

# Aberrant interactions of cortical networks in chronic migraine

## A resting-state fMRI study

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## Abstract

### Objective

We investigated resting-state (RS)-fMRI using independent component analysis (ICA) to determine the functional connectivity (FC) between networks in chronic migraine (CM) patients and their correlation with clinical features.

### Methods

Twenty CM patients without preventive therapy or acute medication overuse underwent 3T MRI scans and were compared to a group of 20 healthy controls (HC). We used MRI to collect RS data in 3 selected networks, identified using group ICA: the default mode network (DMN), the executive control network (ECN), and the dorsal attention system (DAS).

### Results

Compared to HC, CM patients had significantly reduced functional connectivity between the DMN and the ECN. Moreover, in patients, the DAS showed significantly stronger FC with the DMN and weaker FC with the ECN. The higher the severity of headache, the increased the strength of DAS connectivity, and the lower the strength of ECN connectivity.

### Conclusion

These results provide evidence for large-scale reorganization of functional cortical networks in chronic migraine. They suggest that the severity of headache is associated with opposite connectivity patterns in frontal executive and dorsal attentional networks.

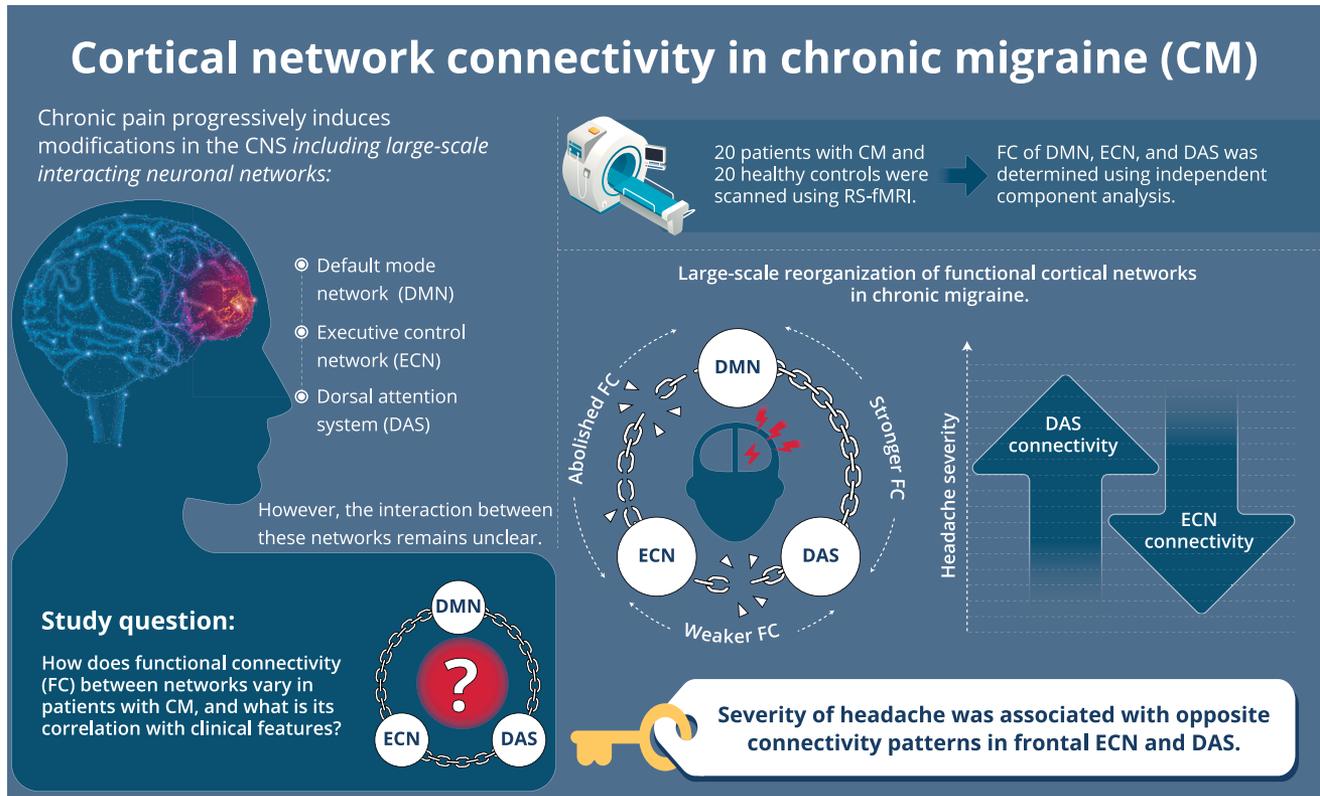
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## Glossary

**BOLD** = blood oxygenation level–dependent; **CM** = chronic migraine; **DAS** = dorsal attention system; **DMN** = default mode network; **ECN** = executive control network; **EPI** = echoplanar imaging; **HC** = healthy controls; **IC** = independent component; **ICA** = independent component analysis; **ICHD-3** = International Classification of Headache Disorders, 3rd edition; **MPRAGE** = magnetization-prepared rapid gradient echo; **RS-fMRI** = resting-state functional MRI.



