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RESEARCH ARTICLE

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The longitudinal influence of tDCS on occipital GABA and glutamate/glutamine levels in episodic migraineurs

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Abstract

This study investigated differences in the concentration of gamma-aminobutyric acid (GABA) and the combination of glutamine and glutamate (as GLX) in the early visual cortex of patients with episodic migraine and the influence of transcranial direct current stimulation (tDCS) on GABA and GLX. In this single-blind, sham-controlled trial, we randomly assigned patients with episodic migraine to receive daily anodal tDCS or sham stimulation. In addition, we included healthy controls. We acquired proton MR spectroscopy data of the visual cortex with 3 Tesla MRI at baseline and from migraine patients directly after the stimulation period and 4 months later. In 22 migraineurs and 25 controls, the GABA and the GLX concentrations did not differ at baseline between the groups. tDCS resulted in reduced concentrations of GABA but not GLX or the migraine frequency directly after the stimulation period, but not 4 months later. The changes in the levels of GABA in the early visual cortex of patients with episodic migraine in the interictal period suggest an effect of tDCS that allowed for subsequent changes in the migraine frequency. However, we might have missed relevant variations in the concentrations of these neurotransmitters during the follow-up period, as changes in migraine frequency appeared after the first MRI and disappeared before the second.

KEYWORDS
episodic, migraine, neurostimulation, spectroscopy, tDCS

Abbreviations: CI, confidence interval; CRLB, Cramér-Rao lower bounds; FUP1, first follow-up visit; FUP2, second follow-up visit; GABA, gamma-aminobutyric acid; GLX, Glutamine/Glutamate; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; IU, institutional units; LCM, linear combination modeling; MEGA-PRESS, Mescher–Garwood Point Resolved Spectroscopy; MIDAS, Migraine Disability Assessment; MRS, Magnetic Resonance Spectroscopy; n. r., not reported; SD, standard deviations; tDCS, transcranial direct current stimulation.

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1 | INTRODUCTION

Migraine attacks intermittently interrupt everyday life by imposing photophobia, phonophobia, nausea, vomiting, and pain on the afflicted individuals (Dodick, 2018). However, even in the absence of an attack, during the inter-ictal period, there are differences compared with healthy controls. A prominent example is the inability to habituate to repeated visual or acoustic stimuli because of changes in cortical excitability or responsiveness (Coppola et al., 2007; Judit et al., 2000; Schoenen et al., 1995).

Several studies have provided evidence for altered cortical excitability in migraine patients in the inter-ictal period. For example, electrophysiological examinations suggest increased excitability of the visual cortex (Brigo et al., 2013; Mulleners et al., 2001; Young et al., 2008). Interestingly, modifying excitability through transcranial direct current stimulation (tDCS) can prevent migraine attacks (Antal et al., 2006; Pohl et al., 2021; Rocha et al., 2015; Vigano et al., 2013). Consequently, cortical excitability may hold a central place in the pathophysiology of migraine.

The concerted influence of inhibitory and excitatory neurotransmitters regulates cortical excitability. Consequently, previous studies hypothesized an imbalance of neurotransmitters as part of the pathophysiology of migraine. Accordingly, Magnetic Resonance Spectroscopy (MRS) studies indicated elevated gamma-aminobutyric acid (GABA) concentrations in adult patients with frequent migraine attacks—but not in patients suffering fewer attacks (Aguila et al., 2015; Peek et al., 2021; Staermose et al., 2019). Some authors reported increased glutamate concentrations in migraine patients during the inter-ictal period (Bell et al., 2021; Gonzalez de la Aleja et al., 2013; Zielman et al., 2017).

Thus, if (i) the concentrations of GABA and glutamate reflect cortical excitability, (ii) cortical excitability is altered in patients with migraine, and (iii) tDCS influences cortical excitability, then applying tDCS should also alter the concentrations of GABA and glutamate. This study aims to test this hypothesis by (i) comparing the concentrations of excitatory and inhibitory neurotransmitters in migraine patients and healthy controls and (ii) investigating the longitudinal influence of anodal tDCS on the concentrations of GABA and GLX in the early visual cortex of patients with episodic migraine.

2 | PATIENTS AND METHODS

This article reports a pre-planned analysis of the study data; we have already published our clinical findings separately (Pohl et al., 2021). In short, tDCS resulted in a significant reduction of monthly migraine days. However, the effect was small (an average reduction of 1.7 ±.5 migraine days per month in the active tDCS group during the 4 months following the stimulation period), set in belatedly, and was short-lived.

Significance

Cortical pre-activation levels may be lower between migraine attacks. In this study, we used occipital anodal transcranial direct current stimulation (tDCS) in patients with episodic migraine. To quantify the effect, we measured changes in the concentrations of gamma-aminobutyric acid (GABA) and glutamate in the visual cortex. tDCS reduced GABA concentrations of but not glutamate directly after the 4-week stimulation period. After that measurement, migraine frequency dropped transiently. Four months later, there were no detectable changes anymore. Thus, tDCS may increase the pre-activation level of the visual cortex by reducing GABA concentrations, allowing for a subsequent transient decrease in migraine frequency.

