Alterations in the Excitatory and Inhibitory Coupling in Migraine: A Magnetic Resonance Study

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Research article

Keywords: Migraine, GABA, GLX, thalamus, subgenual anterior cingulate cortex, magnetic resonance spectroscopy

Posted Date: November 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-100062/v1

Abstract

Background: There is evidence suggesting that an imbalance between the levels of the excitatory neurotransmitter, glutamate, and inhibitory neurotransmitter, gamma aminobutyric acid (GABA), leads to migraine attacks; however, the pathophysiology and specific diagnostic markers remain unknown.

Methods: Twenty-one migraine patients (18 female, 3 male, mean age=40.63 14.23years) and 11 healthy controls (9 female, 2 male, mean age=39.78 15.31 years) were included in this study. We used ^{1}H-MRS at 3 Tesla with voxels-of-interest located in the bilateral thalamus and subgenual anterior cingulate cortex (SG ACC) to quantify the GABA and GLX (glutamate-glutamine complex) concentrations measured via the Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) sequence in migraineurs and healthy controls.

Result: Statistical analyses revealed significantly decreased GLX/NAA (N-acetylaspartate) in the right thalamus of migraine patients compared to healthy controls. However, we found no group differences in GABA levels in the SG ACC and bilateral thalamus.

Conclusion: The right thalamus may be involved in the pain modulation process of migraineurs through changes in the GLX levels. Decreased GLX levels within the right thalamus might be associated with the disruption of "excitation-inhibition" homeostasis in migraine.

Trial registration: ClinicalTrials.gov, NCT02580968. Registered 30 October 2015, https://clinicaltrials.gov/ct2/show/study/NCT02580968

Background

Migraine is the most prevalent neurological disorder, characterized by recurrent attacks of headache and multiple sensory symptoms, and ranked sixth among the leading causes of years lived with disability according to the 2016 Global Burden of Disease Study(1, 2). Migraine leads to various neurological disorders that represent more than half of the causes for neurological years lived with disability, which contribute to a growing number of individual- and societal-level burdens, owing to the associated pain and sensitivity(3).

Despite the high prevalence of migraine, the diagnosis relies solely on non-specific symptoms and signs, and there is a lack of a definitive diagnostic tool and method. While there is still significant controversy corresponding to the pathophysiology of migraine, convergent evidence generated from brain imageology and electrophysiology indicates that the disruption of the excitatory-inhibitory balance leads to migraine(4). Further, several studies have reported on evidence indicating that an alteration in the glutamate or gamma aminobutyric acid (GABA) levels is involved in migraine attacks, thereby providing a potential foundation for the presence of a hyperexcitable brain in migraineurs, including elevated glutamate in the brain region of the visual cortex(5) and decreased GABA levels in the occipital region(6).

However, some studies have reported the opposite, suggesting reduced levels of glutamate in the visual cortex(7) and elevated GABA levels in the posterior cingulate cortex in migraineurs(8).

Glutamate and GABA are key signal transduction receptors in the pain-processing pathways and are involved in various pain modulation mechanisms(9, 10). Research in this realm suggests that the dysregulation of GABA and glutamate in the brain may lead to distinctness in different pain regulation processes and may, thus, serve as biomarkers in different pain conditions(11, 12). In recent years, the study of migraine events caused by the imbalance of the excitatory-inhibitory neurotransmitters involved in the pathogenesis of migraine by magnetic resonance spectroscopy (MRS) has been controversial(13).

To address whether migraine is associated with abnormal neurochemical changes in the thalamocortical pathway, we hypothesized the presence of an imbalance between the excitatory and inhibitory neurotransmitters of the subgenual anterior cingulate cortex (SG ACC) and bilateral thalamus. The ACC is a key structure involved in multiple processing pathways in pain, including its involvement in descending modulation, salience circuits, and analgesia mechanisms(14), as well as in the affective and pain-related negative emotional states(15). The thalamus plays an important role in transferring sensory signals from the periphery to the cortex that connects multiple cortical, subcortical, and brainstem regions(16). In the intrinsic brain networks, thalamic trigeminovascular neurons may have significant effects on thalamic functional connectivity through dynamically modulating various neurochemical transmitters during a migraine attack and an interictal state to maintain homeostasis(4, 17). Several studies have demonstrated the association of thalamocortical pathway dysfunction with migraine(18), particularly with the frequency of migraine attacks(19). This previous finding also suggests that the inhibition of the mediodorsal thalamic to ACC pathway projection by reducing the excitation / inhibition balance is associated with aversion in the chronic pain state(20). In addition, the ACC is connected to the thalamus through the dimensions of its anatomical structure and functional connectivity(21). The above brain regions have been implicated to be related to central sensitization and abnormal excitability in migraine in previous studies(18, 22).

