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Clinical Research Article

Effect of upper cervical mobilization on activation of sensory areas of the brain: an fMRI study in migraine patients

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ABSTRACT

Introduction: Given the sensory network dysfunction observed in migraine, this study aimed to investigate the effects of upper cervical mobilization on sensory brain activation using functional magnetic resonance imaging (fMRI) during trigeminal pain stimulation.

Methods: Thirty-nine migraine patients were randomized into an intervention group ($n = 22$), receiving upper cervical mobilization, or a sham group ($n = 17$). All participants underwent fMRI scans before and after ten sessions. Trigeminal pain was induced using intranasal ammonia, and pain intensity was rated using the Visual Analog Scale (VAS). Brain activity was analyzed in sensory-related regions, including the primary somatosensory cortex (S1), angular and supramarginal gyri, superior parietal lobule (SPL), and thalamus. Outcomes included mean Z-score (statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). using ANCOVA (adjusted for baseline), with effect sizes reported using epsilon squared (ε^2) or partial eta squared (η^2).

Results: The mobilization group showed a greater pain reduction (Cohen's $d \approx 2.60$) than the sham group ($r \approx 0.64$). Voxel count in bilateral supramarginal gyri decreased significantly ($\eta^2 \approx 0.21, 0.11$), as did BOLD signal in right SPL ($\varepsilon^2 \approx 0.08$). Right S1 activation deviation correlated with pain reduction ($r = 0.69$). Pain reduction also correlated negatively with thalamic PSC ($\rho \approx -0.36$) and right angular gyrus COPD ($\rho \approx -0.35$).

Conclusion: Upper cervical mobilization significantly reduced migraine pain and modulated activity in brain regions associated with pain and sensorimotor processing, suggesting a potential neurofunctional mechanism of action.

Keywords:
Migraine
fMRI
Cervical mobilization
Sensory brain network
Trigeminal pain

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Introduction

Upper cervical mobilization is a physical therapy intervention known for its potential to modulate neural and physiological functions (Jafari et al., 2024). A study in 2017 demonstrated the immediate benefits of cervical mobilization, revealing significant enhancements in neck mobility and overall quality of life among individuals suffering from neck pain (Malo-Urriés et al., 2017). This technique may also be effective in neurological rehabilitation (Maden et al., 2022). Recent research has begun to underscore the efficacy of upper cervical mobilization in terms of headache alleviation (Fernández-de-Las-Peñas et al., 2023). These beneficial effects are likely linked to mechanical stimulation that initiates a series of biomechanical and neurophysiological responses, potentially involving the activation of descending pain modulation pathways through corticospinal projections originating from the periaqueductal gray matter (Malo-Urriés et al., 2017).

Migraine is a debilitating neurological condition characterized by severe headaches and heightened sensitivity to various stimuli (Steiner et al., 2020). It is primarily classified into two main subtypes: migraine with aura and migraine without aura (Kincses et al., 2019). However, studies that focusing specially on the treatment of migraine through the cervical spine mobilization are limited. In a study conducted in 2018, by Davidson et al. implemented cervical spine mobilization (C0-C3) on a cohort of 101 migraine patients, which resulted in significant reductions in pain intensity, frequency, and duration, as well as to improve medicines use (Davidson et al., 2018). When compared to standard care provided by general practitioners, the mobilization technique yielded even greater improvements in headache duration, frequency, intensity, medication use, and overall disability (Haghdoost and Togha 2022). The underlying mechanisms through which upper cervical mobilization alleviates migraine symptoms present a compelling area for further research. Initial studies indicate several possible mechanisms, including neuromodulation (Tiwari and Agrawal 2022), reduction of muscle tension (Repiso-Guardeño et al., 2023), enhanced blood circulation (Chaliha et al., 2020), improved joint mobility and proprioception (Peng et al., 2021), and decreased stress levels (Maleki et al., 2012). Furthermore, the combination of manual therapy and medication may offer additional benefits for individuals experiencing both migraines and neck pain by normalizing levels of central sensitization (Jafari et al., 2024).

Previous studies assessing the efficacy of manual therapy have frequently relied on subjective measures, suggesting that its effects may be associated with alterations in the central nervous system and brain function (Bialosky et al., 2018; Roura et al., 2021). Nevertheless, few objective studies have directly explored the impact of manual therapy on the brain and its pain-related regions (Isenburg et al., 2021; Jafari et al., 2024). This study employed functional magnetic resonance imaging (fMRI) to address this gap and objectively investigate these effects.

fMRI studies have revealed functional brain alterations associated with migraine, contributing to an improved understanding of its underlying pathophysiology (Messina et al., 2022). In task related functional imaging, brain responses to stimuli such as trigeminal activation have been used to assess neural function in individuals with migraine, providing insights into the mechanisms underlying sensory hypersensitivity and migraine pathophysiology (Schramm et al., 2023). Findings from fMRI studies have demonstrated heightened brain responses to trigeminal stimuli in specific brain regions among individuals with migraine (Schramm et al., 2023; Schwedt et al., 2015). Furthermore, studies have provided evidence of a dysfunctional sensory network in individuals with migraine during the pain-free (interictal) phase, which may underlie altered sensory processing between migraine attacks (Meylakh and Henderson 2022). The current study aims to investigate the effects of upper cervical mobilization on the activation of sensory brain regions using fMRI, ultimately enhancing our understanding of the therapeutic potential of manual therapy in modulating pain processing mechanisms.

Material and Methods

Study design

This semi-experimental, randomized clinical trial was designed to assess the effects of upper cervical (C0-C3) mobilization on sensory brain area activation. Initially, imaging was performed on all participants to compare sensory area activation between healthy subjects and individuals with migraines. The migraine group was then randomly divided into treatment and sham groups. The treatment group received the main intervention, while the sham group received a placebo intervention. Final imaging was conducted to evaluate the effects of the intervention. The study was approved by the appropriate institutional research ethics committee.

Settings

This study was conducted in Shiraz, Iran. Participants were recruited from specialized headache clinics in Shiraz between January and June 2022. Brain imaging was performed at the imaging center of Shahid Faghihi Hospital, affiliated with Shiraz University of Medical Sciences. The therapeutic intervention took place in the physiotherapy department of Doran Hospital in the same city between July and August 2022. Data were collected in two phases: before and after ten treatment sessions.

Participants

A total of 39 migraine patients (32 females and 8 males) and 10 healthy controls (5 females and 5 males) were recruited for this study. The eligibility criteria for both groups were as follows: Migraine group: Participants were aged 20-55 years, experienced 2-5 headache attacks per month, and had a minimum disease duration of one year. Control group: Healthy controls were aged 20-55 years and had no history of headaches, pain syndromes, or any neurological or psychiatric diseases. Exclusion criteria for both groups included: Contraindications to MRI, Current use of psychotropic or prophylactic medications, Neck pain or trauma during the study, Any signs of psychotic or medical disorders that might affect MRI results, Not receiving any non-pharmacological treatments for migraine in the past six months (Badveli et al., 2021). Dissatisfaction at any stage of the study.

Migraine patients were recruited from specialized headache clinics in Shiraz, Iran. Diagnosis was confirmed by a neurologist according to the International Classification of Headache Disorders (ICHD-3) criteria (Olesen 2018). Control Selection: Healthy controls were recruited from the general population, ensuring they met the eligibility criteria (i.e., no history of headaches or neurological disorders). They were matched by age and gender to the migraine group to minimize demographic bias. Clinical data collection was performed using structured interviews to gather detailed personal and headache-related characteristics from each participant. Migraine subjects were randomly divided into two groups (22 treatment /17 sham) using a simple random sampling method without replacement (srswor). All participants were given detailed information about the study and signed an informed consent form to participate.

Variables

The primary outcomes in this study were the brain activity (measured using fMRI. The ammonia-induced trigeminal pain contrast (pain > baseline) was modeled at the subject level. Significant activation region of interest (ROI) was identified using a voxel-wise Z-threshold of > 3.1 and a cluster-corrected significance threshold of $p < 0.05$ (Gaussian random field theory). The key indices to evaluate the brain activity were:

Mean Z-stat (Mean Z-statistics) were extracted for each significant cluster using the cluster results table in FEAT output, reflecting the average statistical strength of activation relative to background noise. These values were mapped back to spatial clusters for verification.

Percent signal change (PSC): PSC values were calculated from the %signal change time series extracted for each significant cluster using the FSL Featquery tool, relative to the baseline condition.

Voxel count (activation volume): Activation volume was determined as the total number of suprathreshold voxels within specified ROIs, (from FSL FEAT (FMRI Expert Analysis Tool, version 6.64). cluster report output).

Contrast of parameter estimates (COPE): COPE values were extracted directly from the general linear model (GLM) parameter estimate outputs, representing the contrast-weighted amplitude of task-related BOLD responses. These values were also visualized in Featquery for regional accuracy.

As a secondary outcome, pain intensity was assessed using the Visual Analog Scale (VAS). The study was approved by the Ethics Committee of Tarbiat Modares University, Tehran, Iran (Ethics ID: IR.

MODARES.REC.1400.349).

Measurement

fMRI scans were conducted at the Shahid Faghihi Hospital Imaging Center, affiliated with Shiraz University of Medical Sciences. To ensure comparability, identical acquisition protocols were applied to both the treatment and sham groups. Imaging was performed at two time points: at baseline and post-intervention (following the completion of the 5-week treatment period).

