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# Characteristic early changes of Glu and Cho in brain regions affected by different types of subjective cognitive decline and their clinical significance

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**Abstract**

To discuss the early changes of Glu and Cho in the affected areas of different types of subjective cognitive decline, including amnestic MCI (aMCI), non-amnestic MCI (naMCI) and vascular cognitive impairment no dementia (VCIND), using Proton Magnetic Resonance Spectroscopy ($^1$H-MRS) technology. Routine head MRI and $^1$H-MRS examinations were performed on 50 clearly diagnosed aMCI patients, 44 naMCI patients, 44 VCIND patients, and 44 elderly individuals with normal cognitive function. Measure the volume of the patient bilateral hippocampus. Using the bilateral hippocampus, left posterior cingulate gyrus (PCG), and frontal lobe as regions of interest, the scope under the peak of N-acetylaspartate (NAA), choline complex (Cho), glutamate (Glu), Metabolic Images (mI), and creatine (Cr) was tested. Perform a correlation analysis between the NAA/Cho/Cr values of the VCIND group and the MoCA score. All experimental subjects were right-handed. The NAACr values in both hippocampus of the VCIND were greatly lower than those in control ($P < .05$). The NAA/Cr values on both sides of the VCIND were correlated with the MoCA score ($P < .05$). The NAA/Cr values in the LHp and PCG of subjects in the aMCI and naMCI groups were lower than those in the NC group ($P < .05$). The NAA/Cr values in the left frontal lobe of the aMCI and naMCI showed no obvious decrease compared to the NC. The Glu/Cr of subjects in the aMCI was lower in the left PCG than those in the naMCI and NC ($P < .05$). The discrepancy between the naMCI and the NC was $P > .05$. In the LHp and frontal lobe, in contrast with the naMCI and NC, the mI/Cr values in the LHp and PCG of subjects in the aMCI were higher ($P < .05$). In the left frontal lobe, relative to the aMCI and NC, the mI/Cr values in the naMCI were higher ($P < .05$). The changes in the concentration of 1H-MRS metabolites in the hippocampus can indicate the presence of hippocampal neuronal damage before morphological changes occur in the hippocampus. $^1$H-MRS NAA/Cr can reflect the cognitive function changes of patients to a certain extent. There are regional differences in mI and Glu metabolism in the brain between aMCI and naMCI groups. $^1$H-MRS provides an effective basis for clinical differentiation between aMCI and naMCI.

**Abbreviations:** 1H-MRS = Proton Magnetic Resonance Spectroscopy, aMCI = Amnestic MCI, Cho = choline complex, Cr = creatine, Glu = glutamate, MI = Metabolic Images, NAA = acetylaspartate, naMCI = non-amnestic MCI, PCG = posterior cingulate gyrus, VCI = vascular cognitive impairment, VCIND = vascular cognitive impairment no dementia.

**Keywords:** $^1$H-MRS, choline complex, Glu, non-demented vascular cognitive impairment

## 1. Introduction

The vascular cognitive impairment no dementia (VCIND) is a very early, mild, and highly insidious stage of vascular cognitive impairment (VCI), which is the most common form of VCI in the elderly. VCI is not a single disease, but refers to a syndrome of mild cognitive impairment (MCI) to dementia caused by risk factors for cerebrovascular disease (CVD), obvious or unclear CVDs. Its clinical manifestations are very complex, mainly including impairment in memory, execution ability, attention, language, emotions, personality, and other aspects. VCIND is considered a pre dementia state. Scholars have found during follow-up that nearly 34% of patients develop dementia, and 14% of patients return to normal cognitive impairment (CI). It can be seen that the risk of VCIND developing into dementia is high, but not all patients will develop into dementia, and the condition is reversible. MCI is an intermediate transitional state between normal aging and early dementia. According to the presence or absence of memory impairment, MCI can be divided into amnestic MCI (aMCI) and non-amnestic MCI (naMCI).[1,2] aMCI generally progresses to Alzheimer disease (AD), while naMCI mostly

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progresses to vascular dementia (VD), frontotemporal dementia (FTD), and body lewy dementia (DLB). Making correct judgments about aMCI and naMCI as early as possible will effectively guide clinical treatment and improve prognosis. In the study of CI diseases, the region of interest of $^1$H-MRS is mainly located in anatomical regions related to cognitive function, such as the frontal lobe (FL), hippocampus, cingulate gyrus, and other parts. The hippocampus has been proven to be related to memory ability and plays a very important role in memory storage and retrieval.[3] However, the hippocampus is highly susceptible to damage due to ischemia and hypoxia. There are literature reports that the most sensitive cells to ischemia and hypoxia are a type of conical cell located in the hippocampus. When the hippocampus is damaged, the concentration level of NAA changes, which is significantly correlated with memory ability.[4] In cognitive dysfunction diseases, the hippocampus is the earliest and most prone to pathological changes.[5] So while the exact pathogenesis of vascular CI still needs further research. Early monitoring of the hippocampus, which is associated with various cognitive disorders, may be helpful for the judgment and mechanism understanding of cognitive states. The comprehensive application of technologies and methods such as neuroimaging and neuropsychological assessment to study the relationship between CVD and CI has become an important research approach in this field. This study utilized $^1$H-MRS to investigate whether there are cellular level metabolic variations in the hippocampus of VCIND cases, and analyzed the characteristics of changes in $^1$H-MRS metabolite parameters in the hippocampus of patients and their relationship with diseases. The purpose is to provide valuable imaging evidence for the early diagnosis and treatment of VCIND, aMCI, and naMCI patients.

