

REVIEW

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One-month atogepant treatment induces rapid changes in delta-band functional connectivity in migraine: an HD-EEG study

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Abstract

Background Atogepant is a novel oral calcitonin gene-related peptide (CGRP) receptor antagonist approved for the preventive treatment of migraine. While its peripheral mechanisms are well characterized, little is known about its potential effects on central functional brain networks. This study aims to investigate changes in resting-state functional connectivity (FC) using high-density EEG (HD-EEG) after one month of atogepant treatment in patients with migraine, and to assess the relationship between these changes and clinical response.

Methods Twelve patients with high-frequency episodic migraine (HFEM; $n = 7$) or chronic migraine (CM; $n = 5$) underwent HD-EEG recordings at two time points: before starting Atogepant administration (T0) and after one month of treatment (T1). Fifteen healthy controls (HC) were also enrolled. Clinical evaluations included: monthly migraine days (MMD), monthly symptomatic drugs intake (MSI), modified Migraine Disability Assessment (mMIDAS), the headache impact test (HIT-6), the Migraine-Specific Quality of Life Questionnaire (MSQ), the 12-item Allodynia Symptom Checklist (ASC-12), and the Migraine Interictal Burden Scale (MIBS-4). EEG-based FC was analyzed in source space using the weighted Phase Lag Index (wPLI) across δ , θ , α , β , low- γ , and high- γ bands. To identify changes related to treatment, we applied Network-Based Statistics (NBS), while Spearman correlation was used to explore the relationship between clinical improvements and functional changes.

Results Compared to HCs, HFEM + CM patients exhibited increased δ band functional connectivity (FC) in temporo-parietal, orbitofrontal, insular, and limbic regions. After one month of atogepant treatment, a significant reduction in this aberrant FC was observed, particularly in bilateral temporo-parietal, cingulate, insular, and prefrontal cortices. Baseline δ -band FC correlated with greater clinical disability (mMIDAS, MSQ), while treatment-induced FC changes (Δ mNC) were associated with improvements in mMIDAS, HIT-6, and ASC-12 scores, highlighting the clinical relevance of δ band network modulation.

Conclusions This pilot study provides preliminary evidence that atogepant modulates δ band functional brain connectivity after one month of treatment in patients with episodic and chronic migraine. These changes in central

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brain networks are associated with clinical improvement and may serve as a neurophysiological marker of CGRP receptor antagonist efficacy. Larger-scale studies are needed to confirm and extend these findings.

Keywords Migraine, Atogepant, HD-EEG, Functional connectivity

Background

Migraine is a complex neurological disorder characterized by recurrent headache attacks and widespread disruptions in sensory processing and brain functional connectivity (FC) [1, 2]. Recent neuroimaging studies have shown that migraine involves dynamic alterations in large-scale brain networks, particularly during the interictal phase, the period between attacks [3–5]. These changes are believed to reflect heightened cortical excitability and impaired thalamo-cortical modulation [2, 6, 7].

In a subset of individuals, migraine can progress into a more persistent and treatment-resistant form [8]. The transition from episodic to chronic migraine is well documented, particularly in the presence of risk factors such as medication overuse or inadequate preventive therapy [9]. This chronification process is believed to involve progressive sensitization of the nociceptive pathways, beginning at the peripheral level and extending to second-order neurons within the central nervous system. The resulting dysfunction in sensory integration and increased cortical excitability contributes to symptom persistence and diminished treatment responsiveness [1].

In this context, effective clinical management of migraine requires a comprehensive approach that addresses both acute attacks and long-term disease burden. Although the precise pathophysiology of migraine remains debated, there is strong consensus that both peripheral and central mechanisms are critically involved in initiation, progression, and response to treatment [10].

High-density electroencephalography (HD-EEG) provides a non-invasive, high-temporal-resolution method to explore brain network dynamics. HD-EEG investigates pathophysiological features of neurological disorders, including neurodegenerative disorders like Parkinson's Disease (PD), where HD-EEG has highlighted specific cortical FC features of early-onset PD and differentiated between clinical phenotypes [11–13]. By capturing frequency-specific oscillatory activity and enabling source reconstruction, HD-EEG has also been used to examine FC alterations related to migraine pathophysiology and the network-level effects of preventive treatments [2]. However, findings to date have often been inconsistent, highlighting the need for further investigation.

Among the latest therapeutic innovations targeting the calcitonin gene-related peptide (CGRP) pathway, atogepant represents a novel significant advancement. Unlike monoclonal antibodies, which require subcutaneous or intravenous administration, atogepant is a

small-molecule CGRP receptor antagonist that is orally administered, enabling greater flexibility and patient adherence. Clinical trials and ongoing real-life studies [14] have demonstrated that atogepant has a rapid onset of action [15], with efficacy evident within 4 weeks of treatment.

While both monoclonal antibodies and gepants effectively reduce peripheral sensitization, emerging evidence suggests that CGRP-targeted therapies may exert a more pronounced effect on central sensitization, especially in relation to non-headache symptoms such as cutaneous allodynia. Supporting this, Montisano et al. (2024) [16] reported that onabotulinumtoxinA (OBTA), a treatment primarily acting at the peripheral level [17], is significantly less effective than CGRP-targeted therapies in alleviating migraine-associated symptoms, particularly allodynia. These findings highlight the clinical importance of central mechanisms in mediating migraine-related disability.

Complementary evidence from functional MRI (fMRI) studies has shown that galcanezumab, a monoclonal antibody targeting CGRP, can attenuate resting-state hyperexcitability in key cortical regions within the limbic pain network, likely through the reduction of afferent nociceptive input [18].

In a previous study by our group [2], we demonstrated that patients with chronic migraine exhibit FC abnormalities that are both network- and frequency-specific during the interictal phase, when compared to controls. Notably, a single session with OBTA resulted in a reversal of these alterations, restoring FC patterns toward a physiological state. Our observation strongly supports the peripheral modulatory effect of OBTA on a central level pain dynamic.

This study aims to investigate the effects of atogepant on resting-state FC as measured by HD-EEG after one month of treatment in patients with high-frequency episodic migraine (HFEM) and chronic migraine (CM). Specifically, we seek to characterize how CGRP receptor antagonism modulates large-scale brain networks, and whether changes in FC correlate with clinical improvements in migraine frequency, severity, disability, and central sensitization. By integrating neurophysiological and clinical data, this study may shed light on the central mechanisms underlying migraine pathophysiology and provide empirical support for the use of EEG-based biomarkers for personalized preventive therapies.

Methods

Study subjects

This mixed-design study, combining a baseline case-control design with a longitudinal observational approach, enrolled patients admitted to the Headache Centre at Tor Vergata University Hospital in Rome between July 2024 and December 2024.

