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Research Submissions

Cognitive Networks Disarrangement in Patients With Migraine Predicts Cutaneous Allodynia

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Background.—Two-thirds of patients with migraine without aura (MwoA) complain ictal cutaneous allodynia (CA), clinical sign of central nociceptive pathway sensitization, and independent predictor for migraine chronification.

Aim.—We aimed to investigate whether functional abnormalities, structural, or microstructural changes of the main cognitive networks (default mode network [DMN], salience network [SN], and central executive network [CEN]) could predict the development of CA in patients with MwoA.

Methods.—Baseline 3-Tesla MRI images of 50 patients with MwoA were analyzed between 2009 and 2015. Over a three-year period, patients were then stratified into 2 groups based on CA development and compared with matched healthy controls (HC). Group-level independent components analysis was used to investigate intrinsic functional connectivity (FC) differences within the cognitive resting-state networks. Voxel-based morphometry (VBM) was used to assess whether group differences in cognitive network FC were related to structural differences. Tract-based spatial statistical analyses (TBSS) were conducted to assess the microstructural properties of white matter tracts. We also compared internetwork connectivity between patients. Finally, a logistic regression analysis was used to investigate baseline imaging predictors of CA development.

Results and Discussion.—We observed a significantly reduced FC of both DMN and CEN in patients with MwoA developing CA (MwoA $_{d}$CA) when compared with both patients with MwoA not developing CA (MwoA $_{nd}$CA) and HC. Within the DMN, the PCC/precuneus is a key hub aimed to anti-nociception and multisensory integration. The reduced intrinsic PCC/precuneus FC observed in patients with MwoA $_{d}$CA could subtend abnormal inputs integration, from different sensory modalities, allowing the development of CA. On the other hand, within the CEN, a central role in pain modulation as well as in executive functions is played by ACC and MFG. Our finding of reduced ACC and MFG FC in MwoA $_{d}$CA may represent the neuronal substrate of both subclinical impairment of complex executive functions and dysfunctional anti-nociceptive pathway, making these patients more prone to migraine chronification. TBSS analyses showed a statistically significant reduced corpus callosum (CC) FA in patients with MwoA $_{d}$CA as previously demonstrated in migraine patients with other chronification factors such as medication overuse or affective disorders. No VBM differences in both global and local volumes were revealed between groups. No significant correlations have been found between the observed functional and microstructural changes and clinical parameters of disease severity. Logistic regression analysis indicated that the full model containing all predictors was statistically significant while the decreased ACC-FC was significantly associated with CA development.

Conclusion.—We suggest that DMN and CEN FC abnormalities as well as CC microstructural changes could represent a prognostic imaging biomarker able to identify migraine patients more prone to experiencing CA and therefore, more inclined

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to chronic migraine. In the new pharmacological scenario, it would be useful to address therapeutic resources to specific migraine populations with a high risk of more severe clinical phenotype.

Key words: migraine, allodynia, chronification, corpus callosum, cognitive networks

Abbreviations: ACC anterior cingulate cortex, AD axial diffusivity, ASC-12 Allodynia Symptom Checklist, BOLD blood oxygenation level dependent, CA cutaneous allodynia, CC corpus callosum, CEN central executive network, DMN default mode network, DTI diffusion tensor imaging, FA fractional anisotropy, FC functional connectivity, fMRI functional magnetic resonance imaging, HARS Hamilton Anxiety Rating Scale, HC healthy controls, HDRS Hamilton Depression Rating Scale, HIT-6 Headache Impact Test, MD medial diffusivity, MFG middle frontal gyrus, MIDAS Migraine Disability Assessment Scale, mPFC medial prefrontal cortex, MwoA $_{d}$CA migraine without aura developing CA, MwoA $_{nd}$CA migraine without aura not developing CA, MwoA migraine without aura, PCC posterior cingulate cortex, RD radial diffusivity, RS resting state, SN salience network, TBSS tract-based spatial statistics, VBM voxel-based morphometry

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INTRODUCTION

About two-thirds of patients with migraine report, during or between headache episodes, cutaneous allodynia (CA), a perception of pain induced by trivial stimuli to normal skin, known to represent a risk factor for migraine chronification.[1,2]

The mechanisms underlying CA in migraine have been clarified by neurophysiological studies demonstrating the sensitization phenomenon at different levels of the trigemino-talamo-cortical nociceptive pathway.[3] Specifically, the involvement of the first-order trigeminal neurons in ictal CA as well as the second- and third-order trigeminal neurons in cephalic and extracephalic interictal CA, respectively, has been widely clarified.[3]

The involvement of the ascending trigeminal nociceptive pathway but also of the descending pain modulatory system have been further supported by neuroimaging studies in patients with migraine and CA, suggesting dysfunctional analgesic compensatory mechanisms in these patients.[4,5]

Moreover, CA in migraine patients may be related to abnormal functional connectivity (FC) between cortical and sub-cortical regions implicated in processing and modulation of pain and pain-related cognitive and emotional experiences, constituting the so-called "neurolimbic pain network."[6,7]

More recently, decreased intrinsic resting-state (RS)-FC of cognitive networks (eg, DMN, SN, and CEN) has been demonstrated in chronic migraine patients with a statistically significant correlation between the dysfunctional networks and CA.[8]

Nevertheless, to the best of our knowledge, no studies have been conducted to investigate the prognostic role of intrinsic RS-FC abnormalities of cognitive networks in the development of CA in migraine patients. Therefore, in the present study, we aimed to assess, for the first time, whether specific intra- and inter-network RS-FC changes can discriminate in a group of MwoA patients not experiencing CA (MwoA CA-) those who will not develop CA (MwoA $_{nd}$CA) from those who will develop CA (MwoA $_{d}$CA) over time.

Conflicts of Interest: The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Prof. Russo has received speaker honoraria from Allergan, Lilly, Novartis, and Teva and serves as an associate editor of Frontiers in Neurology (Headache Medicine and Facial Pain session). Dr. Bisecco has received speaker honoraria and/or compensation for consulting service from Biogen, Merck, Roche, Celgene, and Genzyme. Prof. Tessitore has received speaker honoraria from Novartis, Schwarz Pharma/UCB, Lundbeck, Abbvie, and Glaxo. Prof. Tedeschi has received speaker honoraria from Sanofi-Aventis, Merck Serono, Bayer Schering Pharma, Novartis, Biogen-Dompé AG, Teva, and Lilly; has received funding for travel from Bayer Schering Pharma, Biogen-Dompé AG, Merck Serono, Novartis, and Sanofi Aventis; and serves as an associate editor of Neurological Sciences. The other authors have nothing to declare.

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We hypothesize that patients with MwoA $_{d}$CA would show abnormal intrinsic FC in cognitive networks (eg, DMN, SN, and CEN) during interictal period even before the occurrence of CA complaint.

Furthermore, based on recent data from an imaging sub-classification of migraine patients supporting the critical role of CA in determining structural and microstructural abnormalities,[9] we used voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) techniques to assess whether morphological brain differences could precede CA and subtend putative RS-FC changes as well.

