Functional connectivity during spontaneous migraine attacks compared to pain-free periods: a resting-state fMRI study

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November 2019

Abstract

Motivation: Migraine is a common and debilitating brain disorder, yet, its pathophysiology remains misunderstood. Migraine attacks are characterized by a throbbing headache, often accompanied by altered sensory stimuli processing and cognitive dysfunction.

Objective: To investigate migraine mechanisms by evaluating the functional connectivity (FC) in migraineurs during spontaneous migraine attacks, compared to pain-free periods.

Methods: Eleven female migraine patients without aura underwent two sessions of resting-state functional magnetic resonance imaging: during a spontaneous attack (ictally) and in a pain-free period (interictally). A data-driven independent component analysis (ICA) was performed in order to identify independent components (ICs) associated with well-established resting-state networks (RSNs). Both whole-brain and region of interest (ROI) FC analyses were performed on the selected ICs to identify differences between the two sessions. ROI-averaged FC was further correlated with patients' clinical features.

Results: ROI-based FC analysis revealed decreased within-network FC ictally in two components, one representing the sensorimotor and posterior insular cortices, and another consisting in the left frontoparietal network. Both networks' FC negatively correlated with clinically relevant migraine features.

Conclusions: This study identified abnormal ictal FC in several brain regions involved in pain perception, sensory processing, cognition and executive control. These findings contribute with novel evidence to the limited literature concerning migraineurs ictally, further supporting the view of migraine as a complex disorder.

Keywords: episodic migraine, resting-state functional magnetic resonance imaging, functional connectivity, independent component analysis, seed-based analysis.

Introduction

Migraine is a severe neurological brain condition, listed as the sixth most prevalent disorder globally and one of the main causes of disability worldwide by the World Health Organization [1]. This disorder predominantly affects women, 3:1, mainly upsetting the patients' quality of life during years of higher productivity (between the ages of 22 and 55), thus representing a significant financial burden on global economies [2]. Despite imposing significant health and financial burdens, migraine remains unattended in terms of research resource allocation and priority setting in health services. Consequently, its pathophysiology is not yet completely understood and the clinical management of migraine patients remains suboptimal [3].

Migraine is a disorder of cyclical nature, with intermittent attacks (ictal phase) alternating with attack-free (interictal) periods. Based on monthly attack frequency, migraine can be classified as episodic, if patients have up to 14 headache days per month or chronic, characterized by 15 or more headache days per month, with migraine-associated features present in at least 8 of those days [2].

Attacks are mainly characterized by a moderate to severe unilateral and throbbing head pain. As the headache progresses, it may be accompanied by a variety of non-painful symptoms, as for example autonomic symptoms (nausea, vomiting and yawning, among others), sensory symptoms, with up to 90% of patients reporting hypersensitivities to visual (photophobia) and auditory (phonophobia) stimuli, and affective symptoms (depression and irritability) [4]. An additional frequent manifestation of migraine

attacks is cognitive dysfunction. During the headache phase, the most common cognitive symptoms reported by migraineurs are "impaired thinking", "feeling distracted or slow" and "speech difficulties", suggesting attentional and executive dysfunctions. Cognitive symptoms are often under valued by clinicians, however, given that these greatly contribute to the disability associated to migraine, should instead be perceived as important therapeutic targets [5].

In some patients the headache begins with no warning signs, however, the majority of migraineurs experience a prodrome phase before headache onset, mainly characterized by changes in mood and activity, irritability, fatigue, depression, food cravings, neck stiffness, increased yawning and abnormal sensitivity to light and sound [6]. Prodromal cognitive complaints include speech and reading difficulties, as well as concentration deficits, classified as reliable predictors of the incoming attack [5]. About 10-15% of migraineurs experience migraine with aura, characterized as one or more transient and cortically mediated neurological symptoms, classified as either visual (most common), sensory, motor, speech, brainstem or retinal. The aura phase may initiate during the headache or precede it [4].

After the headache phase has ended, some patients undergo a postdrome phase defined by symptoms such as tiredness, difficulties in concentrating and neck stiffness [2]. Regarding the upper mentioned manifestations, it is possible to identify four main phases during an attack: the prodrome, the aura, the headache and the postdrome phases. Within an attack, these phases can overlap and will most probably vary both between attacks within the same patient and between patients.

