Volumetric alterations of subcortical brain structures in female migraineurs

PhD thesis

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1. Introduction

Migraine is a frequent neurological condition characterized by recurring episodes of headaches along with osmophobia, photophobia, phonophobia, and cutaneous allodynia. It affects about 15–20% of the overall population and is associated with a substantial personal and social burden. Migraine is more common in women, and the prevalence at its peak among women is more than 25%. Usually, women are three times more likely to have migraines, and the female to male ratio peaks at 3.25 among those between 18 and 29 years of age. Besides the epidemiologic evidence of sex differences, there are also structural and functional sex differences in patients suffering migraine, which were supported by brain magnetic resonance imaging (MRI) studies. Gonadal hormones and psychological mechanisms may contribute to these sex differences.

MRI is a useful diagnostic tool in migraine and shows migraine-related structural complications, e.g., hemispheric white matter lesions (WMLs) as well as cortical and subcortical volume changes of different structures. The WMLs are clinically mute, mostly progressive microvascular tissue damages, which are areas of focal axonal and glial cell injuries in association with decreased intracellular energy metabolism due to impairment of mitochondria. It is plausible that abnormalities in axons passing through these lesions might cause gray matter changes.

Migraine aura is described as transient neurological symptoms, and refers to a sequence of absolutely reversible visual, sensory or language disturbances, which occur and spread gradually, and either precede or accompany a migraine attack. It is widely accepted that cortical spreading depression (CSD) accounts for the aura, but mechanisms of triggering CSD in the structurally normal, well-nourished cortex of migraineurs still remain unknown. Synaptic drive from subcortical sensory processing structures (brainstem and/or thalamocortical networks) could evoke depolarization of hyperexcitable cortical neurons sufficient to initiate the regenerative spreading depression process. Animal studies demonstrated that the regional blood flow in the brainstem was transiently increased during spreading depression.

The pathophysiology of migraine is complex and not fully understood. Previous

studies have indicated that the brainstem plays a critical role in migraine attacks and is even considered to be associated with migraine generators. The thalamus is served as a key nociceptive relay station with nerve fibers not merely projecting out information to the cerebral cortex but also receiving feedback information from these multiple cortical areas. It is a central area for the processing and integration of pain stimuli, and it has an important role in allodynia, central sensitization, and photophobia in migraine. The hippocampus is involved in memory consolidation, spatial navigation, and in pain-related stress response, as well as in pain processing, pain-related attention, and anxiety. Episodic migraine attacks can be considered as repeated stressor.

Previously, brain regions were usually segmented manually, and manual segmentation is also considered as the gold standard for accuracy. However, this method is subjective and extremely time-consuming. A segmentation for the whole brain could take days, and also prone to errors. Therefore, automated segmentation tools will be a good alternative for medium and large-scale studies. FreeSurfer is one of the most commonly used software for brain segmentation. The high reliability of FreeSurfer-derived measures in subcortical structures have been confirmed by previous studies.

2. Research Background and Objectives

Previous studies demonstrated volume changes in subcortical structures in migraine. However, findings are partly inconsistent. Structural changes can be sexually dimorphic in migraine that may have an impact on previous studies examining combined male and female groups. Therefore, only females were included in the present study.

Part I The Volume of the Thalamus and Hippocampus in a Right-Handed Female Episodic Migraine Group

Based on the current literature, some subcortical structures may be functionally impaired in migraine, thereby we hypothesized that WMLs, aura and the migraine characteristics (disease duration and frequency) may affect the volume of thalamus and

hippocampus. To test our hypothesis, we measured the volumes of the thalami and hippocampi of migraine patients based on brain MRI and investigated the potential role of WMLs and the migraine characteristics on volumetric changes.

Part II Volumetric Alteration of Brainstem in Female Migraineurs With and Without Aura

It was reported that there are white matter microstructural differences between migraine patients with aura (MwA) and migraine patients without aura (MwoA), highlighting the importance of taking the aura into consideration. Moreover, none of the previous studies investigated the influence of aura on brainstem volume specifically. We hypothesized that the aura may cause brainstem volume changes in migraineurs as an independent risk factor. For that reason, we investigated migraine patients subdivided into two groups (MwA and MwoA), when assessing the effects of migraine on the volumes of the whole brainstem and its subfields.

3. Patients and Methods

A total of 161 females with episodic migraine were prospectively enrolled to this study. As controls, 40 age-matched female healthy controls (HC) were included. All migraineurs and controls reported right-handedness. Migraineurs had no other types of headaches. Brain MRI studies of healthy participants did not show any structural abnormalities.