PATIENTS AND METHODS

Study Population and Study Design.—Fifty right-handed patients with episodic MwoA, according to the International Headache Society criteria (Headache Classification Subcommittee of the International Headache Society, 2004 and 2013) were prospectively recruited between 2009 and 2015 from the migraine population referring to the Headache Center of the Department of Neurology at the University of Campania "Luigi Vanvitelli."[10] All patients filled in the Allodynia Symptom Checklist-12 (ASC-12) questionnaire to investigate CA experience during migraine attacks: patients with CA (eg, at least 1 item with positive response) were not enrolled in the study.[11] Demographic data were obtained from the patients with MwoA CA – as well as the following clinical features: age of migraine onset, disease duration, frequency of migraine attacks (day/month), average of pain intensity of migraine attacks (assessed using a visual analogic scale – VAS), and related disability (using Migraine Disability Assessment Scale – MIDAS and Headache Impact Test – HIT-6)[12,13] (Table 1). Moreover, patients with MwoA completed the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS),[14,15] and Montreal Cognitive Assessment (MoCA). Finally, an extensive neuropsychological evaluation was performed in patients with MwoA and healthy controls (HC), as previously described.[16]

Similarly, patients with pregnancy, claustrophobia, hypertension, diabetes mellitus, heart disease, chronic systemic diseases, stroke, cognitive impairment, substance abuse, chronic pain, psychiatric disorders as well as other neurological diseases were excluded. To avoid the confounding interference of migraine attack or pharmacologic interference with RS-fMRI

Table 1.—Demographic and Clinical Characteristics of Patients With MwoA dCA, Patients With MwoA ndCA, and HC

Parameter	Group	Mean ± SE	*P* Value
Gender	MwoA dCA	4M; 16F	.17†
	MwoA ndCA	7M; 10F	.56‡
	HC	6M; 13F	.42§
Age (years) T^0	MwoA dCA	31.3 ± 1.97	.84†
	MwoA ndCA	30.7 ± 2.15	.46‡
	HC	28.8 ± 1.45	.32§
Disease duration (years) T^0	MwoA dCA	13.8 ± 1.77	.62
	MwoA ndCA	12.4 ± 2.38	
Frequency (days/month) T^0	MwoA dCA	4.4 ± 0.94	.33
	MwoA ndCA	3.3 ± 0.57	
Frequency (days/month) T^1	MwoA dCA	4.7 ± 1.01	.37
	MwoA ndCA	3.5 ± 0.71	
MIDAS T^0	MwoA dCA	14.8 ± 2.57	.46
	MwoA ndCA	13.3 ± 2.45	
MIDAS T^1	MwoA dCA	15.9 ± 2.36	.30
	MwoA ndCA	12.2 ± 2.68	
HIT-6 T^0	MwoA dCA	59.8 ± 1.65	.07
	MwoA ndCA	55.1 ± 1.81	
HIT-6 T^1	MwoA dCA	59.7 ± 1.66	.08
	MwoA ndCA	55.4 ± 2.23	
NRS of attack intensity T^0	MwoA dCA	8.2 ± 0.31	.28
	MwoA ndCA	7.9 ± 0.36	
NRS of attack intensity T^1	MwoA dCA	8.4 ± 0.26	.21
	MwoA ndCA	7.9 ± 0.34	
ASC-12 T^0	MwoA dCA	0	
	MwoA ndCA	0	
ASC-12 T^1	MwoA dCA	7.7 ± 1.00	1.38×10^{-8}
	MwoA ndCA	0	
MoCA T^0	MwoA dCA	22.7 ± 2.74	.57†
	MwoA ndCA	22.3 ± 2.35	.03‡
	HC	25.4 ± 2.56	.04§
MoCA T^1	MwoA dCA	23.1 ± 2.95	.65†
	MwoA ndCA	22.9 ± 2.37	.03‡
	HC	24.9 ± 2.76	.04§
HARS T^1	MwoA dCA	5.7 ± 0.96	.28
	MwoA ndCA	5.3 ± 0.89	
HDRS T^1	MwoA dCA	5.1 ± 0.82	.18
	MwoA ndCA	4.8 ± 0.76	

ASC-12 = Allodynia Symptoms Checklist-12; F = female; HADR = Hamilton Anxiety Rating Scale; HC = healthy controls; HDRS = Hamilton Depression Rating Scale; HIT-6 = Headache Impact Test-6; M = male; MIDAS = Migraine Disability Assessment Scale; MoCA = Il Montreal Cognitive Assessment; MwoA dCA = patients with migraine without aura developing cutaneous allodynia; MwoA ndCA = patients with migraine without aura non developing cutaneous allodynia; NRS = numerical rating scale.
†MwoA dCA vs MwoA ndCA.
‡MwoA ndCA vs HC.
§MwoA dCA vs HC.

investigation, all patients were both migraine free and not taking medications for migraine attacks at least 3 days before scanning. All patients were interviewed 3 days after scanning to ascertain if they were migraine free also during the post-scan days. Finally, patients were naïve for any commonly prescribed migraine preventive medications. Three patients were excluded from the final analyses due to migraine attacks within 3 days after the fMRI scan. For this reason, final analyses were conducted on 47 patients.

After 3 years from the first fMRI scan, from the initial group 37 patients were re-called (10 drop-out patients) to obtain an assessment of clinical parameters at a distance from the baseline. Moreover, migraine patients filled in again the ASC-12 questionnaire, to investigate if patients had developed CA symptoms during migraine attacks. Similarly, information regarding migraine-related disability (using MIDAS and HIT-6) as well as HDRS, HARS, and MoCA were re-collected. So, 20 patients with MwoA with CA and 17 patients with MwoA without CA were identified. Therefore, based on the observed disease evolution, we identified, in the baseline group of patients, those who will not develop CA (MwoA $_{nd}$CA) and those who develop CA (MwoA $_{d}$CA) over time (Suppl_1).

Nineteen age- and gender-matched, right-handed subjects with less than a few spontaneous nonthrobbing headaches per year, with no family history of migraine, pregnancy, claustrophobia, hypertension, diabetes mellitus, heart disease, other chronic systemic diseases, stroke, cognitive impairment, substance abuse, chronic pain, as well as other neurological or psychiatric disorders were recruited as HC.

Standard Protocol Approvals, Registrations, and Patient Consents.—The study was approved by the Ethics Committee of University of Campania "Luigi Vanvitelli", and written informed consent was obtained from all subjects according to the Declaration of Helsinki.

Imaging Parameters.—Magnetic resonance images were acquired on a General Electric 3-Tesla MRI scanner equipped with an 8-channel parallel-head coil. fMRI data consisted of 240 volumes of a repeated gradient-echo planar imaging T2*-weighted sequence (TR, 1508 ms; axial slices, 29; matrix, 64 × 64; field of view 256 mm; thickness 4 mm; interslice gap 0 mm). During the functional scan, subjects were asked to simply stay motionless, awake, and relaxed, and to keep their eyes closed; no visual or auditory stimuli were presented at any time during functional scanning. Three-dimensional high-resolution T1-weighted sagittal images (GE sequence IR-FSPGR; TR, 6988 ms; TI, 1100 ms; TE, 3.9 ms; flip angle, 10; voxel size, $1 \times 1 \times 1.2$ mm^3) were acquired for registration and normalization of the functional images as well as for atrophy measures and VBM analysis. The criterion used to exclude scans was formulated on the basis of head movements as estimated during the motion correction procedures. To include scans, the estimated translation parameters were to be higher than the dimension of the functional voxel used for the analysis (3 mm isotropic), and the rotation parameters were to be not higher than 3 degrees.

