



Structural alterations of the brainstem in migraine

Catherine D. Chong^{a,*}, Jonathan D. Plasencia^b, David H. Frakes^{b,c}, Todd J. Schwedt^a



^aMayo Clinic-Arizona, Department of Neurology, Phoenix, AZ, USA

^bArizona State University, School of Biological and Health Systems Engineering, Tempe, AZ, USA

^cArizona State University, School of Electrical, Computer and Energy Engineering, Tempe, AZ, USA

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ABSTRACT

Atypical brainstem modulation of pain might contribute to changes in sensory processing typical of migraine. The study objective was to investigate whether migraine is associated with brainstem structural alterations that correlate with this altered pain processing.

MRI T1-weighted images of 55 migraine patients and 58 healthy controls were used to: (1) create deformable mesh models of the brainstem that allow for shape analyses; (2) calculate volumes of the midbrain, pons, medulla and the superior cerebellar peduncles; (3) interrogate correlations between regional brainstem volumes, cutaneous heat pain thresholds, and allodynia symptoms.

Migraineurs had smaller midbrain volumes (healthy controls = 61.28 mm³, SD = 5.89; migraineurs = 58.80 mm³, SD = 6.64; $p = 0.038$), and significant ($p < 0.05$) inward deformations in the ventral midbrain and pons, and outward deformations in the lateral medulla and dorsolateral pons relative to healthy controls. Migraineurs had a *negative* correlation between ASC-12 allodynia symptom severity with midbrain volume ($r = -0.32$; $p = 0.019$) and a *positive* correlation between cutaneous heat pain thresholds with medulla ($r = 0.337$; $p = 0.012$) and cerebellar peduncle volumes ($r = 0.435$; $p = 0.001$).

Migraineurs with greater symptoms of allodynia have smaller midbrain volumes and migraineurs with lower heat pain thresholds have smaller medulla and cerebellar peduncles. The brainstem likely plays a role in altered sensory processing in migraine and brainstem structure might reflect severity of allodynia and hypersensitivity to pain in migraine.

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1. Introduction

Migraine is a common and debilitating neurological disorder associated with hypersensitivities to light, sound, touch and odor. Oftentimes, migraine patients describe that normally non-painful stimuli, such as light touch of the skin, are experienced as painful during a migraine attack, a phenomenon called cutaneous allodynia. Cutaneous allodynia is believed to be related to abnormal modulation of descending pain signals (Bingel and Tracey, 2008; Moulton et al., 2008). Although these hypersensitivities are magnified during the ictal phase of migraine (Bigal et al., 2008; Kelman, 2004; Lipton et al., 2008; Russell et al., 1996; Wober-Bingol et al., 2004) these hypersensitivities can also persist during the interictal phase of migraine (Ashkenazi et al., 2009; Main et al., 1997; Schwedt et al., 2011, 2015), when patients are pain-free. Several studies have shown that migraine patients demonstrate hypersensitivities during the interictal phase including lower thresholds to heat-induced pain (Schwedt et al., 2015), higher sensitivity to touch and light using self-report questionnaires (Chen et al., 2015; Cucchiara et al., 2015; Lovati et al., 2008), and altered functional brain activation

patterns to painful heat stimuli (Chen et al., 2015; Schwedt et al., 2014a, 2015).

The descending pain system of the brainstem has reciprocal connections with cortical regions involved with nociceptive processing. It is believed that brainstem regions might play a pivotal role in the generation and perpetuation of the migraine attack and that dysfunction of these brainstem regions could contribute to migraine-specific hypersensitivities such as allodynia. Several imaging studies using positron emission tomography (PET) showed increased dorsal pons and dorsal rostral brainstem activation in migraine patients during the attack phase (Afridi et al., 2005; Bahra et al., 2001; Weiller et al., 1995; Wober-Bingol et al., 2004) and results from functional magnetic resonance imaging studies (fMRI) showed increased functional connectivity between the periaqueductal gray matter and cortical and subcortical regions involved in nociceptive processing (Mainero et al., 2011; Schwedt et al., 2013). Although these imaging results suggest functional alterations in localized brainstem regions, whether these *functional* alterations underlie *structural* changes in the brainstem anatomy remains unknown.

