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Preliminary MRS study of critical values of relevant brain metabolites in elderly Chinese patients with post-stroke cognitive impairment

MengQi Li [a], LingLing Yao [c], ZengXin Lu [d], LiMing Yang [d], Hong Fan [b],*

[a] *School of Medicine, Shaoxing University, Shaoxing, Zhejiang, PR China*
[b] *Department of Geriatrics, Shaoxing People's Hospital (The First Affiliated Hospital of Shaoxing University), Shaoxing, Zhejiang, PR China*
[c] *Department of Rehabilitation, Shaoxing People's Hospital (The First Affiliated Hospital of Shaoxing University), Shaoxing, Zhejiang, PR China*
[d] *Department of Radiology, Shaoxing People's Hospital (The First Affiliated Hospital of Shaoxing University), Shaoxing, Zhejiang, PR China*

ABSTRACT

Objective: Proton magnetic resonance spectroscopy (^{1}H-MRS) was applied in this study to detect metabolite changes in the brain of post-stroke cognitive impairment (PSCI) and normal volunteers. The levels of N-acetylaspartate (NAA) and creatinine (Cr) and in the frontal lobe, hippocampus and cingulate gyrus were measured to distinguish patients with post-stroke cognitive impairment (PSCI) and normal control group (NC). The relationship between them and cognitive function was explored and a critical value of the metabolite ratio was predicted. This study may serve as a reference for the diagnosis of cognitive dysfunction after stroke.
Methods: A total of 46 patients with PSCI (PSCI group, all patients are unilateral cerebral infarction or intracerebral haemorrhage) were screened by the Mini-Mental Status Examination (MMSE), and 35 healthy volunteers were selected as normal control group (NC group). The general information of gender, age, and education level was matched between the two groups. Two groups of subjects were examined using MRS and evaluated for cognitive function using the MMSE test and the Montreal Cognitive Assessment Scale (MoCA). The correlation between MRS and neurobehavioral scale (MMSE test and MoCA scale) was analysed, and the possible demarcation points of the brain metabolism of PSCI were evaluated.
Result: The MMSE and MoCA scores of patients with PSCI were lower significantly when compared with those of the NC group ($P < 0.05$). The NAA/Cr values of the bilateral hippocampus, bilateral frontal lobe and bilateral anterior and posterior cingulate gyrus in the PSCI group were lower than those in the NC group ($P < 0.05$). The NAA/Cr cut-off value for the right frontal lobe was 1.533, and the NAA/Cr sensitivity, specificity and Youden index for the right frontal lobe were 0.943, 0.935, and 0.878.
Conclusion: NAA/Cr values in the MRS bilateral frontal, bilateral hippocampus and bilateral anterior and posterior cingulate gyrus were reduced in the cognitively impaired post-stroke patients compared to the normal control group. MRS was also found to be correlated with the score of neurobehavioral scale (MMSE test and MoCA scale) and the combination of the two could evaluate cognitive dysfunction more comprehensively and objectively. NAA/Cr value of the right frontal lobe < 1.533 indicated that PSCI may occur. In accordance with this cut-off point, PSCI could be detected as early as possible and timely intervention could be carried out.

Introduction

Post-stroke cognitive impairment (PSCI) refers to the deterioration of executive function, dyscalculia and memory loss of patients poststroke often with also the alteration of processing speed and attention (Verstraeten et al., 2023; Hara et al., 2021); it is one of the most common complications of post-stroke (Rohde et al., 2019). Currently, there's no real effective treatment of PSCI, and cognitive function may decline even with an effective care. PSCI is diagnosed using criteria, including stroke evidence, cognitive decline (memory, attention, etc.), temporal link to stroke, exclusion of other causes, functional impact, and objective assessments. These criteria guide healthcare professionals in tailoring interventions and support for affected individuals, improving their daily functioning and quality of life (Salvadori et al., 2013; Jacquin et al., 2014). A hospital population-based cohort study showed rates of cognitive impairment ranging from 17% to 66% within three months of

