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ORIGINAL COMMUNICATION

# Increased neural connectivity between the hypothalamus and cortical resting-state functional networks in chronic migraine

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## Abstract

**Objective** The findings of resting-state functional MRI studies have suggested that abnormal functional integration between interconnected cortical networks characterises the brain of patients with migraine. The aim of this study was to investigate the functional connectivity between the hypothalamus, brainstem, considered as the migraine generator, and the following areas/networks that are reportedly involved in the pathophysiology of migraine: default mode network (DMN), executive control network, dorsal attention system, and primary and dorsoventral visual networks.

**Methods** Twenty patients with chronic migraine (CM) without medication overuse and 20 healthy controls (HCs) were prospectively recruited. All study participants underwent 3-T MRI scans using a 7.5-min resting-state protocol. Using a seed-based approach, we performed a ROI-to-ROI analysis selecting the hypothalamus as the seed.

**Results** Compared to HCs, patients with CM showed significantly increased neural connectivity between the hypothalamus and brain areas belonging to the DMN and dorsal visual network. We did not detect any connectivity abnormalities between the hypothalamus and the brainstem. The correlation analysis showed that the severity of the migraine headache was positively correlated with the connectivity strength of the hypothalamus and negatively with the connectivity strength of the medial prefrontal cortex, which belongs to the DMN.

**Conclusion** These data provide evidence for hypothalamic involvement in large-scale reorganisation at the functional-network level in CM and in proportion with the perceived severity of the migraine pain.

**Keywords** Chronic migraine · Resting state · fMRI · Default mode network · Dorsal visual network

## Introduction

During the last decade, modern neuroimaging techniques have allowed the accumulation of new information regarding the pathophysiology of episodic migraine. This information has enabled researchers to develop new pharmacological [1] and non-pharmacological therapies [2]. However, knowledge is lacking on the pathophysiology of migraine when it becomes chronic, i.e. when it occurs at least 15 days within a month and for at least 3 months, with clear migraine characteristics in at least 8 days per month [3]. Among the various brain structures considered to be involved in the pathophysiology of headaches, the hypothalamus appears to be playing an important role in primary headaches. In migraine, several studies have reported that the hypothalamus is involved in the various stages of the migraine cycle: interictal, preictal, and ictal [4]. Recently, some studies have also described

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the involvement of the hypothalamus in the pathophysiology of chronic migraine (CM). Unfortunately, however, these studies were limited by the fact that they enrolled patients who were sometimes in prophylactic therapy [5, 6], had undergone treatment of de-addiction from excessive use of symptomatic drugs, were under clear medication overuse [6], or lacked a direct comparison with healthy controls [6, 7]. We recently observed abnormalities in functional connectivity between brain networks on a large scale in a group of patients with de-novo CM who were not on prophylactic therapy and had no history of medication overuse [8].

The aim of the present study was to determine, using resting-state fMRI and a ROI-to-ROI approach, the functional connectivity between the hypothalamus and the brain networks that have been previously found to be involved in CM. Moreover, considering the important role that the brainstem reportedly plays in the pathophysiology of migraine [9–11], we also verified the connectivity between the hypothalamus and the brainstem. Finally, we verified whether there were relationships between any functional brain abnormalities and various clinical features of CM.

## Methods

### Participants

Twenty patients with de-novo CM were prospectively recruited in accordance with the third revision of the International Classification of Headache Disorders beta version (ICHD-IIIbeta, code 1.3) [12]. A posteriori, patients enrolled in the study also met the criteria for the diagnosis of CM set out in the 2018 third edition of the International Classification of Headache Disorders [3]. No patient enrolled in the study had history of acute medication overuse or had previously received a CM diagnosis. Before the diagnosis of CM, all participants had a clear clinical history of episodic migraine without aura. The participants in this study underwent a series of neuroimaging tests; part of the results of these tests were published elsewhere [8, 13]. With the exception of four patients who had a mild headache [mean of 2.5 out of 10 on the visual analogue scale (VAS)] without clear migraine characteristics, we managed to perform the MRI scans during the headache-free interval. The criteria for inclusion were lack of history of other neurological diseases, systemic hypertension, diabetes or other metabolic disorders, connective or autoimmune diseases, medically treated depression, and/or any other type of primary or secondary headache. Patients had not received any migraine-prevention treatment in the 3 months prior to the study. Fourteen of 20 patients had never received prophylactic migraine therapy. There was no clear lateralisation of the headache in any of the participants. For comparative purposes, we recruited 20 healthy controls (HCs), matched for age and sex, who were selected among university students and medical professionals. For the HCs, the inclusion criteria were the absence of personal or family history of migraine, as well as of any other type of primary headache or other medical condition at the time of the study for which they had to use medication on a regular basis. All female participants in the study were scanned outside their pre-menstrual and menstrual periods. Recording sessions were always carried out in the afternoon, between 4 p.m. and 7 p.m. Patients and HCs were randomly scanned during the same experimental session.