## 2. Materials and Methods

### 2.1. General information

This study was approved by the Ethics Committee of the Third Hospital of Wuhan (No. 25). This study selected 44 patients who met the diagnosis of VCIND in the neurology department of our hospital from May 2020 to December 2020. Among them, 14 are male patients and 30 are female, their average age is in 71.71 ± 5.43 years. 50 with aMCI were selected, including 24 males and 26 females (average age: 66.43 ± 5.01 years). 44 patients with naMCI were selected, with 20 males and 24 females (average age: 68.23 ± 5.90 years).

Inclusion criteria: The patient has a complaint of memory impairment and has evidence from an informed individual. Memory loss is not consistent with age and education level, and memory test scores are 1.5 standard deviations (SDs) lower than the normal control. The diagnostic criteria for dementia were not met, and the patient was determined to be 0.5 by the Clinical Dementia Rating (CDR). There is no significant impairment in daily living ability. The patient was assessed on the Activities of Daily Living (ADL) scale and scored <26 points. The patient MoCA score was <26 points as measured by the Montreal Cognitive Assessment (MoCA). The CI of patients is caused by CVDs, such as risk factors for CVDs, obvious or inconspicuous CVDs. There are corresponding focal neurological signs or imaging data to confirm the presence of CVD in auxiliary examinations. The patient was evaluated on the Hachinski Ischemic Score (HIS) and scored no <8 points.

Exclusion criteria: CI caused by reasons other than CVD. Have a history of alcohol dependence and abuse of other psychoactive substances. Patients with severe aphasia, loss of use, loss of recognition, and various reasons who cannot cooperate with cognitive function tests. No history of CI induced drug use, or cessation of such drugs for more than 6 months.

This project is approved by the Medical Theory Committee of our hospital. All guardians of the children have signed informed consent forms.

### 2.2. Inspection method

The experiment was conducted using magnetic resonance imaging, using a German SIEMENS 1.5T Avanto superconducting magnetic resonance scanner and a skull coil. All subjects underwent routine MRI scans. The specific scanning parameters are as follows: cross-sectional T1WI: TR = 550ms, TE = 8.7ms, with 8.4mm thick layer, 1.4mm layer spacing, FOV220*220mm, and matrix size 512 * 512. Cross section T2WI: TR = 4000ms, TE = 99ms, thick layer 8.4mm, 1.4mm layer spacing, FOV220 * 220mm, matrix size 512 * 512. Cross section DWI: TR = 3400ms, TE = 102ms, thick layer 8.4mm, layer spacing 1.4mm, FOV230 * 230mm. Cross section FLAIR: TR = 8200ms, TE = 102ms, thick layer 8.4mm, layer spacing 1.4mm, FOV220 * 220mm. $^1$H-MRS advanced brain function 3D imaging sequence scanning, and completed transverse and coronal images parallel and perpendicular to the hippocampus and the long axis of the hippocampus based on sagittal images. It will serve as the positioning image for MRS. In the coronal image, the edges of the hippocampus were delineated using the Brenasconi and Press methods. Use the automatic generation function of Tools software to calculate the area of the area. The obtained result value is multiplied by the layer thickness to obtain the hippocampal volume of that layer. Finally, add the volumes of each layer to obtain the volume of the hippocampus on that side. $^1$H-MRS uses CSI matrix sequence scanning. This sequence defaults to the absence of adipose tissue in the intracranial region. The magnetic resonance scanner automatically completes baseline calibration, shimming, and water suppression, so that the half peak of water is <10 Hz, and then performs automatic scanning. The scanning related parameters are set to TR = 1500ms, TE = 135ms, multi-dimensional pixel phase matrix 16 * 16, voxel thickness = 10mm, FOV = 160mm, and imaging time around 12min. After the scanning is completed, the raw data is transmitted to the workstation and the original phase map of the spectrum is obtained through Fourier transform. This includes Chemical shift images (CSI), Spectra (S), MI, and Overlay of Metabolism and Anatomy (AI + MI). Record the area under peak curves of NAA, Cho, Glu, and Cr in AI + MI, and calculate the NAA/Cr, Cho/Cr, Glu/Cr ratios. Another 44 volunteers were selected as the Normal Control (NC) in the experiment, and compared with the VCIND, aMCI, and naMCI groups. The age and education level of NC group volunteers are similar to those of the control group, and there is no clear CI or neurological disease. Under CDR, ADL, and MoCA tests, their scores were all within the normal range.

