

Macro- and Microstructural Alterations in Migraine and Cluster Headache

PhD Thesis

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Table of contents

ORIGINAL PUBLICATIONS RELATED TO THE THESIS	4
ORIGINAL PUBLICATIONS NOT DIRECTLY RELATED TO THE THESIS	4
REVIEW PUBLICATIONS	6
ABBREVIATIONS	7
INTRODUCTION	8
MIGRAINE	8
CLUSTER HEADACHE	11
OBJECTIVES	12
METHODS	12
PARTICIPANTS	12
IMAGE ACQUISITION	13
IMAGE ANALYSIS	13
RESULTS	16
MIGRAINE	16
FOCAL WHITE MATTER MICROSTRUCTURE ALTERATIONS	16
SUBCORTICAL STRUCTURES' VOLUME IN MIGRAINEURS AND CONTROLS	18
THALAMIC VOLUME CHANGES ACCORDING TO THE ATTACK FREQUENCY AND DISEASE DURATION IN MIGRAINE	18
SURFACE CHANGES OF THE THALAMI IN MIGRAINEURS	20
CLUSTER HEADACHE	21
WHITE MATTER MICROSTRUCTURAL ALTERATIONS	21
DISCUSSION	22
MIGRAINE	23
MICROSTRUCTURAL ALTERATIONS IN MIGRAINE	23
THALAMIC VOLUMETRY	24
THE RELATION OF OUR FINDING TO MIGRAINE PATHOMECHANISM	25
CLUSTER HEADACHE	28

<u>LIMITATIONS</u>	<u>30</u>
<u>CONCLUSIONS</u>	<u>30</u>
<u>ACKNOWLEDGEMENT</u>	<u>31</u>
<u>REFERENCES</u>	<u>32</u>

Original publications related to the thesis:

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VI. Zsigmond Tamas Kincses, Daniel Hořínek, Nikoletta Szabó, Eszter Tóth, Gergő Csete, Irena Štěpán-Buksakowska, Jakub Hort, László Vécsei: The Pattern of Diffusion Parameter Changes in Alzheimer's Disease, Identified by Means of Linked Independent Component

Analysis. Journal of Alzheimer's Disease: JAD 03/2013; DOI:10.3233/JAD122431I.

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Abbreviations

AD	Axial diffusivity
CGRP	Calcitonin gene related peptide
CH	Cluster headache
CSD	Cortical spreading depression
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDT	FMRIB's Diffusion Toolbox
FSL	FMRIB Software Library
MD	Mean diffusivity
MMP	Metalloproteinase
MRI	Magnetic resonance imaging
PAG	Periaqueductal gray matter
PD	Perpendicular diffusivity
PET	Positron emission tomography
ROI	Region-of-interest
SPSS	Statistical Package for Social Sciences
TBSS	Tract based spatial statistics
TFCE	Threshold free cluster enhancing approach

Introduction

Migraine

Migraine is the most common primary headache disorder. The disease commonly presents in the form of intense pulsing or throbbing unilateral headache. Migraine usually starts in adolescence but tends to affect predominantly people aged between 35 to 45 years. The socio-economic importance of the disease is that approximately 20% of the population suffers from disabling attacks of migraine during lifetime [1]. The pain commonly accompanied by nausea, vomiting and extreme sensibility to light, smell and sound. In one quarter of the patients the headache is preceded by transient central nervous system symptoms, mostly visual or sensory, called aura.

While environmental factors like hormonal changes, stress, changes in wake-sleep pattern or the environment, foods and drinks, medications and sensory stimuli could trigger migraine headache [2], scientific data suggest a predominantly genetic origin of the disease (see for review: [3,4]).

The underlying pathophysiological process of migraine is not entirely understood and established indicators of the disease are missing. There are evidences, that the trigeminovascular pathway and hemispheric brain structures also must have a central role in the pathomechanism, which suggest the multilevel origin of the disease. Dural perivascular trigeminal activation and the release of calcitonin gene related peptide (CGRP) and substance P [5,6] are involved in migraine pathomechanism and that cause neurogenic inflammation. The nociceptive information is then transmitted by the sensory neuron, residing in the trigeminal ganglion, to the trigeminal nucleus caudalis [7,8] wherefrom it is mediated to the thalamus and forth to cortical centres [9]. Most of the migraineurs also report allodynia during the attacks when non-nociceptive stimuli cause pain either in the trigeminal or extracephalic areas, which is associated with the disease duration and attack frequency [10]. This process involves the central sensitisation of the secondary and tertiary neurons of the trigeminal system [11]. Trigeminal sensitisation might arise from two distinct but not necessarily exclusive processes:

stimulation might arise from the cortical spreading depression (CSD) [12] that stimulates trigeminal endings [13] or alternatively top-down modulation of the trigeminal system from higher-level cortical systems [14]. The altered excitability of the cerebral cortex in the interictal state seems to be fundamental in the brain's susceptibility to migraine attacks [15].

To understand the parallel steps of the pathogenesis we should examine the migraine with extended methods. Beyond the investigation of animal models (the relevance of which is limited) and laboratory tests, functional and structural imaging techniques have a crucial role to investigate *in vivo* alterations in migraine patient's central nervous system.

The first functional imaging studies were based on positron emission tomography (PET). PET studies found increased activity in visual cortex during migraine attack and photophobia [16,17]. Migraineurs in interictal period showed altered brain activity compared to controls [18,19]. In patients, hypometabolism was found in the bilateral insula, bilateral anterior and posterior cingulate cortex, left premotor and prefrontal cortex, and left primary somatosensory cortex [19]. The cerebellum and the white matter of the posterior brain-parts showed decreased glucose metabolism [18]. Moreover, based on PET studies the role of the 5HT(1A) receptors was described in the pontine raphe nuclei, the left orbitofrontal cortex, the temporal pole and the precentral gyrus [20,21]. Functional magnetic resonance imaging (fMRI) examinations confirmed the results of the PET studies. The pain-related areas showed altered activation during migraine attack [22-25] and in interictal [26-29] period.

Structural magnetic resonance imaging (MRI) studies, despite of the different methodological process, consistently revealed loss of gray matter in pain related brain regions, including the frontal cortex, temporal lobe, insula, and brainstem [30-34]. Kim and coworkers described that increasing headache duration and increasing headache frequency lead to progressive reduction of the gray matter volume of the migraineurs suggesting that repeated migraine attacks may cause selective alteration to several brain regions involved in migraine pain processing [30].

White matter microstructure changes, as defined by diffusion-weighted MRI, are receiving more and more attention. Diffusion-weighted MRI is sensitive to

diffusion of water molecules, which in the brain is largely restricted by the membranes of the cellular particles (Figure 1.). Diffusion weighted MRI is tuned to measure diffusion in certain directions and by fitting a diffusion tensor model to the measured diffusion profile, it is possible to calculate diffusion parameters that reflect the microscopic organisation of the measured volume [35].