Inclusion criteria were: (1) patients of both sexes of legal age (>18 years); (2) diagnosis of either HFEM or CM, according to the International Headache Society (International Classification of Headache Disorders, 3rd edition [19]); (3) prescription with atogepant 60 mg daily, in accordance with the criteria established by the Italian Medicines Agency (AIFA), and continued treatment for at least one month (T1); (4) no migraine attack or acute medication intake 72 h before the start of the protocol, to exclude the post-ictal phase.

Exclusion criteria included: (1) treatment with migraine preventive oral standard of care in the previous four weeks; (2) treatment with onabotulinumtoxinA or anti-CGRP monoclonal antibodies in the last six months; (3) history of other neurological, psychiatric, autoimmune, or systemic diseases potentially altering EEG; (4) presence of significant abnormalities on brain MRI, including large or confluent white matter hyperintensities (WMH), cortical lesions, or other structural alterations; (5) altered consciousness, organ failure, or severe infections that could interfere with clinical follow-up; (6) medication overuse; (7) occurrence of a migraine attack within 48 h after EEG recording, to avoid inclusion of the pre-ictal phase.

To note, all included HFEM-CM patients had experienced at least three previous failures of preventive migraine therapies, such as beta-blockers, tricyclic antidepressants, antiepileptics, or onabotulinumtoxinA (for CM patients), in accordance with Italian Medicines Agency (AIFA) guidelines. Treatment failure was defined as a lack of clinically meaningful improvement after a minimum of 6 months, poor tolerability, or contraindications. Among the enrolled subjects, five had received unsuccessful treatment with anti-CGRP monoclonal antibodies (erenumab, $n=1$; galcanezumab, $n=2$; fremanezumab, $n=2$), and five with onabotulinumtoxinA. In accordance with exclusion criteria, a washout period of at least six months was observed before starting atogepant for both anti-CGRP monoclonal antibodies and onabotulinumtoxinA, and at least four weeks for oral preventive medications.

Thirty-two adult patients with migraine were considered eligible for the study. Among them, twelve patients (7 with HFEM and 5 with CM) initiated atogepant treatment according to clinical practice. As a control group, we enrolled fifteen age- and sex-matched healthy controls (HCs) with no history of neurological, psychiatric,

autoimmune, or systemic disease, and with no significant lesion in brain MRI (exclusion criteria 3–4). The recruitment process is summarized in the flow diagram of Fig. 1.

Notably, all participants underwent brain MRI within six months prior to study enrollment. Subjects with clinically significant structural abnormalities, such as large or confluent white matter hyperintensities (WMH), cortical lesions, or other alterations affecting brain function, were excluded from the study, as described above.

The study was conducted following the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Policlinico Tor Vergata (protocol code RS 16/17), and all participants provided written informed consent.

This study does not qualify as a clinical trial according to the WHO/ICMJE definition. All patients received atogepant as part of routine clinical care, independently prescribed by their treating neurologist in accordance with national (AIFA) and European (EMA) regulations. The study followed an observational, pre-post design.

Assessments

All patients underwent a thorough clinical history assessment, focusing on the characteristics of their migraine attacks—including duration, monthly migraine days (MMD), use of symptomatic medications, pain location and quality, associated symptoms (such as autonomic and/or dopaminergic signs), and the presence of cutaneous allodynia. Data were also collected on prior preventive treatments, comorbidities, and concomitant therapies. A routine neurological examination was conducted to rule out focal neurological deficits. Migraine-related disability and associated symptoms were evaluated at baseline (T0) and after one month of treatment (T1) using standardized, validated clinical scales commonly used in clinical practice. These included: the modified (monthly) Migraine Disability Assessment (MIDAS) questionnaire (measured as a 4-week recall period vs. a 3-month recall of standard MIDAS [20, 21]), the Headache Impact Test (HIT-6) [22], the Migraine-Specific Quality of Life Questionnaire (MSQ) [23], the 12-item Allodynia Symptom Checklist (ASC-12) [24], and the Migraine Interictal Burden Scale (MIBS-4) [25]. Adverse events (AEs) were recorded for all patients throughout the study.

Finally, HFEM+CM patients were categorized as responders or non-responders based on clinical outcome thresholds. Responders were defined a priori as patients achieving a $\geq 50\%$ reduction in the number of monthly migraine days (MMD) from baseline to follow-up, consistent with established criteria in migraine prevention trials [26].