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It is well-known that chronic pain progressively induces modifications at multiple levels in the CNS, from synaptic sites to large-scale interacting neuronal networks.<sup>1</sup> For instance, functional organization of the default mode network (DMN), salience network, and executive control network (ECN), subtending dynamic pain-cognition interactions, undergoes plastic changes in response to acute or chronic presentation of pain.<sup>2</sup> Previous research has shown that the same effects on the brain's functional organization can occur in response to repetitive attacks in episodic migraine.<sup>3</sup> One would expect that such cerebral plastic reorganizations may be more pronounced in chronic migraine. Resting-state functional MRI (RS-fMRI) is commonly used to investigate communications between brain areas by analyzing spontaneous coherent fluctuations of the blood oxygenation level-dependent (BOLD) signal at rest.<sup>4</sup> Independent component analysis (ICA) is a semi-automatic method to recognize coherent spatial patterns of spontaneous BOLD activity, called functional connectivity.<sup>5</sup> Previous studies in chronic migraine (CM) investigated RS-fMRI using an a priori hypothesis that a specific brain area would be involved in its pathophysiology.<sup>6–11</sup> Hence,

studies exploring functional brain connectivity, not between single brain areas, but between large-scale independent networks, are missing in CM. We therefore performed this RS-fMRI study using ICA to search for changes in functional network connectivity maps at rest in typical CM patients, that is, patients without ongoing or past acute medication overuse, and compared them with healthy controls (HC). We also searched for possible correlations between connectivity patterns and clinical features of CM.

## Methods

### Participants

Twenty patients (table) among those consecutively admitted to our headache clinics provided informed consent to participate in the present study. The 20 patients were diagnosed as having de novo CM during their first visit; that is, they did not have a past or present history of medication overuse, as in agreement with the ICHD-3-beta criteria (code 1.3).<sup>12</sup> To confirm this, we made sure that the patients had not surpassed

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

|  | HCs (n = 20) | CM (n = 20) |
|--|--------------|-------------|
| Women, n                                   | 13           | 14          |
| Age, y                                     | 28.5 ± 4.1   | 31.3 ± 10.2 |
| Days with headache/month, n                |              | 23.0 ± 6.8  |
| Disease duration, y                        |              | 15.0 ± 13.1 |
| Severity of headache (0-10)                |              | 7.6 ± 1.6   |
| Duration of the chronic headache phase, mo |              | 17.1 ± 29.3 |
| Tablet intake/month, n                     |              | 3.0 ± 3.2   |

Data are expressed as mean ± SD.

the threshold for the mean monthly tablet intake (table) set by the International Classification Committee for medication overuse.<sup>13</sup> Patients took a comprehensive series of neuroimaging tests including RS-fMRI. The same participants were studied using voxel-based morphometry and the results have been published elsewhere.<sup>14</sup> Before the diagnosis of CM, all patients had a diagnosis of having a history of episodic migraine without aura (ICHD-3 code 1.1) and used nonsteroidal anti-inflammatory drugs to control migraine symptoms. MRI recordings were made of all patients during a headache-free interval, except in 4 patients who had experienced a mild headache (mean visual analogue scale score = 2.5) without migrainous features. Recruitment criteria for patients was as follows: no history of other neurologic diseases, systemic hypertension, diabetes, or other metabolic disorders, connective or autoimmune diseases, medically treated depression, or any other type of primary or secondary headache. Patients did not always have a headache on the same side. No preventive treatments were allowed during the previous 3 months. In order to make a comparison, we enrolled 20 HC of comparable age and sex distribution, who were selected among medical school students and health care professionals. There was no personal or familial history (first- or second-degree relatives) of migraine or any detectable medical conditions among the HC and they were not on any regular medication. Participants, including HC, were randomly scanned during the same experimental session. Given the possibility of variations due to menstruation, female participants were recorded outside of their premenstrual or menstrual periods. Scanning sessions took place in the afternoon (4–7 PM). For all participants, additional exclusion criteria were abnormal structural MRI of the brain or pathologic findings, including white matter lesions.

### Standard protocol approvals, registrations, and patient consents

All participants received a complete description of the study and granted written 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 participants were scanned using a Siemens (Munich, Germany) Magnetom Verio 3T scanner with a 12-channel head coil.