### 2.3. Statistical methods

The study used Windows system and IBM SPSS 23.0 software for data analysis. The obtained quantitative data is represented using the method of mean and SD. The comparison between the 2 groups was conducted using independent sample t-tests, while intra-group comparison was conducted using paired t-tests. If the data does not conform to normality and the variance is homogeneous, non-parametric testing is used. The correlation analysis was conducted using Spearman. When the $P < .05$, it means that the difference in comparison is statistically significant.

## 3. Results

### 3.1. General data analysis

The general data comparison results of the 4 groups of subjects are shown in Table 1. The difference in general

**Table 1**

**Comparative data for each group of subjects.**

| / | aMCI | naMCI | VCIND | NC | Statistic | P |
|---|---|---|---|---|---|---|
| Number of cases | 50 | 44 | 44 | 44 | / | / |
| Age | 66.43 ± 5.01 | 68.23 ± 5.90 | 71.71 ± 5.43 | 70.71 ± 5.32 | $F = 0.03$ | .35 |
| Gender (male/female) | 24/26 | 20/24 | 14/30 | 20/22 | $\chi^2 = 3.53$ | .07 |
| Years of Education Primary/Middle/High/University | 10/20/14/6 | 9/18/12/5 | 8/18/14/4 | 10/18/10/6 | $\chi^2 = 1.44$ | .75 |

General data comparison results, $P < .05$ is considered significant.

**Table 2**

**Comparison results of relevant parameters between distinctive test groups.**

| / | aMCI | naMCI | VCIND | NC |
|---|---|---|---|---|
| Left hippocampus (LHp) | 2.50 ± 0.11 | 2.52 ± 0.11 | 2.48 ± 0.13 | 2.49 ± 0.09 |
| Right hippocampus (RHp) | 2.52 ± 0.10 | 2.53 ± 0.12 | 2.50 ± 0.12 | 2.52 ± 0.08 |
| *t* | −1.63 | −1.66 | −1.75 | −2.61 |
| *P* | >0.05 | >0.05 | >0.05 | >0.05 |

Comparison of hippocampal volume on both sides of each group, $P < .05$ is considered significant.

information such as age, gender, and education level among them is $P > .05$.

### 3.2. Comparison of hippocampal volume among 4 groups of subjects

In Table 2, the results of hippocampal volume on both sides of the experimental subjects in each group expressed $P > .05$ among the 4 groups.

### 3.3. Comparison of MRS indicators between the VCIND and the NC on both sides of the hippocampus

The comparison results of various indicators between VCIND and NC hippocampus under $^1$H-MRS detection are shown in Table 3. In the LHp, the distinction in NAA/Cr ratio between VCIND and NC was $P < .05$; Cho/Cr ratio ($P > .05$). In the RHp, the NAA/Cr between VCIND and NC was $P < .05$; The Cho/Cr was $P > .05$.

Figure 1A and 1B show the 1H MRS detection results of the LHp and RHp of patients in the VCIND. The Cr2 ratio in 1(a) is 0.67, the Cho ratio is 0.78, and the NAA ratio is 0.77. The Cr2 ratio in 1(b) is 0.73, the Cho ratio is 1.20, and the NAA ratio is 1.23. In the results, the Cho and NAA ratios of LHp and RHp in the VCIND appeared a certain decrease, and the left side was more pronounced.

### 3.4. Comparatuve MRS indicators for the VCIND and the NC groups in the LHp

Figure 2A and 2B show the 2 groups' results of $^1$H-MRS detection in the LHp. The Cr2 ratio in 2(a) is 0.67, the Cho ratio is 0.78, and the NAA ratio is 0.77. The Cr2 ratio in 2(b) is 0.73, the Cho ratio is 0.95, and the NAA ratio is 0.95. The left NAA ratio in the VCIND obviously decreased, indicating $P < .05$.

### 3.5. Correlation analysis results between VCIND group and MoCA

As shown in Figure 3A and 3B represent the 2's scatter plots of the connection between NAA/Cr values and MoCA scores in the LHp, as well as the correlation between Cho/Cr values and MoCA scores. The correlation coefficient in 3(a) is 0.77, $P < .05$; In 3(b), it is −0.13, $P > .05$.

In Figure 4A and 4B show scatter plots of the correlation between NAA/Cr and MoCA, Cho/Cr and MoCA in the RHp of the VCIND and NC, respectively. The correlation coefficient in 4(a) is 0.61, which is $P < .05$. The correlation coefficient in 4(b) is −0.06, with a $P > .05$.

