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STUDY TO DETERMINE THE ANATOMICAL ALTERATIONS IN BRAIN STEM OF PATIENTS WITH MIGRAINE

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Abstract:

Background: *Atypical modulation of brainstem pain may contribute to the changes in sensory processing typical of migraine. The aim of the study was to investigate whether migraine is associated with structural changes in the brainstem that correlate with this altered pain processing.*

Place and Duration: *In the Neurology and Radiology department of Holy Family Hospital, Rawalpindi for one-year duration from June 2019 to June 2020.*

Methods: *T1-weighted MRI images of 55 migraine patients and 58 healthy controls were used to: (1) create deformable mesh models of the brainstem that enable shape analysis; (2) calculate the volume of the midbrain, pons, medulla and upper pedicels of the cerebellum; (3) examine the correlations between regional brainstem volumes, cutaneous heat pain thresholds, and symptoms of allodynia.*

Results: *People with migraines had smaller volumes of the midbrain (healthy controls = 61.28 mm3, SD = 5.89; migraine = 58.80 mm3, SD = 6.64; p = 0.038) and significant (pb 0.05) internal deformities ventral midbrain and bridges, and external deformities of the lateral spine and dorsolateral bridge in relation to healthy subjects. In people with migraine, a negative correlation was found between the severity of ASC-12 allodynia symptoms and the volume of the midbrain (r = −0.32; p = 0.019) and a positive correlation between the thresholds of thermal cutaneous pain with the core (r = 0.337; p = 0.012) and the volume of peduncle of the cerebellum (r = 0.435; p = 0.001).*

Conclusion: *Migraine with more symptoms of allodynia has smaller volumes of the midbrain, and migraine with a lower threshold of thermal pain has a smaller core and pedicels of the cerebellum. The brainstem likely plays a role in altered sensory processing in migraine, and the structure of the brainstem may reflect the severity of allodynia and hypersensitivity to pain in migraine.*

Keywords: *Migraine, Magnetic resonance imaging, Brainstem, Allodynia*

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INTRODUCTION:

Migraine is a common and debilitating neurological disorder associated with sensitivity to light, sound, touch and smell. Often, migraine patients describe that normally painless stimuli, such as a light touch of the skin, are felt to be painful during a migraine attack, a phenomenon known as cutaneous allodynia. Cutaneous allodynia is believed to be associated with abnormal modulation of descending pain signals (Bingel and Tracey, 2008; Moulton et al., 2008). While these hypersensitivity increases during the paroxysmal phase of migraine (Bigal et al., 2008; Kelman, 2004; Lipton et al., 2008; Russell et al., 1996; Wober-Bingol et al., 2004), these hypersensitivities may also persist. occurs in the interictal phase of migraine (Ashkenazi et al., 2009; Main et al., 1997; Schwedt et al., 2011, 2015), when patients are painless. Several studies have shown that migraine patients exhibit interictal hypersensitivity, including a lower threshold for 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 patterns of functional brain activation to painful thermal stimuli (Chen et al., 2015; Schwedt et al., 2014a, 2015).

The descending pain system of the brainstem is interconnected with cortical regions involved in nociceptive processing. It is believed that brainstem regions may play a key role in generating and perpetuating a migraine attack, and that dysfunction in these regions may contribute to migraine-specific hypersensitivity such as allodynia. Several positron emission tomography (PET) imaging studies have shown increased activation of the dorsal bridge and dorsal brainstem in patients with onset migraine (Afridi et al., 2005; Bahra et al., 2001; Weiller et al., 1995; Wober-Bingol et al., 2004), and the results of functional magnetic resonance imaging (fMRI) studies showed increased functional connectivity between the periapical gray matter and the cortical and subcortical regions involved in nociceptive processing (Mainero et al., 2011; Schwedt et al., 2013). While these imaging results suggest functional changes in localized areas of the brainstem, it is not known whether these functional changes underlie structural changes in the brainstem anatomy. In a recent volumetric study, Bilgic et al. Demonstrated a lower brain stem volume in patients with chronic migraine compared to healthy controls (Bilgic et al., 2016). Similarly, the results of Jin et al. Show a lower cerebellum and brainstem density in migraine without aura compared to healthy controls using voxel-based morphometry (Jin et al., 2013). Whether migraine is associated with specific subregional volume changes in the brainstem structures has not yet been investigated. Until recently, parceling of brainstem substructures could not be achieved using automated brain parcelling algorithms, which left relatively unexplored changes in the structural anatomy of individual brainstem structures in migraine. The latest Free Surfer 6.0 structural pipeline includes the ability to segment the brainstem regions and shows good performance compared to manual labeling techniques which are time consuming and operator dependent (Iglesias et al., 2015).

