Abstract

In migraine with aura visual stimulation can induce changes in the functional connectivity of resting state networks evaluable through ICA fMRI

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Purpose: Migraine is the most frequent primary headache and one of the most disabling diseases in the world. During migraine attacks, the headache can be of moderate-to severe intensity, with a combination of nausea, vomiting, and hypersensitivities to external stimuli, such as visual, auditory, olfactory, and somato-sensory stimuli (Headache Classification Committee of the International Headache Society, 2018; Schwedt, 2013). These can represent also common triggers for the attack (Kelman, 2007). Moreover, between migraine attacks, a persistent hypersensitivity to visual, olfactory, auditory, and somatosensory stimuli has been often observed (Schwedt, 2013). About a third of the patients with migraine have experienced aura (MA), especially the visual one (Russell & Olesen, 1996).

Functional and structural abnormalities would seem to be part of the pathophysiological scenario that leads to the susceptibility to migraine and the recurrence of the crises (Schwedt et al., 2015).

Many techniques going beyond the usual morphological magnetic resonance imaging (MRI) and potentially carrying a high information contribution are currently available. In particular, functional magnetic resonance imaging (fMRI) studies of the brain could be useful to understand the underlying mechanisms of migraine, as well as sensorial hypersensitivities in migraine condition.

In this study, we hypothesized that in MA, the visual stimulation might induce different functional connectivity between interacting neuronal networks and that this might depend on the recurrence of aura symptoms.

Thus, in collaboration with the Sapienza University and IRCCS-Fondazione Bietti of Rome, we performed at the Perugia University Hospital a rs-fMRI study using independent component analysis (ICA) to investigate the potential role of visual stimulation in modulating the interictal neural connectivity of patients with MA. The results of this study could lead to an improved understanding of pathophysiology of migraine.

Methods and materials: This study was approved by the Institutional Review Board and the local Ethical Committee and complied with the Declaration of Helsinki.

25 MA patients and 18 healthy controls were enrolled at the Headache Centre of the Neurologic

Clinic, University of Perugia, Italy. An informed consent was obtained from all participants. 4 MA patients did not complete the scanning sessions. For each MA patient, we collected clinical data about migraine clinical characteristics.

Subjects underwent MRI acquisition on a 3T Philips Achieva clinical system, using an 8-channel head-coil. The acquisition protocol included a 3D sagittal T1 and rs-fMRI data that were obtained using an axial EPI gradient-echo.

In our MRI acquisition protocol, two rs-fMRI acquisitions were performed before and after a 4 min visual stimulus presented on an MRI-compatible monitor and visualized by the participant through a mirror during the MRI study; the visual stimulus was designed to display a 4 Hz flashing checkerboard pattern for 15 s and 15 s fixation which is repeated 8 times. Each of the rs-fMRI acquisition was collected in a 7 min 30 s run, during which subjects were instructed to relax, avoid motion, and keep their eyes closed.

The two rs-fMRI data-series of each subject were preprocessed with SPM12 involving the following steps: i) realignment and reslicing of fMRI images; ii) co-registration with the corresponding 3D structural T1 data; iii) spatial normalization to the MNI152 template and transformation into a common stereotactic space, resampled by 3 mm on each direction.; iv) spatial smoothing with a 3D isotropic 8 mm full-width at half maximum (FWHM) Gaussian kernel.

Therefore, grouped spatial ICA was performed by GIFT separately on HC and MA patient datasets including both the within-session rs-fMRI acquisitions (pre and post visual stimulus). The version of the minimum description length (MDL) criterion implemented by GIFT (Li et al., 2007) was adopted to determine the number of independent components (ICs) from the two datasets.

After data decomposition into ICs, two expert neuroradiologists visually inspected all grouped ICs blindly, plotting them to the anatomical MRI template provided by GIFT. The clinicians discarded ICs located in CSF or white matter, or with low correlation to gray matter that can be connected to artifacts.

Therefore, the selected networks were processed by means of FNC toolbox in two separate sessions respectively for HC and MA groups to determine the temporal correlations among ICA component time courses, according to a published method (Jafri et al., 2008). Correlation and lag values between networks were calculated for all subjects and were later averaged for groups separately, where correlation values represented the dependency of two resting state networks on each other.

