, Chao AC, Sheng WY, Soong BW, Hu HH. Transient global amnesia: cerebral venous outflow impairment-insight from the abnormal flow patterns of the internal jugular vein. *Ultrasound Med Biol.* (2007) 33:1727–35. doi: 10.1016/j.ultrasmedbio.2007.05.018
30. Chao AC, Chung CP, Hsu HY, Hu HH. Analysis of internal jugular vein insufficiency-a comparison of two ultrasound methods. *Ultrasound Med Biol.* (2008) 34:689–90. doi: 10.1016/j.ultrasmedbio.2007.09.016
31. Traboulsee AL, Knox KB, Machan L, Zhao Y, Yee I, Rauscher A, et al. Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study. *Lancet* (2014) 383:138–45. doi: 10.1016/S0140-6736(13)61747-X

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A Neuroimaging Marker Based on Diffusion Tensor Imaging and Cognitive Impairment Due to Cerebral White Matter Lesions

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Background: The peak width of skeletonized mean diffusivity (PSMD) is a new, fully automated, robust imaging marker for cerebral small vessel disease (SVD), strongly associated with processing speed. However, it has never been applied to cerebral white matter lesions (WMLs). Our study aimed to investigate the correlation between PSMD and cognition, particularly in the executive function of patients with WMLs.

Methods: A total of 111 WML patients and 50 healthy controls (HCs) were enrolled, and their demographic information and cardiovascular disease risk factors were recorded. Subjects were divided into three groups: WMLs with normal cognition (WMLs-NC), WMLs with vascular cognitive impairment (WMLs-VCI), and HCs. They underwent conventional head magnetic resonance imaging and diffusion tensor imaging (DTI), followed by neuropsychological and psychological examinations, including the Montreal Cognitive Assessment (MoCA), and the executive function tests. We compared executive function and PSMD among the three groups and analyzed the correlation between PSMD and cognitive function in all subjects.

Results: There were no significant differences in demographic characteristics (age, sex, education level, and cardiovascular disease risk factors) among the three groups ($P > 0.05$), but there were significant differences in global cognition ($P < 0.0001$), executive function ($P < 0.0001$), and PSMD ($P < 0.0001$). The average PSMD value ($\times 10^{-4}$ mm^2/s) was 2.40 ± 0.23, 2.68 ± 0.30, and 4.51 ± 0.39 in the HC, WMLs-NC, and WMLs-VCI groups, respectively. There was no correlation between PSMD and cognition in the HC group, but PSMD was significantly correlated with MoCA scores ($r = -0.3785$, $P < 0.0001$) and executive function ($r = -0.4744$, $P < 0.0001$) in the WMLs-NC group and in the WMLs-VCI group ($r = -0.4448$, $P < 0.0001$ and $r = -0.6279$, $P < 0.0001$, respectively).

Conclusions: WML patients have higher PSMD and worse cognitive performance than HCs, and PSMD is strongly associated with global cognition and executive functions in WML patients. This result provides new insights into the pathophysiology of cognitive impairment in WML patients. PSMD could be a surrogate marker for disease progression and could thus be used in therapeutic trials involving WML patients.

Keywords: white matter lesions, vascular cognitive impairment, magnetic resonance imaging, diffusion tensor imaging, white matter structural integrity

INTRODUCTION

On computed tomography (CT), cerebral white matter lesions (WMLs) appear as hypodense bilateral and symmetrical areas in the WM of the periventricular region and centrum semiovale (1) and are indicators of cerebral small vessel disease (SVD). The Leukoaraiosis And Disability (LADIS) study confirmed a significant impairment of cognitive function in WML patients (2–4). WMLs are closely correlated to cognitive impairments in attention, executive function, and information processing speed (5). However, some patients may have severe cognitive dysfunction in the absence of widespread WMLs on magnetic resonance imaging (MRI). One of the factors may be the loss of microstructure integrity in the largest part of white matter, which can be visualized with conventional MRI, but can be investigated with DTI.

DTI is a sensitive technique for evaluating disease progression, allowing the quantification of microstructural tissue changes (6). The typical diffusion change pattern in WMLs consists of a decrease in fractional anisotropy (FA) and an increase in mean diffusivity (MD). However, the reliability in multicenter and long-term studies seems questionable. In addition, there are some limitations to the wide application of DTI measures due to the large amount of data postprocessing and the subjective operation errors in methods based on brain regions of interest.

Recently, Baykara et al. (7) proposed the assessment of SVD through DTI parameters which use a WM skeleton to measure the peak width of mean diffusivity in the brain. The new imaging marker was called peak width of skeletonized mean diffusivity (PSMD). Calculations of this marker appear to be robust and promising for studies of large populations. The derived measures were strongly correlated with processing speed and performed better than other neuroimaging markers for SVD, such as WM hyperintensities (WMHs) and the numbers and volumes of lacunes. The method eliminated cerebrospinal fluid contamination and increased the sensitivity in capturing SVD-related changes. A longitudinal analysis revealed the smallest sample size estimate for PSMD when compared with whole brain mean diffusivity peak height, normalized WMH volume, brain parenchymal fraction, processing speed score, or normalized lacune volume. PSMD may thus have a great practical value for clinical research and applications. However, no study has assessed the relationship between PSMD and cognitive function in patients with WMLs, yet.

In the present study, we aimed to examine the relationship between whole WM microstructural integrity, as assessed by PSMD, and cognitive function, in patients with WMLs. We hypothesized that WML patients would show poorer cognitive performance and a higher PSMD than HCs. Further, we aimed to assess the correlation between this new DTI marker and cognition, particularly executive function, in patients with WMLs.

MATERIALS AND METHODS

Subjects

WML patients were recruited from the neurology clinic of the Beijing Tiantan Hospital, Capital Medical University, China, between January 2014 to March 2017. WML was diagnosed independently and unanimously by two radiologists, who visually evaluated the fluid-attenuated inversion recovery (FLAIR) MR images without knowledge of the participants' clinical profiles. The inclusion criteria for WML patients were as follows: (a) age 50–85 years and (b) presence of WMHs on MRI scans, according to a revised version of the Fazekas scale (8). The exclusion criteria were as follows: (a) cardiac or renal failure, cancer, or other severe systemic diseases; (b) unrelated neurological diseases such as epilepsy, traumatic brain injury, or multiple sclerosis; (c) chronic cerebral infarction or other lesions; (d) leukoencephalopathy of non-vascular origin; (e) dementia of non-vascular origin; (f) psychiatric diseases or drug addiction; (g) consciousness disruption or aphasia; or (h) inability or refusal to undergo brain MRI. Initially, 113 WML patients were enrolled. In addition, 48 age-, sex-, and education level-matched normal volunteers were recruited as control subjects. Their age ranged between 50 and 85 years, and their MRI results were normal. The exclusion criteria for the healthy controls were the same as those for the WML patients.

All subjects were administered the Beijing version of the MoCA (9) and the Clinical Dementia Rating (CDR) scale under the supervision of a physician. Based on the results of these cognitive tests, the subjects were divided into three groups: (a) WML patients with normal cognition (WMLs-NC), defined as MoCA $\geq$ 26 and CDR = 0; (b) WML patients with vascular cognitive impairment (WMLs-VCI), defined as MoCA $<$ 26 and CDR $>$ 0; and (c) healthy controls (HC), defined as MoCA $\geq$ 26 and CDR = 0.

This study was approved by the Ethics Committee of the Beijing Tian Tan Hospital. All patients or their legal representatives provided written informed consent.

MRI Scanning Protocol

MRI scans of all participants were performed using a 3.0T Signa scanner (Magnetom Trio Tim, Siemens, Germany). The general MRI protocol included the following sequences: T1-weighted 3-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (TR/TE/TI 2300/3.28/1200 ms; flip angle 9°; voxel size 1.0 × 1.0 × 1.0 mm), a FLAIR sequence (TR/TE/TI 8000/94/2200 ms; voxel size 1.0 × 1.2 × 5.0 mm, interslice gap 1 mm), and DTI sequences (TR/TE 4900/93 ms; voxel size 2.5 × 2.5 × 2.5 mm; 4 unweighted scans, 30 directions with b-value 1,000 s/mm^2). Two radiologists blinded to the clinical information assessed the MRI data.

Processing of PSMD

DTI data were corrected for quick visual inspection to exclude large artifacts. The fully automated calculation of the new marker consists of two steps: Skeletonization of the DTI data and histogram analysis. All study samples were processed with the same pipeline. First, DTI data were skeletonized using the Tract-Based Spatial Statistics procedure included in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL) (10). The fractional anisotropy (FA) data of each subject were projected onto a skeleton derived from a standard space template. The mean diffusivity image was then projected onto the skeleton using FA-derived projection parameters. This process avoids contamination of the skeleton through partial volume effects of cerebrospinal fluid and fornix. The fully automated PSMD calculation pipeline is available at http://www.psmd-marker.com/ as a shell script including all processing steps (including pre-processing). No further human intervention is required during the processing pipeline.

Neuropsychological Testing

Neuropsychological assessment followed the LADIS protocol (11). In the test battery, the MoCA was considered to be a measure of global cognitive function. Executive function was assessed by computing compound measures from the Stroop color and word test (SCWT), trail-making test (TMT), symbol-digital replacement task (DST), and verbal fluency test (VFT).

Statistical Analyses

SPSS 23.0 was used for data processing, and SAS 9.4 for statistical analysis. To allow direct comparisons between the imaging marker and neuropsychological tests results, we generated z scores, representing the position of a score value within the score distribution. Executive functions = z scores of ((Stroop3-2) + (TMB-TMA) + symbol digit + verbal fluency)/4.The sign of each z-score was changed if necessary, to make positive scores correspond to better performance. The results of the MoCA were also transformed into z scores.

The numerical variables were reported as mean ± standard deviation (SD), and as median and interquartile ranges for parameters with skewed distributions. Normally distributed continuous variables were compared by one-way analysis of variance(ANOVA), and the Kruskal-Wallis test was used to compare non-normally distributed variables. A chi squared test was used to compare categorical variables. Multivariate regression analysis was used to assess the relative contribution of PSMD measures to performance in different cognitive domains. Regression analysis was performed with two levels of adjustment for covariates: Model 1 adjusted for age, sex, and level of education; model 2 extended model 1 by the addition of hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking status, drinking, and BMI. Furthermore, using Pearson correlation analysis, we examined the association between PSMD value and cognitive functions. *P*-values <0.05 were considered statistically significant.

RESULTS

A total of 163 subjects were enrolled in this study. Among them, there were 35 and 78 patients in the WMLs-NC and WMLs-VCI groups, respectively, and 48 healthy controls. The baseline characteristics of all subjects are listed in **Table 1**. There were no statistically significant differences in age, sex, years of education, or incidence of cerebral vessel risk factors in terms of hypertension, hyperlipidemia, coronary heart disease, smoking, drinking, and BMI among the three groups ($P < 0.05$).

As shown in **Table 2**, there were significant differences in cognitive status among the three groups, as measured by the MoCA z score ($P < 0.0001$), and in executive functions ($P < 0.0001$). There were significant differences in PSMD among the three groups ($P < 0.0001$). The mean PSMD values were 2.40 ± 0.23 × 10^{-4} mm^2/s, 2.68 ± 0.30 × 10^{-4} mm^2/s, and 4.51 ± 0.39 × 10^{-4} mm^2/s in the healthy controls, WMLs-NC, and WMLs-VCI, respectively.

As seen in **Table 3**, when assessing the relationship between PSMD and global cognitive function, no significant associations were seen with test results in the HC or WMLs-NC groups after correction for age, sex, and education level (model 1) or after adjustment for hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking status, drinking, and BMI (model 2). However, the association with global cognitive function in the WMLs-VCI group was significant in the fully adjusted model (ß=-0.513; standard error [SE] = 0.091; $P < 0.001$). When assessing the relationship between PSMD and executive function, the association remained significant in both model 1 and model 2. In the latter model the coefficients were: HCs: ß = −2.155; SE = 0.714; $P = 0.005$; WMLs-NC: ß = −1.629; SE = 0.741; $P = 0.039$; and WMLs-VCI: ß = −0.372; SE = 0.107; $P < 0.001$.

As seen in **Table 4**, there were no significant associations between PSMD and cognitive performance in the healthy control samples ($P = 0.56$–0.88). Negative correlation was found between PSMD and global and executive function in the WMLs-CN samples, with correlation coefficients −0.3785 and −0.4744, respectively, and also in the WMLs-VCI samples, with correlation coefficients −0.4448 and −0.6279, respectively.

The correlation analysis between cognitive performance and PSMD in healthy controls and WML patients is shown in **Figure 1**. Linear regression showed no significant association between PSMD and MoCA scores (**Figure 1A**) or executive function (**Figure 1B**) in the healthy controls. The WMLs-CN group showed associations between PSMD and MoCA

TABLE 1 | Characteristics of the study population.

Characteristics	HC ($n = 48$)	WMLs-CN ($n = 35$)	WMLs-VCI ($n = 78$)	*P*-value
DEMOGRAPHICS				
Male	24 (50.00)	18 (51.43)	42 (52.50)	0.9631[a]
Age, y	56.83 ± 4.72	61.94 ± 8.50	63.03 ± 9.37	0.0031[b]
Years of education	12.38 ± 3.19	11.54 ± 3.06	11.48 ± 3.05	0.3175 [b]
VASCULAR RISK FACTORS				
Hypertension	21 (43.75)	18 (51.43)	47 (58.97)	0.0902[a]
Diabetes	8 (16.67)	7 (20.00)	18 (23.08)	0.3337[a]
Hyperlipidemia	16 (33.33)	12 (34.29)	30 (38.46)	0.1270[a]
Coronary heart disease	5 (10.42)	5 (14.29)	14 (17.95)	0.2300[a]
Smoking	19 (39.58)	10 (28.57)	19 (24.36)	0.2189[a]
Drinking	13 (27.08)	8 (22.86)	20 (25.64)	0.9498[a]
BMI	24.29 ± 2.24	24.25 ± 2.08	24.77 ± 2.33	0.3125[b]

Categorical variables are expressed as number (percentage), and continuous ones as mean ± SD. HC, healthy controls; WMLs-CN, cognitively normal white matter lesion patients; WMLs-VCI, white matter lesion patients with vascular cognitive impairment; BMI, body mass index. [a]The P-value was obtained by chi squared (χ^2) test. [b]The P-value was obtained by ANOVA.

TABLE 2 | Cognitive function measures and the peak width of skeletonized mean diffusivity in the study population.

Characteristics	HC ($n = 48$)	WMLs-CN ($n = 35$)	WMLs-VCI ($n = 78$)	*P*-value
GLOBAL COGNITIVE FUNCTION				
MoCA	27.81 ± 1.53	26.74 ± 1.09	20.76 ± 3.46	<0.0001
z score	0.00 ± 2.43	0.00 ± 1.00	0.01 ± 1.01	<0.0001
EXECUTIVE FUNCTIONS				
SCWT- B (s)	43.60 ± 1.01	44.37 ± 2.50	68.04 ± 7.58	<0.0001
SCWT- C (s)	63.30 ± 4.20	64.15 ± 2.72	93.13 ± 3.40	<0.0001
SCWT (C-B) (s)	19.40 ± 4.14	19.78 ± 3.07	25.09 ± 4.39	<0.0001
TMT-A (s)	30.77 ± 0.87	32.05 ± 1.77	42.54 ± 1.92	<0.0001
TMT-B (s)	80.49 ± 0.74	81.17 ± 1.47	89.86 ± 5.90	<0.0001
TMT (B–A) (s)	49.72 ± 0.96	49.12 ± 1.22	47.32 ± 4.27	0.0347
DST	47.90 ± 2.98	45.51 ± 2.29	33.94 ± 4.92	<0.0001
VFT	11.07 ± 0.84	10.83 ± 0.98	7.81 ± 1.28	<0.0001
z scores	0.00 ± 2.04	−0.53 ± 3.42	−0.66 ± 1.57	< 0.0001
PSMD ($10^{-4}mm^2/s$)	2.40 ± 0.23	2.68 ± 0.30	4.51 ± 0.39	<0.0001

Variables and z scores are shown as mean ± SD. HC, healthy controls; WMLs-CN, cognitively normal white matter lesion patients; WMLs-VCI, white matter lesion patients with vascular cognitive impairment; MoCA, Montreal Cognitive Assessment; SCWT, Stroop color and word test; TMT, trail-making test; DST, symbol-digital replacement task, VFT, verbal fluency test; PSMD, peak width of skeletonized mean diffusivity.

scores (**Figure 1C**) as well as executive function (**Figure 1D**). The WMLs-VCI group showed strong associations between PSMD and MoCA scores (**Figure 1E**) as well as executive function (**Figure 1F**).

DISCUSSION

In this study, we analyzed PSMD and cognitive function in HC subjects and WMLs patients, with or without cognitive impairment. We also investigated the relationship between PSMD and cognitive functions.

There were no significant differences in age, sex, years of education, and vascular risk factors between the WML patients and the healthy controls, largely eliminating the influence of possible confounders on cognitive assessment. Extensive neuropsychological assessment was performed by two investigators, and multivariate regression analysis included adjustment for potential confounders. Global cognitive function was measured using MoCA scores, which have been proposed as a screening tool for vascular cognitive impairment (12). Pasi et al. demonstrated that DTI-measured WM microstructural damage is more related to MoCA results than to mini mental state examination performances in SVD patients (13), indicating that MoCA is suitable for the cognitive screening of patients with small vessel disease. Yuan et al. demonstrated that the cognitive domains affected in patients with WMLs were attention, executive function, and information processing speed (2012).

TABLE 3 | Associations between the peak width of skeletonized mean diffusivity and cognitive performance.

Cognitive function	HC	WMLs-CN	WMLs-VCI
GLOBAL COGNITIVE FUNCTION (Z SCORES)			
Model 1			
ß	−0.598	−1.505	−0.558
SE	1.484	0.953	0.088
P	0.689	0.125	< 0.001
Model 2			
ß	−0.272	−1.549	−0.513
SE	1.690	1.149	0.091
P	0.873	0.191	< 0.001
EXECUTIVE FUNCTIONS (Z SCORES)			
Model 1			
ß	−1.838	−1.583	−0.382
SE	0.657	0.555	0.100
P	0.008	0.008	< 0.001
Model 2			
ß	−2.155	−1.629	−0.372
SE	0.714	0.741	0.107
P	0.005	0.039	0.001

Model 1: adjusted for age, sex, and level of education. Model 2: same as model 1, additionally adjusted for hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking status, drinking and BMI. SE, standard error.

TABLE 4 | Correlation between cognitive function and the peak width of skeletonized mean diffusivity.

Cognitive function	HC	WMLs-CN	WMLs-VCI
GLOBAL COGNITIVE FUNCTION (Z SCORES)			
r	0.0355	−0.3785	−0.4448
P	0.88	<0.0001	<0.0001
EXECUTIVE FUNCTIONS (Z SCORES)			
r	−0.0979	−0.4744	−0.6279
P	0.56	<0.0001	<0.0001

HC, health controls; WMLs-CN, cognitively normal white matter lesion patients; WMLs-VCI, white matter lesion patients with vascular cognitive impairment. r, Pearson's correlation coefficient.

The loss of memory is not common in patients with cognitive impairment due to WMLs, which is one of the differences between vascular dementia and Alzheimer's disease (14).

In our study, executive function was assessed by computing compound measures from the SCWT, TMT, DST, and VFT, which examine the cognitive domain of psychomotor speed, fluency, concept shifting, and attention. We found that the global cognitive and executive functions of WML patients were significantly worse than those of healthy subjects. Further, WMLs-NC patients had better executive function performance than WMLs-VCI patients. These findings are consistent with those of other studies (15).

The characteristics of cognitive impairment in individuals with WMLs depend on the location, degree, and size of the lesions. Diffusion tensor tractography study showed that the location of WMLs was related to the damaged cognitive domain (2). As cognitive disturbances in subjects with cerebral small vessel disease are related to microstructural integrity of multiple WM fibers (within WMH and normal-appearing WM) connecting different cortical and subcortical regions, we examined the relation between the microstructural integrity of the whole WM and cognitive performance in subjects with WMLs. In addition, whole brain histogram analysis is particularly appropriate when quantifying total disease burden (16). In this study, we measured PSMD as an imaging marker to measure the microstructural integrity of the whole WM in HC subjects and WML patients. Our results showed that WML patients had higher PSMD values than control subjects. Moreover, we found that in WML patients the severity of cognitive impairment increased with PSMD.

DTI measures are more sensitive than conventional MRI markers in capturing changes associated with SVD. Histograms of MR parameter values measured in the whole brain are increasingly being used to characterize subtle disease that affects large parts of the brain. Studies have shown that histogram peak height measures were associated with cognitive function and can capture disease burden in SVD (17, 18). PSMD is a combination of DTI, skeletonization and histogram analysis of WM tracks, and is therefore superior in assessing the burden of disease (19).

In this study, we examined the relationship between PSMD and cognitive performance in the three groups. We found that there were no significant associations between PSMD and cognition performance in the healthy controls. However, in the WML group, PSMD was associated with executive dysfunction, a pattern that has been associated with SVD (20). The associations were also reflected in the MoCA scores, which give a global measure of cognitive function. Our study found a clear inverse relationship between PSMD and cognition: High PSMD values were associated with lower scores for cognitive functions, and especially for executive performance. As PSMD is a whole-brain measure computed from DTI scans, but not a local estimate of possible changes in the microstructure within the brain, subjects with the same WMH loads may show different cognitive performances. We demonstrated that PSMD was highly correlated with executive function in WML patients. Moreover, the correlation was more significant in WML patients with cognitive impairment. This imaging marker is therefore highly sensitive to vascular cognitive impairment and could therefore be used in addition to conventional MRI to investigate cognitive dysfunction.

A major strength of this study is that all subjects were assessed by multiple MRI sequences, including 3D T1, FLAIR, and 30-direction DTI acquisition. Therefore, accurate and comprehensive original image data were acquired. Another strength is the use of novel imaging techniques: Image data are processed by the online scanning software. All the processing steps are simple and fully automated, without any manual intervention. Furthermore, our study is a single-center study, with all subjects examined by only two investigators, using manual segmentation of the WML, without prior knowledge of the clinical data.

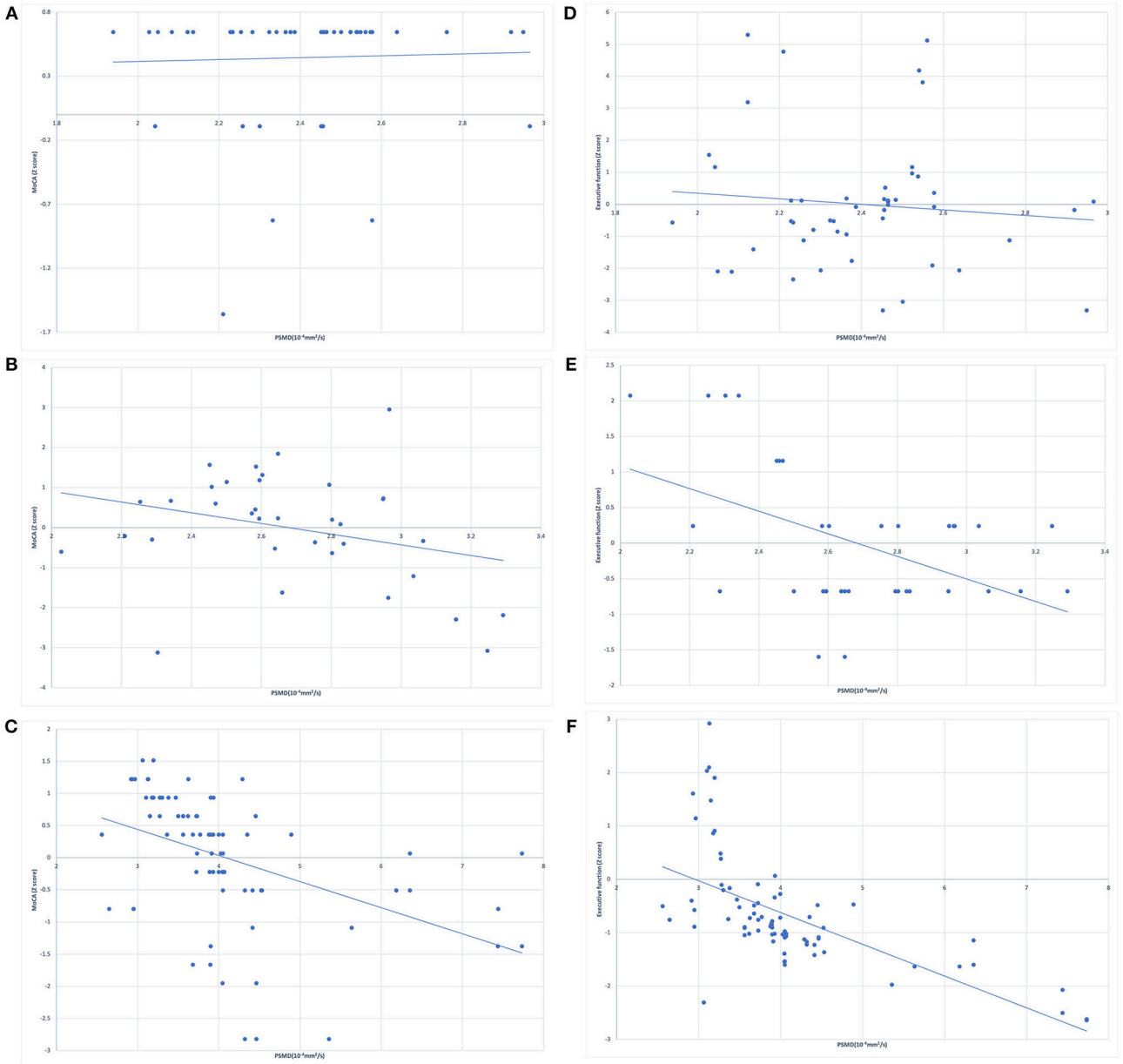

FIGURE 1 | Simple linear regression between peak width of skeletonized mean diffusivity (PSMD) and z scores of MoCA in **(A)** healthy controls, **(B)** cognitively normal WML patients, **(C)** WML patients with vascular cognitive impairment, and for the z scores of executive function in **(D)** healthy controls, **(E)** cognitively normal WML patients, **(F)** the WML patients with vascular cognitive impairment.

Our study also had limitations. First, the study was hospital-based, and patients who did not meet the inclusion criteria were excluded. This may result in selection bias and influence the measurement of cognitive function in WML patients. Second, PSMD mostly reflects SVD-related alterations or primary neurodegenerative pathology, and the subjects should be grouped based on the degree of WM damage, but this could not be done in the present study. In future studies, it is desirable to combine the measurements of cognitive impairment and WMH load with PSMD, in order to elucidate the correlations between brain microstructural integrity and cognitive function associated with WMLs. Third, our study is cross-sectional, and the causal interpretation of the results is limited. Future studies with larger sample sizes may further clarify the interactions between cognitive impairment and brain microstructural characteristics.

To summarize, the present study comprehensively investigated the characteristics of PSMD in WML patients and compared them with those of HC subjects. We demonstrated that PSMD is significantly correlated with

cognitive impairment in WML patients. Our findings suggest that microstructural integrity of the whole WM should be considered when investigating the relationship between WMLs and cognitive function. PSMD could therefore serve as an addition to a conventional MRI in order to investigate cognitive dysfunction. This result provides new insights into the pathophysiology of cognitive impairment in WML patients. PSMD could be a surrogate marker for disease progression and could thus be used in therapeutic trials involving WML patients.

AUTHOR CONTRIBUTIONS

NW and YZ designed the study and drafted the manuscript. YD, WJ, QS, and JW performed the measurements and collected the data. HC performed the brain MRI data acquisition. LY participated in the brain imaging data analysis. YP and HY performed the statistical analysis. YZ and YW participated in the critical discussion of the manuscript.

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REFERENCES

1. Hachinski VC, Potter P, Merskey H, Leukoaraiosis. *Arch Neurol.* (1987) 44:21–3. doi: 10.1001/archneur.1987.00520130013009
2. Defrancesco M, Marksteiner J, Deisenhammer E, Kemmler G, Djurdjevic T, Schocke M. Impact of white matter lesions and cognitive deficits on conversion from mild cognitive impairment to alzheimer's disease. *J Alzheimers Dis Jad.* (2013) 34:665–72. doi: 10.3233/JAD-122095
3. Tully PJ, Qchiqach S, Pereira E, Debette S, Mazoyer B, Tzourio C. Development and validation of a priori risk model for extensive white matter lesions in people age 65 years or older: the Dijon MRI study. *BMJ Open.* (2017) 7:e018328. doi: 10.1136/bmjopen-2017-018328
4. Li R, Lai Y, Zhang Y, Yao L, Wu X. Classification of cognitive level of patients with leukoaraiosis on the basis of linear and non-linear functional connectivity. *Front. Neurol.* (2017) 8:2. doi: 10.3389/fneur.2017.00002
5. Yuan JL, Wang SK, Peng P, Guo XJ, Gu H, Li SJ, et al. Characteristics of cognitive impairment in patients with leukoaraiosis. *Zhonghua Yi Xue Za Zhi* (2012) 92:147–51. doi: 10.3760/cma.j.issn.0376-2491.2012.03.002
6. Croall ID, Lohner V, Moynihan B, Khan U, Hassan A, O'Brien JT, et al. Using dti to assess white matter microstructure in cerebral small vessel disease (svd) in multicentre studies. *Clin Sci.* (2017) 131:1361–73. doi: 10.1042/CS20170146
7. Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, et al. A novel imaging marker for small vessel disease based on skeletonization of white matter tracts and diffusion histograms. *Ann Neurol.* (2016) 80:581–92. doi: 10.1002/ana.24758
8. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *Ajr Am. J. Roentgenol.* (1987) 149:351–6. doi: 10.2214/ajr.149.2.351
9. Wen HB, Zhang ZX, Niu FS, Li L. The application of montreal cognitive assessment in urban Chinese residents of Beijing. *Zhonghua Nei Ke Za Zhi* (2008) 47:36–9. doi: 10.3321/j.issn:0578-1426.2008.01.012
10. Smith SM, Jenkinson M, Johansenberg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* (2006) 31:1487–505.doi: 10.1016/j.neuroimage.2006.02.024
11. Madureira S, Verdelho A, Moleiro C, Ferro JM, Erkinjuntti T, Jokinen H, et al. Neuropsychological predictors of dementia in a three-year follow-up period: data from the ladis study. *Dement Geriatr Cogn Disord.* (2010) 29:325–34. doi: 10.1159/000278333
12. Pendlebury ST, Cuthbertson FC, Welch SJV, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by mini-mental state examination versus the montreal cognitive assessment in patients with transient ischemic attack and stroke a population-based study. *Stroke* (2010) 41"1290–3. doi: 10.1161/STROKEAHA.110.579888
13. Pasi M, van Uden IW, Tuladhar AM, de Leeuw FE, Pantoni L. White matter microstructural damage on diffusion tensor imaging in cerebral small vessel disease: clinical consequences. *Stroke* (2016) 47:1679–84. doi: 10.1161/STROKEAHA.115.012065
14. Jang YK, Na YJ, Kim YJ, Cheo YS, Lee KH, Kim ST, et al. Early- versus late-onset subcortical vascular cognitive impairment. *Alzheimers Dement.* (2015) 11:P245. doi: 10.1016/j.jalz.2015.07.299
15. Dijk EJV, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences. *Stroke* (2008) 39:2712–9. doi: 10.1161/STROKEAHA.107.513176
16. Tofts PS, Davies GR, Dehmeshki J. Histograms: measuring subtle diffuse disease. *Quant MRI Brain* (2003) 2003:581–610. doi: 10.1002/0470869526.ch18
17. Tuladhar AM, van Norden AG, de Laat KF, Zwiers MP, van Dijk EJ, Norris DG, et al. White matter integrity in small vessel disease is related to cognition. *Neuroimage Clin.* (2015) 7:518–24.doi: 10.1016/j.nicl.2015.02.003
18. Jokinen H, Schmidt R, Ropele S, Fazekas F, Gouw AA, Barkhof F, et al. Diffusion changes predict cognitive and functional outcome: the ladis study. *Ann Neurol.* (2013) 73:576–83. doi: 10.1002/ana.23802
19. de Groot M, Verhaaren BF, de Boer R, Klein S, Hofman A, van der Lugt A, et al. (2013). Changes in normal-appearing white matter precede development of white matter lesions. *Stroke* 44:1037–42. doi: 10.1161/STROKEAHA.112.680223.
20. Price CC, Jefferson AL, Merino JG, Heilman KM, Libon DJ. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. *Neurology* (2005) 65:376–82. doi: 10.1212/01.wnl.0000168877.06011.15

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REVIEW
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Effect of Inflammation on the Process of Stroke Rehabilitation and Poststroke Depression

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A considerable body of evidence has shown that inflammation plays an important role in the process of stroke rehabilitation and development of poststroke depression (PSD). However, the specific molecular and cellular mechanisms involved remain unclear. In this review, we summarize how neuroinflammation affects stroke rehabilitation and PSD. We mainly focus on the immune/inflammatory response, involving astrocytes, microglia, monocyte-derived macrophages, cytokines (tumor necrosis factor alpha, interleukin 1), and microRNAs (microRNA-124, microRNA 133b). This review provides new insights into the effect of inflammation on the process of stroke rehabilitation and PSD and potentially offer new therapeutic targets of stroke and PSD.