### 3.6. Comparison of NAA/Cr values among subjects in aMCI group, naMCI group, and NC group

The difference in NAA/Cr values between the 3 groups in the LHp and posterior cingulate gyrus (PCG) was $P < .05$. Pairwise comparison between groups showed that the NAA/Cr values in the LHp and PCG of subjects in the aMCI and naMCI were lower, in constrast with the NC ($P < .05$). This time, the NAA/Cr values in both aMCI and naMCI were $P > .05$. The NAA/Cr values in the left FL of the aMCI and naMCI had no obvious decrease compared to the NC group, and between the 3 groups, it was $P > .05$ (Table 4).

### 3.7. Comparison of Glu/Cr values among subjects in aMCI, naMCI, and NC

The difference in Clu/Cr values in the left PCG between the 3 groups was $P < .05$. Pairwise comparison between groups showed that the Glu/Cr of subjects in the aMCI were lower in the left PCG than those in the naMCI and NC ($P < .05$). Within the naMCI and the NC groups, there was $P > .05$. Glu/Cr values between the 3 groups in the LHp and FL, $P > .05$ (Table 5).

### 3.8. Comparison of mI/Cr values among subjects in naMCI, aMCI, and NC

The mI/Cr values of the LHp, PCG, and left FL among the 3 groups were all $P < .05$. Pairwise comparison indicated that the mI/Cr values in the LHp and PCG of subjects in the aMCI outperformed than those in the naMCI and NC ($P < .05$), while the mI/Cr in the naMCI were lower than the NC ($P > .05$). In the left FL, the mI/Cr in the naMCI were greater than those in the aMCI and NC, both $P < .05$ (Table 6).

## 4. Conclusion

VCIND is the early stage of VCI, with a concealed onset and slow progression. It is considered a pre dementia state and the most common subtype of MCI in China.[5] There is no definite treatment method at home and abroad that can prevent the progression of VCIND, so early diagnosis and intervention, delaying or even reversing the development of CI, are particularly important. The hippocampus is located inside the temporal lobe, one on each side, and is a part of the brain limbic system. It has been proven to be related to memory ability and plays a very important role in memory storage and retrieval.[6] MCI is currently a

**Table 3**

**Comparative data of MRS indicators between 2 groups of bilateral hippocampus.**

| Position | Index | VCIND group | NC group | *F* value | *t* value | *P* value |
|---|---|---|---|---|---|---|
| LHp | NAA/Cr | 0.91 ± 0.09 | 1.20 ± 0.19 | 3.02 | −4.28 | **.00** |
| | Cho/Cr | 1.02 ± 0.24 | 1.11 ± 0.14 | 2.04 | −0.92 | .31 |
| RHp | NAA/Cr | 1.03 ± 0.13 | 1.27 ± 0.19 | 1.56 | −3.07 | **.01** |
| | Cho/Cr | 1.14 ± 0.39 | 1.25 ± 0.39 | 3.52 | −0.68 | .33 |

*P* < .05 is considered significant and is bolded in the table.