In a recent volumetric study, Bilgic et al. demonstrated less brainstem volume in chronic migraine patients relative to healthy control subjects (Bilgic et al., 2016). Similarly, results by Jin et al. demonstrate less cerebellar and brainstem density in migraine patients

* Corresponding author at: Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, AZ 85054, United States.

E-mail address: Chong.Catherine@mayo.edu (C.D. Chong).

without aura relative to healthy controls using voxel-based morphometry (Jin et al., 2013). Yet, whether migraine is associated with specific subregional volume alterations of brainstem structures has not yet been interrogated. Until recently, parcellation of brainstem sub-structures could not be achieved using automated brain parcellation algorithms, leaving changes in the structural anatomy of individual brainstem structures in migraine relatively unexplored. The most recent structural pipeline of FreeSurfer 6.0 includes the capability to segment brainstem regions, and shows good performance relative to manual labeling techniques, which are time-consuming and operator-dependent (Iglesias et al., 2015).

This study assesses brainstem (midbrain, pons, medulla, superior cerebellar peduncle) volume differences and alterations in the brainstem shape between migraineurs and healthy controls and interrogates whether morphologic alterations in the brainstem correlate with symptoms of allodynia and heat pain sensitivity in migraine patients.

2. Methods

This study included 55 migraineurs and 58 healthy controls and was approved by the Institutional Review Boards at Mayo Clinic and Washington University School of Medicine in St. Louis. Written informed consent was obtained from all subjects prior to study participation. Migraine patients were recruited through the headache clinic and diagnosed using the International Classification of headache disorders II criteria (ICHD-II) (*The International Classification of Headache Disorders: 2nd edition, 2004*). Migraine patients had no history of neurological disorder other than migraine and were pain-free for at least 24 h prior to their scanning appointment. All migraine patients had migraine for a minimum of 3 years, and did not take migraine preventive medication or opiates for pain control. Healthy controls were community dwelling individuals without chronic pain or headache symptoms and without a history of neurologic disorder. Healthy controls were excluded if they had more than three tension-type headaches per month. Subject demographics are shown in Table 1.

All subjects were evaluated during a single, 2½-hour appointment which included MRI (T1 and T2) scanning, evaluation of cutaneous heat pain thresholds using quantitative sensory testing (QST), and completion of questionnaire data. All subjects completed the state and trait anxiety inventory (STAI, Form Y-1 and Form Y-2) measuring acute and general levels of anxiety (Spielberger et al., 1983), the Beck Depression Inventory II (BDI-II) (Beck et al., 1996) evaluating presence or absence of depression and the Allodynia Symptom Checklist 12 (ASC-12) to assess symptoms of allodynia (Lipton et al., 2008). QST included a standardized protocol using the Medoc pathway system and a 30 mm × 30 mm thermode. The thermode was placed on the subject's medial forearm and subjects were instructed to press a button the moment they felt a change from the sensation of heat to the sensation of

pain. This moment was defined as the 'pain-threshold'. During QST, the thermode was set to slowly warm up (1 °C/s) starting at 32 °C. The heating process was stopped immediately when the subject pressed the button, and the thermode quickly cooled back to the baseline temperature. Pain thresholds were tested three times at the right forearm and three times at the left forearm, and the average of the three measurements at each body location was considered the heat pain threshold at that location. For the purposes of determining correlations between heat pain thresholds and brainstem structure, the heat pain threshold was the average of the right and left forearm measurements.

2.1. Imaging parameters

All imaging was conducted on 3-Tesla Siemens Magnetom scanners using the following sequences: Washington University parameters (scanner I): T1-weighted imaging; TR = 2400 ms; TE = 3.16 ms; flip angle = 8 degrees. T2-weighted imaging; TE = 88 ms, TR = 6280 ms, flip angle = 120 degrees, 1 × 1 × 4 mm³ voxels. Mayo Clinic parameters (scanner II): T1-weighted imaging; TR = 2400 ms; TE = 3.06 ms; TI = flip angle = 8 degrees. T2-weighted imaging; TE = 84 ms, TR = 6800 ms, flip angle = 150 degrees, 1 × 1 × 4 mm³ voxels. Healthy controls: 32 subjects were scanned on scanner I, and 26 subjects were scanned on scanner II. Migraine patients: 32 patients were scanned on scanner I, and 23 patients were scanned on scanner II.