Keywords: stroke, immune/inflammation, rehabilitation, poststroke depression, pharmacotherapy

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INTRODUCTION

Stroke is defined as permanent tissue damage caused by a sudden loss of brain blood supply as a result of occlusion or a hemorrhage. Stroke includes two main types, ischemic stroke and intracerebral hemorrhage (ICH). Approximately 85% of strokes belong to the ischemic type and 12% are ICHs (3% are subarachnoid hemorrhage). Neural plasticity can be affected by different risk factors of stroke, medical management, and anti-inflammatory interventions during the process of stroke rehabilitation.

The immune/inflammatory response can be triggered by several factors, such as ischemia or hemorrhage. Microglia, astrocytes, and endotheliocytes are involved in immune/inflammatory activation induced by ischemic stroke. These cells can communicate with each other by proinflammatory and anti-inflammatory factors, such as cytokines and adhesion molecules. Inflammatory cells, such as neutrophils and macrophages, are activated, reach the ischemic area, and contribute to the inflammatory response (1). These immune responses following the initial ischemic insult can be long lasting and subsequently modulate synaptic plasticity alterations during the process of stroke rehabilitation (2). In ICH, ambient microglia and astrocytes can also exert modulatory effects during ICH rehabilitation (3).

Poststroke depression (PSD), a critical psychiatric complication of stroke, involves several major symptoms including sleep and appetite disturbance, psychomotor agitation, and fatigue (4). As the inflammatory response may modulate neuroplasticity during stroke and altered neuroplasticity may be associated with the onset of PSD, the stroke-induced immune response in the brain can also affect the PSD process. It was found that several inflammatory markers, pro-inflammatory cytokines, and the pro-inflammatory/anti-inflammatory ratios were increased and the complementary expression was reduced in the PSD process (5).

In this review, we describe the two different types of stroke (ischemic stroke and ICH) and respectively summarize the effects of inflammation on the process of stroke rehabilitation. We then describe PSD and summarize the effects of inflammation on PSD. Finally, we discuss the potential efficacy of using anti-inflammatory medication for stroke rehabilitation and PSD prevention.

STROKE

Stroke refers to several conditions caused by occlusion or a hemorrhage of the brain blood vessels. Stroke is a worldwide neurological disease with few effective treatments and preventative measures (6). Neuroinflammation involves damage-associated molecular patterns, instead of microbial pathogens (7). Importantly, neuroinflammation plays a key role in several neurological diseases such as a hemorrhage and ischemia (8). There are certain complicated connections between immune/inflammatory processes and stroke rehabilitation.

Ischemic Stroke

Ischemic stroke, the most common type of brain ischemic injury in humans, is the leading cause of mortality and long-term disability (9). Ischemic stroke is mainly caused by an ischemic core induced by brain artery occlusion, surrounded neuronal loss, and glial scarring (10). In ischemic stroke, the most relevant inflammatory-cellular component is the microglial and astrocytic responses, chemokines and cytokines, and infiltrating peripheral blood cells (9).

There are two types of models in ischemic stroke: the middle cerebral artery (MCA) occlusion model and the photothrombotic MCA stroke model. The photothrombotic MCA stroke model is created by a laser beam irradiating a photosensitizing dye in the MCA. The latter can slowly substitute the former because of the ease of application and reproducibility of the model. However, the latter delays microglial and astrocytic invasion of the ischemic core but elevates the levels of inflammatory cytokines or chemokines and their infiltration from the circulatory system (11). In an experimental striatal stroke model induced by endothelin-1, focal ischemic neuronal loss appeared, with intense microglia activation in 3–14 postlesion days (maximum at 7 postlesion days). Astrocytosis was also maximal at 7 postlesion days (12). In ischemic brains, local inflammation involves astrocytes, activated resident microglia, and infiltrating monocytes or monocyte-derived macrophages (MDMs), with upregulated expression of proinflammatory factors [interleukin (IL)-6, nitric oxide synthase-2, IL-1β, tumor necrosis factor alpha (TNF-α)] and anti-inflammatory factors (CCL22,Ym1, CXCL13,TGFβ,CD163) (13).

Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; ICH, intracerebral hemorrhage; IL, interleukin; MCA, middle cerebral artery; MDM, monocyte-derived macrophage; MiRNA, microRNA; MSC, multipotent mesenchymal stromal cell; PSD, poststroke depression; TNF-a, tumor necrosis factor alpha.

Astrocytes

Astrocytes are the largest specialized cells in the central nervous system (CNS). Astrocytes play a significant role in neural development and neuroprotection via supporting synaptic connections, ionic homeostasis, and glutamate clearance. It is considered that astrocytes are involved in the local inflammatory response via modulating proinflammatory and anti-inflammatory cytokines (14–16). It was found that astrocytes can enhance neuronal viability through the uptake of glutamate and the release of neurotrophins; astrocytes also compromise neuronal viability by producing inflammatory cytokines or releasing glutamate, and contribute to angiogenesis and neuronal plasticity several days after stroke (17).

The ring- or crescent- shaped "peri-infarct" form is mainly localized around the infarct region and significantly grows after stroke. Microglia and macrophages are mainly localized in the lesion infarct core, rather than in the infarct region (18). One of the pathological alterations of the infarct region is reactive astrogliosis and the formation of glial scarring. Astrocytes in the "peri-infarct" region respond adaptively to stroke, which is known as reactive astrogliosis. Astrocytes can proliferate and be centrally involved in glial scar formation in the "peri-infarct" region, which separates the damaged infarct tissue from the normal tissue. The intertwined connection of astrocytes in and around the infarct region forms the mature glial scar and impedes neuronal rehabilitation after stroke. Early dysfunction and subsequent function recovery after stroke, through the destruction and remodeling of intertwined connection around the infarct region, is associated with neuroinflammation (18, 19).

Reactive astrogliosis and glial scar formation after stroke is considerable during the rehabilitation process, with a change in gene expression, morphology, and proliferation of reactive astrocytes (14, 16). In addition, the main characteristic of astrogliosis is hypertrophic astrocytes with a high expression of proinflammatory cytokines, neurotrophic factors, and neuronal and proliferation markers (8). As major components of the neuroinflammatory process after ischemic stroke, reactive astrocytes have both positive and negative effects on pathological progression (18). Reactive astrogliosis actively protects the neurons in the CNS and regulates their homeostasis to limit the size of the infarct region in the early stage of ischemic stroke. However, if not resolved in time, reactive astrogliosis can also inhibit plasticity and regeneration in the CNS (20). At the early stage of ischemia, perivascular astrocytes can release excess cytokines, which subsequently activate metalloproteases and disrupt the blood-brain barrier (BBB) and vasogenic edema. At the later stage of ischemia, perivascular astrocytes can uptake excess extracellular glutamate, contributing to the regeneration of the BBB (21).

After ischemic stroke, maladapted morphological and functional plasticity of astrocytes occurs in the neurovascular unit, which may result in disorders of the neurovascular unit and disrupt the BBB and astrocyte membrane homeostasis in the CNS during stroke rehabilitation (22). In response to oxidative stress, a typical feature of reactive astrocytes is the high expression of intermediate filament proteins (nanofilament proteins) and remodeling of the intermediate filament system in astrocytes,

with a high expression of many characteristic morphological hallmarks. A characteristic morphological hallmark of reactive astrocytes is the presence of hypertrophic astrocytes with increased production of nanofilament proteins, glial fibrillary acidic protein, vimentin, nestin, and synemin (20, 23). Another typical feature of reactive astrocytes is the expression and remodeling of ion channels, which modulate the function of astrocytes by altering the transporters and neurotransmitter receptors. Consequently, alterations in neuronal excitability might lead to secondary neurological disease, such as ischemia and epilepsy during stroke rehabilitation (10). Although astrocytes are not electrically-excitable cells, they can mediate neuron-glia bidirectional interactions through modulating the Ca^{2+} signaling of synapses. It was reported that astrocytes can enhance Ca^{2+} excitability and modulate synaptic function and plasticity during stroke rehabilitation (16). G protein-coupled calcium-sensing receptor expression is also a feature of reactive astrocytes with astrocyte hypertrophy and high expression of glial fibrillary acid protein in ischemic stroke (24).

Microglia

Microglia are resident immune cells involved in physiological and pathological processes in the CNS. Physiologically, microglia are long-living resident immune cells that support a stable chemical and physical microenvironment in the CNS. Pathologically, microglia are dynamic immune cells that respond to nervous damage, repair, and regeneration in the CNS. Microglia can be activated and recruited by the injury signals or stimulation and can elicit a quick response to infection or injury by releasing proinflammatory or anti-inflammatory cytokines. The BBB in the CNS consists of microglia, astrocytes, endothelial cells, and pericytes and selectively separates the sensitive brain parenchyma from the circulatory system. Microglia bidirectionally survey the influx of blood-borne components into the CNS and may stimulate the BBB to open, to extravasate leukocytes resulting in angiogenesis (15, 25, 26).

Another pathological change in ischemic stroke is the activation of resident microglia and infiltrating monocytes/macrophages (27). Activated microglia have both positive and negative effects on the pathological progression of ischemia. Early activated microglia contribute to ischemic injury by releasing TNF and IL-1 and can engulf the cellular debris and invading pathogens. Activated microglia also contribute to resolving the inflammatory response by producing IL-10 and TGFβ and inhibiting the ischemia-induced astrocytic response as a neuroprotective effect during stroke rehabilitation (21, 28, 29). Activated microglia participate in attenuating neuronal apoptosis and enhancing neurogenesis after ischemic stroke (30) and they can contribute to nervous reconstruction and repair during stroke rehabilitation together with reactive astrocytes (4). Nevertheless, chronically activated microglia may cause neuronal death by releasing excessive inflammatory mediators (28). Activated microglia appear after ischemia, and microglial survival depends on signaling through the colony-stimulating factor I receptor during stroke rehabilitation. Therefore, depletion of microglia via colony-stimulating factor I receptor inhibitor PLX3397 exacerbates ischemic infarction and augments the production of inflammatory mediators, leukocyte infiltration, and cell death after ischemic stroke (29).

For instance, P2X4 receptors (P2X4Rs) on microglia modulate the inflammatory response to ischemia. In acute ischemia, P2X4R activation leads to microglial activation and proliferation to exacerbate the inflammatory response of ischemia. In chronic ischemia, stimulation of P2X4Rs on microglia leads to release of brain-derived neurotrophic factor to support synaptic plasticity and strengthen behavioral rehabilitation. Therefore, knockout of P2X4R on microglia protects against stroke at the early stage of ischemia but exacerbates behavioral recovery at the late stage of ischemia (27).

Modulating microglial overreaction and microglia-mediated neuroinflammation is considered a therapeutic strategy against ischemic damage. For instance, triggering receptor expressed on myeloid cells 2 (TREM2) was mostly expressed in microglia, but not in neurons, astrocytes, or oligodendrocytes in ischemic stroke. TREM2 responds to inflammation after ischemia to protect against cerebral ischemia/reperfusion. Targeting TREM2 to inhibit the inflammatory response in ischemic stroke may be a new therapeutic option (31). Electroacupuncture is also reported as a safe and effective therapy to attenuate the overactivation of Iba-1 and ED1 positive microglia and the expression of TNF-α, IL-1β, and IL-6 and leads to reduced neurological and sensorimotor impairment in ischemia (32).

MDMs

MDMs recruited to the injured area at the early stage of ischemia contribute to behavioral rehabilitation by resolving the inflammatory response. The infiltrating monocytes compromise the neurogenesis from endogenous new striatal neurons from neural stem/progenitor cells. The depletion of circulating monocytes early after ischemic stroke most likely increases the short-term survival of the newly formed neoblasts to enhance neurogenesis, using the anti-CCR2 antibody MC21 (33). Incubation of exogenous peroxiredoxin with murine RAW264.7 macrophages leads to nuclear translocation of transcription factor κB p65 and production of proinflammatory mediators (NO, TNF-α, IL-6) (34). Transcription factor κB is also essential to the upregulation of pro-inflammatory genes, which participate in microglial activation and proliferation during stroke rehabilitation (35).

Two Phenotypes of Microglia and MDMs

Microglia and MDMs differentiate toward two phenotypes: the M1 phenotype is the classical one, pro-inflammatory, and detrimental, whereas the M2 phenotype is the alternative one, anti-inflammatory, and protective. The two phenotypes of microglia and MDMs suggest their dual roles. The M1 phenotype, which is activated by toll-like receptors or IF-r, promotes injury, whereas the M2 macrophage or N2 neutrophil phenotype, which is activated by regulatory mediators, such as ILs 4, 10, 13; or TGFβ, prompts tissue remodeling and repair (dualistic role) (21).

These mononuclear phagocytes including microglia and macrophages respond to ischemic stroke dynamically, from the M1 phenotype to the M2 phenotype. After stroke

onset, monocytes and microglia infiltrate into the infarct core, peaking 3 days after stroke. Before day 7, MDMs with the pro-inflammatory phenotype dominate, and at day 7, half of the infiltrating MDMs are found to be of the proinflammatory phenotype and the other half of the anti-inflammatory phenotype, but the anti-inflammatory phenotype dominates during the subsequent 2 weeks. Similarly, microglia are predominantly of the proinflammatory phenotype at days 3 and 7 after stroke (12, 36). Therefore, instead of broad suppression, there is a need of shifting the polarization of microglia/macrophages into the protective, anti-inflammatory M2 phenotype during stroke rehabilitation (36, 37). For example, ST2, a member of the IL family, and its ligand IL-33 play critical roles in neuroinflammatory responses after ischemic stroke. There is increased expression of ST2 in microglia during stroke rehabilitation, which enhances the expression of M2 polarization markers on microglia/macrophages and impairs the expression of M1 polarization markers. The absence of ST2 shifted the polarization of microglia/macrophages into a proinflammatory M1-like phenotype. There is also increased expression of IL-33 in astrocytes during stroke rehabilitation, and IL-33 and ST2 serve as immune regulatory brakes on the process of stroke rehabilitation (7).

Cytokines

Some cytokines and chemokines have been found to affect the inflammatory response to stroke in the process of stroke rehabilitation. Two important inflammatory mediators of the neuroinflammatory response during stroke rehabilitation are TNF-α and IL-1. We next describe how these two cytokines affect stroke rehabilitation.

TNF-α

A common proinflammatory cytokine is TNF-α, which is involved in every phase of the stroke rehabilitation process. When there are certain stimuli, such as ischemia or hemorrhage, TNF-α is synthesized and released by astrocytes, microglia, or neurons in response to the stimuli and is involved in many pathophysiological processes of ischemic stroke or ICH. TNF-α can activate microglia and astrocytes and have a modulatory effect on BBB permeability, and may also have several positive and negative effects on synaptic transmission and synaptic plasticity during stroke rehabilitation (1, 38).

Inhibition of TNF-α R1 signaling can reportedly preserve brain plasticity during stroke rehabilitation. Etanercept, which is a biologic TNF antagonist, can decrease microglial activation in experimental stroke models and has been used therapeutically in animal stroke models. It has been shown that intravenous administration of etanercept is not therapeutic during stroke rehabilitation because biologic TNF inhibitors can be reengineered for BBB penetration. However, intravenous IgG-TNFR fusion protein is reported to have a therapeutic effect on stroke rehabilitation by significantly reducing stroke volume and neural damage (1, 39, 40).

Interleukin-1

Another common inflammatory cytokine is IL-1, which affects both systemic and local inflammation and is also an important driver of central and peripheral immune responses to infection or injury. There is considerable experimental and clinical evidence that it is valuable to inhibit IL-1 by IL-1 receptor antagonism as an effective treatment in ischemic stroke. The IL-1 receptor antagonist appears to be a promising treatment target in stroke and is being studied for its therapeutic potential (41).

MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression post-transcriptionally by inhibiting the translation of select target genes. MiRNAs are involved in chronic microglial inflammation and lead to progression of neurological diseases such as Alzheimer's disease, amyotrophic lateral sclerosis and stroke (15). In astrocytes and microglia, miRNAs are critical regulators in the mitochondrial response to ischemic stroke. Thereby, MiRNA-targeted therapies have become a viable intervention to optimize mitochondrial function in astrocytes and microglia and improve clinical outcome after ischemic stroke (42).

MiRNA-124 and MiRNA 133b are reportedly involved in the inflammatory response in stroke rehabilitation. Their effects are discussed in detail below.

MiRNA-124

MiRNA-124 is the most common brain-specific MiRNA in the CNS and has recently been reported to shift the polarization of activated microglia and infiltration of macrophages into the anti-inflammatory M2 phenotype and while also maintaining microglial activation in the acquiescent state. Early injection of MiR-124 significantly increases the number of microglia/macrophages of the M2-like phenotype and neuronal survival and reduces ischemic core formation by inhibiting reactive astrocytes (36, 37). Moreover, liposomated miR-124 administration before the peak of the proinflammatory process in ischemic stroke can shift the predominantly proinflammatory microglia/macrophage phenotype into the anti-inflammatory M2 phenotype most effectively and enhance stroke rehabilitation in the subacute phase (36).

MicroRNA 133b

Compared with naïve multipotent mesenchymal stromal cells (MSCs), MSCs with overexpressed MiRNA 133b significantly contribute to stroke rehabilitation in animal models of MCA occlusion. Exosomes releasenaïvenaive MSCs are beneficial mediators in the MSC treatment of ischemic stroke. Ex-miR-133b+ significantly increases the release of exosomes from astrocytes by promoting neurite branching and elongation of cortical embryonic neurons, whereas Ex-miR-133b- significantly decreases the release (43).

ICH

ICH is the most critical subtype of stroke and lacks effective treatment (44). ICH also leads to neuronal loss, cerebral edema, and neuropathological alterations, including activation

of astrocytes and microglia/macrophages and the invasion of neutrophils and T lymphocytes from the blood circulation after ICH (34). There are two types of ICH models: the collagenase-induced model and the autologous arterial whole blood-induced model (45). ICH also leads to neuronal loss, cerebral edema, and neuropathological alterations, including microglial/macrophage and astrocytic activation, and neutrophil and T lymphocyte invasion after ICH (34). After ICH, microglia and astrocytes in brain tissue adjacent to the hematoma may modulate brain cellular plasticity (3). Microglia are among the first non-neuronal cells in the innate immune response to ICH. Microglia become activated by the classical pro-inflammatory M1 phenotype or alternative anti-inflammatory M2 phenotype (44). Astrocytes have differential roles in the recovery pattern of ischemic and hemorrhagic stroke. However, there is similar long-term GFAP-positive astrocytic plasticity after both ischemic stroke and ICH (46). Astrocyte HO-1 overexpression shows distinct neuroprotection after ICH (47). Moreover, ICH stimulates expression and release of Prx 1, activation of toll-like receptor4/nuclear factor κB, and production of cytokines (TNF-α, IL-6, and IL-17) (34). Prostaglandins such as PGE2 also mediate secondary brain injury in the inflammatory response to ICH. The EP2 receptor, which can be activated by PGE2, is expressed in neurons but not in astrocytes or microglia after ICH. The neuronal EP2 receptor shows neuroprotection after ICH by suppressing inflammatory responses, oxidative stress, and matrix metalloproteinase-219 activity, which is involved in brain injury after ICH (45).

PSD

PSD is a critical psychiatric complication after stroke that frequently occurs at ∼3–6 months and remains for 2–3 years after ischemic stroke or ICH. It is reported that the prevalence rate of PSD is ∼33% in ischemic stroke and it is 15% at 1 year after ICH. It is independently associated with increased morbidity and mortality in stroke because PSD may hinder rehabilitation. To wit, alleviating PSD can improve the outcomes and quality of life in patients after stroke. PSD is reportedly associated with late worsening of disability, but not with initial damage severity after stroke (4, 48, 49).

The mechanisms between cerebrovascular diseases and depressive disorders are intertwined. As the inflammatory response in stroke affects stroke rehabilitation, some studies have confirmed that an immunological hypothesis is one of the pathophysiological mechanisms of PSD and the inflammatory response in PSD affects its outcome. However, the specific mechanisms of the inflammatory effects on stroke and PSD reportedly differ. It has been shown that patients with PSD have early increased inflammatory markers (such as high-sensitivity C-reactive protein, ferritin, neopterin, and glutamate), increased proinflammatory cytokines (TNF-α, IL-6, IFN-γ), increased pro-inflammatory/anti-inflammatory ratios (TNF-α/IL-10, IL-6/IL-10), and lowered complement expression (5). Recent investigations have revealed imbalances in inflammatory cytokine levels and increased oxidative DNA damage in association with PSD, as well as the involvement of inflammatory and immune mechanisms and elevated oxidative stress level in PSD (49–52). It has also been reported that cytokines can drive intrinsic apoptotic factors to increase the risk of PSD through intracellular calcium and glutamate excitotoxicity after ischemic damage; pro-inflammatory cytokines may amplify the proinflammatory processes by activating indoleamine 2, 3-dioxygenase and reducing serotonin production, which sequentially results in PSD. Cytokines can provoke the dysregulation of several growth factors, such as BDNF, fibroblast growth factor-2, and contribute to PSD and other comorbidities (53–55).

PHARMACOTHERAPY

Pharmacotherapy in Stroke Rehabilitation

Using anti-inflammatory drugs along with neurorehabilitation therapy is useful for neuroprotection and functional recovery (56). Anti-inflammatory drugs may enhance brain plasticity after stroke but need to be used in conjunction with neurorehabilitation therapy (57). Therefore, anti-inflammatory treatment has the most potential as a therapy to enhance neurorehabilitation after stroke (58).

The findings of recent studies on anti-inflammatory treatments for stroke are listed below. Multimodal intervention of minocycline (pharmacotherapy, anti-inflammatory drug used to modulate the dynamics of the immune system) together with cerebral stimulation using transcranial direct-current stimulation and repetitive transcranial magnetic stimulation (neurorehabilitation therapy used to enhance functional recovery after stroke) may augment plasticity, rehabilitation, and neurorestoration (48). Simvastatin (statin class of cholesterol-lowering drugs), alters the release of cytokines and trophic factors from microglia, including IL-β, TNF-α, and brain derived neurotrophic factor in a cholesterol-dependent manner, but inhibits phagocytosis in a cholesterol-independent manner (59). Vinpocetine (a potent anti-inflammatory agent) improves neuronal plasticity and reduces the release of inflammatory cytokines and chemokines from microglia, macrophages, endothelial cells, and vascular smooth muscle cells (60). Omega-3 polyunsaturated fatty acids provide anti-inflammatory neuroprotective function in ischemic stroke by targeting astroglia and microglia and preventing the release of cyclooxygenase 2, hypoxia-inducible factor 1α, nitric oxide synthase, and IL-1β and have clinical potential as a therapeutic treatment in stroke (61). Trypsin inhibitor ulinastatin (anti-inflammatory drug) provides neuroprotective function in synaptic plasticity and spatial memory in cerebral ischemia-reperfusion injury (62). The melanocortin MC4 receptor agonist RO27-3225 (used to reduce expression of TNF-α, BAX, ERK1/2, JNK1/2, and cascapse-3 and counteract prolonged/recurrent inflammatory and apoptotic responses) provides neuroprotective function and promotes functional recovery in ischemic stroke (63). Scutellarin (a potential Chinese herbal extract, a putative therapeutic agent, used to improve neurological function), ameliorates neuroinflammation by suppressing microglial activation and

enhances astrocytic reaction by upregulating the expression of neurotrophic factors (8, 28).

Sex differences are involved in the frequency of intracellular astrocyte Ca2+ elevation and microglial volume immediately in ischemic stroke and are foundational for future sex-specific stroke therapeutic treatments (64). Female sexual hormones (estradiol and progesterone, anti-inflammatory), modulate the cellular and immune response to ischemic stroke (9). The corticotropin-releasing hormone type 1 receptor actively alters neuronal injury and inflammation, neuronal plasticity, and functional recovery in ischemic stroke (65).

The vascular endothelial growth factor mediates reactive astrocyte transdifferentiation into new mature neurons and enhances neurogenesis in ischemic stroke (66). The vascular endothelial growth factor also suppresses the inflammatory response in ischemic stroke to promote neuronal plasticity and neuronal remodeling (67). High-mobility group box 1 (amphoterin or HMG1) promotes neuronal necrosis and influx of damaging inflammatory cells in the acute stage of ischemic stroke but promotes beneficial plasticity and neuronal recovery in the delayed stage after stroke (68). The vagus nerve system regulates the immune system through the cholinergic anti-inflammatory pathway (69). Acetylcholine-alpha 7 nicotinic acetylcholine receptor on macrophages or microglia also provides neuroprotection through the cholinergic anti-inflammatory pathway. Nicotine (an acetylcholine receptor agonist, anti-inflammatory), inhibits microglial activation and production of proinflammatory cytokines and cholinesterase by activated astrocytes, which is partly medicated by COX-2 (70). Therefore, treatments inhibiting cyclooxygenases enhance neuronal plasticity after ischemic stroke (71). Therapeutic hypothermia is another potential treatment for ischemic stroke. Novel neurotensin receptor1 (NTR1) agonists induce hypothermia to inhibit microglial activation and decrease the expression of proinflammatory (M1) chemokines and cytokines and protect against neuronal damage in ischemic stroke and ICH (6).

Pharmacotherapy in PSD

Anti-cytokine modulators are new therapeutic targets for the treatment of PSD, especially in subjects affected by inflammatory processes. For instance, an investigation revealed that anti-inflammatory treatment, such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and statins decrease the risk of PSD, and inflammation contributes to PSD depending on the onset of PSD (72).

CONCLUSIONS

Stroke comprises ischemic stroke and ICH. The immuno-inflammatory process is involved in neural plasticity following events such as a hemorrhage or ischemic stroke. After ischemia, astrocytes, microglia, and MDMs play important roles during rehabilitation with the modulation of cytokines or chemokines, such as TNF-α and IL-1. Moreover, MiRNAs are also important posttranscriptional regulators in these glial mitochondrial responses to cerebral ischemia. ICH involves processes similar and different to those seen in ischemia, including neuronal injury, astrocytic and microglial/macrophage activation, and neutrophil and T lymphocyte invasion after ICH. Immunological hypothesis is also one of the pathophysiological mechanisms of PSD. To date, many pharmacotherapies have been suggested as having an anti-inflammatory function in stroke rehabilitation, including those involving minocycline, melanocortin, omega-3 polyunsaturated fatty acids, UTI, statin, vinpocetine, RO27-3225, scutellarin, and sexual hormones. Other potential therapies involve the vascular endothelial growth factor, high-mobility group box 1, corticotropin-releasing hormone type 1 receptor, the vagus nerve system, nicotine and cyclooxygenase 2, and therapeutic hypothermia. In PSD, very few anti-inflammatory treatments have been studied, including the use of acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and statins.

AUTHOR CONTRIBUTIONS

MF, LZ, and XJ wrote the first draft. RC and WY provided the organization and framework of the article. SG, JL, BL, and TL provided the critical revisions. All authors approved the final version of the manuscript for submission.

