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Sensory migraine aura is not associated with structural grey matter abnormalities

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ABSTRACT

Migraine with aura (MA) is characterized by cortical dysfunction. Frequent aura attacks may alter cerebral cortical structure in patients, or structural grey matter abnormalities may predispose MA patients to aura attacks. In the present study we aimed to investigate cerebral grey matter structure in a large group of MA patients with and without sensory aura (i.e. gradually developing, transient unilateral sensory disturbances). We included 60 patients suffering from migraine with typical visual aura and 60 individually age and sex-matched controls. Twenty-nine of the patients additionally experienced sensory aura regularly. We analysed high-resolution structural MR images using two complimentary approaches and compared patients with and without sensory aura. Patients were also compared to controls. We found no differences of grey matter density or cortical thickness between patients with and without sensory aura and no differences for the cortical visual areas between patients and controls. The somatosensory cortex was thinner in patients (1.92 mm vs. 1.96 mm, $P = 0.043$) and the anterior cingulate cortex of patients had a decreased grey matter density ($P = 0.039$) compared to controls. These differences were not correlated to the clinical characteristics. Our results suggest that sensory migraine aura is not associated with altered grey matter structure and that patients with visual aura have normal cortical structure of areas involved in visual processing. The observed decreased grey matter volume of the cingulate gyrus in patients compared to controls have previously been reported in migraine with and without aura, but also in a wide range of other neurologic and psychiatric disorders. Most likely, this finding reflects general bias between patients and healthy controls.

1. Introduction

The hallmark of migraine with aura (MA) is recurrent attacks of transient cortical dysfunction (Headache Classification Committee of the International Headache Society (IHS), 2013). The most common migraine aura symptoms are visual and sensory disturbances (Russell and Olesen, 1996). The pathological features that specifically predispose MA patients to aura attacks, and the effects on the brain from repeated MA attacks are largely unknown. Recently, magnetic resonance imaging (MRI) studies have suggested a relation between aura and altered grey matter structure (Granziera et al., 2013; Granziera et al., 2006). MA patients definitively have *dysfunctional* cortex during, (Hadjikhani et al., 2001) and likely also between, (Datta et al., 2013; Hougaard et al., 2014b) attacks. Therefore, MA patients could indeed be expected to have specific structural grey matter abnormalities accompanying abnormal neuronal functioning. Such abnormalities could hypothetically represent cortex that is more susceptible to eliciting waves of cortical spreading depression (CSD), the underlying pathophysiological phenomenon of the aura (Granziera et al., 2006), or they could be a result of frequent CSD episodes. In animals, CSD has been shown to alter cortical microstructure (Dreier, 2011).

We previously investigated interhemispheric structural grey matter differences in a selected group of MA patients with frequent visual aura consistently occurring in the same hemifield and found no structural changes in the contralateral hemisphere (Hougaard et al., 2015a). However, MA patients may exhibit structural brain abnormalities on the whole-brain level or changes may be present only in subgroups of patients, depending on the aura symptoms.

In the present study, we investigated a large group of MA patients with visual aura in the interictal phase. Approximately half of these patients, in addition, experienced sensory aura regularly. We further included a group of carefully individually matched healthy controls. State of the art high-field T1 weighted MRI was applied to investigate

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cortical and subcortical grey matter structure in these groups. We hypothesised that MA patients with visual and sensory aura exhibit structural differences compared to patients with visual aura only, and that grey matter structure of MA patients is different from that of matched controls.

2. Methods

2.1. Study design

We used two complementary approaches to investigate differences in grey matter structure between MA patient subgroups and in patients vs. controls:

1) Voxel-based morphometry (VBM) and 2) Surface-based morphometry (SBM). VBM gives a mixed measure of grey matter volume and density, while SBM can selectively estimate cortical thickness (Hutton et al., 2009). Thus, a combination of these two methods is useful to both detect and specify the underlying grey matter changes. For both methods we applied whole-brain analyses as well as analyses of preselected regions of interest (ROIs). All analyses were carried out with and without the addition of nuisance variables: age, gender, attack frequency and disease duration.

