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Altered brainstem–cortex activation and interaction in migraine patients: somatosensory evoked EEG responses with machine learning

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Abstract

Background To gain a comprehensive understanding of the altered sensory processing in patients with migraine, in this study, we developed an electroencephalography (EEG) protocol for examining brainstem and cortical responses to sensory stimulation. Furthermore, machine learning techniques were employed to identify neural signatures from evoked brainstem–cortex activation and their interactions, facilitating the identification of the presence and subtype of migraine.

Methods This study analysed 1,000-epoch-averaged somatosensory evoked responses from 342 participants, comprising 113 healthy controls (HCs), 106 patients with chronic migraine (CM), and 123 patients with episodic migraine (EM). Activation amplitude and effective connectivity were obtained using weighted minimum norm estimates with spectral Granger causality analysis. This study used support vector machine algorithms to develop classification models; multimodal data (amplitude, connectivity, and scores of psychometric assessments) were applied to assess the reliability and generalisability of the identification results from the classification models.

Results The findings revealed that patients with migraine exhibited reduced amplitudes for responses in both the brainstem and cortical regions and increased effective connectivity between these regions in the gamma and high-gamma frequency bands. The classification model with characteristic features performed well in distinguishing patients with CM from HCs, achieving an accuracy of 81.8% and an area under the curve (AUC) of 0.86 during training and an accuracy of 76.2% and an AUC of 0.89 during independent testing. Similarly, the model effectively identified patients with EM, with an accuracy of 77.5% and an AUC of 0.84 during training and an accuracy of 87% and an AUC of 0.88 during independent testing. Additionally, the model successfully differentiated patients with CM from patients with EM, with an accuracy of 70.5% and an AUC of 0.73 during training and an accuracy of 72.7% and an AUC of 0.74 during independent testing.

Conclusion Altered brainstem-cortex activation and interaction are characteristic of the abnormal sensory processing in migraine. Combining evoked activity analysis with machine learning offers a reliable and generalisable tool for identifying patients with migraine and for assessing the severity of their condition. Thus, this approach is an effective and rapid diagnostic tool for clinicians.

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Keywords Migraine, EEG, Sensory processing, Brainstem, Primary somatosensory cortex, Primary motor cortex, Insula, Spectral Granger causality analysis, Support vector machine, Machine learning

Introduction

Migraine is a highly prevalent neurological disorder affecting more than one billion people worldwide. The World Health Organization's Global Burden of Disease study reported a global age-standardised prevalence of 14.4% [1]. Patients with migraine experience considerable functional disability, particularly as the disorder progresses from episodic migraine (EM) to chronic migraine (CM); CM is defined by headaches occurring ≥ 15 days per month for > 3 months [2]. This progression also leads to a considerable economic burden [3]. Migraine is recognised as a complex brain network disorder with a strong genetic basis, in which interactions among various neuronal systems contribute to a wide range of symptoms. Central dysfunctions play a critical role in the neuropathology of migraine [4, 5], particularly regarding the potential generators or mediators of migraine attacks in the subcortical regions of the brain.

In patients with migraine, alterations in sensory processing often involve changes in the transmission and processing of sensory information from the peripheral nervous system to the brain [6]. Consequently, patients with migraine frequently exhibit increased sensitivity to sensory stimuli, such as touch, light, temperature, and pain, leading to an exaggerated perception of pain or abnormal pain responses, even to nonpainful stimuli. Neurophysiological and neuroimaging evidence suggests that altered brainstem [7] and cortical activation [6], sensory habituation deficits [8], and abnormal connectivity from subcortical areas, such as the brainstem, to higher cortical areas may characterise the impaired sensory integration and modulation observed in patients with migraine. However, it remains to be determined whether this atypical sensory processing exhibits consistent characteristics across different migraine phases, potentially serving as a distinct neural signature for identifying patients with migraine.

Supervised machine learning (ML) approaches can be used to diagnose migraine on the basis of its characteristic changes in sensory processing [9]. Supervised ML can also provide tailored recommendations, making it suitable for routine use in clinical settings. Given its affordability, wide availability, and potential for mobility and scalability to large patient populations, electroencephalography (EEG) combined with ML algorithms may be particularly effective for establishing a migraine classification model [10].

This study employed EEG to directly capture neural activity, with an experimental design specifically developed for examining brainstem and cortical responses to sensory stimulation [11]. We examined the changes in the amplitude of the evoked responses in brainstem and cortical regions as well as the oscillatory effective connectivity between the brainstem and cortical regions in patients with migraine, irrespective of the migraine phase. To mitigate the effects of volume conduction in EEG recordings, we conducted source-based analyses through distributed source modelling, specifically employing weighted minimum norm estimates (MNEs). Classification models were used to identify the electrophysiological and psychometric features associated with the frequency of headache. These models differentiated patients with CM and patients with EM from healthy controls (HCs) and distinguished patients with CM from patients with EM. To ensure generalisability, the models were validated using an independent testing dataset. Additionally, this study aimed to reveal the signatures of altered brainstem–cortex activation and interaction that contribute to the neuropathology of migraine chronification, providing an effective and rapid diagnostic aid in clinical scenarios where migraine severity is challenging to accurately assess.

Materials and methods

1. Participants

All participants were aged between 20 and 60 years, were right-handed, had no history of systemic or major neurological disorders, and had normal results on physical and neurological examinations. They were recruited from the headache clinic at Taipei Veterans General Hospital. EM and CM were diagnosed according to *International Classification of Headache Disorders, Third Edition* [2]. All patients were naïve to preventive migraine treatments. The exclusion criteria were the overuse of headache medications, as defined by the diagnostic criteria of medication-overuse headache [2], as well as the regular (daily) use of migraine prophylactic drugs, hormones, or other medications. None of the HCs had a personal or family history of primary headaches, nor had they experienced any significant pain conditions in the previous year. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHTPE: IRB 2019–07-001B), and all participants provided written informed consent prior to the study.

