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Cortical plasticity in episodic and chronic cluster headache

Steffen Naegel[a,*], Dagny Holle[a], Nathalie Desmarattes[a], Nina Theysohn[b], Hans-Christoph Diener[a], Zaza Katsarava[a], Mark Obermann[a]

[a]Department of Neurology, University of Duisburg Essen, Hufelandstr. 55, Essen 45122, Germany
[b]Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Hufelandstr. 55, Essen 45122, Germany

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ABSTRACT

Cluster headache (CH) is characterized by recurrent episodes of excruciatingly painful, unilateral headache attacks typically accompanied by trigeminal autonomic symptoms. Due to its rhythm with alternating episodes of pain and no-pain, it is an excellent model to investigate whether structural brain changes detected by magnetic resonance based voxel-based-morphometry (VBM) reflect the cause of the disease, may be a consequence of the underlying disease other than pain, or may simply be caused by the sensation of pain itself. We investigated 91 patients with CH in different stages of their disease using VBM and compared them to 78 age- and gender-matched healthy controls. We detected distinct regional gray matter (GM) changes in different brain regions including the temporal lobe, the hippocampus, the insular cortex and the cerebellum. The extent, location and direction of observed GM alterations depended on the state of disease and appeared dynamic in relation to pain state (i.e., pain vs. no-pain). No hypothalamic changes were detected in CH patients compared to healthy controls. The GM changes observed in this study are highly dynamic and thereby reflect the cortical plasticity of the brain in regard to pain. This observed dynamic may provide an explanation of the diverse results of previous VBM studies in pain. Regarding CH the results suggest that the disease is more likely to be caused by a network dysfunction rather than by a single malfunctioning structure.

1. Introduction

In contrast to the former belief of a static adult brain without structural changes past full development, considerable plasticity of the adult brain has been well described now. This not only specifically applies to changes caused by training and learning, but also was shown for many other external influences. In regard to pain and headache, numerous studies showed structural brain changes in different conditions that were reversible in parallel to the cessation of pain (Obermann et al., 2009; Rodriguez-Raecke et al., 2009; Gwilym et al., 2010). In experimentally induced pain, structural changes most likely reflect alterations caused by the noxious input, while in disorders like chronic headache the question of cause or consequence of pain and disease is much more difficult to answer.

Cluster headache (CH) as primary headache disorder with strict circannual and circadian rhythm of headache attacks and symptom free episodes is a promising model condition to differentiate structural brain changes primarily related to the headache disorder itself from changes caused by the sensation of pain in general. There are three different stages of disease in CH: 1) episodic CH (eCH) in bout (i.b.) with acute pain attacks up to eight times a day, 2) episodic CH out of bout (o.b.) — an attack free phase that may last months to years, and 3) chronic CH (cCH) without attack free remission periods lasting beyond 1 month. Approximately 10–20% of all CH patients suffer from cCH (Headache Classification Committee of the International Headache Society, 1988).

The clinical characteristics of CH with trigeminal autonomic symptoms (i.e., lacrimation, conjunctival injection, tearing, facial sweating, nasal congestion, miosis and ptosis) as well as the circadian rhythm suggest involvement of the hypothalamus. This involvement was confirmed in several functional imaging studies (May et al., 1998; Sprenger et al., 2004; Morelli et al., 2009). An early voxel-based morphometry (VBM) study detected an isolated regional gray matter increase in the posterior hypothalamus which was thought to be responsible for the development of CH (May, et al, 1999). However, this pathognomonic pathophysiological connection became more and more disputed recently as many other primary headache disorders and different painful conditions showed hypothalamic involvement in imaging studies and newer VBM studies were not able to reconfirm structural hypothalamic alterations in CH (Denuelle et al., 2007; Holle et al., 2011; Kupers et al., 2000; Rosen et al., 1994; Blankstein et al., 2010; Matharu, 2006; Absinta et al., 2012; Yang et al., 2013). It was suggested that the hypothalamus might be unspecific and simply a part of the pain modulating network (Tracey and Mantyh, 2007; Holle et al., 2011).

* Corresponding author. Tel.: +49 201 723 83222; fax: +49 201 723 5953.
E-mail address: steffen.naegel@uk-essen.de (S. Naegel).

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Since not all studies on different painful disorders were able to show changes in all structures that presumably take part in human pain processing, it remains unclear which structural changes may be caused by the disease itself, which are related to pain in general, and which are a consequence of the underlying disease other than the sensation of pain (Iannetti and Mouraux, 2010).

In this study we used magnetic resonance imaging (MRI) based VBM to 1.) identify different GM change patterns corresponding to different stages of disease in order to differentiate GM changes associated with CH in general from changes related to the sensation of pain itself and 2.) reconfirm the presence of structural GM changes in the hypothalamus and other brain regions known to be associated with trigeminal pain processing.

2. Material and methods

2.1. Subjects

Ninety-seven patients (75 men, 22 women) with CH were investigated. Clinical characteristics and demography of the ninety-one subjects included into the final analysis are shown in Table 1. Patients were recruited from a tertiary headache center (West-German Headache Center) between April 2009 and August 2011. The study protocol was approved by the local ethics committee and all participants gave their written informed consent according to the Declaration of Helsinki prior to study inclusion. The diagnosis was re-confirmed in a face-to-face interview by headache experienced neurologists (D.H., M.O.) according to the International Classification of Headache Disorders (ICDH-II) (Headache Classification Committee of the International Headache Society, 2004). Inclusion criteria were age over 18 years and confirmed diagnosis of CH. Exclusion criteria were other primary headaches, psychiatric co-morbidities, and other serious somatic illnesses and pain conditions. Patients were compared to 78 healthy age- and gender-matched controls (56 males, 22 females). All subjects included were interviewed using a standardized questionnaire.