2.2. Patients and controls

We recruited 60 patients (42 F, 18 M, mean age 33.36 years [range 18–59 years]) suffering from migraine with typical aura (MA) according to the second edition of The International Classification of Headache Disorders (The International Classification Of Headache Disorders, 2nd edition, 2004). We also included 60 individually age and sex matched healthy controls (42 F, 18 M, mean age 33.39 years [range 18–59 years]). Data from 20 of these patients have been included in three previously published studies (Hougaard et al., 2014b; Hougaard et al., 2015a, 2015b), data from 20 of the controls have been included in two previous studies (Hougaard et al., 2014b, 2015b), while data from another 20 patients and 20 controls have been included in one study (Hougaard et al., 2015b). The remaining patients ($n = 20$) and controls ($n = 20$) were included for the present study specifically. Exclusion criteria for both groups were any other type of headache except infrequent tension-type headache, serious somatic or psychiatric conditions, or intake of daily medication including prophylactic migraine treatment. We excluded controls if they had a history of any type of migraine or first-degree relatives with a history of any type of migraine (including, but not limited to migraine with aura). A thorough medical history was taken in patients and controls and all participants underwent a complete neurological examination.

The median MA attack frequency was 12 attacks per year [range 2–96 attacks/year]. Prior to inclusion, patients gave a very detailed description of their aura symptoms. All patients reported visual aura symptoms in every attack. Twenty-nine patients additionally experienced typical sensory aura regularly (in one third of attacks or more) (7 males, median MA attack frequency 36 attacks/year, mean age 32.22 years) while the remaining 31 patients reported visual aura only (11 males, median MA attack frequency 12 attacks/year, mean age 34.43 years). All patients experienced headache following aura episodes. All patients were migraine free at least 48 h before and after the MRI scan.

The Ethics Committee of the County of Copenhagen (H-KA-20060083) approved the study, which was undertaken in accordance with the Helsinki Declaration of 1964, as revised in 2008. The study was carried out at Glostrup Hospital, Copenhagen Area, Denmark between April 2011 and June 2014. All subjects gave written informed consent to participate in the study.

3. MRI procedure

MRI was performed on a 3.0 T Philips Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands) using a 32-element phased-array receive head coil. Anatomical images were acquired using a T1-weighted three-dimensional turbo field-echo sequence (170 sagittal slices of 1 mm thickness; in-plane resolution 1×1 mm; repetition time 9.9 s; echo time 4.6 ms; and flip angle 81 degrees). The T1-weighted images were reviewed by an experienced neuroradiologist (VAL), who did not find structural abnormalities in any of the subjects.

4. Data analysis

4.1. Voxel-based morphometry

Structural data were analysed with FSL-VBM (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) (Douaud et al., 2007), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and grey matter segmentation was performed before the images were registered to the Montreal Neurological Institute (MNI) 152 standard space using non-linear registration. The resulting images were averaged to create a left–right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific average template and “modulated” to correct for local expansion or contraction due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm, i.e. approximately full width half maximum (FWHM) of $3 \times 2.3 = 6.9$ mm. We compared 1) patients with vs. patients without sensory and 2) patients vs. matched controls aura in a two-group design in a voxel-wise general linear model (GLM) using permutation-based non-parametric testing (Nichols and Holmes, 2002), correcting for multiple comparisons across space by threshold-free cluster enhancement (Smith and Nichols, 2009) (cluster-wise $P < 0.05$). Age, gender, disease duration, and attack frequency were included in the model as nuisance variables.

4.2. Surface-based morphometry

Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl and Dale, 2000). Using this approach, the grey and white matter surfaces were defined by an automated brain segmentation process. An experienced investigator, who was blinded with respect to whether subjects were patients or controls, then manually corrected the automated segmentation. Cortical thickness was estimated at each point across the cortex by calculating the distance between the grey/white matter boundary and the cortical surface. Individual whole brain surface maps were then registered to a common FreeSurfer template surface (fsaverage) by the FreeSurfer spherical registration system (Fischl et al., 1999) and smoothed with a 10 mm 2D Gaussian smoothing kernel (Fischl et al., 1999). We compared a) patients with vs. patients without sensory aura and b) patients vs. controls in a vertex-wise GLM using an unpaired design while applying cluster-wise correction for multiple comparisons using a permutation-based non-parametric analysis (cluster-wise $P < 0.05$). Age, gender, disease duration, and attack frequency were included in the model as nuisance variables. Additionally, we measured the volume of the thalamus, caudate, putamen, amygdala and hippocampus bilaterally for each subject, as well as the total intracranial volume, total grey matter volume, total cortical volume, and total subcortical grey matter volume using FreeSurfer's automated segmentation.