Structural anatomic scans were performed using T1-weighted sagittal magnetization-prepared rapid gradient echo (MPRAGE) series (repetition time 1,900 ms, echo time 2.93 ms, 176 slices,  $0.508 \times 0.508 \times 1 \text{ mm}^3$  voxels).

Functional imaging data were collected using a BOLD contrast-sensitive sequence (echo time 25 ms, flip angle  $90^\circ$ , resolution  $3.906 \times 3.906 \times 3 \text{ mm}$ ); whole-brain echoplanar imaging (EPI) volumes (MRI frames) of 40 contiguous, 3-mm-thick axial slices were obtained every 3 seconds.

Functional BOLD data were collected in a 7.5-minute run, during which participants were instructed to relax with their eyes closed.

### Data processing and analysis

Image data were processed using SPM 12 ([fil.ion.ucl.ac.uk/spm](http://fil.ion.ucl.ac.uk/spm)), GIFT v4.0, FNC ([mialab.mrn.org](http://mialab.mrn.org)), in MATLAB environmental ([mathworks.com](http://mathworks.com)).

SPM 12 was used to preprocess the data involving the following steps.

Single participant EPI images were realigned using a 6-parameter rigid body process, resliced by a cubic spline interpolation. The structural (T1-MPRAGE) and functional data were coregistered for each participant dataset. Normalization procedure transformed structural and realigned EPI images into a common stereotactic space based on Talairach and Tournoux,<sup>15</sup> resampled by 3 mm on each direction. Finally, the spatially normalized functional images were smoothed isotropically at  $8 \times 8 \times 8 \text{ mm}$ .

### Group ICA

Grouped spatial ICA was performed for all 40 participants using the infomax algorithm.<sup>16</sup>

Two separate group spatial ICAs were also carried out in HCs and CM patients to ensure that the resulting components had similar resting-state fluctuations in the 2 groups as in the resulting components obtained from all 40 participants combined.

Therefore, data were automatically decomposed into 30 components by GIFT software.

A priori probabilistic maps provided by GIFT were used to inspect all 30 components and those whose patterns consisted above all of gray matter rather than non-gray matter were selected.<sup>17</sup> We discarded components located in CSF or white matter, or with low correlation to gray matter, because they can be of an artefactual nature, for instance eye movements, head motion, or ballistic artefacts. With FNC toolbox in MATLAB, after removing all the artefactual components, only 3 independent components (ICs) survived for further analysis: DMN (IC3), ECN (IC4), and left dorsal attention system (DAS) (IC6).

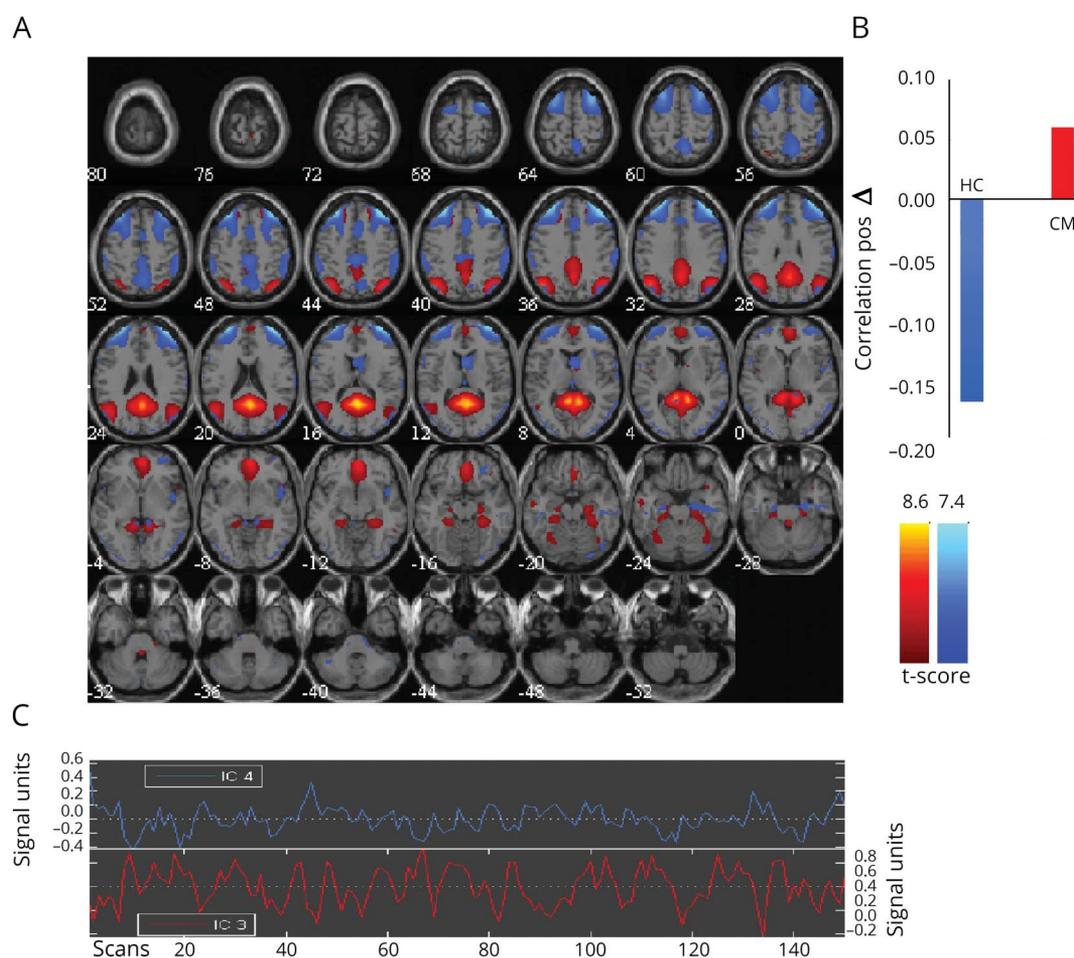
The resulted component time courses were band-pass filtered between the frequencies of 0.1 and 0.4 Hz. Correlation and lag for each pair of resulted ICs were computed for CM patients, HCs, and their possible differences, as reported elsewhere.<sup>4</sup> Each IC consists of a temporal waveform and an associated spatial map; the latter is expressed in terms of Z scores that reflect the degree to which a given voxel time-course correlates with the specific IC temporal waveform, that is, a way to measure the strength of the IC.<sup>18</sup> Furthermore, to search for a correlation between regional RS-fMRI network changes and clinical features, the Zmax scores (voxel-wise analysis) of each IC network were extracted for each participant.