2. Study design

All participants completed semi-structured questionnaires on their background characteristics. Moreover, they received psychometric assessments, including the Hospital Anxiety and Depression Scale (HADS) [12], Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI). For patients with migraine, additional information in terms of headache profiles, such as the number of headache days per month (headache days), disease duration (in years) since the onset of first headache (disease duration), average headache intensity over the past year (severity of last year), and number of acute headache medications per month, was obtained. Furthermore, the Migraine Disability Assessment (MIDAS) questionnaire was administered to evaluate migraine-related disability [13]. Following recruitment, all patients maintained a headache diary, in which they recorded the details of their headaches, including the date and time of attacks, pain intensity, associated symptoms, medication use (if any), and menstrual periods. For each participant, EEG recordings were conducted on the same day they completed the questionnaires and provided demographic information. Notably, dynamic changes in brain activation were observed across different migraine phases, particularly during the preictal period [11]. Given the difficulties in accurately assessing the migraine phase for each patient in clinical scenarios, patients in the present study were recruited regardless of their current migraine phase to facilitate a more rapid diagnostic approach.

3. EEG recording and analysis

Figure 1 outlines the data acquisition and analysis pipeline. Scalp EEG data were recorded using a 64-electrode BrainVision actiCAP system (Brain Products GmbH, Munich, Germany), which adheres to the extended International 10–20 system. In this system, for impedance conversion, active circuits are integrated into the streamlined actiCAP electrodes, providing superior signal quality even at higher impedance, compared with conventional passive electrodes. Crucially, an electronic circuit is integrated into each active electrode for performing impedance conversion directly at the scalp,

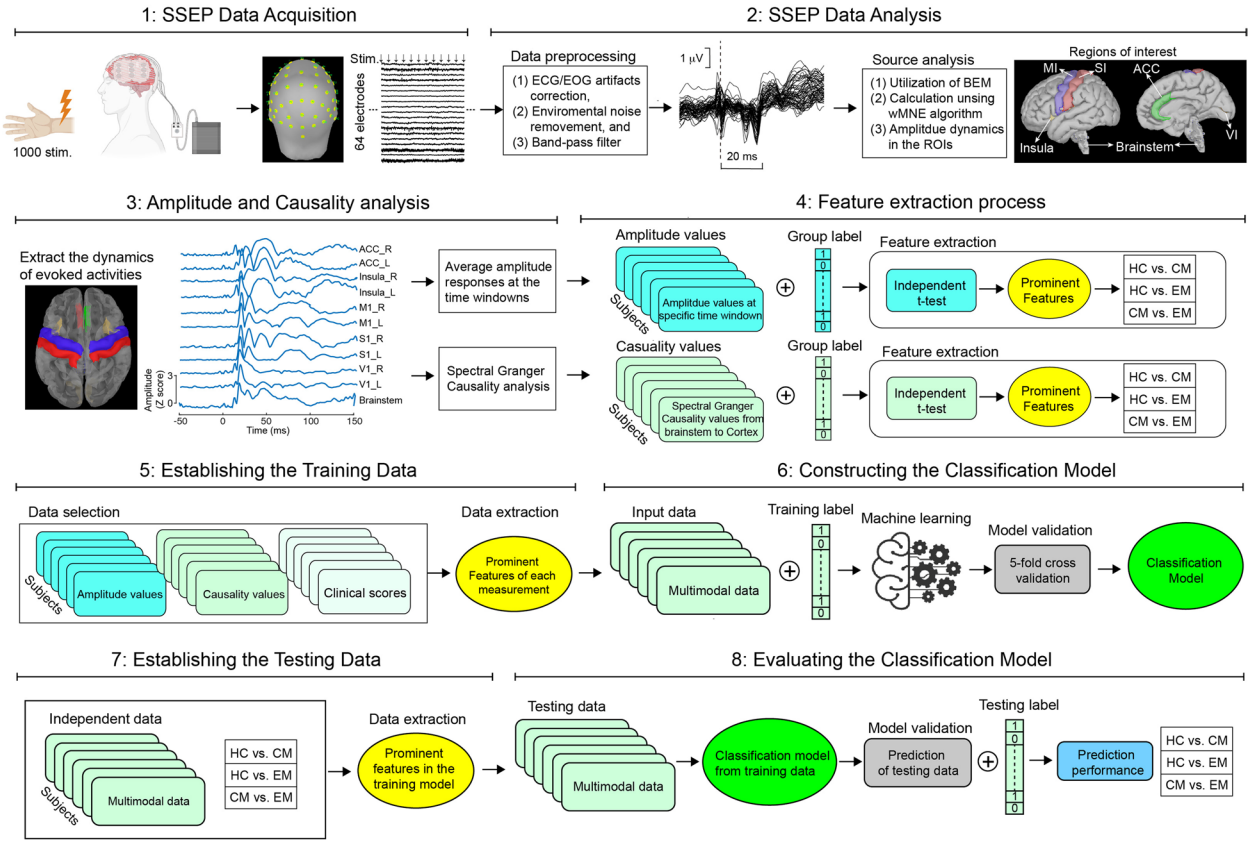

Fig. 1 Procedure of EEG experiment and data analysis. Pipeline of the somatosensory evoked potential data acquisition, data preprocessing and analysis, and the development and validation of machine learning analysis. SSEP, somatosensory evoked potential; Stim., stimulus; ECG, electrocardiography; EOG, electrooculography; BEM, boundary element modelling; wMNE, weighted minimum norm estimates; ROIs, regions of interest; CM, chronic migraine; HCs, healthy controls; EM, episodic migraine

offering the acquisition of high-quality EEG signals that remain unaffected by extraneous noise or movements possibly affecting the electrode cables. The electrodes were referenced online to an electrode positioned at the Fz plane, with a common ground connection established at the FPz site. EEG signals were amplified and digitised at a sampling rate of 1,000 Hz by using a BrainAmp DC amplifier (Brain Products GmbH) that was interfaced with Brain Vision Recorder software (version 2.1, Brain Products GmbH). For the offline elimination of artefacts, electrooculography (EOG) and electrocardiography (ECG) recordings were simultaneously obtained.