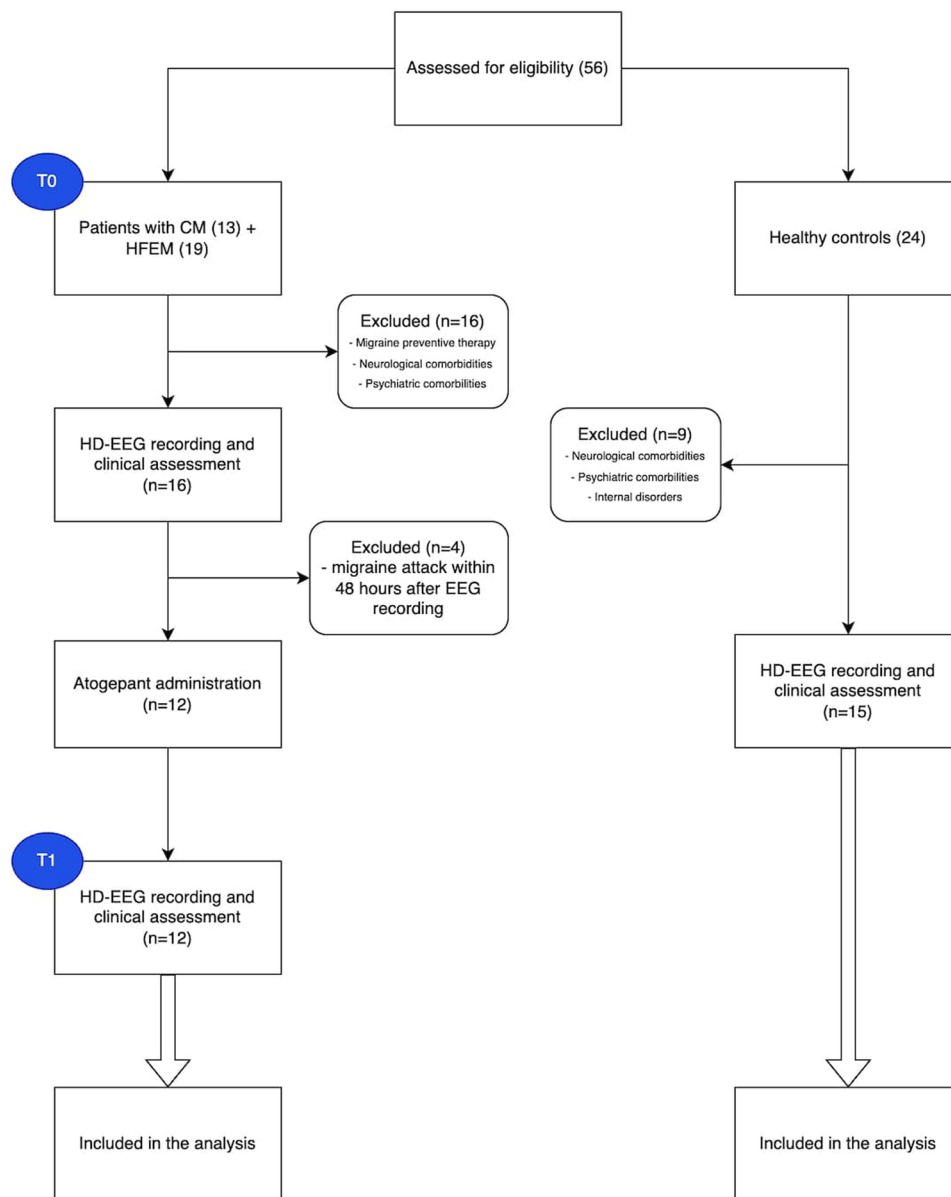


Fig. 1 Flowchart of the recruitment process of the study. Abbreviations: CM, Chronic Migraine; HD-EEG, high-density electroencephalography; HFEM, High Frequency Episodic Migraine

Atogepant administration

Atogepant was administered orally at a dose of 60 mg once daily, in accordance with the recommendations of the European Medicines Agency (EMA) (EMA/361998/2023). Participants were instructed to take the medication in the evening, approximately at 10:00 p.m., after dinner. The treatment began at baseline (T0) and continued uninterrupted throughout the entire month until the post-treatment assessment (T1) and was maintained thereafter.

EEG recording

HD-EEG recordings were performed in patients with HFEM and CM for 10 min at a sampling rate of 1024 Hz, band-pass filtered at 0.5–100 Hz using a 64-channel EEG system (EbNeuro BePlus-ProStandard). Electrodes were positioned according to the 10–10 International System [27]. Impedance was kept below 5 k Ω . In line with previous EEG studies [2, 12, 13], HD-EEG recording was performed in the eyes-closed (EC) resting state (RS). Subjects were instructed to keep their eyes closed while staying awake for 5 min. Then, reactivity to eye opening and activation tests was performed to exclude the appearance of epileptiform elements in the EEG data. EEG data were

recorded in migraine patients in the interictal phase (at least 72 h after and 48 h before a migraine attack or acute medication intake). Patients were contacted by phone 48 h after the EEG recording to ensure that they had not had a migraine attack. Indeed, patients with migraine in a pre-ictal phase were excluded from the analysis (T0 $n=4$ excluded, T1 $n=0$ excluded), as indicated in Fig. 1. In cases where a migraine episode occurred within 72 h before the planned T1 recording (28–30 Days of treatment), the session was postponed accordingly. However, in all patients, the T1 assessment was completed within 72 h from Day 30 of treatment, ensuring protocol adherence and temporal consistency across subjects. The same HD-EEG recording was obtained in HC. Both the HD-EEG recordings and the clinical evaluations were performed at the baseline screening visit (enrolment – T0), just before the start of atogepant treatment, and one month (T1) from the start of therapy.

To ensure that EEG recordings were not influenced by peri-ictal cortical changes, all sessions were performed during the interictal phase, defined as at least 72 h after the last migraine attack or acute medication intake. Patients were instructed to promptly report any migraine occurrence during the final days of treatment. If a migraine attack occurred within 72 h of the scheduled post-treatment (T1) recording, the EEG session was postponed complying with protocol criteria. However, in all cases, the T1 EEG was conducted within 72 h from Day 30 of atogepant administration, ensuring consistency across the cohort.

FC analysis

Primary FC analyses were then conducted on the data collected. The data analyses were performed in a blind manner to the clinical examinations. HD-EEG recordings in the EC condition were segmented into epochs of 30 s each for visualization purposes [28, 29]. The first epoch of each recording was discarded. Then, we manually selected the first six consecutive low-artifact epochs (total 180s), that were retained for the following analysis. The same method was used for HFEM + CM patients and HCs.

Independent component analysis (ICA) was used to remove the residual EEG artifacts [30]. Then, we proceeded with EEG source localization. EEG channels and MRI template (ICBM152) were co-registered through the identification of the same anatomical landmarks, and the Boundary Element Method (BEM) [31] was used to solve the forward problem. We used weighted minimum-norm estimation (wMNE) to solve the inverse problem [32]. The sources obtained were divided into 68 brain regions, using the Desikan–Killiany atlas [33].

FC was calculated in source space using the values of weighted phase lag index (wPLI), a measure known to

reduce conduction volume artifacts, noise artifacts, and bias from small samples [34]. Phase information from the preprocessed signals had been computed using the Hilbert transform in δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), low- γ (30–50 Hz), and high- γ (50–100 Hz) frequency bands. Dynamic FC matrices were computed between any pair of regions in the above EEG bands, on segments of 1-second length, with an overlap of 50%, according to Welch's method [35]. Those matrices were averaged across time epochs to obtain static FC matrices.

A pipeline of the study protocol is provided in Fig. 2.

Statistical analysis

Descriptive statistics – including mean, median, standard deviation, and percentiles – were calculated for all study variables. Due to the limited sample size (27 subjects; 15 healthy controls and 12 migraine patients), the normality of data distribution was assessed using the Shapiro-Wilk test. Since most variables did not follow a normal distribution, non-parametric statistical methods were used for subsequent analyses.

Group comparisons between healthy controls (HC) and HFEM + CM patients in terms of sex, age, and body mass index (BMI) were performed using the chi-square test and the Mann-Whitney U test. Within the HFEM + CM group, changes in clinical scale scores (ASC-12, HIT-6, MSQ, MIDAS, and MIBS-4) and monthly migraine days (MMD) between baseline (T0) and post-treatment (T1) were analyzed using the Wilcoxon signed-rank test. Finally, due to the presence of only one non-responder, comparative analyses between responders and non-responders were not statistically feasible.

Differences in EEG-FC across different frequency bands between HFEM + CM patients at T0 and HCs, and between HFEM + CM patients at T0 and at T1 were analyzed using the network-based statistic (NBS) [36]. Age and sex were considered confounding factors in NBS.