### Statistical analyses

Group differences for demographic data were estimated using 2-sample *t* test.

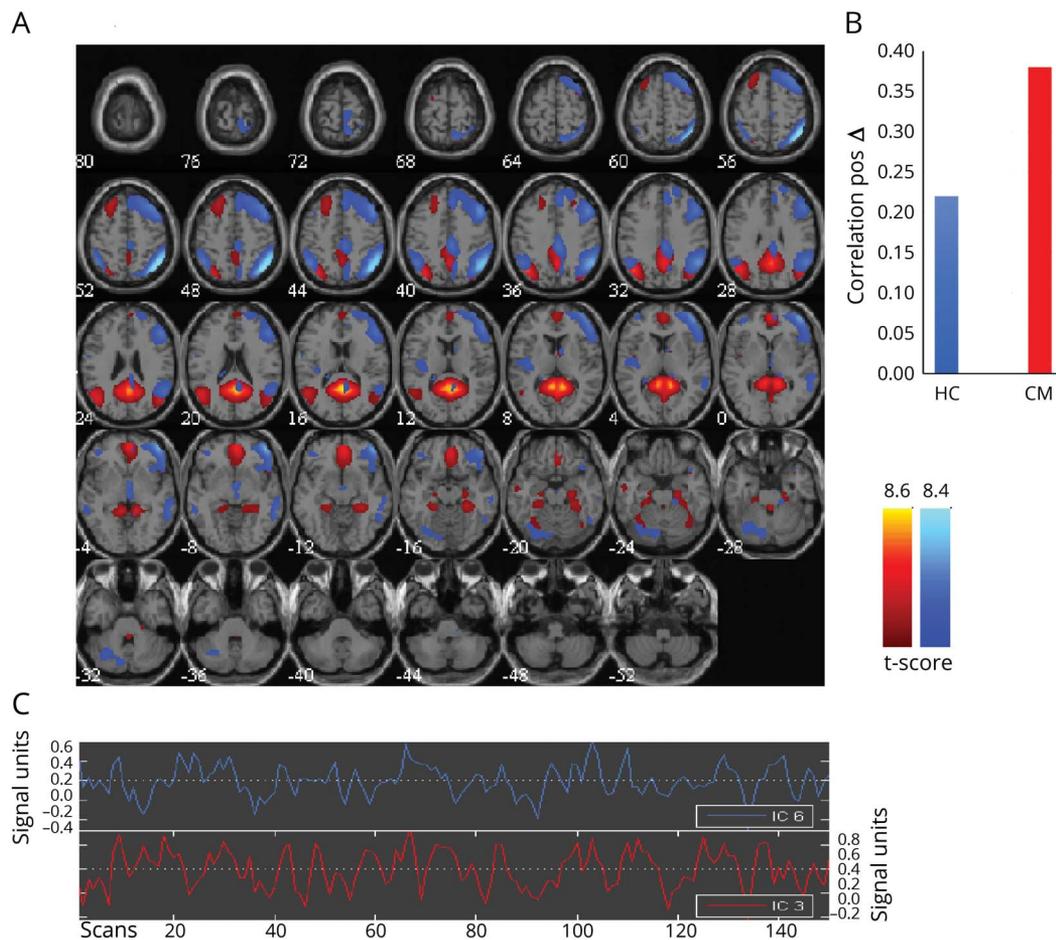
Three statistically significant differences in correlation between IC values for group 1 HCs and group 2 CM patients