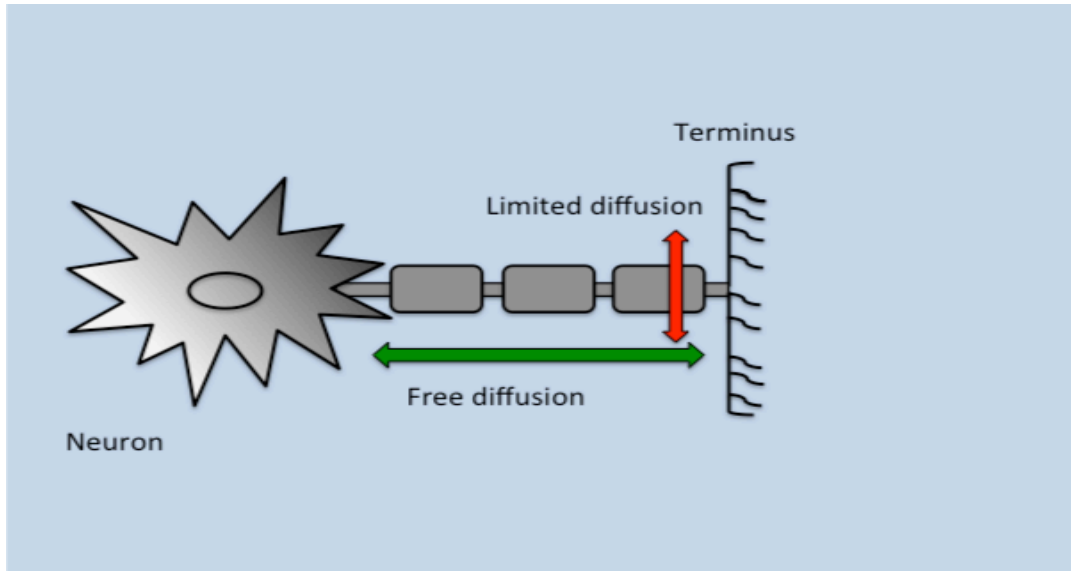


Figure 1. The restricted diffusion of water in brain tissue can be measured with diffusion tensor imaging. The movement of the water is free parallel to the axons and restricted perpendicular to the membranes. Imaging techniques allow getting information about the integrity of the white matter tracts.

A number of studies reported altered white matter microstructure in migraine with different methodological approaches. For example, lower white matter mean diffusivity (MD) and increased fractional anisotropy (FA) were found in migraine patients by means of a histogram analysis [36]. Li and co-workers, in a region-of-interest (ROI) analysis showed reduced FA in the genu, splenium, and body of the corpus callosum [37]. Similarly, in another ROI-based analysis, Rocca and colleagues found reduced FA and higher MD in the right optic radiation of patients with aura [38]. Using a voxel-based morphometry style analysis, lower FA was described in the thalamocortical tract of migraineurs, and similar alterations were found in the trigeminothalamic tract and in the periaqueductal gray matter (PAG) of patients with and without aura, respectively [39]. By using a similar approach, Granziera and colleagues found reduced FA in the visual motion-processing network [40].

Cluster headache

Cluster headache (CH), a primary headache disorder within the group of trigeminal autonomic cephalalgias, is characterised by paroxysmal hemicrania and ipsilateral craniofacial autonomic symptoms [2]. Cluster periods may last from weeks to months, usually followed by remission periods when the headache attacks stop completely. During remission, no headaches occur for months and sometimes even years. One period lasts from 6 to 12 weeks. Migraine-like symptoms can occur over an attack usually on one side. The main risk factors of CH are the smoking, alcohol use and positive family history. The first CH attack occurs between 20 and 50 years. The prevalence of the CH is about 0.1%. Although the appearance of CH is much rare compared to migraine, it usually presents with a very severe headache, which causes significant disability during the attack.

The pathomechanism of CH is not fully understood but involves both central and peripheral mechanisms [41]. Due to the periodic appearance of the attacks, there has been numerous studies suggesting the role of the hypothalamus [42]. Positron emission tomography studies showed that the anterior cingulate cortex, the contralateral thalamus, the ipsilateral basal ganglia and both insulae were activated in CH [43,44]. Most importantly, pain related to the emotional and autonomic response is known to be the main activator of the mentioned structures. Nevertheless, the activation of the hypothalamus seems to be a specific feature of cluster attacks [43], indicating its pivotal role in the pathogenesis and pain regulation in CH. Since the hypothalamic activation can influence the pain-matrix [45] these findings point to the multifocal origin of the CH, the dysfunction of the pain-matrix [41,46]. Structural MRI studies found gray as well as white matter alterations in CH [47] similar to those found in migraine [30,34,48]. A recent diffusion tensor imaging (DTI) study in CH found reduced FA in the pain matrix [49]. Contrarily, another study found no microstructural alterations (investigated FA and MD) in CH [47]. While these results may be contradictory, imaging markers could be a powerful tool to describe disease progression and reveal important clues on the pathomechanism.

Objectives

The aim of our study was to seek biomarkers of primary headache disorders and examine the microstructure of the white matter in migraine and cluster headache. Furthermore, thalamic morphology was examined in migraine using structural MRI methods.

Methods

Participants

Twenty-one female migraine patients and thirteen patients with episodic CH, without any history of other neurological disorder, were chosen from the Headache Outpatient Clinic of the Department of Neurology, University of Szeged. The diagnosis was based on the criteria of the International Headache Society [50]. In order to rule out possible confounding factors, patients were all screened for depression by means of the Hamilton Depression Rating Scale [51]. Based on this, four patients were excluded from the study.

All patients underwent a clinical interview, which covered the time since the onset of headaches, frequency, quality, intensity, duration, localization of pain, provoking factors and associated symptoms. Headache-related allodynia was evaluated based on Lipton and coworkers' work [10]. The allodynia symptom checklist measures the cephalic and the extracephalic allodynia. All subjects were right-handed; none of them had a history of head injury or met the criteria of chronic headache. None of the patients had any other neurological or psychiatric diseases. None of the patients reported aura symptoms. MRI scans were acquired in the interictal period. Demographic data of the study groups listed in Table 1 and Table 2. As controls, seventeen age-matched, right-handed, healthy female individuals and sixteen controls, with no history of migraine, CH, long-term headache or other neurological or psychiatric diseases were included in the migraine and CH study respectively. The study was approved by the local ethics committee (authority number: 87/2009), and all the subjects provided written consent according to the Declaration of Helsinki.