NBS is a cluster-based statistical method that has been shown to provide greater statistical power than traditional correction methods, such as Bonferroni or FDR [13, 28, 37]. Nevertheless, choosing the NBS threshold t represents an arbitrary parameter, even though control of the family-wise error rate (FWER) is guaranteed regardless of the threshold selection. In this study, we adopted a data-driven approach by selecting the smallest t threshold that yielded a statistically significant NBS network ($p < 0.05$, 5000 permutations for the permutation test) with at least a “medium” effect size, already used in a previous study of our group [38]. This strategy was implemented to avoid the detection of overly large networks that, while significant, might include numerous weak effects and obscure the truly meaningful alterations in FC. The effect size associated with each t threshold was estimated using Cohen's d , as the general linear model

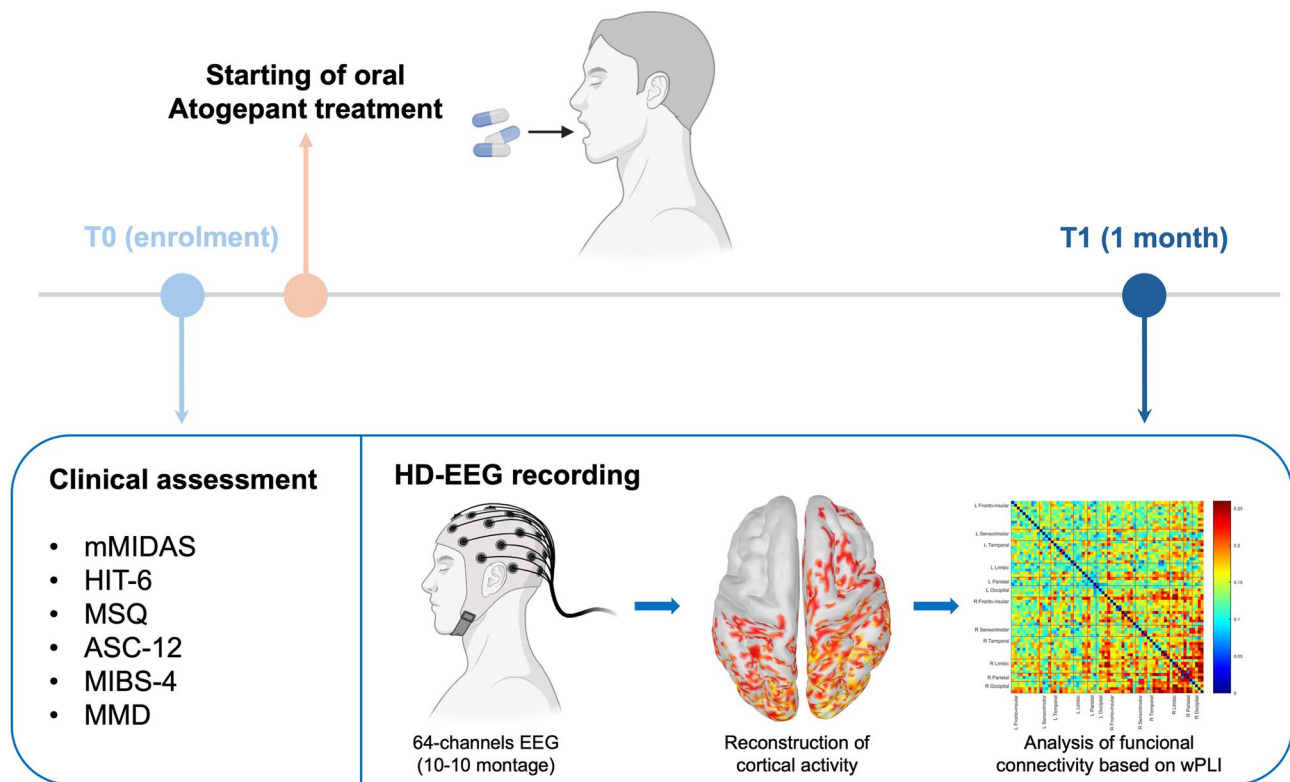


Fig. 2 Pipeline of the study. In each patient with chronic migraine (HFEM + CM), high-density electroencephalography (HD-EEG) recordings and clinical evaluations were performed at baseline (T0, enrolment visit), immediately before the initiation of atogepant treatment, and after 1 month of therapy (T1). Atogepant was administered orally at a dose of 60 mg once daily in the evening, approximately at 10:00 p.m., after dinner. Cortical activity was reconstructed from the EEG signals, and functional connectivity (FC) matrices were computed for each frequency band using the weighted phase lag index (wPLI). Abbreviations: ASC-12, Allodynia Symptom Checklist; CM, chronic migraine; FC, functional connectivity; HD-EEG, high-density electroencephalography; HIT-6, Headache Impact Test; MIBS-4, Migraine Interictal Burden Scale; mMIDAS, modified (monthly) Migraine Disability Assessment Test; MMD, Monthly Migraine Days; MSQ, Migraine Specific quality of life Questionnaire; wPLI, weighted phase lag index. Figure created with BioRender.com

(GLM) for NBS applied in this case was a two-sample t-test. A Cohen's $d > 0.5$ was considered indicative of a medium effect size.

Mean network connectivity (mNC) was defined as the average connectivity within an NBS network, following established methods [2, 12, 13]. Spearman's correlation was used to examine the relationship between mNC of the altered functional network in the combined HFEM and CM group compared to HCs at baseline and clinical scores, including ASC-12, mMIDAS, MIBS-4, MSQ, and HIT-6. Additionally, we calculated Spearman's correlations between the change in mNC (Δ mNC, defined as the difference between T1 and T0) and the changes in clinical measures (Δ ASC-12, Δ mIDAS, Δ MIBS-4, Δ MSQ, and Δ HIT-6) within the HFEM + CM group.

All statistical analyses were two-tailed, and a significance level of $p < 0.05$ was adopted. No a priori power calculation was conducted, as the sample size was determined based on data availability and prior experience with the design of EEG-FC studies using network-based statistics (NBS).

Cross-validation methods

We evaluated the reliability of our NBS results by implementing a predictive modeling approach based on support vector machines (SVM). To assess the generalizability of the model, we used leave-one-out cross-validation (LOOCV), an exhaustive and unbiased validation method. We calculated several performance metrics for each cross-validation fold to evaluate the ability of the identified network to discriminate between the two groups. Specifically, we estimated accuracy (the proportion of correctly classified links out of the total number of links), precision (the proportion of true positive links among all links predicted as positive), Cohen's kappa (a chance-corrected measure of agreement between predicted and actual classifications), sensitivity (the proportion of true positive links correctly identified), specificity (the proportion of true negative links correctly identified), and the area under the receiver operating characteristic (ROC) curve, which illustrates the trade-off between sensitivity and specificity across different thresholds. This analysis allowed us to quantify the robustness and

discriminative power of the functional connectivity networks identified through NBS.