stroke (Zuo et al., 2017). The progress of PSCI is typically a hidden continuous progress. If no effective treatment is provided, the cognitive function of the patient may gradually decline. Currently, diagnosis of PSCI relies on clinical presentation and neurobehavioral assessment scales, of which MMSE and MoCA are the most widely used cognitive screening tools in the country and abroad. MMSE is sensitive to memory and language cognition and has high sensitivity and specificity to screen for moderate and severe cognitive impairment, while MoCA has high sensitivity and specificity to identify mild cognitive impairment (Zhu et al., 2020). However, there were differences in the associated rating scales due to the age, cultural background and educational level of the patients. In addition, the neurobehavioral scale could not assess patients with aphasia after stroke (especially those with sensory aphasia and total aphasia) (Wang et al., 2020; Burton and Tyson, 2015; Chen et al., 2016; Sharma et al., 2020). It is therefore worthwhile to explore a tool that can objectively and accurately predict the incidence of PSCI in stroke patients during early hospitalization.

With the continuous development of imaging technology, proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive technology used to detect changes in brain neurotransmitters and thus could detect the activity and function of brain neurons. A recent study found that injuries to the frontal, hippocampus and cingulate gyrus are heavily associated with cognitive decline and that they are involved in the occurrence and development of PSCI (Egerton, 2021; Rivera et al., 2020). Therefore, they are treated as regions of interest in the present study. N-acetylaspartate (NAA) is an amino acid that mainly exists in the neurons, dendrites and axons of the central nervous system. It actively participates in the synthesis of myelin sheaths, which may reflect the damage or loss of neurons in quantitative regions. It has been widely used as a marker of neuronal density and neurometabolic adaptability in the MRS study of neurodegenerative diseases (Igarashi et al., 2021). Creatine (Cr), mainly including intracellular Cr and phosphate Cr, could be used as a marker of energy metabolism in the brain and it is regularly used as an internal reference for measuring the content of different metabolites in various spectral studies (Fayed et al., 2017; Zhang et al., 2015).

Currently, few studies on MRS changes in cognitively relevant brain regions in PSCI patients and the relationship between brain metabolites and cognitive function scores and cutoffs can be found in both domestic and international studies of PSCI patients. This study aims to explore metabolite changes in different parts of brain tissue under different cognitive states and their relevance to the cognitive function assessment scale, to clarify the diagnostic value of the ^{1}H-MRS in the early stages of PSCI, and to guide clinical early intervention to reduce the occurrence of adverse prognoses.

Methods

Participants

Patients with PSCI

The participants were patients in the geriatric and rehabilitation departments of Shaoxing People's Hospital from January 2020 to August 2021.

Inclusion criteria

Patients who (1) met Chinese guidelines for the diagnosis and treatment of acute stroke (Oz et al., 2014); (2) had their first stroke diagnosed as unilateral cerebral infarction or intracerebral haemorrhage by cranial CT or magnetic resonance imaging (MRI) (3) met the PSCI diagnostic criteria, that is, there is a clear diagnosis of stroke, there are manifestations of cognitive impairment, and cognitive impairment occurs after a stroke event (Wang et al., 2018); (4) had a course of disease ≤ 12 weeks, stable condition and age of 18–80 years; (5) had no metal implants in the body, such as cardiac pacemaker; (6) had acquired cognitive impairment and no evident cognitive impairment before onset

and (7) had informed consent form signed by himself or an authorised agent were included.

Exclusion criteria

Patients (1) with cognitive impairment caused by epilepsy, Alzheimer's disease, mental illness or other reasons; (2) severe organ function damage; (3) serious visual, hearing or language impairment and cannot cooperate with the examination were excluded.

According to the evaluation results of the Mini-Mental Status Examination (MMSE), 46 patients (male 26, female 20), with an age of 67.5 (57.75–74) and a length of education of 6 (6–9) years, were included in the PSCI group, data are expressed as median between 25th and 75th percentiles [M (P25–P75)].