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REFERENCES

1. Tuttolomondo A, Pecoraro R, Pinto A. Studies of selective TNF inhibitors in the treatment of brain injury from stroke and trauma: a review of the evidence to date. *Drug Design Dev Ther*. (2014) 8:2221–38. doi: 10.2147/DDDT.S67655
2. Kriz J, Lalancette-Hébert M. Inflammation, plasticity and real-time imaging after cerebral ischemia. *Acta Neuropathologica*. (2009) 117:497–509. doi: 10.1007/s00401-009-0496-1
3. Neves JD, Aristimunha D, Vizuete AF, Nicola F, Vanzella C, Petenuzzo L, et al. Glial-associated changes in the cerebral cortex after collagenase-induced intracerebral hemorrhage in the rat striatum. *Brain Res Bull*. (2017) 134:55–62. doi: 10.1016/j.brainresbull.2017.07.002
4. Nakase T, Tobisawa M, Sasaki M, Suzuki A. Outstanding symptoms of poststroke depression during the acute phase of stroke. *PLoS ONE*. (2016) 11:e0163038. doi: 10.1371/journal.pone.0163038
5. Levada OA, Troyan AS. Poststroke Depression biomarkers: a narrative review. *Front Neurol*. (2018) 9:577. doi: 10.3389/fneur.2018.00577
6. Lee JH, Wei ZZ, Cao W, Won S, Gu X, Winter M. et al. Regulation of therapeutic hypothermia on inflammatory cytokines, microglia polarization, migration and functional recovery after ischemic stroke in mice. *Neurobiol Dis*. (2016) 96:248–60. doi: 10.1016/j.nbd.2016.09.013
7. Freeman L, Guo H, David CN, Brickey WJ, Jha S, Ting JP. NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes. *J Exp Med*. (2017) 214:1351–70. doi: 10.1084/jem.20150237

8. Wu CY, Fang M, Karthikeyan A, Yuan Y, Ling EA. Scutellarin attenuates microglia-mediated neuroinflammation and promotes astrogliosis in cerebral ischemia - a therapeutic consideration. *Curr Med Chem*. (2017) 24:718–27. doi: 10.2174/0929867324666161118142045
9. Perez-Alvarez MJ, Wandosell F. Stroke and neuroinflammation: role of sexual hormones. *Curr Pharm Des*. (2016) 22:1334–49. doi: 10.2174/1381612822101603041128 34
10. Pivonkova H, Anderova M. Altered homeostatic functions in reactive astrocytes and their potential as a therapeutic target after brain ischemic injury. *Curr Pharmaceut Design*. (2017) 23:5056–5074. doi: 10.2174/1381612823666170710161858
11. Cotrina ML, Lou N, Tome-Garcia J, Goldman J, Nedergaard M. Direct comparison of microglial dynamics and inflammatory profile in photothrombotic and arterial occlusion evoked stroke. *Neuroscience*. (2017) 343:483–94. doi: 10.1016/j.neuroscience.2016.12.012
12. Lima RR, Santana LN, Fernandes RM, Nascimento EM, Oliveira AC, Fernandes LM, et al. Neurodegeneration and glial response after acute striatal stroke: histological basis for neuroprotective studies. *Oxidat Med Cell Longevity*. (2016) 2016:3173564, 2016. doi: 10.1155/2016/3173564
13. Wattananit S, Tornero D, Graubardt N, Memanishvili T, Monni E, Tatarishvili J, et al. Monocyte-Derived macrophages contribute to spontaneous long-term functional recovery after stroke in mice. *J Neurosci*. (2016) 36:4182–95. doi: 10.1523/JNEUROSCI.4317-15.2016
14. Choudhury GR, Ding S. Reactive astrocytes and therapeutic potential in focal ischemic stroke. *Neurobiol Dis*. (2016) 85:234–44. doi: 10.1016/j.nbd.2015.05.003
15. Karthikeyan A, Patnala R, Jadhav SP, Eng-Ang L, Dheen ST. MicroRNAs: Key players in microglia and astrocyte mediated inflammation in CNS pathologies. *Curr Med Chem*. (2016) 23:3528–46. doi: 10.2174/0929867323666160814001040
16. Ding S. Ca(2+) signaling in astrocytes and its role in ischemic stroke. *Adv Neurobiol*. (2014) 11:189–211. doi: 10.1007/978-3-319-08894-5_10
17. Zhao Y, Rempe DA. Targeting astrocytes for stroke therapy. *Neurotherapeutics*. (2010) 7:439–451. doi: 10.1016/j.nurt.2010.07.004
18. Hao XZ, Yin LK, Zhang XX, Tian JQ, Li CC, Feng XY, et al. Combining systemic and stereotactic MEMRI to detect the correlation between gliosis and neuronal connective pathway at the chronic stage after stroke. *J Neuroinflammation*. (2016) 13:156. doi: 10.1186/s12974-016-0622-7
19. Sims NR, Yew WP. Reactive astrogliosis in stroke: Contributions of astrocytes to recovery of neurological function. *Neurochem Int*. (2017) 107:88–103. doi: 10.1016/j.neuint.2016.12.016
20. Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. *Neurosci Lett*. (2014) 565:30–38. doi: 10.1016/j.neulet.2013.12.071
21. Amantea D, Micieli G, Tassorelli C, Cuartero MI, Ballesteros I, Certo M, et al. Rational modulation of the innate immune system for neuroprotection in ischemic stroke. *Front Neurosci*. (2015) 9:147. doi: 10.3389/fnins.2015.00147
22. Wang YF, Parpura V. Central role of maladapted astrocytic plasticity in ischemic brain edema formation. *Front Cell Neurosci*. (2016) 10:129. doi: 10.3389/fncel.2016.00129
23. de Pablo Y, Nilsson M, Pekna M, Pekny M. Intermediate filaments are important for astrocyte response to oxidative stress induced by oxygen-glucose deprivation and reperfusion. *Histochem Cell Biol*. (2013) 140:81–91. doi: 10.1007/s00418-013-1110-0
24. Pak HJ, Riew TR, Shin YJ, Choi JH, Jin X, Lee MY. Enhanced expression of the calcium-sensing receptor in reactive astrocytes following ischemic injury *in vivo* and *in vitro*. *J Neurol Sci*. (2016) 366:102–9. doi: 10.1016/j.jns.2016.05.015
25. Bronstein R, Torres L, Nissen JC, Tsirka SE. Culturing microglia from the neonatal and adult central nervous system. *J Visual Exp*. (2013) 78:50647. doi: 10.3791/50647
26. Dudvarski Stankovic N, Teodorczyk M, Ploen R, Zipp F, Schmidt MHH. Microglia-blood vessel interactions: a double-edged sword in brain pathologies. *Acta Neuropathol*. (2016) 131:347–63. doi: 10.1007/s00401-015-1524-y
27. Verma R, Cronin CG, Hudobenko J, Venna VR, McCullough LD, Liang BT. Deletion of the P2X4 receptor is neuroprotective acutely, but induces a depressive phenotype during recovery from ischemic stroke. *Brain Behav Immunity*. (2017) 66:302–12. doi: 10.1016/j.bbi.2017.07.155
28. Yuan Y, Fang M, Wu CY, Ling EA. Scutellarin as a potential therapeutic agent for microglia-mediated neuroinflammation in cerebral ischemia. *Neuromol Med*. (2016) 18:264–73. doi: 10.1007/s12017-016-8394-x
29. Jin WN, Shi SX, Li Z, Li M, Wood K, Gonzales RJ, et al. Depletion of microglia exacerbates postischemic inflammation and brain injury. *J Cerebr Blood Flow Metabol*. (2017) 37:2224–36. doi: 10.1177/0271678X17694185
30. Ma Y, Wang J, Wang Y, Yang GY. The biphasic function of microglia in ischemic stroke. *Progr Neurobiol*. (2016) 157:247–72. doi: 10.1016/j.pneurobio.2016.01.005
31. Wu R, Li X, Xu P, Huang L, Cheng J, Huang X, et al. TREM2 protects against cerebral ischemia/reperfusion injury. *Mol Brain*. (2017) 10:20. doi: 10.1186/s13041-017-0296-9
32. Liu W, Wang X, Yang S, Huang J, Xue X, Zheng Y, et al. Electroacupunctre improves motor impairment via inhibition of microglia-mediated neuroinflammation in the sensorimotor cortex after ischemic stroke. *Life Sci*. (2016) 151:313–22. doi: 10.1016/j.lfs.2016.01.045
33. Laterza C, Wattananit S, Uoshima N, Ge R, Pekny R, Tornero D, et al. Monocyte depletion early after stroke promotes neurogenesis from endogenous neural stem cells in adult brain. *Exp Neurol*. (2017) 297:129–37. doi: 10.1016/j.expneurol.2017.07.012
34. Liu DL, Zhao LX, Zhang S, Du JR. Peroxiredoxin 1-mediated activation of TLR4/NF-kappaB pathway contributes to neuroinflammatory injury in intracerebral hemorrhage. *Int Immunopharmacol*. (2016) 41:82–89. doi: 10.1016/j.intimp.2016.10.025
35. Madinier A, Bertrand N, Mossiat C, Prigent-Tessier A, Beley A, Marie C, et al. Microglial involvement in neuroplastic changes following focal brain ischemia in rats. *PLoS ONE*. (2009) 4:e8101. doi: 10.1371/journal.pone.0008101
36. Hamzei Taj S, Kho W, Aswendt M, Collmann FM, Green C, Adamczak J, et al. Dynamic modulation of microglia/macrophage polarization by miR−124 after Focal Cerebral Ischemia. *J Neuroimmune Pharmacol*. (2016) 11:733–748. doi: 10.1007/s11481-016-9700-y
37. Hamzei Taj S, Kho W, Riou A, Wiedermann D, Hoehn M. MiRNA−124 induces neuroprotection and functional improvement after focal cerebral ischemia. *Biomaterials*. (2016) 91:151–65. doi: 10.1016/j.biomaterials.2016.03.025
38. O'Connor JJ. Targeting tumour necrosis factor-alpha in hypoxia and synaptic signalling. *Irish J Med Sci*. (2013) 182:157–62. doi: 10.1007/s11845-013-0911-4
39. Liguz-Lecznar M, Zakrzewska R, Kossut M. Inhibition of Tnf-alpha R1 signaling can rescue functional cortical plasticity impaired in early post-stroke period. *Neurobiol Aging*. (2015) 36:2877–84. doi: 10.1016/j.neurobiolaging.2015.06.015
40. Sumbria RK, Boado RJ, Pardridge WM. Brain protection from stroke with intravenous TNFalpha decoy receptor-Trojan horse fusion protein. *J Cerebr Blood Flow Metabol*. (2012) 32:1933–8. doi: 10.1038/jcbfm.2012.97
41. Denes A, Pinteaux E, Rothwell NJ, Allan SM. Interleukin-1 and stroke: biomarker, harbinger of damage, and therapeutic target. *Cerebrovasc Dis*. (2011) 32:517–27. doi: 10.1159/000332205
42. Li L, Stary CM. Targeting glial mitochondrial function for protection from cerebral ischemia: relevance, mechanisms, and the role of MicroRNAs. *Oxidat Med Cell Longevity*. (2016) 2016:6032306. doi: 10.1155/2016/6032306
43. Xin HQ, Wang FJ, Li YF, Lu QE, Cheung WL, Zhang Y, et al. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from microRNA 133b-overexpressed multipotent mesenchymal stromal cells. *Cell Transplant*. (2017) 26:243–57. doi: 10.3727/096368916X693031
44. Lan X, Han X, Li Q, Yang QW, Wang J. Modulators of microglial activation and polarization after intracerebral haemorrhage. *Nat Rev Neurol*. (2017) 13:420–33. doi: 10.1038/nrneurol.2017.69
45. Wu H, Wu T, Han X, Wan J, Jiang C, Chen W, et al. Cerebroprotection by the neuronal PGE2 receptor EP2 after intracerebral hemorrhage in middle-aged mice. *J Cerebr Blood Flow Metabol*. (2017) 37:39–51. doi: 10.1177/0271678X15625351
46. Mestriner RG, Saur L, Bagatini PB, Baptista PP, Vaz SP, Ferreira K, et al. Astrocyte morphology after ischemic and hemorrhagic experimental stroke

has no influence on the different recovery patterns. *Behav Brain Res*. (2015) 278:257–61. doi: 10.1016/j.bbr.2014.10.005
47. Chen-Roetling J, Kamalapathy P, Cao Y, Song W, Schipper HM, Regan RF. Astrocyte heme oxygenase-1 reduces mortality and improves outcome after collagenase-induced intracerebral hemorrhage. *Neurobiol Dis*. (2017) 102:140–6. doi: 10.1016/j.nbd.2017.03.008
48. Stern-Nezer S, Eyngorn I, Mlynash M, Snider RW, Venkatsubramanian C, Wijman CAC, et al. Depression one year after hemorrhagic stroke is associated with late worsening of outcomes. *NeuroRehabilitation. (*2017*)* 41:179–87. doi: 10.3233/NRE-171470
49. Villa RF, Ferrari F, Moretti A. Post-stroke depression: mechanisms and pharmacological treatment. *Pharmacol Ther*. (2018) 184:131–44. doi: 10.1016/j.pharmthera.2017.11.005
50. Chen CY, Chen CL, Yang YH, Ho CH, Tseng WC. Poststroke depressive symptoms are associated with increased oxidative deoxyribonucleic acid damage. *J Neuropsychiatry Clin Neurosci*. (2018) 30:139–44. doi: 10.1176/appi.neuropsych.17050108
51. Zhao W, Jiang F, Zhang Z, Zhang J, Ding Y, Ji X. Remote ischemic conditioning: a novel non-invasive approach to prevent post-stroke depression. *Front Aging Neurosci*. (2017) 9:270. doi: 10.3389/fnagi.2017.00270
52. Nguyen VA, Carey LM, Giummarra L, Faou P, Cooke I, Howells DW, et al. A pathway proteomic profile of ischemic stroke survivors reveals innate immune dysfunction in association with mild symptoms of depression - a pilot study. *Front Neurol*. (2016) 7:85. doi: 10.3389/fneur.2016.00085
53. Pascoe MC, Crewther SG, Carey LM, Crewther DP. Inflammation and depression: why poststroke depression may be the norm and not the exception. *Int J Stroke*. (2011) 6:128–35. doi: 10.1111/j.1747-4949.2010.00565.x
54. Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. *Mol Psychiatry*. (2006) 11:984–91. doi: 10.1038/sj.mp.4001879
55. Anisman H, Hayley, S. Inflammatory factors contribute to depression and its comorbid conditions. *Sci Signal*. (2012) 5:pe45. doi: 10.1126/scisignal.2003579
56. Alam MA, Subramanyam Rallabandi VP, Roy PK. Systems biology of immunomodulation for post-stroke neuroplasticity: multimodal implications of pharmacotherapy and neurorehabilitation. *Front Neurol*. (2016) 7:94. doi: 10.3389/fneur.2016.00094
57. Witte OW, Kossut M. Impairment of brain plasticity by brain inflammation. *Zeitschrift Für Psychologie*. (2016) 224:133–8. doi: 10.1027/2151-2604/a000247
58. Greifzu F, Schmidt S, Schmidt KF, Kreikemeier K, Witte OW, Löwel S. Global impairment and therapeutic restoration of visual plasticity mechanisms after a localized cortical stroke. *Proc Natl Acad Sci USA*. (2011) 108:15450–5. doi: 10.1073/pnas.1016458108
59. Churchward MA, Todd KG. Statin treatment affects cytokine release and phagocytic activity in primary cultured microglia through two separable mechanisms. *Mol Brain*. (2014) 7:85. doi: 10.1186/s13041-014-0085-7
60. Zhang L, Yang L. Anti-inflammatory effects of vinpocetine in atherosclerosis and ischemic stroke: a review of the literature. *Molecules*. (2014) 20:335–347. doi: 10.3390/molecules20010335
61. Zendedel A, Habib P, Dang J, Lammerding L, Hoffmann S, Beyer C, et al. Omega-3 polyunsaturated fatty acids ameliorate neuroinflammation and mitigate ischemic stroke damage through interactions with astrocytes and microglia. *J Neuroimmunol*. (2015) 278:200–11. doi: 10.1016/j.jneuroim.2014.11.007
62. Cao LJ, Wang J, Hao PP, Sun CL, Chen YG. Effects of ulinastatin, a urinary trypsin inhibitor, on synaptic plasticity and spatial memory in a rat model of cerebral ischemia/reperfusion injury. *Chin J Physiol*. (2015) 54:435–42. doi: 10.4077/CJP.2011.AMM058
63. Spaccapelo L, Bitto A, Galantucci M, Ottani A, Irrera N, Minutoli L, et al. Melanocortin MC(4) receptor agonists counteract late inflammatory and apoptotic responses and improve neuronal functionality after cerebral ischemia. *Eur J Pharmacol*. (2011) 670:479–86. doi: 10.1016/j.ejphar.2011.09.015
64. Morrison HW, Filosa JA. Sex differences in astrocyte and microglia responses immediately following middle cerebral artery occlusion in adult mice. *Neuroscience*. (2016) 339:85–99. doi: 10.1016/j.neuroscience.2016.09.047
65. de la Tremblaye PB, Benoit SM, Schock S, Plamondon H. CRHR1 exacerbates the glial inflammatory response and alters BDNF/TrkB/pCREB signaling in a rat model of global cerebral ischemia: implications for neuroprotection and cognitive recovery. *Prog Neuropsychopharmacol Biol Psychiatry*. (2017) 79:234–78. doi: 10.1016/j.pnpbp.2017.06.021
66. Shen SW, Duan CL, Chen XH, Wang YQ, Sun X, Zhang QW, et al. Neurogenic effect of VEGF is related to increase of astrocytes transdifferentiation into new mature neurons in rat brains after stroke. *Neuropharmacology*. (2016) 108:451–61. doi: 10.1016/j.neuropharm.2015.11.012
67. Herz J, Reitmeir R, Hagen SI, Reinboth BS, Guo Z, Zechariah A, et al. Intracerebroventricularly delivered VEGF promotes contralesional corticorubral plasticity after focal cerebral ischemia via mechanisms involving anti-inflammatory actions. *Neurobiol Dis*. (2012) 45:1077–85. doi: 10.1016/j.nbd.2011.12.026
68. Hayakawa K, Qiu J, Lo EH. Biphasic actions of HMGB1 signaling in inflammation and recovery after stroke. *Ann N Y Acad Sci*. (2010) 1207:50–7. doi: 10.1111/j.1749-6632.2010.05728.x
69. Møller AR. The role of neuroplasticity and the immune system in recovery from strokes and other forms of brain trauma. *J Neurol Stroke*. (2014) 1:16. doi: 10.15406/jnsk.2014.01.00016
70. Revathikumar P, Bergqvist F, Gopalakrishnan S, Korotkova M, Jakobsson PJ, Lampa J, et al. Immunomodulatory effects of nicotine on interleukin 1beta activated human astrocytes and the role of cyclooxygenase 2 in the underlying mechanism. *J Neuroinflammation*. (2016) 13:256. doi: 10.1186/s12974-016-0725-1
71. Jablonka JA, Kossut M, Witte OW, Liguz-Lecznar M. Experience-dependent brain plasticity after stroke: effect of ibuprofen and poststroke delay. *Eur J Neurosci*. (2012) 36:2632–9. doi: 10.1111/j.1460-9568.2012.08174.x
72. Wium-Andersen IK, Wium-Andersen MK, Jørgensen MB, Osler M. Anti-inflammatory treatment and risk for depression after first-time stroke in a cohort of 147 487 danish patients. *J Psychiatry Neurosci*. (2017) 42:320–30. doi: 10.1503/jpn160244

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Anxiety in Patients With Acute Ischemic Stroke: Risk Factors and Effects on Functional Status

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Background: Anxiety is prevalent after a stroke. The pathophysiological mechanisms underlying the development of poststroke anxiety (PSA) remain unclear. The aim of this study was to investigate the clinical and neuroimaging risk factors for development of PSA and examine the effects of PSA on activities of daily living (ADL) and quality of life (QOL) in Chinese patients with ischemic stroke.

Methods: Two hundred nineteen patients with acute ischemic stroke were recruited to the study. A series of comprehensive assessments, including Hamilton Anxiety Rating Scale (HARS), Hamilton Depression Rating Scale (HDRS), Lawton ADL Scale, and the Stroke-Specific Quality of Life (SSQOL) Scale, were conducted in the acute stage and 3 months after stroke. Magnetic resonance imaging assessment focused on evaluation of infarctions, white matter lesions, and brain atrophy.

Results: In the acute stage and 3 months after stroke, 34 (16%) and 33 (15%) patients had PSA, respectively. Multiple logistic regression analysis indicated that HDRS (OR = 1.269, 95% CI = 1.182–1.364, $P < 0.001$) and acute infarcts in cerebral hemispheric white matter (CHWM; OR = 2.902, 95% CI = 1.052–8.007, $P = 0.040$) were significant correlates of PSA in the acute stage of stroke. Three months after stroke, these correlates remained significant predictors, along with male sex. Multiple linear regressions showed that age, NIHSS, HARS, and HDRS in the acute stage were significant predictors for both ADL and SSQOL at 3 months after stroke.

Conclusion: Depressive symptoms are the major correlates of PSA while more severe PSA is associated with poorer ADL and health-related QOL. Acute lesions involving CHWM may correlate with PSA in ischemic stroke patients with mild-to-moderate neurologic deficits, supporting a lesion-location hypothesis in PSA.

Keywords: anxiety, depression, functional status, quality of life, stroke, cerebral hemispheric white matter

INTRODUCTION

Anxiety is prevalent after stroke and occurs in about one-quarter of stroke survivors (1, 2). Poststroke anxiety (PSA) may have a negative impact on quality of life (QOL) of stroke survivors, affecting their rehabilitation (3). Furthermore, one prospective study found that severe anxiety symptoms were associated with increased risk for incident stroke, independent of other risk factors (4). Despite high prevalence of anxiety after stroke, understanding of PSA is limited.

Risk factors related to PSA include depression (5–7), cognitive impairment (5, 8), fatigue (9), age (10–12), female sex (10, 12), lesion location (13, 14), and sleep disturbance (9, 15), indicating PSA might be multifactorial. Apart from stress due to acute ischemic stroke, the biological mechanisms of PSA should also be considered. Anxiety-related neural circuits span a wide range of brain structures, including subcortical white matter and the limbic system (16, 17). Neuroimaging techniques, e.g., magnetic resonance imaging (MRI), can locate the infarction precisely. Thus, studying the neuroimaging correlates of PSA may be helpful in understanding the pathophysiology of PSA. However, few studies have evaluated the association between PSA and neuroimaging variables. The lesion-location hypothesis of PSA might be presumed as the infarction may damage brain structures involved in anxiety. Recently, a large-scale MRI study involving 239 stroke patients was performed, but no association was found between brain lesion location and PSA (18). Thus, the underlying pathophysiological mechanisms of development of PSA remain unclear.

Functional status, including the ability to perform activities of daily living (ADL) and QOL, is an important outcome of stroke in many studies (3, 19, 20). However, few studies have explored the subsequent effect of PSA in the acute phase on patient QOL and functional outcomes in the chronic stage.

The purpose of this prospective study was twofold. The first purpose was to investigate the associated clinical and MRI risk factors for PSA, testing the lesion-location hypothesis of PSA. The second purpose was to examine the effects of PSA on patient ADL and QOL following ischemic stroke. We assumed that lesions in specific locations (e.g., structures related to emotional modulation) might be more likely to result in PSA. Severity of PSA in the acute stage is a significant factor independently contributing to poor ADL and QOL in the chronic stage.

METHODS

Participants and Setting

Patients with first-ever or recurrent acute ischemic stroke admitted to the Department of Neurology, Dongguan People Hospital, between July 2013 and June 2014 were screened for this study. Patients were enrolled in the study if they met the following criteria: 1) age 40 to 80 years; 2) had an acute, first, or recurrent ischemic stroke that occurred within 7 days prior to admission; if they had a previous stroke, the modified Rankin Scale score before the index stroke was <2. Patients were excluded if they 1) had significant neurological illness other than stroke, e.g., Parkinson's disease, brain tumor, or multiple sclerosis; 2) had no MRI scans or poor-quality MRI scans on admission; 3) had a severe stroke, which received a National Institutes of Health Stroke Scale (NIHSS) total score of ≥15; 4) had severe aphasia (defined as NIHSS best language subscore ≥2) or dysarthria; 5) had severe cognitive impairment, defined by a Mini-Mental State Examination (MMSE) total score of <17; 6) had a history of anxiety disorders, depression, substance abuse/dependence, or other psychiatric disorders before the index stroke; and 7) had comorbid severe diseases of the heart, lung, kidney, liver, or malignant tumors. This study was carried out in accordance with the recommendations of the World Medical Association's Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Dongguan People's Hospital. Consent forms were obtained from the patients or their legally authorized representative.

Collection of Demographic and Clinical Data

Patient demographics (age, sex, and education level) and clinical characteristics including vascular risk factors (e.g., hypertension, diabetes mellitus, hyperlipidemia, and smoking history) and previous stroke history were collected from medical records. The severity of stroke was assessed by the NIHSS from medical records.

Assessment of PSA

The Chinese version of the 14-item Hamilton Anxiety Rating Scale (HARS) (21, 22) was used to evaluate anxiety symptoms in all participants in the acute stage when they were medically stable (5–14 days after the index stroke) and at the 3-month follow-up. Assessments of clinical anxiety were performed by two trained neurologists (WL and HW) who were blinded to the MRI results of the stroke survivors. The Chinese version of the 14-item HARS has been widely used in the Chinese population, as well as in Chinese stroke patients (22), indicating good reliability and validity. PSA in this study was defined by a HARS score ≥14 (22). HARS was repeatedly conducted at 3 months after stroke by the same raters. PSA was defined as a HARS score ≥14 at 3 months after stroke. If the patients were diagnosed with anxiety at baseline and received anti-anxiety treatment, they were also judged to have PSA even if they had a HARS score lower than 14.

Assessment of Other Psychological Status in the Acute Stage of Stroke

The Chinese version of the MMSE (scores range from 0 to 30, with lower scores indicating greater deficits) (23) was used to measure basic cognitive function by the two trained neurologists (WL and HW). They also administered the Chinese version of the 24-item Hamilton Depression Rating Scale (HDRS) (22, 24), which was used to evaluate the severity of depressive symptoms, with an internal consistent Cronbach's $\alpha = 0.88–0.99$ (22).

Assessment of Functional Status at 3 Months After Stroke

The two raters administered the Lawton ADL Scale (25) and the Chinese version of the Stroke-Specific Quality of Life (SSQOL) Scale (26). The Lawton ADL Scale, which contains six items assessing self-maintenance and eight items evaluating instrumental activities, was used to measure functional level of patients with stroke. Each item was rated from 1 to 4, and the total ADL score was calculated by summing the scores of all items. Higher scores indicate poorer performance. The test–retest kappa of the Chinese version of the Lawton ADL Scale is 0.502 (22). The Chinese version of the SSQOL Scale, which was used to assess patient QOL and proved to have good reliability and validity, consists of 49 questions grouped into 12 domains, with scores rated from 1 (worst outcome) to 5 (best outcome). The internal consistent reliability is high (Cronbach's $\alpha = 0.76$) (26, 27).

Before the first interview, the two neurologists selected 10 patients with ischemic stroke to test the interrater reliability of the rating instruments. The intraclass correlation coefficients (ICCs) of the above scales between the two raters ranged between 0.83 and 0.91.

Magnetic Resonance Imaging Assessment

MRI acquisition was performed using a 1.5-T scanner (Achieva Phillip Medical System, Best, the Netherlands) within 7 days of the index stroke. The sequences of MRI scanning included diffusion-weighted imaging (DWI), gradient echo sequences, and T1- and T2-weighted, fluid-attenuated inversion recovery sequences. A trained neurologist (YL), who was blinded to patient clinical information, assessed the MRI variables as follows:

1. Infarcts: The location, number, and volume of acute infarcts were examined in DWI. The sites of acute infarcts were denoted by brain region as follows: frontal, parietal, temporal, and occipital lobes; corpus callosum; coronal radiate; centrums semiovale; internal capsule; basal ganglia; thalamus; brainstem; and cerebellum. If the patient had infarcts in more than two sites, both sites would be recorded as presence. Cerebral hemispheric white matter (CHWM) was defined as any supratentorial white matter structure including the corpus callosum, coronal radiate, centrums semiovale, and internal capsule.
2. The total volume was calculated by multiplying the total area by the sum of the slice thickness and the gap. The number of old lacunar infarcts was also recorded.
3. White matter lesions (WMLs). The extent of WMLs was graded using the four-point scale of Fazekas et al. (28). Deep white matter hyperintensities (DWMH) and periventricular hyperintensities (PVH) were scored on fluid-attenuated inversion recovery (FLAIR) images.
4. Ventricle-to-brain ratio (VBR). VBR is an indicator of global brain atrophy (29). The slice showing the longest vertical length of the lateral ventricle at the middle was selected. The VBR was defined as the ratio of the diameter of the width of the lateral ventricle divided by the width of the brain along the same line (30).
5. Medial temporal lobe atrophy (MTLA). MTLA was measured using Schelten's scale (31). This visual rating scale yields standard images with different severity of MTL atrophy on coronal MRI sections, ranging from 0 to 4, from "no atrophy" to "severe atrophy." The MTLA score was determined using the sum of left and right medial temporal lobes.

Intrarater reliability activities were performed on 10 patients by the same MRI rater at two time points (interval ≥2 months). The intrarater agreements of the MRI measurements were good to excellent, as reported in our previous study (32).

Statistical Analysis

All statistical tests were performed using SPSS for Windows (Release 16.0, SPSS Inc., Chicago, IL, USA). In the acute stage of stroke, all patients were divided into two groups, the PSA and non-PSA groups, according to the HARS cutoff. The demographic and clinical variables were compared between the PSA and non-PSA groups using χ^2 test, two independent *t* tests, or Mann–Whitney *U* tests, as appropriate, in order to screen for potential predictors. Variables with $P < 0.1$ in univariate comparisons were entered as independent variables in multiple stepwise logistic regression analysis with PSA as the dependent variable. The same statistical procedures were performed at 3 months after stroke. Subsequently, multiple linear regressions were performed to explore the effects of HARS in the acute stage on ADL and SSQOL at 3 months after stroke (ADL and SSQOL were used as dependent variables) after adjusting for age, sex, NIHSS, and HDRS. The significance level was set at 0.05 (two-sided).

RESULTS

A total of 435 patients aged 40 to 80 years with acute ischemic stroke were admitted and screened. Two hundred nineteen patients (50.3%) fulfilled the study criteria and were included in the study. Compared to those who were excluded, participating patients were younger (61.4 ± 11.2 *vs.* 64.8 ± 12.7 years; $P < 0.001$), had a lower NIHSS score at admission (median, 3.0 [range, 0–15] *vs.* 5.0 (0–35), $P < 0.001$), but had a comparable frequency of male sex (73.1% *vs.* 68.1%; $P = 0.252$).

Demographic and Clinical Characteristics

The study cohort consisted of 219 patients who satisfied the study criteria (**Table 1**). One patient died and three patients were lost to follow-up before the 3-month assessment. In the acute stage and 3 months after the index stroke, there were 34 (15.5%) and 33 (15.1%) patients who were judged to have PSA, respectively. Compared to patients without PSA, patients with PSA were more likely to be female and to have more severe depressive symptoms (**Table 1**). No MRI variables were significantly different between the two groups, although patients with PSA trended toward more CHWM infarcts in both the acute stage and 3 months after stroke ($P = 0.075$ and $P = 0.071$, respectively; **Table 2**).

TABLE 1 | Comparisons of demographic and clinical variables between the PSA and non-PSA groups.

Variables	PSA in the acute stage		*P*	PSA at 3 months after stroke		*P*
	Yes (*n* = 34)	No (*n* = 185)		Yes (*n* = 33)	No (*n* = 182)	
Age (years)*	63.1 (9.6)	60.9 (11.6)	0.281	63.8 (9.7)	60.7 (11.7)	0.141
Female sex (*n*, %)†	14 (41.2%)	45 (24.3%)	0.042	14 (42.4%)	43 (23.6%)	0.024
Education level†						
Secondary and tertiary	10 (29.4%)	60 (32.4%)	0.728	8 (24.2%)	62 (34.1%)	0.268
Hypertension (*n*, %)†	24 (70.6%)	139 (75.1%)	0.576	24 (72.7%)	135 (74.2%)	0.862
Diabetes (*n*, %)†	9 (26.5%)	49 (26.5%)	0.998	8 (24.2%)	50 (27.5%)	0.700
Hyperlipidemia (*n*, %)†	12 (37.5%)	62 (36.7%)	0.930	8 (26.7%)	65 (38.9%)	0.201
Previous stroke (*n*, %)†	6 (17.6%)	27 (14.6%)	0.647	6 (18.2%)	26 (14.3%)	0.563
NIHSS on admission‡	4 (3–5)	3 (2–5)	0.101	4 (2–7)	3 (2–5)	0.069
MMSE†	24.1 (3.9)	25.3 (4.8)	0.175	23.7 (4.0)	25.4 (4.8)	0.055.
HDRS‡	19.6 (6.2)	6.2 (5.5)	<0.001	18.9 (9.2)	3.9 (3.7)	<0.001
HARS‡	18.2 (4.9)	4.8 (3.6)	<0.001	16.4 (6.8)	5.2 (4.3)	<0.001

PSA, poststroke anxiety; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale.

**Mean (SD), t test; †n (%), chi-square test; ‡ median (25%Q–75%Q), Mann–Whitney U test.*

TABLE 2 | Comparisons of MRI variables between the PSA and non-PSA groups.

Variables	PSA in the acute stage		*P*	PSA at 3 months after stroke		*P*
	Yes (*n* = 34)	No (*n* = 185)		Yes (*n* = 33)	No (*n* = 182)	
Acute infarcts (*n*, %)*						
Frontal lobe	4 (11.8%)	30 (16.2%)	0.615	4 (12.1%)	29 (15.9%)	0.793
Parietal lobe	3 (8.8%)	21 (11.4%)	1.000	4 (12.1%)	19 (10.4%)	0.761
Temporal lobe	1 (2.9%)	14 (7.6%)	0.476	1 (3.0%)	14 (7.7%)	0.477
Occipital lobe	1 (2.9%)	12 (6.5%)	0.697	1 (3.0%)	12 (6.6%)	0.697
Corpus callosum	2 (5.9%)	8 (4.3%)	0.656	2 (6.1%)	8 (4.4%)	0.653
Corona radiata	12 (35.3%)	46 (24.9%)	0.205	13 (39.4%)	46 (25.3%)	0.094
Centrums semiovale	2 (5.9%)	18 (9.7%)	0.746	3 (9.1%)	17 (9.3%)	1.000
Internal capsule	6 (17.6%)	18 (9.7%)	0.174	5 (15.2%)	19 (10.4%)	0.429
Basal ganglia	9 (26.5%)	31 (16.8%)	0.178	9 (27.3%)	31 (17.0%)	0.164
Thalami	2 (5.9%)	16 (8.6%)	0.746	1 (3.0%)	16 (8.8%)	0.481
Brainstem	4 (11.8%)	38 (20.5%)	0.343	5 (15.2%)	36 (19.8%)	0.533
Cerebellum	0 (0.0%)	12 (6.5%)	0.221	0 (0.0%)	12 (6.6%)	0.220
CHWM	19 (55.9%)	73 (39.5%)	0.075	19 (57.6%)	74 (40.7%)	0.071
Volume of acute infarcts (ml)†	0.9 (0.5–3.8)	0.9 (0.3–3.0)	0.753	1.0 (0.4–4.0)	0.9 (0.2–2.9)	0.578
Number of acute infarcts†	1 (1–2)	1 (1–2)	0.578	1 (1–2)	1 (1–2)	0.594
Number of old infarcts†	0 (0–2)	0 (0–2)	0.412	0 (0–2)	0 (0–2)	0.442
PVH	1 (0–2)	1 (1–2)	0.298	1 (0–2)	1 (1–2)	0.879
DWMH	1 (0–2)	1 (1–2)	0.330	1 (0–2)	1 (1–2)	0.805
VBR‡	17.9 (5.4)	18.8 (4.2)	0.248	18.4 (5.8)	18.8 (4.2)	0.689
MTLA†	0 (0–2.25)	0 (0–2)	0.941	0 (0–3)	0 (0–2)	0.989

PSA, poststroke anxiety; CHWM, cerebral hemispheric white matter; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; VBR, ventricle-to-brain ratio; MTLA, medial temporal lobe atrophy.