Image acquisition

MR imaging was carried out on a 1.5T GE Signa Excite HDxt MRI scanner. During the scanning, each subject laid supine in the scanner with eyes closed and head motion was restricted with foam padding around the head, and the necessity of head immobility was explained to each subject. Scanner noise was attenuated with earplugs. 3D spoiled gradient echo (FSPGR: TE: 4.1ms, TR: 10.276ms, matrix: 256x256, FOV: 25x25cm, Flip angle: 15 degree, in-plane resolution: 1x1mm, slice thickness: 1mm) and 60 direction diffusion weighted images with 6 non-diffusion-weighted reference volume (TE: 93.8ms, TR: 16000ms, matrix: 96x96, FOV: 23x23cm, Flip angle: 90 degree, in-plane resolution: 2.4x2.4mm slice thickness: 2.4mm, b: 1000s/m², NEX: 2, ASSET) were acquired for all the subjects.

Image analysis

Processing of diffusion data

Correction for eddy currents and movement artifacts by 12 DOF affine linear registration to the first non-diffusion-weighted reference image was the first step of the preprocessing [52]. Diffusion gradient directions were reoriented according to the result of eddy current correction [53]. Diffusion tensors at each voxel of the brain were fitted by an algorithm of FMRIB's Diffusion Toolbox (FDT) in FSL (v. 4.0, www.fmrib.ox.ac.uk/fsl; [54]). FA, MD, and AD (λ_1) and PD ($(\lambda_2 + \lambda_3)/2$) to the principal diffusion direction were calculated for the whole brain. In CH study, images were mirrored to the midsagittal axis according to the side affected by the headache. In order to minimize the possible mistakes arising from misalignment of the images, we used the tract based spatial statistical (TBSS) method [55]: All subjects' FA data were aligned into a common space derived from 58 high-resolution FA images of healthy subjects, using the FMRIB's Nonlinear Registration Tool, FNIRT [56] which uses a b-spline representation of the registration warp field [57]. A mean FA image was created and then thresholded at FA = 0.2, deriving a mean FA skeleton that represents the centres of all tracts common to the group. Each participant's aligned FA data were then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics.

Modeling and inference using standard general linear model design set-up was accomplished using permutation-based cluster analysis (5000 permutation) [58] as implemented in FSL. The design encoded for group membership and clinical variables.

In the migraine study clusters were formed according to a defined threshold ($t = 2.3$) and corrected for multiple comparisons (across space) within the permutation framework by building up the null distribution of the maximum cluster size for each permutation ($p < 0.05$). We also carried out a region of interest analysis on the white matter regions whose FA values differed significantly between groups. We tested for differences in FA, MD, longitudinal, and perpendicular diffusivity.

Connectivity of the identified differences in white matter integrity was defined by probabilistic tractography (FDT, part of FSL: www.fmrib.ox.ac.uk/fsl/fdt/) in migraineurs. We fitted a multifibre diffusion model [59] that estimates probability distributions of the direction of 1 or more fibre populations at each brain voxel. Probabilistic tractography was then performed from any brain voxel by tracing streamline samples through these probabilistic distributions on fibre direction. For tractography, we generated 5000 streamline samples from each seed voxel to build up a connectivity distribution. The number of these samples passing through each brain voxel is interpreted as proportional to the probability of connection to the seed voxel. By fitting a multifibre model to our diffusion data, we were able to follow pathways through regions of fibre crossing [59]. Cluster-masks of the TBSS analysis were used as a binary seed masks.

In CH study after using permutation test (5000 permutation), statistical images were thresholded by the novel threshold free cluster enhancing approach (TFCE) [60]. Similar analysis were carried out for the MD, perpendicular (PD) and axial diffusivity (AD). The diffusivity parameters were extracted from the regions indicated by the thresholded results of the TBSS analysis and these parameters were correlated with the number of cumulative headache days using Statistical Package for Social Sciences (SPSS 17 for OS X, SPSS Inc., <http://www.spss.com>). Laterality index was calculated for every diffusion parameter from the number of suprathreshold voxels [61]:

$$LI = \frac{N_L + N_R}{N_L - N_R},$$

where N_L and N_R are the number of suprathreshold voxels in the left and right hemisphere.

Volumetric analysis

Volumetric analysis of the thalamus was carried out using tools of FSL (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>) [55]. A deformable-model-based segmentation-registration tool employing a Bayesian Appearance Model (FMRIB's Integrated Registration Segmentation Toolkit), FIRST was used, which can automatically segment the thalami [62]. For the automatic segmentation of basal ganglia, shape and intensity variations of subcortical structures were constructed from a training set of 336 images. To study the cross-subject vertex correspondence, surface meshes were obtained with a deformable model. At each vertex a sample was taken from the normalized intensities along the surface normal. Then the vertex intensity and location variation were modeled as a multivariate Gaussian distribution. Finally, maximizing the posterior probability of the shape given the observed intensities, this model was fit to new images [62]. The boundary voxels on the edge of the structure were corrected by FAST, which classifies these boundary voxels according to intensity [63]. The obtained segmentation quality was evaluated by visual inspection. Given our primary interest of volume changes related to the sensitization of the thalamic neuron, our prior hypothesis was centered on the thalamus. The other subcortical structures were also segmented.

Volumetric comparison of the segmented thalami across groups was performed using the Statistical Package for Social Sciences (SPSS 17 for OS X, SPSS Inc., <http://www.spss.com>). Testing the normality of the data Shapiro-Wilk test was used and Student t-test was used to compare groups. Pearson correlation was calculated between the size of the thalami and the clinical parameters.

Shape changes of the subcortical structures

A surface mesh model was fit to the individual thalami. The corresponding vertices can be compared across groups since the number of vertices are fixed and correspond with one another across subjects. The meshes were then aligned

(rotation and translation) to the mean surface in MNI152 space, and group comparisons of corresponding vertex locations were performed by calculating vertex-wise F statistics to investigate localized shape differences [62]. Since, this was only performed as a post-hoc localisation of the significant changes, identified with the volumetric analysis, uncorrected p-values were used.

Connectivity of focal thalamic volume changes

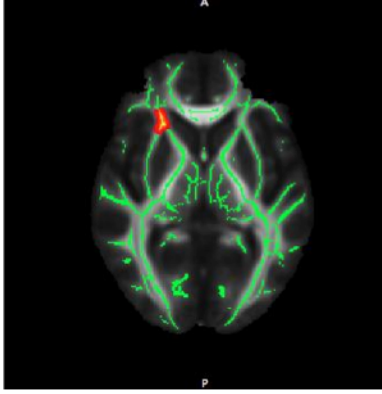
Probabilistic tractography was started from the described focal thalamic shape changes (thresholded at $p < 0.05$, uncorrected). The mesh surface vertices in MNI152 space were used as seed locations for tractography (FMRIB's Diffusion Toolbox, part of FSL: www.fmrib.ox.ac.uk/fsl/fdt/). We fitted a multi-fibre diffusion model [59] that estimates probability distributions on the direction of one or more fibre populations in each seed brain voxel. Probabilistic tractography was then performed from any voxel of the brain by tracing streamline samples through these probabilistic distributions on fibre direction. We generated for tractography 5000 streamline samples from each seed voxel to build up connectivity spacing. The number of these samples passing through each brain voxel is interpreted as being proportional to the probability of connection to the seed voxel. By fitting a multi-fibre model to our diffusion data, we were able to trace pathways through regions of fibre crossings [59]. The individual connectivity maps were registered to standard MNI152 brain. Individual tractography results were thresholded at 1000 particles (20%), binarised and summed over subjects to represent the group level connectivity pattern.