2.1 | Participants

Adults with episodic migraine diagnosed according to the criteria published in the International Headache classification (Headache Classification Committee of the International Headache Society (IHS), 2018) and healthy controls (HC) who did not suffer from any headache disorder were eligible to enroll. We excluded patients with less than two monthly migraine days (MMD) during the baseline period and HC who scored more than 0 points in the Migraine Disability Assessment (MIDAS). Furthermore, we excluded patients and HC if they suffered from severe cardiovascular disorders (e.g., severe hypertension), severe psychiatric disorders (e.g., acute psychosis), or other neurologic disorders (e.g., stroke, neck injury, traumatic brain injury, epilepsy, and cerebrovascular disease).

Both migraineurs and healthy controls were enrolled during the same period. All participants were recruited specifically for this research project. We had not aimed for a specific number of participants, as no preliminary data had been available allowing power calculations. Hence, the available data determined the sample size.

2.2 | Design

We conducted this single-blind, sham-controlled, randomized trial at the University Hospital Zurich (Switzerland). After a 28-day baseline period, we allocated migraine patients at the baseline visit to the sham or the active tDCS group applying block randomization (block size = ten). The baseline visit marked the beginning of the 28-day stimulation period during which all patients used the tDCS device daily. We scheduled a first follow-up visit (FUP1) directly after the stimulation period and a second follow-up visit (FUP2) about 4 months later. Healthy controls were examined only once. We obtained magnetic resonance (MR) scans from all participants at each

study visit. All participants completed the HADS (Hospital Anxiety and Depression scale) (Zigmond & Snaith, 1983) and the MIDAS (Stewart et al., 2000) at baseline; migraine patients also filled in both questionnaires at each follow-up visit. All migraine patients kept headache diaries throughout the study to identify migraine days; we distinguished them from non-migraine headache days as published (Tassorelli et al., 2018). Participants were allowed to take acute medication as needed and prescribed. However, we asked them not to change their prophylactic treatment during the study period. Figure 1 summarizes the study design.

2.3 | Transcranial direct current stimulation

We used a one-channel stimulator (DCSTIMULATOR PLUS) with rubber electrodes (active electrode size: 5 ×7 cm; reference electrode size 10 cm×10 cm) from NeuroConn (Ilmenau, Germany) for the anodal tDCS. Following detailed instructions, participants placed the reference electrode over Cz and the active electrode over Oz themselves and conducted once-daily stimulation sessions at a convenient time, each lasting 20 min. In the active tDCS group, the device maintained a stimulation intensity of 1 mA for the whole stimulation period. Sham stimulation also had an intensity of 1 mA but lasted only 30 s and was then followed by intermitted impedance checks during the remaining 19.5 min.

2.4 | MR acquisition and spectroscopy analysis

We acquired the imaging data on a 3-Tesla MRI Philips Ingenia scanner (version 5.1.8) with a 15-channel head coil. Using T1-weighted anatomical images, we placed the $30\times30\times30\,mm^3$ (27 ml) voxel in the midline early visual cortex (Brodmann areas 17 and 18, see Figure 2). We focused on the early visual cortex as previous MRS and structural brain imaging studies suggested alterations in the visual cortex in patients with migraine (Gonzalez de la Aleja et al., 2013; Zielman et al., 2017).

GABA-edited MR spectra were acquired with a macromolecule-minimized Mescher-Garwood Point RESolved Spectroscopy (MEGA-PRESS) sequence (repetition time (TR)/echo time (TE) = 1800/68 ms) (Henry et al., 2001), applying a 20 ms editing pulses at 1.9 and 1.5 ppm (number of averages: 256).

We then estimated the concentrations of GABA and GLX using a linear-combination modeling algorithm (LCModel, Version 6.3-1N (Provencher, 1993)), quantified them relative to water (ATTH20 = .86, WCONC = 55,556), and corrected them for relaxation and tissue-specific contributions according to Gasparovic and co-workers (Gasparovic et al., 2006). Specifically, the data were pre-processed with GANNET (v.3.0) (Edden et al., 2014) run with MATLAB (R2022b, v.9.13), doing the following steps (as described in the manual): read-in data in sdat file format, time-domain frequency-and-phase correction using spectral correction (Near et al., 2015), apply exponential apodization (line-broadening and zero-filling), followed by Fourier transformation and time averaging. Then, the data with editing pulse on and the data with editing pulse off are separated to generate the difference spectra and extract the off spectra. Next, the data are saved in sdat format before quantification is conducted with LCModel. All metabolite amplitudes are reported in institutional units (IU). For spectral fitting, we used the basis sets obtained from the laboratory of U. Dydak (Purdue University, USA) incorporating the coupling properties available (Dydak et al., 2011; Govindaraju et al., 2000; Kaiser et al., 2008).

To assess the quality of the data, we calculated Cramér-Rao lower bounds (CRLB) as published (Bolliger et al., 2013). We inspected spectra visually and excluded them if there were ghosting (i.e., stimulated echo) artifacts or increased noise levels.

Table S1 provides a study overview according to the consensus recommendation MRSinMRS (Lin et al., 2021).