MRS is a unique, non-invasive technique for investigating brain chemical metabolites in vivo. The homeostasis of neurotransmitter metabolism is supposed to be responsible for altered pain modulation and manifestation in migraine. Therefore, to address whether migraine is associated with imbalanced neurotransmitter levels in the thalamocortical circuit, we aimed to use proton (^{1}H)-MRS to detect the levels of GABA and the glutamate and glutamine complex (GLX) in the bilateral thalamus and SG ACC regions, and to compare these levels between migraine patients and healthy controls. We considered that the accurate detection, separation, and quantification of GABA and GLX could illuminate the role of neurotransmitters in migraine and elucidate the neurobiological pathogenesis of migraine.

Methods

Participants

We recruited participants at the headache clinic of Longhua Hospital, Shanghai University of Traditional Chinese Medicine. Migraine patients were diagnosed based on the criteria from The International Classification of Headache Disorders, 3rd edition (ICHD-Ⅲ)(2). The study was approved by the Ethics Committee of Longhua Hospital that is affiliated with the Shanghai University of Traditional Chinese Medicine (2015LCSY012), which was conducted in accordance with the Helsinki Declaration of 1964 with later revisions. Participants provided written informed consent after receiving detailed oral and written information regarding the study.

All participants were aged between 19 and 64 years. Participants in the migraine patient group were included if they were diagnosed with migraine by their attending neurologist/physician because they fulfilled the ICHD-Ⅲ criteria for migraine with or without aura and had at least two migraine attacks per month for the last 3 months, and if they had an established migraine diagnosis for at least 3 years. The exclusion criteria included the following: medication use (migraine prophylactic drugs, antidepressants, narcotics, antiepileptic drugs, mood stabilizers, and anxiolytics); pregnant or breast-feeding women; significant acute or chronic neurologic, psychiatric, endocrine, or medical problems; a history of conditions that could compromise the spectroscopic data (e.g., implants, dental braces, tattoos); another primary chronic headache disorder, any secondary headache disorder, or headache medication overuse; a history of having used medications known to alter GABA and GLX levels; and a history of neck injury or claustrophobia. Participants in the control group were aged-matched healthy individuals with no history of migraine. Participants were included in the healthy control (HC) group if they did not experience regular headaches and had no headache in the last 3 months. The exclusion criteria were the same as those applied in the migraine patient group with the added criterion of positive family history of migraine among first-degree relatives.

A total of 32 participants were enrolled in the study, and MRI data were collected. Four datasets were discarded due to poor spectral quality. Twenty-eight participants, including 19 in the patient group and 9 in the HC group, were considered in the final analysis. Patients were allowed to take analgesic medications, such as non-steroidal anti-inflammatory drugs. They were all assessed interictally at least 24 h after their last attack.

MRI Acquisition

MRI data were obtained using a 3 Tesla Siemens Verio MR scanner with a 32-channel head coil (Siemens AG, Erlangen, Germany). The head position was fixed with foam padding to minimize movement artifacts.

Anatomical T1-weighted images were acquired using a three-dimensional magnetic preparation fast gradient echo (3D-MPRAGE) sequence with the following parameters: echo time (TE) = 3.65 ms, repetition time (TR) = 2530 ms, field of view (FOV) = 240 × 240 mm^2, 256 × 256 matrix, slice thickness = 1.0 mm, and 224 continuous sagittal slices. The T1-weighted images were used to localize the voxels-of-interest (VOIs) in the following MRS acquisition.

The MRS data were acquired using a Mescher-Garwood point resolved spectroscopy (MEGA-PRESS) sequence with the following parameters: TR = 1500 ms, TE = 68 ms, 328 averages with water suppression, and eight averages without water suppression. The VOIs in the SG ACC (25 × 25 × 25 mm^3), left thalamus (25 × 25 × 18 mm^3), and right thalamus (25 × 25 × 18 mm^3) were localized in the mid-sagittal and transverse slices, respectively (Figure 1). Six orthogonal fat saturation bands were placed surrounding the VOIs to avoid signal interference. Automated shimming followed by manual shimming were conducted to reduce the water signal full width at half maximum (FWHM) below 25 Hz.

