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Region-specific changes in brain glutamate and gamma-aminobutyric acid across the migraine attack in children and adolescents

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Abstract

In patients with migraine, an excitation–inhibition imbalance that fluctuates relative to attack onset has been proposed to contribute to the underlying pathophysiology of migraine, but this has yet to be explored in children and adolescents. This prospective, observational, cohort study examined glutamate and gamma-aminobutyric acid (GABA) levels across the phases of a migraine attack and interictally in children and adolescents using magnetic resonance spectroscopy. Macromolecule-suppressed GABA (sensorimotor cortex and thalamus) and glutamate (occipital cortex, sensorimotor cortex, and thalamus) were measured in children and adolescents (10-17 years) with a migraine diagnosis with or without aura 4 times over 2 weeks. Linear mixed-effects models examined changes in glutamate and GABA during the 72 hours leading up to, and after the onset of an attack. We found significant region-specific changes in glutamate and GABA. Specifically, sensorimotor GABA significantly increased leading up to the headache phase, whereas glutamate significantly decreased following the headache onset in the occipital cortex and the thalamus. Post hoc analyses examined the 24 hours leading up to or following the onset of the headache phase. In the 24 hours before the headache onset, sensorimotor glutamate, occipital glutamate, and thalamic GABA decreased. In the 24 hours post headache onset, sensorimotor glutamate continued to decrease. Our results suggest changes in glutamate and GABA that are consistent with the thalamocortical dysrhythmia hypothesis. These findings provide insight into developmental migraine pathophysiology and may open future avenues for treatment targets specific to children and adolescents.

Keywords: Migraine, Pediatrics, Excitation, Inhibition, Thalamocortical dysrhythmia, MRS, Glutamate, GABA

1. Introduction

Migraine is a common neurological disorder affecting approximately 8% of children and adolescents.[1] For children, the debilitating symptoms associated with migraine decrease the quality of life and cause disability in the home, at school, and in social relationships.[12] Despite its prevalence, the pathophysiology of migraine is still unclear.

Migraine attacks have been characterized by 4 phases: prodrome, aura, headache, and postdrome; each of these phases have accompanying symptoms.[47] Changes in the brain align with the occurrence of these phases, such as functional connectivity alterations in the occipital cortex, somatosensory network, thalamic network, and hypothalamus.[36,48,52] Transcranial magnetic stimulation (TMS),[19,20] magnetoencephalography (MEG),[14,58] electroencephalograph,[27,40] and evoked potential[10,30] studies in adults and children have suggested that there may be an excitation–inhibition imbalance underlying migraine. Interestingly, excitation and inhibition have been observed to fluctuate with the different phases of the attack.[19,20,40] The excitation–inhibition imbalance hypothesis[41] has brought forth the primary neurochemicals involved in excitation and inhibition, glutamate and gamma-aminobutyric acid (GABA), respectively, as candidates for further investigation.

In migraine pathophysiology, the thalamus is central to the trigeminovascular system as it contains the third-order afferent nociceptive neurons and receives information for nociceptive processing from a variety of brain regions.[60] The third-order thalamic neurons then project to cortical regions, including the sensorimotor and occipital cortices, which are thought to have primary roles in migraine symptoms such as pain and aura. Aligning with this, neurophysiological studies have reported that individuals with migraine have altered sensorimotor integration

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during migraine attacks.[2,56] The occipital cortex is one of the most studied brain regions in the migraine literature due to one of the clinical hallmarks of migraine being photophobia and the fact that visual aura is the most common aura type. Studies also show that individuals with migraine with or without aura have alterations in visual network function compared with healthy controls.[28,38,46] These 3 regions are consistently studied in the pediatric migraine literature using various imaging modalities, including magnetic resonance spectroscopy (MRS),[8] functional magnetic resonance imaging (fMRI),[39] structural MRI,[22] and arterial spin labelling.[54]

Magnetic resonance spectroscopy is a noninvasive method of measuring in vivo concentrations of neurochemicals. To date, only 4 studies have measured glutamate and/or GABA concentrations before or during an attack, and these studies have made measurements in the occipital cortex or pons.[4,42,59,61] All 4 studies measured glutamate, but only one measured GABA.[42] Across all 4 studies, there were no changes in glutamate from the interictal to headache phases. Onderwater et al.[42] measured GABA in the occipital cortex over the course of a provoked attack in adults and showed that GABA increased from the interictal to preictal phase in those with migraine as compared with controls. Only one study has measured glutamate and GABA in children and adolescents with migraine.[8] This cross-sectional study measured glutamate and GABA at one time point and found that lower interictal GABA levels in the thalamus were associated with proximity to the next attack, which was measured based on data from daily headache diaries. Therefore, there remains a need to explore both glutamate and GABA longitudinally.

To our knowledge, no study has measured glutamate and GABA in youth with migraine across all phases of migraine. Studies in the pediatric population are critical to improve knowledge and care of pediatric migraine as evidence suggests that migraine in children is different from migraine in adults. Compelling evidence of differences in migraine between children and adults is the differences seen in treatment response: a large clinical trial reported no difference in outcomes when comparing response to migraine medications used in adults and placebo in children and adolescents with migraine.[34] Clinically, headache is more bilateral in children and unilateral in adults, and headache duration in children ranges from 2 to 72 hours, whereas in adults, it can range 4 to 72 hours.[29] Finally, a recent study found that children with migraine had lower levels of occipital glutamate compared with healthy controls,[8] whereas in the adult literature, individuals with migraine consistently have higher levels of glutamate compared with healthy controls.[43]

Here, we measured glutamate and GABA in children and adolescents at different times relative to the onset of the next headache phase. We hypothesized that leading up to the headache phase, glutamate would increase and GABA would decrease in the occipital cortex, the sensorimotor cortex, and the thalamus. During and after the headache, we expected that neurochemistry would "reset" with glutamate decreasing and GABA increasing to interictal levels.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

This was a prospective observational cohort study approved by the Conjoint Health Research Ethics Board (CHREB), University of Calgary (REB21-0733). Recruitment and data collection were conducted between August 2021 and December 2022. Upon enrollment, participants provided written informed assent, and their parents provided written informed consent. In the case of mature minors, participants provided their own informed consent.

2.2. Participants

Participants completed 4 MRI scanning sessions within a 2-week time window with the goal of capturing different parts of the attack. Children and adolescents between the ages of 10 to 17 years (inclusive) with migraine were recruited from headache clinics at a tertiary care children's hospital in Western Canada. Participants were eligible if they had (1) a diagnosis of migraine with or without aura based on the International Classification of Headache Disorders 3rd Edition (ICHD-3) criteria[29] as ascertained by a headache neurologist or nurse practitioner, (2) self-reported having 4 to 20 headache days per month at the time of enrollment, and (3) maintained stable use of medications over the past month. Although a change in dosage was permitted, a change in medication excluded or delayed participation until one month had passed from the time of the change. Limiting the headache frequency to 4 to 20 headache days per month allowed for some degree of fluctuation in symptoms (ie, not always in the headache or interictal phases) over the 2 weeks of study participation. To scan across multiple time points during the migraine attack, participants were scanned at a scheduled time of convenience that was not tied to whether they were experiencing a migraine attack. However, participants were provided the option to reschedule in the event of a migraine attack. A flowchart outlining the study design can be seen in **Figure 1**.