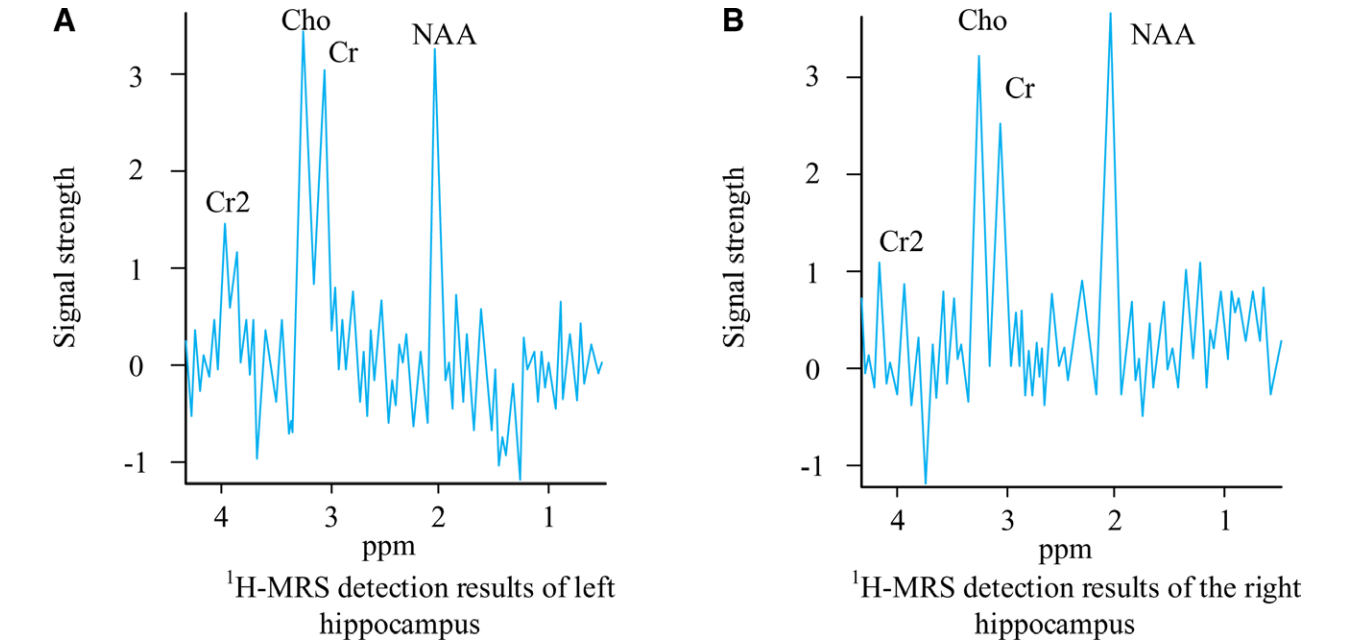


**Figure 1.** ¹H-MRS detection results of bilateral hippocampus in patients with VCIND group. VCIND = vascular cognitive impairment no dementia.

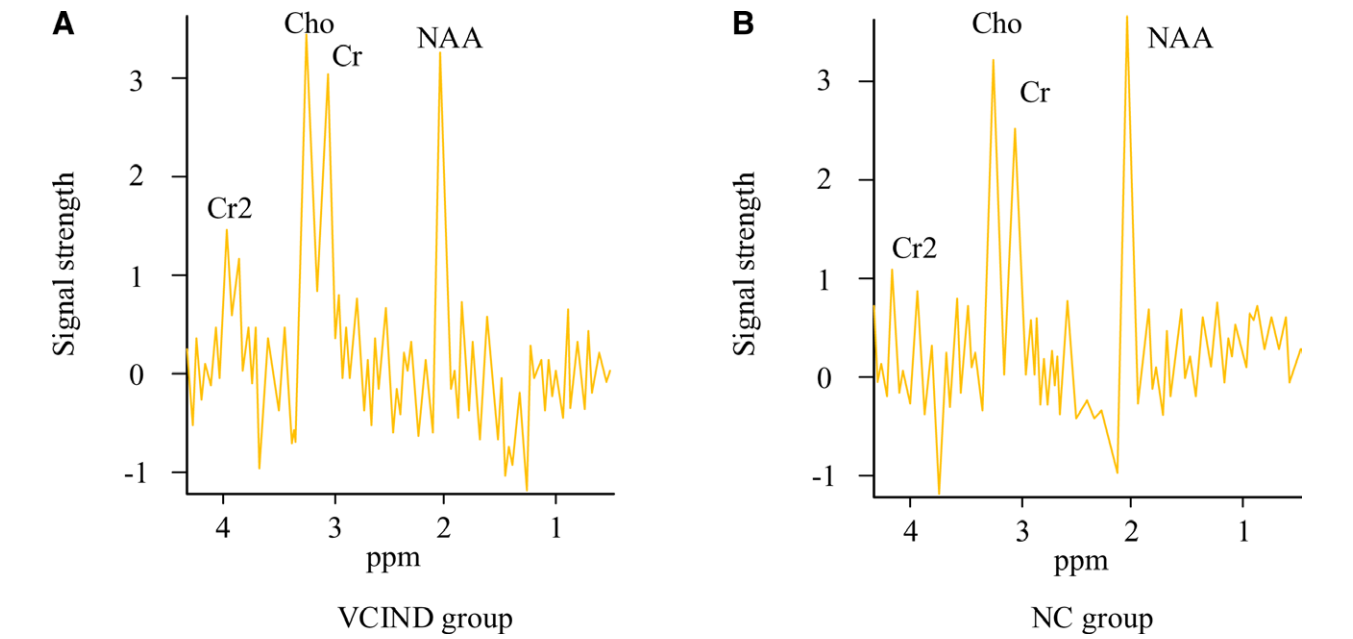


**Figure 2.** ¹H-MRS detection results of LHp in VCIND group patients and NC group patients. VCIND = vascular cognitive impairment no dementia.

broad concept that includes various pre dementia states caused by neurodegeneration, vascular factors, or other factors. Due to the irreversible development of various CIs into dementia, some studies even suggest that as long as there is sufficient time, most or all MCIs will develop into dementia. The distinct outcomes of aMCI and naMCI lead to significant differences in clinical treatment and prognosis, making early identification of MCI subtypes particularly important. There are literature reports that the most