Spectrum Quantification

MRS raw data were processed using the LCModel software, version 6.3-1P Stephen (Provencher, 2016) (23, 24). Water-scaled GABA and GLX concentrations were quantified based on the LCModel package and LCMgui. The edited spectra were fitted using LCM-basis functions that were generated from phantom measurements using the MEGA-PRESS sequence with the appropriate acquisition parameters(25). The GABA peak arose at 3.01 ppm, and the GLX peak, at 3.74 ppm(26) (Figure 1). The levels of GABA and GLX were expressed as ratios with respect to the N-acetylaspartate (NAA) peak at 2.01 ppm. The criteria for reliable metabolite concentrations were based on the % standard deviation (SD) of the fit for each metabolite, reflecting the Cramer-Rao lower bounds (CRLB) in the LCModel analysis(24, 27, 28). Only results with a %SD below 30% were included in the following analysis(23, 26).

Tissue Segmentation

To calculate the proportion of grey matter (GM), white matter (WM), and cerebrospinal (CSF) contained in the VOIs, the 3D MPRAGE T1 images were segmented using the SPM8 software (The Wellcome Centre for Human Neuroimaging, 2008) (29). The voxel CSF content in each subject was evaluated by extracting the location of the voxel from the spectra file headers and using an in-house software developed in Visual Studio 2013 (Microsoft, 2013, USA) to calculate the proportions of GM, WM, and CSF contents based on the segmented T1-weighted images. To correct the spectroscopy results for the partial volume effect of CSF contamination, each metabolite value was corrected for the CSF content in the VOI using the following formula: corrected metabolite level = uncorrected metabolite level/(1 − C), where C is the fractional CSF content in the VOI(30).

Statistical Analysis

All the statistical analyses were conducted using SPSS v.22.0 (IBM Inc, 2014, Armonk, NY, USA). The normality of the distribution of all the independent variables, including age, weight, height, and metabolite concentrations, was examined using Kolmogorov-Smirnov tests. Demographic variables and GM, WM, and CSF volumes within the VOIs were compared between the two groups using a t test. Chi-squared tests were performed to assess the group effect on sex and handedness. An independent sample t test was performed to compare group differences in the GABA and GLX levels in each VOI. All tests were two tailed and the level of statistical significance was set at $P < 0.05$.

Results

After four participants with poor study quality were excluded 28 participants, including 19 in the patient group and 9 in the HC group, partook in the final analysis.

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the two groups are presented in Table 1. There were no significant differences in age, sex, height, weight, and handedness between the two groups.

Table 1: Demographic and clinical characteristics among migraine patients and healthy controls.

	Patient	**HC**	***p*-value**
Group Size	19	9	-
Age (years old)(Mean SD)	40.63 14.23	39.78 15.31	*P*=0.89[a]
Gender (male/female)	1/18	2/7	*P*=0.23[b]
Height(cm)	160.5 5.7	164.2 7.6	*P*=0.16[a]
Weight(kg)	55.9	53.7±10.4	*P*=0.12[a]
Handness(left/right)	0/19	1/8	*P*=0.32[b]
Headache laterality(uni-/bi-lateral)	12/7	Na	-
Max. headache severity (0–10)	5.42 1.5	Na	-
Migraine history (years)	9.4 3.0	Na	-

[a] Kolmogorov-Smirnov tests. [b] Chi-squared tests or Fisher's exact test.

Voxel Tissue Composition and Metabolite Level

No between-group differences were found in the proportions of GM (*P* = 0.74, 0.68), WM (*P* = 0.083, 0.44), or CSF (*P* = 0.12, 0.41) in the VOIs of the SG ACC and right thalamus, and no between-group difference was observed in the proportion of GM (*P* = 0.27) in the left thalamus. However, significant differences in the proportions of WM (*P* = 0.054; Table 2) and CSF (*P* = 0.022) were found in the left thalamus. The composition proportions of GM, WM, and CSF in each VOI are presented in Table 2.