The brain activity measured via task-related fMRI.

Nociceptive stimulation was administered to the trigeminal nerve using gaseous ammonia, delivered through a custom-made, MR-compatible olfactometer (Hosseini et al., 2020), which targeted the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve to induce brief stinging or stabbing pain (Stankewitz et al., 2010). Prior to the fMRI experiment, participants were familiarized with the stimulation method outside the scanner. The concentration of the ammonia solution was calibrated to induce pain levels between 5 and 7 on the Visual Analogue Scale (VAS). A 2.5% ammonia solution in pure water, maintained at 20°C, was used for this purpose. The olfactometer was positioned in the operator's room, connected to the MRI room via an 8-meter nasal cannula passed through a dedicated cannula passage. Gaseous ammonia was delivered through a tube placed in the subjects' nostrils, which was secured with hypoallergenic leucoplast tape. Participants were instructed to breathe orally during the experiment to minimize fluctuations in stimulus concentration caused by respiratory airflow.

Additional considerations included maintaining a neutral head and neck position, avoiding motion, fear, anxiety, smoking, and abstaining from medication or coffee intake for at least two hours before imaging. The influence of low-level carbon monoxide (CO) exposure on blood oxygen level-dependent (BOLD) fMRI signals was also considered (Bendell et al., 2020). To eliminate sound interference and stabilize the participant's head, ear protection was provided. Compressed pillows were placed around the head and ears to minimize movement.

Data Acquisition Protocol

Assessment of Migraine Pain Intensity

Migraine pain intensity was assessed using the Visual Analog Scale (VAS), ranging from 0 (no pain) to 10 (worst imaginable pain). Pain intensity was assessed daily using a visual analogue scale (VAS). The preintervention score was calculated as the mean VAS value over the two weeks preceding the baseline fMRI scan. Following the initiation of the intervention (cervical mobilization or sham), participants recorded their pain intensity daily for five weeks; the mean of these daily scores was defined as the post-intervention pain intensity. Finally, pre- and post-intervention mean scores were compared to evaluate treatment-induced changes in pain intensity.

Imaging

MRI data were acquired using a 1.5-Tesla Siemens MAGNETOM Amira scanner (A-Tim, version XA12) equipped with an 18-channel head coil. Functional imaging utilized a BOLD contrast-sensitive asymmetric echo-planar imaging (EPI) sequence with the following parameters: 48 axial slices, voxel size of 3 × 3 × 4 mm, 25% slice gap, repetition time (TR) of 3000 msec., echo time (TE) of 50 msec., flip angle of 80°, field of view (FOV) of 192 × 192 mm, slice thickness of 4 mm, and an acquisition matrix of 64 × 64.

Structural scans included high-resolution T1-weighted sagittal three-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) sequences with the following specifications: TE = 3.16 msec., TR = 2.4 s, flip angle = 8°, 176 slices, voxel size of 1 × 1 × 1 mm, and FOV of 256 × 256 mm^2. The lowest slice was positioned at the caudal part of the cerebellum, serving as a reference point.

Task Design

The stimulation paradigm consisted of 12 trials, each lasting 1 minute. During each trial, stimuli were administered via 2.5% ammonia in both nostrils for 12 seconds. Imaging was conducted both before and after the treatment using the same protocol.

Manual therapy protocols: Participants in the intervention group were positioned supine with the cervical spine in a neutral position. The treatment in this group consisted of a 30-minute session of MT. The therapist applied 30-second manual stretching (distraction) using four fingers (index, middle, ring, and little) on the posterior aspect of the subject's head, while the other hand guided the tension from under the chin, returning slowly to the neutral position (Malo-Urriés et al., 2017). A mobilization force was applied dorsally from the shoulder until resistance was felt, followed by a slight increase in pressure to perform a stretching mobilization, classified as Maitland grades 3 and 4. No pain was reported during the treatment (Hengeveld and K 2014). The mobilization involved the 1st, 2nd, and 3rd cervical vertebrae, including extension, rotation to both sides, and lateral flexion to both sides (30 glides each). The frequency of mobilization was 1 to 2 Hz (Chiu and Wright 1996). Translatory mobilizations of the upper cervical spine

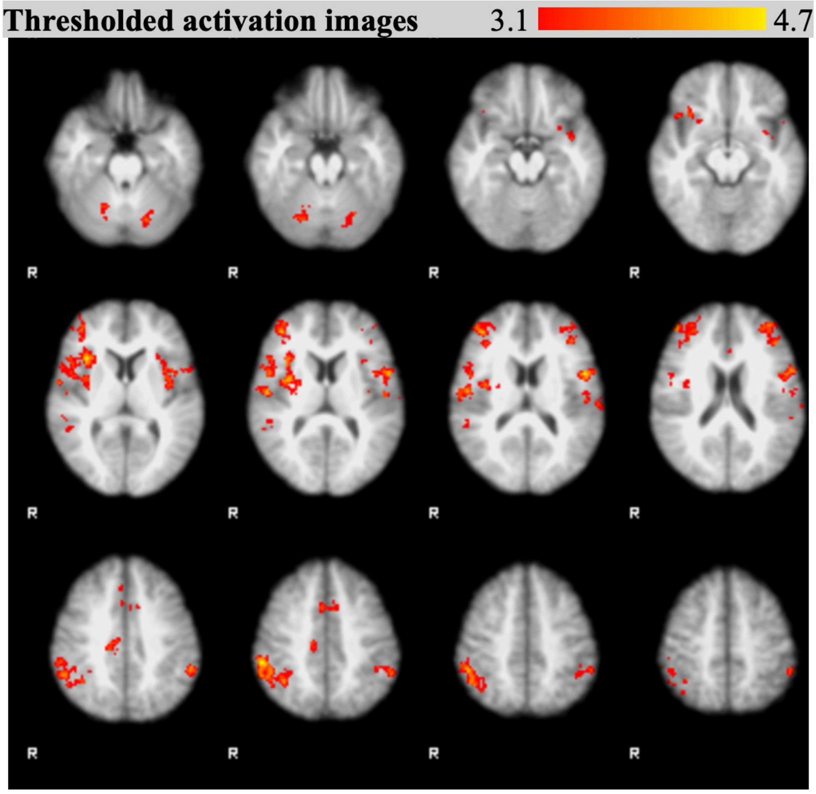

FIGURE 1. Group-level statistical activation map is a qualitative illustration of brain responses to trigeminal pain stimulation in healthy controls. The maps display the spatial distribution, activation intensity, and voxel-wise activation patterns. Color intensity represents Z-statistic values, with warmer colors (yellow to red) indicating stronger activation (Z = 3.1 to 4.7). Each row corresponds to a different axial slice, arranged in descending anatomical order. These thresholded images depict typical neural responses to trigeminal stimulation in individuals without migraine.

were performed with 10-second rest periods between sets, ensuring a complete return of movement (Hengeveld and K 2014). The session concluded with an additional 30-second stretch. The sham group remained in a supine position for 30 minutes (similar in position and duration to the intervention group) while receiving gentle periodic hand touch. The treatment protocols were administered by a therapist with a specialized training in orthopedic MT (39). In this study, the treatment was administered twice a week for a total of 10 sessions over five weeks.

Image Processing and Statistical Analysis—fMRI: All preprocessing and General Linear Model (GLM) estimation of whole-brain activation patterns were conducted using the FMRIB Software Library (FSL) version 6.64. Functional images were first realigned to the mean volume in the series and then motion-corrected. These images were subsequently aligned to each individual's structural images, normalized to the standard stereotaxic space using the Montreal Neurological Institute (MNI 152) template, and smoothed with a 5 mm full-width at half-maximum (FWHM) Gaussian kernel.

For each subject, a first-level analysis was performed, identifying clusters with a $Z > 3.1$. (a threshold value, representing the ratio of the difference between the mean values of the activated and non-activated signals to the standard deviation of the signal). It is calculated based on the difference in signal intensity before and after the task in fMRI and a significance threshold of $P < 0.05$. Group-level analyses were conducted using FLAME (FMRIB's Local Analysis of Mixed Effects), employing simple ordinary least squares (OLS) modeling. Significant clusters of voxels were anatomically defined using the Montreal Neurological Institute (MNI) brain template in conjunction with the Talairach atlas. Figure 1.