**n (%), chi-square test; †median (25%Q–75%Q), Mann–Whitney U test; ‡mean (SD), t test.*

Correlates of Poststroke Anxiety in the Acute Stage of Stroke

HDRS, sex, and acute infarcts in CHWM were evaluated by multiple logistic regressions. HDRS (odds ratio [OR] = 1.269, 95% CI = 1.182–1.364, $P < 0.001$) and acute infarcts in CHWM (OR = 2.902, 95% CI = 1.052–8.007, $P = 0.040$) were significant correlates of PSA in the acute stage of stroke (**Table 3**).

Correlates of Poststroke Anxiety at 3 Months After Stroke

HDRS, sex, NIHSS, MMSE, and acute infarcts in CHWM were evaluated by multiple logistic regression. HDRS (OR = 1.232, 95% CI = 1.150–1.320, $P < 0.001$), female sex (OR = 3.214, 95% CI = 1.124–9.189, $P = 0.029$), and acute infarcts in CHWM (OR = 2.904, 95% CI = 1.033–8.162, $P = 0.043$) significantly correlated with PSA (**Table 4**).

TABLE 3 | Correlates of PSA in the acute stage of ischemic stroke.

Variables	β	*P*	OR	95% CI
HDRS	0.238	<0.001	1.269	1.182–1.364
Acute infarcts in CHWM	1.065	0.040	2.902	1.052–8.007
Sex (female)	2.521	0.112	2.307	0.811–6.564-

Total R^2 = 0.536; PSA, poststroke anxiety; HDRS, Hamilton Depression Rating Scale; CHWM, cerebral hemispheric white matter.

TABLE 4 | Correlates of PSA at 3 months after stroke.

Variables	β	*P*	OR	95% CI
HDRS	0.209	<0.001	1.232	1.150–1.320
Acute infarcts in CHWM	1.066	0.043	2.904	1.033–8.162
Sex (female)	1.168	0.029	3.214	1.124–9.189
MMSE	1.524	0.217	0.931	0.831–1.044
NIHSS	0.173	0.678	0.942	0.801–1.108

Total R^2 = 0.491; PSA, poststroke anxiety; HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; CHWM, cerebral hemispheric white matter.

Effects of Anxiety in the Acute Stage on Activities of Daily Living and Stroke-Specific Quality of Life at 3 Months After Stroke

Multiple linear regressions showed that age, NIHSS, HARS, and HDRS in the acute stage were significant predictors for both ADL and SSQOL at 3 months after stroke (**Table 5**). Patients with PSA in the acute stage were more likely to have a poorer performance in ADL and SSQOL at 3 months after stroke.

Sensitivity Analysis After Excluding Patients With Previous Stroke

Analyses including only patients with their first-ever stroke are summarized in the supplemental tables. Acute infarcts in CHWM remained a significant correlate of PSA in the acute stage, but not at 3 months after stroke. HARS score in the acute stage significantly contributed to poorer ADL and SSQOL 3 months after stroke after adjusting for age, sex, NIHSS, and HDRS.

TABLE 5 | The effects of PSA in the acute stage on ADL and SSQOL at 3 months after stroke.

Dependent variable	Independent variables			
	3-month ADL		3-month SSQOL	
	Adjusted β	*P*	Adjusted β	*P*
HARS in the acute stage	0.282	<0.001	−0.252	0.014
Age	0.155	0.011	−0.142	0.012
Sex (female)	−0.013	0.837	0.087	0.124
NIHSS	0.318	<0.001	−0.225	0.001
HDRS in the acute stage	0.281	<0.001	−0.258	0.014
R^2	0.255		0.360	

PSA, poststroke anxiety; ADL, activities of daily living; SSQOL, Stroke-Specific Quality of Life; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; NIHSS, National Institutes of Health Stroke Scale.

DISCUSSION

In this prospective and longitudinal study, we found that frequency of PSA in the acute stage and 3 months after a mild-to-moderate ischemic stroke was 15.5% and 15.1%, respectively. HDRS and acute infarcts in CHWM correlated with PSA in both the acute stage and 3 months after stroke. Severity of PSA was a significant indicator for both ADL and SSQOL. To the best of our knowledge, studies investigating the effects of PSA on functional status are very limited. Our study represents a significant contribution to literature on the significance of PSA.

Anxiety symptoms were common after stroke. A meta-analysis study estimated that PSA affected 25% of stroke survivors (1). A summary of studies on PSA is shown in **Table 6**. In our study, we used HARS to assess anxiety symptoms with a cutoff of mean HARS ≥14 and found that frequency of PSA was about 15% in stroke survivors, which was lower than most previous studies (33–37). This may be due to the inclusion of a stroke sample with relatively mild neurological deficits (median NIHSS, 4) and exclusion of severe neurologic deficits or aphasia. Patients excluded from this study might be more likely to have PSA. Differences in assessment tools for PSA might also contribute to the differences between our results and previous studies.

Sudden occurrence of neurological deficits might cause stress or anxiety in stroke patients. We assessed PSA at two time points, including the acute stage (5–14 days) and months after stroke. The time point of 5–14 days was chosen for the first time point because this is when patients are typically medically stable. The 3-month time point was selected as the acute effects of stress related to an adverse life event might have diminished, and is a common time point used in previous studies (5, 13). As PSA might be multifactorial, we collected comprehensive data to the extent possible, including clinical, physical, psychological, and neuroimaging variables. The present study showed that PSD was significantly associated with PSA both in the acute stage and 3 months after stroke, indicating that PSD and PSA may share a common pathophysiological mechanism. This comorbidity has been confirmed by other studies (2, 5, 37).

Available clinical data on the relationship between PSA and lesion location are conflicting. Tang et al. (13) found that patients with acute frontal lobe infarction were more likely to have PSA. Similar to other studies (8, 18, 40), we could not locate a single lesion location that was directly related to PSA. However, we found that patients with acute infarction in the CHWM were more likely to have PSA in the acute stage of stroke, as well as 3 months after stroke. This finding has not been reported previously. CHWM includes a wide range of regions of connected neural fibers in the cerebral hemisphere, e.g., corpus callosum, corona radiata, centrums semiovale, and internal capsule. Neural circuits associated with emotion regulation are widely distributed in the cerebral hemispheres, such as the fronto-subcortical circuits or the limbic system (41, 42). Brain white matter abnormalities have also been implicated in development of anxiety (17). Thus, acute CHWM lesions are logical potential contributors to PSA. However, the wide range of OR in CHWM in prediction of PSA indicates that this preliminary finding should be carefully repeated in further studies. Furthermore, after excluding patients

TABLE 6 | Summary of studies assessing the correlates or prevalence of anxiety in patients with ischemic stroke.

Study	Source of sample and sample size	Mean age	Sex (male)	Assessment tool of PSA	Assessment of ADL	Assessment of SSQOL	MRI assessment	Assessment time point	Frequency of PSA	Significant correlates
The present study	Hospital (*n* = 219)	61.4	73.1%	HARS	Yes	Yes	Yes	Acute stage and 3 m	15.5% (acute) 15.1% (3 m)	HDRS, acute infarcts in CHWM (acute) HDRS, male, acute infarcts in CHWM (3 m)
Schultz et al. (10)	Hospital (*n* = 142)	58.1	57%	*DSM-IV*	Yes	No	No	3 m 6 m 1 year 2 years	19% (acute) 22.1% (3 m) 25.3% (6 m) 11.4% (1 year) 18.2% (2 years)	Depression, ADL, and female
Chun et al. (38)	Hospital (*n* = 175)	69.6	60%	*DSM-IV*	No	Yes	No	3 m	22%	Pre-stroke depression, pre-stroke anxiety, EQ-5D5L, and young age
De Wit et al. (33)	European rehabilitation centers (*n* = 532)	69.5	53.3%	HADS-A	No	No	No	2 m 4 m 6 m	25% (2 m) 22% (4 m) 22% (6 m)	No significant correlates
Vuletić et al. (34)	Hospital (*n* = 40)	71.1	50%	HADS-A	No	No	No	Acute stage	40%	MMSE, BI
Wu et al. (36)	Hospital (*n* = 226)	63.13	62.84%	HARS	No	No	No	1 m	26.6%	Vitamin D deficiency
D'Aniello et al. (35)	Hospital (*n* = 81)	62	59.2%	HADS-A	No	No	No	Undefined	55.6%	No correlates
Vicentini et al. (12)	Hospital (*n* = 34)	NR	64.7%	BAI	No	No	Yes	Undefined	11.8%	Disruption of DMN
Liu et al. (18)	Hospital (*n* = 203)	63.5	64.5%	HARS	No	No	Yes	Acute stage	24.1%	MDA, GPX, SOD, and CAT
Lincoln et al. (37)	European rehabilitation centers (*n* = 220)	67.5	54%	HADS-A	No	No	No	5 years	29%	No correlates
Broomfield et al. (39)	Community (*n* = 3831)	70.39	55.3%	HADS-A	No	No	No	Undefined	16.1%	Age, gender, and socioeconomic deprivation
Tang et al. (13)	Hospital (*n* = 693)	65.6	61%	HADS-A	No	No	Yes	3 m	6.1%	Frontal infarcts

PSA, poststroke anxiety; ADL, activities of daily living; SSQOL, Stroke-Specific Quality of Life; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; CHWM, cerebral hemispheric white matter; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision; EQ-5D5L, EuroQoL-5D5L; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; MMSE, Mini-Mental State Examination; BI, Barthel Activities of Daily Living Index; BAI, Beck Anxiety Inventory; DMN, Default Mode Network; MDA, malondialdehyde; GPX, glutathione peroxidase; SOD, superoxide dismutase; CAT, catalase; NR, not recorded.

with previous strokes, CHWM only contributed to PSA in the acute stage, but not 3 months after stroke.

The role of CHWM in development of PSA remains unclear. Recently, studies have focused on lesions involving neuronal network or circuits rather than single locations. Fornito et al. (43) reported that functional neuronal network disruption may be more critical than lesion location to explain PSA. Vicentini et al. (12) reported that PSA was not associated with infarct location but correlated with disruption of the default mode network (DMN) in the brain. Accordingly, examining the effects of the integrity of brain networks or neural circuits rather than a single location on PSA might be another direction for further research.

The severity of PSA in the acute stage was inversely associated with performance of ADL in this study. Schultz et al. (10) reported that association of anxiety and impairment in ADL were present only at the initial evaluation (in the acute stage of ischemic stroke), with independent effects only for women. It can be postulated that PSA patients may have poor adherence to rehabilitative efforts because of a significant decrease in both physical and mental energy, which, in turn, impairs performance of ADL.

Stroke frequently reduces the level of health-related QOL (HRQOL) of survivors. Our study indicated that the severity of PSA in the acute stage was a significant contributor to poorer SSQOL 3 months after stroke. PSA may reduce physical and mental energy, motivation, and activity, which then inversely affects HRQOL. A cross-sectional study also found that poorer QOL was associated with greater levels of physical disability, anxiety, and depression, and reduced social interaction (44). Thus, assessment and intervention of PSA as well as PSD in the acute stage may be helpful to predict outcomes of functional status.

Our study has several strengths. First, we conducted a face-to-face interview to evaluate functional and psychological measures, which was rarely reported in other studies. Second, we obtained comprehensive MRI data from all participants. However, there were also several limitations to our study. First, only patients with mild-to-moderate ischemic stroke without severe cognitive impairment and aphasia were recruited, which limits the generalization of our findings. Second, we did not collect medication or rehabilitation after discharge, though most patients would have follow-up visits with neurologists or general physicians in community clinics. Third, we only used a screening tool (HDRS) rather than the standard psychiatric interview to define PSA, as there are no sufficient psychiatric professionals in our hospital. Lastly, the associations between PSA and QOL or ADL did not indicate causality due to the study design.

In general, anxiety is common in the acute and chronic stages of ischemic stroke with mild-to-moderate neurologic deficits. The lesion-location hypothesis of PSA might be relevant but remains uncertain. PSA in the acute stage may have a significant impact on ADL and HRQOL in stroke patients in the chronic stage. Early detection of anxiety symptoms may facilitate functional recovery and improve QOL in stroke patients. Careful evaluation of PSA should be integrated into clinical care of stroke patients.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Operational Guidelines for Ethics Committees That Review Biomedical Research, World Health Organization (2000), Ethics Committee of Dongguan People's Hospital" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the "Ethics Committee of Dongguan People's Hospital."

AUTHOR CONTRIBUTIONS

YC and WX designed the study. WL, JQ, and GL screened and collected the patients. WL and HW performed the psychological assessments. XF designed and trained the MRI assessment. YL assessed the MRI variables. WL and YC wrote the manuscript.

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REFERENCES

1. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. *Int J Stroke* (2013) 8(7):545–59. doi: 10.1111/j.1747-4949.2012.00906.x
2. Wright F, Wu S, Chun HY, Mead G. Factors associated with poststroke anxiety: a systematic review and meta-analysis. *Stroke Res Treat* (2017) 2017:2124743. doi: 10.1155/2017/2124743
3. Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS. Impact of anxiety on health-related quality of life after stroke: a cross-sectional study. *Arch Phys Med Rehabil* (2013) 94(12):2535–41. doi: 10.1016/j.apmr.2013.07.012
4. Lambiase MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke* (2014) 45(2):438–43. doi: 10.1161/STROKEAHA.113.003741
5. Barker-Collo SL. Depression and anxiety 3 months post stroke: prevalence and correlates. *Arch Clin Neuropsychol* (2007) 22(4):519–31. doi: 10.1016/j.acn.2007.03.002
6. Schottke H, Giabbiconi CM. Post-stroke depression and post-stroke anxiety: prevalence and predictors. *Int Psychogeriatr* (2015) 27(11):1805–12. doi: 10.1017/S1041610215000988
7. White JH, Attia J, Sturm J, Carter G, Magin P. Predictors of depression and anxiety in community dwelling stroke survivors: a cohort study. *Disabil Rehabil* (2014) 36(23):1975–82. doi: 10.3109/09638288.2014.884172
8. Fure B, Wyller TB, Engedal K, Thommessen B. Emotional symptoms in acute ischemic stroke. *Int J Geriatr Psychiatry* (2006) 21(4):382–7. doi: 10.1002/gps.1482
9. Galligan NG, Hevey D, Coen RF, Harbison JA. Clarifying the associations between anxiety, depression and fatigue following stroke. *J Health Psychol* (2016) 21(12):2863–71. doi: 10.1177/1359105315587140
10. Schultz SK, Castillo CS, Kosier JT, Robinson RG. Generalized anxiety and depression. Assessment over 2 years after stroke. *Am J Geriatr Psychiatry* (1997) 5(3):229–37. doi: 10.1097/00019442-199700530-00007
11. Carod-Artal FJ, Ferreira CL, rizotto DS, Menezes MC. Poststroke depression: prevalence and determinants in Brazilian stroke patients. *Cerebrovasc Dis* (2009) 28(2):157–65. doi: 10.1159/000226114

12. Vicentini JE, Weiler M, Almeida SRM, de Campos BM, Valler L, Li LM. Depression and anxiety symptoms are associated to disruption of default mode network in subacute ischemic stroke. *Brain Imaging Behav* (2017) 11(6):1571–80. doi: 10.1007/s11682-016-9605-7
13. Tang WK, Chen Y, Lu J, Liang H, Chu WC, Tong Mok VC, Frontal infarcts and anxiety in stroke. *Stroke* (2012) 43(5):1426–8. doi: 10.1161/STROKEAHA.111.640482
14. Astrom M. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. *Stroke* (1996) 27(2):270–5. doi: 10.1161/01.STR.27.2.270
15. Leppävuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T. Generalized anxiety disorders three to four months after ischemic stroke. *Cerebrovasc Dis* (2003) 16(3):257–64. doi: 10.1159/000071125
16. Allsop SA, Vander Weele CM, Wichmann R, Tye KM. Optogenetic insights on the relationship between anxiety-related behaviors and social deficits. *Front Behav Neurosci* (2014) 8:241. doi: 10.3389/fnbeh.2014.00241
17. Westlye LT, Bjørnebekk A, Grydeland H, Fjell AM, Walhovd KB. Linking an anxiety-related personality trait to brain white matter microstructure: diffusion tensor imaging and harm avoidance. *Arch Gen Psychiatry* (2011) 68(4):369–77. doi: 10.1001/archgenpsychiatry.2011.24
18. Liu Z, Cai Y, Zhang X, Zhu Z, He J. High serum levels of malondialdehyde and antioxidant enzymes are associated with post-stroke anxiety. *Neurol Sci* (2018) 39(6):999–1007. doi: 10.1007/s10072-018-3287-4
19. Raju RS, Sarma PS, Pandian JD. Psychosocial problems, quality of life, and functional independence among Indian stroke survivors. *Stroke* (2010) 41(12):2932–7. doi: 10.1161/STROKEAHA.110.596817
20. Jeong BO, Kang HJ, Bae KY, Kim SW, Kim JM, Shin IS, et al. Determinants of quality of life in the acute stage following stroke. *Psychiatry Investig* (2012) 9(2):127–33. doi: 10.4306/pi.2012.9.2.127
21. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* (1959) 32(1):50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x
22. Zhang MY. Depression and anxiety. In: Zhang MY, editor. *The rating scale for psychiatry*., 1st edn. Changsha: Hunan Science and Technology Press (1998). p. 30–2.
23. Katzman R, Zhang MY, Ouang-Ya-Qu, Wang ZY, Liu WT, Yu E, et al. A Chinese version of the mini-mental state examination; impact of illiteracy in a Shanghai dementia survey. *J Clin Epidemiol* (1988) 41(10):971–8. doi: 10.1016/0895-4356(88)90034-0
24. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
25. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* (1969) 9(3):179–86. doi: 10.1093/geront/9.3_Part_1.179
26. Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. *Stroke* (1999) 30(7):1362–9. doi: 10.1161/01.STR.30.7.1362
27. Tang WK, Chen YK, Lu JY, Chu WC, Mok VCT, Ungvari GS, et al. Cerebral microbleeds and depression in lacunar stroke. *Stroke* (2011) 42(9):2443–6. doi: 10.1161/STROKEAHA.111.614586
28. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* (1987) 149(2):351–6. doi: 10.2214/ajr.149.2.351
29. Papageorgiou C, Ziroyannis P, Vathylakis J, Grigoriadis A, Hatzikonstantinou V, Capsalakis Z. A comparative study of brain atrophy by computerized tomography in chronic renal failure and chronic hemodialysis. *Acta Neurol Scand* (1982) 66(3):378–85. doi: 10.1111/j.1600-0404.1982.tb06859.x
30. Victoroff J, Mack WJ, Grafton ST, Schreiber SS, Chui HC. A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. *Neurology* (1994) 44(12):2267–76. doi: 10.1212/WNL.44.12.2267
31. Galton CJ, Gomez-Anson B, Antoun N, Scheltens P, Patterson K, Graves M, et al. Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. *J Neurol Neurosurg Psychiatry* (2001) 70(2):165–73. doi: 10.1136/jnnp.70.2.165
32. Chen YK, Qu JF, Xiao WM, Li WY, Li W, Fang XW, et al. Intracranial atherosclerosis and poststroke depression in Chinese patients with ischemic stroke. *J Stroke Cerebrovasc Dis* (2016) 25(4):998–1004. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.038
33. De Wit L, Putman K, Baert I, Lincoln NB, Angst F, Beyens H, et al. Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. *Disabil Rehabil* (2008) 30(24):1858–66. doi: 10.1080/09638280701708736
34. Vuletić V, Sapina L, Lozert M, Lezaić Z, Morović S. Anxiety and depressive symptoms in acute ischemic stroke. *Acta Clin Croat* (2012) 51(2):243–6. doi: 10.1016/j.jstrokecerebrovasdis.2018.09.037
35. D'Aniello GE, Scarpina F, Mauro A, Mori I, Castelnuovo G, Bigoni M, et al. Characteristics of anxiety and psychological well-being in chronic post-stroke patients. *J Neurol Sci* (2014) 338(1–2):191–6. doi: 10.1016/j.jns.2014.01.005
36. Wu C, Ren W, Cheng J, Zhu B, Jin Q, Wang L, et al. Association between serum levels of vitamin D and the risk of post-stroke anxiety. *Medicine (Baltimore)* (2016) 95(18):e3566. doi: 10.1097/MD.0000000000003566
37. Lincoln NB, Brinkmann N, Cunningham S, Dejaeger E, De Weerdt W, Jenni W, et al. Anxiety and depression after stroke: a 5 year follow-up. *Disabil Rehabil* (2013) 35(2):140–5. doi: 10.3109/09638288.2012.691939
38. Chun HY, Whiteley WN, Dennis MS, Mead GE, Carson AJ. Anxiety after stroke: the importance of subtyping. *Stroke* (2018) 49(3):556–64. doi: 10.1161/STROKEAHA.117.020078
39. Broomfield NM, Scoular A, Welsh P, Walters M, Evans JJ. Poststroke anxiety is prevalent at the population level, especially among socially deprived and younger age community stroke survivors. *Int J Stroke* (2015) 10(6):897–902. doi: 10.1111/ijs.12109
40. Sharpe M, Hawton K, House A, Molyneux A, Sandercock P, Bamford J, et al. Mood disorders in long-term survivors of stroke: associations with brain lesion location and volume. *Psychol Med* (1990) 20(4):815–28. doi: 10.1017/S0033291700036503
41. Jiao Q, Ding J, Lu G, Su L, Zhang Z, Wang Z, et al. Increased activity imbalance in fronto-subcortical circuits in adolescents with major depression. *PLoS One* (2011) 6(9):e25159. doi: 10.1371/journal.pone.0025159
42. Calhoon GG, Tye KM. Resolving the neural circuits of anxiety. *Nat Neurosci* (2015) 18(10):1394–404. doi: 10.1038/nn.4101
43. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Nat Rev Neurosci* (2015) 16(3):159–72. doi: 10.1038/nrn3901
44. Howitt SC, Jones MP, Jusabani A, Gray WK, Aris E, Mugusi F, et al. A cross-sectional study of quality of life in incident stroke survivors in rural northern Tanzania. *J Neurol* (2011) 258(8):1422–30. doi: 10.1007/s00415-011-5948-6

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CASE REPORT
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Does the Use of Antidepressants Accelerate the Disease Progress in Creutzfeldt–Jakob Disease Patients With Depression? A Case Report and A Systematic Review

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Background: Creutzfeldt–Jakob disease (CJD) is a fatal neurodegenerative disorder characterized by rapidly progressive dementia. Growing evidence suggests that antidepressant usage was associated with dementia. Given the commonality of depression in CJD, it is necessary to investigate the effect of antidepressants on CJD.

Methods: First, we report a case of sporadic CJD (sCJD) with depression where the condition worsened rapidly after using a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant. Second, a systematic literature survey was conducted to investigate the effect of antidepressants on the survival time of sCJD patients with depression. Thirteen cases plus our case were included for qualitative analysis. Twelve subjects were included in the Kaplan–Meier survival and Cox regression analysis. Finally, we provide a postulation of pathophysiological mechanism in CJD.

Results: The median survival time of all patients was 6.0 months, of which patients with SNRIs were significantly shorter than those with first-generation antidepressants (2.0 vs. 6.0 months; log rank, P = .008) and relatively shorter than those with nonselective serotonin reuptake inhibitors (SSRIs; 4.0 vs. 6.0 months; log rank, P = .090). In comparison with first-generation antidepressants, the use of SNRIs [hazard ratio (HR), 23.028; 95% confidence interval (CI), 1.401 to 378.461; P = .028] remained independently associated with shorter survival time.

Conclusions: The use of antidepressants, especially SNRIs, was associated with a shorter survival time of sCJD patients. The possible changes in neurotransmitters should be emphasized. Scientifically, this study may provide insights into the mechanism of CJD. Clinically, it may contribute to the early diagnosis of CJD.

Keywords: depression, Creutzfeldt–Jakob disease, antidepressant, neurotransmitters, sleep wake disorders

INTRODUCTION

Depression is common in the elderly. Its prevalence rate is as high as 11.19%, and this increases progressively with worsening cognitive impairment (1). The presence of depression is an acknowledged risk factor for dementia (2); it can even double the risk for Alzheimer's disease (AD) (3, 4). Many reasons lie behind the prescription of antidepressant drugs, which increased dramatically from 1999

to 2014 (5). However, some studies have questioned whether antidepressants confer any benefits in terms of cognitive decline (6–9). Recently, a meta-analysis indicated that antidepressant usage was associated with AD/dementia (10). Tricyclic antidepressants (TCA) may be associated with a reduced risk (11) or no risk of dementia (12) for depressed patients, whereas nonselective serotonin reuptake inhibitors (SSRIs) antidepressant drugs, including monoamine oxidase (MAO) inhibitors, and serotonin and noradrenaline reuptake inhibitors (SNRIs) have been reported to possess an intermediate risk (11–13).

Creutzfeldt–Jakob disease (CJD), a fatal neurodegenerative disorder characterized by rapidly progressive dementia, is divided into the sporadic (sCJD), familial (fCJD), variant (vCJD), and iatrogenic (iCJD) subtypes (14). sCJD accounts for the majority, i.e., 85% of all CJD cases, with an annual worldwide incidence of one to two cases/million population (15). Although rare, the overall mortality rate of sCJD has been increasing since 1993 (16). There is no effective treatment for CJD, so it is important to identify modifiable risk factors for CJD and to delay disease progression. Psychiatric manifestations are often the first symptoms to appear in vCJD. Recent studies have shown that they are also more prevalent in sCJD than previously thought. Most commonly, these are exhibited as depression in 16%–37% of cases (17–19). While treatment of the psychiatric symptoms with hypnotics, anxiolytics, or antipsychotic drugs may offer relief to CJD patients, it appears that antidepressant drugs are ineffective (19). As is the case in some other dementias, the implication is that antidepressants may also fail to benefit CJD patients.

Here, we report a case of sCJD in which depression was the first symptom, and the condition worsened rapidly after the administration of an SNRI antidepressant. Subsequently, a systematic review of the literature was undertaken to explore the characteristics of sCJD patients with depressive symptoms as well as the effect of treatment with antidepressants on sCJD. This report aims to provide novel insights into the underlying causes and treatment of CJD and dementia.

CASE REPORT

Ms. S was a 63-year-old female with no previous medical or psychiatric history. In July 2017, she presented with dizziness, weakness, chronic shoulder pain, and high blood pressure. She informed her family that she felt helpless and sick. The preliminary examination revealed nothing but multiple lacunar infarcts in brain magnetic resonance imaging (MRI) scans. On September 17, 2017, she exhibited anhedonia, fear, anxiety, impatience, and a propensity to cry after being annoyed with others. She was examined in the psychiatric unit of the local hospital. Her value on the Self-rating Depression Scale (SDS) was 53.75, which pointed to mild depression, whereas on the Hastgawa Dementia Scale (HDS), she scored 13.0, which suggested probable dementia (education: primary school). The memory quotient (MQ) of Wechsler Memory Scale (WMS) was 59. Her sleep was normal. She was diagnosed with depression, and sertraline 50 mg/day was prescribed. Her symptoms nonetheless worsened with insomnia, garrulity, irritability, and gait imbalance. Her memory function deteriorated, and she became disoriented. The psychiatrist changed the antidepressant drug to venlafaxine 75 mg/day on October 8, 2017. However, instead of improving, the condition rapidly worsened. Her speech became hypophonic and monotonous with a paucity of content. She was sleepy during the day and sometimes burst into tears. Her arms curled up, indicating panic. She developed psychomotor retardation, responded poorly to questions, experienced visual hallucination, and suffered from a rigid posture with paroxysmal myoclonus and an inability to walk. The changes in her symptoms were initially considered to be side effects of venlafaxine. Two weeks later, she had deteriorated further and was unable to talk, exhibiting dysphagia and suffering from urinary incontinence. The symptoms did not improve after the withdrawal of the antidepressant. An assessment of her electroencephalogram (EEG) revealed generalized slow activity (**Figure 1A**). She was then transferred to the neurologic ward of our hospital where the following neurological findings were detected: akinetic mutism (AM), normal muscle strength, increased muscle tension, brisk tendon reflexes, and unresponsive pathologic reflexes. We performed a hematology screen for endocrine, metabolic, autoimmune, neoplastic, and infectious diseases, which were all negative. Cerebrospinal fluid (CSF) studies, including a paraneoplastic, an autoimmune antibody panel, and a tubercular, fungal antibody survey were also negative. Fluid-attenuated inversion recovery (FLAIR) of the brain MRI showed hyperintensities in the bilateral frontal lobe, corona radiate, and near the anterior and posterior horns of the lateral ventricle (**Figure 2A**). Diffusion-weighted imaging (DWI) showed hyperintensities in the bilateral caudate nucleus and putamen (**Figure 2B**). A diagnosis of CJD was considered. One week after admission, the second EEG was performed, revealing partially periodic sharp wave complexes (PSWC; **Figure 1B**). No gene mutations associated with genetic CJD were found, but methionine homozygotes were detected at codon 129 of the prion protein gene. The final diagnosis was probable sCJD according to the diagnostic criteria for sCJD (20, 21). Antibiotics, antiviral, and corticosteroid therapies had been tried since admission, but none of them worked. Ultimately, she was discharged from the hospital.

METHODS

Search Strategy and Study Selection

We searched PubMed, EMBASE, and PsycINFO up to May 2018 for previous cases using the key words "Creutzfeldt–Jakob disease AND depression." The reports were restricted to those published and unpublished in English and those including human subjects. The inclusion criteria were as follows: case reports, case series, previous literature reviews, or systematic reviews describing sCJD patients with depression as the first symptom and receiving the treatment for depression. The CJD patients had to meet the WHO or 2009 Consortium diagnostic criteria for definite or probable sCJD (20, 21). To minimize confounders, such as the effect of other medications on outcomes, the included cases were those in which depression was the only symptom diagnosed initially. Two authors independently decided on the selection.