A t-test was used to compare the metabolite levels in the VOIs of the SG ACC and right thalamus between the two groups. The results revealed a lower GLX/NAA in the right thalamus of the migraine patient group in comparison to the HC group (t = -2.57, *P* = 0.016). There was no significant difference between groups in GLX/NAA in the SG ACC (t = -0.52, *P* = 0.61). We also did not observe significant differences in GABA/NAA in the two VOIs (t = -0.59, *P* = 0.56 for SG ACC; t = -1.33, *P* = 0.20 for right thalamus; Table 2

and Figure 2) between the two groups. An analysis of covariance (ANCOVA) with WM proportion and CSF proportion as covariates was performed to compare the between-group differences in the metabolite levels in the left thalamus. The results did not reveal any significant differences in GABA/NAA (F = 0.55, *P* = 0.47) or GLX/NAA (F = 0.98, *P* = 0.33; Table 2).

Table 2 Means (SD) for metabolites level and tissue composition in the three VOIs in migraine patients and healthy controls (HC).

		Metabolites		Tissue Composition		
Brain Region	Group	GABA/NAA	GLX/NAA	CSF fraction	GM fraction	WM fraction
SG ACC	HC	0.33(0.10)	1.36(0.32)	0.135(0.029)	0.591(0.042)	0.272(0.037)
	Patient	0.32(0.05)	1.31(0.21)	0.155(0.031)	0.596(0.027)	0.248(0.024)
Left Thalamus	HC	0.35(0.078)	0.57(0.17)	0.043(0.020)	0.198(0.024)	0.757(0.035)
	Patient	0.31(0.064)	0.55(0.21)	0.062(0.016)	0.212(0.043)	0.723(0.052)
Right Thalamus	HC	0.39(0.097)	0.85(0.22)	0.051(0.026)	0.189(0.030)	0.757(0.045)
	Patient	0.38(0.075)	0.64(0.19)	0.059(0.015)	0.194(0.031)	0.743(0.038)

GM = grey matter, WM = white matter, CSF = cerebrospinal fluid, SG ACC = subgenual anterior cingulate cortex

Discussion

The purpose of this study was to investigate the differences in the GLX and GABA levels in the thalamus and ACC, to compare them between migraine patients and healthy controls, and to determine whether the balance of these neurotransmitters could explain the homeostasis of migraine excitement and inhibition. Our findings revealed that the level of GLX in the right thalamus was significantly lower in patients with migraine, but that there were no differences in the GABA levels in the VOIs between the groups. Participants with migraine had a higher CSF fraction and lower WM fraction in the left thalamus, but the covariate analysis with the metabolite levels revealed no between-group differences. These findings suggest that the decreased concentration of GLX in the right thalamus may be a pathophysiological mechanism that leads to migraine attacks in migraineurs.

Contrary to results of similarly-designed previous studies, our results revealed decreased concentrations of the excitatory neurotransmitter, GLX, in migraineurs(31, 32). Furthermore, some studies have shown that changes in GLX levels are not associated with migraine(13). These discrepancies may be due to differences in demographics, MRI scanning parameters, and the size of the regions of the VOIs. However, the thalamus is not only involved in pain regulation and transmission, but it is also related to sensory hypersensitivity in the visual, somatosensory, and auditory systems in migraineurs(17). Hemispheric lateralization in the thalamus has previously been observed both functionally and structurally and may be the process involved in pain(33), vestibular system disorders(34), schizophrenia(35) and developmental dyslexia(36). A study showed that a right thalamic lesion was present on the predominant hemisphere in thalamic pain syndromes, as an obvious result of which lateralization in post-thalamic stroke-related pain appears(33). A resting state functional (rs-f)MRI study reported that connectivity between the right thalamus and several pain relevant regions was decreased during spontaneous migraine attacks(37). We speculate that the right side of the thalamus is responsible for the hemispheric functional dominance in pain modulation in migraineurs.

Glutamate, involved in energy metabolism, plays a critical role in the central metabolism associated with nitrogen assimilation and amino acid biosynthesis. Glutamine is also associated with neurotransmitter synthesis and may play a role as the precursor to GABA. The homeostatic mechanisms involved in the degradation, synthesis, and transport of glutamine, glutamate, and GABA among different cellular compartments contribute to maintaining the metabolic flux of the elements in the GABA-glutamate-glutamine cycle and the delicate balance between excitatory and inhibitory neurotransmission(38). One hypothesis is that increasing the glutamate levels in the extracellular synaptic cleft in order to disrupt the balance of excitation and inhibition can lead to cortical hyperexcitability and can enhance the susceptibility to cortical spreading depression (CSD)(4, 39). A study observed that the levels of GLX across the brain pain regions are positively correlated with pain sensitivity(11). A growing amount of attention is being paid to the role of GABA in migraine, due to its functions in the alterations in neuronal excitability, pain processing and modulation in CSD, and sensitization of the trigeminovascular system in migraine(9). In the present study, we utilized the MEGA-PRESS sequence specific for quantifying GABA compared to previous studies(6); however, the concentrations of GABA in the bilateral thalamus and ACC in the patient group was similar to those in the HC group.