The intra- and inter- patient variability, along with the great diversity of symptoms experienced by migraineurs, adds greater intricacy to this disorder. It is now widely accepted that migraine should be considered as much more than a headache, instead, a complex neurological disorder, probably affecting multiple cortical, subcortical and brainstem regions to account for the pain and wide variety of symptoms characterized in the attack [3].

Nevertheless, several questions remain unanswered when it comes to the neural mechanisms involved in initiating the migraine attacks and driving the symptoms [4]. One pathway that has frequently shown to be associated to migraine biology (especially in the headache phase) is the trigeminovascular system, which conveys nociceptive information from the meninges to central areas of the brain located in the brainstem. The brainstem then fires

to the thalamus, where trigeminal thalamocortical neurons have projections to a diffuse network of cortical regions, including the primary and secondary motor (M1/M2), somatosensory (S1/S2) and visual (V1/V2) cortices [2].

In the last two decades, the number of resting-state functional magnetic resonance imaging (rs-fMRI) studies in migraine has increased significantly, showing a remarkable potential for bringing new insights into migraine's pathophysiology [7].

The rs-fMRI technique is conducted when subjects are not performing any explicit task, thus relying on spontaneous, low frequency fluctuations of the blood oxygenation level dependent (BOLD) signal [8]. Through correlation between the signal of different voxels, the rs-fMRI allows the study of functional connectivity (FC) within and between different brain regions, under the assumption that functionally related structures behave similarly [9]. Throughout the years, studies investigating brain's resting FC allowed the identification of different resting-state networks (RSNs), each consisting of temporally synchronized structures in the brain. These networks have shown to be reproducible across individuals, sessions, scanners and methods, but their spatial extent and connectivity strength are affected by physiologic parameters and pathological conditions. Therefore, rs-fMRI has emerged as a new window to the brain, enabling the identification of functional disconnection in psychiatric and neurological disorders, providing rich and sensitive markers of disease [10].

In previous literature, migraine patients have shown atypical resting-state FC in the default mode network, salience network, frontoparietal network, executive network and sensorimotor network, with the extent of FC abnormalities being positively correlated with markers of migraine burden, such as disease frequency and duration [8]. On the basis of emerging evidence regarding atypical FC in migraineurs, the present study aims to investigate attack-specific FC alterations in migraine without aura (MwoA) through a whole-brain exploratory approach, thus avoiding any *a priori* hypothesis about the source of possible functional disconnections in migraine.

Materials and Methods

Participants and study design

Fourteen female episodic MwoA patients, according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) [11], were prospectively recruited among Hospital da Luz staff and patients from the acute care outpatient clinic.

Exclusion criteria were as follows: presence of aura; previous history of chronic migraine; a history of other headache types; pregnancy; contraindication for MRI; and claustrophobia-suffering volunteers. To avoid any pharmacological interference, the only allowed medication was oral contraception and patients were not under any prophylactic regimen for migraine prevention. Demographic data and the following clinical characteristics were obtained from the patients: usual duration of migraine attacks, migraine frequency (day/month) and usual pain intensity of migraine attacks. The later was assessed by visual analogue scale (VAS), measured on a paper-based 10-cm graduated line. In order to obtain an accurate assessment of the patients' headache-related disability, participants completed the HIT-6 (Headache Impact Test), in which scores vary between 36 and 78, with higher scores corresponding to higher impact, i.e. reduced functioning and productivity (see table 1 for demographic and clinical features).

Table 1: Demographics and usual attack clinical features, averaged across the participants.

Parameter	mean ± SD
Age (y)	35.7 ± 7.35
Attack duration (h)	32.6 ± 25.3
Headache intensity (0-10 VAS)	7.38 ± 1.26
Frequency (attacks/month)	2.38 ± 1.56
HIT-score	62.0 ± 4.00

y=years; h=hours; VAS=Visual Analogue scale; HIT=Headache impact test.

This study adopted a longitudinal approach, with each subject being evaluated in two different phases of the migraine cycle. The first session evaluated the subjects during the headache phase of a spontaneous MwoA attack (ictal phase) while in the second session the subjects were in the interictal (attack-free) period of the migraine cycle. The second session was always performed at least one month after the first evaluation and with a minimal 48 h delay from the last migraine attack. In the first session, information regarding the duration and headache intensity of the ongoing attack was collected. Participants were also asked to rate the expression of several migraine-defining symptoms using a VAS. The clinical parameters characterizing the ongoing attack in the first session are presented in table 2. Only 11 of the 14 patients enrolled in this study were able to perform the two scanning sessions as initially designed, hence, only data from these 11 participants was considered for further analysis.