Bias

To minimize potential sources of bias in this study,

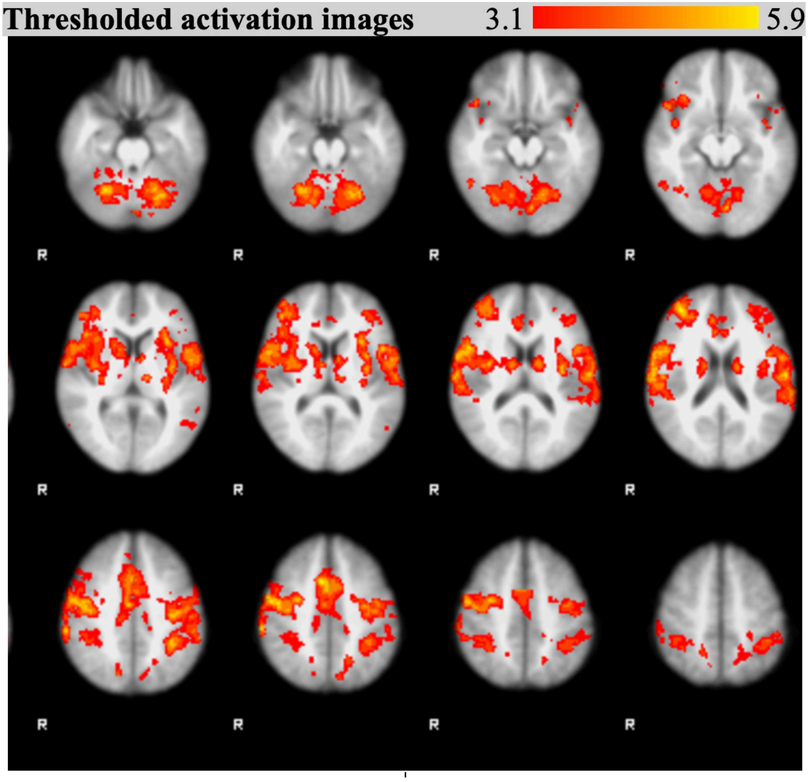

FIGURE 2. Group-level statistical activation map is a qualitative illustration of brain responses to trigeminal pain stimulation in migraine patients prior to upper cervical mobilization. The maps display the spatial distribution, activation intensity, and voxel-wise activation patterns. Color intensity represents Z-statistic values, with warmer colors (yellow to red) indicating stronger activation (Z = 3.1 to 5.9). Each row corresponds to a different axial slice, arranged in descend-ing anatomical order. These thresholded images depict the pre-treatment neural activation profile in migraine pa-tients.

several measures were implemented. Participants were randomly assigned to either the treatment or sham group. Both participants and researchers were blinded to group assignments to prevent performance bias and expectation bias. Participants were unaware of whether they were receiving the active treatment or a placebo, and the researchers conducting the assessmnts (e.g., fMRI scans) were also blinded to group allocation. All outcomes were assessed using standardized, validated instruments, which helped reduce measurement bias. Strict eligibility criteria were applied to ensure that only participants who met the specific diagnostic criteria for episodic migraine without aura were included, thereby minimizing the risk of selection bias. Statistical analyses were performed on an intention-to-treat basis, meaning that all participants, regardless of whether they completed the intervention, were included in the final analysis. This approach helped minimize analysis bias and ensured the results were more generalizable.

Statistical Methods

Data analysis was conducted using the Python programming language, and various statistical techniques were employed to evaluate the data. The PyTorch framework was utilized for dataset augmentation through Generative Adversarial Networks (GANs) to enhance the data (Paszke et al. 2019, Qiang et al., 2023). The Pandas library was used for generating and manipulating datasets in Comma-Separated Values (CSV) format within Excel (Khadka 2019). For computing basic statistical measures such as mean and standard deviation, as well as performing additional numerical operations, the NumPy library was used (Gupta and Bagchi 2024). The Q-Q plot method and the SciPy library were employed to assess the normality of the data (Chmielowiec and Klich 2021). Between-group differences were analyzed using ANCOVA for normally distributed variables (with baseline covariates) and the Kruskal-Wallis H test for non-normally distributed data. Within-group comparisons used paired t-tests for normally distributed

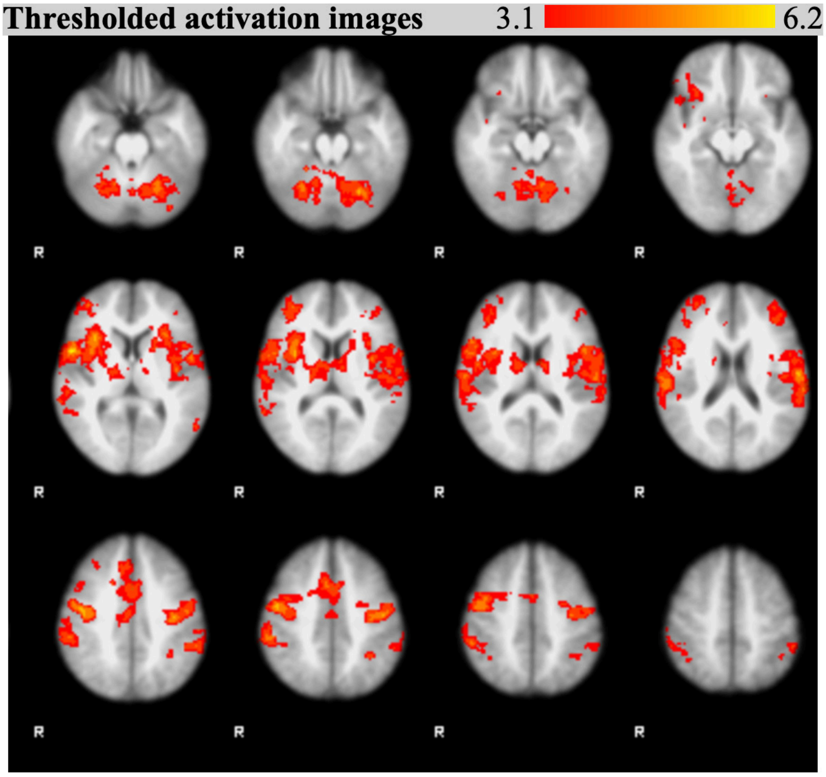

FIGURE 3. Group-level statistical activation map is a qualitative illustration of brain responses to trigeminal pain stimulation in migraine patients following upper cervical mobilization. The maps display the spatial distribution, activation intensi-ty, and voxel-wise activation patterns. Color intensity represents Z-statistic values, with warmer colors (yellow to red) indicating stronger activation (Z = 3.1 to 6.2). Each row corresponds to a different axial slice, arranged in de-scending anatomical order. These thresholded images highlight post-treatment changes in brain activation patterns.

data and the Wilcoxon signed-rank test for non-normally distributed data.

Effect sizes were reported as partial eta-squared (η^2) for ANCOVA, Cohen's d for paired t-tests, and rank-biserial correlation (r) for the Wilcoxon signed-rank and Kruskal-Wallis to examine the correlation between changes in brain analysis parameters and pain relief, Pearson's correlation coefficient (r) was used for parametric data, and Spearman's rank-order correlation (ρ) was applied for non-parametric data.

Missing Data Handling and Sensitivity Analysis: Missing data were addressed using multiple imputation techniques to ensure that all available cases contributed to the final analysis. To evaluate the robustness of the findings, sensitivity analyses were performed, including assessments under varying assumptions about the nature and pattern of the missing data.

Results

Participants: A total of 39 individuals with migraine (32 females and 8 males) and 10 healthy participants (control group: 5 female and 5 male) were enrolled in the study. Among the migraine individuals, 10 did not complete all intervention sessions, primarily due to neck pain or scheduling conflicts. However, all migraine participants underwent post-intervention imaging and were included in the final data analysis.

Demographic Characteristics of Study Participants: (Tables I)

Demographic data from 39 migraine patients were analyzed, with a female-to-male ratio of 31:8 and a mean age of 37.10 ± 7.71 years (range: 21-53 years). The study included 22 individuals in the intervention group, 17 in the sham group, and 10 healthy participants. In the intervention group, the female-to-male ratio was 17:5, with a mean age of 36.45 ± 7.53 years (range: 21-53 years). The sham group had a female-to-male ratio of 14:3, with a mean age of 37.94 ± 8.09 years (range: 24-48 years). The healthy group had an equal gender dis-

TABLE I: Demographic characteristics of study participants

Group	Number	Female/Male Ratio	Age (Mean ± SD)	Disease Duration (Mean ± SD)/ y
Healthy	10	5/5	33.5 ± 7.36	Not applicable
Migraineurs	49	31/9	37.10±7.71	16.44±8.46
Treatment	22	17/5	36.45 ± 7.53	15.23 ± 1.74
Sham	17	14/3	37.94 ± 8.08	18.59 ± 8.72

Note. SD: standard deviation; y:years: y: year

TABLE II: Sensory Brain Regions with Significant Differences Between Healthy Controls and Migraine Patients (Treatment and Sham Combined)

Score Type	Brain region (BA)	Side	Healthy (Mean ± SD)	Migraine (Mean ± SD)	Effect Size d/r
Z-stat	Angular Gyrus BA 39	Right	3.84 ± 0.91	2.94 ± 1.523*	d≈-0.714
Voxel count	Thalamus	Left	166.3 ± 13.56	168.77 ± 14.16*	d ≈0.178
COPE	post central Gyrus BA 5	Right	133.05 ± 94.98	212.57 ± 220.79*	r ≈ 0.34
PSC	Primary somatosensory BA1	Left	0.03 ± 0.03	0.05 ± 0.07*	r ≈ 0.37

Note. SD, standard deviation; BA, Brodmann Area; Z- statistic (Z-stat; statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). BOLD, blood-oxygen-level dependent;
Effect Size Measures: d = Cohen's d (t-test), r = rank-biserial correlation (Mann–Whitney U); (Cohen 2013) thresholds for d (small = 0.2, medium = 0.5, large = 0.8), and classification for rank-biserial correlation (Vargha and Delaney 2000), (small = 0.11–0.28, medium = 0.28–0.43, large ≥ 0.43).
Statistical significance between independent groups baseline (Healthy Controls vs. Migraine Patients, combining Treatment and Sham groups) was determined using independent t-tests or Wilcoxon tests is indicated by asterisks.: p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001, ***** p < 0.00001.

tribution, with a mean age of 33.50 ± 7.36 years (range: 23-44 years). The intervention group reported an average disease duration of 15.23 ± 1.74 years, while the sham control group reported a mean disease duration of 18.59 ± 8.73 years. Demographic characteristics of migraineurs and healthy subjects and both groups, are summarized in Tables I.