Results

Migraine

Focal white matter microstructure alterations

As evaluated by group level voxelwise FA differences in the centre of white matter fibre bundles, the white matter microstructure was significantly changed in migraine patients as compared to controls. The differences were observed in the right frontal white matter (maximal t-score at voxel location $x = 25$ mm, $y = 24$



mm, $z = 5$ mm standard space coordinates; Figure 2.).

Figure 2. Reduced FA in the right frontal white matter in migraine patients was detected with TBSS. The mean FA skeleton is rendered in green. The t-scores are depicted in red-to-yellow colours within the significant cluster.

Specifically, FA was lower (Figure 3.), while MD and PD were significantly higher in patients than in controls ($p < 0.0088$ and $p < 0.0002$, respectively, Figure 3.). AD, on the other hand, was not different between groups ($p > 0.101$, Figure 3.).

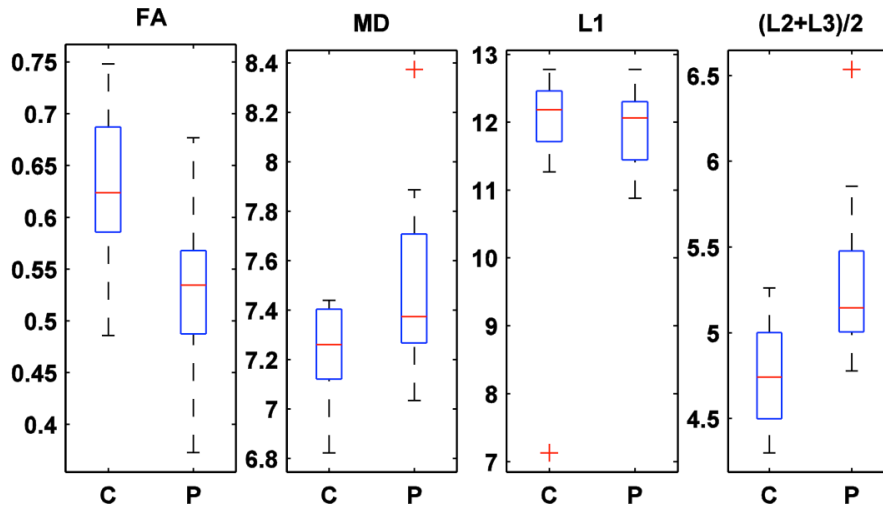


Figure 3. FA, MD, axial (L1), and perpendicular ((L2 + L3)/2) diffusivity in the cluster where reduced FA was found ($x=25$ mm, $y=24$ mm, $z=5$ mm). MD was higher in migraine patients ($p < 0.0088$), which was explained by the increase in perpendicular diffusivity ($p < 0.0002$). L1 did not differ between the groups ($p > 0.101$). On the box-plot, the central mark is the mean, the boxes represent the 25% and 75% percentiles, and outliers are depicted as red crosses.

In a whole brain analysis, neither MD nor the axial/perpendicular diffusivity showed any significant difference between patients and controls. In order to further characterize the microstructural alterations found in migraine, we carried out a correlation analysis between clinical data and local FA by using an ROI approach. No correlation was found between the observed FA and disease duration or attack frequency.

Connectivity of focal FA changes in migraine

The probabilistic tractography indicated that fibres of the right frontal white matter showing the FA alteration (identified by the TBSS analysis) were connected to the ipsilateral prefrontal cortical regions, insula, thalamus, dorsal, and ventral midbrain. Fibres proceeded in the direction of the occipital cortex through the putative inferior fronto-occipital fasciculus. Some fibres also crossed the midline through the corpus callosum (Figure 4).

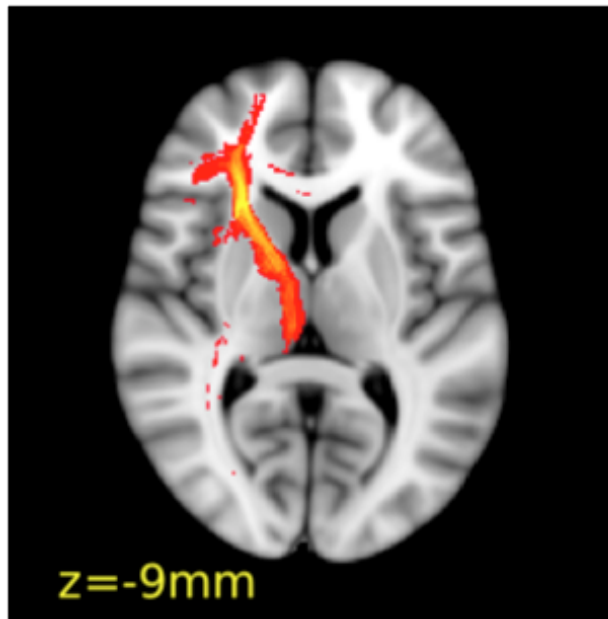


Figure 4. Connectivity of the white matter cluster showing significantly lower FA in migraine patients than in controls. The binary cluster masks were used as seed mask for each patient.

Subcortical structures' volume in migraineurs and controls

The data showed normally distribution as we tested with Shapiro-Wilk test (right thalamus: $p < 0.323$; left thalamus: $p < 0.529$). The size of the left ($p < 0.04$) as well as the right ($p < 0.047$) thalami was significantly larger in patients. There was no significant difference between the size of the left and right thalamus either in case of the patients ($p < 0.467$) or the healthy subjects ($p < 0.299$). The volume of the other subcortical structures was not difference between patients and controls ($p > 0.05$).

The relationship of thalamic volume changes and clinical features

We correlated the size of the thalami in migraineurs with the frequency of their attacks (the number of migraine attacks within one year, and also the total number of the attacks over the course of disease) and the duration of the disease. The

number of attacks within one year significantly correlated with the size of the left ($R=0.550$; $F(1,15)=6.491$; $p<0.022$) and right thalamus ($R=0.496$; $F(1,15)=4.881$; $p<0.043$) (Figure 5.).