2.5 | Statistical analysis

The analysis was conducted in the modified intention-to-treat population, which consisted of the patients who met the inclusion criteria and had received tDCS treatment.

We first compared demographic data of migraineurs and healthy controls and then of migraine patients in the active and sham groups using the Mann–Whitney *U*-test for ordinal (i.e., the total MIDAS score) and continuous variables and the two-sided Fisher's exact test for dichotomous categorical variables. Then, we calculated means and standard deviations (SD) to report continuous variables; categorical variables are reported as frequencies.

When comparing the concentrations of GABA and GLX of migraineurs and HC at baseline, we used a *t*-test if the data were

FIGURE 1 Overview of the study design: After a 28-day baseline period followed the baseline visit. Then patients self-applied transcranial direct current stimulation once daily for 28 days and were examined at the first follow-up visit (FUP1). After a subsequent 4-month follow-up period, patients were examined again at the second follow-up visit (FUP2).

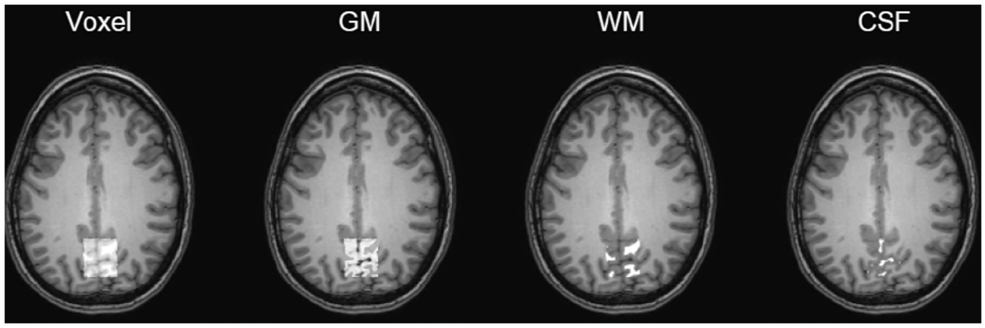

FIGURE 2 Region of interest in one patient. The voxel (white rectangle) covered Brodmann areas 17 and 18. Anatomical data was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). MRS data in the voxel was tissue-composition corrected for CSF content.

TABLE 1 Baseline data of the included sample; all patients diagnosed with migraine with aura also had attacks without aura

	Active tDCS ($N = 11$)	Sham tDCS ($N = 11$)	*p*-Value	Migraine patients ($N = 22$)	Healthy controls ($N = 25$)	*p*-Value
Age, years	41 ± 15	34 ± 10	.197	37 ± 13	33 ± 10	.293
No. of females (%)	10 (90.9)	11 (100)	>.999	21 (95.5)	20 (80.0)	.194
No. of patients with migraine with aura	7 (63.6)	6 (54.5)	>.999	13 (59.1)	0	–
Baseline migraine days	5 ± 2	7 ± 3	.086	6 ± 3	0	–
Baseline headache days	7 ± 3	8 ± 2	.253	8 ± 3	0	–
Baseline acute medication days	4 ± 3	6 ± 3	.217	5 ± 3	0	–
Baseline total MIDAS score	20 ± 20	32 ± 20	.045	25 ± 21	0	–
Baseline HADS-A score	7 ± 4	6 ± 3	.519	6 ± 3	4 ± 3	.483
Baseline HADS-D score	4 ± 2	4 ± 3	.606	4 ± 3	2 ± 2	.606

Abbreviations: HADS, hospital anxiety and depression scale; MIDAS, migraine disability assessment.

normally distributed and otherwise, the Mann–Whitney *U* test. We calculated Cohen's *d* for *t*-tests and r for the Mann–Whitney *U* test to estimate effect sizes as published (Fritz et al., 2012). We checked for the normal distribution with the Shapiro–Wilk test.

Next, we investigated correlations between the migraine frequency and the transmitter concentrations with Spearman's Rho.

Then, we analyzed the changes from baseline to FUP1 and FUP2 in the concentrations of the neurotransmitters building a mixed-effects model. The neurotransmitter concentration (GLX or GABA) was the dependent variable, and the group allocation (active vs sham tDCS) entered the model as fixed effects; the time between the first stimulation day and the follow-up visit as well as the number of stimulation days were considered random effects. Estimated marginal means are reported with their confidence intervals (CI). Finally, we tested the normal distribution of the residuals with the Shapiro–Wilk test.

We used IBM SPSS statistics version 26 for the statistical analysis with the significance level set at .05 and did not impute missing data; missing data are indicated as "not reported" (n. r.).

3 | RESULTS

Twenty-five controls and 22 migraine patients were enrolled in the study. Table 1 summarizes their baseline data (see also Pohl et al., 2021).

Even though we had instructed patients to stimulate daily for 28 days, some continued afterward. The average number of stimulation days was 30 ± 3 days in the active (median 29 days, range 28 to 37 days) and 28 ± 0 days in the sham group (median 28 days, range 28 to 29). The difference was not statistically significant ($p = .116$, $r = .38$); the numbers of stimulation days were not normally distributed ($p < .001$).