Compared individuals with migraine to healthy controls (original): (Table II)

At baseline, individuals with migraine showed significant differences in sensory-related brain regions compared to healthy controls (Table II). In the right angular gyrus (Brodmann area [BA] 39), migraine patients demonstrated significantly lower Z-stat (mean ± SD: 2.94 ± 1.53) than controls (3.84 ± 0.91), with a large effect size (Cohen's d ≈ –0.71). Voxel-based analysis of the left thalamus showed a slight increase in activation in migraine patients (168.77 ± 14.16) relative to controls (166.30 ± 13.56), though the effect size was small (d ≈ 0.18). Additionally, the consistency of participation (CoP) in the right postcentral gyrus (BA 5) was higher in the migraine group (212.57 ± 220.79) compared to healthy participants (133.05 ± 94.98), indicating a moderate effect size (rank-biserial r ≈ 0.34). Similarly, percent signal chang (PSC) in the left primary somatosensory cortex (S1; BA 1) was greater in the migraine group (0.048 ± 0.067) than in controls (0.026 ± 0.027), with a moderate effect size (r ≈ 0.37).

Migraine pain intensity in the Treatment and Sham groups: (Table III)

Analysis of pain intensity, measured via the Visual Analog Scale (VAS), revealed a significant reduction in self-reported migraine pain in the treatment group following the intervention (Table III). The mean VAS score in this group decreased from 8.18 ± 1.50 at baseline to 4.70 ± 1.16 post-intervention, yielding a very large within-group effect size (Cohen's d ≈ 2.60), indicative of a strong analgesic response to upper cervical mobilization. In contrast, the sham group also showed a statistically significant, albeit smaller, reduction in VAS scores—from 8.31 ± 1.50 to 7.39 ± 1.79—with a moderate-to-large effect size (r ≈ 0.64, calculated using the Wilcoxon signed-rank test). Between-group comparisons post-intervention demonstrated a large differential

TABLE III: Comparison of Mean Pain Intensity (VAS) Before and After Intervention in Treatment and Sham Groups

Group	(VAS) Before Intervention (Mean ± SD)	(VAS) After Intervention (Mean ± SD)	Effect size d/ r/ δ
treatment	8.18 ± 1.50	4.70±1.160****	d ≈ 2.60
sham	8.31± 1.50	7.39 ± 1.79***	r≈ 0.64
between groups	-	-	δ ≈0.70+

Note. d = Cohen's d; r = rank-biserial correlation; δ = Cliff's delta. Interpretation thresholds: Cohen's d (small = 0.2, medium = 0.5, large = 0.8; (Cohen 2013), rank-biserial correlation (small = 0.11–0.28, medium = 0.28–0.43, large ≥ 0.43; (Vargha and Delaney 2000), and Cliff's delta (negligible < 0.147, small = 0.147–0.33, medium = 0.33–0.474, large ≥ 0.474; (Romano et al., 2006).
Statistical significance within-group pre–post changes (paired t-test or Mann-Whitney-U test) is indicated by asterisks: $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$

effect in favor of the treatment condition, with a Cliff's delta (δ) ≈ 0.70, suggesting that the observed reduction in pain was not attributable to placebo or time effects alone. These findings support the clinical relevance of the intervention in alleviating migraine-related pain and reinforce the potential role of cervical mobilization as a complementary therapeutic approach.

Comparison Between Treatment and Sham Groups (original)" (Table IV)

Analyses revealed significant intervention-related changes in several sensory brain regions when comparing the treatment and sham groups before and after the intervention (Table IV).

In the left primary somatosensory cortex (S1), Brodmann area (BA1), Z-stat values significantly increased in the sham group but decreased in the treatment group following the intervention. The between-group analysis yielded a partial eta squared effect size ($\eta^2 = 0.11$), indicating a moderate to large overall effect. Within-group comparisons demonstrated a moderate-to-large effect in the sham group (Cohen's d = 0.68) and a negligible effect in the treatment group (d = –0.08).

In the right angular gyrus (BA 39), COPD values increased significantly in both groups post-intervention. The Kruskal–Wallis test indicated a moderate between-group effect (epsilon squared, $\varepsilon^2 = 0.08$). Within-group non-parametric effect sizes were small in the sham group (r = 0.17) and small-to-moderate in the treatment group (r = 0.23), suggesting a general enhancement of sensory integration in this region following the intervention. The left thalamus, assessed using the PSC parameter, exhibited significant between-group differences, with a large effect size ($\varepsilon^2 = 0.32$). The effect size within the sham group was minimal (r ≈ 0.05), whereas the treatment group demonstrated a small-to-moderate effect (r ≈ 0.25), indicating greater thalamic responsiveness to the intervention. Collectively, these findings support the hypothesis that manual mobilization induces measurable functional changes in key sensory processing areas. However, the type of parameter exhibiting change varied across regions. This inconsistency raised concerns regarding statistical sensitivity.

Despite the observed regional differences, the variability in which specific neural parameters Z-stat, COPE, PSC were affected in each region raised methodological concerns regarding statistical sensitivity and sample size limitations.

To address these issues and enhance the robustness and reliability of the findings, data augmentation was performed using Generative Adversarial Networks (GANs) implemented in PyTorch. This technique enabled synthetic generation of additional data points that preserved the distributional characteristics of the original dataset, thereby increasing the effective sample size and representing a forward-looking methodological advancement in neuroscience research particularly in studies constrained by small sample sizes and region-specific variability in neurophysiological response (Paszke et al., ; Qiang et al., 2023). The application of GAN-based augmentation improved the statistical power of subsequent analyses, allowing for more stable estimation of effect sizes and reducing the likelihood of Type II errors.

Compared Individuals with Migraine to Healthy controls (Augmented): (Table V)

Functional MRI analysis comparing interictal migraine patients (combined treatment and sham groups) with healthy controls revealed significant differences across multiple sensory brain regions. Following data augmentation—which involved the generation of 50 synthetic migraine and 50 synthetic healthy datasets us-

TABLE IV: Sensory Brain Regions with Significant Differences Between Treatment and Sham Groups Pre- and Post-Intervention

Brain Region (BA)	**Side**	**Variable**	**Group**	**Pre (Mean ± SD)**	**Post (Mean ± SD)**	**Effect Size Between group (η^2 / ε^2)**	Effect size Whitin grop (d / r)
S1 (BA 1)	**left**	Z- state	sham	5.46 ± 1.74	6.63 ± 1.68*	η2=0.11	d= 0.68
			treatment	5.48 ± 2.05	5.30 ± 2.17		d=-0.08
angular gyrus (BA 39)	right	COPE	sham	120.52 ± 137.69	163.64 ±103.18*	ε^2=0.08	r= 0.17
			treatment	87.65 ± 54.11	119.52 ± 77.78		**r** = 0.23
Thalamus	left	**PSC**	sham	0.151 ± 0.10	0.160 ± 0.07	ε^2=0.32	r≈0.05
			treatment	0.086 ± 0.05	0.114 ± 0.06****		r≈0.25

Note. BA = Brodmann Area; S1 = Primary Somatosensory Cortex; Z- statistic (Z-stat; statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). BOLD, blood-oxygen-level dependent; Effect size measures: ε^2 = Epsilon squared with interpretation thresholds: negligible (0.00 < 0.01), weak (0.01 ≤ 0.04), moderate (0.04 ≤ 0.16), relatively strong (0.16 ≤ 0.36), strong (0.36 ≤ 0.64), and very strong (0.64 ≤ 1.00);(Tomczak and Tomczak 2014); η^2 = Partial eta squared with thresholds: small (0.01), medium (0.06), large (0.14); Cohen 2013); d = Cohen's d; r = rank-biserial correlation; Interpretation thresholds: Cohen's d (small = 0.2, medium = 0.5, large = 0.8; (Cohen 2013), rank-biserial correlation (small = 0.11–0.28, medium = 0.28–0.43, large ≥ 0.43; (Vargha and Delaney 2000), Statistical significance between-group differences base line (Intervention vs. Sham) post-treatment (ANCOVA adjusted for baseline or Kru- skal-Wallis test) is indicated by asterisks: $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$.

ing Generative Adversarial Networks (GANs)—a greater number of regions exhibited statistically significant group differences across key neuroimaging parameters:

Z-stat analysis indicated increased activation in the left superior parietal lobule (SPL) in migraine patients compared to controls ($p = 0.003$, Cohen's $d \approx 0.44$), reflecting a medium effect size. In contrast, the angular gyrus showed decreased activation bilaterally: in the right hemisphere ($p = 0.0006$, $d \approx 0.51$; medium effect), and in the left hemisphere ($p = 0.045$, $d \approx 0.29$; small effect). The postcentral gyrus exhibited increased activation in both hemispheres. On the right, this difference was statistically significant ($p = 0.013$, $d \approx 0.37$), indicating a small-to-medium effect size, and on the left ($p = 0.002$, $d \approx 0.46$), corresponding to a medium effect size. Additional increases in activation were observed in the left thalamus ($p = 0.003$, $d \approx 0.45$) and the right primary somatosensory cortex (S1) ($p = 0.011$, $d \approx 0.33$), both representing small-to-medium effect sizes.