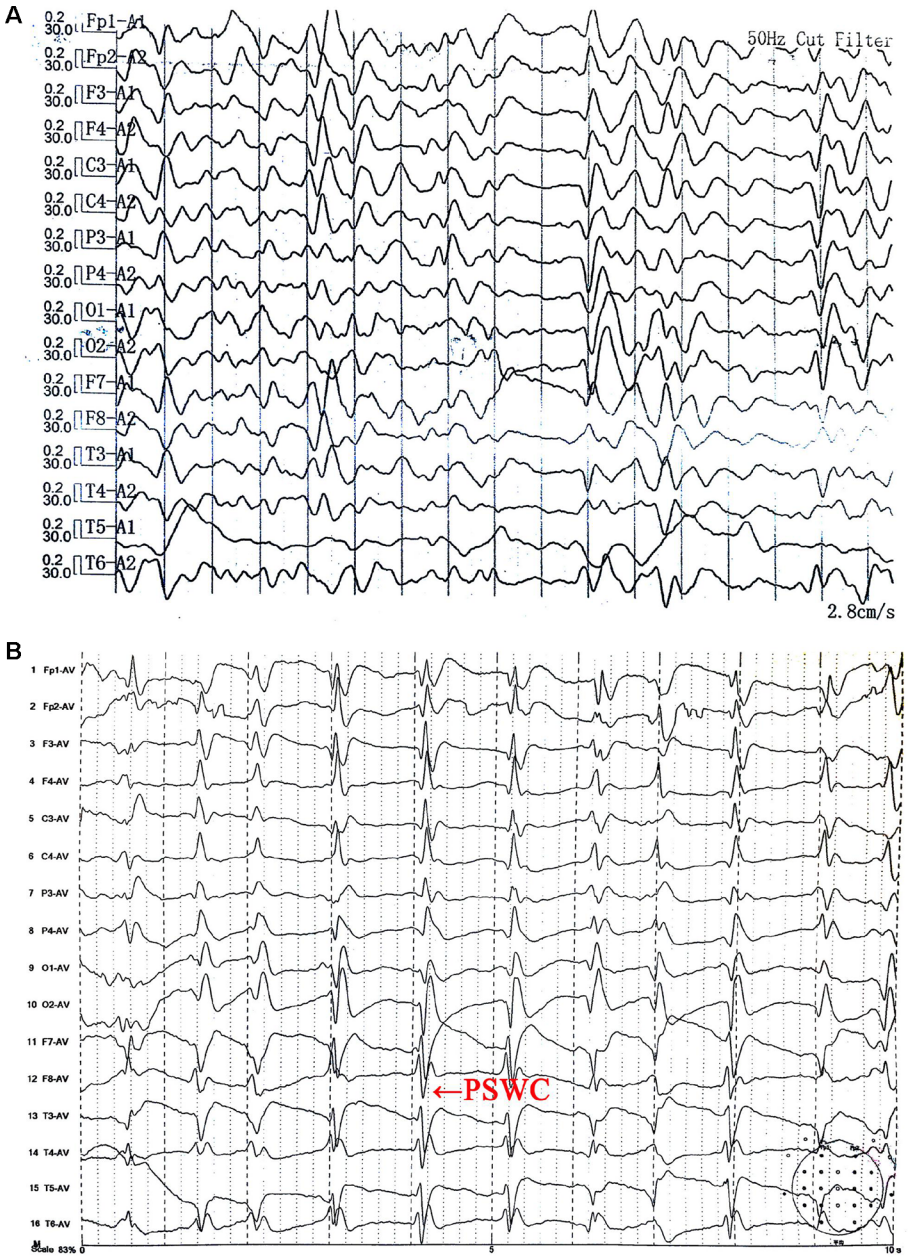

FIGURE 1 | Electroencephalogram (EEG) **(A)** on October 26, 2017 showed generalized slow activity. The second EEG **(B)** on November 2, 2017 showed partially periodic sharp wave complexes (PSWC).

Data Extraction

The data extracted included study name, study characteristics, patient characteristics, and the duration, institutional care, symptoms, examinations, treatments, and diagnosis of distinct phases. The duration of CJD patients was divided into three phases based on the main symptoms. The first phase was the prodromal phase, with mental manifestations; the second phase was the intermediate phase, with progressive dementia, myoclonus, psychiatric disorder, pyramidal signs, and extrapyramidal performance; the third phase was the late phase, with incontinence, AM, coma, or decorticate rigidity. If an article did not distinguish between the duration of the second and third phases, we utilized a value of half of the total duration of the two periods as their respective durations. Data were graded by two authors independently according to the Oxford Centre for Evidence-Based Medicine levels of evidence (22).

Statistical Analysis

A systematic analysis was performed. Categorical variables were described using proportions and continuous variables using medians and interquartile range (IQR). A Kaplan–Meier

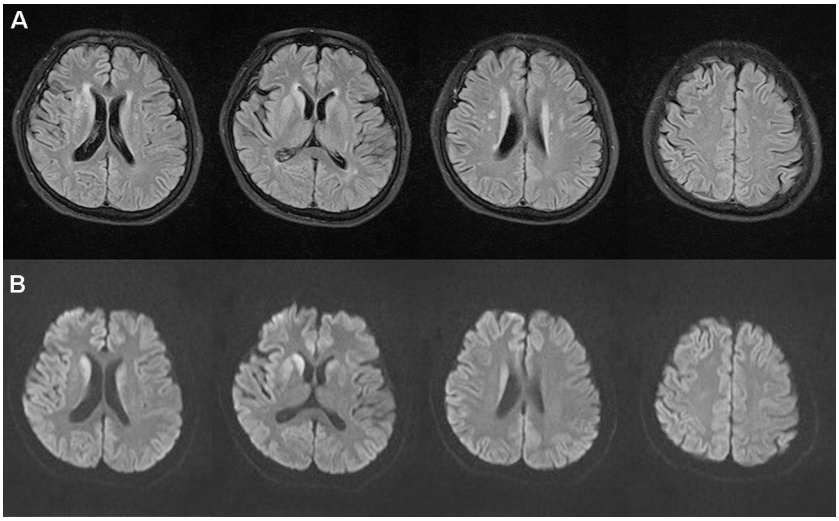

FIGURE 2 | Brain magnetic resonance imaging magnetic. Fluid-attenuated inversion recovery **(A)** showed hyperintensities in the bilateral frontal lobe, corona radiate, and near the anterior and posterior horns of the lateral ventricle. Diffusion-weighted imaging **(B)** showed hyperintensities in the bilateral caudate nucleus and putamen on November 1, 2017.

survival analysis was conducted in those patients for whom we had data on the three-phase duration and the use of antidepressants. Antidepressants were categorized into three classes, SSRIs, newer non-SSRI antidepressants (mostly SNRIs), and first-generation antidepressants (mostly TCA) according to the Anatomical Therapeutical Chemical (ATC) classification system (World Health Organization, 1999). The log rank test was used to compare the survival distributions of different groups. Finally, a multivariate Cox regression analysis with Enter was undertaken to determine the predictors of survival. Due to the small number of cases, we considered only three factors: gender, age, and antidepressant type. The model with a significant score test and a smaller deviance in likelihood ratio test will be preferred. Significance was set at $P < .05$ (two-sided test). Statistical analysis was completed using SPSS v17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study Identification and Characteristics

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (23). The PRISMA flow diagram is depicted in **eFigure** in the **Supplementary Material**. In our literature search, we identified 13 cases from 12 articles that met our inclusion criteria for qualitative analysis (24–35). Subsequently, 11 cases from 10 articles were included for qualitative analysis (24–26, 28, 30–35). With the addition of our case, a total of 12 subjects could be included in the Kaplan–Meier survival and multivariate Cox regression analysis.

The characteristics and evidence levels of the 14 cases published from 1993 to 2017 are shown in **eTable** in the **Supplementary Material**. All included articles were case reports. The age of all subjects was 58.8 (55.5–61.5) years with 11 (79%) being female. After administration of antidepressants, only 1 case out of 13 (8%) showed improved depressive symptoms.

Survival Time of Sporadic Creutzfeldt–Jakob Disease Patients with Different Antidepressants

A Kaplan–Meier survival curve for all of the sCJD patients who had used antidepressants is shown in **Figure 3**. The median survival time of all of the cases was 6.0 months. The cumulative incidences with survival times less than 3, 6, and 12 months were 30.0%, 90.0%, and 100%, respectively. All of the patients died within 1 year after onset.

The use of antidepressants in 12 cases is as follows: 3 (25%) were given SNRIs (1 censored), 4 (33%) were administered SSRIs (2 censored), and 5 (42%) were treated with first-generation antidepressants. The median survival times for cases with SNRIs, SSRIs, and first-generation antidepressants were 2.0, 4.0, and 6.0 months, respectively. The median survival time of patients with SNRIs was significantly shorter than those treated with first-generation antidepressants (log rank, $P = .008$) and relatively shorter than those with SSRIs (log rank, $P = .090$). Furthermore, the median survival time of patients receiving SSRIs was nonsignificantly shorter than those with the first-generation antidepressants (log rank, $P = .615$).

Predictors of Survival Time in Sporadic Creutzfeldt–Jakob Disease Patients With Depression

The Cox regression model including age and antidepressant types (**Table 1**) was preferred (likelihood ratio test, deviance = 25.469; score test, $P = .043$). Compared to first-generation antidepressants, the use of SNRIs [hazard ratio (HR), 23.028; 95% confidence interval (CI), 1.401 to 378.461; $P = .028$] remained

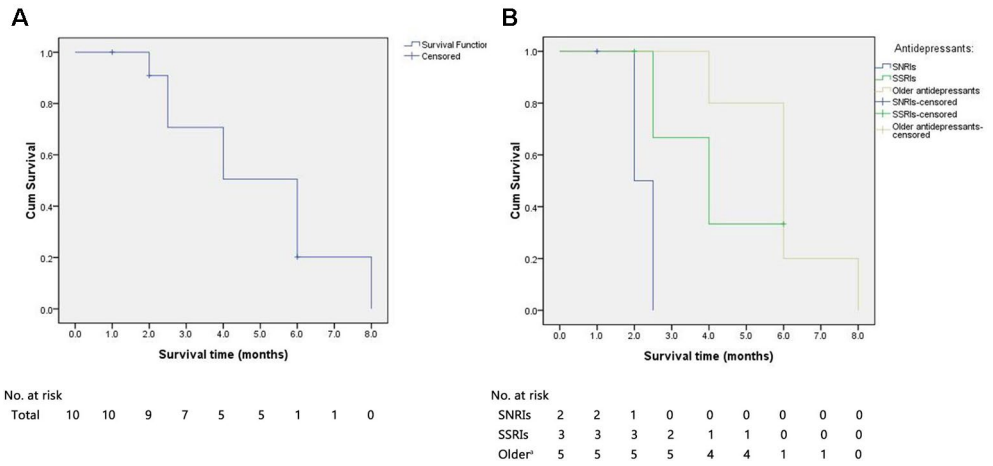

FIGURE 3 | The Kaplan–Meier survival curves for sCJD patients with antidepressants. **(A)** Survival time for all patients. **(B)** Survival time for patients stratified according to the type of antidepressant. X-axis represents survival time (months) and Y-axis represents survival probability. sCJD = sporadic Creutzfeldt–Jakob disease; SNRIs = serotonin and noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors. [a]Referred to first-generation antidepressants.

TABLE 1 | Cox regression analysis of survival time in sCJD patients with depression.

Factors	Unadjusted		Adjusted[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.015 (0.947–1.087)	.677	1.042 (0.955–1.136)	.354
Antidepressants	NA	.103	NA	.086
SNRIs	15.665 (1.215–201.884)	.035*	23.028 (1.401–378.461)	.028*
SSRIs	1.432 (0.256–8.018)	.683	2.689 (0.295–24.498)	.380
First-generation antidepressants (reference)	NA	NA	NA	NA

sCJD, sporadic Creutzfeldt–Jakob disease; HR, hazard ratio; C, confidence interval; NA, not applicable (outcome not investigated); SNRIs, serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a]Adjusted for age and antidepressant types.

**P < .05.*

independently associated with significantly shorter survival time in sCJD patients with depression.

DISCUSSION

Since depression is one of the most common global mental health conditions, the use of antidepressant drugs has increased dramatically with almost half of the prescriptions being for some off-label indication (36). However, our investigation revealed that almost none of the sCJD patients experienced any relief of their depressive symptoms after the antidepressant treatment. Furthermore, the median survival time of sCJD patients receiving SNRI therapy was shorter than the average survival of sCJD patients (2.3 vs. 4.6–17.4 months) (16). Thus, antidepressants do not seem to have any beneficial effect on sCJD patients with depression, a finding consistent with previous clinical studies not only on sCJD patients but also those with dementia (10, 19). Likewise, the efficacy characteristics of antidepressants indicate that antidepressants appear to display relatively poor efficacy in people older than 65 years (37). Based on the neurotransmitter receptor hypothesis of antidepressant drugs, the amount of neurotransmitter changes rapidly after an antidepressant is administered. But the clinical effects appear only weeks later (usually 6–12 weeks) (37). Due to the rapid progress of the disease, sCJD patients often use antidepressants for only a brief period. Therefore, the drugs usually cannot achieve clinical efficacy but are instead likely to exert unwanted side effects.

The question arises as to why patients with sCJD receiving antidepressants seem to deteriorate faster. Since antidepressants mainly alter neurotransmitter levels, we postulate that this deterioration must be related to these changes. Several independent lines of evidence support this postulation. sCJD resembles the degenerative dementias. Studies of AD, the best-known of the degenerative dementias, have proved that the accumulations of β-amyloid (Aβ) and tau proteins damage neurons and synapses, whereas the change in neurotransmitters such as acetylcholine (ACh) occurs at the initial stage (38). Similarly, the cause of sCJD neuropathological changes has also proved to be a reversible process, such as synaptic or neuronal dysfunction (39). Interestingly, patients with sCJD also have higher concentrations of Aβ and tau proteins in their serum and CSF (40, 41). Aβ may be propagated in a prion-like manner (42, 43). Similar observations have been made for tau (44). Because sCJD and AD share these common features (45), perhaps we can also attempt to delay the

progress of sCJD by regulating the level of neurotransmitters. Furthermore, the typical lesions in MRI and histologic appearance in sCJD consist of cortical, basal ganglia, and cerebellum (46, 47). It was observed that the clinical target areas in the brainstem of prion-infected mice were the locus coeruleus, the nucleus of the solitary tract, and the pre-Bötzinger complex (48). These brain areas are exactly those in which the neuronal cell bodies generating neurotransmitters are mainly located or the areas innervated by their axonal projections.

How do these neurotransmitters modulate disease progression? According to our study, the survival period of sCJD patients is related to the type of antidepressants. By analyzing the pharmacological characteristics, we postulate that elevations in 5-hydroxytryptamine (5-HT) and norepinephrine (NE) may worsen the condition, although the sedative effects mediated by anti-histamine (HA), anti-ACh, and blockade of α-1 adrenoceptors may contribute to the relief of symptoms. Acute stimulation of the 5-HT can produce symptoms similar to sCJD (37). Neurotransmitters exist in many brain areas, but which area plays the key role? When SSRI treatment is initiated, the concentrations of 5-HT are elevated to a much greater extent at the somatodendritic area located in the midbrain raphe, rather than in the brain areas where the axons terminate (37). Therefore, SSRIs may exert more significant effects on the brainstem in patients with sCJD. However, the pathological changes in sCJD do not occur in the brainstem but rather in the projection pathways of neurotransmitters, such as cortical, basal ganglia, and cerebellum. This raises the question of how changes in the brainstem's neurotransmitter activities affect other brain areas. Taking into account the symptoms (such as myoclonus that occurs at night, AM) of patients with sCJD, we postulate that one pathway through which brainstem's neurotransmitter activities trigger cognitive impairment encountered in sCJD patients may be through its disruption of sleep centers in the brainstem. AM is a disorder caused by damage to the ascending reticular activating system (ARAS) centered on the brainstem. Arousal is regulated by ARAS, which is influenced in large part by five key neurotransmitters: HA, dopamine (DA), NE, 5-HT, and ACh. Changes in these neurotransmitters can cause sleep disorders, i.e., rapid eye movement (REM) sleep without atonia (RSWA), and nonrapid eye movement (NREM) sleep disruption. Clinical studies have shown that SSRIs and SNRIs are associated with a higher prevalence of RSWA (49), explained in part by the theories about REM sleep initiation that advocate for a double switch model, possibly triggered by neurons located in the brainstem (50). Sleep disorders can cause many symptoms similar to sCJD, such as psychiatric symptoms (fear, anger, aggressive behavior, etc.), increased muscle tone, and most notably, cognitive impairment. For example, REM sleep behavior disorder (RBD) is by far the strongest clinical predictor of onset of neurodegenerative diseases (51). The presence of RBD in Parkinson's disease (PD) is associated with higher risk of cognitive decline (52). The reduced NREM slow-wave activity (SWA) generation was associated with impaired hippocampus-dependent memory consolidation (53). The Aβ burden in the medial prefrontal cortex correlates significantly with the severity of impairment in NREM SWA generation (53). Even one night of sleep deprivation could result in a significant increase in Aβ burden in the brain (54). Thus, the dual excitatory effects of 5-HT and NE may exacerbate the sleep deprivation encountered in sCJD patients, causing a cascading effect and then triggering cognitive impairment.

Why is the effect of neurotransmitters so rapid in sCJD patients? One reason may be the pathological overactivity of the brain's serotonergic system in this disease. This hypothesis is supported by the evidence that the mean tryptophan hydroxylase (TPH)-positive cell size was significantly greater and cells were more intensely stained in CJD compared to controls (55). This may result in an increase in release of 5-HT. Coupled with the cascade effect of neurotransmitters, the actual effects may be amplified. The increase in 5-HT also reduced the release of DA in the prefrontal zone by negative feedback regulation (37). The reduction of DA may cause some symptoms similar to sCJD, such as cognitive impairment and apathy. Another reason could be that synapses in sCJD may be more vulnerable. The pathological features of CJD indicate that the vacuole in the cytoplasm is the cystic dilation of neurons and necrosis of the necrotic membrane. The cell membrane damage of CJD seems to be more serious than AD, where amyloid plaques form outside the neurons and neuron fibers entangle within the neurons. Damage to the synaptic membrane leads to a decrease in neurotransmitter receptors. In response to this change, the remaining receptors may be in a hypersensitivity state, or the number of receptors may increase (37), which may further enhance the effects of neurotransmitters such as 5-HT.

Many of the families of patients with sCJD complain of the delay in diagnosis and the plethora of misdiagnoses (56). Expediating a sCJD diagnosis is of great significance. Almost half of patients were misdiagnosed first as "psychiatric patients" (57). Consequently, it is very important for psychiatrists to consider CJD among the possible differential diagnoses in elderly patients. Our investigation suggests that it may be helpful to use imaging such as functional MRI and positron emission computed tomography (PET) to detect earlier changes in patients with sCJD.

Of course, our study has some limitations. First, the number of available cases is too small, and in many cases, the description of psychiatric symptoms and details of the antidepressants were inadequate. Second, because case reports tend to report exceptional situations, there is inevitably some bias. However, we think it is a reasonable approach to study CJD by undertaking case analysis or studies of one single individual. Due to the rapid progression of CJD, studies on population samples often overlook certain unique changes.

Investigations into sCJD have mainly focused on autopsy-based pathology, but little is known about neurophysiological changes. We hope this study will draw attention to the depressive symptoms of sCJD patients and the underlying neurophysiological mechanisms.

CONCLUSIONS

The use of antidepressants was associated with a shorter survival time of sCJD patients, especially the use of SNRIs. The possible neurotransmitter changes may be due to a pathophysiological

mechanism in CJD. Functional imaging and use of the polysomnogram to detect earlier changes in sCJD patients may be worth trying.

ETHICS STATEMENT

This case study was carried out in accordance with the recommendations of the Ethical Committee of China Medical University. The case study has been approved by the Ethics Committee of China Medical University. The subject gave written informed consent in accordance with the Declaration of Helsinki. Written informed consent was also obtained from each patient for the publication of this case report.

AUTHOR CONTRIBUTIONS

CZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CZ and YLia contributed to the study concept and design. YLi contributed to the case report. YLia, YLi, MG, and SZ contributed to the acquisition, analysis, or interpretation of data. YLia, HW, and XC drafted the manuscript. CZ conducted the critical revision of the manuscript for important intellectual content. All authors performed the statistical analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00297/full#supplementary-material

REFERENCES

1. Steffens DC, Fisher GG, Langa KM, Potter GG, Plassman BL. Prevalence of depression among older Americans: the Aging, Demographics and Memory Study. *Int Psychogeriatr* (2009) 21:879–88. doi: 10.1017/S1041610209990044
2. WHO. *Dementia*. Fact sheet [Updated December 2017]. Geneva, Switzerland: World Health Organization (2017). Available at www.who.int/mediacentre/factsheets/fs362/en/
3. Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *Eur J Pharmacol* (2010) 626:64–71. doi: 10.1016/j.ejphar.2009.10.022
4. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease: a longitudinal analysis. *Neurology* (2015) 84:617–22. doi: 10.1212/WNL.0000000000001238
5. Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over: United States, 2011–2014. *NCHS Data Brief, no. 283*. Hyattsville, MD: National Center for Health Statistics (2017). Available at https://www.cdc.gov/nchs/data/databriefs/db283.pdf
6. Dawes SE, Palmer BW, Meeks T, Golshan S, Kasckow J, Mohamed S, et al. Does antidepressant treatment improve cognition in older people with schizophrenia or schizoaffective disorder and comorbid subsyndromal depression. *Neuropsychobiology* (2012) 65:168–72. doi: 10.1159/000331141
7. Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder. *Int Clin Psychopharmacol* (2011) 26:316–22. doi: 10.1097/YIC.0b013e32834ace0f
8. Rosenberg PB, Mielke MM, Han D, Leoutsakos JS, Lyketsos CG, Rabins PV, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. *Int J Geriatr Psychiatry* (2012) 27:1248–57. doi: 10.1002/gps.3769
9. Årdal G, Hammar Å. Is impairment in cognitive inhibition in the acute phase of major depression irreversible? Results from a 10-year follow-up study. *Psychol Psychother* (2011) 84:141–50. doi: 10.1348/147608310X502328
10. Moraros J, Nwankwo C, Patten SB, Mousseau DD. The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: A systematic review and meta-analysis. *Depress Anxiety* (2017) 34:217–26. doi: 10.1002/da.22584
11. Lee CW, Lin CL, Sung FC, Liang JA, Kao CH. Antidepressant treatment and risk of dementia: a population-based, retrospective case–control study. *J Clin Psychiatry* (2016) 77:117–22. doi: 10.4088/JCP.14m09580
12. Kessing LV, Søndergård L, Forman JL, Andersen PK. Antidepressants and dementia. *J Affect Disord* (2009) 117:24–9. doi: 10.1016/j.jad.2008.11.020
13. Wang C, Gao S, Hendrie HC, Kesterson J, Campbell NL, Shekhar A, et al. Antidepressant use in the elderly is associated with an increased risk of dementia. *Alzheimer Dis Assoc Disord* (2016) 30:99–104. doi: 10.1097/WAD.0000000000000103
14. Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, et al. Mortality from Creutzfeldt–Jakob disease and related disorders in Europe, Australia, and Canada. *Neurology* (2005) 64:1586–91. doi: 10.1212/01.WNL.0000160117.56690.B2
15. Mead S, Stumpf MP, Whitfield J, Beck JA, Poulter M, Campbell T, et al. Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. *Science* (2003) 300:640–3. doi: 10.1126/science.1083320
16. Chen C, Dong XP. Epidemiological characteristics of human prion diseases. *Infect Dis Poverty* (2016) 5:47. doi: 10.1186/s40249-016-0143-8
17. Krasnianski A, Bohling GT, Harden M, Zerr I. Psychiatric symptoms in patients with sporadic Creutzfeldt–Jakob disease in Germany. *J Clin Psychiatry* (2015) 76:1209–15. doi: 10.4088/JCP.13m08915
18. Rabinovici GD, Wang PN, Levin J, Cook L, Pravdin M, Davis J, et al. First symptom in sporadic Creutzfeldt–Jakob disease. *Neurology* (2006) 66:286–7. doi: 10.1212/01.wnl.0000196440.00297.67
19. Wall CA, Rummans TA, Aksamit AJ, Krahn LE, Pankratz VS. Psychiatric manifestations of Creutzfeldt–Jakob disease: a 25-year analysis. *J Neuropsychiatry Clin Neurosci* (2005) 17:489–95. doi: 10.1176/jnp.17.4.489
20. WHO. Human transmissible spongiform encephalopathies. *Wkly Epidemiol Rec* (1998) 73:361–5.
21. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt–Jakob disease. *Brain* (2009) 132:2659–68. doi: 10.1093/brain/awp191
22. OCEBM Levels of Evidence Working Group. *The Oxford 2011 levels of evidence*. Oxford, England: Oxford Centre for Evidence-Based Medicine (2016). Available at www.cebm.net/index.aspx?o=5653
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* (2009) 151:264–9. doi: 10.7326/0003-4819-151-4-200908180-00135
24. Azorin JM, Donnet A, Dassa D, Gambarelli D. Creutzfeldt–Jakob disease misdiagnosed as depressive pseudodementia. *Compr Psychiatry* (1993) 34:42–4. doi: 10.1016/0010-440X(93)90034-2
25. Goetz KL, Price TR. Electroconvulsive therapy in Creutzfeldt–Jakob disease. *Convuls Ther* (1993) 9:58–62.

26. González-Duarte A, Medina Z, Balaguer RR, Calleja JH. Can prion disease suspicion be supported earlier? Clinical, radiological and laboratory findings in a series of cases. *Prion* (2011) 5:201–7. doi: 10.4161/pri.5.3.16187
27. Grande I, Fortea J, Gelpi E, Flamarique I, Udina M, Blanch J, et al. Atypical Creutzfeldt–Jakob disease evolution after electroconvulsive therapy for catatonic depression. *Case Rep Psychiatry* (2011) 2011:791275. doi: 10.1155/2011/791275
28. Jardri R, DiPaola C, Lajugie C, Thomas P, Goeb JL. Depressive disorder with psychotic symptoms as psychiatric presentation of sporadic Creutzfeldt–Jakob disease: a case report. *Gen Hosp Psychiatry* (2006) 28:452–4. doi: 10.1016/j.genhosppsych.2006.05.005
29. Jiang TT, Moses H, Gordon H, Obah E. Sporadic Creutzfeldt–Jakob disease presenting as major depression. *South Med J* (1999) 92:807–8. doi: 10.1097/00007611-199908000-00012
30. Milanlioglu A, Ozdemir PG, Cilingir V, Ozdemir O. Catatonic depression as the presenting manifestation of Creutzfeldt–Jakob disease. *J Neurosci Rural Pract* (2015) 6:122. doi: 10.4103/0976-3147.143220
31. Muayqil T, Siddiqi ZA. Sporadic Creutzfeldt–Jakob disease with worsening depression and cognition. *Can J Neurol Sci* (2007) 34:464–6. doi: 10.1017/S031716710000737X
32. Onofrj M, Fulgente T, Gambi D, Macchi G. Early MRI findings in Creutzfeldt–Jakob disease. *J Neurol* (1993) 240:423–6. doi: 10.1007/BF00867355
33. Power B, Trivedi D, Samuel M. What psychiatrists should know about sporadic Creutzfeldt–Jakob disease. *Australas Psychiatry* (2012) 20:61–6. doi: 10.1177/1039856211430145
34. Wang YT, Wu CL. Probable sporadic Creutzfeldt–Jakob disease mimicking a catatonic depression in an elderly adult. *Psychogeriatrics* (2017) 17(6):524–5. doi: 10.1111/psyg.12264
35. Yang HY, Huang SS, Lin CC, Lan TH, Chan CH. Identification of a patient with sporadic Creutzfeldt–Jakob disease in a psychiatric ward. *Psychiatry Clin Neurosci* (2013) 67:280–1. doi: 10.1111/pcn.12049
36. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. *BMJ* (2017) 356:j603. doi: 10.1136/bmj.j603
37. Stahl SM. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 4th ed. New York: Cambridge University Press (2014).
38. Wang L, Benzinger TL, Su Y, Christensen J, Friedrichsen K, Aldea P, et al. Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between β-amyloid and tauopathy. *JAMA Neurol* (2016) 73:1070–7. doi: 10.1001/jamaneurol.2016.2078
39. Soto C, Satani N. The intricate mechanisms of neurodegeneration in prion diseases. *Trends Mol Med* (2011) 17:14–24. doi: 10.1016/j.molmed.2010.09.001
40. Thompson AGB, Luk C, Heslegrave AJ, Zetterberg H, Mead SH, Collinge J, et al. Neurofilament light chain and tau concentrations are markedly increased in the serum of patients with sporadic Creutzfeldt–Jakob disease, and tau correlates with rate of disease progression. *J Neurol Neurosurg Psychiatry* (2018) 89(9):955–61. doi: 10.1136/jnnp-2017-317793
41. Leitão MJ, Baldeiras I, Almeida MR, Ribeiro MH, Santos AC, Ribeiro M, et al. CSF Tau proteins reduce misdiagnosis of sporadic Creutzfeldt–Jakob disease suspected cases with inconclusive 14-3-3 result. *J Neurol* (2016) 263:1847–61. doi: 10.1007/s00415-016-8209-x
42. Frontzek K, Lutz MI, Aguzzi A, Kovacs GG, Budka H. Amyloid-β pathology and cerebral amyloid angiopathy are frequent in iatrogenic Creutzfeldt–Jakob disease after dural grafting. *Swiss Med Wkly* (2016) 146:w14287. doi: 10.4414/smw.2016.14287
43. Jucker M, Walker LC. Neurodegeneration: amyloid-β pathology induced in humans. *Nature* (2015) 525:193–4. doi: 10.1038/525193a
44. Alonso AD, Beharry C, Corbo CP, Cohen LS. Molecular mechanism of prion-like tau-induced neurodegeneration. *Alzheimers Dement* (2016) 12:1090–7. doi: 10.1016/j.jalz.2015.12.014
45. Debatin L, Streffer J, Geissen M, Matschke J, Aguzzi A, Glatzel M. Association between deposition of beta-amyloid and pathological prion protein in sporadic Creutzfeldt–Jakob disease. *Neurodegener Dis* (2008) 5:347–54. doi: 10.1159/000121389
46. Fragoso DC, Gonçalves FAL, Pacheco FT, Barros BR, Aguiar LI, Nunes RH, et al. Imaging of Creutzfeldt–Jakob disease: imaging patterns and their differential diagnosis. *Radiographics* (2017) 37:234–57. doi: 10.1148/rg.2017160075
47. Liberski PP. Spongiform change—an electron microscopic view. *Folia Neuropathol* (2004) 42 Suppl B:59–70.
48. Mirabile I, Jat PS, Brandner S, Collinge J. Identification of clinical target areas in the brainstem of prion-infected mice. *Neuropathol Appl Neurobiol* (2015) 41:613–30. doi: 10.1111/nan.12189
49. Lee K, Baron K, Soca R, Attarian H. The prevalence and characteristics of REM sleep without atonia (RSWA) in patients taking antidepressants. *J Clin Sleep Med* (2016) 12:351–5. doi: 10.5664/jcsm.5582
50. Peever J, Luppi PH, Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci* (2014) 37:279–88. doi: 10.1016/j.tins.2014.02.009
51. Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol* (2006) 5:572–7. doi: 10.1016/S1474-4422(06)70476-8
52. Vendette M, Gagnon JF, Décary A, Massicotte-Marquez J, Postuma RB, Doyon J, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology* (2007) 69:1843–9. doi: 10.1212/01.wnl.0000278114.14096.74
53. Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, et al. β-Amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* (2015) 18:1051–7. doi: 10.1038/nn.4035
54. Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A* (2018) 115:4483–8. doi: 10.1073/pnas.1721694115
55. Fraser E, McDonagh AM, Head M, Bishop M, Ironside JW, Mann DM. Neuronal and astrocytic responses involving the serotonergic system in human spongiform encephalopathies. *Neuropathol Appl Neurobiol* (2003) 29:482–95. doi: 10.1046/j.1365-2990.2003.00486.x
56. Paterson RW, Torres-Chae CC, Kuo AL, Ando T, Nguyen EA, Wong K, et al. Differential diagnosis of Jakob–Creutzfeldt disease. *Arch Neurol* (2012) 69:1578–82. doi: 10.1001/2013.jamaneurol.79
57. Abudy A, Juven-Wetzler A, Zohar J. The different faces of Creutzfeldt–Jacob disease CJD in psychiatry. *Gen Hosp Psychiatry* (2014) 36:245–8. doi: 10.1016/j.genhosppsych.2014.02.002

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CASE REPORT
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Clinical Study of Restless Leg Syndrome Accompanied by Psychological Symptoms Induced by High-Dose Treatment With Madopar

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Objectives: Some neurological disorders demonstrate indistinguishable psychological symptoms at an early stage, especially when accompanied by jitters similar to those in Parkinson's disease. During dopamine replacement therapy, some patients display restless leg syndrome (RLS)-like symptoms. Therefore, we aimed to analyze treatment strategies and the prognosis of RLS caused by high-dose Madopar.