Subjects in the normal group

A total of 35 healthy controls (15 males and 20 females) with an age of 65(49–70) years and a length of education of 8(6–9) years were selected by the physical examination centre of Shaoxing People's Hospital in the same period, data are expressed as M (P25–P75). The admission criteria were as follows: (1) age of admission = 18–80 years old, (2) simple mental state scale (MMSE Chinese version): 27–30 points and disability without physical function in accordance with the instrument activities of daily living scale (ANON, 2018). (3) the MoCA scale had 30 points in total, and > 26 points indicated normal. The exclusion criteria were: a history of serious cardiovascular and cerebrovascular disease, a history of mental and psychological disorders, and a history of severe central nervous system disease. Due to the fact that this study is a case-control study and the sample size is small at each level, stratified randomization was not used.

Assessment and data collection

MRS data acquisition and post-processing

The 3.0 T Siemens superconducting MRI system (Siemens, Verio 3.0 T) was used to collect the multi-voxel spectrum of the PSCI group and the normal control (NC) group. A point resolved spectroscopy-chemical shift imaging (PRESS-CSI) sequence was applied to ^{1}H-MRS scanning, and the parameters of the ^{1}H-MRS scans were as follows: TR/TE = 1700/135 ms; bandwidth = 1200 Hz; field of view (FOV) = 160 mm × 160 mm; flip angle = 90°; and matrix size = 16 × 16. The volume of interest (VOI) was 60 mm×60 mm×15 mm for bilateral hippocampus (HIP), and 120 mm×120 mm×20 mm for bilateral frontal lobe (FL), posterior cingulate gyrus (PCG) and anterior cingulate gyrus (ACG). The voxel size was 10.0 mm×10.0 mm×15.0 mm for HIP and 10.0 mm×10.0 mm×20.0 mm for bilateral FL, PCG and ACG.The HIP VOI size was designed to match the bilateral HIP, which was located in the skull base, to avoid interference from other factors, i.e., the skull or cerebrospinal fluid. An automatic prescanning program was used to adjust the gain of the voxel, receive/transmit, for semiautomatic shimming, weak water suppression, full width at half maximum (FWHM) < 25 Hz, and water suppression level > 95%. After the scan, a sequence of postprocessing steps were employed to get the MRS data, including the water reference processing, filter, zero-filling, Fourier transformation, frequency shift correction, baseline correction, phase correction, and curve fitting. The regions of interest were segmented using MRI techniques and software. Firstly, a cortical segmentation algorithm based on sulcus and gyrus patterns is used to segment the cerebral cortex into different regions, including the frontal lobe, hippocampus, and cingulate gyrus. Finally, visualize the segmented area and make corrections with the help of neuroimaging experts. The post-processing software we use is LCmodel. The chemical shifts of metabolites were 2.02 ppm for NAA, 3.03 ppm for Cr. Cr was considered as internal parameter, the NAA/Cr ratios were calculated (Bhinderwala et al., 2022).

Neuropsychological assessment

Cognitive function assessment included MMSE (Chinese version) and

MOCA (Beijing version) (Melikyan et al., 2021). MMSE included time/place of orientation, immediate word recall, computational power, delayed recall, language function (naming, retelling, and understanding instructions) and structural imitation, with a maximum total score of 30. MOCA included visuospatial and executive function, naming, memory (no score), attention, language, abstraction, delayed recall and orientation. The maximum total score was 30 points. If the length of education ≤ 12 years, 1 point was added, and < 26 points indicated cognitive impairment. All tests were scored by professionals trained in neuropsychological testing.

Statistical processing

The SPSS 26.0 was used for data processing and frequency analysis, rate statistics, R (version 3.6.3) statistical analysis and visualisation. The GLM function was used to construct the logistics model, and the results of proc (for analysis) and ggplot2 (for visualisation) packages were statistically analysed. Inconsistent M (P25–P75) is adopted to describe the measurement data of state distribution, and the counting data is adopted Described by frequency and percentage, Mann Whiteny U test was used between the two groups. The Spearman correlation analysis was used for non-normally distributed data to evaluate the correlation between cognitive score and brain metabolite level. The receiver operating characteristic (ROC) curve of brain metabolites was drawn and the best cut-off value of the related brain metabolites in patients with PSCI were predicted in accordance with the corresponding maximum area under the ROC curve (AUC) and the maximum value of Youden index (YDI).