Voxel count analysis revealed significant group differences in several sensory regions. The supramarginal gyrus showed reduced voxel counts bilaterally in migraine patients compared to healthy controls: right hemisphere ($p = 0.02$, Cohen's $d \approx 0.34$) and left hemisphere ($p = 0.0024$, $d \approx 0.46$), corresponding to small-to-medium effect sizes. An increase in voxel count was observed in the left superior parietal lobule (SPL; $p = 0.02$, $d \approx 0.35$), also indicating a small-to-medium effect. The angular gyrus demonstrated bilateral reductions in voxel counts: right ($p = 0.001$, $d \approx 0.48$) and left ($p = 0.009$, $d \approx 0.45$), with medium effect sizes. A significant increase was noted in the left thalamus ($p = 5.05 \times 10^{-8}$, $d \approx 0.55$), reflecting a medium-to-large effect size.

In the COPE analysis, the angular gyrus again showed reduced values bilaterally: right ($p = 0.04$, $r \approx 0.23$) and left ($p = 0.02$, $r \approx 0.21$), corresponding to small-to-medium effect sizes. In contrast, increases were observed in the left postcentral gyrus ($p = 0.01$, $r \approx 0.25$) and the right primary somatosensory cortex (S1; $p = 0.047$, $r \approx 0.29$), both reflecting medium effect sizes.

PSC analysis revealed increased activation in the right SPL ($p = 0.009$, $r = 0.24$) and decreased activation in the left SPL ($p = 0.009$, $r = 0.24$), both showing small-to-medium effect sizes. A slight increase was detected in the left angular gyrus ($p = 0.05$, $r = 0.20$; small effect size). Decreases were observed in the left postcentral gyrus ($p = 0.006$, $r = 0.28$) and right thalamus ($p = 0.048$, $r = 0.20$), with medium and small-to-medium effect sizes, respectively. The left S1 displayed a significant increase in activity ($p = 0.01$, $r = 0.25$), consistent with a medium

TABLE V: Sensory Brain Regions with Significant Differences Between Healthy Controls and Migraine Patients (Treatment and Sham Combined) (Augmented):

score	side	Variable	Healthy Group (Mean ± SD)	Migraineur Group (Mean ± SD)	d/ r
Z-state	Left	SPL BA 7	3.595 ± 1.057	4.421 ± 1.639***	d≈0.437
	Right	Angular Gy BA 39	3.839 ± 0.905	2.94 ± 1.529****	d≈0.513
	Left	Angular Gy BA 39	3.476 ± 1.044	3.047 ± 1.198*	d≈ 0.287
	Right	post central Gy BA 5	2.456 ± 1.46	3.4 ± 2.158**	d≈0.369
	Left	post central Gy BA 5	2.655 ± 1.241	3.152 ± 1.587***	d≈ 0.457
	Left	Thalamus	4.237 ± 1.462	5.016 ± 1.671***	d≈ **0.447**
	Right	S1 BA 1	5.159 ± 1.669	5.474 ± 2.391***	d≈ 0.328
Voxel count	Right	Supramarginal G BA 40	79.302 ± 11.809	74.384 ± 8.565**	d≈ 0.336
	Left	Supramarginal Gy BA 40	80.599 ± 10.998	79.128 ± 7.176***	d≈0.460
	Left	SPL BA 7	172.302 ± 18.757	182.154 ± 27.802**	d≈ 0.346
	Right	Angular Gy BA 39	48.503 ± 8.11	42.385 ± 9.802***	**d≈ 0.482**
	Left	Angular G BA 39	48.196 ± 7.989	46.999 ± 6.508***	d≈0.445
	Left	Thalamus	166.298 ± 13.553	168.769 ± 14.161****	d≈550
COPE	right	Angular Gy BA 39	110.196 ± 45.544	101.982 ± 100.898*	r≈0.233
	Left	Angular Gy BA 39	110.196 ± 45.544	101.982 ± 100.898*	r≈0.205
	Left	post central Gy BA 5	90.064 ± 60.741	154.997 ± 139.153**	r≈0.250
	right	S1 BA 1	234.302 ± 192.69	309.014 ± 237.366***	r≈0.288
PSC	right	SPL BA 7	0.028 ± 0.012	0.059 ± 0.126**	r=0.239
	left	SPL BA 7	0.059 ± 0.051	0.046 ± 0.087***	r=0.247
	left	Angular Gy BA 39	0.023 ± 0.025	0.033 ± 0.038*	r=0.197
	left	post central Gy BA 5	0.084 ± 0.148	0.03 ± 0.045***	r=0.275
	right	Thalamus	0.142 ± 0.044	0.132 ± 0.093*	r=200
	left	S1 BA 1	0.03 ± 0.021	0.049 ± 0.067**	r=0.247

Note. Z- statistic (Z-stat; statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). BOLD, blood-oxygen-level dependent; SD: standard deviation; BA: Brodmann Area; Gy: Gyrus; S1: primary somatosensory area Effect size measures: d = Cohen's d; r = rank-biserial correlation; Interpretation thresholds: Cohen's d (small = 0.2, medium = 0.5, large = 0.8; (Cohen 2013), rank-biserial correlation (small = 0.11–0.28, medium = 0.28–0.43, large ≥ 0.43; (Vargha and Delaney 2000), Statistical significance between independent groups Augmented (Healthy Controls vs. Migraine Patients, combining Treatment and Sham groups) was determined using independent t-tests or Wilcoxon tests and is indicated by asterisks.: $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$.

effect size. These findings are summarized in Table V.

Comparison Between Treatment and Sham Groups (Augmented): (Tables VI and VII)

The effects of the intervention were evaluated across key sensory brain regions, comparing sham and mobilization groups before and after treatment (Table VI).

Z-stat analysis: The right angular gyrus (BA 39) showed baseline similarity between sham (2.89 ± 1.86) and treatment groups (2.99 ±1.209). Post-intervention,

TABLE VI: Sensory Brain Regions with Significant Differences Between Treatment and Sham Groups Pre- and Post-Intervention (Augmented).

Brain Region (BA)	Side	Variable	Group	Pre (Mean ± SD)	Post (Mean ± SD)	Effect Size Between group (η^2 / ε^2)	Effect size Whitin grop (d / r)
Angular Gyrus (BA 39)	Right	Z- state	Sham	2.88 ± 1.86	4.30 ± 1.02 **	$\eta^2 = 0.07$	d = 0.95
			Treatment	2.99 ± 1.21	3.55 ± 1.66		d = 0.38
Primary Somatosensory Cortex (BA 1)	Right	Z-state	Sham	5.83 ± 2.58	6.66 ± 1.55**	$\eta^2 \approx 0.01$	d = 0.39
			Treatment	5.20 ± 2.19	5.37 ± 2.09		d = 0.08
Supramarginal Gyrus (BA 40)	Right	Voxel Count	Sham	75.24 ± 7.87	80.65 ± 8.22 *****	$\eta^2 \approx 0.21$	d = 0.67
			Treatment	73.72 ± 9.00	72.54 ± 6.79		r = –0.15
Supramarginal Gyrus (BA 40)	left	Voxel Count	Sham	78.41 ± 8.1	79.681 ± 6.311	$\eta^2 \approx 0.105$	d=0.24
			Treatment	79.10 ± 5.10	74.86 ± 9.38****		d = -0.60
Angular Gy BA 39	right	COPE	Sham	120.53 ± 137.68	163.64 ± 103.18 ***	$\varepsilon^2 \approx 0.09$	r ≈0.28
			Treatment	87.66 ± 54.11	119.52 ± 77.78		r≈ 0.35
Angular Gy BA 39	left	PSC	Sham	0.02 ± 0.02	0.07 ± 0.07 ***	$\varepsilon^2 \approx 0.09$	r= 0.39
			Treatment	0.04 ± 0.04	0.07 ± 0.10		r=0.41
SPL BA 7	right	PSC	Sham	0.04 ± 0.052	0.062 ± 0.053	$\varepsilon^2 \approx 0.08$	r=0.41
			Treatment	0.078 ± 0.157	0.058 ± 0.067		r = –0.18
Thalamus	right	PSC	Sham	0.123 ± 0.63	0.0.169 ± 0.073	$\varepsilon^2 \approx 0.06$	r= 0.35
			Treatment	0.136 ± 0.109	0.174 ± 0.12		r = 0.31

Note. BA: Brodmann Area; SPL: Superior Parietal Lobule; S1: Primary Somatosensory Cortex; Gy: Gyrus; Z- statistic (Z-stat; statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). BOLD, blood-oxygen-level dependent; Effect size measures: ε^2 = Epsilon squared with interpretation thresholds: negligible (0.00 <0.01), weak (0.01 ≤ 0.04), moderate (0.04 ≤ 0.16), relatively strong (0.16 ≤ 0.36), strong (0.36 ≤ 0.64), and very strong (0.64 ≤1.00); (Tomczak and Tomczak 2014); η^2 = Partial eta squared with thresholds: small (0.01), medium (0.06), large (0.14); Cohen 2013); d = Cohen's d; r = rank-biserial correlation; Interpretation thresholds: Cohen's d (small = 0.2, medium = 0.5, large = 0.8; (Cohen 2013), rank-biserial correlation (small = 0.11–0.28, medium = 0.28–0.43, large ≥ 0.43; (Vargha and Delaney 2000), Statistical significance be- tween-group Augmented differences (Intervention vs. Sham) post-treatment (ANCOVA adjusted for baseline or Kruskal-Wallis test) is indi- cated by asterisks: $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$

the sham group exhibited a significant increase in activation (4.3±1.022) with a large within-group effect size (d = 0.95). The treatment group also increased (3.6± 1.658) but with a smaller effect size (d = 0.38). The between-group effect size was moderate ($\eta^2 = 0.07$). The therapeutic effect of cervical mobilization in these patients and the correlation between changes in the Z-stat of right angular gyrus and the Migraine pain was Pearson's r ≈ –0.06 means: There is no significant correlation between change in right BA39 activity and change in VAS pain in treatment group.

