Interictal alterations of the trigeminal somatosensory pathway and periaqueductal gray matter in migraine

Alexandre F.M. DaSilva[a], Cristina Granziera[a], David S. Tuch[a], Josh Snyder[a], Maurice Vincent[c] and Nouchine Hadjikhani[a,b]

[a]Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, [b]Division of Health Sciences and Technology, MIT, Cambridge, Massachusetts, USA and [c]Department of Neurology, Faculty of Medicine of UFRJ, Rio de Janeiro, Brazil

Correspondence to Dr Nouchine Hadjikhani, MD, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Bldg. 120, 110 Sixth Street, Room 217, Charlestown, Massachusetts 02129, USA
Tel: + 1 617 724 5625; fax: + 1 530 309 4973; e-mail: nouchine@nmr.mgh.harvard.edu

Current address of Alexandre F.M. DaSilva, P.A.I.N. Group, Brain Imaging Center, McLean Hospital, Harvard Medical School, Belmont, Massachusetts, USA

Migraine has been traditionally considered a nonprogressive, paroxysmal disorder with no brain abnormalities between attacks. We used diffusion tensor imaging to examine interictal diffusion properties of the brains of migraineurs with aura, migraineurs without aura and matched healthy controls. Areas of lower fractional anisotropy were present in migraineurs along the thalamocortical tract. In addition, migraineurs with aura had lower fractional anisotropy in the ventral trigeminothalamic tract, and migraineurs without aura had lower fractional anisotropy in the ventrolateral periaqueductal grey matter. Our results indicate the presence of permanent interictal changes in migraineurs, pointing to an effect of migraine on the trigeminal somatosensory and modulatory pain systems. *NeuroReport* 18:301–305 © 2007 Lippincott Williams & Wilkins.

Keywords: brain, diffusion tensor imaging, imaging, migraine, periaqueductal grey, trigeminal somatosensory system

Introduction

Migraine is a common neurological disorder affecting around 10–20% of the population worldwide [1], characterized by paroxysmal attacks of unilateral, throbbing, severe headache, usually accompanied by nausea, vomiting, photophobia and phonophobia. Attacks may be preceded by transitory focal neurological dysfunctions named aura, mostly of a visual nature (migraine with aura).

The pathophysiology of migraine is not fully understood. Strong evidence exists indicating that genetically predisposed [2], abnormally hyperexcitable [3] areas of the central nervous system may be the source of an abnormal series of events ultimately leading to the migraine attack. Spreading depression, a self-propagating neurophysiologic phenomenon characterized by a spreading wave of depolarization associated with a reduction of the cortical activity, probably underlies migraine aura [4] and possibly also occurs in migraine without aura [5]. Although spreading depression fits as the cause of aura, controversy remains as to how pain develops in migraine. Spreading depression induces trigeminal activation [6], and spreading vascular changes including a short hyperperfusion immediately followed by longer-lasting hypoperfusion. Trigeminal activation may in turn induce neurogenic inflammation, a reaction characterized by vasodilation and plasma extravasation. Pain is experienced from peripherally generated trigeminal noxious stimuli conveyed to the correspondent somatosensory cortex throughout the somatosensory pathway by successive synapses (Fig. 1e).

Migraine is a paroxysmal disorder. The general idea that migraine does not induce pathology in the brain on a permanent basis and that migraineurs are indistinguishable from controls between attacks has been challenged by recent reports showing that migraine may be related to silent white matter lesions and stroke [7,8].

Diffusion tensor imaging (DTI) is a magnetic resonance imaging tool used to visualize orientation and anisotropy of grey and white matter [9]. DTI is typically used to examine white matter affecting ailments such as multiple sclerosis, stroke, brain tumours, diffuse axonal injury, degenerative diseases and HIV infection [10]. DTI has also been used to address the effects of ageing [11]. One of the DTI parameters, fractional anisotropy (FA), reflects cellular and subcellular tissue components and their preferable orientation, allowing identification of tracts separately.