Exclusion criteria for participation included contraindications to MRI, inability to read or understand English, concussion within the past 3 months, and diagnosis of psychosis, schizophrenia, autism, developmental delay, intellectual disability, or major comorbidities such as epilepsy or arthritis.

2.3. Clinical measures

All participants completed a standardized, baseline, headache characterization questionnaire before their first MRI visit. Information collected included demographics (age, sex, gender, and ethnicity), description of headaches (location, time since onset, duration, accompanying symptoms, diagnosis of aura, frequency, and medication), and family history of headache. The baseline headache questionnaire included the Pediatric Migraine Disability Assessment Scale (PedMIDAS) to measure migraine-related burden.[26] Before their first visit, participants also completed the Pubertal Scale Questionnaire, a validated questionnaire used to determine pubertal status.[13]

2.4. Daily headache diary

Participants completed daily headache diaries starting 2 days before their first MRI scan until 2 days after their last scan. If the participant had an attack on any given day, they were asked headache characterization questions aligned with ICHD-3 criteria, such that migraine attack days (vs. other headache days) could be ascertained. These included details such as start and end time of headache, medication(s) taken, severity, location, and presence of aura.

2.5. MR acquisition

All imaging data were acquired on a 3T GE 750w MR scanner with a 32-channel head coil. Total scan time was 48 minutes 36

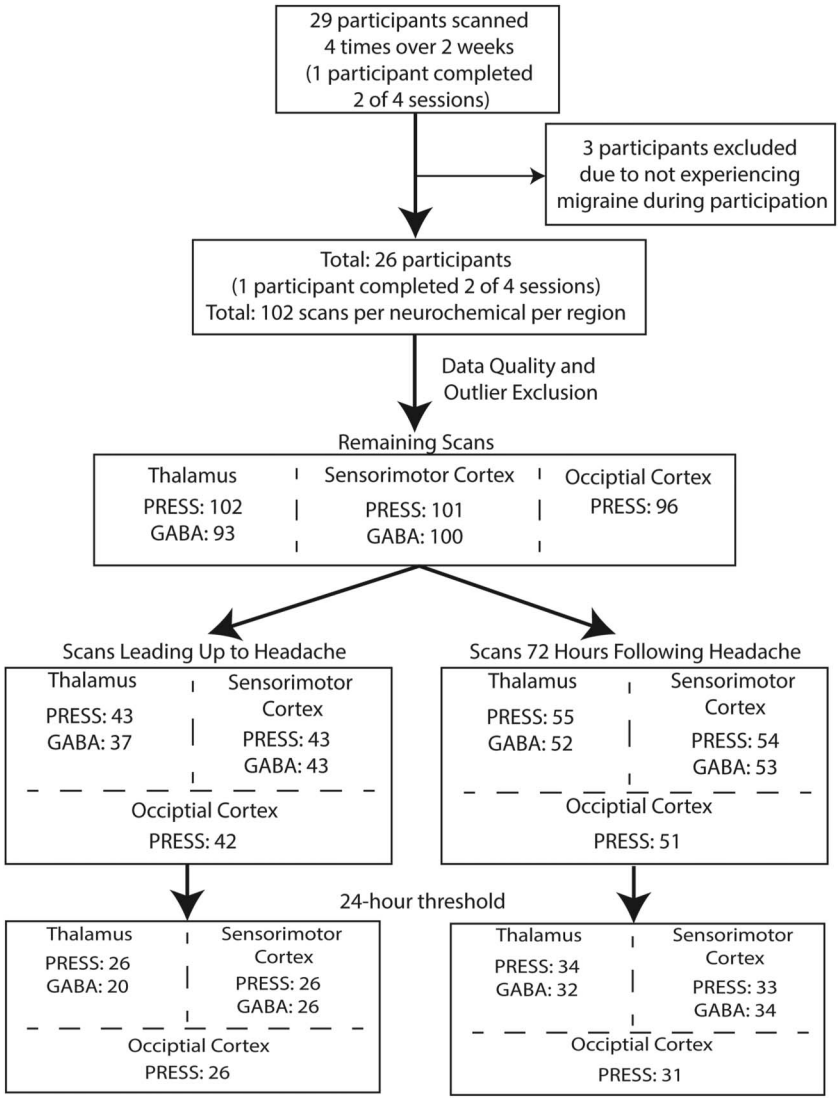

Figure 1. Flowchart outlining study design, along with the number of scans included for each step of analyses.

seconds. Before MRS data acquisition, a T1-weighted anatomical image (BRAVO, 230 slices, TR/TE = 7.4 ms/2.7 ms, 1.0 mm^3 isotropic voxels, matrix 240 × 240, 4 minutes 10 seconds) was obtained for voxel placement and tissue segmentation. In cases where a participant moved, a T2-weighted anatomical image (FAST, 36 slices, TR/TE = 7611 ms/83.2 ms, 0.45 × 0.45 × 3.6 mm^3, 11 seconds) was acquired and used for MRS voxel placement during the scan.

Point-resolved spectroscopy (PRESS) was used to measure glutamate in the right sensorimotor cortex and thalamus with 30 × 30 × 30 mm^3 voxels (TR/TE = 1800 ms/30 ms, 64 averages, 2 minutes 31 seconds) and occipital cortex with a 20 × 20 × 20 mm^3 voxel (TR/TE = 1800 ms/30 ms, 112 averages, 3 minutes 58 seconds) (**Fig. 2**). Macromolecule (MM)-suppressed GABA-edited MRS (Mescher-Garwood Point Resolved Spectroscopy, MEGA-PRESS) was used to measure GABA in the sensorimotor cortex and thalamus (TR/TE = 1800 ms/80 ms, 20 ms editing pulses at 1.9 and 1.5 ppm, 256 averages, 8 minutes 13 seconds, same voxels as used for PRESS data). Macromolecule-suppressed MEGA-PRESS is a novel acquisition method that aims to eliminate the variable macromolecule signal thought to contaminate approximately 45% of the GABA signal, providing a measurement more specific to GABA.[24]

In the occipital cortex, only PRESS data were collected because previous work showed no significant differences in GABA levels in the occipital cortex in children and adolescents with migraine compared with controls, and no association of occipital GABA levels with migraine disease severity or attack frequency.[8] This decision enabled using a smaller voxel to increase regional specificity in the occipital cortex.