In the right primary somatosensory cortex (S1), baseline values were 5.83 ± 2.58 (sham) and 5.20 ± 2.19 (treatment). Following intervention, the sham group worsened (6.66 ± 1.55, d = 0.39), indicating a small to medium negative change, while the treatment group remained nearly stable (5.37 ± 2.09, d = 0.08). The between-group effect size was small to medium ($\eta^2 \approx 0.096$). The Pearson correlation between the change in right S1 activation and pain reduction in the mobilization group is: positive correlation (r = 0.69) means: Greater increases in S1 activation are associated with smaller reductions—or even increases—in pain.

Voxel Count Analysis: In the right supramarginal gyrus (Brodmann area 40), baseline voxel counts were comparable between groups (sham: 75.24 ± 7.87; treatment: 73.72 ± 9.01). Post-intervention, the sham group demonstrated a significant increase (80.65 ± 8.22), corresponding to a medium-to-large within-group effect size (Cohen's d ≈ 0.67). In contrast, the treatment group

TABLE VII: Correlations between pain reduction and parameter changes in sensory brain regions

Parameter	side	Brain Region	Correlation (r / ρ)	Interpretation
z-state	right	primary somatosensory cortex	r = 0.69	moderately strong, positive correlation
z-state	right	angular Gyrus	r ≈ –0.06	minimal, no significant. negative correlation
voxel count	right	supramarginal Gyrus	r ≈ -0.17	small, no significant. negative correlation
voxel count	left	supramarginal Gyrus	r ≈ –0.15	small, no significant negative correlation
COPE	right	angular Gyrus	ρ ≈ –0.35	Moderate, negative correlation
PSC	left	angular Gyrus	ρ ≈ -0.31	small to moderate, negative correlation
PSC	right	superior parietal lobule	ρ ≈ 0.30	small to moderate, positive correlation
PSC	right	thalamus	ρ ≈ –0.36	moderate, negative correlation

Note. Z- statistic (Z-stat; statistical strength of brain activation relative to background noise), percent signal change (PSC; percentage change in regional BOLD signal relative to baseline), voxel count (activation volume), and contrast of parameter estimates (COPE; amplitude of the trigeminal pain–related BOLD response). BOLD, blood-oxygen-level dependent; r: Pearson Correlation (r); ρ: Spearman's correlation (ρ); For both Spearman and Pearson correlation coefficients, values near 0.00 indicate a negligible association; approximately ±0.10 indicate a weak association; ±0.38 to ±0.40 indicate a moderate association; ±0.68 to ±0.70 indicate a strong association; and ±0.89 to ±0.90 indicate a very strong association. The sign of the coefficient indicates the direction of the relationship (positive or negative). These interpretations thresh- olds are applied consistently for comparative purposes (dapted from Cohen 2013).

A positive correlation indicates that greater increases are associated with smaller reductions in pain—or even increases in pain. A negative correlation indicates that greater increases are associated with greater reductions in pain—or even decreases in pain.

Positive correlation = greater increases associated with smaller pain reduction or increased pain; Negative correlation = greater increases associated with greater pain reduction or decreased pain.

exhibited a slight decrease (72.54 ± 6.79, d ≈ –0.15). The between-group effect size was large (partial eta squared, $\eta^2 \approx 0.209$). A small and likely non-significant negative correlation was observed between changes in voxel count and pain reduction in the treatment group (Pearson's r ≈ –0.17), indicating limited therapeutic relevance.

For the left supramarginal gyrus, baseline values were similarly matched (sham: 78.41 ± 8.10; treatment: 79.68 ± 6.31). Following the intervention, the sham group showed a minor increase (79.99 ± 5.10, d = 0.24), while the treatment group exhibited a more notable decrease (74.86 ± 9.38, d ≈ –0.60). The between-group effect size was medium to large ($\eta^2 \approx 0.105$). Correlation between voxel change and pain reduction in the treatment group was again small and likely non-significant (r ≈ –0.15), suggesting limited clinical association.

COPE analysis: COPE in the right angular gyrus showed considerable variability at baseline (sham: 120.53 ± 137.68; treatment: 87.66 ± 54.11). Post-intervention, both groups improved (sham: 163.64 ± 103.18, r ≈ 0.28; treatment: 119.52 ± 77.78, r ≈ 0.35). The between-group effect size was small to medium (epsilon squared, $\varepsilon^2 \approx 0.093$), with slightly greater gains observed in the sham group. A moderate negative Spearman correlation (ρ ≈ –0.35) between COPE change and pain reduction suggests that increased participation may be modestly associated with greater pain relief.

percent signal change (PSC; percentage change in regional BOLD signal relative to baseline) analysis: In the left angular gyrus, PSC increased significantly in the sham group (from 0.02 ± 0.02 to 0.07 ± 0.07), with a very large within-group effect (r ≈ 0.39). The treatment group also demonstrated an increase (from 0.040 ± 0.041 to 0.07 ± 0.109), although the effect size was moderate (r ≈ 0.41). The between-group effect was small to moderate ($\varepsilon^2 \approx 0.0903$). Spearman correlation analysis revealed a moderate negative association between PSC increase and pain reduction (ρ ≈ –0.35), suggesting that larger PSC increases were associated with pain relief. In the right superior parietal lobule (rSPL), PSC decreased in the treatment group (from 0.078 ± 0.157 to 0.058 ± 0.067), which may reflect therapeutic benefit due to reduction in hyperactivity. Conversely, the sham group exhibited an increase (from 0.040 ± 0.052 to 0.062 ± 0.053). Between-group effect size was small to moderate ($\varepsilon^2 \approx 0.0835$). Within-group analyses indicated moderate worsening in the sham group (r ≈ 0.41) and a small improvement in the treatment group (r ≈ –0.18). A weak-to-moderate positive correlation between PSC reduction and pain relief was observed (ρ ≈ 0.30), suggesting that decreased rSPL activation was modestly associated with improved clinical outcomes.

Thalamic Activation: Baseline PSC values in the right thalamus were similar across groups (sham: 0.123 ± 0.063; treatment: 0.136 ± 0.109). Post-intervention increases were observed in both groups (sham: 0.169 ± 0.073; treatment: 0.174 ± 0.120), with small to medium within-group effect sizes (sham: $r \approx 0.35$; treatment: $r \approx 0.31$) and a small to moderate between-group effect ($\varepsilon^2 \approx 0.0629$). Given the thalamic hypoactivity often reported in migraine, these findings suggest functional improvement. A moderate negative Spearman correlation ($\rho \approx -0.36$) between PSC change and pain reduction indicates that larger increases in thalamic activity were associated with greater symptom improvement. Tables VI and VII.

Correlation Between Brain Activation and Pain Reduction : (Tables VII)

A detailed correlation analysis was conducted to examine the relationship between changes in migraine pain intensity (measured by the Visual Analog Scale, VAS) and alterations in functional parameters across sensory-related brain regions. In the present study, pain change was defined as [Ppost – Ppre]. Therefore, a positive correlation indicates that greater increases in the variable of interest were associated with smaller pain reduction or increased pain. As shown in Table VII (p. 48, lines 1–22), several region-specific associations were observed. A moderate negative correlation was found between changes in the COPE value of the right angular gyrus and pain reduction ($\rho \approx -0.35$), as well as between the PSC in the right thalamus ($\rho \approx -0.36$). Conversely, a moderately strong positive correlation emerged in the Z-stat of the right primary somatosensory cortex ($r = 0.69$), and a small-to-moderate positive association was observed in the PSC value of the right superior parietal lobule ($\rho \approx 0.30$).

positive correlation indicates that greater increases [in brain activity] are associated with smaller reductions in pain—or even increases in pain.

A negative correlation indicates that greater increases [in brain activity] are associated with greater reductions in pain—or even decreases in pain.”

Discussion

According to the results of this study, the fMRI analysis in sensory brain regions in migraineurs in the interictal phase, had significant changes compared to healthy controls. This study revealed distinct neurofunctional alterations in migraineurs compared to healthy controls across multiple sensory and associative cortical regions, corroborating prior literature on migraine-related brain changes.