Moreover, we estimated the out-of-sample performance of the Spearman correlation analysis bootstrapping (BS) as a cross-validation method. This resampling technique allowed us to assess the stability and generalizability of our correlation estimates by repeatedly sampling subsets of the data and simulating different training and testing datasets. The number of BS iterations we used was 1000. In the results, we provided a 95% confidence interval (BS-95%CI) of the BS distribution of correlation coefficients, as an estimation of the robustness of our findings.

Statistical analyses of clinical and demographic variables were performed using IBM SPSS Statistics (Version XX, IBM Corp., Armonk, NY). The EEG-FC analysis was performed using a custom-written script based on MATLAB 2024b, combined with Brainstorm and NBS toolboxes. Graphs were based on MATLAB 2024b and R (ggplot2 package).

Table 1 Clinical and demographic data of the study population

	MG T0 N = 12	MG T1 N = 12	HC n = 15	p-value
Age	44 (35.3 57.0)	/	44.6 (36 54)	1.000
F/M	10/2		12/3	0.612
BMI	22.3(21.3 24.6)	/	22.5(21.6 24.3)	0.880
DDY	15(9 42)	/	/	/
HFEM/CM	7/5	/	/	/
Responders/non-responders	/	11/1	/	/
MMD	13(10 23.7)	5.5 (4.3 9.8)	/	< 0.001*
MSI	10(7 13.8)	0 (0 1.8)	/	< 0.001*
ASC-12	3(2 8.8)	0 (0 3.5)	/	0.005*
HIT-6	66.5(61.5 69)	58 (53.8 58)	/	0.002*
mMIDAS	47.5(28 67.5)	13.5 (10.3 20)	/	0.001*
MSQ	12.5(9 25.3)	39.5(26.3 57)	/	0.002*
MIBS-4	8.5(6 10.5)	6 (2)	/	0.001*

Data are expressed as median [25th, 75th percentiles] of variables. Age is expressed in years

Abbreviations MG-T0 migraine group at baseline, CM-T1 migraine group one month after treatment, F females, BMI body mass index, HCs healthy controls, M males, DDY disease duration years, HFEM high frequency episodic migraine, CM chronic migraine, MMD monthly migraine days, MSI Monthly symptomatic drugs Intake, ASC-12 allodynia symptom checklist, HIT-6 Headache Impact Test, mMIDAS modified (monthly) Migraine Disability Assessment Test, MSQ migraine specific quality of life questionnaire, MIBS-4 migraine interictal burden scale

*Statistical significance

Results

Demographic and clinical characteristics of HCs and HFEM + CM patients at baseline are reported in Table 1, including clinical scores after 1 month of atogepant treatment (T1).

Comparison of EEG-FC between HCs and HFEM + CM patients

Through NBS analysis, we found a network in the δ frequency band ($t=2.6$, $p=0.045$), where FC was significantly increased in the HFEM + CM group compared to HCs (Fig. 3, Panels A-B-D). This network included 40 nodes and 58 links and was well distributed between the two hemispheres (52.5% right). ROIs with the highest degree were mainly located in temporal regions (including bilateral middle and inferior temporal gyri, and right temporal pole), limbic areas (such as bilateral parahippocampal cortex and posterior cingulate), frontal regions (notably left lateral orbitofrontal and bilateral pars orbitalis/triangularis), and parietal cortices (especially right precuneus and superior parietal lobule). The most represented connections were temporo-limbic (13.8%), fronto-temporal (12.1%), and intra-temporal (10.3%). The mNC was significantly higher in the HFEM + CM group compared to HC ($p<0.001$) (Fig. 3, Panel C). To note, no significant differences in the mNC of the differential NBS network emerged between HFEM and CM patients.

Moreover, we found significant positive Spearman's correlations between mNC of the δ FC network and mMIDAS score at T0 ($r=0.60$, $p=0.042$, BS-95% CI [0.10, 0.89]) (Fig. 3, Panel E) and a negative Spearman's correlations between δ FC mNC and MSQ score at T0 ($r=-0.78$, $p=0.003$, BS-95% CI [-0.93, -0.38]) (Fig. 3, Panel F). No other correlations between the mNC of the altered network and other clinical scores were found.

Accuracy, precision, Cohen's κ , sensitivity, and specificity for ROC analysis (HFEM + CM vs. HC) of the identified NBS network were calculated using an SVM approach and a CV LOO algorithm (Table 2).

No significant differences in FC between HFEM + CM patients and HCs were observed in the other bands.

Comparison of EEG-FC between T0 and T1 in HFEM + CM patients

A network in the δ frequency band was identified through NBS analysis ($t=2.6$, $p=0.008$), showing significantly decreased FC following one month of treatment with atogepant (T1 < T0) in HFEM + CM patients (Fig. 4, Panels A-B-D). This network included 51 nodes and 112 links and was bilaterally distributed, with 51% of the nodes located in the right hemisphere. ROIs with the highest degree were primarily located in frontal regions (notably right rostral middle frontal, frontal pole, and bilateral lateral orbitofrontal and pars opercularis/triangularis),