For each participant, somatosensory-evoked potentials (SSEPs) were elicited through an electrical stimulation task. Participants received stimulation using a Digitimer DS7A device (Digitimer, Welwyn Garden City, Hertfordshire, UK), which delivered constant-current square-wave pulses (0.2-ms duration, proximal cathode) at a frequency of 4 Hz. The stimulation intensity was set to twice the subjective sensory threshold of the right median nerve at the wrist. Consistent with previous findings, no pain response or visible twitching of the flexor digitorum superficialis was observed [14, 15]. Participants were comfortably seated in an illuminated room and were instructed to remain awake with their eyes closed during the stimulation. A total of 1,000 SSEP epochs were recorded, and each trial comprised a 50-ms prestimulus baseline period and a 100-ms poststimulus period. According to a previous study [16], this number of epochs is sufficient to reliably capture subcortical responses, particularly those from the brainstem.

To isolate source-based neural activity and to mitigate the effects of volume conduction in EEG recordings, distributed current source modelling was performed using depth-weighted MNEs [14, 15, 17]. This method enables the precise localisation of the source, even for deep neural generators [18, 19]. The neuronal dynamics of both cortical and subcortical sources were modelled using a mixed brain model incorporating both volume and surface scouts; the model can identify the characteristic signal patterns produced by a unit dipole. This forward model enabled the realistic distribution of current dipoles across the neocortex and subcortical structures [19]; this model is based on the symmetric boundary element method (BEM) [20]. The model yields more accurate results than spherical models. This study also used the inverse operator from the MNE analysis to estimate the distribution of the current sources of EEG signals. This approach generated distributed and dynamic brain activation maps that were reconstructed onto the surface and volume models for each participant. Subsequently, neural amplitude dynamics in the cortical and subcortical regions were extracted for further analysis. This study analysed time-varying current intensity in regions of interest (ROIs), including the brainstem (volume scout), bilateral insula, anterior cingulate cortex (ACC), primary motor cortex (MI), primary somatosensory cortex (SI), and primary visual cortex (V1) (surface scout). All current density values were transformed into z-scores, reflecting deviations from baseline.

Spectral Granger causality analysis, which is an extension of Granger causality in the frequency domain, was utilised in this study to determine whether one time series can predict another at specific frequencies; thus, this analysis can provide insights into the directional influence between time series across different frequency bands [21, 22]. This method yields valuable insights on the mechanism through which directional interactions occur between different brain regions at various frequencies. In this study, source-based Granger causality analysis in the frequency domain was conducted using the MNE-derived intensity activities of the current sources in each ROI. The analysis was performed across frequencies ranging from 1 to 200 Hz, with a resolution of 1 Hz, and a Granger model order of ≤ 10 was employed. Crucially, to explore ascending somatosensory processes, we examined the causal relationships from the brainstem to cortical regions—including the bilateral insula, ACC, MI, SI, and V1—within the 10–30-ms time window after stimulation.

All data analyses in this study, including preprocessing, source modelling, amplitude measurement, and spectral Granger causality analysis, were conducted using Brainstorm software [23], as partially described in our previous studies [9, 11, 14, 15, 24, 25].

4. Machine learning and statistical analysis

Given that activation measurements and effective connectivity analysis primarily focus on early sensory processing, this study aimed to enhance migraine identification through multimodal data modelling. The multimodal data included clinical scores related to emotion and cognition, such as HADS, PSS, and PQSI scores.

Before model construction, feature selection is essential for improving classification performance, reducing computational complexity, and eliminating irrelevant features. Therefore, in this study, univariate analyses (independent t tests) were applied to identify discriminative features between the groups. These features were then used to construct training and testing datasets (Fig. 1). Notably, the training datasets were derived from the multimodal data of 90% of the participants, and the remaining 10% of the data were applied as the independent testing datasets. This study employed support vector machine (SVM) algorithms to develop classification models for distinguishing

HC vs. CM, HC vs. EM, and CM vs. EM. SVM algorithms map input vectors into a high-dimensional space for constructing a linear classification system. By training the algorithm on the provided data, SVM identified an optimal hyperplane that minimised classification errors and produced an effective model. The supervised learning approach used to train the SVM classifiers enabled the pairwise for examination of the conditions, with appropriate kernel functions and parameters. The selection of hyperparameter values was automated through Bayesian optimisation.

To avoid overfitting, the classification models in this study were trained using a 5-fold leave-one-out cross-validation technique. Classification models were developed and reconstructed using datasets containing three sets of features: (1) prominent amplitude measurements from the brainstem and 10 cortical regions, (2) significant spectral Granger causality values combined with amplitude measurements, and (3) discriminative amplitude and spectral Granger causality values integrated with psychometric scores (HADS, PSS, or PSQI). All ML analyses were conducted using the Machine Learning Toolbox in MATLAB software (R2023b).

The performance of each classification model was assessed in terms of accuracy, sensitivity, specificity, and the area under the curve (AUC). After model reconstruction and evaluation on the training dataset, the models were further validated with the testing datasets to assess the generalisability of the identified features (Fig. 1). The labels for the testing datasets were blinded, and classification models were applied to the discriminative features without further training. Predictive accuracy and AUC were then calculated for each model. Shapley values were computed for each classification model to quantify the contribution of individual features to specific predictions [26]. The Shapley values from models with satisfactory performance were analysed to assess the importance of each feature.