2.6. Processing

PRESS data were preprocessed using FID-A[50] using an automated pipeline included with the software that includes coil combination, removal of bad averages, frequency drift correction, and zero-order phase correction. Outputs from FID-A were then quantified with LCModel version 6.3[45] to provide a quantification relative to water. The basis set for quantification, included alanine, aspartate, glycerophosphocholine, phosphocholine, creatine (tCr), phosphocreatine, GABA, glutamate, glutamine, lactate, inositol, N-acetylaspartate, N-acetylaspartylglutamate, scyllo-inositol, glutathione, glucose, and taurine. This basis set was simulated using FID-A based on scanner specific sequence timings and the shape of radiofrequency pulses used during the acquisition. Neurochemical concentrations were tissue corrected

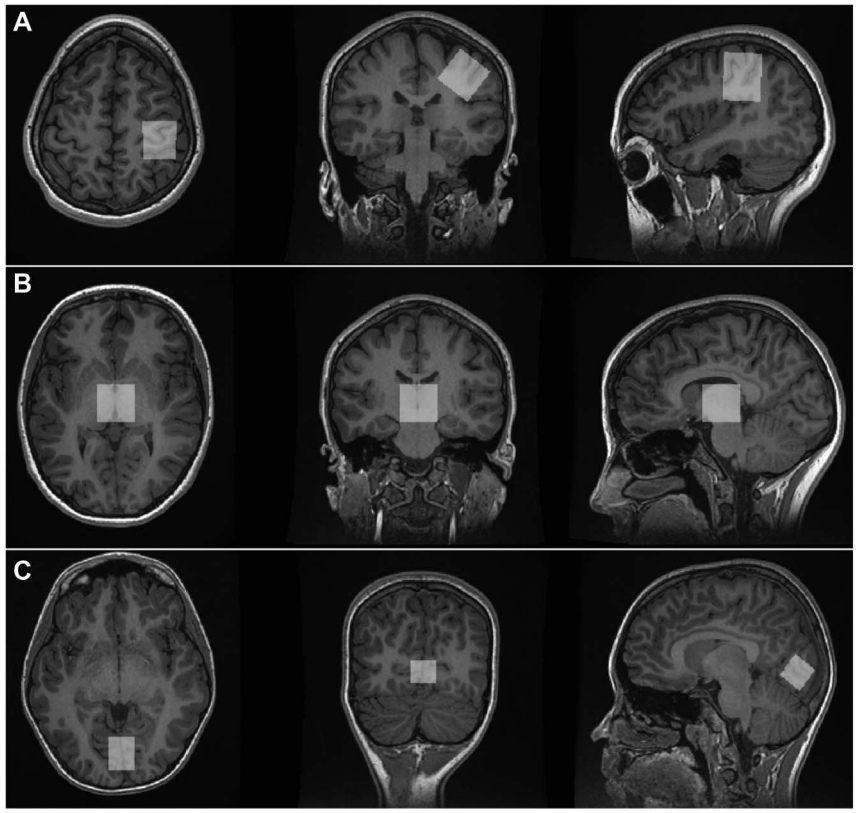

Figure 2. Example voxel placements in the (A) right sensorimotor cortex, (B) thalamus, and (C) occipital cortex.

to account for tissue-specific water visibility and T1 and T2 relaxation. Data quality was assessed through visual inspection and quantitative assessment of the linewidth (FWHM), signal-to-noise ratio (SNR), and Cramer-Rao Lower Bound (CRLB) values provided by LCModel. Both glutamate and Glx (glutamate + glutamine) are reported for completeness. Glx represents glutamate and glutamine because they are similar in chemical composition and are difficult to separate.

Macromolecule-suppressed GABA-edited MRS data were preprocessed and quantified using Gannet 3.2.[21] The pipeline included coil combination, eddy current correction, frequency and phase correction, and downweighting or removal of motion-corrupted averages (depending on which resulted higher-quality data). Tissue correction using the alpha-correction method was applied to account for twice the amount of GABA present in grey matter compared with white matter.[25] Visual inspection and consideration of full-width half-maximum (FWHM) and GABA+/Water fit error values were used for quality assessment of spectral data. Data outliers >3 SD from the group mean were also excluded from analyses for both MM-suppressed GABA-edited and PRESS data.

2.7. Statistical analysis

All statistical analyses were performed using R software (version 4.2.2). Linear mixed-effects models were run using the R "lmer" function,[5] and model assumptions (linearity, homogeneity of variance, collinearity, and normality) were checked using the R "check_model" function.[35] Neurochemical levels were z-scored before modelling to output standardized beta values. Statistical analyses were one sided at 0.05 significance level as we hypothesized neurochemical changes in specific directions.

A priori sample size calculations ($R = 0.53$, $\alpha = 0.05$, $\beta = 0.2$) showed that a minimum of 26 participants were required to have sufficient power for this study. This value was calculated based on a previous case–control cross-sectional study where a significant correlation of $R = -0.53$ was found between interictal thalamic GABA and position in migraine cycle.[8]

Descriptive statistics were used to examine demographics and clinical scores. Shapiro–Wilks tests were used to test for normality of continuous data elements, including age, headache frequency, disease duration, and PedMIDAS. Categorical data were reported using proportions, whereas continuous data were reported as means (SD) for normally distributed data, or medians (IQR) for data that were not normally distributed. Associations between primary neurochemicals of interest (GABA and glutamate) and demographic/clinical measures were explored using univariate linear mixed-effects models with subject included as a random effect. Each of the following demographic/clinical measures were explored in separate models: sex, age, aura diagnosis, headache frequency (≤9 headache days/month, 10-14 headache days/month, and ≥15 headache days/month), chronic migraine status (yes/no), PedMIDAS score, years since migraine onset, intervention type (none, nutraceutical, or pharmacological/procedural), and pubertal status (pre, early, mid, late, and post). Post hoc exploratory analyses were also done to explore the relationship between glutamate and GABA levels and pain severity ratings for headaches that were captured on scan days using univariate linear mixed-effects models with subject as a random effect.

In primary analyses, hours leading up to next headache and following last headache were calculated based on the completed daily headache diary entries for each data point. Casewise deletion was used for data points from individual sessions that

were missing (ie, did not experience headache during participation). Data points were categorized into either (1) "hours leading up to next headache" or (2) "hours following last headache" depending on their temporal proximity (in hours) to the next attack's or last attack's headache phase, with time of headache onset used to anchor the data. Following the headache, a 72-hour threshold was applied, where data acquired later were not included in the analysis (n = 3). This cutoff was applied given that none of the captured headache phases exceeded 24 hours (the maximum duration of the postdrome phase is typically thought to be 48 hours)[31] and would allow us to focus on the more acute neurochemical changes following the headache phase in the most robust manner.

Raw data visualizations suggested larger magnitude changes in the 24 hours leading up to the onset of the next headache phase, which were not captured in the uncensored 72-hour time frame. Therefore, changes within the 24-hour time frame were further explored using post hoc analyses.

Table 1

Participant demographic information and clinical scores recorded at baseline.

Participant demographics	
Characteristic/clinical measures	**Participants**
Sex	
Male	7 (26.9%)
Female	19 (73.1%)
Age (y)	
Median (IQR)	15.0 (3.75)
Range	10–17
Handedness	
Right	22
Left	4
Ethnicity	
White	21 (80.8%)
South Asian	2 (7.7%)
Other	3 (11.5%)
Chronic migraine	
No	19
Yes	7
Aura diagnosis	12 (46.2%)
Visual	5
Sensory	4
Brainstem	1
Visual + sensory	2
No. of headaches per month (d; normalized to 30 d)	
Mean (SD)	10.9 (4.64)
Range	1.15–20.63
PedMIDAS (headache burden)	
Median (IQR)	25.0 (49.8)
Range	0–184
Disease duration (y)	
Median (IQR)	6.00 (5.75)
Range	2–13
Pubertal status	
Pre	1
Early	3
Mid	3
Late	2
Post	17

Data reported in mean (SD), median (IQR), or N (%), with range, as applicable.