Results

Sociodemographic and cognitive assessment

The final sample included 81 participants, including 46 patients with PSCI and 35 with NC. The score of sex, age, education, MMSE (Chinese version), and MoCA (Beijing version) of the two groups is shown in Table 1. Cognitive scores in the PSCI group decreased significantly compared to the NC group ($P < 0.01$).

MRS and cognitive scores results

Magnetic resonance spectroscopy in the PSCI group was compared with that in the NC group: The NAA/Cr values of the bilateral hippocampus, bilateral frontal lobe and bilateral anterior and posterior cingulate gyrus in the PSCI group were lower than those in the NC group, and the difference was statistically significant ($P < 0.01$, Table 2)..

Correlation coefficient

Both the MMSE and MoCA scores were correlated with the different brain regions, with a correlation coefficient of 0.561–0.721 ($P < 0.01$).

ROC curve

The larger the area under the ROC curve (AUC), the better it is at

Table 1

Descriptive data for the general characteristics and cognitive scale scores($N = 81$).

Variable	PSCI ($n = 46$)	NC ($n = 35$)	p-value	Z-value
Sex (% male)	26(56.52%)	16(45.71%)	0.335	
Age (y)	67.5(57.75–74)	65(49–70)	0.188	-1.317
Education level (y)	6(6–9)	8(6–9)	0.267	-1.111
MMSE	22(21–24)	29(28–30)	< 0.001	-7.763
MoCA	17(15–21)	27(27–29)	< 0.001	-7.700

The data of each group are non normal distribution, described by M (P25–P75)

Table 2

MRS test results in two groups ($N = 81$).

Variable	PSCI ($n = 46$)	NC ($n = 35$)	p-value	Z-value
HIP.L NAA/Cr	0.729 (0.417–1.277)	2.459 (1.720–4.299)	< 0.001	-6.607
HIP.R NAA/Cr	0.767 (0.393–1.198)	2.55(1.922–5.678)	< 0.001	-6.188
FL.L NAA/Cr	0.776 (0.399–1.023)	2.134 (1.813–2.693)	< 0.001	-6.855
FL.R NAA/Cr	0.716 (0.408–1.035)	2.590 (1.907–3.937)	< 0.001	-6.922
ACG.L NAA/Cr	0.712 (0.471–1.202)	2.179 (1.546–4.706)	< 0.001	-5.968
ACG.R NAA/Cr	0.645 (0.311–1.086)	1.586 (1.092–2.485)	< 0.001	-5.187
PCG.L NAA/Cr	0.938 (0.518–1.347)	2.885 (2.113–4.459)	< 0.001	-6.674
PCG.R NAA/Cr	0.919 (0.380–1.438)	2.435 (1.625–4.117)	< 0.001	-5.959

The data of each group are non normal distribution, described by M (P25–P75)

indicating a higher diagnostic value. According to Fig. 1A, the curves for bilateral HIP and FL are more sensitive than those for bilateral ACG and PCG, and for bilateral HIP and FL the AUC is larger below the NAA/Cr curve. The value of AUC was the highest in the right FL, the AUC is 0.951, the area [standard error (SE)] is 0.028 ($P < 0.001$), 95% confidence interval (CI) is0.896–1.000, and then in the left FL, the values of AUC is 0.947, the area (SE) is 0.026 ($P < 0.001$), 95% CI is 0.896–0.997 (Table 4 and Fig. 1A). In addition, we analyzed the ROC curves for age and education to compare with the ROC curve of NAA/Cr. The AUC for age is 0.586 with a 95% confidence interval (CI) of 0.456–0.716; For level, the AUC is 0.569 with a 95% confidence interval (CI) of 0.447–0.691 (Table 4 *and* Fig. 1B).

Cutoff value

In agreement with the statistical results of the ROC curves, the sensitivity, specificity, and Jordan exponents of the age, education and the truncated values of NAA/Cr were calculated for the bilateral hippocampus, bilateral frontal lobe, and bilateral cingulate gyrus of the PSCI group to further analyze the discriminative function for different truncated values.