Furthermore, to examine the differences in activation and interaction between the brainstem and cortex across groups (HC, CM, and EM), we conducted a series of analyses. Activation amplitudes at specific time intervals in the brainstem were compared between groups using analysis of variance (ANOVA), as well as cortical activation within the selected ROIs and time intervals. Additionally, Granger causality values across distinct frequency bands were tested via ANOVA. Bonferroni correction was applied for multiple comparisons, and a corrected p-value of < 0.05 was considered statistically significant.

Results

Demographic characteristics and clinical scores of participants

This study included 342 participants—113 HCs, 106 patients with CM, and 123 patients with EM. The demographic and clinical characteristics of all participants are summarised in Table 1. Three groups (HC, CM, and EM) did not differ significantly in terms of age. However, the HC group had a higher proportion of male participants compared to the other two groups. In the psychometric assessments, anxiety (HADS_A) and depression (HADS_D) scores were higher in the CM and EM groups than in the HC group (HC vs. CM: $p < 0.0001$ in the A score, $p < 0.0001$ in the D score; HC vs. EM: $p < 0.0001$ in the A score, $p < 0.0001$ in the D score). Moreover, PSS and PSQI scores were lower in the HC group than in the CM and EM groups (PSS: $p < 0.0001$ for HC vs. CM, $p = 0.001$ for HC vs. EM; PSQI: $p < 0.0001$ for HC vs. CM, $p < 0.0001$ for HC vs. EM). Notably, PSQI scores were higher in the CM group than in the EM group ($p = 0.0003$). Regarding the migraine profile, as expected, patients with CM had more monthly headache days ($p < 0.0001$) and a higher

Table 1 Demographics and clinical profiles of participants (mean ± std.)

	HC	CM	EM	*p*-value
N	113	106	123	
Age (years)	34.1 ± 8.6	36.0 ± 9.8	34.2 ± 8.8	$p = 0.20$
Sex	67 F/46 M	83 F/23 M	93 F/30 M	$p = 0.01$
Psychometrics				
HADS_A	4.3 ± 3.3	7.9 ± 3.4	7.1 ± 3.8	$p < 0.001^{*,\&}$
HADS_D	2.9 ± 2.7	6.2 ± 3.6	5.3 ± 3.4	$p < 0.001^{*,\&}$
PSS	21.2 ± 8.6	26.5 ± 8.8	24.9 ± 8.4	$p < 0.001^{*,\&}$
PSQI	3.8 ± 2.5	8.8 ± 3.7	7.1 ± 3.4	$p < 0.001^{*,\&,\%}$
Migraine profile				
Headache days (/month)	-	19.8 ± 5.5	6.6 ± 4.3	$p < 0.001^{\%}$
Disease duration (years)	-	17.2 ± 9.3	15.4 ± 9.1	$p = 0.76$
Severity of last year (0–10)	-	6.1 ± 1.7	6.3 ± 1.8	$p = 0.27$
Number of acute headache medications (/month)		9.6 ± 8.4	5.3 ± 4.5	$p < 0.001^{\%}$
MIDAS	-	42.8 ± 43.0	21.4 ± 24.3	$p < 0.001^{\%}$

HC: Healthy control; CM: Chronic migraine; EM: Episodic migraine; F: female; M: male;

HADS: Hospital anxiety and depression score; A: Anxiety; D: Depression; PSS: Perceived stress scale;

PSQI: Pittsburgh sleep quality index; MIDAS: Migraine disability assessment scores

*, significant difference between HC and CM; $^{\&}$, significant difference between HC and EM;

$^{\%}$, significant difference between CM and EM

usage of painkiller (per month; $p < 0.0001$) than patients with EM. Furthermore, MIDAS scores were higher in patients with CM than in patients with EM ($p < 0.0001$). However, the disease duration and severity in the preceding year were comparable between the two groups.

Activation dynamics of brainstem and cortex in response to stimulation

After 4-Hz electrical stimulation, the time-varying evoked activities obtained were transformed into z-scores for each participant and were then averaged across subjects. The data for each group are presented in Fig. 2. The waveform profiles were similar for the groups. However, significant peak amplitude changes for the responses indicated alterations in sensory processing in patients with migraine. To compare activation strength between the groups, the averaged amplitude values were extracted at specific time intervals, as follows: 11–15 ms and 16–21 ms for the brainstem and 16–21 ms and 25–30 ms for the cortical regions. Compared with the HC group, the CM and EM groups exhibited reduced brainstem responses at 11–15 ms (HC: 0.784 ± 0.122; CM: 0.317 ± 0.139, $p = 0.0122$; EM: 0.371 ± 0.134, $p = 0.0244$). Additionally, patients with CM exhibited weakened brainstem activation at 16–21 ms (HC: 2.126 ± 0.232; CM: 1.471 ± 0.238, $p = 0.05$).

In the cortical regions, patients with CM exhibited decreased amplitudes at 16–21 ms in the left insula (HC: 1.592 ± 0.206; CM: 0.497 ± 0.259, $p = 0.0011$) and left V1 (HC: 3.464 ± 0.326; CM: 2.569 ± 0.295, $p = 0.0441$). By contrast, patients with EM exhibited reduced activities in the left insula (HC: 1.592 ± 0.206; EM: 0.837 ± 0.203, $p = 0.0098$), bilateral SI (left: HC: 4.715 ± 0.37; EM: 3.581 ± 0.25, $p = 0.0107$; right: HC: 2.227 ± 0.214; EM:

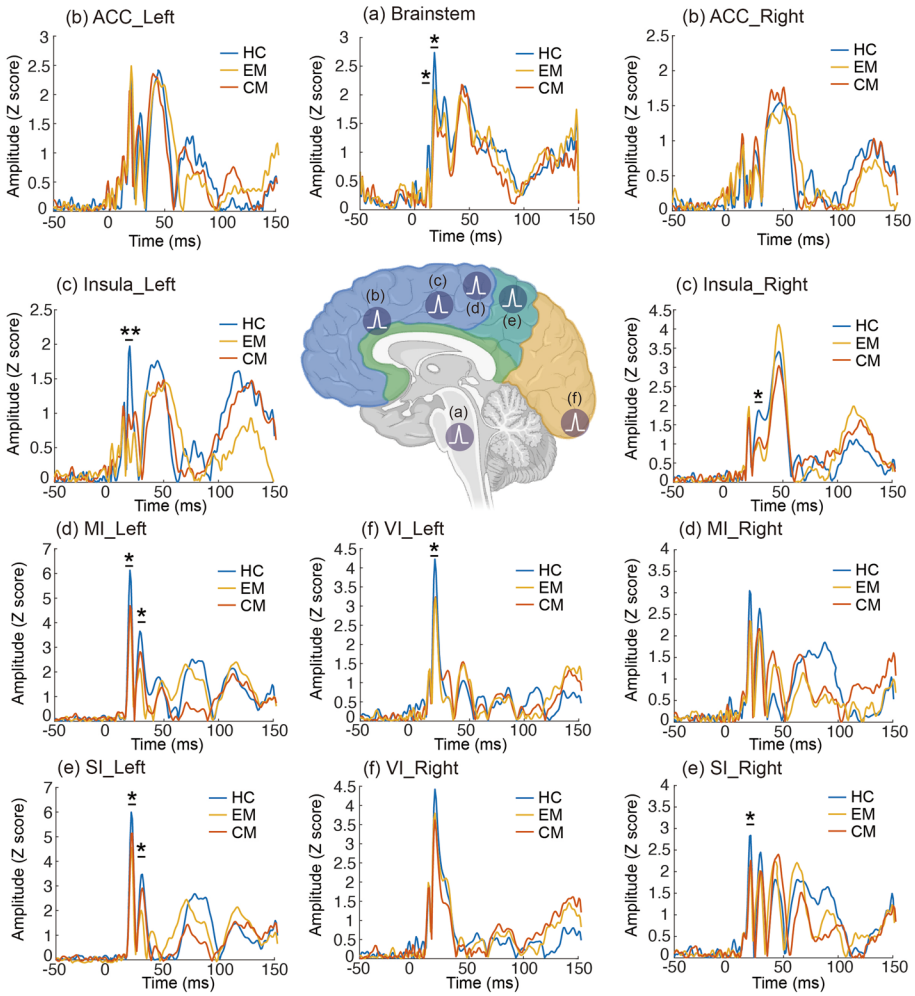

Fig. 2 Altered brainstem and cortical activation in migraine patients**.** Time-varying normalised activation amplitude in the responses to stimulation in the brainstem and bilateral anterior cingulate cortex (ACC), insula, primary somatosensory cortex (SI), primary motor cortex (MI), and primary visual cortex (V1) in the healthy controls (HCs), patients with episodic migraine (EM), and patients with chronic migraine (CM). *, $p < 0.05$; **, $p < 0.01$

1.603 ± 0.19, $p = 0.0297$), and left MI (HC: 4.725 ± 0.408; EM: 3.345 ± 0.274, $p = 0.0048$). Furthermore, at 25–30 ms, patients with EM exhibited significantly decreased amplitudes for the responses in the right insula (HC: 1.797 ± 0.278; EM: 0.94 ± 0.205, $p = 0.013$), left SI (HC: 3.055 ± 0.436; EM: 1.843 ± 0.302, $p = 0.0215$), and left MI (HC: 3.271 ± 0.459; EM: 1.856 ± 0.306, $p = 0.0099$). Notably, the evoked activities in both the brainstem and cortical regions were comparable between the CM and EM groups.

Spectral causality relationships from brainstem to cortical regions

Spectral Granger causality analysis was used to compare the degree of neural oscillatory connectivity from the brainstem to cortical regions between the groups. Figure 3 indicates the significant differences in connections and frequencies, with the colour coding representing the *t* values of the significant differences, with a threshold set for significance. Notably, compared with HCs, patients with CM exhibited prominent increases in connectivity. These alterations in connectivity in patients with CM were characterised by (1) enhanced connectivity from the brainstem to the left insula, right V1, left SI, bilateral MI, and right ACC in the high-gamma (60–200 Hz) range; (2) increased connectivity from the brainstem to the left SI and left MI in the gamma (25–60 Hz) range; and (3) increased connectivity from the brainstem to the right ACC in the alpha (8–13 Hz) band.

EM patients also exhibited notable changes. That is, they exhibited increased connectivity between the brainstem and the right V1, bilateral MI, and right ACC in the high-gamma range as well as increased connectivity between the brainstem and the right insula and