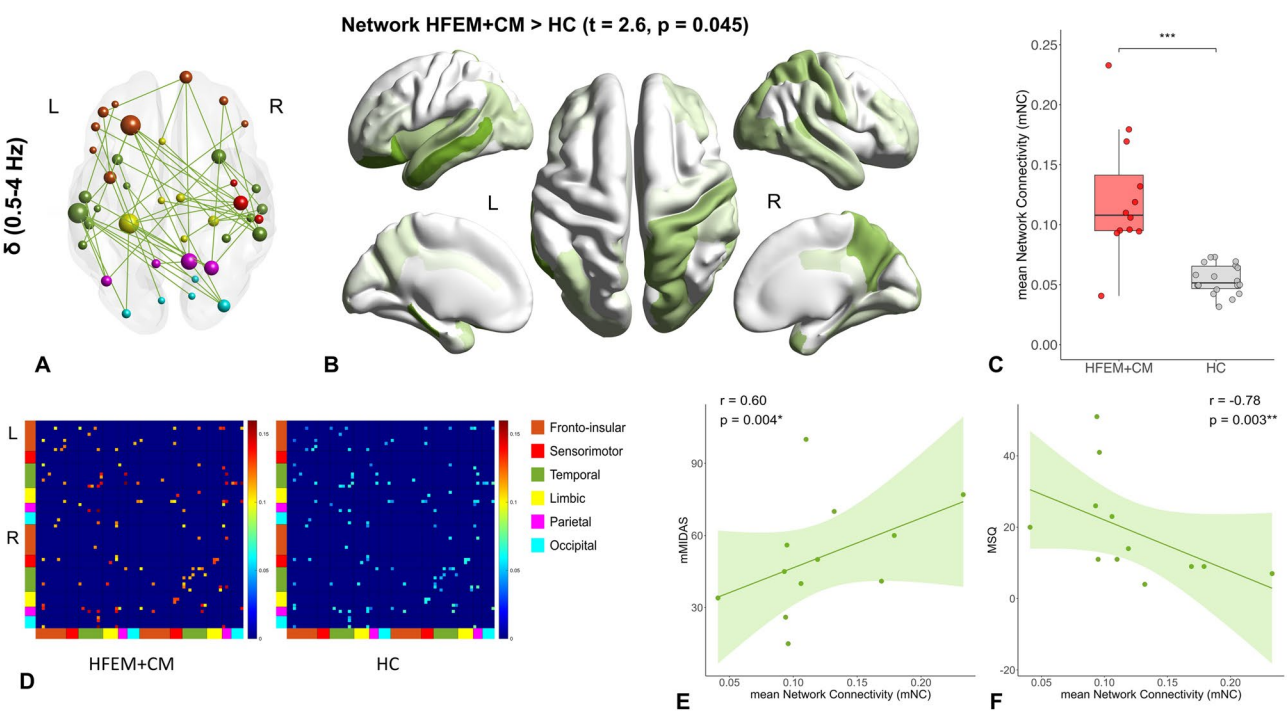


Fig. 3 Graph representation of the differential networks between HFEM+CM and HC in the δ band (A). The color of spheres represents different brain lobes: orange=fronto-insular, red=sensorimotor, yellow=limbic, green=temporal, magenta=parietal, light-blue=occipital; sphere diameters are directly proportional to region of interest (ROI) degrees. Map representation of ROI degrees on the model brain surface of the differential networks in the δ band (B). Box plots represent the mean network connectivity (mNC) values in HFEM+CM and HC groups of the NBS network in the δ band (C). Mean FC matrices of HFEM+CM and HC for NBS networks in the δ band (D). Spearman's correlations between the mNC of the δ network and mMIDAS (E), and MSQ (F) scores in HFEM+CM group

Table 2 Cross-validation of the differential NBS network in HFEM+CM-T0 versus HCs and HFEM+CM T0 versus T1 conditions based on the leave-one-out method						
	Accuracy	Precision	Cohen's κ	AUC	Sensitivity	Specificity
δ network ($t=2.6$)	0.93	1.00	0.86	0.91	0.83	0.96
HFEM+CM-T0 vs. HC	[0.80 1.00]	[1.00 1.00]	[0.66 1.05]	[0.61 1.00]	[0.50 1.00]	[0.90 0.99]
δ network ($t=2.6$)	0.92	1.00	0.83	0.81	0.90	1.00
HFEM+CM T0 vs. T1	[0.77 1.00]	[1.00 1.00]	[0.61 1.05]	[0.72 0.88]	[0.59 1.00]	[1.00 1.00]

temporal cortices (including bilateral middle and inferior temporal gyri, and right transversetemporal), parietal areas (especially right superior and inferior parietal lobules and precuneus), and limbic structures (such as bilateral parahippocampal cortex and posterior cingulate). The most represented connections involved fronto-temporal (12.5%), temporo-limbic (10.7%), and intra-frontal (8.9%) pathways. The mNC was significantly higher at T0 compared to T1 ($t=5.28, p<0.001$), reflecting a reduction in functional connectivity after treatment (Fig. 4, Panel C). No significant differences in the mNC of the T1<T0 network were found between HFEM and CM patients.

Spearman's correlation analysis revealed that the change in mean network connectivity in the delta band (Δ mNC) was significantly associated with clinical improvement. Specifically, Δ mNC positively correlated with reductions in mMIDAS scores ($r=0.75, p=0.005$ BS 95% [0.28 0.94]) (Fig. 4, Panel F), HIT-6 ($r=0.68,$

$p=0.013$ BS 95% [0.20 0.52]) (Fig. 4, Panel G), and ASC-12 ($r=0.60, p=0.036$ BS 95% CI[0.06 0.89]) (Fig. 4, Panel H), suggesting that increased delta-band network variability is linked to better therapeutic response.

Accuracy, precision, Cohen's κ , sensitivity, and specificity of the differential NBS network (T0 vs. T1) were calculated using SVM integrated with CV LOO method (Table 2). ROC curves of predictive models are shown in Fig. 4, Panel E.

Discussion

In this study, we investigated alterations in EEG-based FC within the δ band in patients with HFEM+CM in the interictal phase of migraine. Compared to HCs, HFEM+CM patients showed significantly increased δ band connectivity, which was network-specific, with the most affected regions located in the temporo-parietal, orbitofrontal, insular, and limbic areas. After one month