For all analyses, linear mixed-effects models were used to account for repeated measures. In each model, neurochemical concentration was predicted by the fixed effect of time while controlling for age and sex (fixed effects) and subject identity (random effect). In separate analyses, changes in secondary neurochemicals (N-acetyl aspartate (NAA), creatine (tCr), choline (tCho), and myoinositol (mI)) across the attack were analyzed to confirm the specificity of GABA and glutamate relationships.

2.8. Data availability

Anonymized data may be made available to qualified investigators upon request.

3. Results

3.1. Participants

Participant demographics and clinical characteristics are shown in **Table 1**. Twenty-eight participants completed 4 scanning sessions and 1 participant completed 2 sessions, for a total of 29 participants with 114 scans. Of the 29 participants, 3 did not experience any attacks during the study period and were excluded from the present analyses as time of the last/next headache phase onset were unknown. Therefore, a total of 26 participants were included in the final data set (7 male and 19 female participants; pubertal status: 1 pre, 3 early, 3 mid, 2 late, and 17 post). Characteristics of attacks captured in the daily headache diaries are shown in **Table 2**. Acute and preventive interventions for all participants are shown in **Table 3**. In total, we completed 102 scans, with 10 of these occurring during an attack, 43 leading up to an attack, and 49 following an attack. The number of scans and participants analyzed in each model, as well as mean linewidth and signal-to-noise ratio (SNR) of included scans after quality assessment and outlier exclusions are listed in Supplementary Table 1, http://links.lww.com/PAIN/C68.

3.2. Primary neurochemicals of interest and demographic/clinical measures

In the sensorimotor cortex, both glutamate (beta = −0.16, 95% CI [−0.30, −0.01], P = 0.044; Std. beta = −0.14) and Glx (beta = −0.21, 95% CI [−0.41, −0.02], P = 0.044; Std. beta = −0.13) decreased with age (Supplementary Tables 2 and

Table 2

Participant headache characteristics and acute medications recorded in daily headache diaries.

Headache characteristics	Headaches scanned	All headaches recorded in diaries
N	10	123
Duration (h)	Mean (SD) 5.72 (5.85)	Median (IQR) 3.00 (6.00)
% With aura	0%	4%
% Meeting migraine criteria	70%	69%
Acute medications taken for each headache reported (n)		
NSAIDs	2	38
Triptans	0	5
Other	1	11
None	8	76

Data reported in mean (SD), median (IQR), or N (%), as applicable.

Table 3

Number of acute and preventative interventions recorded at baseline.

Acute interventions	n	Preventative intervention	n
None	2	None	10
Ibuprofen	7	Amitriptyline	2
Naproxen	10	Topiramate	4
Diclofenac	4	Levetiracetam	0
Acetylsalicylic acid	0	Divalproate	1
Acetaminophen/aspirin/caffeine	0	Cyproheptadine	0
Acetaminophen	1	Flunarizine	0
Sumatriptan	0	Propranolol	0
Rizatriptan	3	Pregabalin	0
Zolmitriptan	3	Gabapentin	0
Almotriptan	0	Indomethacin	0
Frovatriptan	0	Verapamil	1
Eletriptan	0	Nortriptyline	0
Naratriptan	0	Venlafaxine	0
Rimegepant	0	Escitalopram	0
Ubrogepant	0	Fluoxetine	0
Lasmiditan	0	Magnesium	6
Sumatriptan/naproxen	0	Coenzyme Q10	9
DHE	0	Riboflavin	3
GONB	0	Vitamin D	0
Trigger point injections	0	Vitamin E	1
Prochlorp	0	Vitamin B6	0
Metoclop	1	GONB	0
Chlorprom	0	Trigger point injections	0
Ketorolac	2	Botox	1
Dexamethasone	0	Erenumab	0
Diphenhydramine	0	Fremanezumab	0
Cefaly TENS device	0	Galcanezumab	0
eNeura sTMS device	0	Eptinezumab	0
GammaCore VNS device	0	Cefaly TENS device	0
Nerivio REN device	0	eNeura sTMS device	0
Washout	0	GammaCore VNS device	0

Six participants were taking more than one acute intervention, and 5 participants were taking more than one preventative intervention.

3, http://links.lww.com/PAIN/C68). Sensorimotor GABA showed significant increases with age (beta = 0.04, 95% CI [0.01, 0.07], P = 0.015; Std. beta = 0.13) (Supplementary Table 4, http://links.lww.com/PAIN/C68). Both sensorimotor glutamate and Glx were significantly associated with pubertal status (Supplementary Tables 2 and 3, http://links.lww.com/PAIN/C68). Specifically, those in the midpuberty state had significantly higher levels of glutamate (beta = 2.13, 95% CI [0.37, 3.90], P = 0.039; Std. beta = 1.86) and Glx (beta = 3.08, 95% CI [0.68, 5.49], P = 0.029; Std. beta = 1.89) than those in the prepubertal stages. None of the other relationships explored demonstrated significant results. Post hoc analyses between GABA and glutamate and pain severity ratings for captured subset of scans taken during the headache phase did not show any significant relationships, although there were few data points of pain ratings at the same time as MRS data.

3.3. Primary neurochemical of interest leading up to or following headache

3.3.1. Sensorimotor cortex

In the sensorimotor cortex, GABA levels significantly increased with time leading up to the onset of the next headache phase (beta = 0.005, 95% CI [0.002, 0.01], P = 0.008, Std.beta = 0.02) (**Fig. 3**). Glutamate and Glx did not change significantly leading up to the headache (Supplementary Figure 5, http://links.lww.com/PAIN/C68). Following headache phase onset, there was no significant effect of time on GABA, glutamate, and Glx levels (Supplementary Figures 5 and 6, http://links.lww.com/PAIN/C68).

3.3.2. Occipital cortex

In the occipital cortex, no significant glutamate and Glx changes were seen leading up to the headache phase (Supplementary Figure 7, http://links.lww.com/PAIN/C68). Following headache phase onset, there was a significant decrease in glutamate as time passed (beta = −0.03, 95% CI [−0.06, −0.01], P = 0.014, Std. beta = −0.02) (**Fig. 4A**). Glx levels across time (beta = −0.04, 95% CI [−0.06, −0.01], P = 0.014, Std. beta = −0.02) also decreased following headache phase onset (Supplementary Figure 7, http://links.lww.com/PAIN/C68).

3.3.3. Thalamus

Glutamate, Glx, and GABA levels in the thalamus did not change significantly leading up to the onset of the headache phase (Supplementary Figures 8 and 9, http://links.lww.com/PAIN/C68). Following headache phase onset, the thalamus showed a significant decrease in glutamate (beta = −0.03, 95% CI [−0.05, −0.01], P = 0.004, Std. beta= −0.02) (**Fig. 4B**) and Glx (beta = −0.03, 95% CI [−0.06, −0.002], P = 0.044, Std. beta = −0.01) with time (Supplementary Figure 8, http://links.lww.com/PAIN/C68).