**Figure 1** Resting-state functional connectivity between the default mode network (IC3) and executive control network (IC4)



(A) Image depicted of the 2 independent components (ICs) IC3 (bright red) and IC4 (bright blue) identified by IC analysis, for which functional connectivity was abolished in chronic migraine (CM) patients compared to healthy controls (HCs). We used the MRI template to coregister all images into the space of the Montreal Neurological Institute template. The numbers underneath each image are in reference to the z coordinate in Talairach space. (B) Time course of spontaneous blood oxygen level-dependent activity fluctuations during resting state and obtained from each of the 2 significant ICs. (C) The bar graph shows correlation between the 2 ICs,  $p < 0.05$ , in HC and CM.

**Figure 2** Resting-state functional connectivity between the default mode network (IC3) and left dorsal attention network (IC6)



(A) Image depicted of the 2 independent components (ICs) IC3 (bright red) and IC6 (bright blue) identified by IC analysis, for which functional connectivity was significantly stronger in chronic migraine (CM) patients compared to healthy controls (HCs). We used the MRI template to coregister all images into the space of the Montreal Neurological Institute template. The numbers underneath each image are in reference to the z coordinate in Talairach space. (B) Time course of spontaneous blood oxygen level-dependent activity fluctuations during resting state and obtained from each of the 2 significant ICs. (C) The bar graph shows correlation between the 2 ICs,  $p < 0.05$ , in HC and CM.

were identified using a 2-sample  $t$  test, choosing a  $p$  value of 0.05 without correction, performed by FNC toolbox. Moreover, connectivity combinations with statistically significant ( $p < 0.05$ ) lag values were also investigated using a 2-sample  $t$  test of the difference between averaged control and patient lags. No lag difference at this level of significance was detected.

We finally used the Pearson test to search for correlations between the individual IC Zmax scores and clinical variables including severity of headache attacks (0–10), duration of migraine history (years), monthly attack frequency (n), attack duration (hours), and days elapsed since the last migraine attack (n). A  $p$  value of less than 0.05 was considered to be statistically significant.

### Data availability

The informed consent signed by all participants in this study did not include a provision stating that individual raw data can be made publicly accessible. Therefore, in

agreement with the Italian data protection law, individual de-identified participant raw data cannot be shared publicly. Researchers meeting the criteria for access to confidential data may access the data upon request, involving the documentation of data access.