Figure 3 shows an overview of all individual spectra (top row) as well as a group-averaged spectrum for the three time points baseline (second row), follow-up 1 (third row), and follow-up 2 (bottom row). First, we compared the baseline concentrations of the studied neurotransmitters in healthy controls and migraine patients. In the latter group, the last migraine day had occurred 5 ± 6 days before the baseline assessment (median 2 days; range 0 to 19 days); the next

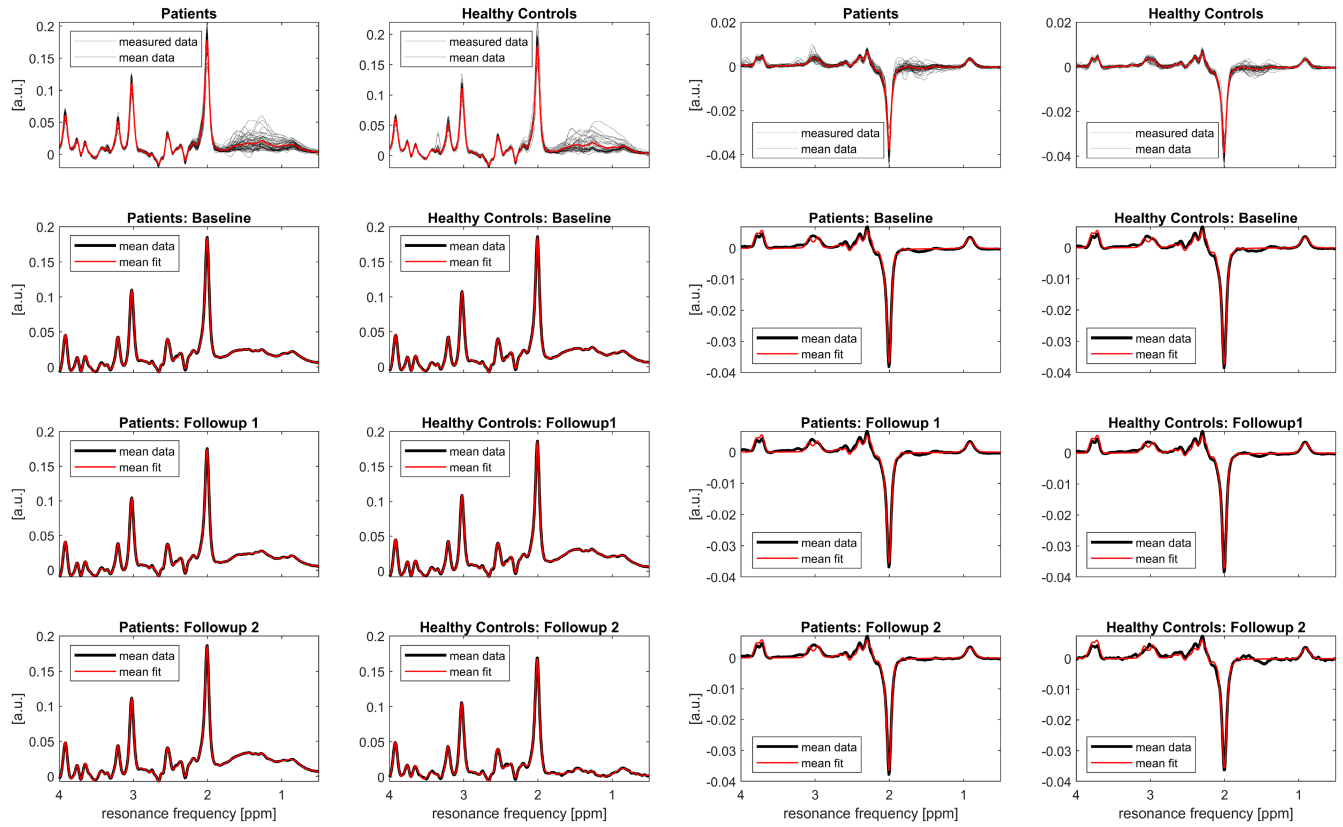

FIGURE 3 This figure illustrates the spectral quality for the two groups at different time points. The first and third columns show the spectra in patients, the second and fourth columns show spectra in healthy controls. In the first row, the measured individual spectra from all subjects are overlaid for the off-pulse scheme (columns 1 + 2) and the difference (on-pulse minus off-pulse) scheme (columns: 3 + 4). The second to last rows show the mean spectra and mean fit of the data for the three time points: Baseline (second row), follow-up 1 (third row), and follow-up 2 (fourth row).

attack after the visit occurred 7 ± 12 days later (median 3 days, range 0 to 41 days).

During the baseline period, patients in the active group had had 5 ± 2 migraine days (median 4 days, range 2 to 9 days) and 7 ± 3 headache days (median 6 days, range 3 to 15 days). Sham-treated patients had had 7 ± 3 migraine (median 7 days, range 3 to 12 days) and 8 ± 2 headache days (median 8 days, range 5 to 12 days). Migraine and headache days were normally distributed ($p = .118$ and $p = .329$, respectively) and did not differ significantly between the groups ($p = .145$, $d = .83$, and $p = .355$, $d = .44$, respectively).