2.2. Statistical analysis of clinical and demographic data

ANOVA with post-hoc Bonferroni analysis using a cutoff significance level of $p < 0.05$ was performed for clinical data, demographics, estimated volumes of different brain tissue classes (using http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) and total intracranial volume (TIV, sum of CSF, gray matter, and white matter) using IBM SPSS Statistics Version 19 (International Business Machines Corporation, Armonk, New York, USA).

2.3. VBM — data acquisition, processing and analysis

Imaging of all patients and controls was performed on a 1.5 Tesla scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) using a standard 8-channel birdcage head coil. No participant was scanned twice. No longitudinal analysis was performed. Prior to analysis all images were rated regarding image quality and pathologies. These were double-checked by an experienced neuro-radiologist (N.T.) blinded to diagnosis and found to be unremarkable in all patients and controls included in the final analysis. T1-weighted magnetic resonance imaging (MRI) 3D datasets were obtained using a magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR: 2400 ms, TE: 3.52 ms, TI: 1200 ms, flip angle: 8, matrix: 256 × 256 mm², 160 slices, resolution: 1 × 1 × 1 mm³).

Data processing and analysis were performed using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK [http://www.fil.ion.ucl.ac.uk/spm/]) including "New Segment", "DARTEL" (Ashburner, 2007) and MATLAB (MATLAB 7.6.0.324, R2008a, The MathWorks, Natick, MA, USA). Preprocessing involved "unified segmentation" (incl. normalization into the Montreal Neurological Institute (MNI) space) and modulation in order to adjust for volume changes during spatial normalization (Wright et al., 1995; Ashburner and Friston, 1997; Friston, 1995; Good et al., 2001). Spatial smoothing was performed with an isotropic Gaussian kernel of 10 mm full-width at half maximum (Ashburner and Friston, 2005). Prior to preprocessing images of patients suffering from left-sided CH were flipped to enhance analysis. Additionally, unflipped analysis was performed to avoid false positive results due to normal brain asymmetry. It showed alterations in the same brain regions, but observed effect strengths were lower. Statistical whole brain analysis tested GM volume differences between CH patients and healthy controls (HC). Post-hoc subgroup analysis was performed comparing the following groups with healthy controls: (1) episodic CH i.b., (2) episodic CH o.b., and (3) cCH. Although gender and age matching was performed these factors were also included into the statistical model along with total intracranial volume. Gray matter changes are reported with a threshold of $p_{FWE} < 0.05$ and correction for multiple comparison (family wise error). To avoid unintentional bias by a priori hypothesis, have better comparability to previous pain VBM studies, and not miss false negative regions a threshold of $p_{unc} < 0.001$ uncorrected and a voxel size greater than 30 voxels were also investigated.

3. Results

3.1. Clinical characteristics and demographics

Table 1 summarizes the clinical characteristics and demographics of study participants. Physical and neurological examination was

Table 1
Demographics and clinical characteristics of different cohorts and subgroups.

	HC	eCH o.b.	eCH i.b.	cCH	CH	p/F
Group size	78	46	22	23	91	
Age [years]	42.78 ± 11.44 [18–64]	44.35 ± 10.95 [18–67]	45.41 ± 9.60 [28–67]	47.96 ± 10.56 [23–65]	45.52 ± 10.61 [18–67]	0.241/1.413
Men/women	56/22	36/10	19/3	16/7	71/20	0.468/0.851
Number of attacks/day	–	3.42 ± 2.34 [1–8]	2.68 ± 1.49 [1–6]	2.57 ± 1.92 [0.5–7]	3.03 ± 2.08 [0.5–8]	0.145/1.973
Last attack [days]	–	241.20 ± 186.83 [16–911]	2.82 ± 4.03 [0–14]	2.39 ± 3.64 [0–12]	123.21 ± 178.46 [0–911]	<0.001/36.260
Duration of disease [years]	–	16.89 ± 9.64 [1–40]	11.73 ± 9.55 [1–33]	12.09 ± 7.63 [2–30]	14.42 ± 9.39 [1–40]	0.039/3.373
Av. attack duration [min]	–	81.63 ± 59.55 [15–180]	55.68 ± 43.60 [15–180]	55.21 ± 33.12 [15–180]	68.68 ± 52.58 [15–180]	0.067/2.794
Total intracranial volume [ml]	1625.04 ± 160.11 [1274.74–1958.03]	1639.53 ± 126.12 [1322.56–1857.49]	1660.43 ± 135.63 [1409.22–1958.30]	1561.27 ± 155.06 [1274.74–1840.63]	1624.80 ± 139.91 [1274.74–1958.3]	0.177/1.994

HC = healthy controls; eCH o.b. = episodic cluster headache outside bout; eCH i.b. = episodic cluster headache inside bout; cCH = chronic cluster headache, CH = all cluster headache patients.