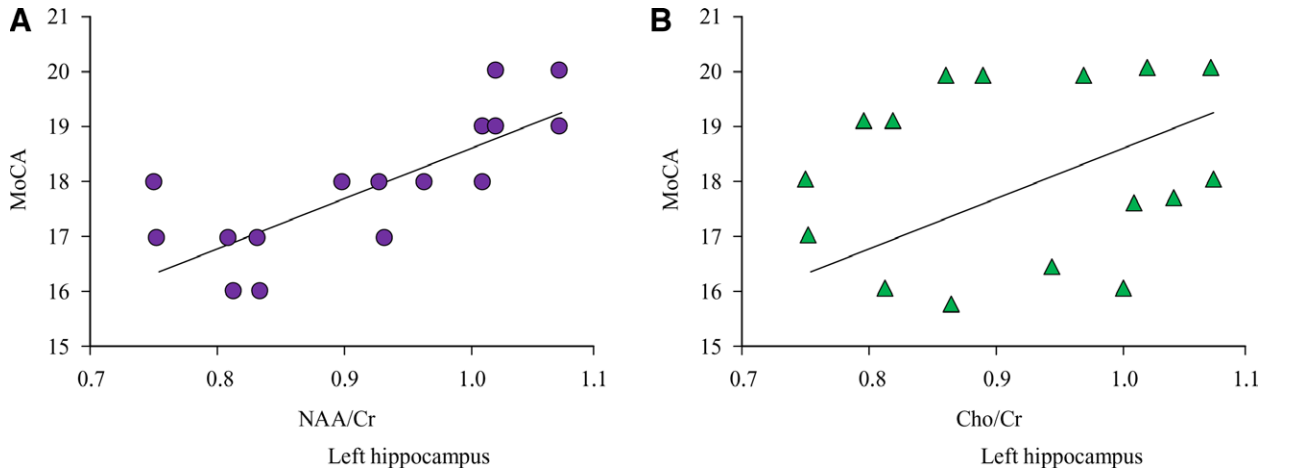


**Figure 3.** Correlation analysis results between NAA/Cr, Cho/Cr, and MoCA scores in the LHp of patients in the VCIND group. VCIND = vascular cognitive impairment no dementia.

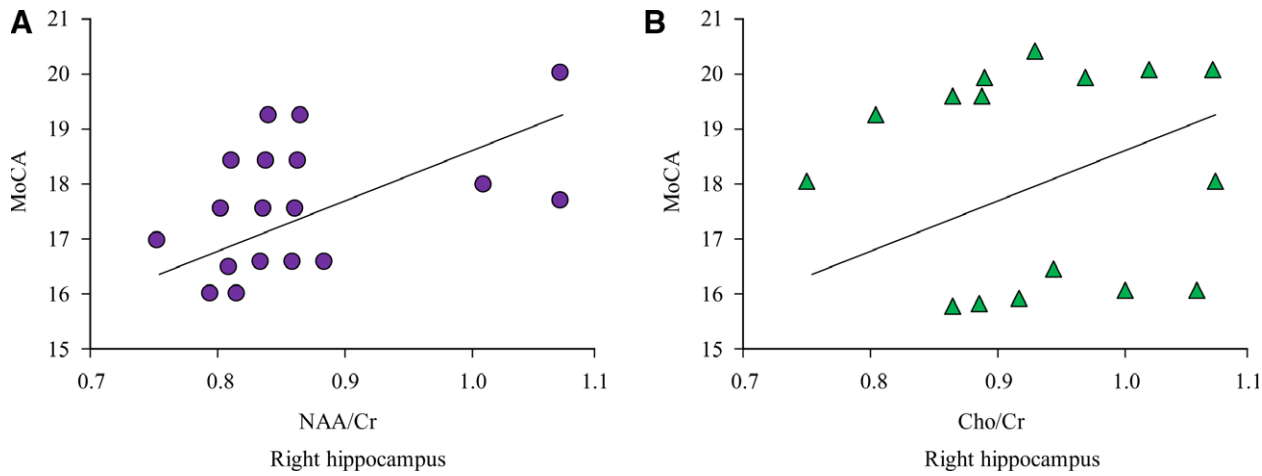


**Figure 4.** Correlation analysis between Cho/Cr values, NAA/Cr values, and MoCA scores in the RHp of patients in the VCIND group. VCIND = vascular cognitive impairment no dementia.