T1 and T2 imaging scans were reviewed and subjects with abnormal findings (i.e., structural abnormalities on MR imaging) were excluded from further analyses.

2.2. Volume analysis

Automated segmentation and volume calculation of the entire brainstem, as well as brainstem subregions was done using FreeSurfer, a freely available automated image analysis software tool with well-established accuracy and reliability for labeling structural anatomy for post-processing neuroimaging data (<http://freesurfer.net>) (Fischl et al., 2001, 2002). The FreeSurfer 6.0 version, which allows for automatic calculation of medulla, pons, midbrain and superior cerebellar peduncle volumes, is based on a probabilistic atlas and a Bayesian segmentation (Iglesias et al., 2015). In order to avoid data irregularities stemming from the use of multiple workstations, all subjects were post-processed on a single Macintosh computer (osX: 10.10.5, Model: MacPro 6.1, Processor: 3.7 Quad-Core Intel Xeon E5, and RAM: 16GB 1866 MHz DDR3 ECC) in accordance with the manual guidelines used by FreeSurfer. Each subject's brain segmentation results were carefully reviewed for errors by a trained technician. Each subject's brainstem volume data was extracted from FreeSurfer, exported in the NIFTI-1 data format, and converted to a TIFF image volume set for importing into Mimics (Materialise, Leuven, Belgium). Within Mimics, the brainstem volume data sets were segmented into a mask and exported as STL surface meshes for further analysis.

Brainstem surface meshes were registered to a single brainstem surface mesh, i.e., a template, using Geomagic Studio (3D Systems, Inc., Rock Hill, South Carolina) via a best-fit alignment function using an iterative closest-point algorithm. This registration algorithm minimizes pair-distances using the least-squares method (<http://support1.geomagic.com/Support/5605/5668/en-US/Article/View/976/How-does-Best-Fit-Alignment-determine-how-the-parts-are-aligned,2016>). Surface analysis of registered surface meshes was performed in 3Matic (Materialise, Leuven, Belgium) wherein subject and template physical space Euclidean surface mesh differences in millimeters were determined using a nearest neighbor technique. The physical space difference measurements were recorded at the corresponding template mesh node coordinates.

Table 1

Subject demographics for migraine patients and healthy controls. f = female, m = male, BDI-II = Beck Depression Inventory (II), STATE/TRAIT = State and Trait anxiety inventory, ASC-12 = Allodynia Symptom Checklist measuring the sensation of pain induced by non-painful skin stimulation during a headache, Headache frequency = days with headache per month, Years with migraine = number of years lived with migraine.

Mean (SD)	Migraine (n = 55)	Controls (n = 58)	p-value
Age	36.1 (11.2)	36.4 (11.0)	0.88
Sex (f/m)	42/13	43/15	0.83
BDI-II	3.8 (4.0)	2.1 (3.8)	0.021
STATE	26.1 (6.6)	24.8 (5.3)	0.21
TRAIT	30.2 (8.5)	28.6 (7.8)	0.28
ASC-12 with headache	5.0 (4.6)	0.5 (1.5)	0.001
Headache frequency	7.9 (5.3)	n/a	n/a
Years with migraine	16.7 (10.6)	n/a	n/a
Aura/no aura	31/24	n/a	n/a

2.3. Statistical analysis

Group demographic and brainstem volume data of migraine patients and healthy controls were compared using either *t*-tests (two-tailed) or a Fisher's exact test, as appropriate. Group differences in brainstem shape between migraineurs versus healthy controls were analyzed using a node-by-node analysis of covariance (ANCOVA). Covariates included age, institute (i.e., where the MRI scan was performed) and sex. *P*-values ≤ 0.05 were considered statistically significant and demonstrated regions of outpouching or dimpling in the migraine population. The Benjamini and Hochberg false detection rate (FDR) was used to correct for null hypothesis false rejections ($\alpha = 0.05$). *P*-value, null hypothesis, and group mean difference values of each surface mesh node were written to a Tecplot file (written in Matlab) and represented as colored contours, i.e., 'heat map', on the brainstem mesh using the 'contour' display function tools within Tecplot (Tecplot Inc., Bellevue, Washington).