Methods: Nine patients who were misdiagnosed with Parkinson's disease, taking a high dose of Madopar, and showed symptoms of anxiety, depression, and somatization were recruited. Clinical data were collected, and strategies of treatment and prognosis were analyzed.

Results: Seven patients demonstrated varying degrees of anxiety and depression, and the other two cases were misdiagnosed as Parkinson's disease. During Madopar treatment, patients gradually showed aggravated symptoms, including swelling, numbness, pain, and other sensory abnormalities in both lower extremities, which spread to both upper extremities in a few patients. Among the seven patients, symptoms of anxiety, depression, insomnia, and somatization significantly worsened during the observation period. The average time from taking Madopar to the appearance of RLS was 2.6 ± 0.6 months, the average time to clinical diagnosis was 18.17 ± 9.40 months, and the average dosage of Madopar was 1.44 ± 0.21 g per day. Gradually reducing the Madopar dosage and administering a small dose of long-acting dopamine preparation greatly alleviated the symptoms after 3 months.

Conclusion: A high dose of Madopar can cause RLS-like symptoms accompanied by anxiety, depression, insomnia, and other mental health symptoms. These symptoms should be more closely monitored by clinicians.

Keywords: Madopar, restless leg syndrome, anxiety, depression, psychological symptoms

INTRODUCTION

Psychiatric symptoms, such as anxiety, depression, insomnia, and somatization, are the clinical manifestations of common psychiatric and neurological diseases. Many neurological disorders show these indistinguishable psychological symptoms in the early stages, especially when symptoms similar to Parkinson's disease (e.g., difficulty walking, stiff limbs, and tremors) are present. These patients are likely to be misdiagnosed with Parkinson's disease and are treated with dopamine replacement therapy; however, in rare cases, increasing the dosage of dopamine can elicit restless leg syndrome (RLS). Extended durations of these psychiatric symptoms can be detrimental to the patient's physical and mental health.

The present study assessed a group of patients who were misdiagnosed with Parkinson's disease and were administered large doses of Madopar. All the patients exhibited rare RLS-like symptoms, such as difficulty in walking, stiff limbs, and tremors, which were accompanied by anxiety, depression, and other psychiatric symptoms. Clinical data of all patients were collected, and strategies of treatment and prognosis were analyzed.

MATERIALS AND METHODS

Patients

The present study was approved by the Ethics Committee of the First People's Hospital of Huainan, and written informed consent was provided. Twelve patients demonstrating symptoms of anxiety, depression, and somatization due to misdiagnosis of Parkinson's disease and taking a large dose of Madopar were identified and recruited from January 2010 to December 2017. Two Parkinson's disease patients did not meet the inclusion criteria, and one patient declined to follow up. Therefore, nine patients (47–78 years old) were enrolled. All nine patients were hospitalized, and after a detailed evaluation of medical history, rigorous neurological physical examination, and related auxiliary tests, they were determined to not meet the criteria for Parkinson's disease according to the British Parkinson's Disease Society (1). Anxiety, depression, insomnia, and somatization symptoms were diagnosed as depression and anxiety disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (2). All patients underwent general routine examinations as well as biochemical and imaging examinations. No abnormalities were noted except for the primary disease. The diagnosis for RLS was based on clinical criteria (3) and included an urge to move the legs, usually associated with unpleasant sensations; symptoms occurring during periods of rest, such as sitting or lying down; symptoms relieved by movement; and worsened symptoms in the evening or night.

The education level of all patients was above primary school, and they could independently complete the questionnaire without communication barriers. All patients agreed to follow up.

Laboratory and Imaging Examinations

Routine blood, urine, fecal, serum glucose level, liver and kidney function, thyroxine, and electrolyte laboratory and physical examinations were conducted. Electroencephalogram and brain magnetic resonance imaging were performed in all patients.

Clinical Evaluation and Follow-Up

Severity of RLS was evaluated on the basis of the International RLS Rating Scale (IRLS-RS) (4). The diagnosis and severity of insomnia, anxiety, and depression in all patients were assessed by two neurologists and a psychiatrist according to the Insomnia Severity Index (ISI) (5), Hamilton Anxiety Rating Scale (Hamilton) (6), Hamilton Depression Rating Scale (HDRS) (7), and DSM-5 diagnostic criteria (2) combined with clinical symptoms and signs. Follow-up data for all patients with RLS were obtained during face-to-face or telephone interviews.

Clinical Research Flow

The clinical study flow is shown in **Figure 1**.

Statistical Analysis

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) version 19.0 (SPSS Inc., Chicago, IL, USA). The normality of the distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed quantitative data were presented as "mean ± standard deviation (SD)." The international RLS scores of patients before and after treatment were compared by *t*-test. The anxiety, depression, and insomnia

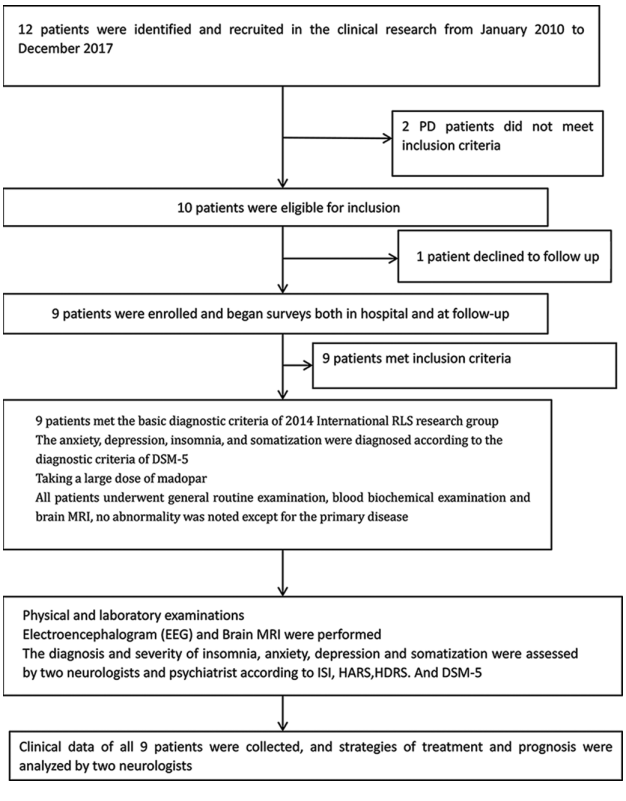

FIGURE 1 | Large doses of Madapor.

scores of patients before and after taking a large dose of Madopar were compared using the Student's *t*-test. *P* values <0.05 were considered significant.

RESULTS

Nine patients took Madopar orally due to being misdiagnosed with Parkinson's disease, and the starting dosage ranged from 1/2 to 1 tablet (0.25 g/tablet). All patients gradually increased the amount of medication administered. Some were under the guidance of a doctor, but then to achieve the "curative effect," patients increased the amount of medication themselves. Some patients increased their doses by themselves from the beginning (i.e., without the doctor's assistance). The amount of medication in most patients was 2–3 tablets per dose, 3–4 times per day, which was at maximum 5 tablets per dose, 3–5 times a day in one case. When the average dosage reached 6–8 tablets per day and the duration of administration lasted 2–4 weeks, the onset of bilateral lower limb discomfort appeared. Initially, the symptoms were minimal, which did not alert the attention of the patients. As the medication dosage and duration increased, so did the symptoms, which appeared as unexplained abnormal sensations in both lower extremities to varying degrees, such as numbness, swelling, crawling, burning, and traction pain at night. The symptoms could be temporarily reduced by activity, which forced patients to stay out of bed for exercises, which affected their sleep. As a result, patients typically increased the dose of Madopar, which could reduce the symptoms, especially when the symptoms were unbearable. The increasing dosage of Madopar could effectively improve the symptoms, and thus forced patients to increase the amount of medication.

During this cycle, when symptoms appeared during the daytime, the upper limbs and occasionally the entire body displayed varying degrees of involvement. As shown in **Table 1**, the average time from the use of the Madopar to the onset of RLS symptoms was 2.61 ± 0.60 months. For symptoms to appear, the minimum of the average daily dose of Madopar was 1.44 ± 0.21 g; moreover, the average duration for the nine patients with RLS from the time of high-dose Madopar administration to the time of hospital admissions was 18.17 ± 9.40 months. The original symptoms of anxiety, depression, insomnia, and general discomfort worsened in seven patients before onset of the disease. The other two cases displayed anxiety, depression, and insomnia, as well as whole-body burning-like and mobile pain, accompanied by the gradually aggravated discomfort of the bilateral lower limbs. As shown in **Table 2**, the symptoms of anxiety, depression, and insomnia were significantly worse in all nine patients after taking a large dose of Madopar ($P < 0.0001$, $P < 0.05$, $P < 0.0001$).

All nine cases were asked to gradually reduce their dose of Madopar. Low doses of long-acting dopamine agents, dopamine receptor agonists, α2δ calcium channel ligands, clonazepam, and other drug treatments were administered. All psychiatric symptoms were greatly alleviated but did not fully disappear and lasted for approximately 2 years. The severity of symptoms in seven patients with more than 6 months of disease course was significantly improved, but after 3 months of treatment, there was no obvious further improvement of symptoms and fluctuations were present.

As shown in **Table 3**, there was a significant difference in the IRLS scores 1 month before and after treatment. During the first month of follow-up, IRLS scores of all patients were significantly lower than the initial assessment [21.22 + 2.05 points (indicative of severe symptoms) compared to 35.33 ± 2.40 points; $P < 0.0001$]. At the 3-month follow-up, the IRLS scores of patients were significantly lower than the first month of follow-up ($P = 0.001$). Finally, at the 6-month follow-up, the IRLS scores were 13.89 ± 5.06 points, indicating moderate severity. Before treatment and at the 1-month follow-up, there was statistically significant difference between IRLS scores ($P < 0.0001$); when the 3-month follow-up was compared to this, although the symptoms were improved, it was not found to be statistically significant ($P = 0.33$). And, at the 12-, 18-, and 21-month follow-ups, when compared with the 6-month follow-up, two cases at the 21-month follow-up demonstrated that the IRLS score continued to decrease, reaching a mild level of severity; however, the subsequent treatment did not provide additional benefits to the remaining seven cases. The RLS symptoms showed no obvious improvements compared to the 6-month follow-up and were still classified as moderately severe symptoms. Another patient died of primary disease (cirrhosis and hemorrhage of upper digestive tract) during the 12 months of follow-up. This demonstrated that improvements were no longer obvious after 3 months, which suggested that early diagnosis and treatment might be the key factor to improving prognosis.

DISCUSSION

RLS is a common nervous system sensory dyskinesia disease, and the clinical manifestations are extreme discomfort during rest and nocturnal sleep. Symptoms can be remitted through movement of the lower extremities, which forces patients to continue to move their limbs, therefore disturbing sleep and rest. According to the etiology, RLS can be divided into two subtypes: primary and secondary. The former etiology is unclear and may be heredity, while the latter is often due to iron deficiency, pregnancy, chronic renal failure, and other causes. In the present study, we reported for the first time that nine patients who had no family history of primary or secondary RLS showed RLS-like symptoms accompanied by anxiety and depressive symptoms, as induced by high-dose Madopar.

Previous reports and case studies have suggested that certain medications may cause or exacerbate RLS. These medications include several classes of antidepressants, including tricyclic antidepressants (8) such as imipramine (9); selective serotonin or norepinephrine reuptake inhibitors (10), such as citalopram (11), escitalopram (12), fluoxetine (13), sertraline (14), paroxetine (15), trazodone (16), venlafaxine (17), dutoxetine (18), and mirtazapine (19); and neuroleptics that have significant dopaminergic blockade (20), such as olanzapine (21), risperidone (22), and quetiapine (23). In addition, antihistamines operating on the H1 receptor (24) and selected antiemetics with dopamine antagonism such as metoclopramide (25) and prochlorperazine (26) have also been associated with RLS. However, as none of the nine patients we observed took the aforementioned drugs, RLS-like symptoms caused by these drugs were excluded.

TABLE 1 | Demographic and clinical characteristics of the nine patients.

Case	Gender	Age (years)	Diagnosis	Madopar dosage (tablets/d)	Time1 (months)	Minimum dosage (g/d)	Time2 (months)	Clinical manifestations						
									LE	UL	GD	AS	DS	IS
1	F	78	Panic disorder	10–18	3	1.25	25	B	0	0	0	++	+	+
								A	+++	++	+++	+++	++	+++
2	F	76	Sleep-associated leg spasms, liver cirrhosis,upper gastrointestinal bleeding	6–12	2.5	1.5	20	B	0	0	0	0	0	0
								A	+++	+	+	++	+	++
3	F	74	Cerebral infarction, poststroke depression	6–10	3	1.25	24	B	0	0	0	+	++	+
								A	+++	++	++	+++	+++	++
4	F	47	Somatization disorder	8–12	2.5	1.25	13	B	0	0	0	++	+	0
								A	++	0	+	+++	++	++
5	M	56	Postencephalitis	6–15	3.5	1.5	4.5	B	0	0	0	0	0	0
								A	+++	+	++	+++	++	++
6	F	52	Anxiety and depressive disorder	9–12	2	1.75	5	B	0	0	+	++	++	++
								A	+++	+	++	+++	++	+++
7	F	67	Anxiety and depressive disorder	6–9	3	1.5	31	B	0	0	0	+	++	+
								A	+++	0	+	++	++	+++
8	F	71	Somatization disorder	6–12	2.5	1.25	15	B	0	0	0	++	+	0
								A	+++	+	++	+++	++	+++
9	M	68	Cerebral infarction, poststroke depression	6–13	1.5	1.75	26	B	0	0	0	0	++	+
								A	++	+	0	++	++	++

M, male; F, female; LE, lower extremity; UL, upper limb; GD, general discomfort; 0, no symptoms; +, mild symptoms; ++, moderate symptoms; +++, severe symptoms. B, before treatment; A, after treatment. Time 1, time of onset of restless leg syndrome (RLS) after taking Madopar; Minimum dosage, minimum dose of Madopar at the onset of RLS; Time 2, time of onset of RLS to visit. Clinical manifestations, clinical manifestations before and after taking Madopar.

TABLE 2 | Comparison of anxiety, depression, and insomnia scores of the nine patients.

		1	2	3	4	5	6	7	8	9	$\bar{x} \pm s$	*P*
HARS	B	25	4	18	25	7	22	16	23	10	16.67 ± 2.66	<0.0001
	A	52	26	50	42	38	45	27	47	26	39.22 ± 3.50	
HDRS	B	22	12	33	22	6	30	30	22	30	23.00 ± 3.03	<0.05
	A	33	25	62	31	32	33	33	32	32	34.78 ± 3.50	
ISI	B	10	7	10	5	3	17	11	5	10	8.667 ± 1.40	<0.0001
	A	26	13	19	21	17	26	25	25	19	21.22 ± 1.54	

B, before taking Madopar; A, after taking large-dose Madopar; HARS, Hamilton Anxiety Rating Scale; HDRS, 24-item Hamilton Depression Rating Scale; ISI, Insomnia Severity Index; p-value, Student's t-test.

The clinical manifestations of anxiety, depression, and somatoform disorders are complex and diverse. Other than the emotional aspects, these illnesses can manifest as different forms of somatic symptoms, such as dizziness, headache, limb weakness (especially in the lower extremities), and difficulty walking, which is likely to be misdiagnosed as a primary disease. Among the nine patients in the present study, seven had varying degrees of anxiety and depression. For example, Case 5 was misdiagnosed with Parkinson's disease and treated with Madopar due to the spasm gait of the double lower limb after encephalitis. Since the effect of treatment was not obvious, the patient increased the dosage by themselves. RLS-like symptoms and severe anxiety, insomnia, and other psychiatric symptoms occurred with an increasing amount of medication. Case 2 was diagnosed with a sleep-related leg spasm according to the predisease clinical manifestation, and then the patient was misdiagnosed with Parkinson's disease and treated with a high dose of Madopar, which induced RLS-like symptoms and anxiety. As one of the effective drugs to treat RLS, Madopar has been widely used in clinical practice; however, the onset of RLS is very rare and its pathogenesis should be further discussed.

In 2016, single-photon emission computed tomography imaging was used to study the pathophysiological mechanisms of RLS at the Tri-Service General Hospital, National Defense Medical Center (27). The results showed a significantly reduced uptake in striatal dopamine transporter (DAT) density and activity in RLS patients (27). This study supported that symptoms of RLS resulted from the striatum due to dopaminergic system dysfunction (27).

To date, many studies have shown that using drugs such as levodopa and other dopamine agonists can significantly improve the symptoms of RLS; therefore, the central dopaminergic nervous system (particularly the nigra-striatum system or intermediate cortical system) has been considered to be associated with the onset of RLS. In the present group, patients displayed RLS symptoms after the use of long-term high doses of Madopar (from the use of Madopar to the onset of RLS-like symptoms), suggesting that the cause was the dysfunction of the central dopamine system. A number of studies have reported that the use of dopamine drugs in the treatment of RLS may promote symptom deterioration, reverse jump, and other adverse reactions. This is especially true after the long-term use of levodopa, as the proportion of deteriorated symptoms is 18–80% (28). Since these adverse reactions are more common in patients with long-term high doses of levodopa treatment, it suggests that the mechanism of symptom deterioration may be associated with dopamine overdose in the central nervous system (29). Therefore, we speculate that the mechanism of RLS-like symptoms in the nine patients of the present study may be caused by excessive dopamine in the central nervous system after the use of long-term high doses of dopaminergic agents.

High concentrations of dopamine can excite D1 receptors and cause D1 receptor-related pain, which results in periodic limb movements. Several studies have shown that certain concentrations of external toxic substances [such as levodopa, dopamine (DA)] may damage dopamine transporters (DAT), therefore significantly reducing their abundance. Additionally, compared to the mitochondria, DAT is more sensitive to injury stimulation from external toxic substances. Before the cells' mass death, the number of DAT on the cell membranes is significantly reduced. The remaining DAT functions display compensatory hyperfunction and are therefore eliminated due to the reciprocal inhibition, which allows them to ingest more dopamine and its metabolites into the cells. This results in a large number of free radicals and the inhibition of the mitochondrial respiratory chain, and eventually causes cell death. Therefore, it is speculated that the long-term use of dopamine in patients of the present study may lead to a reduction in the number of dopamine receptors in the brain and spinal cord or a decrease in DAT function, finally resulting in dopaminergic systemic dysfunction and the occurrence of RLS symptoms.

In the present study, nine patients with long-term high doses of dopaminergic drugs displayed RLS symptoms, while the original symptoms of anxiety, depression, insomnia, and somatization appeared or were aggravated. Current epidemiological studies report that RLS is a common cause of insomnia, and the rate of comorbidity with depression and anxiety is high (30). Winkelmann et al. (31) assessed 238 RLS patients with a standardized diagnostic interview [Munich-Composite International Diagnostic Interview for DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*)]. Rates of anxiety and depressive disorders were compared between them and 2,265 community respondents from a nationally representative sample. RLS patients revealed an increased risk of having anxiety and depressive disorders with particularly strong associations with panic disorder, generalized anxiety disorder, and major depression (31). Moreover, the Baltimore Epidemiologic Catchment Area follow-up study suggested a strong association between RLS and major depressive disorder and/or panic disorder (32). An anonymous survey study in Appalachia suggested that those

TABLE 3 | Treatment and outcome of treatment of the nine patients and follow-up.

Case	RLS score before treatment	Length of treatment at follow-up (months)	IRLS-RS at follow-up (months)						Treatment strategy								
			1	3	6	12	18	21	MAD (tablets/d)	CLSR (tablets/d)	PSRT (mg/d)	PRE (mg/d)	EST (mg/d)	CLO (mg/d)	PAR (mg/d)	DUT (mg/d)	OLA (mg/d)
1	39	38	25	20	16	18	25	20	3	–	50	150	–	0.5	–	60	5
2	31	10	18	12	10	die	–	–	0.5	0.5	50	75–100	–	0.5	–	–	–
3	35	13	22	20	23	18	–	–	1	0.5	50	–	–	1	20	–	2.5
4	34	19	21	18	10	12	15	–	–	1	50–100	150	2	–	–	60	5
5	37	32	20	12	10	12	13	8	–	1	50	150	–	0.5	20	–	2.5
6	36	25	23	16	10	12	10	9	1	–	100	150	–	–	–	60	2.5–5
7	33	23	20	16	16	17	16	–	–	0.5	50	100	2	–	–	60	2.5
8	36	18	22	18	20	16	18	–	–	1	50	100	–	–	–	60–90	5
9	37	36	20	16	10	15	14	12	–	1	50	200	–	0.5	20–30	–	2.5

IRLS-RS, International Restless Legs Syndrome Rating Scale; MAD, Madopar; CLSRT, carbidopa and levodopa sustained-release tablets; PSRT, piribedil SR tablets; PRE, pregabalin; EST, estazolam; CLO, clonazepam; PAR, paroxetine; DUT, dutoxetine; OLA, olanzapine.

with RLS were significantly more likely to indicate a history of depression and anxiety and report sleep impairments both 4 and 7 days/week, with a mean sleep duration <5 h/night (33). These associations increased in both strength and magnitude with increasing symptom frequency (33). More recently, a study on the clinical characteristics of RLS in adult patients from Peking Union Medical College Hospital demonstrated that primary RLS patients suffer from poor sleep and are more susceptible to anxiety and depression (34). The scores of Hospital Anxiety and Depression Scale for depression and anxiety were significantly correlated with those of the Pittsburgh Sleep Quality Index and IRLS (34).

The underlying cause of the high incidence of RLS and anxiety and depression is unclear. It is possible that these illnesses may share a basic pathophysiological mechanism leading to their development. Pan et al. (35) explored the regional gray matter (GM) density in depressed drug-naïve RLS patients using voxel-based morphometry, which showed that GM density of the bilateral anterior cingulate cortex (ACC) was significantly reduced in RLS patients with depressive symptoms (RLS-D) compared to RLS patients without depressive symptoms or healthy controls. Additionally, a significant negative correlation between right ACC density and HDRS scores and duration of depressive symptoms in patients with RLS-D was found (35). It was speculated that depressive symptoms are associated with GM abnormalities in the ACC of patients with RLS.

In the present study, anxiety was more obvious than the depressive symptoms in our patients; however, there is no evidence to suggest its mechanism to date, thereby requiring further discussion. By administering small doses of long-acting dopamine agents, dopamine receptor agonists, α2δ calcium channel ligands, clonazepam, and other treatment to this group of patients, the IRLS score gradually declined and symptoms improved, but RLS symptoms did not completely disappear. Here, the prognosis of RLS was significantly different from secondary RLS patients, as they typically demonstrated complete disappearance of symptoms after cause elimination. It is suggested that long-term high doses of Madopar cause excessive accumulation of dopamine in the central nervous system, thereby irreversibly decreasing the number of dopamine receptors or DAT function, resulting in the persistence of clinical RLS-like symptoms.

The present study reports drug-induced (high-dose levodopa) RLS, which is different from the idiopathic RLS in treatment; however, the method treatment is identical. First, the dose of levodopa was gradually reduced, but as the clinical symptoms of the patients were severe, measures needed to be taken accordingly, depending on the patient's condition and their accompanying anxiety, depression, and insomnia. We referenced the European guidelines on management of restless legs syndrome:report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society (36). According to the recommendations and precautions for drug treatment, the principle of individualization was followed, simultaneously supplemented by physical therapy (hot water bath before sleep,

limb massage, etc). Thus, the clinical symptoms of the nine patients were relieved to varying degrees. The specific method recommends the minimization and withdrawal of the use of Madopar. The therapy was changed to a small dose of a long-acting dopamine agent (Xining 100–200 mg/day) to reduce the risk of dosage increase. Madopar was finally discontinued in five of the nine patients; however, Case 1 was found to have difficulty when the Madopar dose was reduced to 3 pills/day. A small dose of a dopamine receptor agonist and a small-to-moderate dose of a α2δ calcium channel ligand (pregabalin) were added depending on the severity of the patient's symptoms. To improve the symptoms of anxiety, depression, and insomnia, the therapy was supplemented by small-dose paroxetine, duloxetine, and olanzapine; an obvious curative effect was achieved by all of them.

In summary, clinicians should be mindful of differential diagnoses when patients present with walking difficulties and limb stiffness. In addition to the original diseases, anxiety, depression, and somatization disorders should be considered. In particular, clinicians should strengthen the management of patients who use dopaminergic agents to reduce the great physical and mental adverse events due to misdiagnosis and mistreatment.

CONSENT FOR PUBLICATION

The nine patients gave written consent for both participation and publishing the data in a scientific journal. They understood that the information will be published without their names attached, but that full anonymity cannot be guaranteed. They understood that the material may be published and placed on worldwide website and journals. Both the printed version and the website are seen and read by doctors, journalists, and members of the public. The material will not be used for advertising or packaging.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the First People Hospital of Huainan, and written informed consent was obtained from the patient for publication of this case report.

AUTHOR CONTRIBUTIONS

LZ, MZ, WZ: study design and critical revision of the manuscript. LZ, MZ: collection and interpretation of data. LZ: analysis data and drafting of the manuscript. JL, CR, MX, CY: collection data. All authors approved the final version for publication.

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REFERENCES

1. Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* (2009) 373(9680):2055–66. doi: 10.1016/S0140-6736(09)60492-X
2. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* (2013) 170(8):834–51. doi: 10.1176/appi.ajp.2013.12060782
3. Allen RP, Pieehietti DL, Gareia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. *Sleep Med* (2014) 5(8):860–73. doi: 10.1016/j.sleep.2014.03.025
4. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. *Sleep Med* (2003) 4(2):121–32. doi: 10.1016/S1389-9457(02)00258-7
5. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* (2001) 2(4):297–307. doi: 10.1016/S1389-9457(00)00065-4
6. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x
7. Mazure C, Nelson JC, Price LH. Reliability and validity of the symptoms of major depressive illness. *Arch Gen Psychiatry* (1986) 43(5):451–6. doi: 10.1001/archpsyc.1986.01800050053006
8. Leutgeb U, Martus P. Regular intake of non-opioid analgesics is associated with an increased risk of restless legs syndrome in patients maintained on antidepressants. *Eur J Med Res* (2002) 7:368–78.
9. Ware JC, Brown FW, Moorad J, Pittard JT, Murphy M, Franklin D. Nocturnal myoclonus and tricyclic antidepressants. *Sleep Res* (1984) 13:72.
10. Rottach KG, Schaner BM, Kirch MH, Zivotofksy AZ, Teufel LM, Gallwitz T, et al. Restless legs syndrome as side effect of second generation antidepressants. *J Psychiat Res* (2008) 43:70–5. doi: 10.1016/j.jpsychires.2008.02.006
11. Perroud N, Lazignac C, Baleydier B, Cicotti A, Maris S, Damsa C. Restless legs syndrome induced by citalopram: a psychiatric emergency. *Gen Hosp Psychiatry* (2007) 29:72–4. doi: 10.1016/j.genhosppsych.2006.10.006
12. Page RL, 2nd, Ruscin JM, Bainbridge JL, Brieke AA. Restless legs syndrome induced by escitalopram: case report and review of the literature. *Pharmacotherapy* (2008) 28(2):271–80. doi: 10.1592/phco.28.2.271
13. Prospero-Garcia KA, Torres-Ruiz A, Ramierez-Bermudez J, Velazquez-Moctezuma J, Arana-Lechuge Y, Teran-Perez G. Fluoxetine-mirtazapine interaction may induce restless legs syndrome: report of 3 cases from a clinical trial. *J Clin Psychiatry* (2006) 67:1820. doi: 10.4088/JCP.v67n1122d
14. Buskova J, Vorlova T, Pisko J, Sonka K. Severe sleep-related movement disorder induced by sertraline. *Sleep Med* (2012) 13(6):769–70. doi: 10.1016/j.sleep.2012.01.006
15. Chou KJ, Chen PY, Huang MC. Restless legs syndrome following the combined use of quetiapine and paroxetine. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) 34(6):1139–40. doi: 10.1016/j.pnpbp.2010.05.009
16. Patel HC, Bruza D, Yeragani V. Myoclonus with trazodone. *J Clin Psychopharmacol* (1988) 8(2):152. doi: 10.1097/00004714-198804000-00026
17. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. *J Clin Psychiatry* (1997) 58(8):348–50. doi: 10.4088/JCP.v58n0803
18. Belli H, Akbudak M, Ural C. Duloxetine-related galactorrhea and restless legs syndrome: a case report. *Psychiatr Danub* (2013) 25(3):266–7.
19. Chopra A, Pendergrass DS, Bostwick JM. Mirtazapine-induced worsening of restless legs syndrome (RLS) and ropinirole-induced psychosis: challenges in management of depression in RLS. *Psychosomatics* (2011) 52(1):92–4. doi: 10.1016/j.psym.2010.11.009

20. Jagota P, Asawavichienjinda T, Bhidayasiri R. Prevalence of neuroleptic-induced restless legs syndrome in patients taking neuroleptic drugs. *J Neurol Sci* (2012) 314(1–2):158–60. doi: 10.1016/j.jns.2011.10.032
21. Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with olanzapine: a case series. *Curr Drug Saf* (2010) 5(2):129–31. doi: 10.2174/157488610790936187
22. Wetter TC, Brunner J, Bronisch T. Restless legs syndrome probably induced by risperidone treatment. *Pharmacopsychiatry* (2002) 35(3):109–11. doi: 10.1055/s-2002-31514
23. Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. *J Clin Psychophamacol* (2005) 25(6):617–8. doi: 10.1097/01.jcp.0000186870.75042.25
24. O'Sullivan RL, Greenberg DB. H2 antagonists, restless leg syndrome and movement disorders. *Psychosomatics* (1993) 34(6):530–2. doi: 10.1016/S0033-3182(93)71830-7
25. Winkelmann J, Schadrack J, Wetter TC, Zieglgansberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. *Sleep Med* (2001) 2(1):57–61. doi: 10.1016/S1389-9457(00)00025-3
26. Drotts DL, Vinson DR. Prochlorperazine induces akathisia in emergency patients. *Ann Emerg Med* (1999) 34(4 Pt 1):469–75. doi: 10.1016/S0196-0644(99)80048-1
27. Lin CC, Fan YM, Lin GY, Yang FC, Cheng CA, Lu KC, et al. 99mTc-TRODAT-1 SPECT as a potential neuroimaging biomarker in patients with restless legs syndrome. *Clin Nucl Med* (2016) 41(1):e14–7. doi: 10.1097/RLU.0000000000000916
28. Nagandla K, De S. Restless legs syndrome: pathophysiology and modern management. *Postgrad Med J* (2013) 89(1053):402–10. doi: 10.1136/postgradmedj-2012-131634
29. Paulus W, Trenkwalder C. Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome. *Lancet Neurol* (2006) 5(10):878–86. doi: 10.1016/S1474-4422(06)70576-2
30. Becker PM, Sharon D. Mood disorders in restless legs syndrome (Willis-Ekbom disease). *J Clin Psychiatry* (2014) 75(7):e679–94. doi: 10.4088/JCP.13r08692
31. Winkelmann J, Prager M, Lieb R, Pfister H, Spiegel B, Wittchen HU, et al. "Anxietas tibiarum." Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* (2005) 252(1):67–71. doi: 10.1007/s00415-005-0604-7
32. Lee HB, Hening WA, Allen RP, Kalaydjian AE, Earley CJ, Eaton WW, et al. Restless legs syndrome is associated with DSM-IV major depressive disorder and panic disorder in the community. *J Neuropsychiatry Clin Neurosci.* (2008) 20(1):101–5. doi: 10.1176/jnp.2008.20.1.101
33. Innes KE, Flack KL, Selfe TK, Kandati S, Agarwal P. Restless legs syndrome in an appalachian primary care population: prevalence, demographic and lifestyle correlates, and burden. *J Clin Sleep Med* (2013) 9(10):1065–75. doi: 10.5664/jcsm.3084
34. Chen JH, Huang R, Luo JM, Xiao Y, Zhong X, Liu XQ. Restless Legs Syndrome in Adults in Peking Union Medical College Hospital. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* (2016) 38(5):548–53. doi: 10.3881/j.issn.1000-503X.2016.05.010
35. Pan PL, Dai ZY, Shang HF, Xiao PR, Dong CS, Song WG, et al. Gray matter anomalies in anterior cingulate cortex as a correlate of depressive symptoms in drug-naïve idiopathic restless legs syndrome. *Neuroscience* (2014) 277:1–5. doi: 10.1016/j.neuroscience.2014.06.045
36. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *Eur J Neurol* (2012) 19(11):1385–96. doi: 10.1111/j.1468-1331.2012.03853.x.