All participants were fully informed regarding the study and signed informed consent. The ethical review board of the Faculty of Medicine, University of Rome, Italy, approved the project.

### Imaging protocols

To obtain functional and structural images, all study participants were scanned using Magnetom Verio 3 T (Siemens). Structural anatomic scans were performed using T1-weighted sagittal magnetisation-prepared rapid gradient echo (MPRAGE) series [repetition time (TR) = 1900 ms, echo time (TE) = 2.93 ms, 176 slices, $0.508 \times 0.508 \times 1$ mm$^3$ voxels].

A BOLD contrast-sensitive sequence was used for functional imaging (echo time = 25 ms, flip angle = 90°, resolution = $3.906 \times 3.906 \times 3$ mm); whole-brain echo planar imaging volumes (MRI frames) of 40 contiguous, 3-mm thick axial slices were obtained every 3 s.

BOLD data were collected in 7.5-min runs during which the subjects were instructed to relax with their eyes closed.

### Data processing and analysis

All images were processed using SPM 12 (https://www.fil.ion.ucl.ac.uk) and CONN v17f (https://www.nitrc.org) in the MatLab environmental (https://www.mathwork.com).

Pre-processing involved the following steps based on SPM 12 algorithms. All images from a single participant were realigned using a 6-parameter rigid body process, resliced by a cubic spline interpolation. The structural (T1-MPRAGE) and functional data were co-registered for each subject's dataset; data were transformed into a common stereotactic space based on Talairach and Tournoux [14] and resampled isotropically at $3 \text{ mm} \times 3 \text{ mm} \times 3$ mm. Finally, the spatially normalised functional images were smoothed by 8 mm on each direction.

The processing steps listed below were performed with CONN, using the procedure reported by Whitfield-Gabrieli and Nieto-Castanon [15]. First, the toolbox segmented each participant's structural dataset in grey matter, white matter, and CSF. The pre-processing step removed sources of

possible confounding: BOLD signals from white matter and CSF; the realignment parameters (six rigid body head motions) were considered within subject covariates, and the rest effects condition was convolved with the hemodynamic response function (HRF); the bandpass filter values were 0.01 and 0.1 Hz. The third step analysed the functional connectivity of different ROIs in each subject based on the bivariate correlation method. The HRF was selected to weight the scans within each condition. The outcome was the first-level results: seed-to-voxel connectivity maps for each source, for each subject, and for the rest condition. The last step defined the second-level random effect analysis, specifying the contrasts between controls and patients and vice-versa; the sources were the cortical regions belonging to the default mode network (DMN), executive control network (ECN), bilateral dorsal attention system (DAS), hypothalamus, and brainstem. Moreover, as recent studies have shown the involvement of visual processing brain areas in both experimental and endogenous pain [16, 17] as well as in migraine disease progression [18], we added the cortical regions belonging to the primary dorsal (DVN) and ventral visual networks as ROIs. Indeed, the second-level analysis was based on a general linear model with selected subjects as regressors. We performed a ROI-to-ROI analysis selecting the hypothalamus as the seed and the target ROIs mentioned above. The ROI of the hypothalamus was generated according to the MRI atlas of the human hypothalamus [19].