This study assesses differences in brainstem volume (midbrain, pons, medulla, upper cerebellar peduncle) and brainstem changes between people with migraines and healthy controls, and examines whether morphological changes in the brain stem correlate with symptoms of allodynia and sensitivity for heat pain in patients with migraine.

METHODS:

This study was held in the Neurology and Radiology department of Holy Family Hospital, Rawalpindi for one-year duration from June 2019 to June 2020. This study included 55 migraine sufferers and 58 healthy individuals. Written informed consent was obtained from all participants prior to participating in the study. Migraine patients were recruited through clinic and diagnosed using the International Classification of Headache II (ICHD-II) criteria (International Classification of Headache: 2nd Edition, 2004). Migraine patients had no history of neurological disorders other than migraine and were painless for at least 24 hours prior to the scanning visit. All migraine patients have had migraine for at least 3 years and have not been taking migraine prevention drugs or opiates to relieve pain. Healthy controls are those who live in a community with no symptoms of chronic pain or headache, and no history of neurological disorders. Healthy controls were excluded if they had more than three tension headaches per month. The demographic data of the respondents are presented in Table 1.

All subjects were assessed during a one-and-a-half-hour visit, which included an MRI scan (T1 and T2), assessment of cutaneous heat pain thresholds using quantitative sensory testing (QST), and completion of questionnaire data. All subjects completed a state and trait anxiety inventory (STAI, Form Y-1, and Form Y-2) measuring acute and general anxiety levels (Spielberger et al., 1983), Beck Depression Inventory II (BDI-II) (Beck et al. ., 1996) assessing the presence or absence of depression and the Allodynia Symptom Checklist 12 (ASC-12) for assessing the symptoms of allodynia (Lipton et al., 2008). QST includes a

standardized protocol using the Medoc path system and a 30 mm x 30 mm thermode. A thermode was placed on the subject's middle forearm, and subjects were instructed to depress a button as soon as they felt the change from feeling warm to feeling pain. This moment was referred to as the "pain threshold". During QST the thermode was set to slow heating (1 ° C / s) starting at 32 ° C. The heating process was stopped immediately after the subject was pressed, and the thermode quickly cooled back to basal temperature. Pain thresholds were tested three times on the right forearm and three times on the left forearm, and the mean of three measurements at each body site was taken as the thermal pain threshold at that site. For the purpose of determining the correlation between the thermal pain threshold and the structure of the brain stem, the mean value of the measurements of the right and left forearms was taken as the threshold value of thermal pain.

Imaging parameters

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

T1 and T2 imaging scans were reviewed and people with abnormal results (ie, structural abnormalities in MR imaging) were excluded from further analysis.