To specifically test the hypothesis that white and/or organized grey matter diffusional changes along the trigeminal sensory system may be present between migraine attacks, DTI was used to examine migraineurs with and without aura and age-matched and sex-matched healthy controls. Data were correlated with clinical parameters including attack duration, frequency and the disease time span. The present results provide evidence of migraine
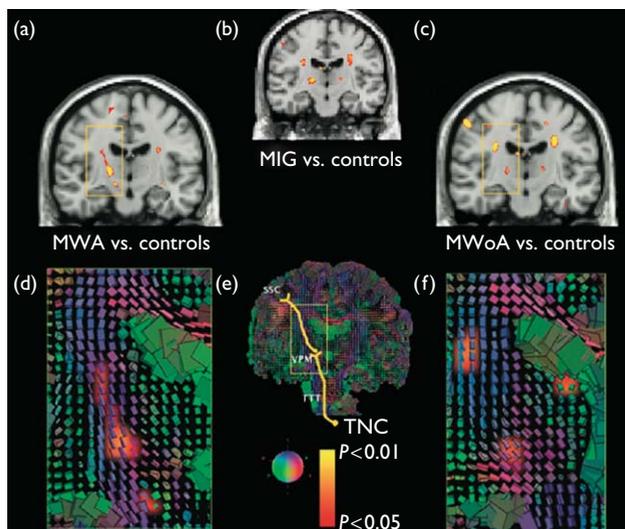
Fig. I Fractional anisotropy (FA) average significance maps superimposed on a TI coronal section comparing migraine with aura (MWA) (a), all migraine patients (MIG) (b) and migraine without aura (MWoA) (c) vs. healthy controls. Panels (d–f) show cuboid maps depicting the diffusion tensor within each voxel. The axes of each cube are placed regarding the main fibres' orientation and are coloured accordingly: green indicates antero-posterior fibres; blue indicates supero-inferior fibres and red indicates medio-lateral fibres. In (d) and (f), cuboid maps are superimposed to the FA maps shown in (a) and (c), respectively. The trigeminal somatosensory pathway is represented in yellow in (e). The rectangular areas in all parts of the figure focus the same anatomical structures. Significantly lower FA values were noticed at the thalamocortical tract (third order neurons) in both migraine subtypes. In addition, the trigeminothalamic tract (TTT) showed also significantly lower FA values in migraineurs with aura (a) (lowest cluster inside the yellow square). In both migraine forms, FA clusters were located at the ventroposterior medial thalamic nucleus (VPM), extending upwards along the thalamocortical sensory pathway. The yellow–red shading code represents P values for lower FA changes. $n=12$ for MWA, MWoA and healthy control groups. SSC, somatosensory cortex; TNC, trigeminal nucleus caudalis.

Fig. 2 Fractional anisotropy (FA) average significance maps comparing migraine with aura (MWA, left panel) and migraine without aura (MWoA, right panel) vs. healthy controls (HCs); and MWA vs. MWoA (middle panel). Significant changes were noticed in the trigeminothalamic tract (MWA vs. HC) and periaqueductal grey area (MWoA vs. HC). FA significant differences were also present between migraine subtypes. The yellow–red shading code represents P values for lower FA changes. The blue shading code represents P values for higher FA changes. $n=12$ for each group. TTT, trigeminothalamic tract; PAG, periaqueductal gray matter.

interictal diffusional changes in brain areas involved with trigeminal pain processing.

Materials and methods
Participants
Twenty-four migraine patients subdivided in two equal groups of 12 individuals (with and without aura) were recruited on the basis of the guidelines of the International Headache Society [12]. In addition, 12 age-matched and sex-matched healthy controls volunteered to participate in this study. The three groups were matched for age (migraine with aura: 33.8 ± 9.2; migraine without aura: 36.0 ± 7.7; healthy controls 31.0 ± 8.0, $P=0.35$). Females predominated in all groups (75, 58.3 and 75%). Patients were considered as migraineurs without aura when no element suggestive of any type of aura was reported. Patients reporting comorbid headaches, chronic pain elsewhere or other neurological condition (e.g. epilepsy) were excluded. Gross asymmetry or clear pathology on magnetic resonance imaging anatomical scans prevented participation in the study. The study was conducted according to the Helsinki Declarations on human experimentation, and was approved by the Institutional Review Boards of the Massachusetts General Hospital (IRB no. 2002P-000652).
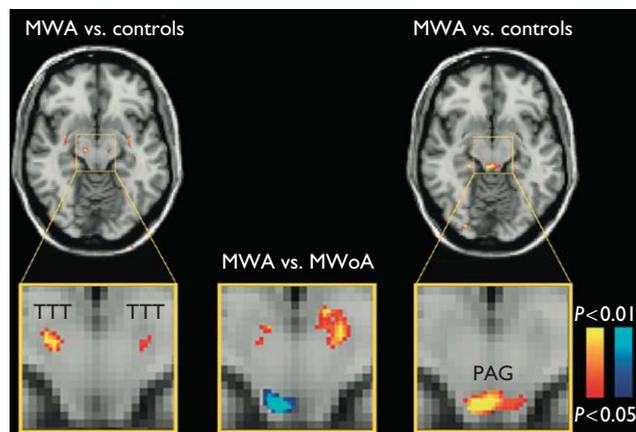
Clinical characteristics
The duration of the migraine history averaged 20 years in both migraine groups (migraine with aura: 20.3 ± 11.2; migraine without aura: 19.5 ± 8.5), with age-at-onset mostly during adolescence (migraine with aura: 13.6 ± 4.6; migraine without aura: 16.5 ± 7.1). Migraine attacks were generally described as moderate-to-severe by the patients. Patients reported a frequency of around four migraine attacks per month (migraine with aura: 4.1 ± 3.6; migraine without aura: 4.0 ± 3.6). Attack duration could not be estimated with precision as the vast majority of the patients used acute medications for pain control. The predominant pain onset side ($>50\%$) was left in four, right in two and bilateral in five of the 12 migraineurs with aura. In migraineurs without aura, pain started predominantly in the right, left and bilateral sides in equal proportions, with four patients in each category. Aura occurred predominantly at the same side of the pain in four patients, at the contralateral side in two, alternating sides in four. Two patients could not indicate the lateralization of their aura. All auras were visual in nature. In addition, four patients also described occasional sensory symptoms. Motor and language disturbances were not found. Other preheadache symptoms in few individuals included olfactory, auditory, emotional and cognitive changes.