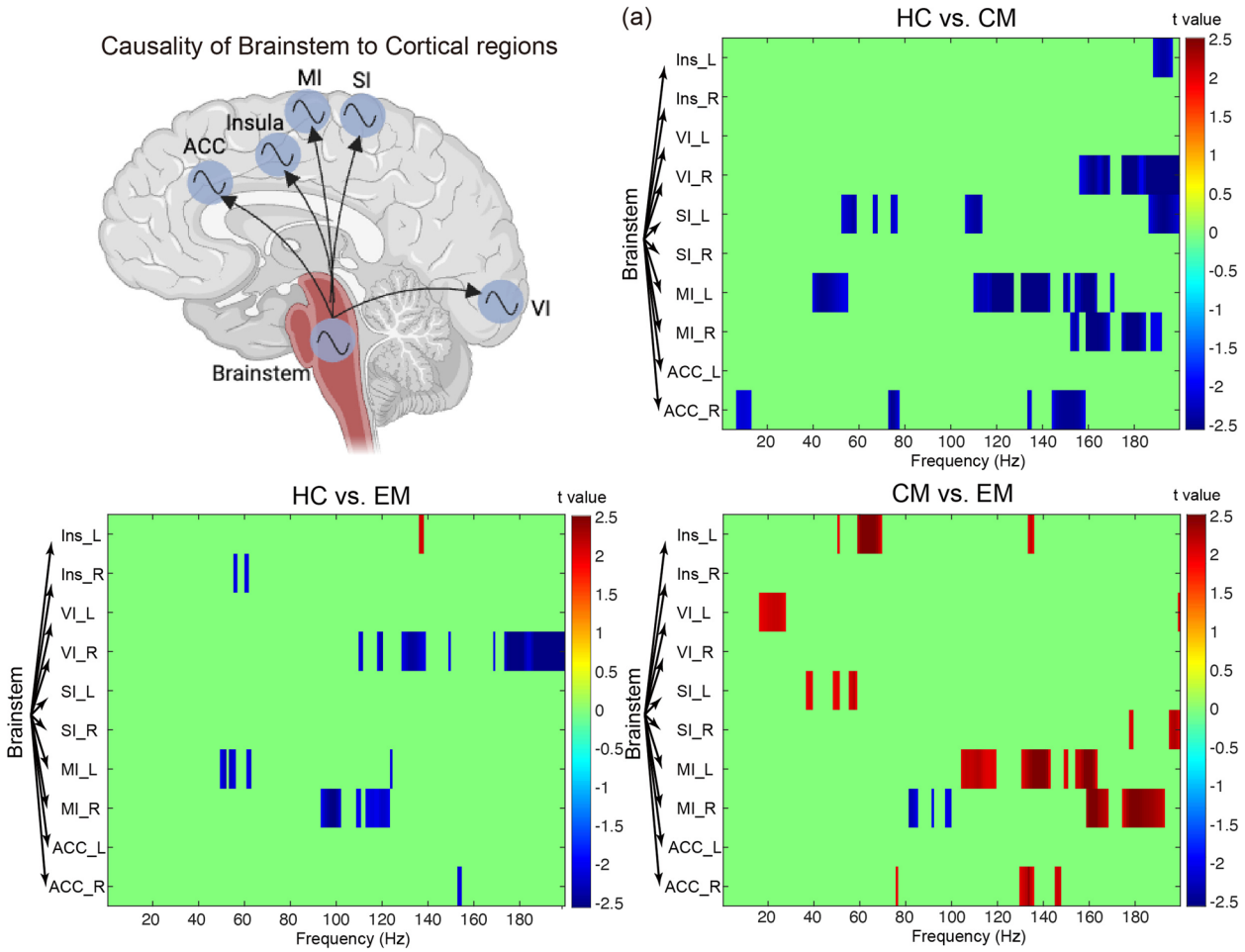

Fig. 3 Aberrant effective connectivity from the brainstem to cortex regions in patients with migraine. The spectral Granger causality analysis between groups was visualised in a *t*-value matrix, where the *x*-axis represents frequency, and the *y*-axis corresponds to distinct brainstem–cortex connections. The plots display significant differences between groups that exceed the statistical threshold, with colour coding representing the corresponding *t* values. HCs, healthy controls; EM, episodic migraine; CM, chronic migraine; Ins, insula; V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex. L, left; R, right

between the brainstem and the left MI in the gamma band. Interestingly, the pattern of oscillatory effective connectivity differed between CM and patients with EM. Specifically, patients with CM exhibited increased connectivity between the brainstem and left insula, right SI, bilateral MI, and right ACC as well as between the brainstem and the left insula and left SI in the gamma band. Additionally, patients with CM exhibited increased connectivity from the brainstem to the left V1 in the beta band, and they also demonstrated decreased connectivity between the brainstem and right MI in the 80–100-Hz frequency range.

Construction and evaluation of classification models using machine learning

In this study, data from 102 HCs, 96 patients with CM, and 111 patients with EM were included in the training dataset, and the independent testing dataset included the data of 11 HCs, 10 patients with CM, and 12 patients with EM. Classification models were developed and applied for conducting three comparisons: HC vs. CM, HC vs. EM, and CM vs. EM. These models were reconstructed using three sets of key features: amplitude responses; amplitude and connectivity measurements; and a combination of amplitude, connectivity, and psychometric assessments scores. Notably, these features used in the model significantly differed across the groups, as indicated in the preceding analyses.

In distinguishing patients with CM from HCs (Fig. 4), classification models achieved an accuracy of 57.1%, an AUC of 0.597, a sensitivity of 0.53, and a specificity of 0.61 when they were based on a Gaussian SVM (kernel scale: 2) and included only amplitude response features. With the addition of connectivity measurements, the performance improved to an accuracy of 71.2%, an AUC of 0.717, a sensitivity of 0.61, and a specificity of 0.80 for the model based on a Gaussian SVM (kernel scale: 201). In the models including the combination of amplitude, connectivity, and psychometric assessment scores and using a Linear SVM (kernel scale: 1), an accuracy of 81.8%, an AUC of 0.863, a sensitivity of 0.77, and a specificity of 0.86 were obtained.

In distinguishing patients with EM from HCs (Fig. 5), classification models that were based on a Gaussian SVM (kernel scale: 2.2) and utilised the amplitudes of the responses alone and achieved an accuracy of 61.0%, an AUC of 0.61, a sensitivity of 0.63, and a specificity of 0.59. With the inclusion of connectivity measurements and by applying a Gaussian SVM (kernel scale: 8.4) in the models, the accuracy of the model improved to 72.3%, with an AUC of 0.742, a sensitivity of 0.63, and a specificity of 0.82. Furthermore, in the models that were based on a Gaussian SVM (kernel scale: 8.6) and incorporated the psychometric assessment scores with the amplitudes of the responses and connectivity and, an accuracy of 77.5%, an AUC of 0.836, a sensitivity of 0.73, and a specificity of 0.82 were obtained.