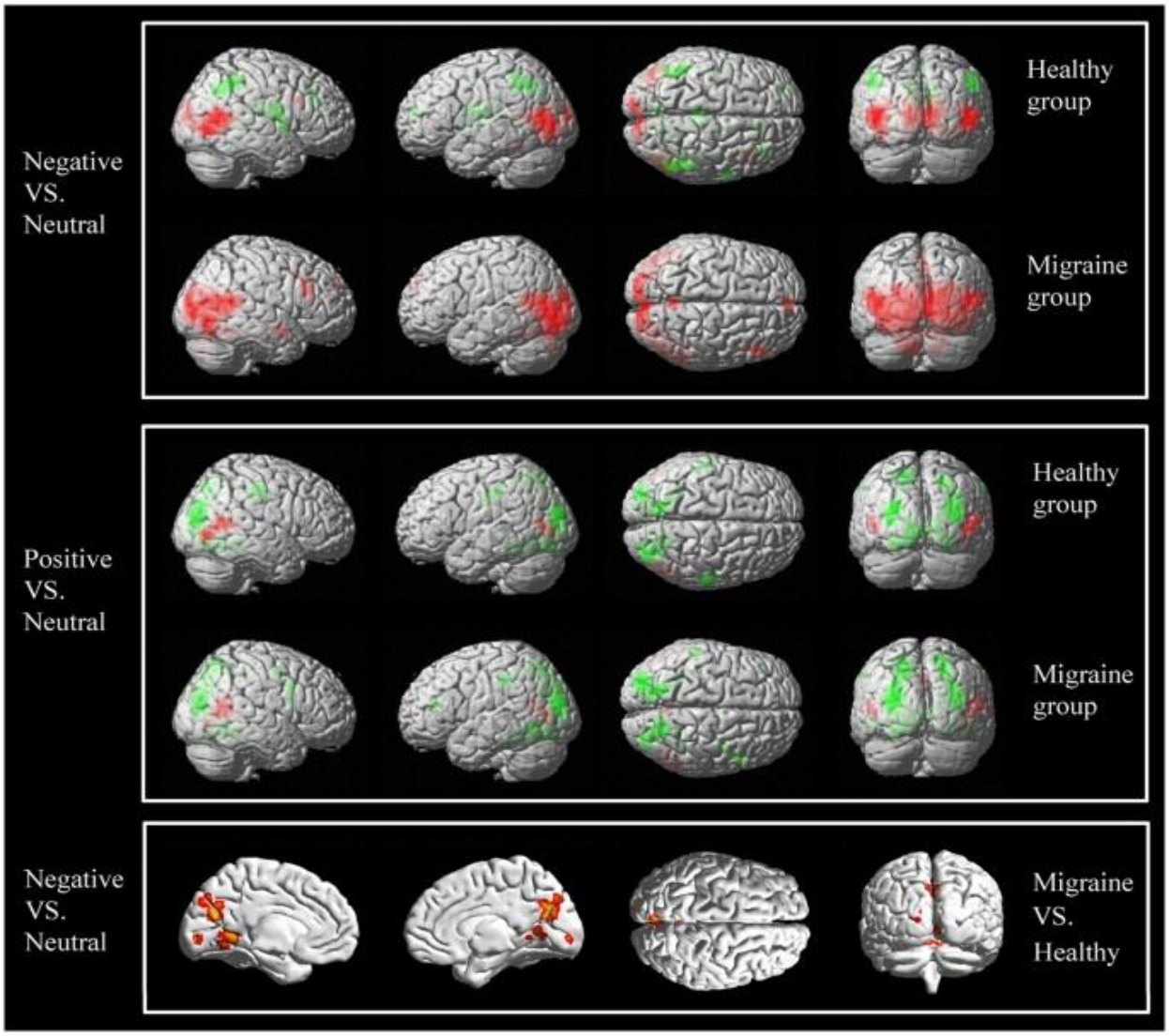
Statistical analysis

Demographic and brainstem volume data of migraine patients and healthy subjects were compared using t-tests (bisection) or Fisher's exact test, respectively. Differences between the brainstem groups between migraine sufferers and healthy controls were analyzed using node-by-node covariance analysis (ANCOVA). The covariates included age, institute (ie, where the MRI was performed), and gender. P values ≤0.05 were considered statistically significant and showed regions of ejection or depression in the migraine population.

RESULTS:

Demographic data

This study included data from 55 people with migraine and 58 healthy controls (Table 1). There were no significant differences in age (people with migraine: mean = 36.1, SD = 11.2; healthy people: mean = 36.4, SD = 11.0; p = 0.88), sex (people with migraine : 42 women, 13 men; healthy people: 43 women, 15 men p = 0.83), state anxiety (migraine: mean = 26.1, SD = 6.6; healthy control group: mean = 24.8, SD = 5.3; p = 0.21) or trait anxiety (migraine: mean = 30.2, SD = 8.5; healthy controls: mean = 28.6; SD = 7.8; p = 0.28). Although there was a significant difference in BDI-II (patients with migraine: mean = 3.8, SD = 4.0; healthy subjects: mean = 2.1, SD = 3.8; p = 0.021), the mean scores of both groups were lowered range.



Volume analysis

Total gray matter volume and cortical white matter volume were calculated for healthy subjects and migraine patients. There were no significant differences between the groups in terms of total gray matter volume (healthy subjects: 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 the volume of white matter cortex (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 total brain volume between groups.

There was a significant difference in the volume of the midbrain between people with migraine and those in the control group (healthy people = 61.28 mm3, SD = 5.89; people with migraine = 58.80 mm3, SD = 6.64; p = 0.038), in people with migraine with smaller volumes of the midbrain compared to healthy people. Group differences remained significant after adjusting for age, gender, and scanner usage (p = 0.023). There were no significant differences between groups in pons (healthy subjects = 146.23 mm3, SD = 18.7; migraine = 143.3 mm3, SD =; 17.63 p = 0.39), spinal cord (healthy controls = 45.56 mm3, SD = 5.19; migraine = 43.94 mm3, SD = 5.1; p = 0.09), upper pedicels of the cerebellum (healthy control group = 2.41 mm3, SD = 0.45; migraine = 2.44 mm3, SD = 0.49; p = 0.70) and volumes of the whole brain stem (healthy control group = 255.5 mm3, SD = 28.3; migraine = 248.5 mm3, SD = 27.9; p = 0.19).