Migraine vs. Healthy Controls

The observed increase in activation of the left SPL (Z-stat and voxel count) supports previous findings that highlight its involvement in spatial attention and sensorimotor integration abnormalities in migraine (Masson 2020). Such hyperactivation may represent compensatory mechanisms or maladaptive plasticity related to migraine pathophysiology. Conversely, decreases in the angular gyrus bilaterally, with a medium effect size noted in the right hemisphere, align with studies reporting altered multisensory integration and disrupted default mode network connectivity in migraineurs (Coppola et al., 2016; Dong et al., 2023). The angular gyrus plays a critical role in integrating sensory inputs, and reduced activation here might contribute to sensory processing deficits observed in migraine. Increases in the postcentral gyrus and S1 indicate enhanced somatosensory cortical activity, consistent with the sensory hypersensitivity and altered nociceptive processing documented in migraine (Boran et al., 2021; Maleki et al., 2011). The small-to-medium effect sizes suggest these are subtle but reliable changes. The significant increase in voxel counts and activation within the left thalamus highlights its central role as a relay station in pain processing and migraine chronification (Chen et al., 2022; Cummings 2025). The medium-to-large effect size for thalamic voxel increases may indicate heightened thalamocortical activity, aligning with prior neuroimaging studies showing altered thalamic function in migraineurs (Jin et al., 2013). COPE parameter decreases in the angular gyrus but increases in the postcentral gyrus and right S1 may reflect complex reorganization within sensorimotor networks, possibly indicating decreased network efficiency in associative areas alongside compensatory increases in primary sensory regions (Kaniewska et al., 2024). The PSC results, showing increased right SPL activity and decreased left SPL activity, suggest lateralized functional alterations, which may relate to the asymmetric clinical presentation of migraine symptoms. The decreased PSC in the left postcentral gyrus and right thalamus further supports dysfunction within key sensory processing nodes. These findings echo previous reports of altered thalamic and somatosensory cortex excitability in migraine patients (Schwedt et al., 2015). Overall, the pattern of increased activity in sensory cortices and thalamus combined with decreased activation in associative regions such as the angular gyrus suggests a dysregulated balance between sensory input and higher-order integration in migraine. These alterations may underlie the sensory disturbances and impaired pain modulation characteristic of the disorder. Further longitudinal studies are warranted to determine whether these neurofunctional changes predict treatment response or migraine progression.

This study demonstrated region - and parameter-specific neural changes following sham and mobilization interventions in migraine patients, with implications for sensory processing and pain modulation. in migraineurs, mobilization of the upper cervical spine and sham treatment reduced pain intensity with very large and larg effect size respectively.

Brain Region Changes Following Intervention

In the right angular gyrus, both the mobilization and sham groups exhibited significant increases in Z-stat. This region implicated in attentional and sensory integration processes (Seghier 2013) .Notably, the sham group demonstrated a larger effect, suggesting that expectancy and non-specific procedural factors may play a substantial role in modulating neural activity. While the mobilization group showed a smaller effect size, this may reflect a more specific but subtler neurophysiological mechanism. These findings highlight the importance of robust control conditions and the potential influence of contextual and placebo-related factors on cortical activation (Barceló and Cooper 2018; Bishop et al., 2015). The pronounced responsiveness of the right angular gyrus may relate to its integrative cognitive role. Although changes in brain activity were not strongly correlated with pain reduction, the direction of effect in the mobilization group may indicate early-stage neuroplastic adaptations. This suggests that even minimal cortical engagement, as seen with manual therapy techniques, may contribute to neural stabilization and prevent clinical decline, despite limited immediate symptomatic relief.

In the primary somatosensory cortex (S1), previous research using fMRI has demonstrated increased excitability in individuals with migraine (Meylakh and Henderson 2022). In the present study, the sham group exhibited increased S1 activation, which may reflect natural disease progression in the absence of active intervention. Conversely, the mobilization group showed relative stability in S1 activation alongside a significant reduction in pain, suggesting a potential stabilizing or protective effect of mobilization therapy on cortical excitability. This finding aligns with the therapeutic hypothesis that maintaining or reducing S1 excitability may help prevent central sensitization and modulate pain perception. Although the between-group effect size was modest, the clinical implication is notable—mobilization appeared to prevent the exacerbation observed in the control condition. These results support previous findings that manual therapies, while not always producing immediate or dramatic symptom relief, may effectively attenuate disease progression over time (Carnes et al., 2010). Furthermore, a significant positive correlation was observed between increased right S1 activation and pain. Greater increases in this variable were associated with increased pain. Overall, these findings underscore the importance of targeting central neural mechanisms, particularly S1 hyperexcitability, in the management of migraine. Future research with larger sample sizes and extended follow-up periods is warranted to further elucidate and confirm these effects.

In the left and right supramarginal gyrus (BA 40), migraine patients exhibited reduced voxel activation when compared to healthy controls during trigeminal pain stimulation. In the right SMG, migraine patients showed lower activity relative to controls, with an effect size of $d \approx 0.34$. Similarly, in the left SMG, activation was lower in the migraine group compared to controls, with a slightly larger effect size of $d \approx 0.46$. These findings suggest that individuals with migraine may exhibit baseline hypoactivation in the supramarginal gyrus during pain-related processing. Given the SMG's known roles in proprioceptive integration, multisensory processing, and attentional reorientation to noxious stimuli, this reduction may reflect altered cortical responsiveness to somatosensory input, potentially contributing to the aberrant sensory perception and body awareness frequently reported in migraine(Nguyen et al., 2024; Singh et al., 2018). The slightly greater reduction in the left hemisphere may be functionally relevant, particularly in right-handed individuals, where the left SMG plays a dominant role in sensory integration and higher-order cognitive modulation. This asymmetry could reflect a hemispheric imbalance in sensory processing networks that predisposes migraineurs to inefficient or distorted interpretation of somatic and pain-related stimuli(de Tommaso et al., 2014). These pre-treatment findings support the idea that migraine is associated with functional alterations in cortical regions involved in pain and body representation, even before therapeutic intervention, highlighting the supramarginal gyrus as a potential target for neuromodulatory approaches.

In the left SMG, following mobilization therapy, voxel activation significantly decreased ($d = –0.60$), while the sham group showed a slight increase ($d = 0.24$), with a between-group effect size of $\eta^2 \approx 0.105$. This reduction in the intervention group, despite marked clinical pain improvement, suggests a normalization of cortical activity. The left SMG is strongly associated with proprioceptive integration and sensory awareness, particularly in right-handed individuals. Reduced activation may reflect restored efficiency in sensory processing circuits no longer burdened by chronic pain signaling. Although the correlation with pain reduction was small ($r \approx –0.15$), the directionality supports the hypothesis of functional downregulation following therapeutic benefit.

In the right SMG, voxel activation increased in the sham group ($d = 0.67$), but slightly decreased in the mobilization group ($d= –0.15$), with a moderate between-group effect size of $\eta^2 \approx 0.21$. The right SMG is involved in multisensory integration and attentional aspects of pain, and its decreased activation post-treatment may similarly indicate a reduced need for compensatory neural engagement. Again, correlation with pain reduction was small ($r\approx –0.17$), but directionally consistent with reduced cortical overactivation in chronic pain. Together, these findings suggest that mobilization therapy contributes to a hemisphere-specific normalization of supramarginal gyrus activity, reflecting more efficient sensory processing mechanisms aligned with clinical improvements.

In the left SMG, the observed reduction in voxel activation may reflect a therapeutic downregulation of hyperactive sensory-processing networks. This likely represents a normalization of function following pain relief, rather than a loss of function, indicating the brain's reduced need for compensatory activation in proprioceptive and attentional pain circuits.

The right angular gyrus is a region critically involved in multisensory integration, spatial awareness, and attentional regulation (Cai et al., 2023). In the present study, both the cervical mobilization and sham intervention groups demonstrated post-treatment improvements in COPE value within the right angular gyrus. The mobilization group exhibited a moderate within-group effect size ($r \approx 0.35$), while the sham group also showed improvement, albeit with a slightly smaller effect ($r \approx 0.28$). The between-group effect size ($\varepsilon^2 \approx 0.093$) modestly favored the sham condition; however, this difference may reflect non-specific therapeutic factors, including expectancy effects, patient–therapist interaction, and contextual cues, as highlighted in prior research (Dugard et al., 2022; Huneke et al., 2025; Lavazza et al., 2021). Enhancements in COPE value within the right angular gyrus (BA 39) may reflect increased neural stability during resting-state conditions, which could be associated with improved attentional control, body schema coherence, and sensorimotor integration—all of which are frequently disrupted in individuals with migraine (Chen et al., 2024; Maleki et al., 2011). Notably, a moderate inverse correlation between COPE increases and pain intensity reduction ($\rho \approx –0.35$) suggests that stabilization in this cortical region may contribute meaningfully to clinical symptom relief. Furthermore, improvements in COPE value in the right angular gyrus observed post-intervention are consistent with previous reports linking this region to proprioceptive processing, spatial attention, and the modulation of migraine-related cortical responses (Seghier 2013; Szabó et al., 2019). While both interventions led to beneficial neural adaptations, the presence of moderate effect sizes and COPE enhancement in the mobilization group supports the hypothesis that upper cervical mobilization may indirectly influence pain perception through modulation of higher-order sensory processing networks (Bishop et al., 2015). These findings underscore the potential therapeutic value of cervical mobilization for addressing sensory disturbances associated with migraine. However, future research is warranted to explore the long-term durability of these effects and to further differentiate specific neurophysiological mechanisms from contextual and placebo-related influences.

*In the left angular gyrus (BA 39), at baseline, migraine patients exhibited greater percent signal change (PSC) compared to healthy controls, with a small effect size.