3.4. Post hoc analyses: thresholding at 24 hours before or after headache onset

3.4.1. Sensorimotor cortex

Using a 24-hour time window threshold, sensorimotor glutamate significantly decreased leading up to headache pain onset (beta = −0.05, 95% CI [−0.08, 0.02], P = 0.033, Std. beta = −0.04) and continued to decrease following headache phase onset (beta = −0.07, 95% CI [−0.12, −0.02], P = 0.009, Std. beta = −0.06) (**Figs. 5A and B**). Glx changes were trend level both 24 hours approaching (beta = −0.05, 95% CI [−0.09, 0.03], P = 0.09, Std. beta = −0.03) and following headache phase onset (beta = −0.07, 95% CI [−0.14, 0.002], P = 0.076, Std. beta = −0.04) (Supplementary Figure 10, http://links.lww.com/PAIN/C68). No changes in GABA were seen 24 hours before or following headache phase onset in the sensorimotor cortex (Supplementary Figure 11, http://links.lww.com/PAIN/C68).

3.4.2. Occipital cortex

Glutamate in the occipital cortex significantly decreased in the 24 hours leading up to headache phase onset (beta = −0.08, 95% CI [−0.15, −0.02], P = 0.029, Std. beta = −0.05) (**Fig. 5C**). In contrast to the primary analyses, there were no significant

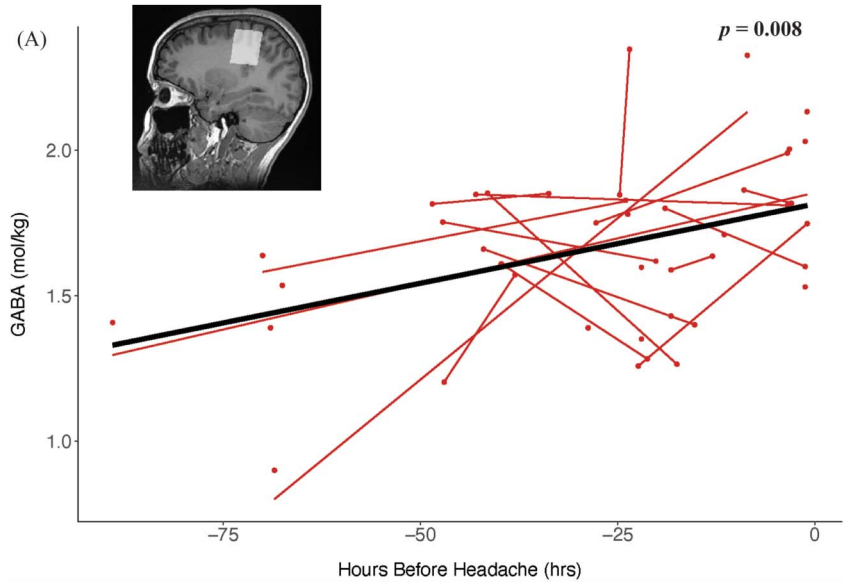

Figure 3. Sensorimotor cortex GABA levels (mol/kg) were seen to increase leading up to the onset of the next headache phase in hours ($P = 0.008$; n = 43). Each point represents one scan session, and each red line represents one participant. Black lines represent overall regression lines averaging the data of all participants included in analyses.

changes in occipital glutamate following headache phase onset (Supplementary Figure 12, http://links.lww.com/PAIN/C68). Glx 24 hours leading up to headache phase onset was trend level (beta = −0.10, 95% CI [−0.20, 0.004], $P = 0.089$, Std. beta = −0.05) but was not significant 24 hours following headache onset (Supplementary Figure 12, http://links.lww.com/PAIN/C68).

3.4.3. Thalamus

Thalamic GABA significantly decreased in the 24 hours leading up to headache phase onset (beta = −0.02, 95% CI [−0.03, −0.01], $P = 0.018$, Std. beta = −0.04) (**Fig. 5D**). No significant changes were seen in thalamic GABA 24 hours following headache phase onset and in the 24 hours before or after headache phase onset for glutamate and Glx (Supplementary Figure 13 and 14, http://links.lww.com/PAIN/C68).

3.5. Secondary neurochemicals: N-acetyl aspartate, choline, creatine, myoinositol

There was no significant effect of time on any of the secondary neurochemicals (tNAA, tCho, tCr, ml), both leading up to and following headache phase onset in all 3 regions (Supplementary Figures 15-20, http://links.lww.com/PAIN/C68).

4. Discussion

In this study, we examined glutamate and GABA fluctuations in children and adolescents with migraine. Overall, we found that sensorimotor cortex GABA increased leading up to the next headache phase, whereas glutamate in the occipital cortex and thalamus decreased following the onset of the attack (**Fig. 6**).

Hyperexcitability in cortical regions is often reported in individuals with migraine.[11,20,23] However, research has reported that patients with migraine also differ from controls in hyperexcitability of subcortical regions, such as the thalamus.[6] We also report changes in excitatory and inhibitory neurochemicals in both cortical and subcortical regions across the attack of migraine. Although we hypothesized that GABA would decrease leading up to the next headache phase, we found that in the sensorimotor cortex, GABA increased as the next headache phase approached. Although different from our initial hypothesis, we propose that these changes support the thalamocortical dysrhythmia hypothesis of migraine (**Fig. 7**).

Thalamocortical dysrhythmia is a model in which the thalamus is functionally disconnected and locked into a state of low-frequency oscillations.[16,33] This leads to further upstream effects, specifically, decreased cortical lateral inhibition, and adjacent cortical regions entering a state of hyperexcitability ("the edge effect"), which has most notably been observed in the visual cortex,[33] but large-scale cortical changes using MEG have also been observed in patients Parkinson disease.[33] More recent fMRI studies have suggested large-scale changes in connectivity, where individuals with migraine showed patterns in thalamocortical networks involving the subcortical, sensory, and visual regions that reflected overall reduced interictal alpha activity and therefore reduced lateral inhibition.[53] Neurophysiological studies also support this hypothesis, whereby changes in cortical excitability have been observed and depend on the proximity to the onset of the next attack, especially in the sensory and motor cortices. Adults with migraine exhibit impaired sensory cortex lateral inhibition interictally, which may increase during attacks.[16] This indicates an increase in regional lateral inhibition leading up to attacks.[16,17,40] We observed increases in sensorimotor GABA leading up to the onset of the next headache phase, which aligns with this previous work suggesting increased lateral inhibition leading up to attacks. It has been proposed in previous adult migraine studies that this increase in sensorimotor lateral inhibition during the attack period is driven by increased thalamocortical connectivity.[16] Increases in cortical GABA have been suggested to be a compensatory homeostatic inhibitory mechanism in response to hyperexcitation or a protective factor in relation to oncoming headache attacks.[9,43] Our results suggest that it may also be a dynamic compensation mechanism.