Post hoc correlation analyzes

In the case of people with migraine, a significant negative correlation was found between the

assessment of allodynia symptoms during headache and the volume of the midbrain (r = -0.32; p = 0.019) and a significant positive correlation between the thresholds of cutaneous thermal pain with the core (r = 0.337; p = 0.012) and the volume of the cerebellar pedicels (r = 0.435; p = 0.001). In healthy controls, no significant correlation was found between the volume (whole brainstem, spine, pons, midbrain) and thermal pain thresholds. Since healthy subjects did not have allodynia, the correlation between brain stem volume and symptoms of allodynia has not been studied.

Since several studies have found a link between major depression and brainstem structure and function (Lai and Wu, 2015; Smith et al., 2015), we examined the relationship between brainstem regions and depression to ensure that depression did not affect our outcomes. Although there was a significant difference between migraine patients and healthy subjects on the Beck Depression Inventory scores, the mean scores for both groups were healthy, non-depressed. The results showed no significant correlation between brain stem volume and depression in healthy controls (r = 0.015, p = 0.91) or migraine patients (r = -0.247, p = 0.07).

Shape analysis

In people with migraine, using the p threshold ≤ 0.05, statistically significant inward deformations in the area of the abdominal midbrain and pons (maximum difference −0.4 mm) and statistically significant deformations outside the right side (maximum difference 0.8 mm) and left (maximum difference 0.6 mm) lateral parts of the core and dorsolateral bridges. The results were corrected by FDR (alpha = 0.05) and adjusted for age, gender, and scanner variability (Fig. 1).

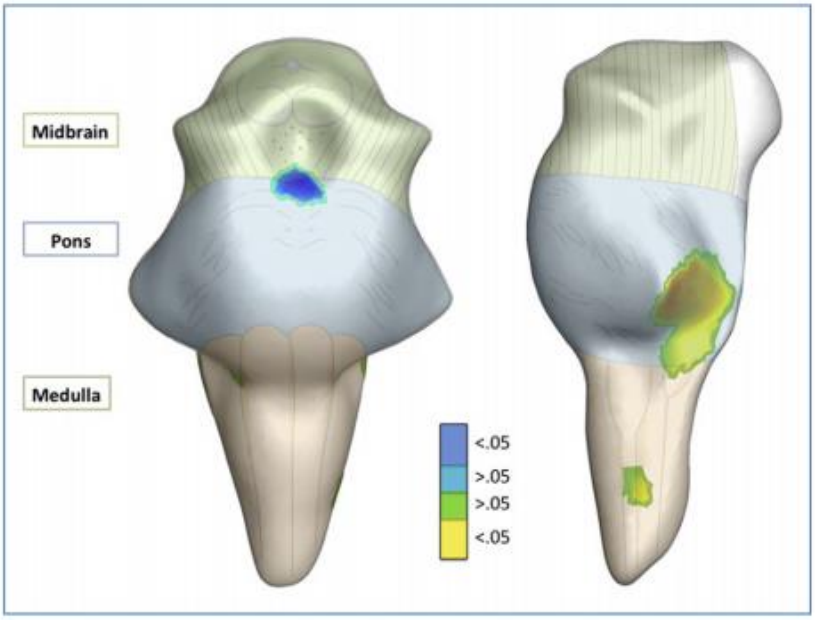


Fig. 1. Shape analysis of the brainstem demonstrating significant regional inward deformations (blue) in the ventral midbrain and pons and outward deformations (orange, yellow) in the lateral medulla and dorsolateral pons in migraineurs relative to healthy controls. Results are FDR corrected at $p <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

DISCUSSION:

This study looked at structural changes to the brain stem in people with migraine and in healthy people. People with migraine had internal deformities in the ventral pons and midbrain, and external deformities in the right and left lateral parts of the spine and in the dorsolateral part of the pons. In addition, people with migraines had a smaller volume of the midbrain compared to healthy people. Results from post hoc analysis showed a significant negative correlation between allodynia and mesencephalic volume in people with migraine, suggesting that more severe symptoms of allodynia were associated with lower mesencephalic volume. Moreover, a significant positive correlation was found between the cutaneous heat pain thresholds and the volume of the spinal cord and the cerebellar peduncle, which indicates that migraine patients who were more sensitive to heat pain had a smaller volume and volume of the cerebellar peduncle.