The maximum values of the Jordan index of NAA/Cr in the frontal lobe left (FL.L) and frontal lobe right (FL.R) were 0.834 and 0.878, respectively. The corresponding optimal truncation values of the frontal lobe left (FL.L) and frontal lobe right (FL.R) were 1.380 and 1.533, respectively. The Youden index was highest in the right frontal lobe. PSCI may occur when the NAA/Cr value of the right frontal lobe is less than 1.533. Consistent with this cut-off, patients with PSCI can be screened. Table 5 shows the specific values.

Case

Fig. 2 A, B show a demonstration of a sample of the selected cases reported in this study, in which, in each part, there is one case with the normal FL.R (A) and one case with PSCI with the FL.R (B).

Discussion

Stroke is one of the world's leading causes of death and disability (Khaw et al., 2021; Writing Group Members et al., 2016). A study shows that even minor stroke can influence activities of daily living (ADLs), cognitive function, and quality of life (Strong et al., 2007). This places a significant financial burden on patients and society, and stroke survivors are at increased risk of cognitive impairment (Fride et al., 2015; Carmona-Torres et al., 2019; Ramos-Estebanez et al., 2012). Post-stroke cognitive impairment (PSCI) has a high morbidity; a recent follow-up

Table 3
The correlation coefficient between cognitive scores and MRS at bilateral hippocampus, bilateral frontal lobe and bilateral anterior and posterior cingulate gyrus (N = 81).

Variable	HIP.L NAA/Cr	HIP.R NAA/Cr	FL.L NAA/Cr	FL.R NAA/Cr	ACG.L NAA/Cr	ACG.R NAA/Cr	PCG.L NAA/Cr	PCG.R NAA/Cr	MoCA
MMSE	0.675 * *	0.688 * *	0.721 * *	0.740 * *	0.671 * *	0.615 * *	0.713 * *	0.641 * *	0.842 * *
MoCA	0.629 * *	0.655 * *	0.714 * *	0.628 * *	0.598 * *	0.561 * *	0.652 * *	0.566 * *	1.000

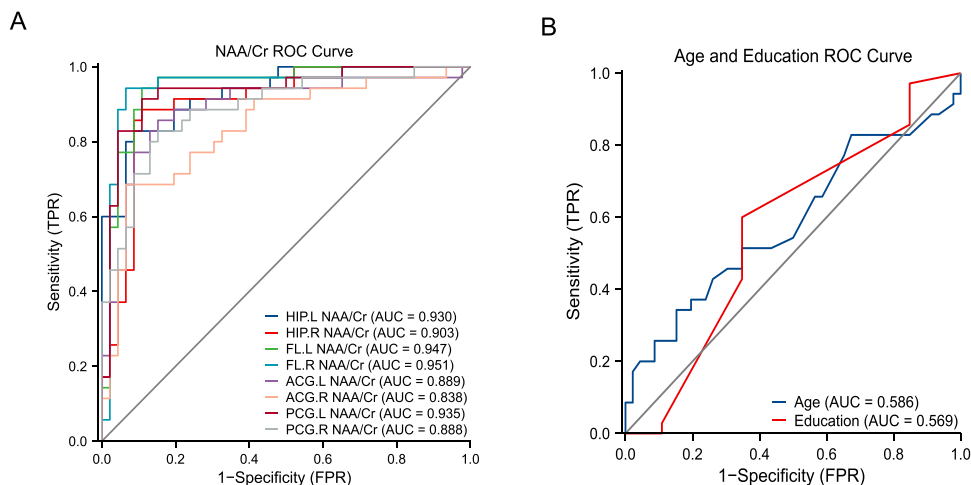* *Correlation is significant at the 0.01 level (two-tailed).