### Statistical analyses

Group differences for demographic data were estimated using two-sample t test. The Chi-square test was performed to assess between-group differences for sex. *T* values and false discovery rate corrected *p* values between the seed and each ROI are reported for the HC and CM groups and their contrasts. We considered statistically significant *p* values lower than 0.05. Moreover, we used the first-level results to obtain the maximum absolute correlation values between the hypothalamus and each ROI for each patient. Finally, we linearly related these correlation values with the patient clinical variables, including duration of migraine history (years), severity of headache attacks (0–10 VAS score), and monthly days with headache (*n*). We consider statistically significant Pearson correlations with *p* values lower than 0.05.

## Results

Table 1 shows the clinical characteristics of the selected patient population. Neither sex distribution (Chi-square = 0.114, $p = 0.736$) nor age ($t = 1.14$, $p = 0.266$) differed significantly between the groups. We found no white matter lesions or evidence of brain atrophy in the study participants.

**Table 1** Clinical and demographic data from patients with chronic migraine (CM) and healthy controls (HCs)

| | HCs | CM |
|---|---|---|
| Female (N) | 13 | 14 |
| Age (years) | 28.5 ± 4.1 | 31.3 ± 10.2 |
| Number of headache days per month | | 23.0 ± 6.8 |
| Years with migraine disease (years) | | 15.0 ± 13.1 |
| Severity of headache attacks (0–10) | | 7.6 ± 1.6 |
| Duration of the chronic headache phase (months) | | 17.1 ± 29.3 |
| Number of acute medications taken per month | | 3.0 ± 3.2 |

Data are expressed as means ± SD

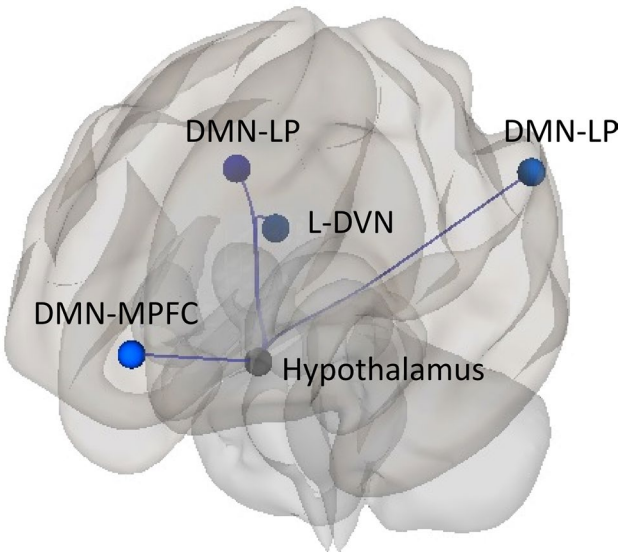


**Fig. 1** ROI-to-ROI functional connectivity with the hypothalamus as the seed area. For display clarity, each ROI is identified by its centroid positions. Results are thresholded at false discovery rate-corrected $p < 0.05$. *DMN* default mode network, *MPFC* middle prefrontal cortex, *LP* lobule parietal, *DVN* dorsal visual network, *L* left

The ROI-to-ROI analysis of the contrast HC > CM did not differ between the groups.

In patients with CM compared to HCs, we found greater functional connectivity between the hypothalamus and some areas belonging to the DMN, such as the medial prefrontal cortex (MPFC) and the bilateral parietal lobules (LP). In addition, in patients with CM, we found greater functional connectivity between the hypothalamus and the left DVN (Fig. 1, Table 2). We found no altered connectivity between the hypothalamus and the brainstem.

In patients with CM, the higher the intensity of the migraine pain, the lower the maximum absolute

**Table 2** Significant brain regions and networks showing altered hypothalamus-seeded resting-state functional connectivity in chronic migraine (CM) patients in comparison with healthy controls (HCs)

| Comparisons | Area/network | *T* | p-FDR corrected |
|---|---|---|---|
| CM > HCs | Left DVN | 3.07 | 0.012 |
| | Left DMN-LP | 2.81 | 0.012 |
| | Right DMN-LP | 2.71 | 0.012 |
| | DMN-MPFC | 2.40 | 0.019 |

*DVN* dorsal visual network, *DMN* default mode network, *LP* lobule parietal, *MPFC* medial prefrontal cortex

functional correlation ($FC_{max}$) between the hypothalamus and the MPFC ($F = 5.98$, $p = 0.026$, $R$-sq(adj) = 21.7%; $FC_{max} = 0.552–0.0373$ VAS). We did not find any other correlation between the neuroimaging data and the clinical features of CM.