While volumetric analysis is able to investigate the loss of volume of the entire structure (i.e., midbrain, pons, medulla, or upper pedicels of the cerebellum), shape analysis can provide information about localized changes in a specific brain structure, which is particularly useful in disease processes that are known by targeting specific subcortical areas.

Therefore, shape analysis was useful for determining regional changes in the basal and thalamic areas in Alzheimer's disease, posterior thalamic deformities in schizophrenia, and was able to provide information on regional structural changes in the brainstem in patients with fibromyalgia (Fallon et al., 2013; Mamah et al., 2016; Tang et al., 2014).

Our results are in line with previous studies that found structural and functional changes to the brainstem in patients with migraine. Bilgic et al. (2016) found lower brainstem volumes in migraine patients compared 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 migraineurs during migraine attacks showed stronger functional activation in the gray periapical region (Weiller et al., 1995), stronger activation in the dorsolateral bridges (Afridi et al., 2005) and stronger functional activation in midbrain regions (Weiller et al., 1995). In addition, Aurora et al. Found increased metabolism in the pons using the transcranial magnetic stimulation paradigm in patients with chronic and episodic migraine between seizures with PET (Aurora et al., 2007), and several studies using functional MRI showed less activation in pons in people with migraine between attacks compared to healthy controls using heat pain stimulation paradigms (Moulton et al., 2011; Russo et al., 2012). The results of studies of functional connectivity at rest showed changes in functional connectivity between the periapical gray areas and the cortical and subcortical areas in patients with migraine and severe allodynia (Mainero et al., 2011; Schwedt et al., 2014b). The hyperactivity and hypo-excitability of the brainstem regions during and between attacks may suggest a reorganization of the brainstem functional networks in migraine patients and possibly indicate changes in pain inhibiting circuits.

Midbrain and allodynia

Our results show structural changes in the midbrain in people with migraine compared to healthy people and show an inverse relationship between the symptoms of allodynia and the volume of the midbrain. These results are consistent with several functional studies that investigated the relationship between midbrain regions and migraine hypersensitivity. A recent PET study by Nascimento et al. Demonstrated increased μ-opioid neurotransmission in the midbrain in patients with migraine and allodynia during attacks (Nascimento et al., 2014). Moreover, the activation of μ-opioids in the gray periapical area and the red nucleus was positively correlated with the severity of allodynia symptoms. Schwedt et al. found stronger functional connectivity in the midbrain areas (periapical gray and sphenoid nucleus) with other areas of pain processing in people with interictal migraine with allodynia compared to those without (Schwedt et al., 2014b). The relationship between the symptoms of allodynia and the structural and functional changes in the midbrain in migraine is intriguing and may suggest a potential role of the midbrain in modulating central sensitization.

Shape deformation in the brainstem

Our results show shape deformations in the ventromedial part of the midbrain and pons (at the level of the hypothalamus floor); however, one should investigate how these shape changes relate to the symptoms of allodynia. In addition, we noticed bilateral changes in the shape of the lateral parts of the core and the dorsolateral bridge. Fallon et al. (2013) showed similar results on changes in the shape of the lateral spinal cord in patients with fibromyalgia, as well as on the total loss of brainstem volume. Moreover, there was a negative correlation between the volume of the brainstem and the points on the manual tenderness scale. Rocca et al. demonstrated higher gray matter density in migraine patients with aura compared to patients without aura in the dorsolateral bridge using voxel-based morphometry (Rocca et al., 2006). Dorsolateral bridge involvement in a migraine attack has been consistently demonstrated in several functional studies that have shown stronger activation of the dorsolateral bridge during a migraine attack (Afridi et al., 2005; Bahra et al., 2001; Cao et al., 2002). Hence, our findings on bilateral external lateral deformities of the spine and dorsolateral bridge may relate to structural changes in basal ganglia involved in nociceptive processing and may contribute to central sensitization and pathophysiology of the brainstem in patients with migraine.

CONCLUSION:

Patients with migraine show morphological changes in the brainstem compared to healthy people. Migraines with more severe symptoms of allodynia and lower thresholds of heat pain show greater loss of volume in specific areas of the brainstem (midbrain, medulla, and spindle), providing further evidence that the brainstem plays a modulating role in the development of central allergy in migraine. However, future research will need to better identify brainstem pain modulating circuits that play a particular role in the development and maintenance of central migraine sensitization.

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