Table 2: Clinical features characterizing the ongoing attack in the ictal session, averaged across the participants.

Parameters	mean ± SD
Attack duration (h)	15.5 ± 18.6
Headache intensity (0-10 VAS)	6.85 ± 1.41
Nausea (0-10 VAS)	4.27 ± 1.54
Photophobia (0-10 VAS)	4.88 ± 1.66
Phonophobia (0-10 VAS)	5.00 ± 2.35
Worsening with physical effort (0-10 VAS)	4.62 ± 2.50

y = years; VAS = Visual Analogue Scale.

Imaging protocol

MRI was performed in a 3 Tesla Siemens Verio MRI system (Siemens, Erlangen, Germany), equipped with a 12-channel head radio-frequency coil. In each session, structural and resting-state functional images were acquired. Functional data consisted of 180 volumes of a repeated gradient-echo echo planar imaging (EPI) T2*-weighted sequence (TR=2250 ms, TE=30 ms, voxel size of 3.5 mm × 3.5 mm × 6.25 mm). Structural T1-weighted images using magnetization-prepared rapid gradient echo (MPRAGE) series (TR=2250 ms, TE=2.26 ms and voxel size of 1 mm × 1 mm × 1 mm) were acquired for registration of the functional images. During scanning, subjects were asked to simply stay motionless, awake and relaxed; no visual or auditory stimuli were presented at any time.

Data processing and analyses

Resting-state data were processed using FMRIB Software Library (FSL). An initial approach on the preprocessing of the functional images followed a standard pipeline, as described in the literature [12], including removal of non-brain structures, motion correction, distortion correction using a fieldmap image, spatial smoothing (5mm full-width at half-maximum Gaussian kernel) and high-pass temporal filtering with a cutoff frequency of 0.01 Hz [13].

Careful noise removal is particularly important in rs-fMRI, given its high sensitivity to artifacts that could reduce the signal to noise ratio, complicate the identification of RSNs and mislead further statistical analysis [14]. Therefore, additional preprocessing strategies were applied in this study, namely motion outliers regression and independent component analysis (ICA)-based denoising. Nuisance regression of motion outliers

accounted for rapid and large movements which could not be corrected by standard motion correction and consisted in the identification of the time points most significantly corrupted by movement, which were further regressed out from data [15]. Afterwards, ICA-based denoising was applied. Being a data-driven approach, this method did not make any prior assumption on the relationship between the sources of noise and resulting changes in rs-fMRI signal, thus accounting for multiple types of noise sources. This strategy's first step consisted in a single-subject ICA (FSL MELODIC [16]), in which data was decomposed into different independent components (ICs), some consisting of signal of interest (i.e. reflecting neural activity) and others of artifactual fluctuations. Automatic classification of the independent components was performed using the FSL tool FIX and further confirmed through visual inspection and analysis of the components' temporal and spectral features [17].

Similarly to previous studies, in order to co-register rs-fMRI images to a standard space, functional images were first registered to each individual's high-resolution T1 anatomical scan and further to the Montreal Neurological Institute 152 (MNI152). The first registration was performed using boundary-based registration, which consists in a linear registration with 6 degrees of freedom, optimized by cost function based on EPI intensity differences between voxels inside and outside of white-matter/grey-matter boundaries (defined by T1-weighted segmentation). The second registration was performed through a non-linear transformation based on a deformation field, thus accounting for the alignment of internal structures [18].

Previous studies suggested ICA to be a reliable method for analyzing resting-state FC, enabling the identification of the different RSNs [19]. Probabilistic group-level ICA (FSL MELODIC [16]) was performed with automatic dimensionality in order to derive the group's RSNs (i.e. considering all subject in both sessions). This analysis resulted in a total of 65 group-ICs, some representing signal of interest and others structured noise sources. Hence, there was the need for identifying which ICs constituted of neural activation through analysis of spatial, temporal and spectral component features, resulting in a total of 21 ICs of interest. Identification of the different well-established RSNs among the 21 ICs was performed through visual inspection, comparison with previous literature on RSNs' architecture and through spatial correlation of each of the 21 ICs with 10 well-matched RSNs templates published by Smith and colleagues [20]. Then, a dual-regression analysis was applied (FSL DualRegression [21]). Using each of the 21 ICs as spatial regressors in a general linear model (GLM), it was possible to extract the temporal dynamics associated with each spatial map. The resulting time courses served as temporal regressors in a GLM in order to generate subject-specific maps of the whole brain for each subject, reflecting the voxel-wise strength of the resting-state FC in that voxel to the corresponding IC.