Six migraineurs without aura were under prophylactic treatment or were taking drugs for other reasons (Diazepam, Amitriptyline, Paroxetine, Metoprolol, Propranolol and Valproate). Four migraineurs with aura were taking prophylactic medications (Verapamil, Amitriptyline, Propranolol and Valproate).

Scanning protocol
Structural imaging
Three-dimensional reconstructions of the brain images were obtained using two high-resolution magnetization-prepared rapid acquisitions with gradient-echoes (MP-RAGE) on a

3.0 T Siemens Allegra Scanner (Erlangen, Germany). The two MP-RAGE sequences ($1.3 \times 1.0 \times 1.3$ mm, 128 slices, 256×256 matrix, echo time (TE)=3.44 ms; repetition time (TR)=2530 ms; flip=$7°$) were motion-corrected and averaged to create a single image volume.

Diffusion tensor imaging
The DTI scans used a single-shot, twice-refocused echo planar sequence [13]. Protocol parameters were TR/TE: 9200/91 ms, 2 mm isotropic resolution, 64 slices, FOV 128×128 mm^2, 1 average, 60 directions of diffusion encoding with b=700 s/mm^2, and 10 encodings with b=0 s/mm^2. Head motion was reduced by the use of padded clamps tightly attached to the head coil. Patients were scanned during interictal periods (no headache), with at least 24 h after the resolution of the last attack.

Analysis
Diffusion data, including diffusion tensor associated eigenvectors, and FA metric were analysed using multiple processes as described by Salat *et al.* [11] as follows: (i) motion and residual distortion correction, (ii) calculation of FA maps from the previous volume normalized to Montreal Neurological Institute (MNI) space, with transformation of each patient's MP-RAGE volume to a MNI-152 T2 template in Talairach space, (iii) resampling of the FA map using the transformation created by the previous step, (iv) manual extraction of region-of-interest FA values on the spatially normalized data of each patient after agreement by two observers, (v) *t*-test voxel-based calculation of group statistics on the spatially normalized data and (vi) multiple comparison by Monte Carlo permutation analysis using 10^4 trials at threshold $P < 0.01$. The group analysis was performed on the FA maps, comparing each migraine subtype group to controls. All data processing was performed using tools available as part of the Freesurfer and FSL (FMRIB, Oxford, UK) streams. The localization of neuronal pathways and structures was defined by superposing the group comparison significance FA maps at $P < 0.05$ onto the red/green/blue cuboid maps, which represent the main orientation vector of each voxel as displayed in Fig. 1d–f.

Clinical correlations
Correlation of FA values with clinical data with disease duration, age-at-onset, frequency of the headache attacks and disease time span was examined. As ageing has been correlated with FA decrease in healthy individuals [11,14], age was specified as a nuisance covariate or confound variable.

All data are shown as mean $\pm$ SD; P values lower than 0.05 were considered significant.

Results
Diffusion tensor imaging changes common to both types of migraine
On the basis of the multiple comparison by Monte Carlo permutation ranking analysis, the lowest FA values were localized and common to all 24 migraineurs in two regions of the brain: the posterior limb of the internal capsule at the proximity of the ventroposterior medial thalamus (right: P=0.004; left: P=0.001), and the corona radiata at the level of

the lateral ventricle horn along the trigeminothalamic tract (right: P=0.001; left: P=0.003) (Fig. 1b).

Diffusion tensor imaging changes specific to migraine subgroups
Statistical differences in FA in the ventroposterior medial thalamus were found between migraineurs with aura and healthy controls (left: P=0.003; right: P=0.007) and between migraineurs without aura and controls (left and right: P=0.01) (Fig. 1a, c).