It is known that thalamic connectivity is involved in higher-level cortical functioning in the cerebrum(19). When it comes to nociceptive and somatosensory information, the more widely acknowledged networks that drive and modulate the activity of relaying thalamic neurons include the excitatory glutamatergic input originating in the spinothalamic, corticothalamic, and medial lemniscus tract neurons as well as the inhibitory GABAergic input involved in the reticular thalamic nucleus(16). This information enabled us to investigate the relationship between the baseline excitatory and inhibitory neurotransmitter levels within the migraineur brain network(4, 17). In our study, we found that GLX levels were decreased in the right thalamus and that there were no differences in GABA levels in the ACC and bilateral thalamus. Our results suggested that the concentration of the GABAergic inhibitory neurotransmitter in the ACC and thalamus is

not high enough to be perceptibly detected by ^{1}H-MRS in the context of heathy controls and migraineurs. Our study findings are similar to those of other MRS studies on the excitatory-inhibitory coupling in migraine, indicating that the changes in GLX levels but not those in GABA levels are related to the pathophysiology of migraine(11, 32). To summarize, the present study demonstrated that the alteration in the GLX levels in the right thalamus may contribute to pain modulation and perception in migraine.

There are a few limitations in this study. Because of the costly nature of capturing MR measurements, ^{1}H-MRS research is usually based on a small sample size. Our study included a high percentage of young women who suffered from repeated migraine attacks; thus, the relation of the excitatory and inhibitory neurotransmitter levels between the two sexes and the potential change in the concentrations with age or with hormonal status have been insufficiently investigated. Furthermore, we are aware that the main limitation of this study is that glutamate and glutamine levels were not separately investigated. Glutamate is commonly measured in combination with glutamine because of the relatively low concentration of glutamine and its spectral overlap with glutamate at 3 Tesla. Finally, single-voxel ^{1}H-MRS measurements are limited in resolution and cannot provide information regarding the cellular or subcellular localization of chemical metabolites.

Conclusions

In conclusion, this study provides evidence, though limited, on altered GLX levels in migraine and contributes to the clarification on the neurobiological mechanisms of migraine. Decreased GLX levels in the right thalamus might be associated with a disruption of the "excitation-inhibition" homeostasis in migraine and provide a basis to further explore the relationship between GLX levels and the pathophysiology of migraine. To innovate on the clinical treatment targets of migraine, future studies need to focus on the interactions between various neurotransmitters and the pathogenesis of migraine.

Abbreviations

^{1}H-MRS: Proton magnetic resonance spectroscopy; GABA: Gamma aminobutyric acid; GLX: glutamate-glutamine complex; SG ACC: Subgenual anterior cingulate cortex; MEGA-PRESS: Mescher-Garwood point-resolved spectroscopy; HC: Healthy control; TE: Echo time; TR: Repetition time; FOV: Field of view; VOIs: Voxels-of-interest; NAA: N-acetylaspartate; GM: Grey matter; WM: White matter; CSF: Cerebrospinal; CSD: Cortical spreading depression

Declarations

Availability of data and materials

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

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Longhua Hospital that is affiliated with the Shanghai University of Traditional Chinese Medicine (2015LCSY012), which was conducted in accordance with the Helsinki Declaration of 1964 with later revisions. Participants provided written informed consent after receiving detailed oral and written information regarding the study.

Acknowledgements

The authors are grateful to all the patients and heathy subjects for their participation in this study. We would like to thank all the doctors and researchers for their help and collaboration with the completion of the research in Longhua Hospital affiliated with the Shanghai University of Traditional Chinese Medicine and Shanghai Key Laboratory of Psychotic Disorders.

Funding

This work was supported by the Financing Scheme of Arising Interdisciplinary Subjects of TCM in Shanghai [grant number Shxxjcxk201709], the TCM genre program of Shanghai Health Bureau [grant number ZY (2018-2020)-CCCX-1006], the key Scientific Research Program of Shanghai Municipal Science and Technology Committee in China [grant numbers 14401971300, 18401970500], and the National Natural Science Foundation of China [grant number 81603697].