3. Results

3.1. Demographic data

Data from 55 migraineurs and 58 healthy controls were included in this study (Table 1). There were no significant differences in age (migraineurs: mean = 36.1, SD = 11.2; healthy controls: mean = 36.4, SD = 11.0; $p = 0.88$), sex (migraineurs: 42 females, 13 males; healthy controls: 43 females, 15 males $p = 0.83$), state anxiety (migraineurs: mean = 26.1, SD = 6.6; healthy controls: mean = 24.8, SD = 5.3; $p = 0.21$), or trait anxiety (migraineurs: mean = 30.2, SD = 8.5; healthy controls: mean = 28.6, SD = 7.8; $p = 0.28$). Although there was a significant difference on the BDI-II (migraineurs: mean = 3.8, SD = 4.0; healthy controls: mean = 2.1, SD = 3.8; $p = 0.021$) the mean scores of both groups were in the average/non-depressed range.

3.2. Volume analysis

Total gray matter volume and cortical white matter volume were calculated for healthy controls and migraine patients. There were no significant differences between groups for total gray matter volume (healthy controls: mean = 623,715.18 mm³, SD = 60,212.8 mm³; migraine patients: mean = 603,053.91 mm³, SD = 72,152.1 mm³; $p = 0.1$) or cortical white matter volume (healthy controls: mean = 455,905.9 mm³, SD = 56,804.1 mm³; migraine patients; mean = 438,140 mm³, SD = 63,845.7 mm³; $p = 0.12$) indicating no difference in overall brain volume between groups.

There was a significant difference in midbrain volume between migraineurs and healthy controls (healthy controls = 61.28 mm³, SD = 5.89; migraineurs = 58.80 mm³, SD = 6.64; $p = 0.038$), with migraineurs having smaller midbrain volumes relative to healthy controls. Group differences remained significant after accounting for the variance in age, sex, and scanner use ($p = 0.023$) There were no significant differences between groups in the pons (healthy controls = 146.23 mm³, SD = 18.7; migraineurs = 143.3 mm³, SD = 17.63 $p = 0.39$), medulla (healthy controls = 45.56 mm³, SD = 5.19; migraineurs = 43.94 mm³, SD = 5.1; $p = 0.09$), superior cerebellar peduncles (healthy controls = 2.41 mm³, SD = 0.45; migraineurs = 2.44 mm³, SD = 0.49; $p = 0.70$) and whole brainstem volumes (healthy controls = 255.5 mm³, SD = 28.3; migraineurs = 248.5 mm³, SD = 27.9; $p = 0.19$).

3.3. Post hoc correlation analyses

For migraineurs, there was a significant *negative* correlation between allodynia symptom scores during headache with midbrain volume ($r = -0.32$; $p = 0.019$) and a significant *positive* correlation

between cutaneous heat pain thresholds with medulla ($r = 0.337$; $p = 0.012$) and cerebellar peduncle volumes ($r = 0.435$; $p = 0.001$).

For healthy controls, there were no significant correlations between volumes (whole brainstem, medulla, pons, midbrain) and heat pain thresholds. As healthy patients did not have allodynia, correlations between brainstem volumes and symptoms of allodynia were not interrogated.

As several studies have demonstrated a relationship between major depression and brainstem structure and function (Lai and Wu, 2015; Smith et al., 2015), we interrogated a relationship between brainstem regions and depression to ensure that our results were not influenced by depression. Although, there was a significant difference between migraine patients and healthy controls on Beck Depression Inventory scores, the average scores of both groups were in the healthy, non-depressed range. Results showed no significant correlations between brainstem volume and depression for healthy controls ($r = 0.015$, $p = 0.91$) or migraine patients ($r = -0.247$, $p = 0.07$).

3.4. Shape analysis

Migraineurs, using the $p \leq 0.05$ threshold, showed statistically significant inward deformations in the ventral midbrain and pons regions (maximal difference of -0.4 mm) and statistically significant outward deformations in the right (maximal difference of 0.8 mm) and left (maximal difference of 0.6 mm) lateral aspects of the medulla and the dorsolateral pons. Results were FDR corrected ($\alpha = 0.05$) and adjusted for age, sex and scanner variability (Fig. 1).