**Table 4**

**Comparison results of NAA/Cr values between 3 groups.**

| Group | Number of cases | LHp | Left buckle back | Left FL |
|---|---|---|---|---|
| aMCI | 50 | 1.08 ± 0.10[ab] | 1.01 ± 0.08[ab] | 1.18 ± 0.11 |
| naMCI | 44 | 1.06 ± 0.07[a] | 1.06 ± 0.09[a] | 1.17 ± 0.11 |
| NC | 44 | 1.19 ± 0.20 | 1.21 ± 0.17 | 1.18 ± 0.09 |
| *F* | / | 9.12 | 8.62 | 1.43 |
| *P* | / | <.05 | <.05 | >.05 |

Compared with the NC group, a represents $P < .05$. Compared with the naMCI group, b represents $P > .05$.

sensitive cells to ischemia and hypoxia are a type of conical cell located in the hippocampus. The limbic system is considered the emotional center. The hippocampal loop is the main circuit of the limbic system, including the hippocampal structure - fornix - papillary body - papillary thalamic tract - anterior optic nucleus - geniculate part of the internal capsule - cingulate gyrus - parahippocampal gyrus - olfactory cortex - perforator pathway - hippocampal formation.[7,8] The hippocampus is highly susceptible to damage caused by ischemia and hypoxia, leading to increased deposition of Aβ and abnormal phosphorylation of tau protein expression in the hippocampal structure. It can also lead to cell apoptosis, thereby exacerbating the loss of neurons in the hippocampal structure and hindering the transmission of hippocampal circuits. When the hippocampus is damaged, the concentration level of NAA changes, which is significantly correlated with memory ability.[9–11] Research has shown that the volume of the hippocampus in dementia patients is significantly reduced compared to normal individuals. The normal volume of the hippocampus is basically between 2.00 and 3.57cm$^3$. There are many reported samples of hippocampal volume in China, but the difference is significant, ranging from 2.06 to 5.34cm3. This indicates that there are significant differences in reports on hippocampal volume, mainly due to the fact that hippocampal volume measurement relies heavily on the subjectivity of the measurer.[12–14] In the study, the volume of the 4 groups of hippocampus was within the normal range of other studies, and there was $P > .05$ compared. This indicates that patients in the VCIND group are in the early stage of VCI, and there is no significant change in hippocampal volume during the early stage of the lesion. $^1$H-MRS displayed a significant deduction in NAA/Cr values on both sides of the hippocampus in the VCIND compared to the normal control group, and both were significantly correlated with MoCA scores. This indicates that the lower the concentration of NAA in the hippocampus, the lower its score, and the poorer its memory ability.

The $^1$H-MRS used in this study is currently the only non-invasive imaging technique that can detect metabolic and biochemical components in the living brain. At present, it is mainly

**Table 5**

**Comparison results of Clu/Cr values between 3 groups.**

| Group | n | LHp | Left buckle back | Left FL |
|---|---|---|---|---|
| aMCI | 50 | 0.46 ± 0.05 | 0.34 ± 0.03[a] | 0.42 ± 0.04 |
| naMCI | 44 | 0.45 ± 0.04 | 0.42 ± 0.03[b] | 0.41 ± 0.02 |
| NC | 44 | 0.43 ± 0.05 | 0.41 ± 0.04 | 0.44 ± 0.03 |
| *F* | / | 0.27 | 8.33 | 0.26 |
| *P* | / | >.05 | <.05 | >.05 |

Compared with the NC group, a represents $P < .05$. Compared with the naMCI group, b represents $P > .05$.

**Table 6**

**Comparison results of mI/Cr values between 3 groups.**

| Group | Number of cases | LHp | Left buckle back | Left FL |
|---|---|---|---|---|
| aMCI | 50 | 0.65 ± 0.06[a] | 0.61 ± 0.06[a] | 0.42 ± 0.04[b] |
| naMCI | 44 | 0.38 ± 0.03[b] | 0.41 ± 0.04[b] | 0.57 ± 0.05[a] |
| NC | 44 | 0.40 ± 0.05 | 0.43 ± 0.05 | 0.42 ± 0.04 |
| *F* | / | 11.36 | 9.30 | 7.72 |
| *P* | / | <.05 | <.05 | <.05 |

Compared with the NC group, a represents $P < .05$. Compared with the naMCI group, b represents $P > .05$.

used to study Alzheimer disease (AD), VaD, etc, while there is relatively little research on VCIND. Among the metabolites that can be detected by $^1$H-MRS, NAA, Cho, Cr, Glu, and mI are the most common substances, and their absolute values or signal intensity ratios are usually used to reflect their concentration changes.[15,16]