Fig. 1. Area under the receiver operating characteristic (ROC) curve and confidence interval (CI): hippocampus left (HIP.L) NAA/ Cr: 0.930 (95% CI: 0.878–0.983) (P < 0.001), hippocampus right (HIP.R) NAA/ Cr: 0.903 (95% CI: 0.834–0.973) (P < 0.001), frontal lobe left (FL.L) NAA/ Cr: 0.947 (95% CI: 0.896–0.997) (P < 0.001), frontal lobe right (FL.R) NAA/ Cr: 0.951 (95% CI: 0.896–1.000) (P < 0.001), left anterior cingulate gyrus (ACG.L) NAA/ Cr: 0.889 (95% CI: 0.809–0.968) (P < 0.001), right anterior cingulate gyrus (ACG.R) NAA/ Cr: 0.838 (95% CI: 0.746–0.929) (P < 0.001), posterior cingulate gyrus left (PCG.L) NAA/ Cr: 0.935 (95% CI: 0.876–0.993) (P < 0.001), posterior cingulate gyrus right (PCG.R) NAA/ Cr: 0.888 (95% CI: 0.814–0.962) (P < 0.001). Age: 0.586 (95% CI: 0.814–0.962) (P > 0.05), Education: 0.569 (95% CI: 0.447–0.691) (P > 0.05).

Table 4
The area under the receiver operating characteristic (ROC) curve.

Variable	AUC	Std. Error	*p-value b*
HIP.L NAA/Cr	0.930	0.027	< 0.001
HIP.R NAA/Cr	0.903	0.035	< 0.001
FL.L NAA/Cr	0.947	0.026	< 0.001
FL.R NAA/Cr	0.951	0.028	< 0.001
ACG.L NAA/Cr	0.889	0.040	< 0.001
ACG.R NAA/Cr	0.838	0.046	< 0.001
PCG.L NAA/Cr	0.935	0.030	< 0.001
PCG.R NAA/Cr	0.888	0.038	< 0.001
Age	0.586	0.574	> 0.05
Education	0.569	0.357	> 0.05

a Under the non-parametric assumption.
b Null hypothesis: true area = 0.5.

study showed a 61% prevalence of PSCI among 10-year stroke survivors (Mijajlović et al., 2017). However, the progress of patients with PSCI may be delayed after drug treatment (such as cholinesterase inhibitor and N-methyl-D-aspartate receptor antagonist) or other nondrug treatment (such as rehabilitation training and repeated transcranial magnetic stimulation) thus early diagnosis and timely intervention are essentia (Oz et al., 2014; Delavaran et al., 2017; Li et al., 2020). There is no clear recommendation for the use of cholinesterase inhibitors, NMDA receptor antagonists, or transcranial magnetic stimulation (TMS) in the treatment of PSCI. However, some studies have investigated the potential benefits of these treatments in PSCI patients (Baskys and Hou, 2007; Wu et al., 2022).

Currently, the most widely used screening tool is the cognitive function scale. MMSE and MoCA serve as quick and effective screening tools for cognitive impairment, with moderate specificity and sensitivity, involving assessments of memory, visual space, executive ability, and attention (Zhu et al., 2020). The sensitivity and specificity of MMSE
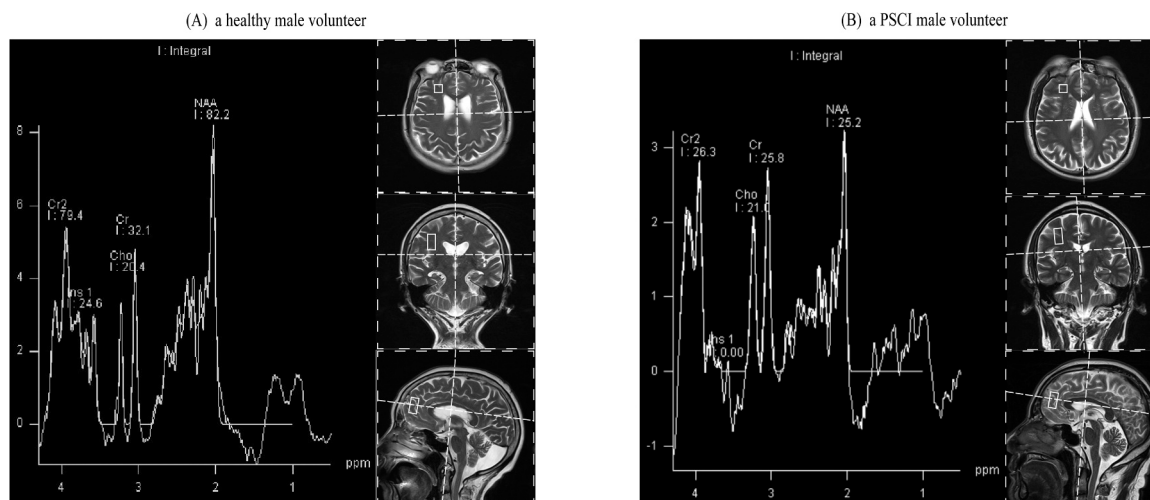
Table 5
Part of ROC related information and data of each prediction variable under their respective best cut off values.