4. Discussion

This study interrogated brainstem structural alterations in migraineurs and healthy controls. Migraineurs had inward deformations in the ventral aspect of the pons and midbrain and outward deformations in the right and left lateral aspects of the medulla and the dorsolateral aspects of the pons. Additionally, migraineurs had less volume in the midbrain relative to healthy controls. Results using a post hoc analysis showed that there was a significant negative correlation between allodynia and midbrain volume in migraineurs suggesting that more severe symptoms of allodynia were related to less midbrain volume. Additionally, there was a significant positive correlation between cutaneous heat pain thresholds and medulla and cerebellar peduncle volume indicating that migraine patients who were more sensitive to heat pain had less cerebellar peduncle and medulla volume.

Whereas volumetric analysis is able to interrogate volume loss over an entire structure (i.e., midbrain, pons, medulla or superior cerebellar peduncles), shape analysis can add information about *localized* alterations of a specific brain structure, which is especially useful for those disease processes that are known to target specific subcortical areas. As such, shape analysis has been useful for defining regional alterations in the basal ganglia regions and the thalamus in Alzheimer's disease, posterior thalamic deformations in schizophrenia, and has been able to provide information about regional structural alterations in the brainstem in patients who have fibromyalgia (Fallon et al., 2013; Mamah et al., 2016; Tang et al., 2014).

Our results are in line with previous studies that have found structural and functional brainstem alterations in migraine patients. Bilgic et al. (2016) found smaller brainstem volumes in migraine patients relative to healthy controls but no correlation between brainstem volume and clinical variables, such as disease duration and MIDAS scores. Positron emission tomography (PET) imaging of migraine patients during migraine attacks have found stronger functional activation in the periaqueductal gray (Weiller et al., 1995) stronger activation in the dorsolateral pons (Afridi et al., 2005) and stronger functional activation in midbrain regions (Weiller et al., 1995). Additionally, Aurora and colleagues have found increased metabolism in the pons using a transcranial magnetic stimulation paradigm in chronic versus episodic migraine

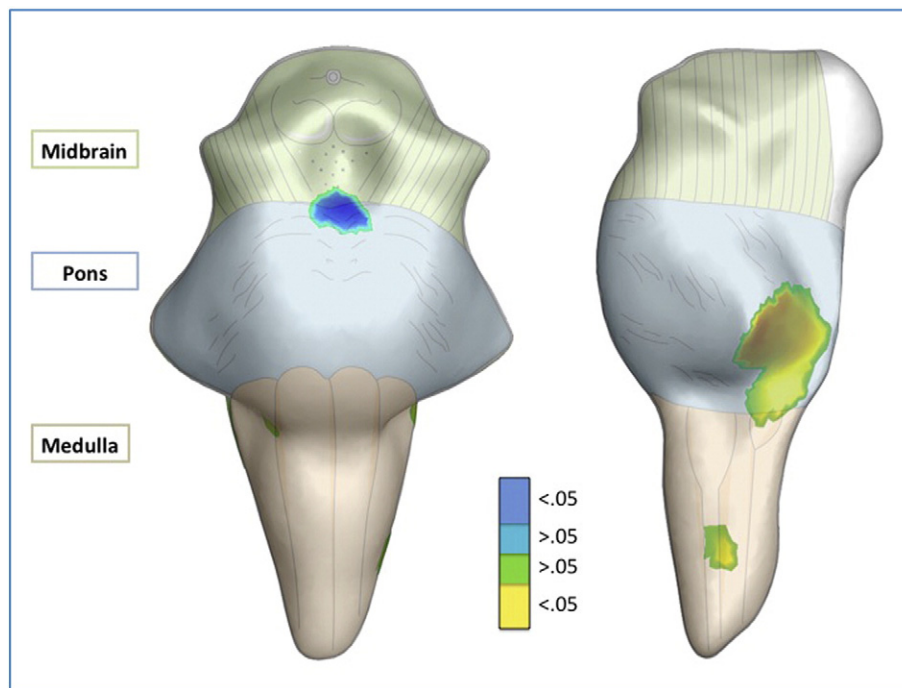


Fig. 1. Shape analysis of the brainstem demonstrating significant regional inward deformations (blue) in the ventral midbrain and pons and outward deformations (orange, yellow) in the lateral medulla and dorsolateral pons in migraineurs relative to healthy controls. Results are FDR corrected at $p < 0.05$.

patients between attacks using PET (Aurora et al., 2007) and several studies using functional magnetic resonance imaging have found less activation in the pons in migraineurs between attacks compared to healthy controls using heat pain stimulation paradigms (Moulton et al., 2011; Russo et al., 2012). Results of resting-state functional connectivity studies have indicated alterations in functional connectivity between the periaqueductal gray to cortical and subcortical regions in migraine patients with severe allodynia (Mainero et al., 2011; Schwedt et al., 2014b). Hyperexcitability and hypoexcitability of brainstem regions during and between attacks might suggest reorganization of brainstem functional networks in migraine patients and perhaps indicate alterations in pain inhibitory circuits.