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Compromised Dynamic Cerebral Autoregulation in Patients With Depression

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Background: Patients with depression tend to have various comorbid neurological symptoms, but the mechanisms remain unclear. The purpose of this study was to analyze the characteristics of dynamic cerebral autoregulation in depressed patients.

Methods: Patients (aged ≥ 18 years) who were diagnosed with depression [17-item Hamilton Depression Rating Scale (HAMD) > 17] or suspected of depression (HAMD > 7) were enrolled in this study. Medically healthy volunteers were recruited as controls. The subjects also received the 7-item HAMD. We simultaneously recorded noninvasive continuous arterial blood pressure and bilateral middle cerebral artery blood flow velocity from each subject. Cerebral autoregulation was assessed by analyzing the phase difference using transfer function analysis.

Results: This study enrolled 54 patients with suspected depression, 45 patients with depression, and 48 healthy volunteers. The mean phase difference values were significantly lower in the patients with depression ($F = 9.071$, $P < 0.001$). In the multiple regression analysis, depression was negatively correlated with the phase difference values.

Conclusions: Dynamic cerebral autoregulation was compromised in patients with depression and negatively correlated with the depression score. Improving dynamic cerebral autoregulation may be a potential therapeutic method for treating the neurological symptoms of depression.

Keywords: depression, dynamic cerebral autoregulation, transcranial Doppler, transfer function, cerebral hemodynamics

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INTRODUCTION

Depression is the most common psychiatric disorder, a leading cause of disability, and affects nearly 15% of the population (1, 2). Core features of this disorder include depressed mood, loss of interest or pleasure, irritability, change in appetite and sleep, and neurocognitive dysfunctions (3, 4). In addition to suicide ideation and behavior, patients with depression also tend to have comorbid medical illnesses, such as cancer, cardiovascular diseases, and diabetes (5, 6). Depression is associated with an increased risk of stroke morbidity and mortality. These combined conditions generally worsen patient outcomes (7–12).

Despite the prevalence of depression and its considerable burden on global health, knowledge about its pathogenesis remains rudimentary. Previous studies have revealed global and regional

changes in the cerebral blood flow of patients with depression compared to healthy individuals (13–15). Cerebral blood flow abnormalities in depression differ in patients, with a varying age of onset (16), disparate responses to antidepressant treatment (17), and diverse family histories (18). Longitudinal research also shows the apparent elevation of regional cerebral perfusion in remissive depression compared to current depression (19). The mechanism of the unusual cerebral blood flow in depressed patients is complex and incompletely understood, and cerebral autoregulation may play a role.

Cerebral autoregulation is the innate ability to maintain appropriate brain perfusion during blood pressure changes. It can be dynamically assessed with transfer function analysis (TFA) between spontaneous fluctuations of arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) (20, 21). To date, cerebral autoregulation has not been well analyzed in patients with depression. In the present study, we hypothesize that dynamic cerebral autoregulation is compromised in patients with depression, and we use TFA to assess dynamic cerebral autoregulation in depressed patients and explore its relationship with the degree of depression.

METHODS

Participants and Clinical Assessment

Patients whose first complaint was poor sleep and with 17-item Hamilton Depression Rating Scale (HAMD) scores > 7 were included from the Department of Neurology, First Hospital of Jinlin University, from September 2017 to June 2018. Two blinded clinical psychiatrists evaluated the patients' mental health status. All patients had never been treated with antidepressants before. Patients with a history of cerebrovascular diseases (that is, cerebrovascular stenosis and stroke), frequent arrhythmias, anemia and unstable blood pressure, and hyperthyroidism were excluded from the study as controls. The patients with hypertension or diabetes took medications, and their blood pressure and blood glucose levels were well controlled. These patients were divided into two groups, those with depression (HAMD ≥ 17) and those suspected of depression (17 > HAMD ≥ 7). Physical health status was assessed using a questionnaire covering cardiovascular, nervous system, thyroid, and metabolic diseases, and information regarding age, smoking, and drinking habits. A total of 48 medically and psychiatrically healthy volunteers were recruited as controls. Liver and kidney function, blood glucose, blood lipid, blood pressure, electrocardiography, transcranial Doppler (EMS-9 PB, Delica, Shenzhen, China), and carotid ultrasound (IU22, Phillips, Andover, MA, USA) tests were used to exclude subjects who did not meet the study standards.

Cerebral Autoregulation Assessment Monitoring

Before the dynamic cerebral autoregulation examination, all of the patients were instructed to avoid caffeine, nicotine, alcohol, and all kinds of sleep medications for at least 24 h. The assessments were performed in a quiet, dedicated monitoring room with minimal external stimuli. The subjects were instructed to breathe spontaneously and assumed a supine position with a head elevation of 30° when baseline ABP (automatic blood pressure monitor, Omron 711) was measured. Signals were recorded after a 10-min rest. Beat-to-beat ABP was noninvasively recorded through servo-controlled finger plethysmography (Finometer Model 1, FMS, Netherlands), and continuous bilateral middle cerebral artery blood flow velocity was recorded with 2-MHz probes with an insonation depth of 45 to 60 mm attached to a customized head frame (MultiDop X2, DWL, Sipplingen, Germany). Stable end-tidal carbon dioxide (CO2) levels were confirmed through a capnograph with a face mask attached to the nasal cannula. Each participant's blood pressure and blood flow velocity were recorded for 10 min. The data were then stored for further dynamic cerebral autoregulation examination analysis.

Analysis of Dynamic Cerebral Autoregulation

The recorded data were analyzed blindly using a laptop computer equipped with MATLAB (MathWorks, Natick, MA, USA). The beat-to-beat alignment of the data was acquired using a cross-correlation function to eliminate possible time lags. By using a cross-correlation function between ABP and CBFV, we may calculate the correlation at each time lag (by sample). We can then find the time lag with the maximum correlation, suggesting that the two signals are synchronized at this time lag. This is considered as the time delay between ABP and CBFV, which is likely caused by the data acquisition devices. We used a third-order Butterworth low-pass filter (cutoff at 0.5 Hz) as an anti-aliasing filter before downsampling the data to 1 Hz. A TFA was applied for evaluating cerebral autoregulation (22). TFA is a frequency domain analysis that calculates the "phase shift" between the CBFV and blood pressure waveforms in the 0.06–0.12 Hz frequency domain to evaluate cerebral autoregulation where the derived parameters were considered most relevant to autoregulation hemodynamics (23). In the current study, a phase shift was accepted for later statistical analysis only if the calculated coherence of one measurement was >0.49 within 0.06–0.12 Hz (24–26), in order to ensure that there was at least 49% linearity between ABP and CBFV. Otherwise, it is invalid to use TFA for the assessment, as it is a linear model.

Statistical Analysis

The statistical data were analyzed using Statistical Program for Social Sciences version 21.0 (SPSS, IBM, West Grove, PA, USA). Continuous and discrete variables were respectively compared between the patients and healthy controls using analysis of variance. Liner multiple regression was used to explore the association between the phases and characteristics of the patients. The relationships between the phase difference values and the HAMD scores were analyzed using Spearman's rank-order correlation analysis. Multiple linear regression analysis was used to investigate the effects of the covariates on the phase difference. P values < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics and Phase Difference

The characteristics of the participants are listed in **Table 1**. This study analyzed 45 patients (median age = 47.95 ± 13.30 years, 12 males) with depression, 154 (median age = 47.19 ± 4.48 years, 57 males) suspected of depression, and 48 healthy controls (median age = 47.29 ± 12.24 years, 19 males). The prevalence of hypertension and hyperlipidemia in the patients with depression and those suspected of depression was higher than in the control group.

There was no significant difference between left and right phase difference values in the patients and the controls. The phases in the patients suspected of depression and in those with depression were significantly lower than in the corresponding hemispheres of the healthy controls (**Table 1**, **Figure 1**).

Multiple Linear Regression Analysis

Age, sex, diabetes, hypertension, hyperlipidemia, tobacco smoking habits, drinking habits, left middle cerebral artery, right middle cerebral artery, mean ABP, and heart rate did not influence the phase averages. However, when the level of depression increased (as evaluated by the HAMD score), the phase difference values were negatively correlated to the HAMD scores (7–17: 95% CI −13.825 to −2.911, P = 0.003; 17: 95% CI −19.725 to −5.802, P < 0.001) (**Table 2**).

DISCUSSION

This study found that dynamic cerebral autoregulation was impaired in patients with depression and the phase difference value was negatively correlated with the HAMD score. Higher levels of depressive symptoms were associated with increased risk of neurological diseases such as stroke or TIA (27). The patients with depression also suffered from dizziness (28). Neurological diseases in patients with depression can be connected to impaired dynamic cerebral autoregulation.

The potential mechanisms underlying this phenomenon are unknown, but there are theoretical possibilities. Recent studies showed that the modulation of neurotransmitters can malfunction in depression (29, 30), and neurotransmitters such as serotonins have a major impact on cerebral vessel tone and could affect cerebral autoregulation (31, 32). In addition, the clinical evidence suggests increased pro-inflammatory markers in patients with depression (increased TNF-α, CRP, and IL-6) (33, 34). These inflammatory factors (35, 36) also can affect the endothelial cells and impair cerebral autoregulation (37). Therefore, depression may influence dynamic cerebral autoregulation through neuroendocrine and immunological/inflammation pathways.

Although various studies (38, 39) indicated that diabetes and hypertension are related to dynamic cerebral autoregulation, we did not find that they have significant influence on cerebral autoregulation. One possible explanation for this disparate finding might be related to the incidence of diabetes and hypertension. This study has a low rate of diabetes and hypertension, and we need to have a larger sample size to further explore their relationship.

In this study, the phase values were correlated with the depression levels. As the HAMD scores increased, the phase difference values (dynamic cerebral autoregulation) tended to decrease. The potential mechanisms are unclear. We supposed that the level of serotonins might be a potential mechanism to explain the relationship between the HAMD scores and the phase values. It has been proven that dysfunction of serotonin is related to major depressive disorder (40). Serotonins also have an impact on cerebrovascular function (41). The study of Edvinsson et al. suggested that serotoninergic projections played a significant role in the regulation of cerebral microvascular tone (42). Nevertheless, a study using PET found that citalopram (a selective serotonin reuptake inhibitor) led to alteration of cerebral hemodynamics (32). In addition, the negative correlation between phase values and the HAMD scale suggests

TABLE 1 | Baseline characteristics and phase differences in the patients and controls.

Factors	Depression (n = 154)	Suspected of Depression (n = 45)	Control (n = 48)	F/χ^2	P
Male, n (%)	57 (37.0%)	12 (26.7%)	19 (39.6%)	2.032	0.362
Age (years)	47.95 ± 13.30	47.27 ± 12.24	47.19 ± 4.48	0.104	0.901
Heart rate	73.10 ± 9.59	75.30 ± 9.79	73.02 ± 8.27	1.007	0.367
Hypertension, n (%)	15 (9.7)	11 (24.4)*	0 (0%)	15.004	0.001
Diabetes, n (%)	7 (4.5%)	2 (4.1%)	0 (0%)	2.254	0.324
Hyperlipidemia, n (%)	12 (7.8%)	5 (11.1%)*	0 (0%)	5.002	0.082
Smoking, n (%)	31 (20.1%)	9 (20.0%)	7 (14.6%)	0.764	0.682
Drinking, n (%)	15 (9.7%)	11 (24.4%)*	0 (0%)	15.004	0.001
Phase difference, degree					
Left hemisphere	48.17 ± 17.15*	42.76 ± 14.01*	56.60 ± 16.00	8.581	<0.001
Right hemisphere	47.78 ± 16.86*	46.38 ± 14.49*	58.25 ± 15.77	8.659	<0.001
Mean ABP, mmHg	89.23 ± 11.84	91.18 ± 9.54	93.26 ± 12.37	2.356	0.097
LCMA velocity	70.05 ± 18.71	66.08 ± 16.39	65.84 ± 14.48	1.583	0.208
RCMA velocity	67.87 ± 16.36	65.72 ± 15.45	64.42 ± 13.10	1.029	0.359
End-tidal CO_2, mmHg	35.71 ± 3.06	35.78 ± 2.81	34.62 ± 2.94	2.644	0.073

**The difference was statistically significant compared to the control group (P < 0.025).*

ABP, arterial blood pressure; LCMA, left cerebral middle artery; RCMA, right cerebral middle artery.

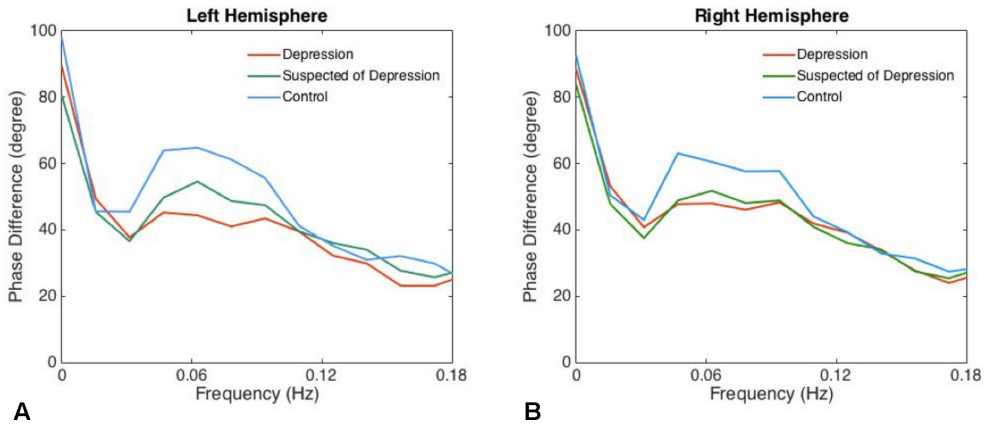

FIGURE 1 | The phase differences of left **(A)** and right **(B)** derived from the transfer function within significant interval 0.06–0.12 Hz are plotted. Phase difference values (parameter of dynamic cerebral autoregulation) were significantly compromised in patients with depression and suspected of depression compared with the controls, indicating an impairment of dynamic cerebral autoregulation in patients with depression.

TABLE 2 | Multiple regression coefficients for the mean phases of the left and right hemispheres.

Factors	Unstandardized coefficients		Standardized coefficients (beta)	95% CI for β		P
	β	Std. error		Lower bound	Upper bound	
Constant	32.594	18.285		–3.433	68.621	0.076
Sex						
Female	Reference					
Male	–1.518	2.384	–0.045	–6.215	3.179	0.525
Hypertension						
No	Reference					
Yes	–3.961	3.786	–0.076	–11.421	3.498	0.209
Diabetes						
No	Reference					
Yes	1.421	5.839	0.017	–10.083	12.926	0.808
Hyperlipidemia						
No	Reference					
Yes	6.383	4.443	0.100	–2.372	15.138	0.152
Smoking						
No	Reference					
Yes	0.250	2.951	0.006	–5.564	6.065	0.932
Drinking						
No	Reference					
Yes	–2.806	3.522	–0.056	–9.746	4.134	0.426
Age	0.022	0.101	0.016	–0.177	0.222	0.826
HAMD						
Control	Reference					
Depression	–8.368	2.770	–0.251	–13.825	–2.911	0.003
Suspected of depression	–12.763	3.533	–0.303	–19.725	–5.802	<0.001
LCMA velocity	–0.100	0.079	–0.109	–0.256	0.056	0.206
RCMA velocity	0.096	0.092	0.093	–0.085	0.278	0.297
Mean ABP, mmHg	0.169	0.094	0.122	–0.017	0.355	0.075
Heart rate	0.123	0.113	0.071	0.100	0.346	0.279
End-tidal CO_2, mmHg	0.001	0.346	0.001	–0.681	0.682	0.999

ABP, arterial blood pressure; LCMA, left cerebral middle artery; RCMA, right cerebral middle artery.

the potential impact of depressive symptoms on dynamic cerebral autoregulation.

The impairment of dynamic cerebral autoregulation in depression indicates that cerebral vascular function may be a therapeutic target of depression. Therefore, improving dynamic cerebral autoregulation may potentially alleviate the neurological symptoms in patients with depression.

This study has some limitations. This was an observational study without in-depth research mechanisms. In addition, the sample size is relatively small. In the future, larger sample sizes and animal studies are needed. In terms of the TFA method, a phase shift is considered valid for further statistical analysis only when the linearity between ABP and CBFV is greater than 49% (24), and TFA is currently the only method that has been studied by multiple centers and standardized by a white paper for the assessment of cerebral autoregulation (23).

CONCLUSIONS

Dynamic cerebral autoregulation was compromised in patients with depression and negatively correlated with depression scores. The mechanism of impaired cerebral autoregulation may play a role not only in the development of cerebrovascular diseases but also as a potential therapeutic method for treating the neurological symptoms of depression.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Declaration of Helsinki and the Ethics Committee of the First Hospital of Jilin University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the First Hospital of Jilin University.

AUTHOR CONTRIBUTIONS

YY, ML, and ZG drafted the manuscript. ZG and ML revised the manuscript. SL, XS, and HM drew the figures. ZW, PZ, HJ was in charge of acquisition of data. YQ and SL performed the data analysis. ML and PZ performed the statistical analysis. XS and YY conceived and designed the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Oakes P, Loukas M, Oskouian RJ, Tubbs RS. The neuroanatomy of depression: a review. *Clin Anat* (2017) 30(1):44–9. doi: 10.1002/ca.22781
2. McCarron RM, Vanderlip ER, Rado J. Depression. *Ann Intern Med* (2016) 165(7):ITC49–ITC64. doi: 10.7326/AITC201610040
3. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature* (2008) 455(7215):894–902. doi: 10.1038/nature07455
4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013). doi: 10.1176/appi.books.9780890425596
5. Smith DJ, Court H, McLean G, Martin D, Langan Martin J, Guthrie B, et al. Depression and multimorbidity: a cross-sectional study of 1,751,841 patients in primary care. *J Clin Psychiatry* (2014) 75(11):1202–8; quiz 8. doi: 10.4088/JCP.14m09147
6. Kessler RC, Birnbaum HG, Shahly V, Bromet E, Hwang I, McLaughlin KA, et al. Age differences in the prevalence and co-morbidity of DSM-IV major depressive episodes: results from the WHO World Mental Health Survey Initiative. *Depress Anxiety* (2010) 27(4):351–64. doi: 10.1002/da.20634
7. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol* (2008) 5(8):466–75. doi: 10.1038/ncponc1134
8. Jackson JL, DeZee K, Berbano E. Can treating depression improve disease outcomes? *Ann Intern Med* (2004) 140(12):1054–6. doi: 10.7326/0003-4819-140-12-200406150-00017
9. Ramasubbu R, Patten SB. Effect of depression on stroke morbidity and mortality. *Can J Psychiatry* (2003) 48(4):250–7. doi: 10.1177/070674370304800409
10. Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care* (2003) 26(10):2822–8. doi: 10.2337/diacare.26.10.2822
11. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, et al. Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* (1996) 78(6):613–7.
12. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* (2011) 306(11):1241–9. doi: 10.1001/jama.2011.1282
13. Wang Y, Zhang H, Tang S, Liu X, O'Neil A, Turner A, et al. Assessing regional cerebral blood flow in depression using 320-slice computed tomography. *PLoS One* (2014) 9(9):e107735. doi: 10.1371/journal.pone.0107735
14. Vakilian A, Iranmanesh F. Assessment of cerebrovascular reactivity during major depression and after remission of disease. *Ann Indian Acad Neurol* (2010) 13(1):52–6. doi: 10.4103/0972-2327.61278
15. Monkul ES, Silva LA, Narayana S, Peluso MA, Zamarripa F, Nery FG, et al. Abnormal resting state corticolimbic blood flow in depressed unmedicated patients with major depression: a (15)O-H(2)O PET study. *Hum Brain Mapp* (2012) 33(2):272–9. doi: 10.1002/hbm.21212
16. Liao W, Wang Z, Zhang X, Shu H, Wang Z, Liu D, et al. Cerebral blood flow changes in remitted early- and late-onset depression patients. *Oncotarget* (2017) 8(44):76214–22. doi: 10.18632/oncotarget.19185
17. Lui S, Parkes LM, Huang X, Zou K, Chan RCK, Yang H, et al. Depressive disorders: focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. *Radiology* (2009) 251(2):476–84. doi: 10.1148/radiol.2512081548
18. Wang S, Wang L, Jing P, Guo P, Zheng W, Li J, et al. Aberrant patterns of brain cerebral blood flow in Chinese han first-episode drug-naive depressive patients with and without a family history of depression. *Oncotarget* (2017) 8(45):79906–13. doi: 10.18632/oncotarget.20306
19. Colloby SJ, Firbank MJ, He J, Thomas AJ, Vasudev A, Parry SW, et al. Regional cerebral blood flow in late-life depression: arterial spin labelling magnetic resonance study. *Br J Psychiatry* (2012) 200(2):150–5. doi: 10.1192/bjp.bp.111.092387
20. Lassen NA. Autoregulation of cerebral blood flow. *Circ Res* (1964) 15(Suppl):201–4.
21. Panerai RB. Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. *Physiol Meas* (1998) 19(3):305–38. doi: 10.1088/0967-3334/19/3/001

22. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol* (1998) 274(1 Pt 2):H233–41. doi: 10.1152/ajpheart.1998.274.1.H233
23. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB. Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab* (2016) 36(4):665–80. doi: 10.1177/0271678X15626425
24. Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Transfer function analysis for clinical evaluation of dynamic cerebral autoregulation—a comparison between spontaneous and respiratory-induced oscillations. *Physiol Meas* (2003) 24(1):27–43. doi: 10.1088/0967-3334/24/1/303
25. Ma H, Guo ZN, Sun X, Liu J, Lv S, Zhao L, et al. Hematoma volume is a predictive factor of disturbed autoregulation after spontaneous intracerebral hemorrhage. *J Neurol Sci* (2017) 382:96–100. doi: 10.1016/j.jns.2017.09.035
26. Kuo TB, Chern CM, Sheng WY, Wong WJ, Hu HH. Frequency domain analysis of cerebral blood flow velocity and its correlation with arterial blood pressure. *J Cereb Blood Flow Metab* (1998) 18(3):311–8. doi: 10.1097/00004647-199803000-00010
27. Everson-Rose SA, Roetker NS, Lutsey PL, Kershaw KN, Longstreth WT, Jr., Sacco RL, et al. Chronic stress, depressive symptoms, anger, hostility, and risk of stroke and transient ischemic attack in the multi-ethnic study of atherosclerosis. *Stroke* (2014) 45(8):2318–23. doi: 10.1161/STROKEAHA.114.004815
28. Kim SK, Kim YB, Park IS, Hong SJ, Kim H, Hong SM. Clinical Analysis of dizzy patients with high levels of depression and anxiety. *J Aud Otol* (2016) 20(3):174–8. doi: 10.7874/jao.2016.20.3.174
29. Ghasemi M, Phillips C, Fahimi A, McNerney MW, Salehi A. Mechanisms of action and clinical efficacy of NMDA receptor modulators in mood disorders. *Neurosci Biobehav Rev* (2017) 80:555–72. doi: 10.1016/j.neubiorev.2017.07.002
30. Niciu MJ, Henter ID, Sanacora G, Zarate CA, Jr. Glial abnormalities in substance use disorders and depression: does shared glutamatergic dysfunction contribute to comorbidity? *World J Biol Psychiatry* (2014) 15(1):2–16. doi: 10.3109/15622975.2013.829585
31. Hilz MJ, Stemper B, Heckmann JG, Neundorfer B. [Mechanisms of cerebral autoregulation, assessment and interpretation by means of transcranial Doppler sonography]. *Fortschr Neurol Psychiatr* (2000) 68(9):398–412. doi: 10.1055/s-2000-11798
32. Geday J, Hermansen F, Rosenberg R, Smith DF. Serotonin modulation of cerebral blood flow measured with positron emission tomography (PET) in humans. *Synapse* (2005) 55(4):224–9. doi: 10.1002/syn.20112
33. Steiner J, Bogerts B, Sarnyai Z, Walter M, Gos T, Bernstein HG, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood–brain barrier integrity. *World J Biol Psychiatry* (2012) 13(7):482–92. doi: 10.3109/15622975.2011.583941
34. Laske C, Zank M, Klein R, Stransky E, Batra A, Buchkremer G, et al. Autoantibody reactivity in serum of patients with major depression, schizophrenia and healthy controls. *Psychiatr Res* (2008) 158(1):83–6. doi: 10.1016/j.psychres.2006.04.023
35. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* (2009) 71(2):171–86. doi: 10.1097/PSY.0b013e3181907c1b
36. White RP, Vallance P, Markus HS. Effect of inhibition of nitric oxide synthase on dynamic cerebral autoregulation in humans. *Clin Sci (Lond)* (2000) 99(6):555–60. doi: 10.1042/cs0990555
37. Armstead WM, Hekierski H, Pastor P, Yarovoi S, Higazi AA, Cines DB. Release of IL-6 after stroke contributes to impaired cerebral autoregulation and hippocampal neuronal necrosis through NMDA receptor activation and upregulation of ET-1 and JNK. *Transl Stroke Res* (2018). doi: 10.1007/s12975-018-0617-z
38. Eames PJ, Blake MJ, Panerai RB, Potter JF. Cerebral autoregulation indices are unimpaired by hypertension in middle aged and older people. *Am J Hypertens* (2003) 16(9 Pt 1):746–53. doi: 10.1016/S0895-7061(03)00947-6
39. Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. *Am J Physiol Heart Circ Physiol* (2015) 308(7):H681–7. doi: 10.1152/ajpheart.00343.2014
40. Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry* (2007) 12(4):331–59. doi: 10.1038/sj.mp.4001949
41. Ueda Y, Walker SA, Povlishock JT. Perivascular nerve damage in the cerebral circulation following traumatic brain injury. *Acta Neuropathol* (2006) 112(1):85–94. doi: 10.1007/s00401-005-0029-5
42. Edvinsson L, Degueurce A, Duverger D, MacKenzie ET, Scatton B. Central serotonergic nerves project to the pial vessels of the brain. *Nature* (1983) 306(5938):55–7. doi: 10.1038/306055a0

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Brain Iron Deposits in Thalamus Is an Independent Factor for Depressive Symptoms Based on Quantitative Susceptibility Mapping in an Older Adults Community Population

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Objectives: With the trend of an aging population, an increasing prevalence of late-life depression has been identified. Several studies demonstrated that iron deposition was significantly related to the severity of symptoms in patients with depression. However, whether brain iron deposits influence depressive symptoms is so far unclear in the community of older adults. We measured iron deposition in deep intracranial nucleus by quantitative susceptibility mapping (QSM) and aimed to explore the relationship between iron deposition and depressive symptoms.

Methods: We reviewed the data of a community population from CIRCLE study, which is a single-center prospective observational study that enrolled individuals above 40 years old with cerebral small vessel disease (SVD), while free of known dementia or stroke. We evaluated regional iron deposits on QSM, measured the volume of white matter hyperintensities (WMHs) on T2 fluid-attenuated inversion recovery, and assessed depressive symptoms by Hamilton depression scale (HDRS). We defined depressive symptom as HDRS > 7.

Results: A total of 185 participants were enrolled. Participants in depressive symptom group had higher QSM value in thalamus than control group (18.79 ± 14.94 vs 13.29 ± 7.64, p = 0.003). The QSM value in the thalamus was an independent factor for the presence of depressive symptoms (OR = 1.055; 95% CI: 1.011-1.100; p = 0.013). The regional QSM values in other areas were not associated with HDRS score (all p > 0.05). No significant correlations were observed between WMHs volume and HDRS score (p > 0.05), or regional QSM values and WMHs volume (all p > 0.05).

Conclusions: Our study demonstrated that iron deposits in the thalamus were related to the depressive symptoms in older adults.

Keywords: iron deposits, white matter hyperintensities, depressive symptoms, quantitative susceptibility mapping, thalamus

INTRODUCTION

With the trend of an aging population, an increasing prevalence of late-life depression has been identified. The devastating effects of depression in older adults have been reported, including increases in suicide, hastened cognitive decline, worsening physical comorbidities, higher caregiver burden and all-cause mortality (1, 2). However, the mechanism of depression in older adults remains uncertain.

As age increases, intracranial iron deposits increase (3, 4). Studies have indicated that increased iron deposits in the deep gray matter of the brain are closely related to neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD) (5). Recent studies also show that increased intracranial iron deposits are associated with emotional behaviors among PD patients, especially depression (6). Moreover, Yao et al. (7) also demonstrated that patients with major depression disorder had a significantly increased susceptibility value in the bilateral putamen than patients with mild-moderate depression or control subjects. Therefore, we presume that in older adults, brain iron deposits might be related to depressive symptoms.

White matter hyperintensities (WMHs), demonstrating related to ischemic, inflammatory and protein deposition, which are commonly seen as confluent or patchy hyperintense areas on T2 weighted or fluid-attenuated inversion recovery (FLAIR) scans, have been reported to be related to both iron deposition and depression in older adults (8). However, the relationship between iron deposits and WMHs is still controversial. Yan et al. (9) observed a significant association between iron deposits in globus pallidus and WMHs volume among patients admitted to hospital, while other study revealed that intracranial iron deposition was not associated with the volume of WMHs (10). Besides, numerous studies have demonstrated that there is a significant but weak association between WMHs and depression (11). However, the relationship between iron deposits, WMHs and depression in older adults remains uncertain.

In previous studies, R2* was usually used to measure iron content, which was easily affected by different factors, such as calcification. The current study has suggested that quantitative susceptibility mapping (QSM) measures iron deposits more accurately (12). Moreover, postmortem study also found that QSM values were directly proportional to iron content (13). Therefore, in this study we evaluated iron deposition in deep intracranial nucleus on QSM, measured the volume of WMHs on T2-FLAIR, and assessed depressive symptoms using the Hamilton depression scale (HDRS), with the aim to explore the relationship between iron deposition and depressive symptoms, and the role of WMHs among them.

MATERIALS AND METHODS

Subjects

The CIRCLE study (ClinicalTrials.gov ID: NCT03542734) was a single-center prospective observational study that enrolled community residents, which aimed to explore the predictors of small vessel disease (SVD) and cognitive deficits. We reviewed the data of consecutive individuals from CIRCLE cohort between 2017 October and 2018 July. Detailed inclusion criteria was: (1) age above 40; (2) SVD imaging markers (WMHs with Fazekas score 1-3 in periventricular or deep white matter, lacunes, microbleeds) visible on MRI; (3) free of known dementia or stroke (both cerebral infarction and hemorrhage); (4) without any MRI contraindications; (5) free of serious head injury (resulting in the loss of consciousness) or received intracranial surgery; (6) not suffering from cancer. Participants with poor image quality due to motion artifact or with the history of psychotropic drugs were excluded. All participants received neuropsychological testing, retinal digital images and multimodal MRI.