Analyzing GABA at baseline, we included the data of 21 patients (1 n. r.) and 14 HC (11 n. r.). The concentrations were normally distributed ($p = .769$) and did not differ statistically significantly between the two groups ($p = .832$, $d = .07$). Migraine patients had mean concentrations of 2.93 ± .53 IU (median 2.82 IU, range 1.94 to 3.92 IU) and healthy controls of 2.98 ± .76. IU (median 2.96 IU, range 1.53 to 4.12 IU). There was no statistically significant correlation between the number of migraine days and the concentration of GABA ($p = .587$, $r = .126$).

The data of 21 patients (1 n. r.) and 14 controls (11 n. r.) entered the analysis of GLX at baseline. The concentrations of the transmitters were normally distributed ($p = .110$) and did not differ statistically significantly between the two groups ($p = .909$, $d = .04$). The average concentrations of GLX were 7.75 ± .61 IU in migraine patients (median 7.92 IU, range 6.31 to 8.92 IU) and 7.72 ± 5.69 IU in HC (median 8.03 IU, range 5.69 to 9.25 IU). Again, there was no statistically significant correlation between the numbers of migraine days and the concentrations of GLX ($r = -.016$, $p = .946$).

Figure 4 depicts GABA and GLX of HC and migraine patients at baseline.

Next, we compared GABA levels in the active and the sham group at baseline. Eleven patients from the active tDCS (0 n. r.) and ten from the sham group (1 n. r.) entered the analysis. The concentrations were normally distributed ($p = .491$) and did not differ between the groups ($p = .374$, $d = .40$). Patients in the active group had an average concentration of 3.03 ± .51 IU (median 3.33 IU, range 2.20 to 3.60 IU) and the in sham group of 2.82 ± .56 IU (median 2.75, range 1.94 to 3.92 IU).

To analyze GLX, the data from 11 patients of the active (0 n. r.) and 10 patients of the sham tDCS group (1 n. r.) were available. In the active group, patients had an average concentration of 16 ± 9.06 IU (median 19.35 IU, range 10.74 to 38.44 IU) and in the sham group of 16.73 ± 3.90 IU (median 17.15 IU, range 10.72 to 23.82). The concentrations were normally distributed ($p = .298$) and did not differ between the two groups ($p = .324$, $d = .44$).

Then, we analyzed the data of the FUP1, which took place 51 ± 8 days after the first day of the stimulation period (median

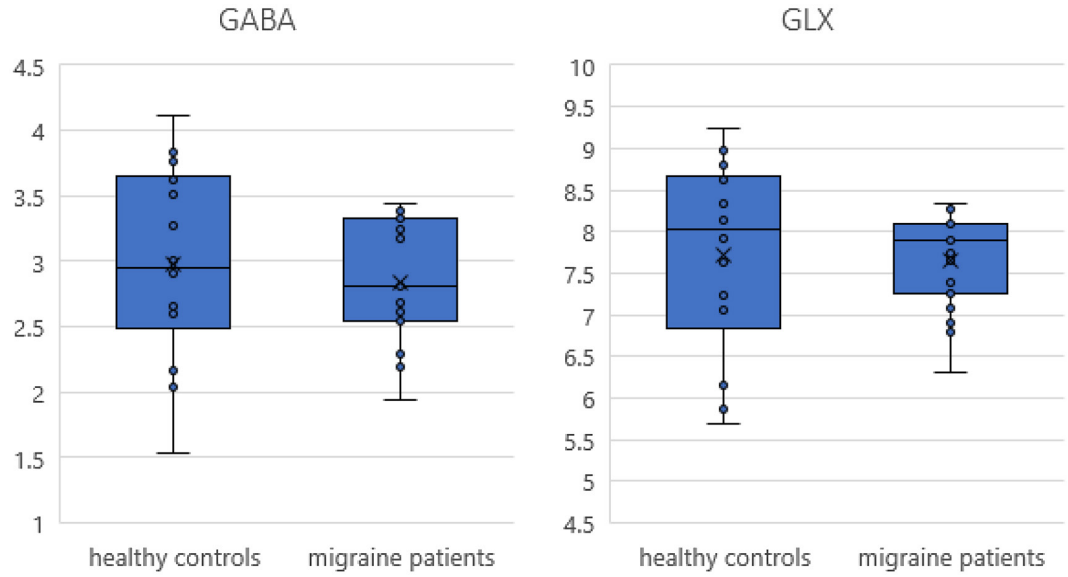

FIGURE 4 Differences in the concentrations of neurotransmitters of healthy controls and migraine patients at baseline; the *y*-axis indicates the concentration of the respective neurotransmitter in institutional units (IU); GABA, gamma-aminobutyric acid including macromolecule contamination; GLX, glutamine and glutamate; the "X" indicates the mean and the circles represent the individual participants.