Finally, in differentiating patients with CM from other patients with migraine (Fig. 6), the model that was based on a Gaussian SVM (kernel scale: 40.2) and included connectivity measurements alone achieved an accuracy of 71.5%, an AUC of 0.714, a sensitivity of 0.59, and a specificity of 0.82. With the incorporation of the PSQI score with connectivity measurements, the model based on a Gaussian SVM (kernel scale: 2.7) maintained good performance with an accuracy of 70.5%, an AUC of 0.735, a sensitivity of 0.66, and a specificity of 0.75. Notably, the features used in each classification model were detailed in supplementary Table 1. Moreover, the importance scores for individual feature in each classification model, calculated using the ANOVA algorithm, are illustrated in Fig. 7 (a). The top 20 most important features are listed. In the classification model, Shapley summary plots (swarm charts) show the ten predictors with the highest mean absolute Shapley values in each model (Fig. 7(b)). In summary, psychometric scores, amplitude and effective connectivity values contributed significantly to the fine performance of the prediction models.

To assess the generalisability of these classification models, we applied them to an independent testing dataset consisting of the data of 11 HCs, 10 patients with CM, and 12 patients with EM (Fig. 8). In distinguishing patients with CM from HCs, the model—based on evoked amplitude, effective connectivity, and psychometric assessment scores—performed well, achieving an accuracy of 76.2%, an AUC of 0.89, a sensitivity of 0.6, and a specificity of 0.91. In distinguishing patients with EM from HCs, the trained model, which also used evoked amplitude, effective connectivity, and psychometric assessment scores, performed well, with an accuracy of 87%, an AUC of 0.886, a sensitivity of 0.83, and a specificity of 0.91. In distinguishing patients with CM from patients with EM, the model—based on effective connectivity and psychometric assessment scores—performed well, with an accuracy of 72.7%, an AUC of 0.745, a sensitivity of 0.6, and a specificity of 0.83. Overall, these classification models performed well (all accuracy values > 72%, AUC values > 0.74) in accurately identifying patients with migraine.

Differences of activation and interaction of brainstem and cortex between groups

In the ANOVA analysis, significant differences in brainstem activation amplitude were observed at 11–15 ms ($F = 3.69$, $p = 0.026$) across the groups. Post hoc analysis indicated that amplitude values were lower in the CM

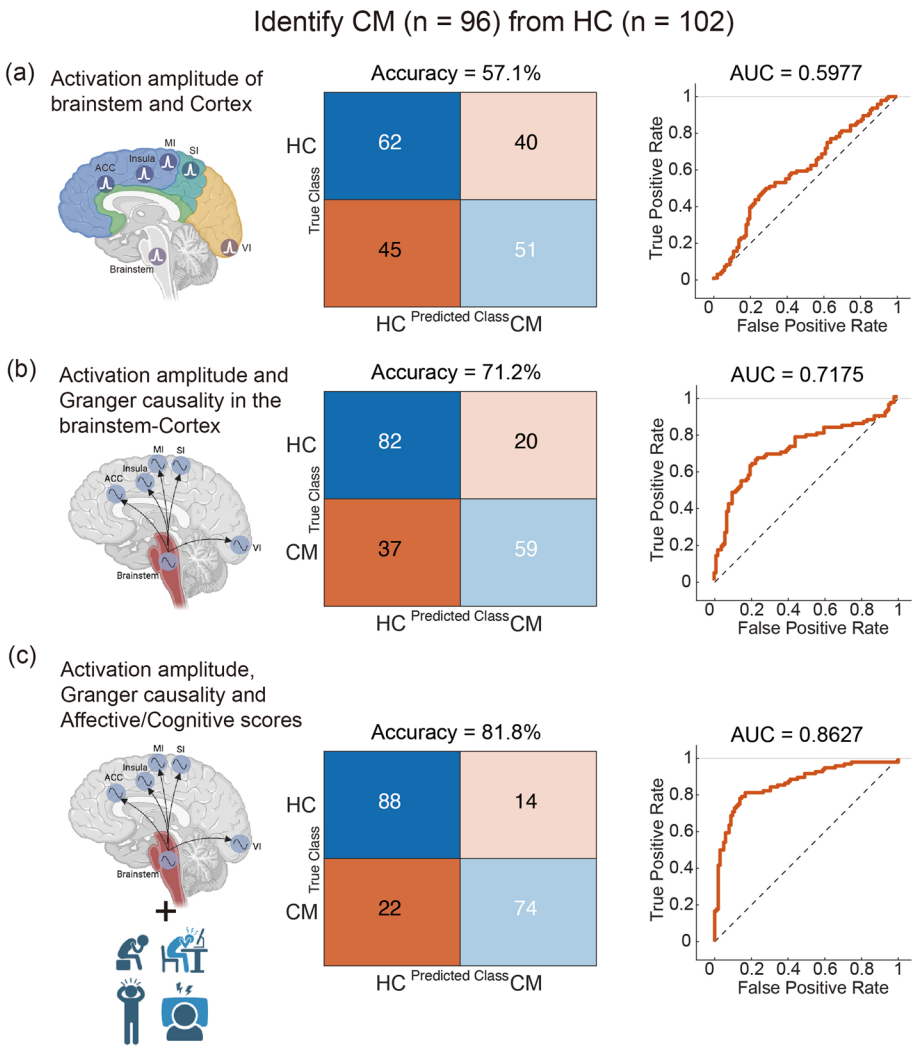

Fig. 4 Performance of classification models for HCs vs. CM. (a) The accuracy and area under the curve (AUC) of the training model including the characteristic feature of activation amplitude in identifying CM. (b) The accuracy and AUC of the training model including the characteristic features of activation amplitude and Granger causality values. (b) The accuracy and AUC of the training model including the characteristic features of activation amplitude, Granger causality values, and psychometric scores. HCs, healthy controls; CM, chronic migraine; V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex