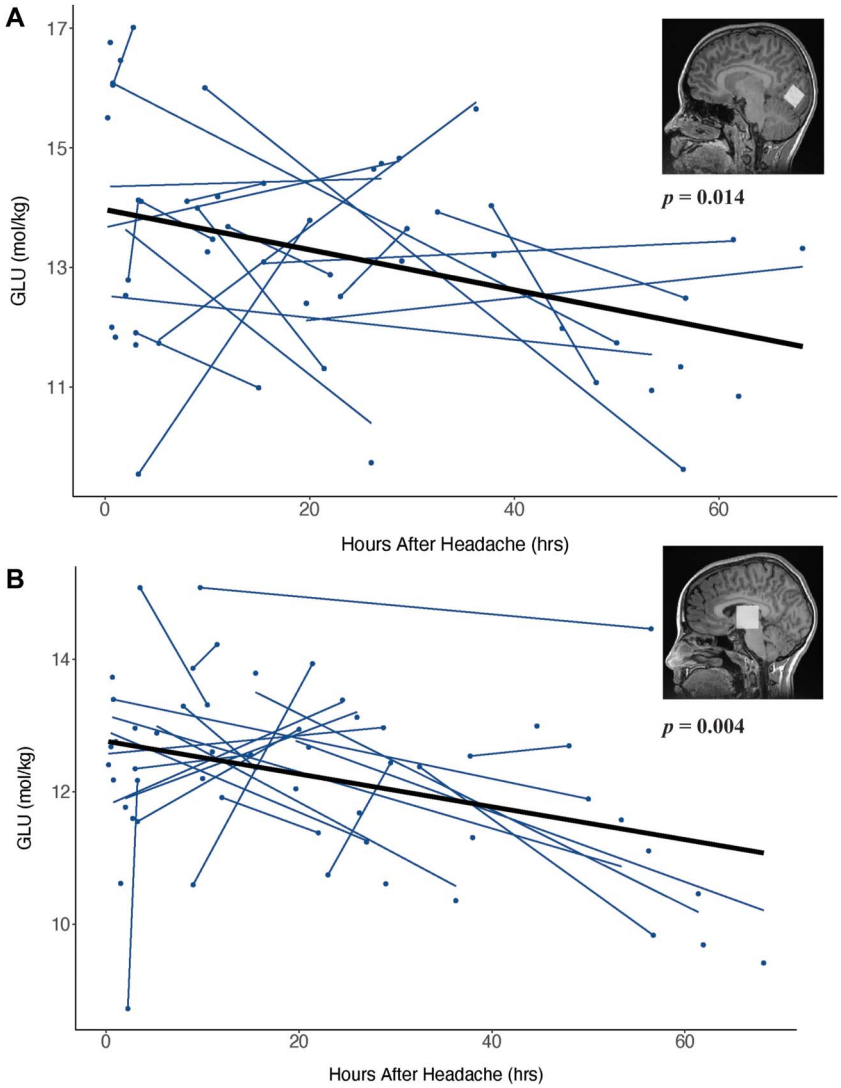

Figure 4. (A) Occipital cortex ($P = 0.014$; n = 54) and (B) thalamic ($P = 0.004$; n = 59) glutamate levels (mol/kg) were both seen to decrease following the onset of the headache phase (shown in hours after headache onset). Ten headaches were captured for glutamate in both the occipital cortex and thalamus. Each point represents one scan session, and each blue line represents one participant. Black lines represent overall regression lines averaging the data of all participants included in analyses.

Although we did not observe sensorimotor glutamate changes leading up to and across 72 hours after headache onset, thresholding at 24 hours before/after headache onset suggested that there may be more acute glutamate decreases both leading up to and following the onset of the headache phase. Interictally, if the thalamus is locked in a state of low-frequency oscillations (ie, thalamocortical dysrhythmia), this would result in high-frequency oscillations in the cortex,[57] which could be associated with increased glutamate because of increased cortical excitability or increased energy demands. We propose that the decrease in sensorimotor glutamate during the 24 hours before the headache attack follows a state of interictal or prodromal hyperexcitation in the sensorimotor cortex, which then decreases immediately before and after the onset of the headache attack. This proposal is consistent with the thalamus and sensorimotor cortex becoming more functionally connected during attacks.[3]

Occipital glutamate decreased 24 hours before and 72 hours following headache onset. Like the sensorimotor cortex, this suggests heightened occipital cortex excitability before the 24 hours before headache phase onset. These findings align with the electrophysiological literature showing an interictal deficit in dishabituation in the occipital cortex for adults with migraine.[15,18] Moreover, the occipital glutamate decrease in the 24 hours leading up to headache phase onset aligns with MEG,[14] fMRI,[49,52] and TMS studies[51] that have shown normalization of multiple metrics during attacks. Although our findings suggest that glutamate levels do not immediately reach baseline at the onset of the headache phase but rather continue to decrease throughout the headache phase and potentially into the postdrome phase, we propose that these observations are consistent with normalisation of glutamate levels. The gradual decrease in glutamate concentration observed may reflect why children and adolescents with migraine can continue to experience clinical symptoms (eg, photophobia) in the postdrome even after pain resolution.

A few adult studies have measured glutamate and/or GABA across different phases of the attack, mostly in the occipital cortex. However, these studies implemented different methods, making comparisons with this study challenging. Although our results suggest that there are dynamic changes in glutamate