51 days, range 36 to 63 days). During the 4 weeks prior, patients in the active group had had 4 ± 3 migraine days (median 5 days, range 1 to 8) and 8 ± 5 headache days (median 7 days, range 2 to 18; 2 n. r.). Sham-treated patients had had 6 ± 1 migraine (median 5.5 days, range 4 to 8 days) and 7 ± 2 headache days (median 6.5 days, range 4 to 10 days; 3 n. r.). Migraine and headache days were normally distributed ($p = .262$ and $p = .071$, respectively) and did not differ significantly between the groups ($p = .191$, $d = .65$, and $p = .595$, $d = .25$ respectively).

The last migraine day had occurred 6 ± 7 days before FUP1 in the active group (median 7 days, range 0 to 17) and 2 ± 3 days before in the sham group (median 1 day, range 0 to 8). The difference was not statistically significant ($p = .746$, $r = .08$; not normally distributed—$p = .002$). The next attack after the visit occurred 12 ± 27 days later in the active (median .5 days, range 0 to 77 days) and 5 ± 6 days later in the sham group (median 3.5 days, range 0 to 17). Again, the difference was not significant ($p = .844$, $r = .16$; not normally distributed—$p < .001$).

Nine patients in the active tDCS (2 n. r.) and five in the sham tDCS group (6 n. r.) entered the analysis of GABA at FUP1. Patients in the active group had an average concentration of 2.61 ± .59 IU (median 2.94 IU, range 1.63 to 3.24 IU), and in the sham group, 3.51 ± .78 IU (median 3.72 IU, range 2.16 to 4.12 IU). The stimulation had significantly influenced the changes in the concentrations of GABA from baseline to FUP1 ($p = .001$). The estimated marginal means of the group allocation were 1.904 (95% CI .245 to 3.563) in the active group and 3.086 (CI: 1.409 to 4.763) in the sham group; negative values indicate a decrease and positive values an increase from baseline in the concentration. The residuals of the mixed-effects model were normally distributed ($p = .056$).

We included nine patients of the active group (2 n. r.) and five of the sham group (6 n. r.) in the analysis of GLX at FUP1. Patients in the active group had a concentration of 7.77 ± 6.72 IU (median 7.77 IU, range 6.72 to 9.02 IU) and 7.97 ± .52 IU (median 7.94 IU, range 7.24 to 8.65 IU) in the sham group. The stimulation had no statistically significant influence on the changes from baseline in the concentration of GLX ($p = .353$); the estimated marginal means were −6.412 (95% CI −10.826 to −1.997) in the active group and −6.065 (95% CI −10.193 to −1.997) in the sham group. The residuals were normally distributed ($p = .982$).

Lastly, we analyzed the data of the FUP2, which took place 232 ± 73 days after the first day of the stimulation period (median 201.5 days, range 161 to 433 days; 6 n. r.). During the 4 weeks prior, patients in the active group had had 5 ± 4 migraine days (median 3.5 days, range 0 to 12) and 7 ± 5 headache days (median 6.0 days, range 0 to 15; 3 n. r.). Sham-treated patients had had 7 ± 3 migraine (median 7 days, range 2 to 12) and 8 ± 4 headache days (median 8 days, range 2 to 12; 4 n. r.). Migraine and headache days were normally distributed ($p = .360$ and $p = .914$, respectively) and did not differ significantly between the groups ($p = .397$, $d = .55$ and $p = .508$, $d = .26$ respectively).

The last migraine day had occurred 13 ± 12 days before FUP2 in the active group (median 8 days, range 1 to 35) and 6 ± 7 days before in the sham group (median 5 days, range 1 to 19). The difference was not statistically significant ($p = .104$, $r = .32$; not normally distributed—$p = .012$).

We analyzed the changes from baseline to the FUP2 in GABA in nine patients in the active tDCS group (2 n. r.) and six patients in the sham group (5 n. r.). The GABA concentration at the FUP2 was 3.24 ± .52 IU in the active tDCS group (median 3.41 IU, range 2.23 to

3.90 IU) and 3.33 ± 1.32 IU in the sham tDCS group (median 2.87 IU, range 2.07 to 5.83 IU). The stimulation had no statistically significant impact on the changes in the concentrations of GABA ($p = .519$). The estimated marginal means were −.064 (95% CI -.609 to .482) in the active group and −.334 (95% CI −1.024 to .356) in the sham group. The residuals were normally distributed ($p = .895$).

We included nine patients from the active group (2 n. r.) and six from the sham tDCS group (5 n. r.) in the analysis of GLX at FUP2. The concentration of GLX was 7.72 ± 1.28 IU in the active group (median 7.91 IU, range 4.71 to 9.24 IU) and 8.38 ± .60 IU in the sham-treated group (median 8.59 IU, range 7.29 to 8.88 IU). The stimulation had not influenced statistically significantly the changes from baseline in GLX ($p = .150$). The estimated marginal means were .160 (95% CI −.407 to .727) in the active group and .808 (95% CI −.091 to 1.525) in the sham group. The residuals were normally distributed ($p = .254$).

Figure 5 depicts the concentrations of GABA and GLX in migraine patients at different time points.