4.1. Midbrain and allodynia

Our results show midbrain structural alterations in migraineurs relative to healthy controls and demonstrate an inverse relationship between allodynia symptoms and midbrain volume. These results are in line with several functional studies that have interrogated a relationship between midbrain regions and migraine hypersensitivities. Results of a recent PET study by Nascimento et al. demonstrated increased μ -opioid neurotransmission in the midbrain in migraine patients with allodynia during attacks (Nascimento et al., 2014). Furthermore, μ -opioid activation in the periaqueductal gray and the red nucleus was positively correlated with severity of allodynia symptoms. Schwedt et al. found stronger functional connectivity in midbrain regions (periaqueductal gray and nucleus cuneiformis) with other pain-processing areas in interictal migraineurs with allodynia compared to those without (Schwedt et al., 2014b). The relationship between symptoms of allodynia and structural and functional midbrain alterations in migraine is intriguing and might suggest a potential role of the midbrain in modulating central sensitization.

4.2. Shape deformations in the brainstem

Our results indicate shape deformations in the ventral-medial aspect of the midbrain and pons (at the level of the hypothalamic floor);

however, how these shape alterations relate to symptoms of allodynia needs to be further interrogated. Additionally, we noted bilateral shape alterations in the lateral aspects of the medulla and dorsolateral pons. Fallon et al. (2013) showed similar findings of shape alterations in the lateral medulla in fibromyalgia patients as well as total brainstem volume loss. In addition, there was a negative correlation between brainstem volume and manual tender point scale scores. Rocca et al. showed more gray matter density in migraine patients with aura compared to those without aura in the dorsolateral pons using voxel-based morphometry (Rocca et al., 2006). The involvement of the dorsolateral pons during a migraine attack has been consistently shown by several functional studies, which have demonstrated stronger dorsolateral pons activation during a migraine attack (Afridi et al., 2005; Bahra et al., 2001; Cao et al., 2002). Henceforth, our findings of bilateral outward deformations in the lateral aspects of the medulla and the dorsolateral pons might relate to structural alterations in the underlying nuclei involved in nociceptive processing and might contribute to central sensitization and brainstem pathophysiology in migraine patients.

4.3. Limitations

Imaging data were acquired using two different 3 T scanners, which is a limitation. An equal proportion of healthy control subjects and migraine patients were scanned on each scanner, limiting the potential impact of using two scanners. Additionally, the use of multiple scanners was included as a covariate in the statistical analysis of this study. Nevertheless, there is still potential that our brain morphology results were influenced to some extent by using two scanners. Future studies, using larger subject cohorts will be needed to validate our results ideally using a single, dedicated MRI scanner. Future studies, using larger sample sizes, are needed to interrogate whether migraine characteristics such as the frequency and intensity of headaches might associate with alterations in brainstem morphology. The brainstem is believed to have a pivotal role in the migraine disease process as it connects via reciprocal pathways to the trigeminovascular system and to supratentorial regions important for pain processing. Although this study showed brainstem morphological alterations in migraineurs

between attacks, as well as a relationship between allodynia symptoms, heat-pain sensitivity and brainstem volume, future studies are needed to interrogate how structural alterations in the brainstem are related to structural alterations in other supratentorial regions. Such studies will further elucidate how changes in brainstem morphology associate with cortical and subcortical changes in regions involved in pain processing.

5. Conclusion

Migraine patients show brainstem morphological changes relative to healthy controls. Migraineurs with more severe symptoms of allodynia and lower heat-pain thresholds show more volume loss in specific brainstem regions (midbrain, medulla and cerebellar peduncles), providing further evidence that the brainstem has a modulatory function in the development of central sensitization in migraine. However, future studies will need to better identify brainstem pain-modulatory circuits that play a specific role in the development and maintenance of central sensitization in migraine.

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Conflict of interest

None declared.

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