Declaration of Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

All the authors have participated extensively in the study and had have proofread the final manuscript. Manuscript preparation and review: Cai YW and Pei J. Supervision and coordination of clinical trials: Pei J. Subject recruitment: Cai YW and Gan MH. Subject assessment: Cai YW and Fu QH. MRS examinations: Tang YY. Statistical analysis: Wang JJ. All the authors have read and approved the final manuscript.

Consent for publication

The article-processing charges for the article has been sponsored by the European Headache Federation.

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Figures

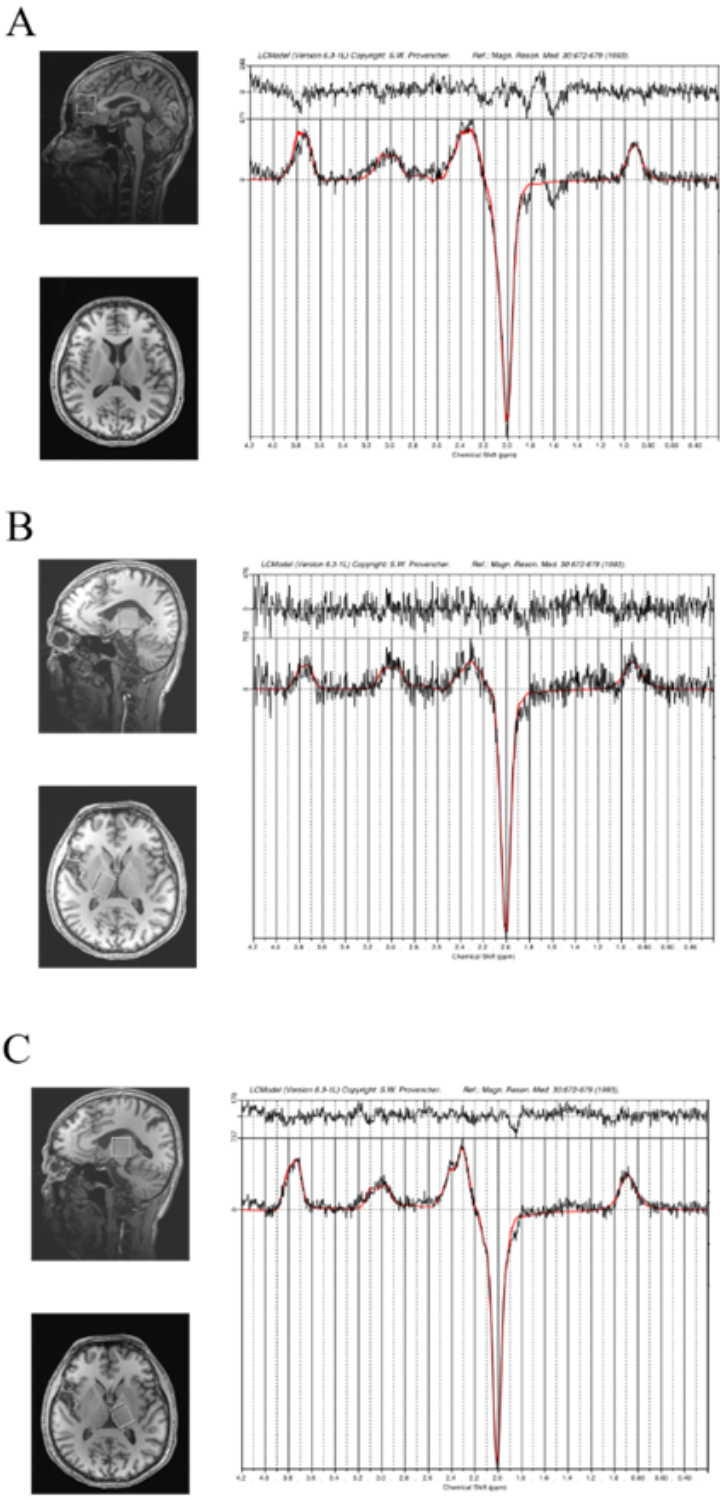

Figure 1

Example spectra of MEGA-PRESS measurement and MRS voxel placement in the SG AGG and bilateral thalamus. Midsagittal and transverse views of the voxel of interest (white square) used for MRS and the representative MRS spectrums of GABA and GLX levels fitted by the LCModel in the SG ACC (A), left thalamus (B), and right thalamus (C). The red line is the model-fitting of the experimental spectrum. The black line is the background signal. The GLX and GABA peaks arise at 3.74 ppm and 3.07 ppm,

respectively. MEGA-PRESS = Mescher-Garwood point-resolved spectroscopy, MRS = Magnetic resonance spectroscopy, SG ACC = Subgenual anterior cingulate cortex, GLX = glutamate-glutamine complex, GABA = Gamma aminobutyric acid