Statistical analysis

FC maps from the second GLM were tested for whole-brain paired differences between the ictal and interictal states in a voxel-wise manner, using non-parametric permutation testing (5000 permutations) with threshold-free cluster enhancement, family-wise error (FWE)-corrected for multiple voxel comparisons (FSL Randomise [22]). A two-sided FWE-corrected $p < 0.05$ was considered statistically significant.

In addition, differences between the two sessions were also investigated regarding the average FC within each IC in a region of interest (ROI)-based analysis. With that purpose, an inclusive mask was created from each of the 21 IC spatial maps, thus defining each ROI, and further applied to the corresponding subject-specific maps from dual regression. Such maps express the relative modulation of each voxel by that IC's activity, hence, by averaging such values, it was possible to obtain measures of mean FC strength within each of the 21 ICs and for each patient. Mean FC was tested for paired differences between the two conditions through a two-sided Wilcoxon signed rank test. Multiple comparison correction was performed via false discovery rate (FDR) correction and a corrected $p < 0.05$ was considered statistically significant [23]. Finally, a post-hoc analysis was performed regarding the ICs to which the mean FC was significantly different between the two sessions, in order to search for relations between within-network FC and several clinical features. Non-parametric Spearman rank correlation [23] was performed between the mean FC values and several migraine clinical parameters. For testing the hypothesis of no correlation against the alternative hypothesis of a nonzero correlation, a significance threshold of 5% was applied.

Results

In this study, 65 ICs were extracted from data through a group-level ICA, with 21 ICs being classified as signal of interest and the remaining as noisy fluctuations. From the 21 ICs representing neural activity, 17 were associated to well-established RSNs, as also reported by Smith and colleagues [20]. Through comparison

between the obtained ICs and literature on RSN's architecture, it was possible to observe that, in some cases, the large-scale RSNs were split into different ICs, i.e. different sub-networks. Therefore, the high dimensionality of the group-ICA allowed for detection of fine-grained RSNs, with increased potential on providing detailed insight into disease-related FC changes [24].

Connectivity maps from each of the 21 ICs were tested voxel-wise for paired differences between the ictal and interictal states. However, non-parametric testing revealed no significant differences in either of the 21 group ICs for a significance threshold of 0.05, FWE-corrected with the TFCE method.

Regarding the ROI-based analysis of within-network FC, the Wilcoxon signed rank test revealed a significant paired difference in the mean FC of IC4 between the ictal and interictal periods (p=0.04, FDR-corrected). This IC showed increased FC during the interictal period when compared to the ictal phase. An interesting tendency has also been observed for IC30 (p=0.02, uncorrected for multiple comparisons), showing an increased FC during the interictal period in comparison to the ictal phase.

Figure 1 displays a comparison between the *Harvard-Oxford Cortical Structural Atlas* and both IC4 and IC30, allowing the identification of the cortical regions involved in these ICs. The boxplots represented in the same figure show the distribution of the mean FC values for each IC in the ictal and interictal periods.

Post-hoc correlation analyses revealed that within-network FC in IC4 was negatively correlated with usual attack duration in both the ictal (ρ= -0.71, p= 0.02) and interictal (ρ= -0.70, p= 0.02) sessions. Moreover, averaged FC values from IC30 in the ictal phase were negatively correlated with the headache intensity of the ongoing attack (ρ= -0.68, p= 0.02). See figure 2 for details on correlation analysis.

Discussion

On one hand, **IC4** (figure 1, upper row) showed activation in regions of the postcentral and precentral gyri that are functionally associated to the sensorimotor cortex, composed by the primary motor cortex (M1) and the S1. Interestingly, IC4 also comprised some regions of the posterior insula, bilaterally. Through comparison between IC4 and RSN templates provided by Smith and colleagues [20], this IC was identified in this study as the sensorimotor RSN, which includes the supplementary motor area, sensorimotor cortex, secondary somatosensory cortex and bilateral middle frontal gyri [20, 10]. Given that the full extent of the network was not included in this IC and the fact that the insula was also

included, this component will be further referred as **sensorimotor-insular network**.