Predictive Variables	Cutoff Value	Youden index	Sensitivity	Specificity	positive predictive value	negative predictive value
HIP.L NAA/Cr	1.496	0.742	0.829	0.913	0.879	0.875
HIP.R NAA/Cr	1.381	0.777	0.886	0.891	0.861	0.911
FL.L NAA/Cr	1.380	0.834	0.943	0.891	0.868	0.953
FL.R NAA/Cr	*1.533*	*0.878*	0.943	0.935	0.917	0.956
ACG.L NAA/Cr	1.324	0.705	0.857	0.848	0.811	0.886
ACG.R NAA/Cr	1.347	0.620	0.686	0.935	0.889	0.796
PCG.L NAA/Cr	1.844	0.806	0.914	0.891	0.865	0.932
PCG.R NAA/Cr	1.544	0.676	0.829	0.848	0.806	0.867
Age	54.500	0.190	0.343	0.848	0.632	0.629
Education	6.500	0.252	0.600	0.652	0.568	0.682

The bold and italics values represent the maximum Youden index value and the corresponding best cutoff value.

Fig. 2. Examples of the data of proton magnetic resonance spectroscopy (^{1}H MRS) obtained in healthy male volunteers and post-stroke cognitive impairment (PSCI) male volunteers. NAA, N-acetyl aspartate; Cr, creatinine. (A) Demonstrates a healthy male volunteer. These ratios are (NAA/Cr = 1.581) in the right frontal lobe. (B) Demonstrates a PSCI male volunteer. These ratios are (NAA/Cr = 0.621) in the right frontal lobe.

and MoCA can be affected by various factors, including the cut-off scores used, the population being tested, and the presence of comorbidities. In the present work, MMSE was used to assess cognitive function in enrolled patients, who were divided into PSCI and NC groups based on their outcomes. MRS was also used to detect differences in brain metabolites between the two groups. The MMSE and MoCA scores of the PSCI group were lower than those of the NC group ($P < 0.001$).

MRS is an MRI-based neuroimaging method. It is currently the only non-invasive technique capable of detecting brain metabolites and biochemical components. It could show information about the function, activity, integrity, energy metabolism, glial overgrowth and other aspects of nerve cells. Compared with conventional MRI, MRS could detect metabolic function changes in minor diseases as early as possible by quantifying brain metabolites, thus helpful for early diagnosis and timely treatment of patients with PSCI30. Related studies have shown that NAA/Cr in the brain decreases to varying degrees prior to dementia and other clinical symptoms in PSCI patients, suggesting that NAA/Cr plays an important diagnostic role in the development of cognitive function (Wang et al., 2021; Eisele et al., 2020). Similar to the previous study, the present study found that the NAA/Cr values of the hippocampus, frontal lobe and cingulate gyrus in the PSCI group were significantly lower than those in the NC group ($P < 0.05$). This result suggests that the decline in cognitive function in patients with PSCI is related to the decline in NAA/Cr values and that the severity of cognitive impairment is positively related to the decline in NAA/Cr. Therefore, the NAA/Cr ratio could effectively reflect the degree of cognitive impairment. This finding may be attributed to the neuronal damage and abnormal activation of glial cells in the corresponding brain regions after stroke. Neurological dysfunction leads to a reduction in the relative concentration of NAA, resulting in the impairment of cognitive function. Therefore, the level of NAA/Cr detected by MRS may reflect the cognitive dysfunction and its severity in stroke patients from a material metabolism perspective, which is of clinical importance for early diagnosis and severity prediction of PSCI.