This suggests subtle hyperactivation in this region, consistent with prior research implicating the angular gyrus in multisensory integration, spatial processing, and pain modulation (Long et al., 2022; Lu et al., 2024). Such findings are often interpreted as markers of maladaptive plasticity or compensatory activation in chronic pain conditions. The angular gyrus plays a key role in spatial attention, sensory integration, and pain modulation, and such hyperactivity may signify either compensatory adaptation or inefficient cortical inhibition (Seghier 2013). Following intervention, both the sham and mobilization groups demonstrated increased PSC in the left angular gyrus. The between-group effect size was $\varepsilon^2 \approx 0.0903$, reflecting a small-to-moderate difference. Within-group analyses revealed moderate-to-large effect sizes in both groups, with $r \approx 0.39$ in the sham group and $r \approx 0.41$ in the treatment group, suggesting substantial neural changes over time in each condition. The greater effect observed in the sham group may be attributable to non-specific contextual factors such as expectancy, placebo responses, attention shifts, or scanner habituation(Dugard et al., 2022; Lavazza et al., 2021). The treatment group's change may reflect a more targeted neuromodulatory effect. Importantly, in the treatment group, a small-to-moderate negative correlation ($\rho \approx -0.31$) was found between PSC change and pain reduction, suggesting that decreased activation in the left angular gyrus may contribute to clinical improvement. This supports the hypothesis that therapeutic benefit may be mediated by normalization of cortical hyperactivity, rather than broad increases in activation. These findings emphasize the importance of including rigorous control conditions in neuroimaging studies, particularly when interpreting intervention effects. Given the non-parametric nature of the PSC data and the observed variability, future research should employ larger samples, improved blinding, and expectancy measurement to clarify specific versus contextual effects. Importantly, a negative correlation between PSC change and pain reduction in the treatment group ($\rho \approx -0.31$) suggests that greater decreases in PSC were associated with greater pain relief. This implies that downregulation of neural activity in the left angular gyrus may represent a therapeutically relevant normalization of previously dysregulated neural processing, potentially reflecting improved integration of sensory, cognitive, and affective information associated with pain perception. In sum, these findings provide preliminary evidence that upper cervical mobilization may exert its effects, in part, through functional modulation of the angular gyrus, a hub implicated in pain and sensory integration. Future studies should aim to isolate specific treatment effects by incorporating expectancy measures, improved experimental blinding, and larger samples, and by tracking the long-term stability of these neural changes.

In the right superior parietal lobule (rSPL), following intervention, a reduction in PSC was observed in the treatment group, suggesting a therapeutic effect through modulation of cortical hyperactivity. In contrast, the sham group exhibited an increase in PSC, potentially indicating a lack of clinical benefit. These changes are consistent with prior evidence showing elevated rSPL activity in individuals with migraine, particularly during rest and pain-related processing tasks (Meylakh 2019; Tessitore et al., 2013).The between-group effect size was small to moderate ($\varepsilon^2 \approx 0.08$), reflecting some differential neural response to the intervention. Within-group analysis revealed a small decrease in the treatment group ($r = -0.18$)—interpreted as a modest improvement—and a moderate increase in the sham group ($r=0.41$), suggesting progression or lack of suppression of cortical excitability. These findings align with previous literature suggesting that non-pharmacologic interventions, such as manual therapy, may exert neuromodulatory effects on cortical regions implicated in pain integration, somatosensory processing, and spatial attention. The reduction in rSPL activity in the treatment group may represent normalization toward patterns observed in healthy controls. Importantly, both reductions in PSC and pain intensity reflect improvement, supporting the hypothesis that neuromodulatory effects on parietal cortical regions may contribute to clinical benefit (Erker et al., 2024). The direction of change in PSC and correlation with pain reduction underscores that: PSC in rSPL has the potential value as a functional imaging biomarker. These findings align with theoretical models of central sensitization, where decreased activity in hyperexcitable cortical areas is associated with symptom resolution (Schwedt et al., 2014; Woolf 2011). Critically, a small to moderate, negative correlation was found between reductions in rSPL PSC and pain relief ($\rho \approx 0.30$). Given that pain reduction was represented by negative change values, this correlation implies that greater decreases in rSPL activation were strongly associated with greater reductions in pain intensity. The right SPL findings further support this, where decreased hyperactivity post-treatment aligns with improved clinical status.

A key observation in the present study was the post-intervention increase in PSC within the right thalamus in both the treatment and sham groups. Although the within-group effect sizes were small to moderate (treatment group r ≈ 0.31; sham group r ≈ 0.35), these findings may reflect alterations in thalamic nociceptive processing. In migraine populations, thalamic hypoactivity is commonly reported during interictal phases, potentially representing adaptive downregulation or sensory desensitization mechanisms (Younis et al., 2017; Chen et al., 2022; Zhe et al., 2023). The observed increases in BSC post-intervention may therefore suggest either a restorative normalization of thalamic function or a disruption of maladaptive compensatory processes. Considering the thalamus's central role within the trigeminothalamocortical system, its modulation may be a neural substrate through which upper cervical mobilization exerts effects on trigeminal pain processing (Cao et al., 2022). Despite this, the between-group effect size was modest ($\varepsilon^2 \approx 0.0629$), and the lack of clear superiority in the treatment group raises the possibility that non-specific factors (e.g., expectancy, attentional modulation, contextual care) contributed to the observed effects. Nevertheless, prior imaging studies have documented partial reversal of thalamic hypoactivity following effective migraine interventions, supporting the potential clinical significance of such neural changes (Coppola et al., 2016).Importantly, a moderate negative correlation (ρ ≈ –0.36) was found between thalamic BSC increases and pain reduction, indicating that greater thalamic engagement was associated with greater symptom relief. These results underscore the potential relevance of thalamic activation as a neurobiological marker of treatment response. However, further longitudinal studies incorporating nucleus-specific thalamic analyses are warranted to clarify the mechanistic and clinical implications of these findings.

The observed correlations between regional brain function and changes in migraine pain provide valuable insights into the potential neural mechanisms underlying the therapeutic effects of cervical mobilization.

Pain Reduction and Brain Changes

As shown in Table VII (p. 48), moderate negative associations in the right angular gyrus (ρ ≈ –0.36) and right thalamus (ρ ≈ –0.35) indicate that reduced pain intensity was related to increased functional engagement or hemodynamic response in these areas. In contrast, a strong positive correlation in the right primary somatosensory cortex (r = 0.69) suggests that greater increases in activation were associated with less pain reduction, potentially indicating maladaptive sensory processing or heightened pain perception.These findings align with current models of sensory network dysfunction in migraine and emphasize the importance of thalamocortical and parietal lobe pathways in pain modulation. Future studies should further explore these correlations to determine causal relationships and potential targets for non-pharmacological interventions

Despite being designed as a control, the sham intervention produced measurable changes across several outcomes, including pain reduction, brain activity (e.g., percent signal change (PSC), amplitud od activity (COPE)). These findings may reflect non-specific treatment effects, such as: Placebo responses driven by participant expectations, therapist-patient interaction and therapeutic context, attention, touch, or engagement effects, which can influence subjective and neurophysiological outcomes, natural variability or spontaneous symptom fluctuations. In some measures (e.g., voxel count or COPE in the right angular gyrus), the sham group even outperformed the treatment group. While this may seem counterintuitive, it aligns with prior literature reporting strong placebo effects in pain-related and neuroimaging studies, particularly when interventions are applied in a structured, clinical environment. These findings emphasize the importance of rigorous control conditions in clinical neuroscience trials and suggest that contextual and psychological factors can play a significant role in modulating both perceived symptoms and brain function.

Collectively, the findings from analyses underscored the capacity of upper cervical mobilization to elicit significant changes in both hemispheres, especially within sensory-related brain areas. These alterations lend support to the notion that this therapeutic approach may effectively modulate sensory processing pathways, thereby contributing to alleviation of symptoms in individuals with migraines. These regions include the right supramarginal gyrus (BA 40), right angular gyrus (BA 39), right primary sensory cortex (BA 1), as well as the left superior parietal lobule (BA 7) and left thalamus. The changes observed in these areas indicate that, despite the limitations of a 1.5T MRI, upper cervical mobilization was capable of eliciting measurable alterations in functional activity and sensory integration across both hemispheres of the brain. While future investigations utilizing higher-field MRI may yield a more comprehensive understanding of these effects, the current evidence strongly indicates that this intervention may be beneficial for improving sensory integration and reducing cortical hyperexcitability in patients with migraines. Subsequent research should investigate the direct effects of cervical mobilization on sensory activation patterns and assess its clinical efficacy in alleviating migraine symptoms by reinstating normal sensory processing

Conclusion

The observed reduction in migraine-related pain following upper cervical spine mobilization appears to be associated with neurofunctional changes in key brain regions. Pain relief was correlated with decreased medium Z-stat in the right primary somatosensory cortex (S1) and reduced percent signal chang (PSC) in the right superior parietal lobule (rSPL), with correlations ranging from moderate to strong. Additional associations were observed between pain reduction and increased PSC in the right thalamus as well as enhanced amplitud of activity (COPE) in the right angular gyrus. A smaller correlation was also noted between PSC increase in the left angular gyrus and pain reduction. These findings suggest that upper cervical mobilization may influence cortical and subcortical regions involved in pain processing, sensorimotor integration, and attentional control. The observed responses in the sham group likely reflect contextual, attentional, or placebo-related mechanisms, underscoring the importance of using rigorous control conditions in studies investigating manual therapy effects.

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Conflict of interests

The authors declare that they have no conflict of interests.

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Data availability

Data are available under reasonable request to the corresponding author

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