## Discussion

In this study, we observed increased connectivity of the hypothalamus with the MPFC and with the parietal lobules bilaterally, i.e. areas that are part of the DMN, and with the left DVN. Moreover, from the correlation analysis, it emerged that the intrinsic connectivity strength between the hypothalamus and the MPFC strictly depends on the intensity of the migraine pain.

During attacks of migraine without aura, an area of increased blood flow was identified in the dorsolateral rostral part of the brainstem in various brain imaging studies [9-11]. This finding, replicated at a time point immediately preceding an attack [20] and in CM [21, 22], was considered to indicate the location of a "generator" of the attack. This putative role was questioned by the findings of hypothalamic activation during the preictal and ictal phases of migraine attacks. Denuelle et al. [23] using the $H_2{}^{15}O$ PET scan method were the first to observe, together with the activation of brainstem areas, activation of the hypothalamic area during spontaneous attacks of episodic migraine without aura. These activations persisted even after the headache was suppressed by sumatriptan. The involvement of the hypothalamus was also observed in the hours prior to a migraine attack. In fact, still using $H_2{}^{15}O$ PET scanning, other authors have observed an increase in brain activity during the premonitory phase of episodic migraine attacks induced by the administration of nitroglycerin [24]. In particular, they observed activation of the posterior hypothalamus and brainstem areas during the early phase premonitory phase of migraine. Activation of the hypothalamus was not seen during the late premonitory phase and during the pain phase, when activation in the brainstem areas persisted. In one patient with episodic migraine with aura, scanned sequentially every day for 30 days [25], the hypothalamus, and not the dorsolateral brainstem, was significantly more activated by a nociceptive trigeminal stimulus administered immediately preictally, when it also showed the greatest functional coupling with the spinal trigeminal nuclei [25]. Whereas, during the attack, the hypothalamus was functionally coupled with the dorso-rostral pons.

More recently, the hypothalamus has also been observed to activate as a function of noxious trigeminal stimulations in patients with CM, especially when scanning during the pain phase compared with HCs and migraineurs that were not experiencing pain at the time of scanning [5]. In patients with CM compared to patients with episodic migraine, some authors have found increased connectivity between the hypothalamus and the trigeminal spinal nucleus as well as with some brain areas that are part of the salience network, such as the insula, caudate nucleus, dorsolateral prefrontal cortex, anterior cingulate cortex, thalamus, and precuneus [6, 7]. A major weakness of the latter studies was the lack of a control group; hence, it is not clear how the presence of CM could have impacted the neuroimaging findings. Even so, as in the studies mentioned above, we did not find altered connectivity between the hypothalamus and brainstem in our patients with CM. In our previous fMRI study carried out with the same subjects, applying an analysis of independent components, we found abnormalities in functional connectivity between large-scale neurocognitive networks, specifically between the DMN, DAS, and ECN, in patients with CM compared to HCs [8]. In our patients with CM compared with HCs, we found that functional connectivity between the DMN and the ECN was disrupted and that between the ECN and DAS was weaker, while that between the DMN and the left DAS was stronger [8]. Now, we used these networks in addition to visual networks (primary, dorsal, and ventral) in a ROI-to-ROI analysis using the hypothalamus as the seed and we showed that patients with CM have greater connectivity of the hypothalamus only with the DMN areas and the left DVN compared to HCs. Between the brain areas that are included in the DMN, the MPFC and LP were the most connected. They seem to play a relevant role in the integrative processing of emotional and cognitive processes by combining emotional biasing signals or markers with decision-making processes [26]. Moreover, from human neurophysiological and neuroimaging studies, it appears that the prefrontal and parietal control regions are concurrently engaged as the neuronal mechanism underlying attention and working memory [27, 28]. The DVN extends from V1 to the extrastriatal areas of the occipital pole [29] and to the parietal lobe [30, 31] and is responsible for spatial perception (location of an object), and when lesioned, it may be responsible for visual spatial (disorientation) cognitive-task impairments, as well as visual, auditory, and somatosensory discrimination impairments [32]. Moreover,