RS-fMRI Pre-Processing.—Image data preprocessing and statistical analysis were performed with BrainVoyager QX (Brain Innovation BV, The Netherlands). Data preprocessing included the correction for slice scan timing acquisition, a three-dimensional rigid-body motion correction based on a 6-parameter rigid body alignment to correct for minor head movements, and the application of a temporal high-pass filter with cut-off set to 3 cycles per time course. Translational motion parameters were verified to be always less than 1 functional voxel for all included participants. Structural and functional data were coregistered and spatially normalized to the Talairach standard space using a 12-parameter affine transformation. During this procedure, the functional images were resampled to an isometric 3-mm grid covering the entire Talairach box. Single-subject and group-level ICA was carried out, respectively, with the fastICA and the self-organizing group ICA (sogICA) algorithms. For each subject, 40 independent components (corresponding to one-sixth of the number of time points) were extracted.[17] All single-subject component maps were then "clustered" at the group level, resulting in 40 single-group average maps that were visually inspected to recognize the main functional resting-state networks, and particularly, to select DMN, SN, and CEN components. The sign-adjusted independent components of all subjects were then submitted to a second-level, multi-subject random effects two-way analysis of variance (ANOVA) that

treated the individual subject map values as random observations at each voxel, cluster memberships as one within-subject factor with 40 levels (corresponding to 40 group components), and subject group as one between-subject factor with 3 levels (corresponding to HC, MwoA $_{d}$CA, and MwoA $_{nd}$CA). Starting from ANOVA, a single-group one-sample *t*-test was used to analyze the whole-brain distribution of the cognitive networks components in each group separately and the resulting t-maps were calibrated at $P = .05$ (Bonferroni corrected over the entire brain). An inclusive mask was also created from the healthy control group maps and used to define a new search volume within-network, between-group comparisons. The resulting statistical maps were overlaid on the standard "Colin-27" brain T1 template. To correct for multiple comparisons, regional effects were only accepted for clusters exceeding a minimum size determined with a nonparametric randomization approach, namely, an initial voxel-level threshold was set to $P = .001$ (uncorrected) and a minimum cluster size was estimated after 1000 Monte Carlo simulations that protected against false-positive clusters up to 5%. Cluster-level correction is a very common and effective way to correct for multiple comparisons in fMRI statistical maps, including random effects maps, obtained from RS-fMRI studies.[16] Individual ICA z-scores for all groups were extracted from DMN, SN, and CEN clusters identified in the above analyses and used for linear correlation analyses with clinical parameters of disease severity and cognitive scores. ICA z-scores express the relative modulation of a given voxel by a specific ICA and hence reflect the amplitude of the correlated fluctuations within the corresponding functional connectivity network.

Regional Atrophy Measurements: Voxel-Based Morphometry.—Data for VBM analysis were processed and examined using SPM12 software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Images were bias-corrected, tissue-classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping) within a unified model with default parameters incorporating the DARTEL toolbox.[18] Subsequently, the warped gray matter (GM) segments were affine-transformed into Montreal Neurological Institute space and were scaled by the Jacobian determinants of the deformations to account for the local compression and stretching that occurs as a consequence of the warping and affine transformation (modulated GM volumes). Finally, the modulated volumes were smoothed with a Gaussian kernel of 8-mm full-width at half maximum (FWHM). The GM volume maps were statistically analyzed using the general linear model. Statistical analysis consisted of an analysis of covariance (ANCOVA) with total intracranial volume (TIV) gender and age as covariates of no interest. We assessed whole-brain regional differences, as well as differences over region of interest (ROI) based on the results of the whole-brain between groups RS-fMRI analysis. Statistical inference was performed at the voxel level, with both a family-wise error correction for multiple comparisons ($P < .05$) and an uncorrected threshold ($P < .001$; cluster size: 100).

Diffusion Tensor Imaging Analysis.—A tract-based spatial statistical (TBSS) approach was used for the group analysis of DTI data.[19] DTI data sets were processed with the Functional MRI of the Brain (FMRIB) Software Library (FSL) software package (http://www.fmrib.ox.ac.uk/fsl). Preprocessing included eddy current and motion correction and brain-tissue extraction. After preprocessing, DTI images were averaged and concatenated into 33 (1 B = 0 + 32 B = 1000) volumes, and a diffusion tensor model was fitted at each voxel, generating axial diffusivity (AD), fractional anisotropy (FA), medial diffusivity (MD), and eigenvalue ($\lambda 1$, $\lambda 2$, and $\lambda 3$) maps. The average of the second and third eigenvalues of the diffusion tensor was used for the definition of radial diffusivity (RD). Images were warped to the Montreal Neurological Institute (MNI) 152 template, available as a standard T1 data set in the FSL software package. TBSS was run with FA maps to create the "skeleton," which represents the center of all fiber bundles common to all subjects, and which was used for all other maps. To this purpose, FA images of all subjects were aligned to a common target (1 × 1 × 1 mm MNI152 FMRIB58_FA standard space) using nonlinear registration. A mean FA skeleton was then created with a threshold of FA > 0.2. Age and gender were considered as covariates. Moreover, the TBSS results were linked to standard anatomic data derived from the International Consortium

of Brain Mapping DTI-81 WM label atlas (Johns Hopkins University, Baltimore, MD).[20,21]

Individual skeleton images were submitted to a general linear model (GLM) analysis with appropriate design matrices and linear contrasts defined for the group comparisons and the correlations between all diffusivity parameters (FA, RD, MD, and AD) and clinical measures migraine severity.

Statistical Analysis.—Comparison between MwoA patients and HC on demographic, neuropsychiatric, and cognitive aspects was performed by means of a multivariate analysis of variance (MANOVA) and Chi-squared, as appropriate. The Shapiro–Wilk normality test was performed to evaluate clinical and imaging variables distribution. For the analysis of differences among groups on demographic, clinical, behavioral, and neuropsychological variables, we used non-parametric tests (Kruskal–Wallis H test to compare 3 samples and the Mann-Whitney U-test to compare 2 samples) to avoid biases because of the small sample size. A value of $P < .05$ was considered statistically significant. Within the sample of MwoA patients, the correlation analysis between the imaging and clinical parameters of disease severity was carried out by means of Spearman's rank correlation coefficient. Although a value of $P < .05$ was considered statistically significant, the Bonferroni correction for multiple comparisons was applied. Logistic regression analysis was run including functional imaging measures to determine the independent predictors of allodynia over time (internetwork connectivity z scores) (Table 2). All analyses were performed using STATA version 14.