On the other hand, **IC30** (figure 1, bottom row) corresponds well to the literature-defined left frontoparietal network, involving prefrontal and parietal cortical areas. Interestingly, although less prominent, this IC also included some areas in the superior frontal, cingulate (posterior division) and paracingulate gyri. These last three regions are usually associated to the executive control network [20], however, this result is not completely irreconcilable with the literature, since the distinction of the structures involved in the frontoparietal and executive networks is not linear across studies, with several authors even gathering the structures form both these networks within one single executive network [25, 26, 27, 9]. Therefore, it can be stated that IC30 corresponds to a **left frontoparietal/executive control network**.

FC of the sensorimotor-insular network

In the present study, a decreased within-network FC has been identified in the IC representing a sensorimotor-insular network during the ictal period when compared to the interictal phase.

The sensorimotor network has shown to be related to pain processing, involved in sensory and affective aspects of pain, therefore, the dysfunction of this network and/or its subregions could cause inefficiency in processing afferent nociceptive information [28]. The S1 is located in the postcentral gyrus on the lateral surface of the hemisphere and areas dedicated to processing sensory information from the different parts of the body are distributed across this surface, with the apportioning of the cortex for a particular part of the body being related to its functional importance (e.g. the face has particularly large areas assigned to it) [29]. Moreover, thalamic neurons within the trigeminal sensory processing system have projections to the S1, most precisely to the region responsible for processing sensory input from the face [30]. In the present study, during the attacks, participants were experiencing head pain, which, according to the literature, would reflect in nociceptive inputs to the trigeminovascular system [2]. Therefore, it would be plausible to expect an increased FC during the ictal phase in the facial regions of S1. However, this was not observed. S1 regions within IC4 did not correspond to the ones responsible for processing sensory input from the face (instead, consist in more medial regions, responsible for processing inputs from the arms and legs) and a decreased FC in these regions was observed during the attacks. Converging evidence suggests that, upon nociceptive stimulation, regional cerebral blood
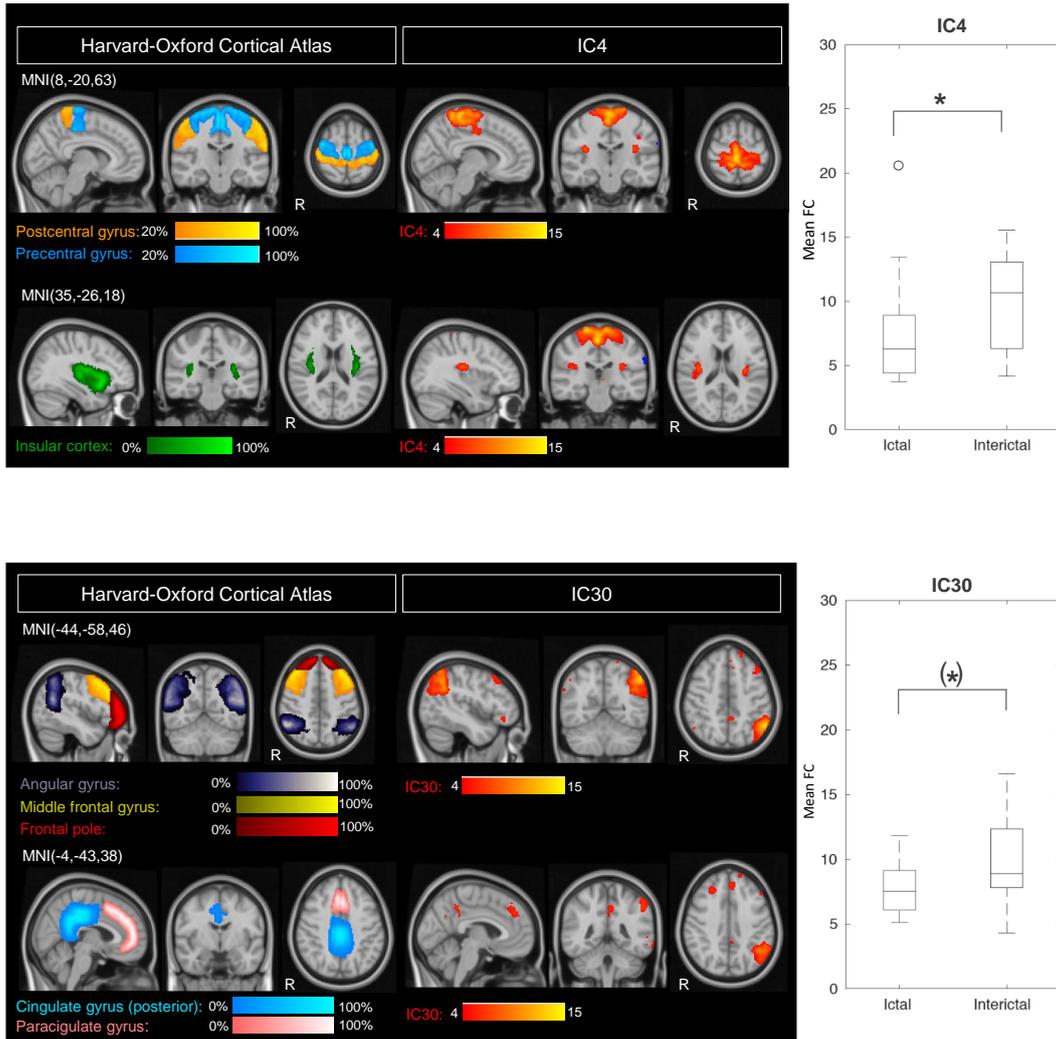
Figure 1: Identification of the cortical structures involved in IC4 (upper row) and IC30 (down row) and, for each IC, boxplot representations of the distribution of mean FC in the ictal and interictal periods. **Left:** Identification of the brain structures in each IC's spatial maps through comparison with *Harvard-Oxford cortical structural atlas*. All images have been coregistered into the standard MNI152 space so that the shown coordinates (in mm) correspond to *x,y,z* in this space. Atlas maps are represented as probabilistic images while the IC maps are represented as thresholded Z statistic maps. R marks the right hemisphere side in the axial representations. **Right:** Boxplot representations of the distributions of the mean FC (y-axis) for each IC in the ictal and interictal periods. The central mark is the median; the edges of the box are the 25th and 75th percentiles; the upper and lower extreme represent, respectively, the maximum and minimum values (excluding outliers).