## Results

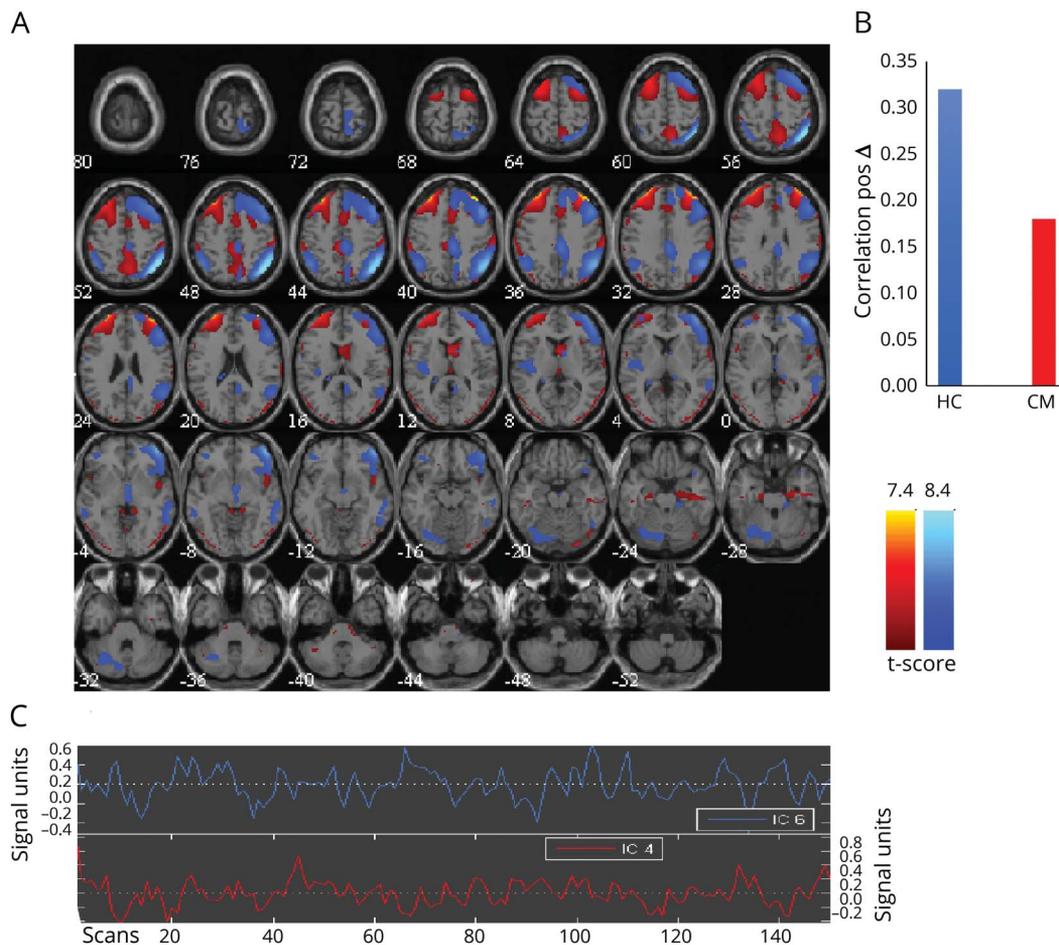
Demographic and clinical features for the 2 groups are summarized in the table. In migraine patients, there were neither white matter lesions nor features indicative of cortical atrophy.

### Resting-state fMRI

Significantly correlated components are represented in figures 1–3.

In HC, we found a significant negative functional connectivity between IC3 and IC4, encompassing interconnected areas of

**Figure 3** Resting-state functional connectivity between the executive control network (IC4) and left dorsal attention network (IC6)



(A) Image depicted of the 2 independent components (ICs) IC4 (bright red) and IC6 (bright blue) identified by IC analysis, for which functional connectivity was significantly weaker in chronic migraine (CM) patients compared to healthy controls (HCs). We used the MRI template to coregister all images into the space of the Montreal Neurological Institute template. The numbers underneath each image are in reference to the z coordinate in Talairach space. (B) Time course of spontaneous blood oxygen level-dependent activity fluctuations during resting state and obtained from each of the 2 significant ICs. (C) The bar graph shows correlation between the 2 ICs,  $p < 0.05$ , in HC and CM.

the so-called DMN and ECN, respectively, as seen on GIFT templates (figure 1). This functional connectivity was disrupted in CM patients.

In CM patients, respective to HC, there was a significantly stronger positive functional connectivity between IC3 and IC6, the latter encompassing interconnected areas of the left DAS, as seen on GIFT templates (figure 2).

In addition, positive functional connectivity between IC4 and IC6 was significantly weaker in CM patients than in HC (figure 3). In fact, the correlation of IC pair IC4–IC6 was significantly lower in CM than in HC.

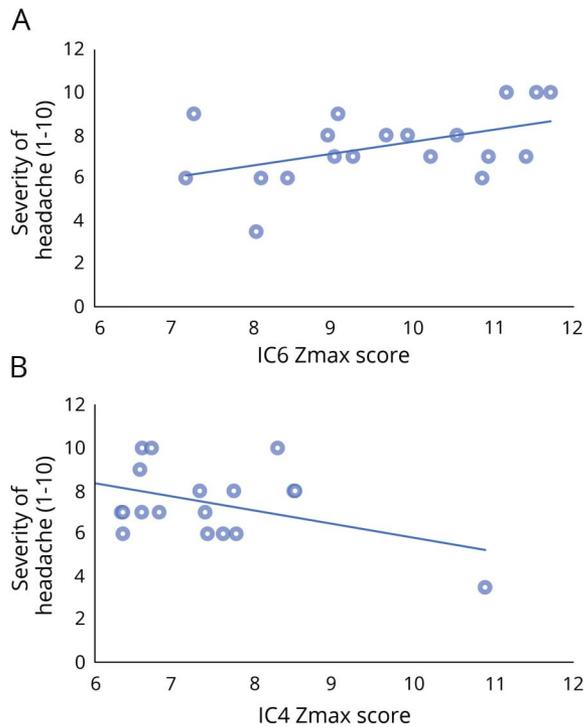
In CM patients, the more severe the headache, the higher the Zmax score of the IC6 ( $F = 4.58$ ,  $p = 0.048$ ,  $R^2[\text{adj}] = 17.4\%$ ) and the lower the Zmax score of the IC4 ( $F = 4.50$ ,  $p = 0.049$ ,  $R^2[\text{adj}] = 17.1\%$ ) (figure 4). There were no other

significant correlations between neuroimaging data and clinical CM features.