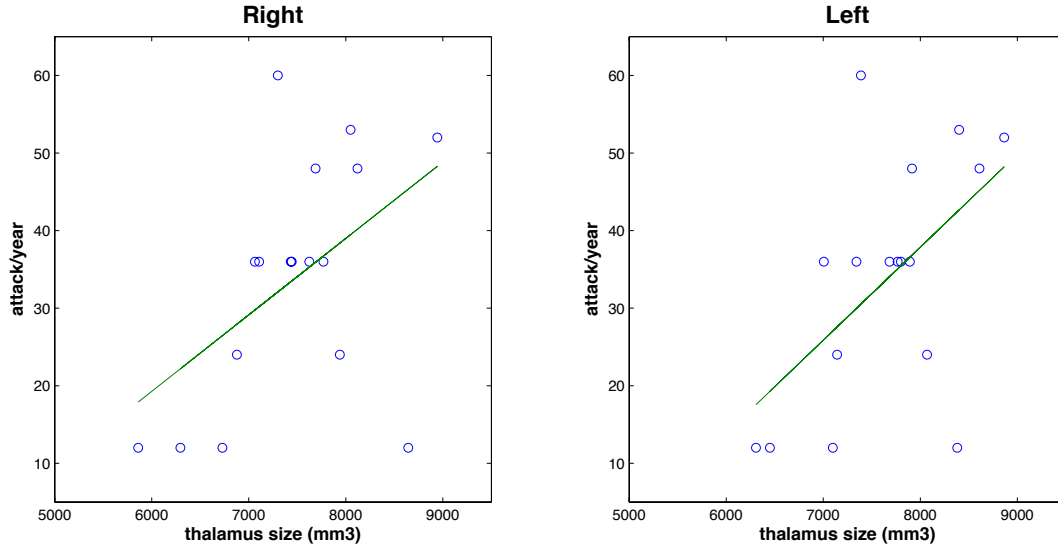


Figure 5. Correlation of thalamic volumes with attack frequency. Correlation was significant on both side: left: $R=0.550$, $p<0.022$; right: $R=0.496$, $p<0.043$.

We found no significant correlation between the number the total attacks and the size of the thalami (right thalamus: $R=0.104$; $F(1,15)=0.164$; $p<0.691$; left thalamus: $R=0.161$; $F(1,15)=0.398$; $p<0.538$). There was no significant correlation between the duration of the disease and the size of the thalami (right thalamus: $R=0.176$; $F(1,15)=0.480$; $p<0.499$; left thalamus: $R=0.137$; $F(1,15)=0.286$; $p<0.601$). Significant correlation was shown between the allodynia score of the patients and the volume of their left thalamus ($R=0.528$; $F(1,15)=5.805$; $p<0.029$) (Figure 6.). It should be noted that this correlation was primarily driven by the highest allodynia scores. There was no significant correlation between the size of the right thalamus and the allodynia score ($R=0.233$; $F(1,15)=0.859$; $p<0.369$).

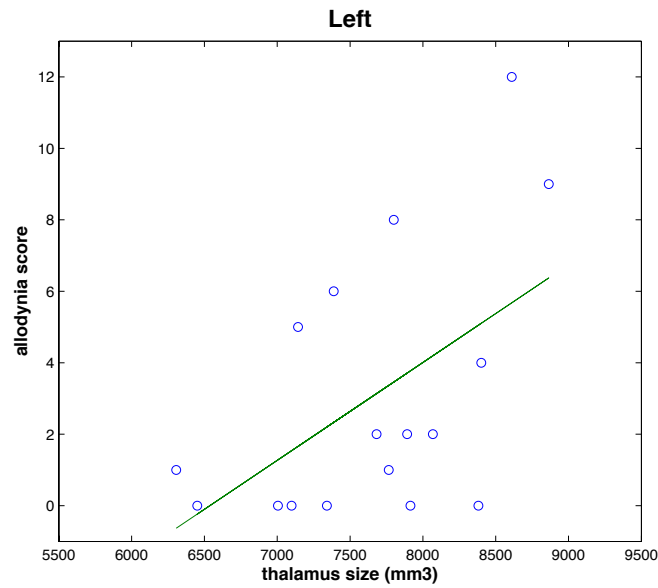


Figure 6. Correlation of the size of the left thalamus with the allodynia score. A significant correlation was found: $R=0.528$, $p<0.029$.

Surface changes of the thalami in migraineurs

The vertex-based analysis of the focal thalamic shape changes showed a local augmentation of size in the ventral region of the right thalamus in patients (Figure 7/A.). Probabilistic tractography of this enlarged area showed consistent connectivity to the dorsal brainstem. In the other direction, the highest connectivity was found to be to the premotor and prefrontal cortices (Figure 7/B.).

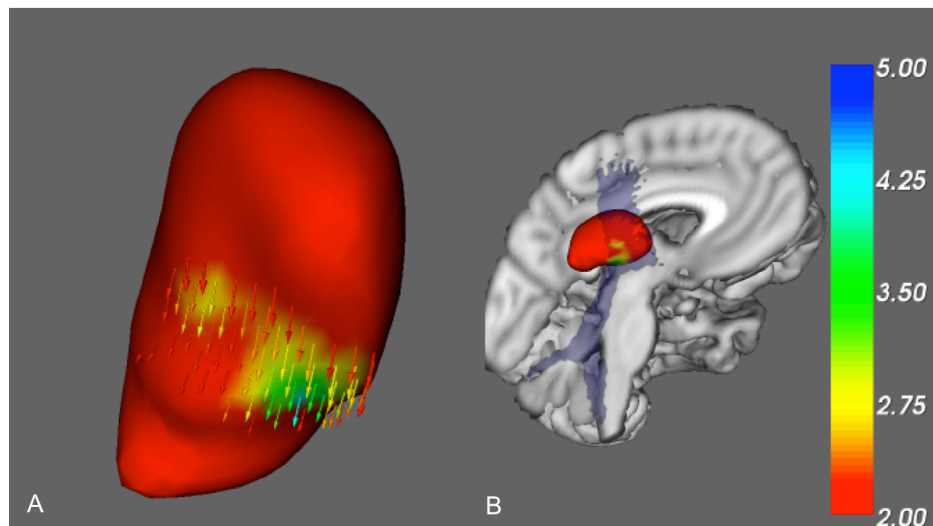


Figure 7. Focal size augmentation of the right thalamus and the connectivity of that region (A). The right thalamus is depicted from the anterior aspect and slightly below. Yellow to blue colours (colour bar on the right represent F-values) represent the location of the size augmentation in patients. The image is thresholded at $p<0.05$, uncorrected. Arrows show the direction of movement of individual

vertices across groups (B). On the 3D image the same right thalamus is depicted with the result of the probabilistic tractography in transparent blue and the connectivity of the affected thalamic region is shown. The red to yellow scale shows super-threshold connectivity values present in two patients.

Cluster headache

White matter microstructural alterations

The whole brain TBSS analysis showed decreased FA ($p < 0.02$, corrected for multiple comparison) in the corpus callosum, bilaterally in the forceps minor and major, right corona radiata, left internal and external capsule, left cerebral peduncle, frontal portion of the left corona radiata, right parietal juxtacortical white matter, left inferior fronto-occipital fascicle (Figure 8/A.).