4 | DISCUSSION

This study quantifies GABA and GLX in the early visual cortex of migraineurs and HC and assesses the influence of tDCS on these neurotransmitters' concentrations. In summary, there was no difference between migraine patients and healthy controls in the baseline concentration of GABA and GLX. Nevertheless, tDCS resulted in a reduced concentration of GABA but not GLX directly after the stimulation period; 4 months later there was no difference anymore between active and sham tDCS. Moreover, there was no correlation between migraine days and the concentrations of GABA and GLX.

The comparison of HC and migraine patients at baseline did not indicate higher GABA concentrations in migraineurs than in HC. This result does not support the hypothesis that an imbalance of excitatory and inhibitory neurotransmitters in the occipital lobe plays an essential role in the pathophysiology of episodic migraine. Moreover, we did not find a correlation between concentrations of GABA and the number of migraine days—unlike Wu and co-workers, who studied the anterior cingulate cortex and the medial prefrontal lobe (Wu et al., 2022). Hence, it is possible that migraine attacks directly influence GABA concentrations only in specific brain regions or do so only in patients with migraine without aura—our sample comprised a higher proportion of migraineurs with aura.

In 1975, Welch and co-workers suspected the importance of GABA in migraine pathophysiology after having detected elevated levels of it in the cerebrospinal fluid during migraine attacks (D'Andrea et al., 2001; Welch et al., 1975). More recently, MRS studies found elevated GABA concentrations in various regions during the interictal period (Aguila et al., 2015; Peek et al., 2020, 2021). We could not demonstrate that GABA concentrations are elevated in the early visual cortex. Thus, the increased GABA concentrations in the cerebrospinal fluid likely stem from specific sources; excitability may not be altered throughout the brain.

A recent study in migraine patients hypothesized that the elevated GABA concentration might counterbalance increased cortical excitability (Peek et al., 2021). However, contrasting this idea and confirming a previous study (Onderwater et al., 2021), we could not prove increased excitability, as the concentration of GABA and GLX did not differ between migraineurs and HC in our sample.

Alternatively, GABA and GLX might not be consistently elevated. Previous studies found the GABA concentration to be *increased* in the posterior cingulate gyrus of patients with migraine without aura

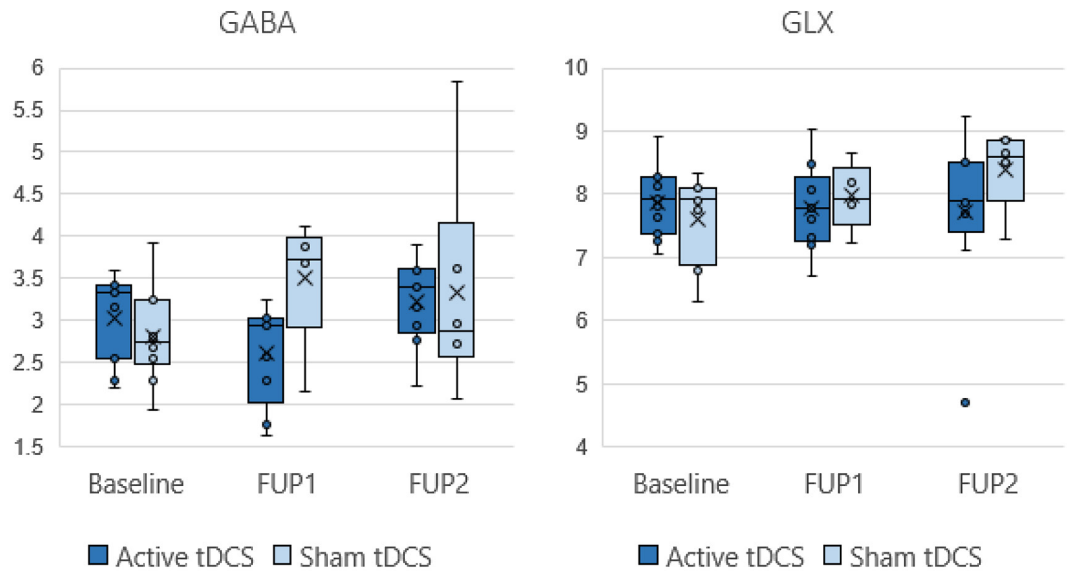

FIGURE 5 Differences in the concentrations of neurotransmitters of migraine patients in the active tDCS and the sham tDCS group; the *y*-axis indicates the concentration of the respective neurotransmitter in institutional units (IU); we scheduled the first follow-up visit about 5 weeks after the first stimulation day and the second follow-up visit about 5 months; the "X" indicates the mean and the circles represent the individual participants.

(Aguila et al., 2015), *decreased* in the occipital cortex of migraineurs with aura (Bridge et al., 2015), and *not changed* in the occipital cortex of migraineurs with and without aura (Bigal et al., 2008; Staermose et al., 2019). Moreover, the extent of the changes compared with HC might depend on other undetermined factors. Finally, the difference between migraineurs and HC may be slight, and its detection could require a larger sample.