Further correlation analysis confirmed a significant correlation between MMSE and MoCA score in brain and metabolite changes. Modrego (Modrego et al., 2011) et al. found that the cut-off for NAA/Cr may be different for different choices, such as brain function regions and ethnicity. In this study of elderly Chinese, we found a cut-off of 1.533 for the ratio of NAA/Cr in the right FL to distinguish normal cognitive impairment from PSCI. Sensitivity, specificity and YDI were 0.943, 0.935 and 0.878 respectively. Therefore, PSCI may occur when the NAA/Cr value of the right frontal lobe is less than 1.533. In addition to

the best performing the NAA/Cr of right FL, the diagnostic accuracy of the ratio of NAA/Cr in other regions is significantly superior to that of clinical factors such as age and educational level. Although the current study may not have comprehensively considered all clinical factors, we have reason to believe that the brain metabolites will demonstrate superior diagnostic advantages in future research.

The PSCI group was found to have a lower NAA/Cr ratio than the NC group. This result suggests that brain metabolites in patients with PSCI begin to modify during the clinical non-emergency or mild cognitive dysfunction phase. MRS is able to sensitively reflect the presence of mild cognitive dysfunction, providing a reference for early diagnosis of cognitive dysfunction. As a non-invasive imaging exam, MRS is unaffected by education and other factors. It has the advantages of strong objectivity and the possibility of early, objective and comprehensive assessment of cognitive impairment. It also provides a modern means for early diagnosis of PSCI and a new basis for building sensitive and reliable models of PSCI assessment and diagnosis in the future.

However, there are additional limitations include: 1. Limited stroke data: The study didn't detail stroke characteristics in the PSCI group, potentially affecting results; 2. No structural abnormality info: Structural issues in the brain weren't reported, which could impact results; 3. Small sample size: With a small sample (46 PSCI patients, 35 controls), findings may not apply broadly; 4. Control group choice: Using only healthy controls limits comparisons to other studies. The study authors acknowledged some of these limitations but more research is needed to validate findings and address these issues in future studies. 5. In terms of methodology, the short echo method was used to detect metabolites in the brain instead of the long echo method. For follow-up studies, deep echo detection methods should be added for comparison with short echo methods, and MRS detection must be performed for additional brain regions of interest.

Statement

No animal studies are presented in this manuscript. The study involving human participants was reviewed and approved by Shaoxing People's Hospital. Patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Raw data supporting the conclusions of this paper will be made available by the authors without undue reservation.

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CRediT authorship contribution statement

MengQi Li: Data curation, Writing − original draft, Investigation, Formal analysis. **LingLing Yao**: Resources, Visualization. **ZengXin Lu**: Project administration. **LiMing Yang**: Validation. **Hong Fan**: Conceptualization, Methodology, Supervision, Funding acquisition, Writing − review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2023.10.002.

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Writing Group Members, Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., Das, S.R., de Ferranti, S., Després, J.P., Fullerton, H.J., Howard, V.J., Huffman, M.D., Isasi, C.R., Jiménez, M.C., Judd, S.E., Kissela, B.M., Lichtman, J.H., Lisabeth, L.D., Liu, S., Mackey, R.H., Magid, D.J., McGuire, D.K., Mohler 3rd, E.R., Moy, C.S., Muntner, P., Mussolino, M.E., Nasir, K., Neumar, R.W., Nichol, G., Palaniappan, L., Pandey, D.K., Reeves, M.J., Rodriguez, C.J., Rosamond, W., Sorlie, P.D., Stein, J., Towfighi, A., Turan, T.N., Virani, S.S., Woo, D., Yeh, R.W., Turner, M.B., American Heart Association Statistics Committee; Stroke Statistics Subcommittee, 2016. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 133 (4), e38–e360. https://doi.org/10.1161/CIR.0000000000000350. Epub 2015 Dec 16. Erratum in: Circulation. 2016 Apr 12;133(15):e599.

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