Each IC consists of a temporal waveform and an associated spatial map; the latter is expressed in terms of T scores reflecting the degree to which a given voxel time-course correlates with the specific IC temporal waveform. To search for correlations between rs-fMRI activation differences and clinical features of MA patients, the voxel-wise T-max scores of each IC network were

obtained for each subject.

Statistically significant correlations from all possible network combinations were extracted for each group using a Student's t-test. Lag values corresponding to the significant correlation combinations were also calculated. Statistically significant differences in correlation between networks pre and post visual stimulation for HC and for MA patient groups were evaluated separately using a paired 2-sample t-test. Moreover, connectivity combinations with statistically significant lag values were also investigated using a paired 2-sample t-test on the difference between averaged lags of networks pre and post visual stimulation for HCs and for MA patients separately. Lastly, correlations between demographic and clinical variables and each significant IC T-max score values were performed by mean of Pearson's correlation test; Spearman's ρ was performed for discrete variable.

Results: The MDL criterion determines 23 IC for HCs and 19 for MA patients.

The blind visual inspection of the IC spatial maps derived from the ICA analysis performed by GIFT resulted in 8 meaningful ICs for HCs: default mode network (IC4), medial visual (IC7), sensory motor system (IC8), left (IC9) and right (IC10) dorsal attention system (DAS), lateral visual (IC11), executive control (ECN. IC12), and visuo-spatial networks (IC21). Whereas, in MA patients the blind visual inspection process resulted in 7 ICs: salience network (SN. IC2), sensory motor network (IC5), lateral visual network (IC6), dorsal attention system (IC10), executive control (IC12), medial visual (IC16), and default mode networks (IC17).

Two statistically significant differences in correlation between networks pre and post visual stimulus for both HCs (IC9, left DAS, vs IC12, ECN, and IC10, right DAS, vs IC12, ECN) and MA patients (IC2, SN, vs IC10, DAS, and IC10, DAS, vs IC12, ECN) were identified by the 2-sample t-test, whereas the 2-sample t-test of the difference between averaged lags of networks pre and post visual stimulus for HCs and for MA patients detected no statistically significant difference.

In HCs, we found that visual stimulation significantly increases functional connectivity between the IC pair left DAS and ECN, and between right DAS and ECN, with no differences in lag. In detail, before visual stimulation the correlations between left DAS and ECN, and between right DAS and ECN were not significant. Instead, after visual stimulation, left DAS and ECN, and right DAS and ECN were significantly positively correlated.

In patients with MA, we found that visual stimulation significantly increased functional connectivity between the IC pair SN and DAS, and between DAS and ECN, with no differences in lag. In detail, before visual stimulation, the correlation between SN and DAS was not significant, whereas the positive correlation between DAS and ECN was significant. Instead, after visual stimulation, both pairs of components were significantly positively.

Correlation test reveals that, after light stimulation, in MA patients the T-max scores of the ECN (IC12) significantly negatively correlated with the monthly frequency of aura.

This study has some limitations that must be considered. First, the data sample was small, and HCs were slightly less than MA patients. Second, as the normal occurrence of the migraine pathology and its subgroups, the MRI-acquired group was predominantly female, even if no significant differences were found between HCs (15/18 females) and MA patients (17/21 females). Third, because of FNC software limitations, we could not examine all together the correlation of HCs and MA patients before and after the visual stimulation.

Conclusion: As it was seen, rs-fMRI provides a powerful tool to evaluate the functional connectivity during rest and to estimate changes in pathological conditions and the application of a methodological approach to the MRI analysis implies that the inferences related to the results of a study can be properly generalized, as well as connected to other experiments performed under the same standard conditions.

Despite the previously discussed limitations of this study, our findings allowed to identify an alteration of functional connectivity between brain cortical networks after a visual stimulation in both HCs and MA patients, and differences in these modified activations between HCs and MA patients. Moreover, the frequency of the aura was negatively correlated with the change in the strength of the intrinsic connectivity of the executive control network collected after visual stimulation.

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