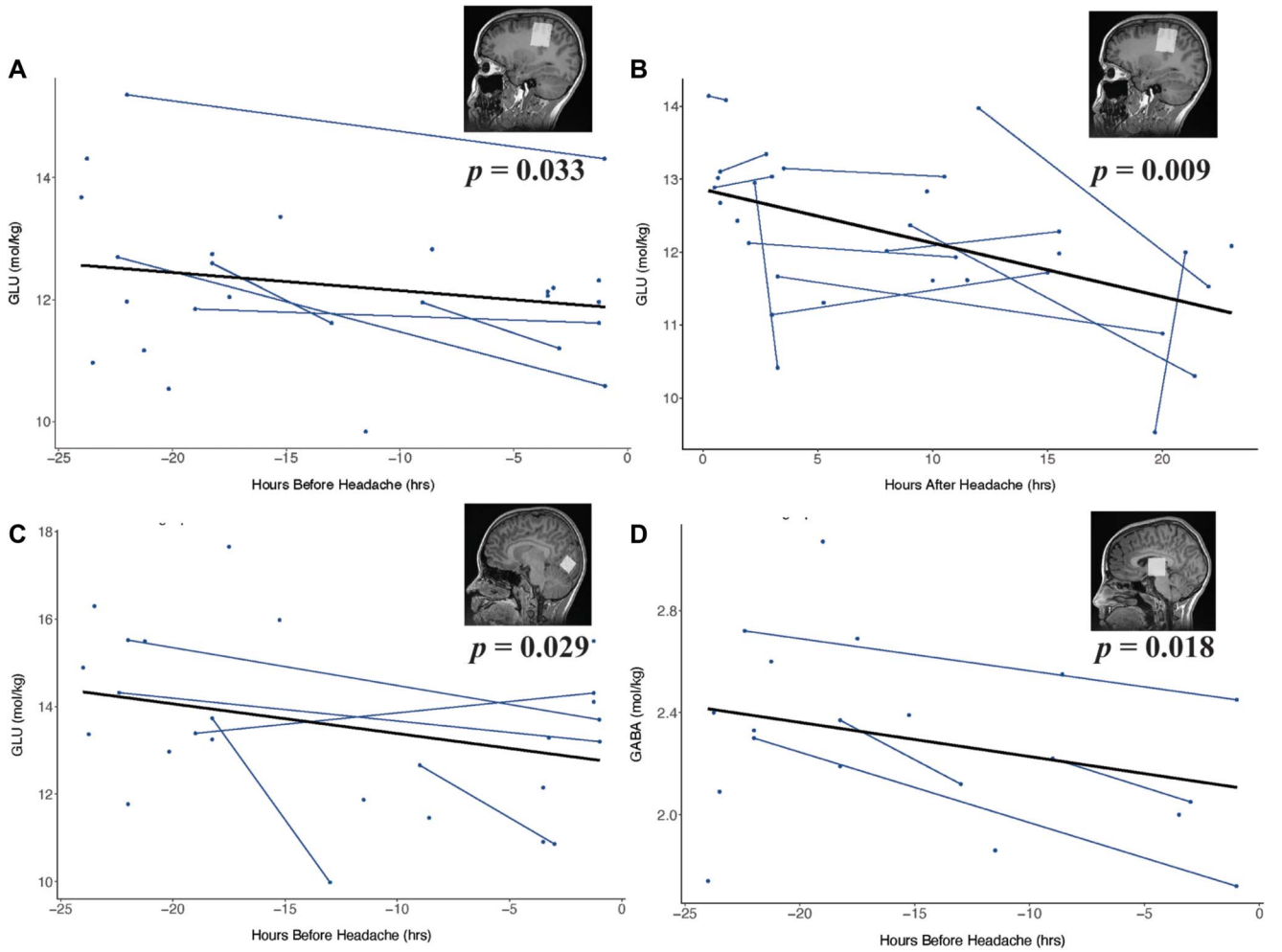

Figure 5. (A) Sensorimotor cortex glutamate levels (mol/kg) decreased 24 hours leading up to the start of the next headache phase ($P = 0.033$; n = 26) and (B) decreased 24 hours following start of the last headache phase ($P = 0.009$; n = 33). (C) Occipital glutamate levels (mol/kg) decreased 24 hours leading up to next headache phase ($P = 0.029$; n = 26). (D) Thalamic GABA levels (mol/kg) decreased 24 hours leading up to the onset of headache phase ($P = 0.018$; n = 20). Ten headaches were captured for the sensorimotor glutamate and occipital glutamate. Eight headaches were captures for thalamic GABA. Each point represents one scan session, and each blue line represents one participant. Black lines represent overall regression lines of all participants included in analyses.

across the attack, perhaps reflective of underlying thalamocortical dysrhythmia, one adult study, comparing occipital glutamate-to-creatine ratios in 6 individuals during an attack and 13 separate individuals interictally, reported no differences between the 2 groups.[61] Moreover, another study of 25 female adults with migraine found no significant changes in occipital glutamate from the interictal to headache phase during a provoked attack.[42] This suggests that the neurobiology of migraine differs between the pediatric and adult populations.[8] Alternately, different methods, such as completing scans during provoked vs unprovoked attacks, cohort design vs case–control design, and using different measurements of time (phases vs continuous), may explain the different findings in our study as compared with prior studies in adults.

The thalamus also exhibited glutamate changes following the onset of the headache phase. The higher level of glutamate and subsequent decrease following the onset of the headache phase could reflect abnormal thalamic control, as is suggested by the thalamocortical dysrhythmia hypothesis. An adult study looking at evoked potentials reported reduced thalamocortical activity between attacks but not during.[16] Another adult fMRI study reported increased functional connectivity between the right thalamus and contralateral motor cortex during attacks.[3] We suggest that these observations are consistent with our results and abnormal thalamic control or a deficit in thalamocortical rhythmicity interictally, which is increased during the headache attack, with a subsequent decrease afterwards. Thalamic GABA decreased in the 24 hours leading up to headache phase onset. This aligns with a previous study from our laboratory showing that lower interictal thalamic GABA was associated with proximity to the next attack in children and adolescents.[8] This may indicate that the thalamus was in a hyperpolarized state before the onset of the headache phase, as thalamocortical relay neurons are thought to be hyperpolarized during thalamocortical dysrhythmia.

Age significantly associated with sensorimotor glutamate, with glutamate decreasing with increasing age. Our findings are consistent with previous work showing glutamate decreases with age, as glutamatergic synapses are pruned during development.[8,37] GABA+ is generally reported to increase with age in childhood then decrease in adulthood[44]; however, MM-suppressed GABA has been reported to show no relationships with age in the thalamus, sensorimotor cortex, and occipital cortex of healthy children and adolescents of 7 to 14 years old.[7] Similarly, our thalamic MM-suppressed GABA data did not show any age associations. However, sensorimotor GABA increased with age. This effect of age on sensorimotor GABA, which was

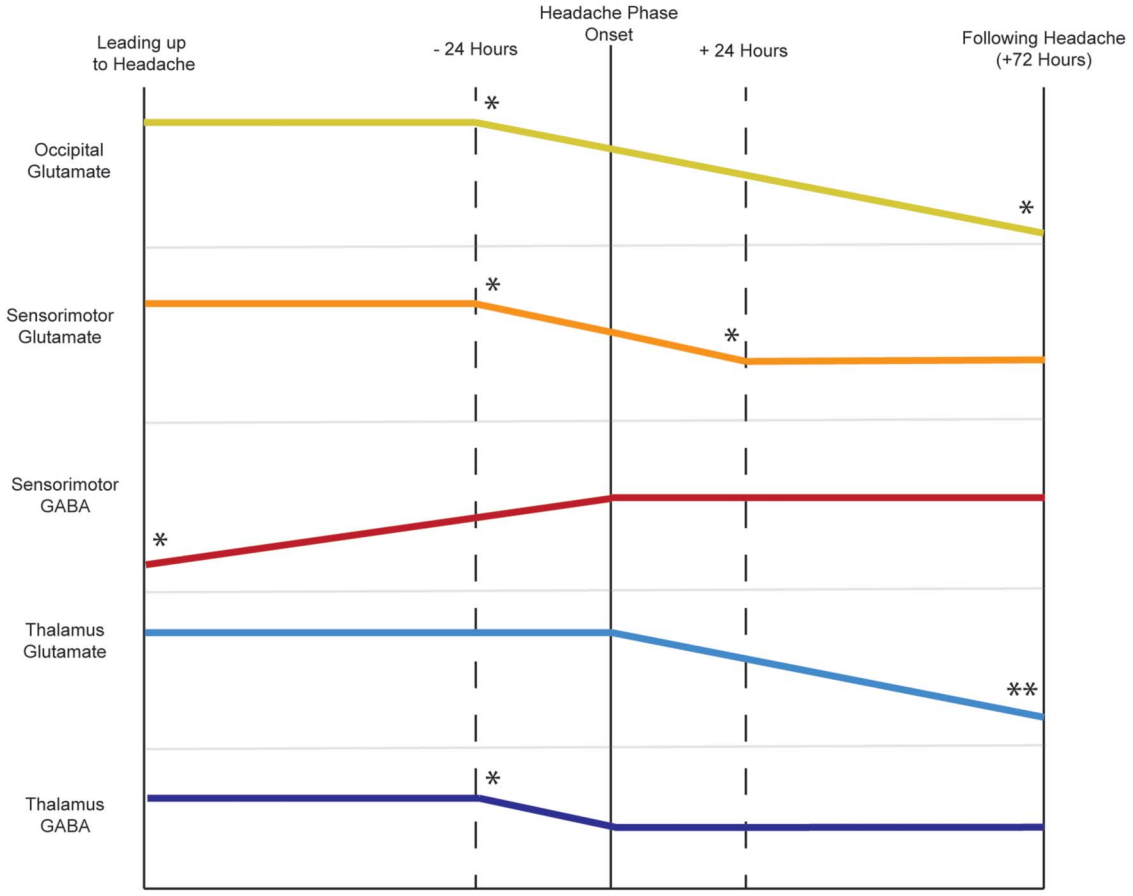

Figure 6. Summary of primary and post hoc analyses for "leading up to headache" and "following headache." Occipital glutamate was seen to significantly decrease 24 hours before the headache phase onset and decreased 72 hours following headache phase onset. Sensorimotor glutamate was seen to significantly decrease in the 24 hours before headache phase onset, as well as decreased in the 24 hours following headache phase onset. Sensorimotor GABA significantly increased leading up to the onset of the headache phase but did not show significant changes both 24 hours and 72 hours following headache phase onset. Thalamic glutamate levels did not show significantly changes leading up to headache phase onset but did show changes in the 72 hours following headache phase onset. Finally, thalamic GABA significantly decreased in the 24 hours before headache phase onset but did not show significant changes following headache phase onset. The slopes of the lines are not representative of the actual increases or decreases in neurochemical concentrations. They are simply representative of the directionality of the change. $^{*}P < 0.05$, $^{**}P < 0.005$.