MRI Protocol

All subjects underwent a multi-model MRI by a 3.0 T MR (HDXT, GE Healthcare, United States) scanner using an 8- channel brain phased array coil, including T1, T2 fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted imaging (SWI) sequence. In order to minimize head motion, foam pads were inserted into the space between the subject's head and the MRI head coil. An axial T2 FLAIR sequence was used to measure the WMHs volume with the following parameters: repetition time = 8000 ms, echo time = 150 ms, FOV = 24 cm × 24 cm, matrix size = 256 × 256, inversion time = 2100 ms, slice thickness = 4.0 mm with no gap (continuous) between slices, and in-plane spatial resolution of 0.4688 mm/pixel × 0.4688 mm/pixel. The whole brain was imaged. The SWI sequence was in an axial orientation parallel to the anterior commissure to posterior commissure line and covered the whole lateral ventricles, using a three-dimension multi-echo gradient-echo sequence with 11 equally spaced echoes: echo time = 4.5 ms [first echo], inter-echo spacing = 4.5 ms, repetition time = 34 ms, FOV = 24 cm × 24 cm, matrix size = 416 × 384, slice thickness = 2.0 mm with no gap between slices, and in-plane spatial resolution of 0.93 mm/pixel × 0.93 mm/pixel. Flow compensation was applied.

Volume Assessment of WMHS

First, the axial T2 FLAIR images were segmented automatically through the lesion segmentation tool (LST) in MATLAB (R2014a) pipeline integrating SPM12 (Wellcome Department of Neurology, University College of London, UK). Then the automatically segmented lesions were manually checked and corrected on mricron (http://www.nitrc.org/projects/mricron) by two experienced neuro-radiologists (WZ and YJ) who were blinded to all other imaging and clinical data after it was coregistered to the T1 images through SPM12. The manual correction process included: (1) division of deep white matter hyperintensities (DWMHs) and periventricular white matter hyperintensities (PVHs); (2) correction of non-white matter area being labeled as WMHs; (3) WMHs area not adequately labeled as WMHs or normal-appearing white matter falsely labeled as WMHs. Afterwards, the volume of WMHs was measured automatically on mricron.

Measurement of the QSM Values

According to the published methods (14), the QSM reconstruction was achieved through the use of a C++ software developed and validated by Wang and his colleagues (15), and

is based on nonlinear morphology-enabled dipole inversion (MEDI), which makes use of the consistency between the susceptibility maps and magnitude images obtained from the Spoiled Gradient Recalled Echo (SPGR) acquisitions. The susceptibility maps are obtained through estimating (nonlinearly) the phase maps, which have to be unwrapped and subsequently undergo dipole inversion. The regularization parameter has been fixed and set to 1000. The regions of interest (ROIs) were manually drawn on QSM maps by two experienced neuro-radiologists (YZ and QL) who were blinded to all other imaging and clinical data. ROIs were put on the slices where the boundaries of target nuclei could be seen most clearly. Susceptibility values were averaged within each ROI from three successive slices. Both left and right sides of the target nuclei were measured, and the average values were calculated based on the volume. Globus pallidus, head of caudate nucleus, putamen, red nucleus, substantia nigra, thalamus, and dentate nucleus were contained in the ROIs (**Figure 1**). The segmentation function of spm12 in MATLAB (R2014a) was used to get the ROIs of white matter and gray matter. Absolute QSM values of the ROIs were measured automatically on mricron software.

Clinical Assessment

We used the Hamilton Depression Rating Scale (HDRS) to assess depressive symptoms and Mini–Mental State Examination (MMSE) to assess cognitive ability at the same time as the MRI scan. According to the HDRS score, the participants were subdivided into two groups: depressive symptom group (HDRS > 7) and control group (HDRS ≤ 7) (16).

Statistical Analysis

Since the WMHs volume was skewed towards the left of mean, we performed natural log transformations of WMHs volume before the correlation analysis. The log-transformed WMHs volume appeared to be acceptably normative. Independent samples' two-tailed t-test was used to compare the demographics, vascular factors, HDRS score and imaging data between depressive symptom group and control subjects. Fisher's Exact test was used for categorical data. We also conducted logistic regression analysis to provide an odds ratio statistic to facilitate comparison with other known risk factors. Partial Pearson's correlation analysis was conducted to determine the correlation among regional QSM values, log-transformed WMHs volume and HDRS scores, by adjusting for baseline sociodemographic and vascular risk factors. Statistical significance was set at a probability value of < 0.05. All statistical analysis was performed with SPSS 17.0 (SPSS Inc., Chicago, USA).

RESULTS

Subject Characteristics

185 consecutive participants were enrolled in this study, after 12 participants were excluded due to poor image quality and 2 participants were excluded due to the history of psychotropic drug use. **Table 1** shows the sociodemographic characteristics, vascular risk factors, volume of WMHs and regional QSM values.

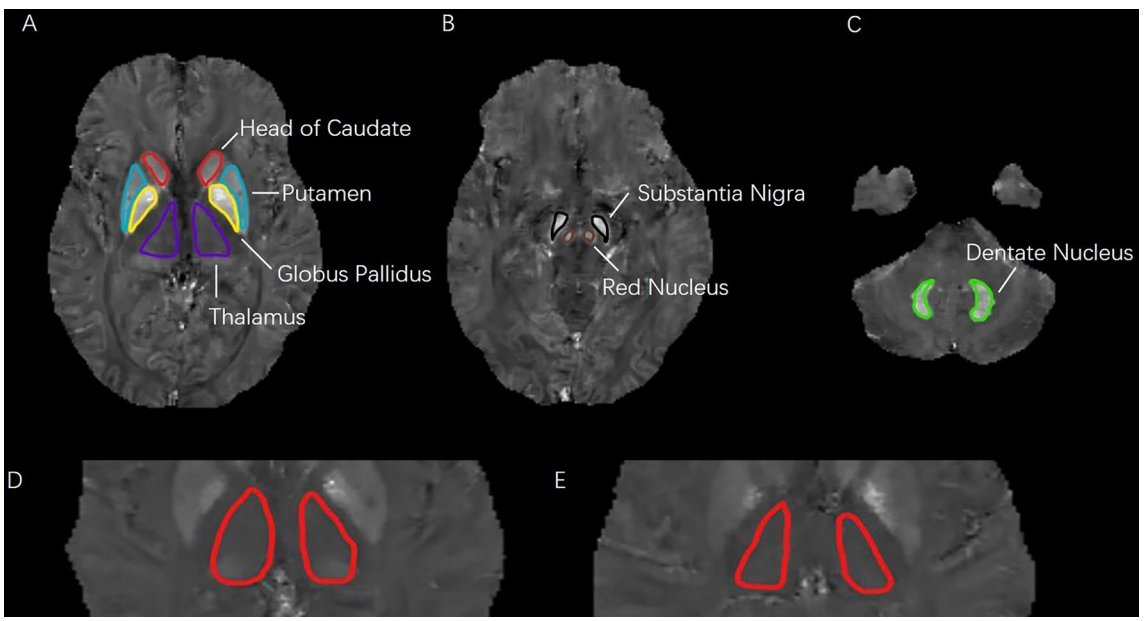

FIGURE 1 | (A–C): Seven regions of interest (ROIs) analyzed in this study. ROIs in three different levels of quantitative susceptibility mapping were including: head of caudate, putamen, globus pallidus, thalamus, substantia nigra, red nucleus, and dentate nucleus. **(D–E)**: Difference in QSM images of bilateral thalamus. **(D)**: depressive symptom with HDRS score of 17; **(E)**: health control with HDRS score of 3.

TABLE 1 | Sociodemographic characteristics, vascular risk factors, white matter hyperintensities (WMHs) volume and regional quantitative susceptibility mapping (QSM) values in all included participants.

	Value (n (%) or mean)
Sociodemographic Characters	
Female	92 (49.7%)
Age, year	59.70 ± 7.15
Year of education, year	8.31 ± 4.69
MMSE	25.17 ± 5.66
HDRS	2.58 ± 4.28
Vascular Risk Factors	
Hypertension	66 (35.7%)
Diabetes mellitus	20 (10.8%)
Hyperlipidemia	22 (11.9%)
Imaging Features	
Volume of WMHs, ml	6.26 ± 9.23
Volume of DWMHs, ml	1.93 ± 3.72
Volume of PVHs, ml	4.33 ± 6.04
QSM value	
Red Nucleus, $\times10^{-3}$ ppm	118.68 ± 43.08
Substantia Nigra, $\times10^{-3}$ ppm	151.77 ± 54.29
Globus Pallidus, $\times10^{-3}$ ppm	197.96 ± 74.39
Putamen, $\times10^{-3}$ ppm	86.79 ± 27.36
Head of Caudate, $\times10^{-3}$ ppm	77.26 ± 21.83
Thalamus, $\times10^{-3}$ ppm	14.04 ± 9.03
Dentate Nucleus, $\times10^{-3}$ ppm	89.56 ± 47.80

MMSE, Mini–Mental State Examination; HDRS, Hamilton Depression Rating Scale DWMHs, deep white matter hyperintensities; PVHs, periventricular white matter hyperintensities.

Reliability of the QSM Value Measurements

The intraclass correlation coefficients (ICCs) were 0.88 for red nucleus, 0.99 for substantia nigra, 0.87 for globus pallidus, 0.96 for putamen, 0.91 for head of caudate, 0.97 for thalamus and 0.97 for dentate nucleus. ICCs were described in detail elsewhere (17).

Proof of QSM Data

Pearson's correlation analysis was conducted to determine the correlation between the mean QSM value of deep intracranial nuclei from the control group in the present study and the mean iron distribution in postmortem samples as reported by Hallgren and Sourander in 1958 (18), which measured the content of iron in different brain regions and found the relationship between increased age and increased iron deposition. Globus pallidus, red nucleus, substantia nigra, putamen, dentate nucleus, and thalamus were selected as reference region for comparison. A significant correlation (r = 0.932, p = 0.007; **Figure 2**) was found and it supported that the QSM data provide a quantitative measure of iron.

Comparison of Iron Deposits and WMHS Volume Between Depressive Symptom Group and Control Group

Table 2 shows the sociodemographic characteristics, vascular risk factors, volume of WMHs and regional QSM values of depressive symptom group and control group. The HDRS scores of the depressive symptom group were significantly higher than the control group (11.43 ± 5.32 vs 1.32 ± 2.06, p < 0.001). There were no differences between two groups in gender, age or vascular risk factors. Participants in depressive symptom group had lower years of education (6.29 ± 4.42 vs 8.64 ± 4.69, p = 0.022), lower MMSE score (22.83 ± 4.38 vs 25.53 ± 5.73, p = 0.028), higher volume of total WMHs (10.87 ± 18.65 vs 5.54 ± 6.63, p = 0.006), higher volume of PVHs (7.18 ± 11.70 vs 3.93 ± 4.65, p = 0.015), higher volume of DWMHs (4.03 ± 7.66 vs 1.63 ± 2.65, p = 0.003) and higher QSM value in thalamus (18.79 ± 14.94 vs 13.29 ± 7.64, p = 0.003; **Figure 1**) than the control group. No differences were observed in other deep nuclei that had been measured. No difference was observed in total grey matter (376.56 ± 21.96 vs 375.22 ± 28.48, p > 0.05) or white matter (176.42 ± 27.10 vs 170.66 ± 27.08, p > 0.05), either.

The binary logistic regression model revealed that the QSM value in thalamus was an independent factor for the presence of depressive symptoms (OR = 1.052; 95% CI: 1.010-1.096; p = 0.015) after adjusting for years of education and MMSE score. Furthermore, the QSM value in thalamus was still an independent factor for depressive symptoms (OR = 1.055; 95% CI: 1.011-1.100; p = 0.013), after adjusting for years of education, MMSE score and the volume of WMHs. In addition, volume of total WMHs, volume of PVHs, or volume of DWMHs were not influencing factors for depressive symptoms after adjusting for years of education and MMSE score (all p > 0.05).

Correlation Analysis Between Iron Deposits, WMHS Volume and HDRS Score in Depressive Symptom Group

As presented in **Table 3**, in the depressive symptom group, none of the QSM values were significantly correlated with HDRS score (all p > 0.05), after adjusting for age, gender, year of education, MMSE score and baseline vascular risk factors. Further adjusting for the volume of WMHs did not change the results (all p > 0.05).

In addition, in the depressive symptom group, no significant correlation was observed between log-transformed WMHs volume and HDRS score (all p > 0.05), and no significant correlations were observed between log-transformed WMHs volume and regional QSM value (all p > 0.05).

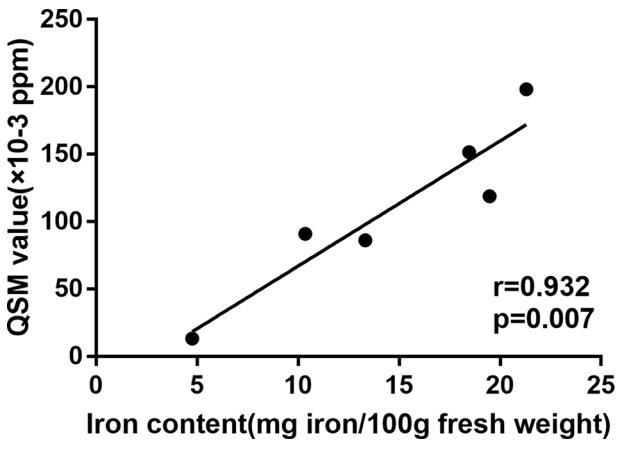

FIGURE 2 | Correlation between the mean QSM value of deep intracranial nuclei from the control group and the mean iron distribution in postmortem samples as reported by Hallgren and Sourande.

TABLE 2 | Comparison of sociodemographic characters, vascular risk factors, white matter hyperintensities (WMHs) volume, and regional quantitative susceptibility mapping (QSM) values between depressive symptom group and control group.

	Depressive symptom group (n = 23)	Control group (n = 162)	P Value
Sociodemographic Characters			
Female (%)	13(56.5%)	79 (48.8%)	0.513
Age, year, mean ± SD	61.96 ± 7.88	59.38 ± 7.01	0.106
Years of education, year, mean ± SD	6.35 ± 4.51	8.59 ± 4.67	0.031
MMSE, mean ± SD	22.74 ± 4.45	25.51 ± 5.74	0.028
HDRS, mean ± SD	11.43 ± 5.32	1.32 ± 2.06	0.000
Vascular Risk Factors			
Hypertension (%)	10 (43.8%)	56 (34.6%)	0.362
Diabetes mellitus (%)	2 (8.7%)	18 (11.1%)	1.000
Hyperlipidemia (%)	3(13.0%)	19 (11.7%)	0.506
Imaging Features			
Volume of WMHs, ml, mean ± SD	11.21 ± 18.99	5.55 ± 6.65	0.006
Volume of DWMHs, ml	4.03 ± 7.66	1.63 ± 2.65	0.003
Volume of PVHs, ml	7.18 ± 11.70	3.93 ± 4.65	0.015
QSM value			
Red Nucleus, $\times10^{-3}$ ppm, mean ± SD	117.17 ± 34.10	118.89 ± 44.30	0.858
Substantia Nigra, $\times10^{-3}$ ppm, mean ± SD	153.05 ± 66.35	151.59 ± 52.60	0.905
Globus Pallidus, $\times10^{-3}$ ppm, mean ± SD	195.73 ± 69.51	198.28 ± 75.25	0.878
Putamen, $\times10^{-3}$ ppm, mean ± SD	91.52 ± 30.61	86.12 ± 26.90	0.377
Head of Caudate, $\times10^{-3}$ ppm, mean ± SD	75.74 ± 18.46	77.48 ± 22.31	0.722
Thalamus, $\times10^{-3}$ ppm, mean ± SD	19.19 ± 14.85	13.31 ± 7.66	0.003
Dentate Nucleus, $\times10^{-3}$ ppm, mean ± SD	80.29 ± 45.19	90.88 ± 48.14	0.321
Grey Matter	376.12 ± 21.96	375.38 ± 28.48	0.906
White Matter	176.42 ± 27.10	170.66 ± 27.08	0.341

MMSE, Mini–Mental State Examination; HDRS, Hamilton Depression Rating Scale
DWMHs, deep white matter hyperintensities; PVHs, periventricular white matter hyperintensities

TABLE 3 | Associations between regional quantitative susceptibility mapping (QSM) values, white matter hyperintensities (WMHs) volume HDRS and Hamilton depression scale (HDRS) score in depressive symptom group.

Brain region	HDRS score		log-transformed WMHs volume
	Partial pearson correlation (model1, r(p))	Partial pearson correlation (model2, r(p))	
Red Nucleus	–0.210 (0.436)	–0.180 (0.522)	–0.232 (0.388)
Substantia Nigra	0.026 (0.923)	0.030(0.917)	–0.019 (0.946)
Globus Pallidus	0.082 (0.762)	0.094 (0.738)	–0.066 (0.808)
Putamen	0.477 (0.062)	0.511 (0.052)	–0.140 (0.606)
Head of Caudate	–0.223 (0.407)	–0.212 (0.448)	–0.090 (0.740)
Thalamus	0.094 (0.730)	0.083 (0.769)	0.077 (0.776)
Dentate Nucleus	–0.097 (0.720)	–0.084 (0.765)	–0.090 (0.740)
log-transformed WMHs volume	0.160 (0.553)	/	/

Model 1 adjusted for age, sex, years of education, MMSE scores and vascular risk factors (hypertension, diabetes, hyperlipidemia); Model 2 adjusted for age, sex, years of education, MMSE scores, vascular risk factors (hypertension, diabetes, hyperlipidemia) and log-transformed WMHs volume; age, sex, years of education, MMSE scores and vascular risk factors (hypertension, diabetes, hyperlipidemia, smoke) were also adjusted for analyzing the association between regional QSM value and log-transformed WMHs volume.

DISCUSSION

Our main findings include: (1) in older adults, iron deposits in the thalamus was an independent factor for depressive symptoms, even after adjusting for WMHs volume; (2) the severity of iron deposits is not related to severity of depression; (3) WMHs volume was not associated with presence of depressive symptoms or brain iron deposits.

In general, the regional QSM value in our study was relatively low, almost the same as the QSM value of healthy older adults in the previous study (the QSM value of Thalamus: our study vs Bettes et al.'s study 0.014 ± 0.009 vs 0.021 ± 0.0008 ppm) (19).

Previous studies have demonstrated that iron deposits in the thalamus were related to the degree of depression among depression patients and post-stroke patients (7, 20). Our study further confirmed that even in older adults, iron deposits in the thalamus were related to depressive symptoms. Although the pathogenesis of depression is still not sufficiently clear, iron deposits might lead to depressive symptoms by multiple mechanisms.

It has been reported that there were abnormal connections in the thalamus-temporal lobes and thalamus-cortex areas in patients with depression (21). Meanwhile, studies have shown that excessive iron could affect functional connectivity (22). Therefore, we speculate that thalamic iron deposits might cause local neuron and neurotransmitter dysfunction, which affects functional connections, finally leading to depressive symptoms.

In addition, the monoamine hypothesis might mediate the relationship between iron deposits and depression. The lack of monoamines, including serotonin, dopamine, norepinephrine, and epinephrine, would lead to depression. Moreover, deficiency of a certain neurotransmitter could lead to a certain depressive symptom (23). Studies have reported that brain iron deposits could affect monoamine function (24). Therefore, brain iron deposits might reduce the activity of monoamines, leading to the occurrence of depressive symptoms.

Furthermore, some studies suggested that inflammation and oxidative stress also could influence depression (25). Cytokines and other pro-inflammatory mediators were involved in the pathophysiological process of mood regulation, such as neurotransmitter metabolism, neuroendocrine function, anterior cingulate cortical activity, and synaptic plasticity (26). Indeed, animal experiments have proven depression-like behaviors could be induced by brain iron overload through apoptosis pathways among adult rats (27). Moreover, Dixon et al. raised the notion of ferroptosis in 2012, which refers to a form of regulated cell death characterized by the iron-dependent accumulation. The accumulation of intracellular iron would induce accumulation of lipid reactive oxygen species (ROS) and the over-accumulation of lipid ROS results in oxidative stress which finally leads to lethal levels for cell deaths (28). Therefore, iron deposits may also cause depressive symptoms by causing an inflammatory reaction and apoptosis.

Yao et al. (7) identified susceptibility values were higher in putamen of patients with major depressive disorder. Whereas, we did not find a correlation between the iron deposits in putamen and depressive symptoms. In addition, our QSM values of putamen met the range of healthy older adults reported before (19, 29). Therefore, given the differences in the study population, we suspect that the putamen might affect different stages of depression. This hypothesis needs to be confirmed in future.

We did not find a relationship between iron deposits and the severity of depression in the depressive symptom group. The mild symptoms of our study population might explain it. We conducted research in old healthy community populations. Although some of their HDRS scores were greater than 7 points, it could only be considered as depressive symptoms rather than depression. In addition, a previous study which found that iron deposits in thalamus were associated with depression severity did not consider cognitive ability, and the cognitive decline in older adults was likely to affect depression scores.

Surprisingly, we did not find the relationship between volume of WMHs and depressive symptoms after adjusting for years of education and MMSE score. According to the vascular depression hypothesis, WMHs may result in mechanistic disconnection and hypoperfusion, which links cerebrovascular diseases with the depression (8). The heterogeneity of the research population might explain the contradiction between our findings and previous research results. Our included population was not diagnosed with depression but was considered to have depressive symptoms based on their HDRS scores. Even in the depressive symptoms group, the HDRS scores were not high (average HDRS score was 11.38). The damage of white matter in our participants might be too slight to affect the depressive symptoms.

We also found no correlation between WMHs and iron deposits. It might also be explained by the difference of research population. The previous positive finding about the relationship between iron deposits and volume of WMHs was based on a population of in-hospital patients, who had severe white matter damage (average volume of WMHs was 35.95 ml) (9), while our current study included a community population with an average WMHs volume of only 6.22 ml. Pathological studies have demonstrated that myelin has a strong ability to store iron without causing damage (30), which may indicate that the damage of iron deposits to myelin is a late manifestation. Moreover, iron deposits might be an early stage of neurodegeneration and might not produce WMHs (10). One possible but hypothetical scenario would be that the early impact of iron deposits on depressive symptoms might be caused by abnormal functional connection, monoamine dysfunction and inflammation reaction, while during the advanced period, iron deposition would aggravate white matter damage and accelerate emotional disorders.

Our study had strength in its methodology. QSM was regarded as a more accurate way to measure iron deposits because it could avoid the loss of signals and the influence of calcifications when measured by R2* (31). We innovatively analyzed the relationship in older adults as there was only one study in the past that examined the relationship between iron deposits and depression by QSM among patients diagnosed as depression. In addition, we excluded the effects of WMHs and cognitive ability, ensuring that the effect of iron deposits on depressive symptoms was an independent process.

Our study had limitations. First, while the total size is close to 200 patients, the group with depressive symptoms is small which can impact the robustness of the results. Second, it was a cross-sectional study that could only analyze the correlation among depression, WMHs and brain iron, and cannot analyze the cause and effect. Further longitudinal study is needed to clarify this. Third, we did not carry out laboratory tests. Therefore, the health status of the enrolled population has not been fully checked, and some factors that may influence emotional behaviors could be ignored. Fourth, voxel-based QSM analysis might further prompt the phenomenon and mechanism, and further study is needed to clarify this. Fifth, the QSM values were measured by manual delineation. Although the consistency was good, there were still measurement errors.

In summary, our finding indicated that in a community population, thalamic iron deposits were an independent factor for depressive symptoms, but WMHs volumes were irrelevant to either increased iron deposits or depressive symptoms. Our results may help to investigate the underlying pathophysiological mechanism of depression in the future studies. It's worthy to explore the relationship between depressive and specific parts of the thalamus in future.

ETHICS STATEMENT

All subjects had given written informed consent prior to the study, and the protocol was approved by the local ethics committee. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

WZ and YZ drafted and revised the manuscript, participated in study concept and design, conducted the statistical analyses, analyzed, and interpreted the data. ML participated in study concept and design, data interpretation and made a major contribution in revising the manuscript. QL, JX, and SY participated in the study design and made contribution in revising the manuscript. YJ and JC assisted in designing the MRI sequences and imaging analysis.

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REFERENCES

1. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry* (1999) 174:307–11. doi: 10.1192/bjp.174.4.307
2. Unutzer J. Clinical practice. Late-life depression. *N Engl J Med* (2007) 357:2269–76. doi: 10.1056/NEJMcp073754
3. Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. *Lancet Neurol* (2014) 13:1045–60. doi: 10.1016/S1474-4422(14)70117-6
4. Gong NJ, Wong CS, Hui ES, Chan CC, Leung LM. Hemisphere, gender and age-related effects on iron deposition in deep gray matter revealed by quantitative susceptibility mapping. *NMR Biomed* (2015) 28:1267–74. doi: 10.1002/nbm.3366
5. Du L, Zhao Z, Cui A, Zhu Y, Zhang L, Liu J, et al. Increased Iron Deposition on Brain Quantitative Susceptibility Mapping Correlates with Decreased Cognitive Function in Alzheimer's Disease. *ACS Chem Neurosci* (2018) 9:1849–57. doi: 10.1021/acschemneuro.8b00194
6. Xu W, Zhi Y, Yuan Y, Zhang B, Shen Y, Zhang H, et al. Correlations between abnormal iron metabolism and non-motor symptoms in Parkinson's disease. *J Neural Transm (Vienna)* (2018) 125:1027–32. doi: 10.1007/s00702-018-1889-x
7. Yao S, Zhong Y, Xu Y, Qin J, Zhang N, Zhu X, et al. Quantitative Susceptibility Mapping Reveals an Association between Brain Iron Load and Depression Severity. *Front Hum Neurosci* (2017) 11:442. doi: 10.3389/fnhum.2017.00442
8. Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, et al. Vascular depression consensus report - a critical update. *BMC Med* (2016) 14:161. doi: 10.1186/s12916-016-0720-5
9. Yan S, Sun J, Chen Y, Selim M, Lou M. Brain iron deposition in white matter hyperintensities: a 3-T MRI study. *Age (Dordr)* (2013) 35:1927–36. doi: 10.1007/s11357-012-9487-6
10. Gattringer T, Khalil M, Langkammer C, Jehna M, Pichler A, Pinter D, et al. No evidence for increased brain iron deposition in patients with ischemic white matter disease. *Neurobiol Aging* (2016) 45:61–3. doi: 10.1016/j.neurobiolaging.2016.05.008
11. Wang L, Leonards CO, Sterzer P, Ebinger M. White matter lesions and depression: a systematic review and meta-analysis. *J Psychiatr Res* (2014) 56:56–64. doi: 10.1016/j.jpsychires.2014.05.005
12. Qiu D, Chan GC, Chu J, Chan Q, Ha SY, Moseley ME, et al. MR quantitative susceptibility imaging for the evaluation of iron loading in the brains of patients with beta-thalassemia major. *AJNR Am J Neuroradiol* (2014) 35:1085–90. doi: 10.3174/ajnr.A3849
13. Langkammer C, Schweser F, Krebs N, Deistung A, Goessler W, Scheurer E, et al. Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. *Neuroimage* (2012) 62:1593–9. doi: 10.1016/j.neuroimage.2012.05.049
14. Ippoliti M, Adams LC, Winfried B, Hamm B, Spincemaille P, Wang Y, et al. Quantitative susceptibility mapping across two clinical field strengths: Contrast-to-noise ratio enhancement at 1.5T. *J Magn Reson Imaging* (2018) 48(5): 1410–20. doi: 10.1002/jmri.26045
15. de Rochefort L, Liu T, Kressler B, Liu J, Spincemaille P, Lebon V, et al. Quantitative susceptibility map reconstruction from MR phase data using bayesian regularization: Validation and application to brain imaging. *Magn Reson Med* (2009) 63(1): 194–206 doi: 10.1002/mrm.22187
16. Yuan H, Zhang N, Wang C, Luo BY, Shi Y, Li J, et al. Factors of Hamilton Depression Rating Scale (17 items) at 2 weeks correlated with poor outcome at 1 year in patients with ischemic stroke. *Neurol Sci* (2014) 35:171–7. doi: 10.1007/s10072-013-1464-z
17. Lee J, Koh D, Ong CN. Statistical evaluation of agreement between two methods for measuring a quantitative variable. *Comput Biol Med* (1989) 19:61. doi: 10.1016/0010-4825(89)90036-X
18. Hallgren B, Sourander P. The effect of age on the non-haemin iron in the human brain. *J Neurochem* (1958) 3:41–51. doi: 10.1111/j.1471-4159.1958.tb12607.x
19. Betts MJ, Acosta-Cabronero J, Cardenas-Blanco A, Nestor PJ, Duzel E. High-resolution characterisation of the aging brain using simultaneous quantitative susceptibility mapping (QSM) and R2* measurements at 7T. *Neuroimage* (2016) 138:43–63. doi: 10.1016/j.neuroimage.2016.05.024
20. Kuchcinski G, Munsch F, Lopes R, Bigourdan A, Su J, Sagnier S, et al. Thalamic alterations remote to infarct appear as focal iron accumulation and impact clinical outcome. *Brain* (2017) 140:1932–46. doi: 10.1093/brain/awx114
21. Brown EC, Clark DL, Hassel S, MacQueen G, Ramasubbu R. Thalamocortical connectivity in major depressive disorder. *J Affect Disord* (2017) 217:125–31. doi: 10.1016/j.jad.2017.04.004
22. Salami A, Avelar-Pereira B, Garzon B, Sitnikov R, Kalpouzos G. Functional coherence of striatal resting-state networks is modulated by striatal iron content. *Neuroimage* (2018) 183:495–503. doi: 10.1016/j.neuroimage.2018.08.036
23. Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. *J Clin Psychiatry* (2008) 69(Suppl E1):4–7.
24. Wu LL, Gong W, Shen SP, Wang ZH, Yao JX, Wang J, et al. Multiple metal exposures and their correlation with monoamine neurotransmitter metabolism in Chinese electroplating workers. *Chemosphere* (2017) 182:745–52. doi: 10.1016/j.chemosphere.2017.04.112
25. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? *J Neurol Neurosurg Psychiatry* (2012) 83:495–502. doi: 10.1136/jnnp-2011-301779
26. Patel A. Review: the role of inflammation in depression. *Psychiatr Danub* (2013) 25(Suppl 2):S216–23.
27. Mehrpouya S, Nahavandi A, Khojasteh F, Soleimani M, Ahmadi M, Barati M. Iron administration prevents BDNF decrease and depressive-like behavior following chronic stress. *Brain Res* (2015) 1596:79–87. doi: 10.1016/j.brainres.2014.10.057
28. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. *Cell* (2012) 149:1060–72. doi: 10.1016/j.cell.2012.03.042

29. Liu M, Liu S, Ghassaban K, et al. Assessing global and regional iron content in deep gray matter as a function of age using susceptibility mapping. *Magn Reson Imaging* (2016) 44(1): 59–71. doi: 10.1002/jmri.25130
30. Heidari M, Johnstone DM, Bassett B, Graham RM, Chua AC, House MJ, et al. Brain iron accumulation affects myelin-related molecular systems implicated in a rare neurogenetic disease family with neuropsychiatric features. *Mol Psychiatry* (2016) 21:1599–607. doi: 10.1038/mp.2015.192
31. Reichenbach JR. The future of susceptibility contrast for assessment of anatomy and function. *Neuroimage* (2012) 62:1311–5. doi: 10.1016/j.neuroimage.2012.01.004

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