flow in S1 (which increases upon neuronal activation in that area, according to the neurocoupling theory) may partially depend on the attention directed to the stimulus. When, during a study with painful stimulus, a decrease in blood flow was observed in portions of the S1 that did not correspond to the stimulated body area [31], authors have explained such effect as resulting from cognitive variables as for example anticipation of pain or focused attention to the site being stimulated.

Therefore the decrease in FC observed in the present study during attacks may result from a decreased activation in sensory areas that do not receive relevant input, perhaps representing an 'economical' brain mechanisms to facilitate stimulus detection by enhancing the contrast between regions concerned or not by stimuli [31].

On the other side, the insula is a very complex structure, associated to a wide variety of functions, such as sensation, homeostasis (including error

IC4

Ictal

$\rho = -0{,}7055$
$p = 0{,}0152$

Mean FC / Usual attack duration

Interictal

$\rho = -0{,}6962$
$p = 0{,}0173$

Mean FC / Usual attack duration

IC30

Ictal

$\rho = -0{,}6842$
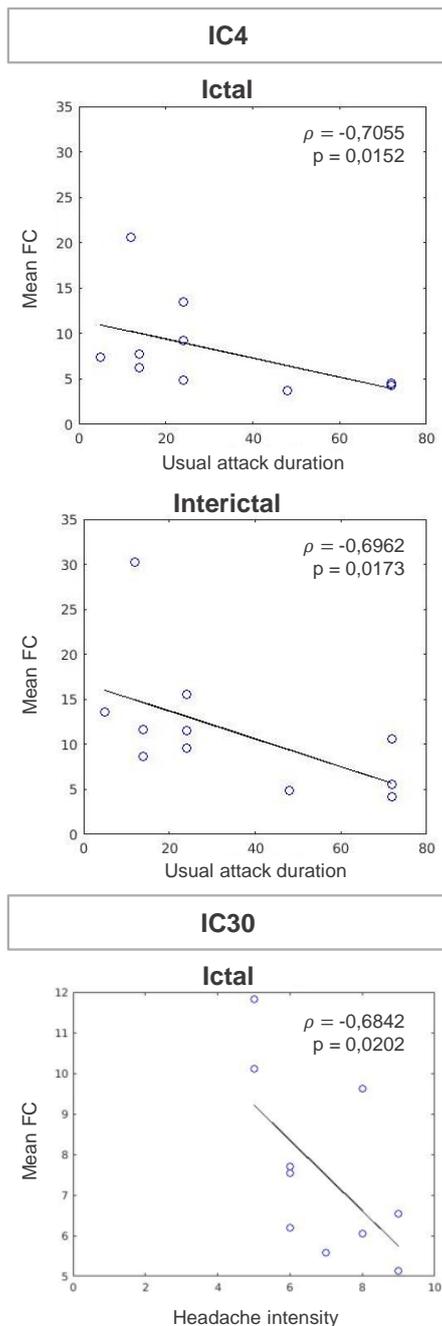$p = 0{,}0202$

Mean FC / Headache intensity

Figure 2: Spearman rank correlation analysis between IC4 and IC30 mean FC and clinical features. The two first images correspond to the correlation between IC4 mean FC (in the ictal and interictal periods, respectively) and usual attack duration. The third image corresponds to the correlation between IC4 mean FC in the ictal period headache instensity of the ongoing attack. The associated Spearman's rank correlation coefficients (ρ) and *p-values* are also displayed.

detection), autonomic function, emotion, salience and awareness. This region also plays an important role in visceral processing, by receiving visceral afferent projections from various body parts [32]. The posterior insula, which is precisely the region identified within IC4, is more closely connected to the premotor, sensorimotor, supplementary motor and middle-posterior cingulate cortices, suggesting its strong involvement in sensorimotor integration [33]. This region has been reported to play a fundamental role in pain perception, since it showed consistent activation in response to noxious stimuli in neuroimaging studies, irrelevant of modality or body part [32]. In patients with insula lesions, acute experimental noxious stimuli produced higher pain intensity ratings, as well as increased levels of responses in the primary sensory cortex when compared with healthy controls (HC) [34].