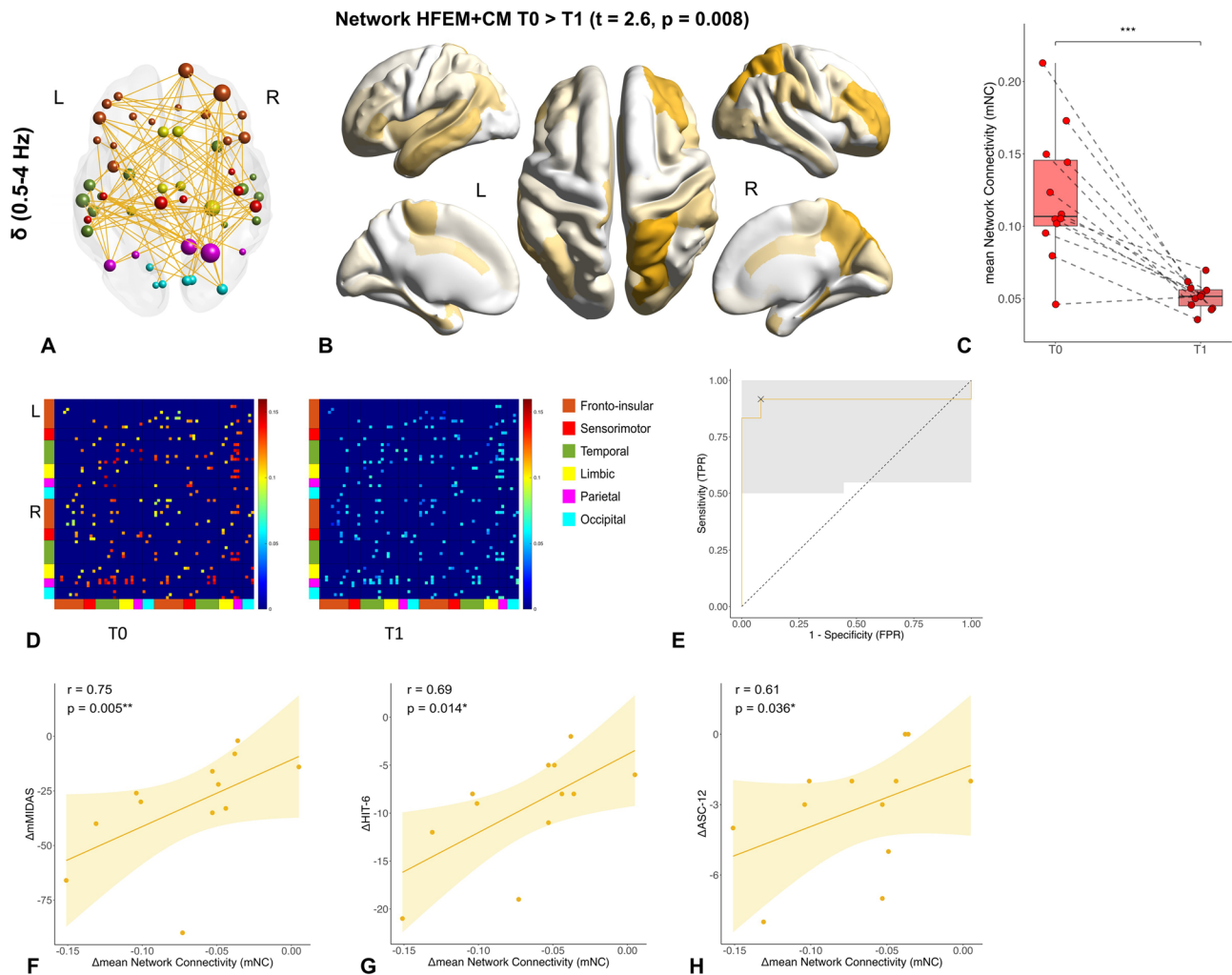


Fig. 4 Graph representation of the differential networks between HFEM+CM at T0 and T1 in the δ band (**A**). The color of spheres represents different brain lobes: orange = fronto-insular, red = sensorimotor, yellow = limbic, green = temporal, magenta = parietal, light-blue = occipital; sphere diameters are directly proportional to region of interest (ROI) degrees. Map representation of ROI degrees on the model brain surface of the differential networks in the δ band (**B**). Box plots represent the mean network connectivity (mNC) values between HFEM + CM at T0 and T1 of the δ band network (**C**). Mean FC matrices of HFEM + CM and HC for NBS networks in the δ band (**D**). ROC curve based on SVM of the δ band differential network between HFEM + CM T1 vs. T0 (**E**). Spearman's correlation between the Δ mNC of the differential network in the δ band and Δ value of the clinical scale (MIDAS (**F**), HIT-6 (**G**), and ASC-12 (**H**)) across T1 and T0 points

of treatment with atogepant, a significant reduction in this dysfunctional δ band connectivity was observed. Notably, the treatment-responsive identified network involved a similar distribution of regions, particularly the bilateral temporo-parietal, cingulate, insular, and prefrontal cortices, suggesting that atogepant may act by selectively reversing the baseline network alterations associated with migraine. Moreover, the network differences observed in both comparisons (migraine patients versus controls and T0 versus T1) were clinically meaningful. In the cross-sectional analysis, mNC positively correlated with baseline scores of the mMIDAS and negatively with MSQ scales, reflecting greater disability and worse quality of life in patients with higher δ -band FC. In the longitudinal analysis, the reduction in mNC (Δ mNC)

significantly correlated with improvement on the mMIDAS, HIT-6, and ASC-12 scales, underscoring the link between δ band network modulation and therapeutic efficacy.

This pattern reflects widespread hyperconnectivity within pain-related brain networks in individuals with migraine. Previous studies – primarily using fMRI – have consistently demonstrated altered resting-state FC among cortical regions involved in the sensory, cognitive, and emotional dimensions of pain processing, collectively known as the “neurolimbic pain network” [39, 40]. Key components of this network include the cingulate cortex and amygdala, which are central to the emotional and affective experience of pain; the orbitofrontal cortex, which contributes to the cognitive appraisal and

regulation of pain; and regions such as the temporal pole, precuneus, and hippocampus, which play a critical role in emotional memory and contextual processing of pain [41].

Consistent with these previous findings, we observed an altered FC at baseline in HFEM+CM patients compared to HCs, primarily involving regions associated with pain processing. Specifically, we found a significant increase in δ band FC mostly in limbic, orbitofrontal, and temporal areas. Moreover, these alterations significantly improved after one month of treatment with atogepant. To note, these results closely parallel those of our previous study investigating the effects of onabotulinumtoxinA (OBTA) in patients with CM, where we similarly observed elevated δ band connectivity at baseline that significantly decreased after treatment, in association with clinical improvement [2]. In both cases, the modulation of δ band FC appears to reflect the normalization of disrupted multisensory integration and nociceptive processing. These converging findings suggest that, despite differing molecular targets, both atogepant and OBTA may exert a common neuromodulatory effect on large-scale brain networks involved in the pathophysiology of migraine.

Importantly, these alterations were not only network-specific but also frequency-specific, consistently emerging within the δ band. Although δ activity is traditionally associated with sleep and unconscious states [42], growing evidence suggests that, in awake adults, it may indicate dysfunctional thalamo-cortical interactions and impaired sensory gating [43, 44]. In the context of CM, studies using EEG-based FC remain limited, though many have examined quantitative EEG spectral characteristics during both interictal and ictal phases [45, 46]. Previous findings have shown increased δ power in fronto-central regions during the interictal phase of CM, potentially reflecting persistent low-frequency thalamic drive or maladaptive cortical inhibition [47]. Similarly, increased δ activity has been observed ipsilateral to the predominant headache side in episodic migraine, possibly reflecting latent cortical spreading depression and impaired cortical homeostasis [48]. According to these findings, our study revealed widespread δ band hyperconnectivity at baseline in HFEM+CM patients compared to HCs. This δ band hypersynchronization may reflect pathophysiological activity within pain-related networks and contribute to migraine chronification through mechanisms of central sensitization.

Consistently, the clinical correlations with dysfunctional δ FC we observed support this hypothesis. The mMIDAS and MSQ are validated measures of migraine-related disability and functional impairment, while the ASC-12 quantifies symptoms related to allodynia [49]. Our finding that δ band mNC correlates positively with

these scales suggests that increased low-frequency FC may reflect an underlying hyper-responsiveness of brain networks to pain-related stimuli and impaired modulatory control.

Notably, the use of HD-EEG-based FC combined with NBS represents a significant advancement over conventional EEG analyses, typically restricted to power spectral density (PSD) measurements derived from low-density montages. Unlike traditional PSD approaches, which primarily focus on localized oscillatory power, our method effectively identifies frequency-specific and network-specific alterations, providing a more comprehensive insight into the large-scale neural dynamics underlying migraine chronification and therapeutic response. Thus, our findings emphasize the potential of δ band FC as a neurophysiological biomarker for migraine chronicity and therapeutic responsiveness.