RESULTS

Clinical Findings.—The three experimental groups (eg, patients with MwoA $_{nd}$CA, patients with MwoA $_{d}$CA, and HC) did not differ in age and male/female ratio, as well as in neuropsychological and psychological assessment (Moca, HADR, and HARS) in both baseline and 3 years' follow-up. Patients with migraine (eg, patients with MwoA $_{nd}$CA and patients with MwoA $_{d}$CA) did not show differences in clinical parameters of migraine severity (disease duration, VAS, MIDAS, and HIT-6) as well as in psychological assessment (HADR and HARS), both at baseline and at 3 years' follow-up. Patients with MwoA did not show significant cognitive impairments when compared to published normative data but, consistent with previous

Table 2.—Logistic Regression Analysis of Baseline Imaging Predictors of CA Development

Number of obs. = 37

LR χ^2 = 34.13

Prob > χ^2 = 0.0000

Pseudo R^2 = 0.6685

Log likelihood = −8.46

	Odds Ratio	Std. Err.	z	$P > \|z\|$	95% CI	
ACC (CEN)	**0.16**	0.14	−2.05	**.04**	0.03	0.92
Left MFG (CEN)	0.50	0.43	−0.81	.42	0.091	2.71
PCC/precuneus (DMN)	0.77	0.38	−0.54	.59	0.29	2.01
Right insula (SN)	1.61	0.61	1.24	.21	0.76	3.41
ACC (SN)	1.01	0.24	0.06	.95	0.63	1.63
Parahippocampal gyrus (SN)	0.60	0.23	−1.31	.19	0.28	1.28
Left insula (SN)	0.55	0.23	−1.41	.16	0.24	1.26
Cons.	300.61	891.96	1.92	.05	0.90	100,841.7

Bold values represent statistically significant data.
ACC = anterior cingulate cortex; CA = cutaneous allodynia; CEN = central executive cortex; DMN = default mode network; MFG = middle frontal gyrus; PCC = posterior cingulate cortex; SN = salience network.

observation, performed significantly lower than HC on the total MoCA score, in particular on visuospatial and executive domains (all $P < .01$ after Bonferroni correction) (Table 1).

RS-fMRI.—*Patients With MwoA vs HC.*—Each group exhibited a DMN connectivity pattern consistent with previous reports, encompassing medial and inferior prefrontal cortices, temporal lobe areas, anterior and posterior cingulate cortices, and precuneus and cerebellar areas.[22-24] Two-sample *t*-tests revealed significant group differences in right and left medial prefrontal cortex (mPFC) (Talairach coordinates x, y, z: 17; 28; 36 $t = -6050$; −19; 19; 36 $t = -7327$), and in the posterior cingulate cortex (PCC)/precuneus (Talairach coordinates x, y, z: 5; −59; 3 $t = 5799$) ($P < .001$). Specifically, patients with MwoA showed a reduced component time course-related activity of the mPFC and an increased component time course-related activity of the PCC/precuneus when compared to HC ($P < .001$) (Fig. 1).

Similarly, the ECN well corresponded with the typically reported central executive network, involving prefrontal cortex (PFC), cingulate, and parietal cortices in both patients with migraine and HC groups. ECN exhibited statistically significant regional differences in the group comparisons between patients with MwoA and HC ($P < .001$). Specifically, the 2-sample *t*-tests revealed significant group differences in anterior cingulate cortex (ACC) (Talairach coordinates x, y, z: 5; 1; 51 $t = -5419$), right medial frontal gyrus (MFG) (Talairach coordinates x, y, z: 38; 34; 24 $t = -6988$) and right insula (Talairach coordinates x, y, z: 42; 4; 4 $t = -5451$), indicating that these areas had a decreased component time course-related activity in patients with MwoA when compared with HC ($P < .001$) (Fig. 1).

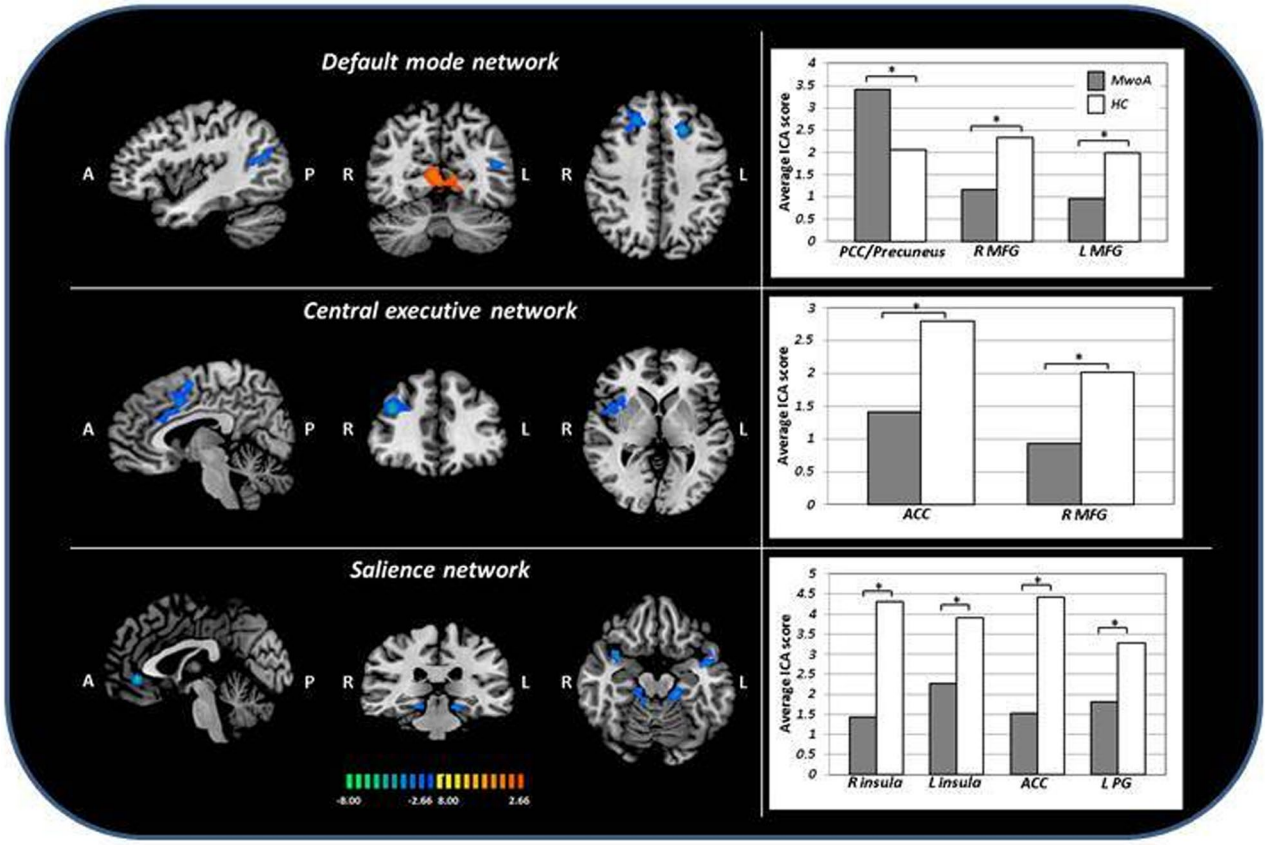

Fig. 1.—T-map of statistically significant differences within the cognitive brain networks between patients with MwoA and HC groups overlaid on the standard "Colin-27" brain T1 template. Corresponding bar graphs of the averaged ICA z-scores for MwoA patients and HC groups. Anterior cingulate cortex (ACC); healthy controls (HC); independent components analysis (ICA); middle frontal gyrus (MFG); migraine without aura (MwoA); parahippocampal gyrus (PG); posterior cingulate cortex (PCC).