## Discussion

This study reveals abnormal large-scale functional connectivity between cortical networks in patients with CM without medication overuse. The results can be summarized as follows: as compared with HC, CM patients had (1) disrupted functional connectivity between the DMN and the ECN, (2) stronger functional connectivity between the DMN and the left DAS, and (3) weaker functional connectivity between the ECN and the left DAS. The severity of perceived migraine headache was correlated positively with the strength of left DAS intrinsic connectivity, and negatively with that of ECN intrinsic connectivity. Altogether, our findings identify a functional reorganization of large-scale brain networks in episodic migraine patients who have evolved to chronic migraine (figure 5).

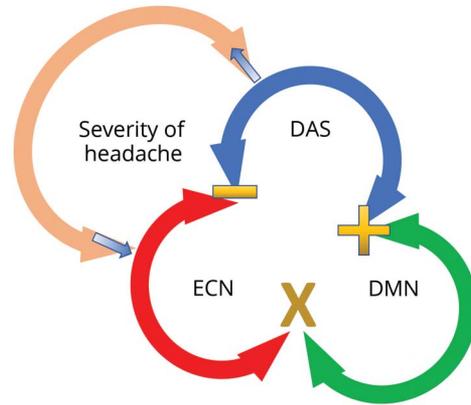
**Figure 4** Correlation analysis



In chronic migraine patients, the severity of headache, as assessed on a visual analogue scale (1–10) correlated positively with Zmax score of (A) the independent component 6 (IC6), encompassing the dorsal attention system, and negatively with Zmax score of (B) the independent component 4 (IC4), encompassing the executive control network.

Using a hypothesis-driven seed-based approach for the analysis of resting-state MRI in CM patients, some authors found that certain brain areas were involved in pain modulation and migraine chronification. Compared with HC, some authors<sup>7</sup> found that CM patients had a decreased functional connectivity between the marginal division (seed), located at the caudal extent of the neostriatum, and the right cuneus and left middle cingulum cortex, and an increased functional connectivity with the bilateral middle frontal gyrus, left hippocampus, and middle temporal gyrus. Assessing regions of interest-based intrinsic resting functional connectivity of the DMN, the salience network, and ECN in a group of 13 women with CM, some researchers<sup>9</sup> reported widespread disruptions between cortical and limbic areas in patients compared to HC, largely attributed to the consequence of medication overuse. In a group of CM patients, the functional connectivity in the brainstem trigeminal nucleus was found to be significantly enhanced during visual stimulation compared to HC and episodic migraineurs.<sup>11</sup> The major sources of bias in such studies were the inclusion of patients with previous or ongoing acute medication overuse and the concomitant use of preventive medications that may have influenced the resting connectivity pattern.<sup>19,20</sup> Here, we have avoided such biases and used a different approach to the analysis of the MRI data, that is, an ICA, to assess functional connectivity between cortical networks at rest. With this analysis, we found

**Figure 5** The cortical neural network model



Schematic representation of information flow describing the cortical neural network model that can encompass the present findings in chronic migraine patients. The severity of headache is positively interrelated with the dorsal attention system (DAS) but negatively with the executive control network (ECN) activity; the direction of the correlation (in shades of blue) is expressed by an arrow. The arithmetic sign (in yellow) reflects increase (+) or decrease (-) between the networks' functional connectivity, while X symbolizes disruption of between-networks functional connectivity. DMN = default mode network.

a complex reorganization of the functional activity of large-scale neuronal networks in CM.

The DMN is considered to be an endogenous neural network that is specialized for self-referential thought and introspection and a central topic in the study of human brain functioning.<sup>21</sup> The ECN is a large-scale network that regulates higher-order cognitive functions such as working memory, goal-directed planning, complex decision-making, also related to pain, and endogenous attention.<sup>22</sup> In studies performed in HC on working memory, an inverse pattern of activation was observed between DMN and ECN depending on the attentional resources, such as those related to an active practice task, a short-memory load, a cognitive load, or an emotional stimulus connotation, suggesting that the human brain is able to use less attentional resources to achieve better or keep stable task performance.<sup>23–26</sup> The spontaneous, low-frequency fluctuations of brain activity that occur in the resting state, without specific task demands, also exhibit patterns of connectivity that strongly resemble that of task-related patterns.<sup>27</sup> Interestingly, it has previously been shown that HC under repeated pain exposure have the same inverse pattern of activation between DMN and middle prefrontal cortex,<sup>2</sup> an area belonging to the ECN, which has been linked to fluctuating attention to pain.<sup>28</sup> In agreement with this evidence, a significant negative functional connectivity between ICs encompassing interconnected areas of the DMN and ECN during rest were detected in our HC. By contrast, DMN–ECN functional connectivity was absent in our CM patients. In previous studies, working memory-related ECN activation under a stressful condition was shown to be accompanied by a failure to suppress activity in DMN regions.<sup>29</sup> It is worth noting that CM patients have difficulties in working