Therefore, a differential interaction between the sensorimotor cortex and the posterior insula during migraine attacks in relation to attack-free periods could be responsible for abnormalities in pain perception. Given that in this study migraineurs served as their own controls, it is not possible to conclude whether altered sensorimotor-insular interactions are characteristic of migraine attacks or if such impairment is a feature of the migraine brain in comparison to healthy subjects. Nevertheless, the fact that the bilateral posterior insular cortex regions have appeared within the same group-IC in this study already consists in an interesting result regarding the migraineurs' brain. In previous studies concerning the sensorimotor cortex such effect was not observed, perhaps because the majority of investigations included HC along with migraineurs. This result may point to an increased need for visceral sensorimotor integration in migraineurs, when compared to healthy subjects.

This network's FC in both the ictal and interictal periods was negatively correlated with the participant's usual attack duration. The fact that similar relations were observed in both the ictal and interictal periods supports the idea of a decreased FC between the insula and S1 as a feature of the migraineurs' brain (perhaps underlying a general pain processing impairment) and not necessarily isolated to the ictal phase (although further decreasing during this period). The observed negative correlations are in accordance with the reported decrease in FC between these structures inside the attacks when compared to interictal periods, supporting an origin of the imaging findings in migraineous mechanisms. However, the direction of such associations is not possible to be clarified, i.e., it is not clear if recurrent and high duration migraine attacks result in progressive maladaptive changes in FC or if, in opposition, worse baseline FC predisposes the patients to have higher duration attacks [8]. If adopting the

second interpretation, it could be hypothesized that impaired sensorimotor-insular interactions in migraineurs result from decreased activity of anti-nociceptive mechanisms.

To our knowledge, only one study has compared the FC within the sensorimotor network between migraine attacks and interictal periods. Such study was performed by Amin and colleagues, who recorded rs-fMRI in migraine patients before and during the early phase of PACAP38-induced migraine attacks. FC was investigated in a seed-based fashion. Concerning the seed representing the sensorimotor network, no significant results were found concerning S1, therefore, results are not directly comparable. Nevertheless, the present investigation holds the great advantage of having scanned the participants during a spontaneous migraine attack, instead of an induced one, therefore allowing more reliable conclusions on migraine mechanisms to be drawn [35]. The sensorimotor network's FC was compared in migraineurs interictally versus HC in an investigation by Zhang et al. through a seed-based analysis, in which seeds were placed in the left and right S1. Although this study compares migraineurs interictally with HC, the results are comparable with the present investigation and further support the previously drawn hypothesis of altered sensorimotor-insular interactions persisting through the interictal phase in migraineurs [28].