Furthermore, as illustrated in Figure 2, each group exhibited a SN connectivity pattern consistent with previous reports, encompassing anterior insula and dorsal ACC. The two-sample *t*-tests revealed significant group differences in right and left insula (Talairach coordinates x, y, z: 37; 9; −11 t = −11,753; −43; 5; −5 t = −7354), in the dorsal ACC (Talairach coordinates x, y, z: −1; 37; 0 t = −8024) and in right and left parahippocampal gyri (Talairach coordinates x, y, z: 14; −20; −18 t = −5025; −16; −29; −12 t = −6423) (P < .01). Specifically, these areas showed a decreased component time course-related activity in patients with MwoA when compared with HC (P < .01) (Fig. 1).

Patients With MwoA $_{d}$CA vs MwoA $_{nd}$CA vs HC.— Our secondary analysis, comparing patients with MwoA $_{d}$CA, patients with MwoA $_{nd}$CA, and HC, showed statistically significant differences in the RS-FC within cognitive networks.

More specifically, within the DMN, a decreased component time course-related activity of PCC/precuneus (Talairach coordinates x, y, z: −7; −62; 27 t = −5636) has been observed in patients with MwoA $_{d}$CA compared with HC and patients with MwoA $_{nd}$CA (P < .001) (Figs. 2 and 3). Similarly, within the CEN, a significantly decreased component time course-related activity of ACC (Talairach coordinates x, y, z: −8; 34; 27 t = −5559) and left MFG (Talairach coordinates x, y, z: −37; 46; 18 t = −5811) has been demonstrated in patients with MwoA $_{d}$CA compared with HC and patients with MwoA $_{nd}$CA (P < .001) (Figs. 2 and 3). Furthermore, although with a less stringent statistical threshold (P < .01), within the SN, both an increased

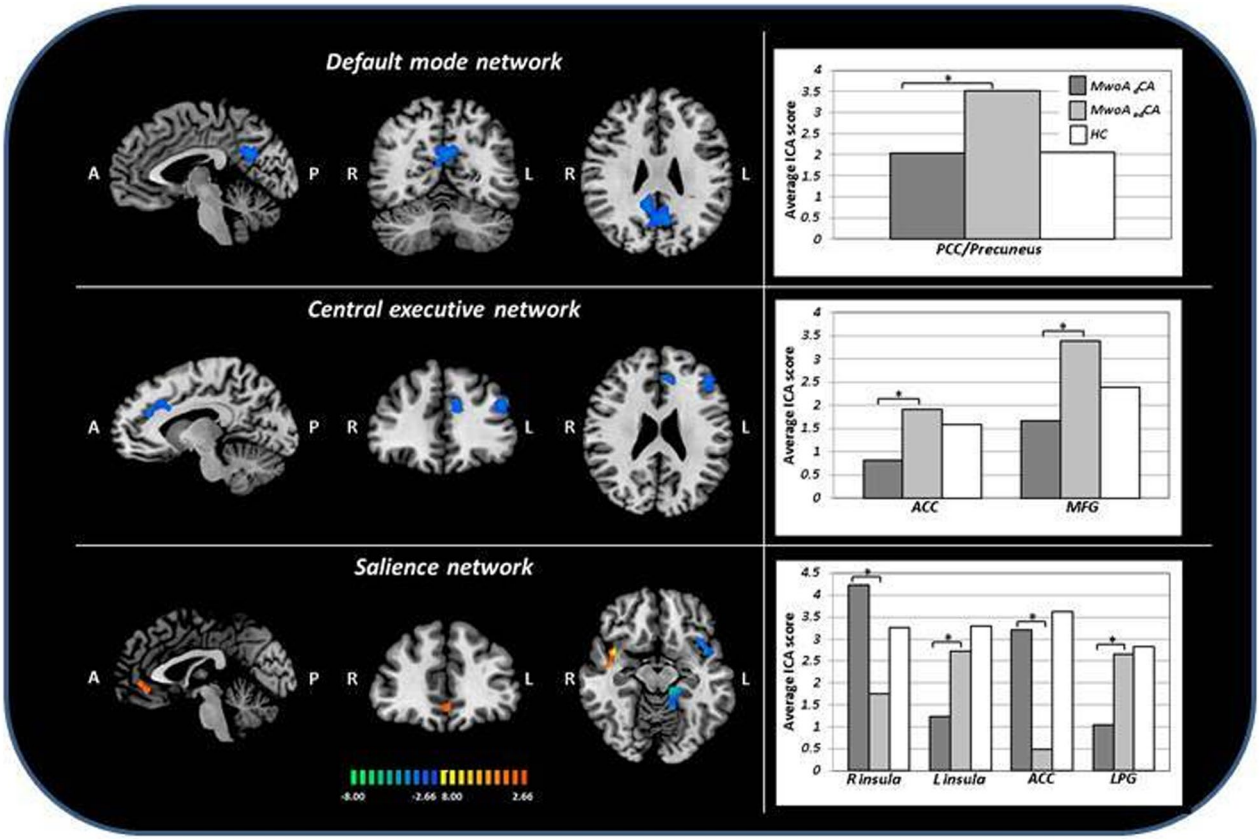

Fig. 2.—T-map of statistically significant differences within the cognitive brain networks between patients with MwoA $_{d}$CA, patients with MwoA $_{nd}$CA and HC groups overlaid on the standard "Colin-27" brain T1 template. Corresponding bar graphs of the averaged ICA z-scores for patients with MwoA $_{d}$CA, patients with MwoA $_{nd}$CA, and HC groups. anterior cingulate cortex (ACC); healthy controls (HC); independent components analysis (ICA); middle frontal gyrus (MFG); migraine without aura developing cutaneous allodynia (MwoA $_{d}$CA); migraine without aura not developing cutaneous allodynia (MwoA $_{nd}$CA); parahippocampal gyrus (PG); posterior cingulate cortex (PCC).