memory tests,<sup>30</sup> memory retrieval, executive function,<sup>31</sup> and rational decision-making,<sup>32</sup> and they have a lower cognitive reserve.<sup>33</sup> These symptoms of a high-order cognitive dysfunction in CM may be mediated by the chronic stress related to the daily or almost daily exposure to head pain. The latter limits selective allocation of processing resources to the ECN and may contribute to disrupt the functional connectivity between DMN and ECN.

Moreover, our ICA detected a functional connection between ECN and left DAS, and between the latter network and the DMN. The dorsal attention system is composed of a group of neural regions responsible for cognitive selection of relevant sensory information, stimulus processing, and preparation of responses or action selection.<sup>17,34,35</sup> Areas belonging to the DAS and those being part of the ECN synergistically constitute the “task-positive network” that typically acts to enhance task-relevant activation, while inhibiting task-irrelevant activation.<sup>27</sup> They are also correlated during the resting state, that is, in the absence of overt task performance,<sup>36</sup> like in our case. In fact, we found here that the ECN is less functionally connected with the left DAS in patients compared with HC. This may be due to the inability of CM patients to allocate relevant attentional resources to pain, which prevents the physiologic engagement of deactivation mechanisms due to a shift from a controlled to an automatic processing of pain, which is normally accompanied by DMN deactivation.<sup>37</sup> This hypothesis is further supported by our finding that in CM, patients have a stronger functional connectivity between left DAS and DMN, probably as a product of both lack of stress-induced DMN deactivation and lack of allocation of more attentional resources to pain,<sup>38</sup> which finally results in the chronic inability to cope with it. This is also supported by earlier observations showing that lower connectivity between DMN and attention networks, and higher connectivity between ECN and attention networks, are associated with variations in meaningful cognitive attributes, such as less purposeful experiences or more experiences focused on themes of personal importance such as pain.<sup>39</sup> In a previous work, we similarly observed a lower functional connectivity between ECN and DAS during spontaneous attacks of episodic migraine.<sup>40</sup> This similarity between functional connectivity of episodic migraine patients recorded during an attack and CM patients, which was also observed for other electrophysiologic features,<sup>41,42</sup> provides functional neuroimaging support to the concept that CM, by various functional brain features, resembles a “never-ending migraine attack.”<sup>43</sup>

Another intriguing finding in our study was that the resting state intrinsic network functional activities are correlated with headache severity. In CM, subjective perception of headache intensity, as assessed on a visual analogue scale, correlated positively with Zmax scores of the DAS intrinsic functional connectivity, but negatively with Zmax scores of the ECN intrinsic functional connectivity. In humans, the visual areas devoted to the attentional systems, of which the DAS is composed, are functionally and anatomically connected with

the trigeminal system,<sup>44</sup> playing a crucial role in pain perception and, under certain experimental condition, in analgesia.<sup>45</sup> That the intrinsic functional connectivity of the ECN is at least in part related to headache severity was also observed in episodic migraine patients during the attack in whom the ECN Z scores were negatively correlated with the number of monthly migraine days.<sup>40</sup> We postulate that the abnormal functional connectivity between large-scale networks in CM may compromise the normal in/outflow activity of the DAS on trigeminal pain, leading to inability of the ECN to engage in goal-directed planning and complex decision-making in response to head pain.

Some important limiting factors of our study have to be considered. First, cognitive functions were not assessed. In future studies, multidomain cognitive tests should be performed before fMRI scanning to search for correlations with the aberrant functional network connectivity underlying attention deficits as found in CM in the present study. Second, our study was cross-sectional and not longitudinal; longitudinal studies will be necessary to evaluate the sensitivity of functional connectivity analyses to disease progression and migraine chronification.

### Author contributions

G. Coppola made substantial contributions to protocol development, interpretation of data, as well as in drafting the manuscript. V.P., M.S., J.S., F.C., V.D.P., and F.P. were implied in the interpretation of data as well as in drafting the manuscript. B.P., V.C., S.T., G. Cartocci, and C.D.L. contributed to participant enrolment. A.D.R. and E.T. were implied in recording, data processing, analysis, and statistics.

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