All subjects were scanned on the same 3T MRI scanner. Whole-brain T1-weighted three-dimensional axial magnetization-prepared rapid gradient-echo (3D MPRAGE) sequence was acquired. Beyond the routine T1- and T2-weighted measurements the scanning protocol also included fluid-attenuated inversion recovery (FLAIR) imaging.

WMLs were considered if visible as hyperintensity on T2-weighted and FLAIR MRI but without low signal intensity lesion on T1-weighted MRI and larger than 3 mm, appearing in at least two consecutive slices. Supratentorial WMLs were delineated manually on the FLAIR images using 3D Slicer software

Left and right thalamus segmentation was performed on the high-resolution three-

dimensional 3D MPRAGE images using Freesurfer 5.3 image analysis suite. The left and right hippocampus and their subfields, as well as brainstem (only included patients without lesions: L-) and as its subfields were segmented using the development version of FreeSurfer on August 31st, 2017.

4. Results

The Volume of the Thalamus and Hippocampus in a Right-Handed Female Episodic Migraine Group

The left hippocampus had a smaller and the left thalamus had a larger total volume than the right one in both the control ($p < 0.001$) and migraine groups ($p < 0.001$). Patients with white matter lesions (L+) showed smaller right thalamus and right hippocampal tail volumes than L- ($p=0.002$ and $p=0.015$, respectively) and controls ($p=0.039$ and $p=0.025$, respectively). For the right hippocampal body, we found significantly smaller volume in L+ patients when compared to L- patients ($p = 0.018$) and a similar trend when compared to the control group ($p = 0.064$). Patients without aura showed larger right hippocampus ($p=0.029$), right hippocampal body ($p=0.012$), and tail volumes ($p=0.011$) than patients with aura. Inverse correlations were found between attack frequency and the volumes of left- and right hippocampal tails ($p=0.018$ and $p=0.008$, respectively).

Volumetric Alteration of Brainstem in Female Migraineurs With and Without Aura

Migraineurs had greater medulla volume (MwoA 3552±459 mm3, MwA 3424±448 mm3) than healthy controls (3236±411 mm3). Statistically, MwA vs. HC $p = 0.040$, MwoA vs. HC $p = 0.002$, MwA vs. MwoA $p = 0.555$. A significant positive correlation was found between disease duration and the volume of medulla in the whole migraine group ($r=0.334$, $p=0.001$). Neither the whole brainstem nor its subfields were significantly different in volume between migraine subgroups.

5. Summary

In this thesis, we firstly tested the hypotheses whether WMLs and the migraine

characteristics (disease duration, frequency, and aura) may affect the volume of both the thalamus and hippocampus in female migraine group, and then explored whether aura and other migraine characteristics may lead to volume changes of brainstem and its subfields for migraineurs without WMLs. For all of these brain structures, we also investigated the potential volume differences between the migraine and the healthy control groups.

The major findings of this research are the following: 1.) the volume of the right thalamus is decreased in migraineurs with WMLs, 2.) the volume of right hippocampal body and tail are smaller in migraineurs with aura or WMLs, 3.) the volumes of both the left and right hippocampal tail are smaller in patients with higher migraine frequency, 4.) the volume of medulla is bigger in migraineurs compared to healthy controls, 5.) aura has no significant impact on the volumetric change of brainstem and its subfields, 6.) the volume of medulla is bigger in migraine patients with longer disease duration.

These structural abnormalities are likely to be the consequence of recurrent migraine headache attacks. The patients need to follow a healthy lifestyle and avoid almost all migraine risk factors, and the doctors need to investigate co-morbidities if suspected and control the attacks with the most effective therapy.

6. List of publications

Articles related to this thesis:

He M, Kis-Jakab G, Komáromy H, Perlaki G, Orsi G, Bosnyák E, Rozgonyi R, John F, Trauninger A, Eklics K, Pfund Z. The volume of the thalamus and hippocampus in a right-handed female episodic migraine group. Frontiers in Neurology. 2023 Oct 19;14:1254628. (IF: 3.4)

He M, Kis-Jakab G, Komáromy H, Perlaki G, Orsi G, Bosnyák E, Rozgonyi R, John F, Trauninger A, Eklics K, Pfund Z. Volumetric alteration of brainstem in female migraineurs with and without aura. Clinical Neurology and Neurosurgery. 2023 Dec 19;236:108089. (IF: 1.9)

Article related to the project this thesis based on:

Komáromy H, **He M**, Perlaki G, Orsi G, Nagy SA, Bosnyák E, Kamson Olayinka D, John F, Trauninger A, Pfund Z. Influence of hemispheric white matter lesions and migraine characteristics on cortical thickness and volume. The Journal of Headache and Pain. 2019 Jan 10;20(1):4.

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