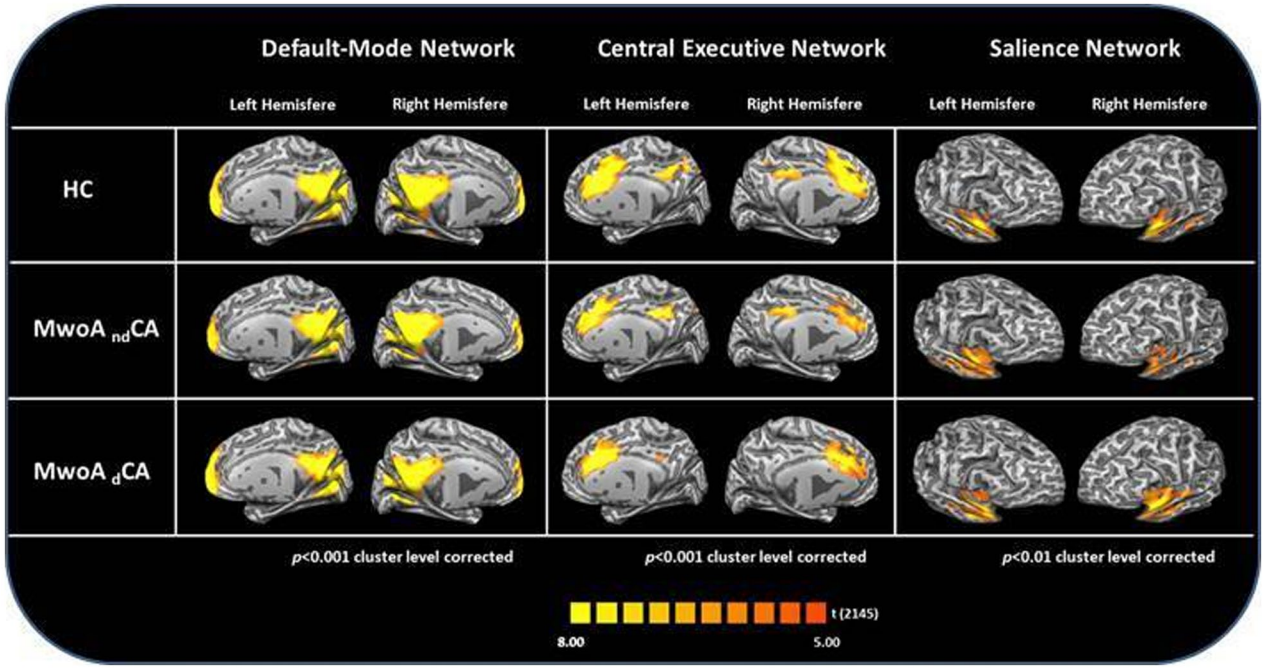

Fig. 3.—Group-level (main effects) functional connectivity of brain cognitive networks in patients with MwoA $_{d}$CA, patients with MwoA $_{nd}$CA, and HC. Statistical maps were obtained overlaying an inflated 3D brain surface from the "Colin 27" atlas. Healthy controls (HC); migraine without aura not developing cutaneous allodynia (MwoA $_{nd}$CA); migraine without aura developing cutaneous allodynia (MwoA $_{d}$CA).

component time course-related activity of the ACC (Talairach coordinates x, y, z: −1; 37; −6 t = 4371) and right anterior insula (Talairach coordinates x, y, z: 37; 8; −9 t = 9918) and a decreased component time course-related activity of left anterior insula (Talairach coordinates x, y, z: −4 3; 8; −5 t = −5128) and left parahippocampal gyri (Talairach coordinates x, y, z: −14; −35; −6 t = −6475) have been shown in patients with MwoA $_{d}$CA compared with HC and patients with MwoA $_{nd}$CA (P < .01) (Figs. 2 and 3).

VBM and DTI.—The whole-brain analyses of global gray matter volume did not reveal any differences between patients with MwoA (as a group) and HC nor between patients with MwoA $_{nd}$CA, patients with MwoA $_{d}$CA, and HC, both at a statistical threshold corrected for multiple comparisons (FEW P < .05) and at an uncorrected threshold (P < .001; cluster size: 100).

Contrariwise, TBSS analyses showed a statistically significant reduced corpus callosum (CC) FA in patients with MwoA $_{d}$CA compared to HC and MwoA $_{nd}$CA (Fig. 4). No significant differences have been found for MD, RD, and AD maps between the groups.

Correlation Analysis and Logistic Regression.—Post hoc analyses did not reveal any statistically significant correlation between RS-FC changes of intrinsic brain cognitive networks and clinical parameters of disease severity, both assessed in baseline and 3 years' follow-up. Similarly, no statistically significant correlation has been found between CC-FA abnormalities and clinical parameters, both assessed in baseline and 3 years' follow-up. Logistic regression analysis indicated that the full model containing all predictors was statistically significant (χ^2 = 34.13, P < .00001, Log likelihood −8.46, R^2 di Mc Fadden: 0.67), and able to distinguish, based only on functional imaging parameters, between those patients who will develop CA and those who will not develop CA over time. Concordant association of predicted probabilities and observed responses was 60.3%. Analysis of odds ratio estimates showed that ACC-FC was significantly associated with the development of CA in patients with migraine over time (odds ratio: 0.16, $P > X^2$: 0.04) (likelihood ratio chi-square 30.82; $P \leq .0000$) (Table 2). Finally, the ROC curve has been calculated (Fig. 5 for ROC curve).

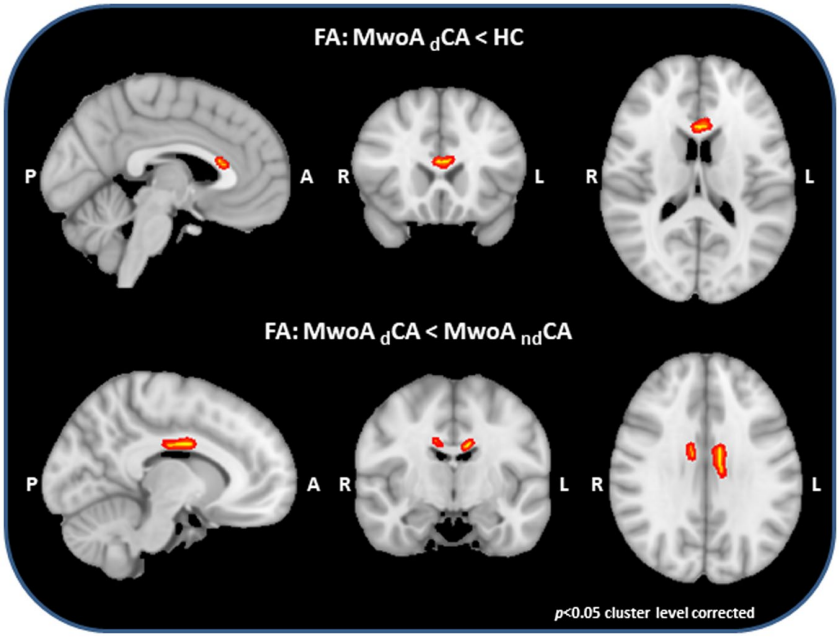

Fig. 4.—Tract-based spatial statistical (TBSS) analysis showing differences in fractional anisotropy values in the genu and splenium of corpus callosum among patients with MwoA $_{d}$CA when compared with patients with MwoA $_{nd}$CA. Fractional anisotropy (FA); migraine without aura developing cutaneous allodynia (MwoA $_{d}$CA); migraine without aura not developing cutaneous allodynia (MwoA $_{nd}$CA).