In research on NAA, its production by mitochondria is a marker of neuronal functional integrity, density, and activity. NAA only exists in neurons and axons, and can reflect the number and functional status of neurons. The decrease usually reflects a decrease in the number of neurons and functional impairment. The NAA/Cr ratio on both sides of VCIND patients was obviously reduced comparing the NC group, and the left side was more pronounced. This indicates that there is neuronal damage in the hippocampus of VCIND patients. When neurons are damaged, the exposed myelin sheath of fibers participates in neural plasticity and motor skill learning. Because myelin damage causes damage to the white matter tract, which subsequently affects these functions and leads to CI. VCIND patients have a lower left side NAA/Cr compared to the right side, which may be due to the asymmetry between the 2 hemispheres in anatomical structure, cognitive function, and biochemical metabolism of the human brain, known as "hemispheric dominance." At the same time, studies have shown that the vast majority of right-handed humans have a left lateral brain. Patients with CI have a higher probability of left hemisphere damage.[17–19] In the study of Cho, it is a precursor of phosphatidylcholine and acetylcholine. The former participates in the formation of cell membranes, while the latter is an important neurotransmitter (nTM) involved in human memory and cognitive processes. Cho is an indicator of cell membrane activity. When cell density increases, the level of Cho increases, which is a sign of cell membrane division and myelin phospholipid lysis. This indicates damage to brain cells. There was no distinction in Cho/Cr between the 2 sides of the hippocampus in the VCIND and NC groups, possibly due to VCIND being the very early stage of VCI. The cholinergic mechanism plays a positive regulatory role in cerebral blood flow. White matter lesions have not yet caused radiative disconnection of the central axonal basal forebrain cholinergic system; The cerebral tissue has not yet shown hypoperfusion; The excitability of nerve cells and brain metabolic rate were not affected; Therefore, there has been no occurrence of focal or diffuse injury.[20–22] In the study, the degree of decrease in NAA/Cr values in both hippocampus of VCIND patients was significantly correlated with MoCA. This indicates that variations in NAA/Cr values can exhibit the severity of CI in VCIND patients, and can serve as important quantitative indicators for early diagnosis, treatment, disease detection, and prognosis of VCIND. The level of Cr in normal brain tissue is relatively stable and is a marker of cellular energy. By storing high-energy phosphate bonds, it acts as a buffer between ATP and ADP, increasing in low metabolic states and decreasing in high metabolic states. It is often used as a reference for the standardization of other metabolites to reflect neuronal damage. The study also used Cr as a reference material to calculate the relative concentrations of other metabolites. In the analysis of MoCA, hippocampal damage is more prone to significant memory impairment (delayed recall), directional ability, abstract ability, and computational ability impairment. Significant memory impairment, especially near memory impairment, can occur when both sides of the hippocampus are damaged.

Glu, as the primary excitatory nTM in the brain, is closely bound up with the learning and memory functions of the brain. The changes in Glu levels highly indicate physiological or pathological changes in neurons and glial cells (GCs). Research has shown that the Glu level in the PCG of aMCI patients is greatly reduced, and the degree of reduction is significantly different from that of the naMCI and normal groups. This indicates that Glu may be an effective indicator for identifying aMCI and naMCI. Since the cingulate gyrus occupies a vital position in the processes such as learning and memory, whether the research results suggest that the posterior structure of the cingulate gyrus in aMCI may be involved earlier than the hippocampus is worth further research. The increase in mI levels to some extent reflects the activation of GCs or micro-GCs. Many studies suggest that mI/Cr values may increase in the initial stages of MCI or AD, so mI may be one of the first metabolites to undergo changes in the brain of MCI or AD patients. However, there have always been different opinions on the value of mI in evaluating CI or dementia.[23–25] Studies have found that aMCI patients exhibit abnormal increases in mI/Cr values in the hippocampus and cingulate zone, while naMCI patients exhibit the same changes in the FL. This indicates that mI may be an important characteristic indicator for distinguishing aMCI from naMCI. The reasons for the regional differences in metabolic changes in the brain between aMCI and naMCI patients are still unclear. The analysis may be related to the different CI patterns between the 2.[19,26,27] CI in aMCI patients belongs to the "temporal neocortex" pattern. Its metabolic changes are centered around the hippocampus and PCG, so the most significant clinical manifestation is a decrease in memory ability. The CI of naMCI is classified as the "frontal subcortical" pattern. Research has shown that the pre-FL is related to executive function, emotional regulation, self-awareness, and social cognitive processes. Damage to the FL will lead to a decrease in executive function. Therefore, the main clinical manifestation is non memory dysfunction, such as execution, computation, etc.[28,29]

In summary, there are changes in the concentration levels of biochemical metabolites in the hippocampus on both sides of VCIND patients. $^1$H-MRS can sensitively detect abnormal metabolic changes in the brain of VCIND patients, which is helpful for early diagnosis and disease monitoring. Studies have shown that although changes in NAA levels lack specificity in distinguishing between aMCI and naMCI patients, there are significant regional differences in mI and Glu indicators between the 2. This indicates that $^1$H-MRS is a good and effective method for clinical differentiation between aMCI and naMCI. The paper shortcomings are the small amount of specimen, the limited selection of regions of interest, and the lack of detailed measurement of metabolite content in the hippocampal structure, resulting in strong subjectivity. All aspects need to be further improved in order to obtain more objective research results.

## Author contributions

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**Data curation:** Zhen Zeng, Jing He, Tao Yao.
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