Indeed, δ band connectivity alterations exhibited notable reversibility following pharmacological intervention with atogepant, paralleling findings from previous research with onabotulinumtoxinA (OBTA). Despite their distinct mechanisms of action, both treatments appear capable of normalizing δ band dysfunctional connectivity, suggesting this neural marker captures key aspects of therapeutic modulation across various pharmacological interventions. Whether this modulation results from direct central effects or from downstream consequences of peripheral CGRP receptor blockade remains debated [50]. Similar questions arise for anti-CGRP monoclonal antibodies [51], whose ability to modulate central sensitization is also documented [16, 49, 52]. Given that atogepant primarily acts outside the central nervous system, the most plausible explanation is that a reduction in peripheral nociceptive input indirectly reshapes brain network activity by decreasing ascending signaling and cortical hyperexcitability.

Whether these EEG-based FC changes represent transient pharmacological modulation or more durable plasticity-related effects remains an open question. Clinical studies on anti-CGRP monoclonal antibodies have shown that discontinuation is often followed by a rapid return of migraine attacks in previously responsive patients [53], suggesting that continuous CGRP pathway inhibition is necessary to maintain clinical benefits. Although no such data are yet available for gepants such as atogepant, it is plausible that a similar mechanism may apply, whereby the observed EEG-FC modulations reflect dynamic and reversible changes that require sustained CGRP receptor blockade to be maintained. Further HD-EEG recordings at 1- or 3-month follow-up after treatment discontinuation would be necessary to assess the temporal persistence of these network-level effects.

These observations support the use of δ band FC as a robust, dynamic biomarker with potential clinical

applications for monitoring disease burden, therapeutic efficacy, and guiding personalized treatment strategies. Future studies should aim to confirm the longitudinal stability, specificity, and predictive utility of δ band connectivity across diverse chronic pain conditions, further establishing its role as a reliable neurophysiological marker in clinical practice and research.

Limitations and strengths

This study has some limitations. First, the sample size was relatively small, and a placebo control group was not included. However, all EEG recordings were conducted during the interictal phase and under carefully controlled conditions to minimize potential confounders such as medication overuse or post-ictal cortical changes. In addition, the use of NBS in combination with cross-validation and bootstrapping methods strengthens the reliability of our findings. Importantly, there were no significant differences in age or sex between the HFEM + CM and healthy control groups, and these variables were included as covariates in the analyses, given their influence on FC [54].

Moreover, the timing of EEG acquisition relative to drug administration ensures that the functional changes observed at T1 were not driven by the acute pharmacodynamic effects of the last atogepant dose. In our protocol, atogepant was administered daily around 10:00 p.m., while EEG recordings at T1 were consistently performed between 4:00 p.m. and 6:00 p.m. the following day, resulting in a mean interval of 18 h between drug intake and data acquisition. Given the pharmacokinetic profile of atogepant [42] characterized by a peak plasma concentration approximately 2 h post-administration and a half-life of approximately 11 h, it is reasonable to assume that the observed effects may reflect a cumulative, long-term neurophysiological change induced by one month of continuous CGRP receptor antagonism, rather than a transient effect related to the single dose.

Another limitation of this study concerns the use of patient-reported outcome measures (PROMs), which, although widely used in headache research, can be influenced by recall bias, mood fluctuations, and variability in individual symptom interpretation [55]. While these tools are essential for capturing patient-centered outcomes, their subjective nature may limit the precision in quantifying clinical changes. Nevertheless, in our cohort, the PROMs employed showed consistent patterns and correlated significantly with EEG-based FC changes, supporting their validity in this specific context.

Finally, another limitation is the lack of specific assessments for psychiatric symptoms. Although patients with formal diagnoses of psychiatric disorders were excluded, we did not administer standardized scales for anxiety or depression (e.g., BDI, STAI), and we cannot exclude the

potential influence of subclinical affective symptoms on FC patterns or treatment response.

Conclusions

In conclusion, our findings suggest that atogepant may produce early neuromodulatory effects on cortico-cortical FC alterations associated with migraine pathophysiology. These network changes appear clinically meaningful, as they correlate with improvement in migraine-related disability and central sensitization symptoms. This supports the emerging perspective that resting-state EEG-based FC, particularly within the δ frequency range, may serve both as a biomarker of disease-related cortical dysfunction and a potential therapeutic target. Future studies with larger sample sizes and extended follow-up are warranted to further investigate the predictive value of the δ band FC in clinical settings.

Abbreviations

AIFA	Italian Medicines Agency
ASC	12–12-item Allodynia Symptom Checklist
BEM	Boundary Element Method
BMI	Body Mass Index
BS	Bootstrapping
BS	95% CI–95% Confidence Interval from Bootstrapping
CM	Chronic Migraine
CGRP	Calcitonin Gene–Related Peptide
EC	Eyes Closed
EEG	Electroencephalography
EMA	European Medicines Agency
FC	Functional Connectivity
FWER	Family–Wise Error Rate
GLM	General Linear Model
HCS	Healthy Controls
HD	EEG–High–Density Electroencephalography
HFEM	High–Frequency Episodic Migraine
HIT	6–Headache Impact Test
ICA	Independent Component Analysis
ICBM	International Consortium for Brain Mapping
ICHD	3–International Classification of Headache Disorders, 3rd Edition
LOOCV	Leave–One–Out Cross–Validation
mMIDAS	Monthly Migraine Disability Assessment
mNC	Mean Network Connectivity
MIBS	4–Migraine Interictal Burden Scale
MRI	Magnetic Resonance Imaging
MSQ	Migraine–Specific Quality of Life Questionnaire
NBS	Network–Based Statistics
OBTA	OnabotulinumtoxinA
PSD	Power Spectral Density
ROI	Region of Interest
RS	Resting State
SVM	Support Vector Machine
T0	Baseline Timepoint
T1	One–Month Post–Treatment Timepoint
wMNE	Weighted Minimum Norm Estimation
wPLI	Weighted Phase Lag Index
Δ mNC	Change in Mean Network Connectivity

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s10194-025-02115-y>.

Supplementary Material 1.

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Institutional review board statement

The study was approved by the Ethics Committee of Fondazione PTV Policlinico Tor Vergata (protocol n° 16.17).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Authors' contributions

Design or conceptualization of the study: MC, MA, and NBM; Drafting of the manuscript: MC and SB; Analysis or interpretation of data: MC, FP, and AS; Major role in the acquisition of data: MC, FC, VF, and VCD; Revising of the manuscript: MA and NBM.

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Data availability

The datasets generated during analysis are available from the corresponding author upon reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

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