not reported previously in a nonclinical population,[7] may reflect changes specific to clinical pediatric migraine as adult migraine studies report group differences in GABA.[43] Moreover, this age-dependent difference in GABA may also provide insight into why medication response is different between the pediatric and adult populations.[34]

Pubertal status was seen to have a significant effect on sensorimotor glutamate and Glx levels. Glutamate and Glx levels in the midpubertal stages were higher than those in the prepubertal stages. Hormonal changes may be a contributing factor to migraine as its prevalence changes from 1 male:1 female during childhood to a 1 male:2 female ratio after puberty.[55] However, these results should be interpreted with caution as most study participants were in the postpubertal stage, with only one participant in the prepubertal stage and 3 participants in the early pubertal stage.

4.1. Strengths and limitations

This study used a novel design to capture neurochemical level changes at multiple time points during each individual's attacks. Despite the knowledge that attacks of migraine are multiphasic and individually unique, studies are often cross-sectional due to the difficulty of capturing different time points relative to attack onset. This study's unique data set adds to the sparse literature on individual phases of an attack with a specific focus on children and adolescents.

Gamma-aminobutyric acid was collected using a MM-suppressed GABA-edited acquisition, the most advanced and specific method of GABA quantification at 3T. This method aims to limit MM contamination in the GABA signal that is a fundamental weakness of conventional GABA+-edited MRS. However, as with all MRS, the voxels used were relatively large, leading to partial volume effects. When considering that each region of interest has, within it, regional specificity in terms of function (eg, thalamic nuclei), this may have been diluted by using relatively large voxels.

Migraine with aura is generally diagnosed in one-quarter of children and adolescents with migraine[32]; however, almost half of our sample had a diagnosis of migraine with aura. This may be a function of our recruitment in a specialist clinic. In addition, 80.8% of our sample was White, and participants were recruited from tertiary care headache clinics. Therefore, our sample is not representative of the general patient population, limiting external validity. This sample may have had a higher disease burden compared with the general migraine population, but the study was designed with the intention of studying migraine with a clinical-level burden because these are the patients who are typical candidates for preventive migraine interventions. In addition, participants with depression and anxiety were also

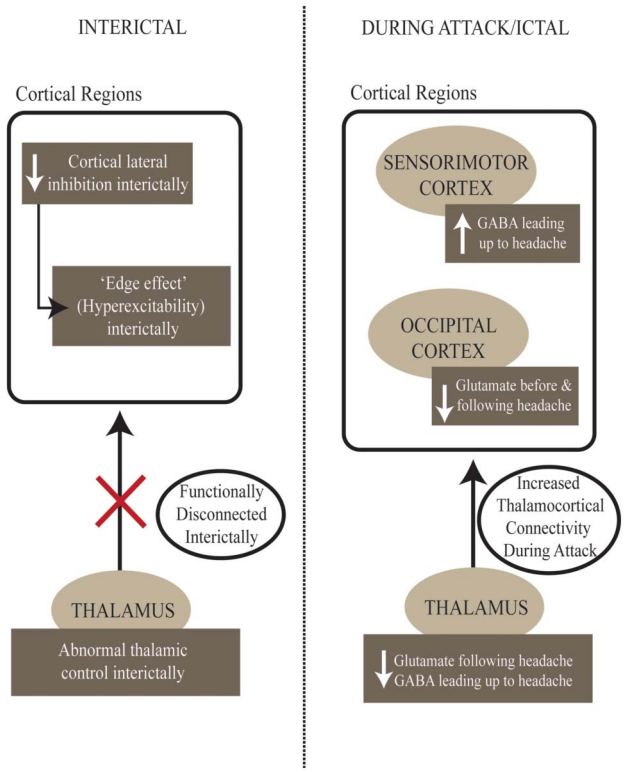

Figure 7. Model of thalamocortical dysrhythmia in children and adolescents with migraine. Interictally, there is abnormal thalamic control in children and adolescents with migraine, leading to a functional disconnect between the thalamus and cortical regions. This thalamocortical dysrhythmia further leads to decreased cortical lateral inhibition in the interictal phase. As a consequence of decreased lateral inhibition, adjacent cortical regions exhibit the "edge effect" where they are hyperexcitable. Our results suggest that moving out of the interictal phase and into the migraine attack, there is an increased functional coherence between the thalamus and cortical regions, as shown by the changes in glutamate and GABA following and leading up to the headache phase onset in the thalamus. This then leads to increased sensorimotor GABA leading up to the headache, suggesting increased cortical lateral inhibition and decreased occipital glutamate leading up to and following the headache phase, suggesting a decrease in occipital cortical excitability.

included in the study as both are common comorbidities with migraine. This may have affected neurochemical levels and could have been a confounder.

5. Conclusion

Sensorimotor GABA increased approaching the next headache phase onset, and thalamic and occipital glutamate decreased following headache phase onset. We suggest that these results support the thalamocortical dysrhythmia hypothesis as an underlying mechanism in migraine. Given that sensorimotor, occipital, and thalamic changes were found, these may inform future targets for neuromodulation-based treatments and provoke questions that should motivate future studies for exploring migraine pathophysiology and ultimately improving care. Overall, our results highlight the importance of considering dynamic changes across the whole attack rather than at a single time point to fully understand migraine biology, particularly in children and adolescents.

Conflict of interest statement

L.Y.C. reports no disclosures relevant to the manuscript. T.K.B. reports no disclosures relevant to the manuscript. L.C. reports no disclosures relevant to the manuscript. K.J.G. reports no disclosures relevant to the manuscript. A.D.Hershey has served as an advisor and/or received funding for his institution or himself from Alder/Lundbeck, Allergan/AbbVie, Amgen, Biohaven/Pfizer, Curelator, Lilly, Teva, Theranica, Upsher-Smith, and NIH. J.K. reports no disclosures relevant to the manuscript. M.S. reports no disclosures relevant to the manuscript. K.M. reports no disclosures relevant to the manuscript. S.L.O. receives royalties from Cambridge University Press. She serves on the editorial boards of Headache, Neurology, and the American Migraine Foundation. She also has research funding from the Canadian Institutes of Health Research and the Alberta Children's Hospital Research Institute. A.D.Harris reports no disclosures relevant to the manuscript.

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Data Availability: Anonymized data may be made available to qualified investigators upon request.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/C68.

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