DISCUSSION

In the present study, we found significant changes in the intrinsic FC of the main cognitive networks (eg, DMN, CEN, and SN) in drug-naïve patients with MwoA who will develop CA over time (ie, 3 years' period), investigated during the interictal period, compared with patients with MwoA who will not develop CA and HC. Aberrant CC FA has been demonstrated exclusively in patients with MwoA who will develop CA over time.

No differences in cognitive inter-networks FC, structural, microstructural, and WMH load have been observed in the three groups under examination. Interestingly, the observed intra-networks FC and microstructural changes did not correlate with clinical parameters of migraine severity.

Intranetwork Resting-State Functional Connectivity in Cognitive Networks.—*Default-Mode Network*.—A DMN-FC decrease in the medial prefrontal cortex (mPFC) and increase in the PCC/precuneus have been observed in drug-naïve patients with MwoA not experiencing CA, as a group, at baseline when compared to HC. However, the main finding of the present study was the significantly weaker DMN-FC centered in PCC/precuneus, observed at baseline in patients with MwoA $_{d}$CA compared with HC and patients with MwoA $_{nd}$CA. No significant correlations have been evidenced between the DMN-FC and the clinical parameters of disease severity both when evaluated at baseline and three years later.

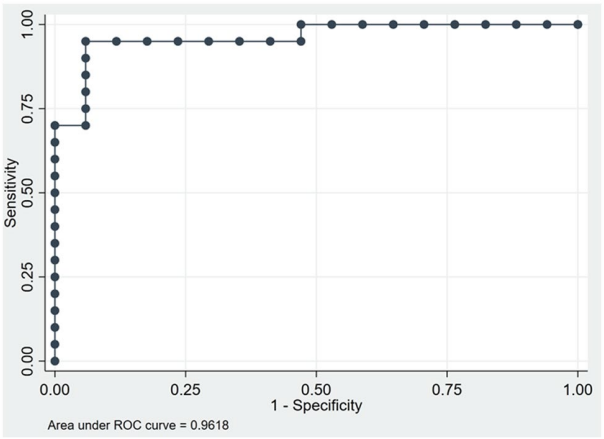

Fig. 5.—ROC curve of Z-scores from cognitive networks functional connectivity for the identification of patients with MwoA $_{d}$CA from patients with MwoA $_{nd}$CA.

In the past years, DMN has been extensively explored in migraine patients suggesting that the repetitive experiences of migraine attacks could affect the ability of DMN regions to stay highly correlated with each other. However, while some studies reported a reduced DMN-FC, other observations demonstrated an increased RS-FC within the same network.[25-28]

More specifically, compelling evidences supported a decreased FC in the anterior nodes of the DMN in patients with MwoA, such as mPFC,[27] involved in an internal/external perception and judgments aimed to face with stressful experiences along with corresponding adaptive and emotional responses.[29] On the other hand, increased RS-FC has been consistently observed in the central posterior nodes of the DMN, such as PCC/precuneus[28] playing a key role in the balance between internally and externally focused attention, engaged in both pain sensitivity and integration of inputs from different sensory modalities (eg, multisensory integration).[30] Our findings, in line with previous data and the well-demonstrated functional differentiation between anterior and posterior DMN nodes characterized by an anti-correlated activity (eg, lower the mPFC response, higher the PCC/precuneus response and vice versa) could further suggest a compensatory adaptive mechanism by which posterior DMN nodes support (or partially replace) the dysfunctional anterior DMN regions.[31,32]

Similarly, although poorly investigated, conflicting results emerged about the FC correlates of CA experienced by patients with migraine. Indeed, in these patients both reduced FC between thalamus and subcortical/cortical structures involved in discriminative and multi-dimensional pain processing and increased FC between brainstem (periaqueductal gray matter and nucleus cuneiformis) and cortical areas implicated in higher order pain modulation have been observed by "seed-based" approach studies.[33]

It is noteworthy that in the present study we found a significantly weak FC of the PCC/precuneus exclusively in patients with MwoA $_{d}$CA. This finding could be read as the failure of the above-mentioned compensatory mechanism, leading to both rising vulnerability in facing stressful experiences (ie, negative prognostic factor for migraine chronicity) and (specifically based on the role of precuneus/PCC) aberrant multisensory integration.[34] The latter may play a role in allowing the future occurrence of ictal CA during migraine attacks (involving trigeminal sensitization) for which trivial stimuli to normal skin, such as hair combing, shaving, wearing glasses, or earrings, are perceived as pain in these patients.

Finally, our RS-fMRI findings did not show correlations with migraine clinical features, both when assessed at baseline and after 3 years, such as disease duration, headache attack severity, frequency and duration of migraine attacks, migraine-related disability and impact on life, and CA in patients with MwA.

Interestingly, the abnormal pattern of RS-FC found in our patients with MwoA d CA, known to be a risk factor for migraine chronification, has been demonstrated also in patients suffering from other primary chronic painful conditions, such as low-back pain and fibromyalgia.[35,36]

These data along with the absence of significant correlations between RS-FC findings and clinical parameters of disease severity suggest that DMN abnormalities observed in patients with MwoA $_{d}$CA at baseline may represent a dysfunctional substrate leading to a greater vulnerability to CA and, in turn, to pain chronicity.

Functional Central Executive Network.—Consistent with previous observations,[16] a significantly decreased CEN-FC has been observed in the ACC, MFG, and insula in drug-naïve patients with MwoA at baseline, as a group (eg, not experiencing CA) when compared to HC. Furthermore, a significantly weaker CEN-FC centered in ACC and MFG has been demonstrated, at baseline, in patients with MwoA $_{d}$CA compared with HC and patients with MwoA $_{nd}$CA. No significant correlations between the CEN-FC and the clinical parameters of disease severity have been evidenced both when assessed at baseline and three years later.

The CEN, encompassing prefrontal, cingulated, and parietal cortices, is considered to represent the underlying[37] functional neuronal correlates of executive function,[38,39] a set of high-order cognitive processes widely involved in several aspects of individual daily living experiences such as planning for the future and adaptation (ie, allostasis).[37]

Interestingly, some cortical areas constituting CEN act as multi-integrative structures, such as ACC

and MFG, involved in both pain perception and modulation but also in attention-for-action, competition monitoring, anticipation, reward assessment and novelty, performance, and conflict and error monitoring.[40,41]

It is noteworthy that, consistent with previous data,[42] migraine patients, explored with extensive neuropsychological examination, showed only *subtle* cognitive dysfunction, at baseline during interictal period.

Our findings of regional reduced CEN-FC in MwoA patients with *subtle cognitive disturbances* in tests exploring executive function integrity could reflect a subclinical impairment of complex executive functions. In other words, MwoA patients, due to the subtle EF deficits, could experience some degree of difficulty in daily living making them more prone (eg, based on the well-known role of the stress as migraine attack trigger) to the development of migraine attacks. Interestingly, the pattern of decreased CEN-FC seems to be further compromised in those patients with MwoA $_{d}$CA when compared with those patients with MwoA $_{nd}$CA, suggesting a role of CEN abnormalities in the development of CA in MWA patients.