FC of the left frontoparietal/executive control network

In the present study, a tendentious decrease in within-network FC during the ictal period has been observed for the IC representing the left frontoparietal/executive control network.

Executive functions require the coordination and goal-orientation of several subprocesses, including decision-making, planning and cognitive flexibility, and such complex operations are involved in a variety of daily living experiences and target-directed activities [20, 36].

Patients consistently report cognitive impairment during migraine attacks, which greatly contributes to the high level of disability attributed to this disorder [37]. Neuropsychological tests performed in migraineurs have already shown decreased cognitive performance during attacks, supporting patients' subjective complaints, with executive functions being among the mostly impaired [5]. These findings point to the existence of a reversible cognitive dysfunction in the ictal phase of migraine and it is of utmost importance to understand the mechanisms that are potentially causing it.

It has been hypothesised that such dysfunction during attacks could be a consequence of pain-cognition interactions. In fact, cognitive and pain networks partially overlap, therefore, if simultaneously active, both systems could be expected to compete for resources. In healthy individuals, concurrent activation of both systems has shown to not affect the performance of either, with acute pain showing little ability to interfere with cognitive activity. In opposition, migraine patients showed decreased cognitive task-related brain activity during painful stimulation suggesting abnormal cognitive-related activity. Therefore, recurrent nociceptive inputs during a migraine attack can compete with cognitive information processing, with cognitive resources being diverted from task-related to pain-reduction-related processes [38, 39].

The interrogation of frontoparietal and executive control network structures during a migraine attack provides an indirect way to study cognitive integrity on a brain network level. In the present study, a tendency for this network's FC to decrease during migraine attacks was observed, possibly resulting from pain-cognition interactions, with nociceptive inputs during head pain hindering the normal functioning of executive networks.

Supporting these findings is an investigation by Coppola et al., which studied the resting-state FC in migraineurs ictally versus HC. Resorting to the ICA approach, the investigators identified two main networks: the executive control network and the dorso-ventral attention networks. Authors have found a decreased FC between the executive control and the dorso-ventral networks during spontaneous migraine attacks, as compared to HC. Such ictal abnormal connectivity was interpreted as the neural substrate for decreased performance in several cognitive domains during migraine attacks, as reported by previous neuropsychological studies. Moreover, authors hypothesized that the impairment of cognitive networks should decrease upon spontaneous termination of the attack, as was found in the present study [36].

The observed negative correlation between this networks' FC in the ictal phase and headache intensity of the ongoing attack supports the neuroimaging findings of a decreased FC during migraine attacks given that during this period migraineurs were experiencing head pain. Moreover, a negative correlation with pain intensity supports the hypothesis of an ictal cognitive dysfunction in migraineurs as a consequence of pain-cognition interactions, as a result of acute pain processing by the brain.

Conclusion

In the present study, by means of a robust ICA approach, all available functional networks were

tested in data from rs-fMRI in 11 migraine patients during and outside of spontaneous migraine attacks. This analysis revealed altered FC within two networks, one comprising the sensorimotor cortex in interaction with the bilateral insula and another representing frontoparietal structures, along with regions responsible for executive control. Such findings point to the involvement of these networks in migraine attack mechanisms. Regions that reported altered FC in the present study are associated to a great variety of brain functions, from somatosensory processing to cognitive functions. Atypical FC within these structures could explain some of the multifaceted migraine symptoms reported by migraineurs during attacks, thus contributing with further knowledge to the limited studies available in the literature that investigated migraineurs during attacks. Furthermore, such variety of findings point to the view of migraine as a complex brain disorder, involving multiple cortical, subcortical and brainstem regions to account for the pain and wide constellation of symptoms characterizing the attack.

The present work is not free from some limitations. One of the main drawbacks of this study is the small number of participants recruited, which strongly limited the statistical power of the analysis, perhaps resulting in less than optimum methods to determine significance and further limiting the generalisability of the results. Knowledge regarding the mechanisms involved in phases of the ictal period other than the headache phase (e.g. the prodrome and postdrome) is still very limited, therefore, added value to future studies would be achieved through scanning migraine patients not only in the ictal versus interictal phases but also repeatedly, over different stages of the ictal period, in order to better understand migraine's pathological mechanisms. Results from such studies would probably allow a more accurate identification of imaging biomarkers for disease management, including the identification of therapeutic targets and the evaluation of treatment response.

Acknowledgments

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