the DVN may participate in cognitive selection of relevant sensory information and can enhance visual attention aiming to cognitively integrate different sensory modalities within the CNS [17, 33]. Recent studies have suggested that chronic pain can capture our attention not only through the salience network (previously called "pain matrix"), but also through significant involvement of the DVN [17]. Pain enhancing neural responses in primary and secondary visual areas have been previously observed approaching and during attacks of episodic migraine [25, 34], and, conversely, visual enhancing functional activity and connectivity have been seen both in patients with episodic migraines and with CM [5, 35], emphasising the deep involvement of the visual areas in the pathophysiology of migraine and its chronification. Taking together this evidence with our present fMRI findings of a hyper-connectivity of the hypothalamus with the DMN and the DVN, we speculate that this pattern of neural connectivity may be an adaptive, presumably ineffective, coping strategy to enhance avoidance learning for events associated with stressful negative outcomes such as persistent chronic headache.

Perhaps in line with the latter interpretation of the fMRI data, we intriguingly found that the strength of the intrinsic connectivity between the hypothalamus and of the MPFC correlated with the subjective perceived intensity of migraine pain. In addition to its ability to regulate the biological rhythms of our body, the hypothalamus reportedly plays an important role in the perception of pain. This function seems to be mediated by orexins, neuropeptides produced in neurons located in the hypothalamus. The antinociceptive effects of orexins have been shown in several pain models including thermally-, mechanically-, and chemically-induced nociception. Orexins modulate pain perception at both the spinal and supraspinal levels [36, 37] through their innervations to the MPFC [38]. In agreement with these experimental data, from the correlation analysis we found that the greater the perceived migraine pain intensity, the lower the strength of the functional connectivity between the hypothalamus and the MPFC. As the MPFC is also considered to mediate attenuation of pain via cognitive-control mechanisms [39], a negative correlation between the perceived pain intensity and the MPFC-to-hypothalamus connectivity in CM could reflect lack of physiological mechanisms to cognitively attenuate pain perception. Remarkably, the correlation between the MPFC and severity of pain has been found in other chronic painful conditions such as, chronic low back pain [40] and fibromyalgia [41].

We postulate that this pattern of hypothalamic-to-network connectivity and of clinical-to-neuroimaging data correlations is related to hyperactivity of the orexinergic system, which is critically involved in coordinating appropriate physiological and behavioural responses to aversive and threatening stimuli [42, 43], such as to headache. Direct and indirect involvements of the orexinergic and non-orexinergic hypothalamic systems in CM come from in-vivo studies of the neuroendocrine system in patients. Significantly higher levels of orexin-A and corticotrophin-releasing factor (CRF), a stress-related hormone also secreted by the hypothalamus (paraventricular nucleus), were detected in the CSF of patients with CM with and without medication overuse compared with control subjects [44]. After CRF administration, ACTH and cortisol concentrations were significantly higher in patients with CM than in controls, and in correlation with disease duration [45]. Some researchers showed that the hypothalamus may play a role in the progression of insulin resistance in CM through the regulation of orexigenic peptides such as neuropeptide Y [46]. Overall, this neuroendocrinological evidence might support the hypothesis that hyperactivity of the hypothalamic orexinergic system could underlie the distinct connectivity pattern found during the resting state in the present study.

As with all scientific studies, ours includes some limitations. First, the design of our study did not include patients who had migraine pain during the scan, which would have helped elucidate if there is a specific hypothalamic connectivity pattern during the experience of headache. Second, the study design was not longitudinal, i.e. did not include imaging before and after resolution of symptoms with migraine preventatives, which could help identify specific connectivity patterns for the chronic phase of migraine.

## Conclusions

This study showed that CM is associated with altered functional connectivity of the hypothalamus with regions of the DMN and DVN and that the connectivity strength between the hypothalamus and MPFC is correlated with the severity of migraine pain. Additional studies are necessary to determine if the imaging findings associated with CM are shared by other primary chronic headaches, other secondary headaches, or non-cephalic pain types or if there are imaging findings specific to CM.

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### Compliance with ethical standards

**Conflicts of interest** The authors declare no financial or other conflicts of interest.

**Ethical standard** The study was approved by ethical review board of the Faculty of Medicine, University of Rome, Italy. Written informed consent was obtained from all participants in this study.

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