When we analyzed the clinical effect of tDCS on migraine days in more detail (published previously) (Pohl et al., 2021), we found a significant overall reduction of 1.7 ±.5 migraine days in the active group compared with the sham group. However, the stimulation effect appeared belatedly and was short-lived, and, unfortunately, the tDCS had no significant influence on migraine days at the time of the MR scans.

However, there was a reduction in the GABA concentration of the early visual cortex that preceded the clinical changes. Consequently, the stimulation effect may not immediately have resulted in a reduction in migraine frequency but have allowed for them. Hence, although implicated in the pathophysiology of migraine, the occipital lobe is unlikely to be the attack generator.

Previous studies reported that anodal tDCS decreases GABA in the occipital cortex both in humans and cats (Stagg et al., 2009; Stagg & Nitsche, 2011; Wilson et al., 2018). Our results are in agreement with the findings of Stagg and co-workers (Stagg et al., 2009). They could indicate that repeated neurostimulation (and lateral inhibition) could have "exhausted" the GABA interneurons or protectively desensitized them by changing their membrane polarity, resulting in lower levels of GABA in the active tDCS group. Yet, this explanation is speculative and should be interpreted with care.

Besides, tDCS may influence neurotransmitters more than our results indicate because we measured them at suboptimal timepoints, and some changes might have remained below the detection threshold. Moreover, other stimulation intensities might have been better suited to induce clinical changes (Vigano et al., 2019).

On the other hand, it should be borne in mind that even if a larger sample and better-timed MR scans did not detect a difference in GLX, altered excitability would still not be excluded. The pathophysiology of migraine could comprise more subtle changes that do not result in gross alterations in GLX concentrations, as suggested by Chan and co-workers (2022).

4.1 | Limitations

The convenience samples of migraineurs and HC included in this study are unlikely to be representative. Consequently, our conclusions may not be generalizable to the whole population. In particular, our sample comprised mostly women and men were therefore underrepresented. In addition, as discussed above, our sample might have been too small to find any statistically significant difference between the active and the sham group.

Moreover, our sample had a relatively high number of migraineurs with aura compared with previous studies (Bell et al., 2021; Gonzalez de la Aleja et al., 2013; Zielman et al., 2017). Since previous studies suggested differing neurotransmitter changes in these groups (D'Andrea et al., 2001), combining them might lump together differing effects. Unfortunately, the small sample size precluded subgroup analyses of patients with and without aura.

While the macromolecule-suppressed scheme for GABA-edited MEGAPRESS offers higher specificity for GABA in comparison to the standard scheme, it is more sensitive to frequency drift and other artifacts like Creatine subtraction artifacts (Chan et al., 2021; Edden et al., 2016). In the present study, we excluded spectra with pronounced artifacts, but due to the small group sizes, some spectra with more subtle Cr subtraction artifacts were included in the analysis. The results should therefore be considered with caution until they can be replicated in a larger sample. In addition, the basis set used in the analysis was not simulated for the macromolecule-suppressed scheme. However, the vendor, pulse timing, and experimental setup matched the study setup. Although preprocessing GABA-edited MEGAPRESS spectra with Gannet prior to fitting in LCModel has previously been shown to offer high reproducibility in comparison to other pipelines (Brix et al., 2017), the zero-filling and line-broadening included in Gannet is generally not recommended prior to LCModel fitting. In particular, these preprocessing steps can invalidate the estimates of LCModel Cramer Rao Lower Bounds (CRLB), and the line broadening can make it harder to separate overlapping multiplet peaks. For GABA-editing, if the CRLB are not used for quality assessment of the spectra, these issues are arguably less problematic since the GABA peak in the subtraction spectrum does not overlap closely with other peaks. However, these issues should be considered carefully for a more general case when preprocessing spectra prior to LCModel fitting.

5 | CONCLUSIONS

Our study did not reveal differences in the concentrations of GABA and GLX in the early visual cortex of patients with episodic migraine in the interictal period. However, we could show that tDCS influences concentrations of GABA. Given the absence of clinical changes at the time of the MRI scans, the stimulation of the early visual cortex might have led to changes in the cortical excitability that allowed for subsequent clinical changes. Hence, more research is required to assess the effect of tDCS on these neurotransmitters and the effect of their changes on migraine pathophysiology.

AUTHOR CONTRIBUTIONS

Conceptualization, L.M.; *Formal Analysis*, H.P., P.W., R.O.; *Investigation*, L.M.; *Project Administration*, L.M.; *Writing – Original Draft*, H.P.; *Writing – Review & Editing*, P.W., P.S.S., J.S., R.L., R.O., F.R., A.R.G., and L.M.

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CONFLICT OF INTEREST

HP received speaking fees and/or honoraria from Novartis, TEVA Pharmaceuticals, and Eli Lilly. ARG has received honoraria for consulting or lecturing from Allergan/AbbVie, Almirall, EliLilly, Grünenthal, Lundbeck, Novartis, Pfizer, and TEVA/Mepha. The listed companies did not play a role in the current study.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.25161.

DATA AVAILABILITY STATEMENT

The anonymized data are available from the corresponding author. However, restrictions by the Swiss legislation on part of the data may apply and will be followed.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. Study overview (consensus recommendation MRSinMRS) (Lin et al., 2021)

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