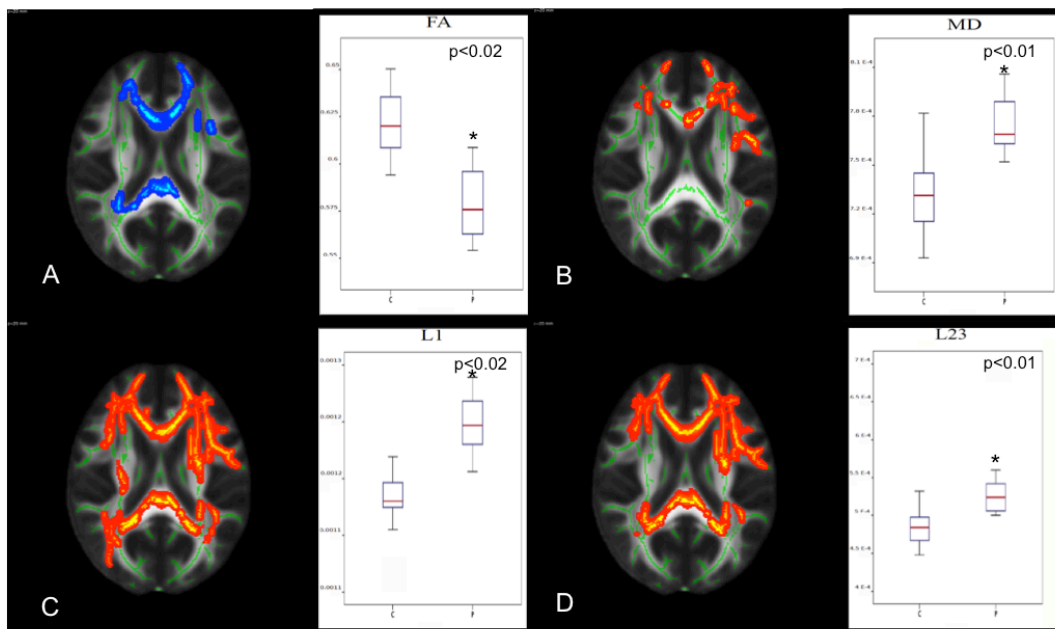


Figure 8. Diffusion parameters in cluster headache patients. Blue colours indicate reduction (A); red-to-yellow colours indicate increment (B-D) in the given diffusion parameters ($x=75\text{mm}$, $y=102\text{mm}$, $z=87\text{mm}$). The mean FA skeleton is shown in green. A thickened version of the significant cluster is used for easier visualisation (red-to-yellow or blue shades). Boxplots show the diffusion parameters of the affected area respectively.

MD was found increased ($p < 0.01$, corrected for multiple correlations) in regions where FA alterations were found, but the alterations were more extensive involving more frontal, parietal and temporal juxtacortical white matter (Figure 8/B.). Axial diffusivity was also found to be increased in widespread white matter regions ($p < 0.02$, corrected for multiple correlations) similar to those of FA changes, but no

significant alteration of axial diffusivity was found in the right parietal lobe in the juxtacortical white matter and the posterior corona radiate (Figure 8/C.). Augmented perpendicular diffusivity ($p < 0.01$, corrected for multiple correlations) was the most extensive among the different diffusion parameters, involved essentially all major white matter fibre bundles, except the right external capsule (Figure 8/D.).

No increased FA or decreased mean, axial, or perpendicular diffusivity was detected. Laterality indices of all measured diffusion parameters showed left dominance (LI_{FA} : 9.8, LI_{MD} : 0.2, LI_{AD} : 0.7, LI_{PD} : 0.2).

There was a significant correlation between the cumulative headache days and axial diffusivity in regions showing significant differences in AD ($p < 0.022$, r : 0.626, corrected for multiple comparisons, Figure 9.). Other diffusion parameters did not show significant correlation.

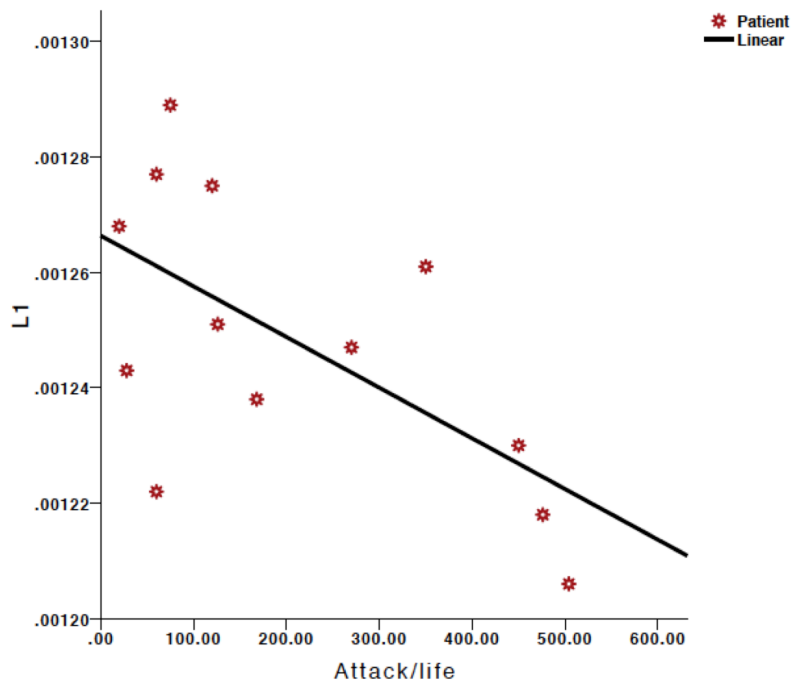


Figure 9.

Augmentation of the axial diffusivity shows inverse correlation with the cumulative headache days in lifetime.

Discussion

In this thesis MRI detected structural alterations are presented in migraine and CH patients: (1) in migraine patients right frontal white matter microstructural

alterations were found and (2) increased thalamic volumes were identified, which is correlated with the attack frequency and the level of allodynia, while (3) in cluster headache similar pattern of diffusion parameter alterations were detected, but more widespread in the white matter and (4) correlation was found between the disease burden and axial diffusivity.

Migraine

Microstructural alterations in migraine

Microstructural white matter alterations as measured by diffusion MRI are frequently reported in migraine. In a histogram analysis lower white matter FA and higher MD was detected in migraineurs [31]. In a region of interest analysis reduced FA was measured in the corpus callosum [37] and in the optic radiation [38]. This later was also confirmed by a voxel based morphometry style analysis [39]. Similar changes (reduced FA, increased MD) was described in the trigemino-thalamic and thalamo-cortical tracts [39]. By using a similar approach, Granziera and colleagues found reduced FA in the visual motion processing network [40].

Despite the undisputed merits of these studies, our investigation overcomes some of the limitations. By investigating only the core of each fibre bundle (as defined by the local maxima of FA) we reduced the effect of the spatial variability [54]. Since this kind of data often violates the requirement of normally distributed data, the use of non-parametric permutation test further enhanced the value of our results.