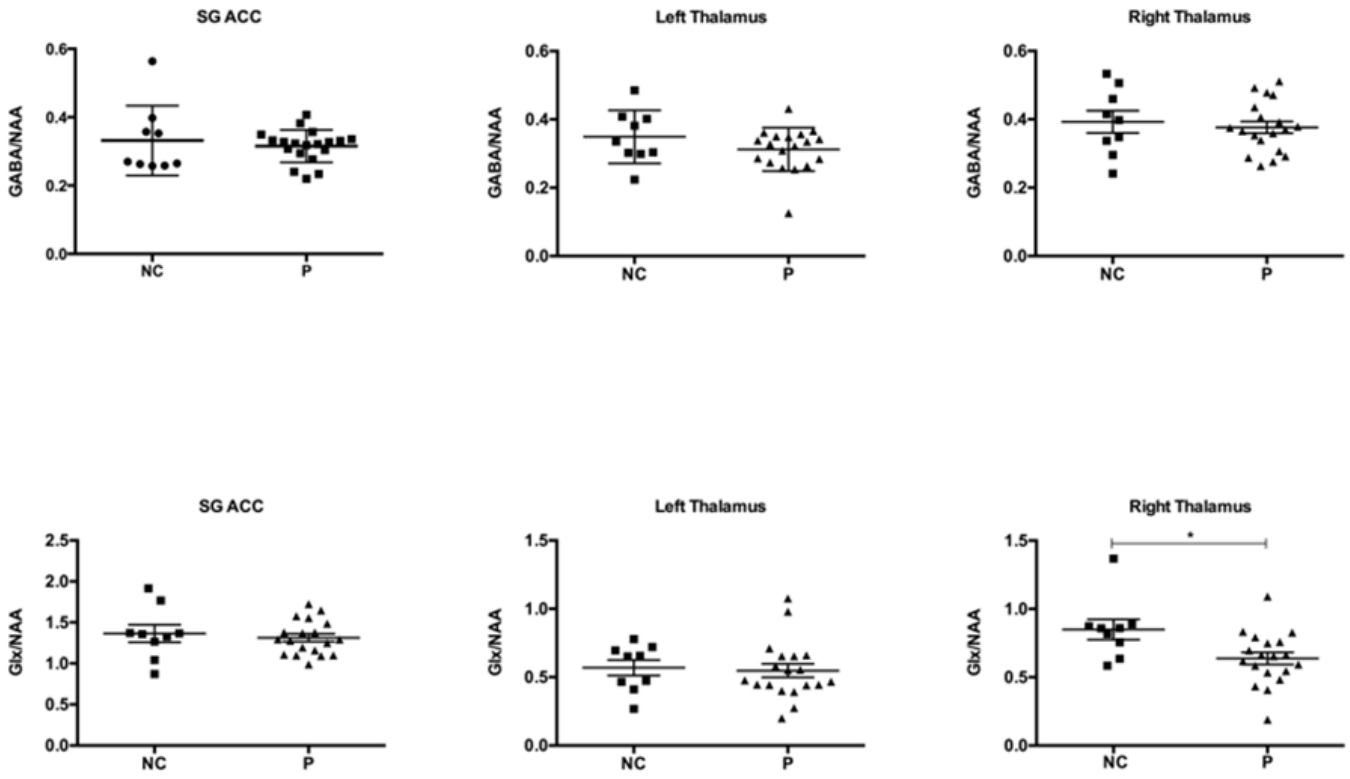

Figure 2

Metabolite concentrations Concentrations of GABA (UPPER) and GLX (BELOW) in the patient and healthy control groups. A lower GLX concentration was found in the right thalamus of migraine patients compared to that of healthy control subjects (*P < 0.05). GABA = Gamma aminobutyric acid, GLX = glutamate-glutamine complex, SG ACC = Subgenual anterior cingulate cortex

Supplementary Files

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- STROBEchecklistv4YiwenCai.doc