In addition, specific regions of reduced FA were found that were specific of the migraine subtype. In migraineurs with aura, lower FA values were present in the ventral trigeminothalamic tract bilaterally (right: P=0.007; left: P=0.02). In migraineurs without aura, lower FA values were observed in the ventrolateral periaqueductal grey matter (right: P=0.01; left: P=0.03) (Fig. 2).

Clinical correlations
We did not find any clear correlation between FA values and the clinical data (duration, age-at-onset, frequency and disease time-span).

Discussion
The present results show that prolonged migraine suffering is associated with changes in the diffusion properties of neuronal structures involved in trigeminal pain processing, the focus of this study. These findings represent changes that are not related to the migraine attack itself, because data were collected interictally.

Diffusion changes in the thalamocortical tract, corresponding to third order neurons, were present in both types of migraineurs. The thalamocortical circuitry is based on mutual feedback loops that show marked plasticity [15]. We interpret these changes as the possible consequence of frequent migraine attacks, with the presence of induced axonal adaptive response in the thalamocortical tract.

FA changes do not necessarily indicate lesions, and can be influenced by different variables such as myelination, axon diameter and axon density [9]. In consequence, interpretation of the present data should also be considered from the functional perspective. Migraine patients present interictal functional abnormalities potentially related to trigeminal sensory system dysfunction, and clinicians have long been aware that migraine patients become abnormally sensitive outside attacks not just to light and sound, but also to cutaneous/mucosal stimuli [16]. Migraine patients appear not to habituate to repetitive nociceptive stimuli [17], and interictal thalamocortical somatosensory spike activity seems to be decreased in both migraine subtypes [18]. Ultimately, this indicates that the thalamocortical tract is an important component of migraine pathophysiology, regardless of the migraine subtype. Pain modulates brain function and repetitive noxious stimulation induces long-term potentiation and hyperalgesia. The central sensitization observed in migraineurs is most probably related to an abnormal activity of the trigeminal sensory pathway.

Chronic or repetitive activation may modify grey and/or white matter structure [19,20]. This has, for example, been shown in brains of individuals trained since childhood to play piano. The authors of this study [19] found a positive

correlation between the number of training hours and FA in the internal capsule, which can be interpreted as a result of an increase in the density of myelinated axon. Paradoxically, intensive motor (piano) training results in lower FA values in the internal capsule of piano players compared with controls in two studies [19,21]. This observation can be interpreted as an increase in axonal diameter in the piano players. Training – or chronic use – may indeed have different results on white matter depending on whether it happens during brain maturation and myelination, or in the mature brain. Although repetitive, abnormally high-frequency pain stimulation occurs in migraineurs, it is possible that low FA signals over the trigeminal sensory pathway do not reflect lesions in the brain, but rather an enlargement of axons as a response to over functioning.

One could argue that white matter changes could be related to cumulative lesions of, for example, vascular origin. Migraine-related lesions, however, have a tendency to be located in posterior circulation areas [7] and not to be related to any particular functional tract as is the case in our findings. The arrangement along a functional tract makes a vascular origin unlikely, and we conclude that the differences observed in migraineurs are most probably related to changes in function at molecular level.

As a critical pain neuromodulating structure, the periaqueductal grey matter has been implicated with the activation of the nervous system in migraine. The ventro-lateral periaqueductal grey is part of a descending pain-inhibiting system from the hypothalamus and frontal cortex projecting to the medullary and spinal dorsal horns. Periaqueductal grey activation inhibits contralateral trigeminovascular nociception in cats [22]. Functional activation of the periaqueductal grey has been observed using PET during migraine attack [23], and the periaqueductal grey of migraineurs contains more iron, a marker of cellular function, with levels increasing with the duration of the disease [24]. We only found changes in the ventrolateral periaqueductal grey in migraineurs without aura, even if pain intensity and frequency were similar in both groups of migraineurs. These findings may indicate a possible dysfunction of the periaqueductal grey in migraineurs without aura, which could result in a lowering of the threshold for initiation of migraine attack through a lack of inhibition of the trigeminal sensory activation.

In conclusion, the data presented here show the presence of alterations in ascending (trigemino-cortical) and descending (periaqueductal grey) sensory pathways and structures in migraineurs, indicating an effect of migraine on the trigeminal sensory system at molecular level.

Further studies with larger amount of patients are required for precise evaluation of possible pharmacologic influences; in addition, comparison with other headache disorders may indicate whether the findings reported in this study are migraine-specific, or are the consequence of nonspecific trigeminal sensory system chronic activation by corollary symptoms.

Acknowledgements

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