Our results are in line with previous reports describing structural and functional alterations of the frontal cortex of subjects with migraine. Frontal cortical atrophy was reported in migraine patients [32,34,64] and frontal cortical gray matter density reduction was correlated to T2-visible lesion load [31]. In migraineurs altered cognitive shift was correlated with the reduced frontal gray matter [65]. In a recent investigation gray matter atrophy was found in the left medial prefrontal cortex, the dorsal anterior cingulate cortex, the right occipital lobe, the cerebellum and brainstem [64]. The volume of the anterior cingulate cortex showed correlation with disease duration [64]. In migraine patients increased functional connectivity was detected between left dorsolateral prefrontal cortex, the bilateral middle temporal lobe, orbitofrontal cortex and the left anterior cingulate cortex [64].

However, there is a potential that alterations of the frontal lobe might not be specific to migraine. In other chronic pain syndromes gray matter loss was frequently reported in the prefrontal cortex [66], cingulate, parahippocampal gyrus, insula [67] amygdalae, hippocampi, postcentral gyri, anterior cingulate gyri, and superior frontal gyri [68]. With chronic pain conditions functional alterations are also observed in medial prefrontal cortex [69], anterior insula, cingulate cortex [70] and ventromedial prefrontal areas [71].

Thalamic volumetry

The thalamus has a cardinal role in pain perception as well as in migraine pathomechanism. It is where the second order neurons project (trigeminothalamic tract) and where the third-order neurons of the thalamocortical tract emerge. Thalamic neurons, which are responding to dural stimulation also were shown to be sensitised by ipsilateral cephalic and extracephalic chemical stimulation [72]. Migraine patients with extracephalic allodynia were shown to have a larger thalamic BOLD response to sensory stimulation than when they were free of migraine [72]. The role of the thalamus in migraine and trigeminal neuralgia was also indicated by the abnormal balance of metabolite levels, detected by MR spectroscopy, in the thalamus [73]. Thalamic activation was described during migraine attacks [74,75]. Shields and colleagues found that naratriptan (see in review: [76]) an effective medication in migraine attack, suppressed the thalamic activation evoked by the stimulation of the superior sagittal sinus in the ventral posteromedial nucleus of the thalamus [77]. Interestingly, in another trigeminal pain disorder, in temporomandibular disorder thalamic and sensory cortical gray matter enlargement was found and shown to correlate with disease duration [78,79]. In contrast, localised thalamic atrophy was detected in trigeminal neuropathy, but not in patients that were classified as having trigeminal neuralgia or temporomandibular disorders [80]. Using MR spectroscopy in the same study, reduced levels of N-acetyl-aspartate, a marker of neuronal viability was found in the affected thalami. The difference between the direction of thalamic volume changes in trigeminal neuropathy and other pain disorder in the trigeminal territory may lie in the different pathomechanisms; peripheral events were proposed in trigeminal neuralgia and temporomandibular disorder, while the reduced volume and neural

viability suggest central mechanisms in trigeminal neuropathy [80]. In a recent study on trigeminal neuralgia gray matter volume reduction was described in the thalamus, insula, anterior cingulate cortex, primary somatosensory and orbitofrontal cortices, secondary somatosensory cortex, cerebellum, and dorsolateral prefrontal cortex [81]. Obermann and co-workers found no influence of the disease duration on thalamic volume [81]. A further study found reduced thalamic volume (contralateral ventral postero-lateral nucleus) in limb amputees with phantom pain [82]. However, this atrophy most probably was related to the loss of sensory input than the pain, as the time since amputation was correlating with the thalamic volume and not the pain index describing the pain intensity and frequency. Contrarily, in neuropathic pain in ankylosing spondylitis increased gray matter volume in the thalamus and putamen was observed [83]. Pain characteristics were correlated with increased gray matter in the motor cortex, anterior cingulate cortex, prefrontal cortex, thalamus, and striatum and with decreased gray matter in the primary somatosensory cortex in patients [83].

The relation of our finding to migraine pathomechanism

In our view there can be alternative interpretations for the white matter alterations and the thalamic enlargement in migraine patients. Degenerative changes and maladaptive plasticity might co-occur in the disease.

(1.) In localized white matter diffusivity alteration (reduced FA) might reflect degenerative process in migraineurs. One hypothesis states that the depolarization wave progressing through the cortex has a central role in migraine pathomechanism [24]. The excessive activation might well be enough to induce in cellular damage, [14] kindle neuroinflammation and consequently cause pain [84-86]. CSD in animals upregulates the matrix metalloproteinase (MMP)-9 [87] and the activation of MMP can elicit the leakage of blood–brain barrier and lead to inflammatory response and neuronal damage [88]. Elevated MMP activity was also detected in human migraineurs [89]. Other markers of neuronal (neuron specific enolase) and glial (S100B) damage was also found in migraineurs [90]. There seems, therefore, to be some evidence for biochemical changes potentially involved in the disintegration of white matter fibre bundles that might be reflected by reduction of FA, increase of MD, and augmented perpendicular diffusivity. Similar patterns of

DTI abnormalities are most frequently reported as a consequence of neurodegenerative processes [91,92]. Reduction of FA and AD reflect axonal loss [93-95], while increased perpendicular diffusivity seems to be a sign of demyelination [93,94]. The serum markers of neuronal and glial damage reported recently [90] might indicate combined damage.

In migraine patients T2 white matter lesions [96] were detected, and the lesions have been widely considered of ischemic nature [97], but not without criticism and alternative hypotheses [98,99]. For instance, the coexistence of antineuronal antibody suggested the inflammatory origin of the altered MRI signal [100]. Reduction of frontal gray matter volume was found to be correlated with the T2 visible lesion load [36]. Retrograde degeneration of axons passing through the macroscopic lesions was the suggested background of this correlation. In our study, however, only one patient had a right frontal T2 visible white matter lesion. Because of the close proximity of the lesion to our cluster of FA difference, we have repeated the analysis with the exclusion of this subject, but the results were essentially unaltered. Hence, it is likely that white matter microstructural alterations are not directly related to the T2 visible lesions in migraine.

(2.) As regarding the increased size of the thalami in migraine the first scenario is the thalami are genuinely larger that could kindle the pathomechanism. Longitudinal imaging studies of normal people, who later develop migraine, or genetically stratified imaging studies could be of use.

Alternatively, and more likely, the increased volume of the thalami is the result of the disease. There are evidences that repeated painful stimuli similarly to training lead to plastic changes in the brain. Gray matter morphological changes due to used-dependent plasticity have already been reported in adults [101,102]. Similar alterations were also found in the white matter with DTI [103]. As an expression of similar mechanisms, repeated pain stimuli were also reported to induce increase of gray matter density in pain processing regions, including the cingulate and the contralateral somatosensory cortex [104].