Interestingly, the stronger abnormal CEN-FC in ACC, MFG, and insula found in our patients with MwoA $_{d}$CA, known to be a risk factor for migraine chronification, are in line with volumetric abnormalities previously reported in the same cortical areas in patients suffering from other primary chronic pain conditions[43] (eg, painful hand osteoarthritis, fibromyalgia, chronic pelvic pain), suggesting a functional re-modeling brain response to pain stimulations in these patients, leading to a greater vulnerability to CA and pain chronification.

Functional Salience Network.—No significant differences have been observed in SN-FC between the three groups under examination with a highly conservative threshold ($P < .001$). On the other hand, with a less stringent threshold ($P < .01$), consistent with previous observations,[8] a decreased SN-FC centered in the ACC, anterior insula, and parahippocampal gyrus has been observed in patients with MwoA at baseline (eg, not experiencing CA) when compared to HC. Furthermore, when patients were stratified according to the development of CA, a significantly higher SN-FC within the ACC and anterior insula has been demonstrated in patients with MwoA $_{d}$CA compared with patients with MwoA $_{nd}$CA.

No significant correlations between SN-FC changes and clinical parameters of disease severity have been found both when assessed at baseline and 3 years later.

The SN is a well-defined brain network involved in the evaluation of specific inputs from external or internal behavior, by assigning the appropriate relevance to stimuli for continuous processing and pain modulation.[44,45] Previous observations found that the strength of SN-FC was both negatively correlated with frequency of migraine attacks and positively correlated with CA in female patients suffering from chronic migraine (with and without medication overuse). It has been suggested that different modulations could simultaneously occur within the SN: while some SN nodes are less synchronously connected as long as headache frequency increases, other SN functional components show more synchronous FC, probably representing the neural surrogate for central sensitization.[8] Similarly, the present observation of increased SN-FC, in patients with MwoA $_{d}$CA compared with patients with MwoA $_{nd}$CA could represent the finding of a "pre-clinical" (or a greater tendency to) central sensitization making these patients more prone to the development of CA or, alternatively, the substrate of a dysfunctional mechanism leading to the excessive attribution of salience to normally nonsalient stimuli (eg, perceiving as painful a trivial stimuli to normal skin during migraine attack).

Internetwork Resting-State Functional Connectivity in Cognitive Networks.—No differences have been found in functional coupling between the three principal cognitive networks in the groups under examination. This finding suggests that the disruption of the internetwork connectivity, previously demonstrated in chronic migraine patients,[46] might represent a late feature, not observed in patients with MwoA, even in those who will develop a chronification factor as the CA (eg, MwoA patients $_{d}$CA).

Structural and Microstructural Findings.—Our data demonstrated, consistent with previous observations, a reduced FA of the genu of CC in patients with MwoA, as a group when compared with HC.

Interestingly, our secondary analysis showed that FA was significantly lower in patients with MwoA

$_{d}$CA when compared with both patients with MwoA $_{nd}$CA and HC. TBSS approach by means of derived indices (FA, MD, AD, and RD) defines highly specific pathophysiological processes subtending WM microstructural changes. In more detail, FA can reflect the structure of axonal cell membranes and myelin sheaths and lower FA may result from several conditions such as demyelination, axonal loss, gliosis, and neuroinflammation.[47] Our results suggest the possibility of an integrity change of CC neurofibrotic microstructures in patients with MwoA, particularly evident in those patients who will develop CA in the three years following the MRI scan.[47,48] The CC, the largest white matter structure in the brain, is formed by commissural fibers providing the main route of communication between the two hemispheres playing a central role in information transmission and integration. Interestingly, gCC-FA abnormalities have been previously reported in patients with MwoA with depression as well as in patients with medication-overuse headache,[49-51] and associated with reduced RS-FC of the ACC.

In the present study, in line with some previous observations, we did not find statistically significant correlation between the FA changes and migraine clinical features, both assessed at baseline and after 3 years, in patients with MwA. Nevertheless, some other studies showed a significant correlation between the FA reductions and both disease duration and migraine attacks frequency suggesting a white matter damage from repetitive MwoA attacks, although they did not evaluate the well-known aging effect on FA.[52]

Therefore, in accordance with the reported association between gCC-FA abnormalities and clinical conditions known to be related to migraine chronification (eg, depression and medication overuse), we believe that gCC-FA disruption, observed in patients with MwoA $_{d}$CA, may precede the development of CA itself (another well-identified factor of migraine chronification) representing a prognostic biomarker of migraine chronification.

CONCLUSION

In the present study, we demonstrated that intrinsic cognitive network functional abnormalities and specific microstructural changes in patients with MwoA might represent advanced neuroimaging prognostic biomarkers able to identify those patients who will develop CA over time and, therefore, more prone to migraine chronification.

In our opinion, the present study has some strengths compared to previous observations.

To overcome one of the major limitations of neuroimaging studies in migraine, that is, the absence of prospective approaches, we investigated patients with MwoA at baseline by advanced neuroimaging techniques. Moreover, we assessed clinical and neuropsychological evaluations, both at baseline and after three years, aimed to follow the clinical story of the disease over time. In this way, we were able to explore whether specific neuronal substrates observed at baseline could both precede and predict, the migraine evolution.

Furthermore, migraine patients and HC have been extensively investigated by means of multiparametric MRI approach (ie, functional, structural, and microstructural).

Finally, we report group differences statistically significant over the entire brain without a priori regional hypothesis on specific pain processing areas.

Nevertheless, we are aware that our study is not exempt from some limitations as well. First of all, despite the absence of correlation between RS functional connectivity findings and disease severity, we cannot exclude that observed differences in RS-DMN are due to functional changes related to some other aspect of migraineous experience. In particular, we did not quantitatively assess migraine sensorineural hypersensitivity symptoms (eg, photophobia, photophobia, and osmophobia) nor at baseline neither after three years. However, no qualitative changes in these symptoms have been reported by the patients during the observation period, using semi-structured clinical interviews. Nevertheless, although it could be speculated that central integrative mechanism may subtend CA as well as other sensorineural hypersensitivity modalities (in particular photophobia and phonophobia), we can further exclude the role of the latter in our results. Indeed, we found a weaker FC in the anterior PCC-precuneus, a sub-region characterized by a good functional segregation and integration in functional task-evoked activations, specifically and exclusively involved in sensorimotor functions.[53]

Moreover, we investigated ictal CA by means of a widely used verbal clinical scale (eg, ASC-12) due to difficulties in testing the presence of dynamic mechanical (brush) allodynia in all patients at the same time point during migraine attacks.

Future perspective advanced neuroimaging studies remain of paramount importance to further clarify the pathophysiological mechanisms underlying CA and migraine worsening up to chronification and the capability of advanced neuroimaging in discriminating specific prognostically unfavorable migraine phenotypes.

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