Apart from the repeated pain in migraineurs, other factors related to the pathomechanism of the disorder might also contribute to maladaptive plasticity: the altered cortical excitability [105-109] might also lead to such changes. Plastic

changes were reported in the central nervous system of animals after induction of CSD [110,111]. A possible energy deficit suggested in migraine [112,113] might also contribute to plastic changes in the brain [114]. The cellular mechanism behind these gray matter volume changes can be suspected similar as proposed in learning-related plastic gray matter enlargements [102], such as synaptogenesis and dendritic arborisation [115,116]. Furthermore, cortical spreading depression itself may induce neurogenesis in the cortex as well as in subcortical structures [117].

Another open question that the above-stated maladaptive plasticity hypothesis, however, is that in chronic pain conditions [66,118,119,67] as well as in migraine [30-34], reduction rather than increase of gray matter size or density has been reported, as seen, for example, in learning [102]. Similarly, white matter alterations due to use-dependent plasticity-like processes were expected to appear in the form of increased FA, as it was reported recently [120]. Explanation of such controversy may lie in a lack of noxious stimulus in chronic pain [121], chronification of the pain condition, compensatory mechanisms [122] or affective components [123], and personality traits related to migraine [124].

Another aspect of our findings that has to be considered is the integration of the thalamic enlargement and the prefrontal white matter alteration in the pain related functional networks. Hadjipavlou and co-workers described the pain network that contains prefrontal cortex, periaqueductal gray and cuneiform nucleus, amygdala, thalamus and hypothalamus, and rostroventral medulla [125]. Our tractography findings are in line with this study; accurately the prefrontal white matter lesion and the enlarged thalamic region are connected to the above-mentioned structures.

The vertex analysis showed that the ventral surface of the thalamus was enlarged in patients. The probabilistic tractography showed that this ventral aspect of the thalamus is the area connected to brainstem structures. These structures cannot be unanimously identified with the current resolution, but might connect thalamus to the PAG or could possibly be the fibres from the putative trigemino-thalamic pathway. Regarding the pathomechanism of migraine each of these pathways could have crucial importance [36,113]. However it has to be pointed out that earlier investigations described the connectivity of PAG to the mediodorsal thalamus [126], rather than to the thalamic region in our analysis. In the other direction the

enlarged thalamic region is connected, with the highest probability, to the frontal cortex. Together with the above-mentioned results it must be emphasized that the role of these regions should not be evaluated individually, but must be seen as part of a network, the parts of which are heavily interconnected [127,125].

We found thalamic volume being related to attack frequency and allodynia reported by the patients. Allodynia (an abnormal sensory state in which normally innoxious stimuli sensed as painful) is a frequently reported feature of migraine [128] and thought to be a sign of neuronal sensitisation. The first order neurons of the trigemino-vascular pathway are in the trigeminal ganglion, which innervate the dural sinuses and project to the spinal trigeminal nucleus. The second order neurons process information from the dural vessels and from both the skin and deep tissue of the periorbital region. The sensitisation of the first order neuron is thought to be related to the throbbing nature of the pain [129]. The sensitisation of the second order neurons is thought to be related to the allodynia around the eye on the affected side and the referred pain [11]. The third order neurons in the thalamus that receive projections from the ipsi- and contralateral second order trigeminal neurons and from all other level of the spinal cord, process multimodal information from the affected and contralateral side of the head as well as from extracranial regions [130]. In a recent parallel rodent electrophysiological and human fMRI investigation extracranial allodynia was associated with the sensitisation of these third order neurons [72]. Furthermore, reduced fractional anisotropy was found in the thalamocortical tracts in migraineurs [39]. It would be tempting to relate the thalamic enlargement to the appearance of extracranial allodynia in our study group also, but almost all the patients having allodynia also reported that as being extracranial, and therefore we do not have appropriate statistical power.

Cluster headache

In the literature there are contradictory results on the diffusion alterations in cluster headache, despite using the same analysis approach as in our study. In a DTI study, Teepker and colleagues described reduction of FA in several brain regions, but no other diffusion parameters were investigated [49]. The extent of the FA alterations was much smaller than in our study. Another investigation on CH patients found no

alteration of FA or MD with similar analytical method [47]. One possible reason why we found more widespread changes than in previous studies could be because of the high angular resolution DTI acquisition, what we have used in our study, thereby providing a higher signal to noise ratio [131].

Correlation between the alteration of diffusion parameters and tissue microstructure is not yet entirely clear. However, the increment of mean and perpendicular diffusivity, which was the most prominent finding of our study, is most probably a sign of increased distances between membranes. This mostly relates to demyelination [94,93], but combined axon and myelin loss may also cause a complex change of diffusion parameters [132]. The increased inter-membrane distance [133] may also cause increased perpendicular diffusivity. One could speculate that the changes in the extracellular space might be related to the sterile inflammation proposed in CH [134]. However recent SPECT study did not find evidence of increased number of intracranial white blood cells in CH [135].

It was previously suggested that the lack of correlation of diffusion abnormalities with attack frequency or disease duration point to a phenotypic biomarker of the disease, reflecting a congenital condition rather than a process related to disease progression over time [47]. However in our current investigation we found a negative correlation between the axial diffusivity and the cumulative headache days. This interesting finding can be explained by observations showing that early stage of axon damage is associated with reduced axial diffusivity [95,94,93,132,136]. However later, the axial diffusivity will pseudo-normalise again as the axon and myelin debris gradually cleared [137,138]. This mechanism could potentially explain our findings, nevertheless it should be emphasized that none of the DTI indices are a direct measurement of specific white matter compartments [139], hence no direct relation can be established between our results and the pathomechanism of CH.

Functional and structural studies on cluster headache found activation and gray matter changes in the contralateral side of the pain [140-143]. Similar lateralisation of the white matter microstructural alterations were found in our investigation. Importantly, this finding point toward a mechanism different from vasodilatation of the intracranial arteries, since that is reported ipsilateral to the pain [144].

Limitations

Our studies are certainly not without limitation. Longitudinal studies are needed in order to reveal if the identified white matter microstructural changes are permanent. Furthermore, it would be important to know if the structural alterations have influence on brain function other than the experienced pain. Earlier studies showed that migraine and CH patients have a decline of memory processing during headache attack, but not between attacks and no progressive cognitive decline was detected [145,146]. While our results are solely structural in nature, given the strong coupling between structure and function in the brain, functional correlates also have to be considered. Our results can be paralleled by recent experiments showing altered resting state fMRI activity in migraine and CH patients [46,147-149]. Furthermore, investigation of the correlation between these microstructural alterations and molecular markers is imperative to get in depth understanding of the pathogenetic relevance of our findings.

Conclusions

Our findings raise the possibility that diffusion imaging and thalamic volumetry in research settings could be a possible biomarker of the primary headache disorders. The pattern of diffusion parameter changes, what we found in CH is similar to what we have described with identical methods in migraine, but the changes in CH are more extensive. However, specificity to migraine as opposed to other chronic pain conditions has to be investigated. While thalamic enlargement seems to be a clue to the pathogenesis of migraine chronification, further investigations into the different phases of the disease would help to elucidate the importance of our findings.

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