group ($p=0.038$) and the EM group ($p=0.063$) compared to the HC group. In terms of cortical activation, evoked amplitude strength at 16–21 ms differed between groups in the left insula ($F=6.17$, $p=0.0023$), left SI ($F=2.95$, $p=0.05$), and left MI ($F=4.08$, $p=0.018$). Post hoc analysis further revealed significant differences, with decreased amplitude responses in the left insula (CM vs. HC, $p=0.0019$; EM vs. HC, $p=0.039$), left SI (EM vs. HC, $p=0.042$), and left MI (EM vs. HC, $p=0.017$). Moreover, significant differences in Granger causality values were observed between the groups (see matrix of F values in Supplementary Fig. 1). In summary, migraine patients exhibited altered effective connectivity, particularly in the pathways from the brainstem to the right insula, right V1, left SI, bilateral MI, and right ACC within the high-gamma frequency range, as well as from brainstem to the left SI within the gamma frequency range.

Discussion

This study demonstrated that the altered sensory processing in patients with migraine is characterised by decreased amplitudes of the responses in the brainstem and cortical regions as well as increased effective connectivity between them in the gamma and high-gamma frequency bands. The key discriminative features of sensory processing were primarily derived from the amplitudes of

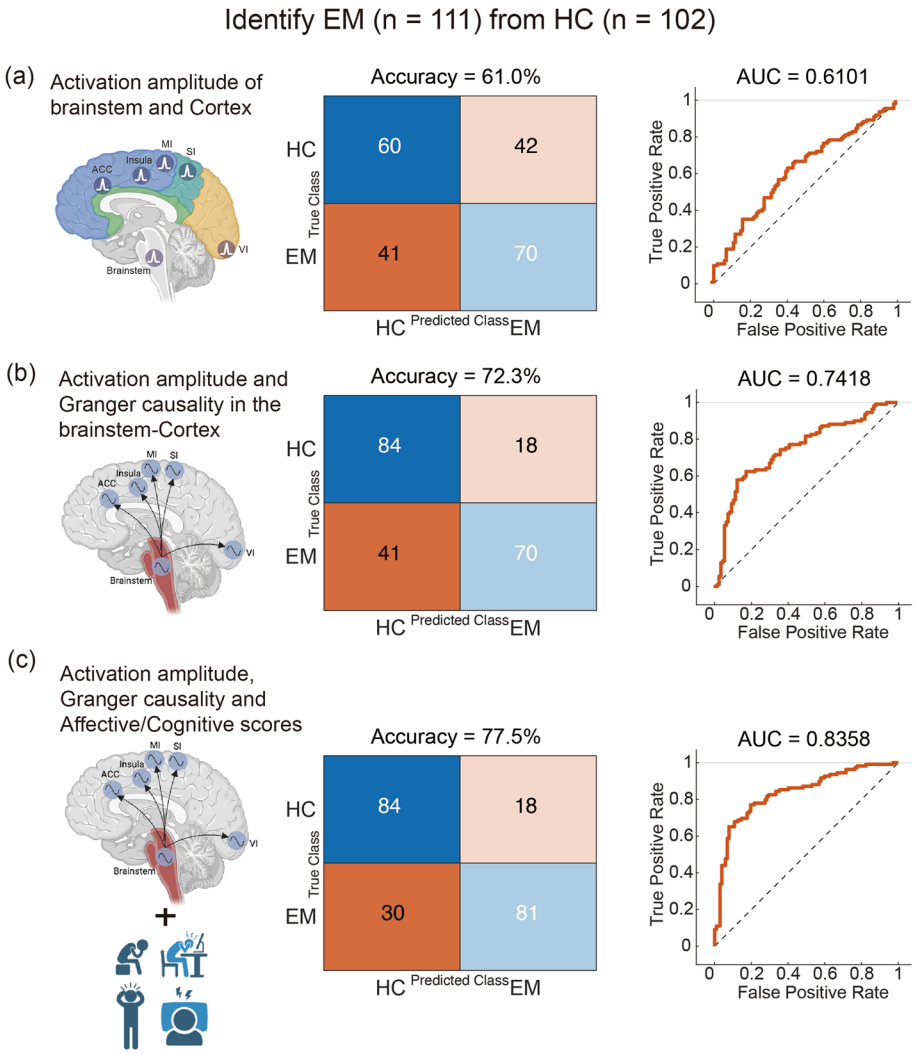

Fig. 5 Performance of classification models for HC vs. EM. (a) The accuracy and area under the curve (AUC) of the training model including the characteristic features of activation amplitude in identifying EM. (b) The accuracy and AUC of the training model including the characteristic features of activation amplitude and Granger causality values. (b) The accuracy and AUC of the training model including the characteristic features of activation amplitude, Granger causality values, and psychometric scores. HCs, healthy controls; EM, episodic migraine; V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex

brainstem activity at 11–15 ms and 16–21 ms as well as the bilateral SI and MI and the left insula and V1 at 16–21 ms. Additionally, the effective interactions of the brainstem with specific cortical regions at 10–30 ms in distinct frequency bands played a significant role in altered sensory processing. Notably, increased effective connectivity was more associated with the chronification of migraine. By integrating these features with the scores of prominent psychometric assessments into SVM models, we identified multimodal data with discriminative features for distinguishing CM or EM patients from HCs. The classification model performed well in differentiating patients with CM (training: accuracy = 81.8%, AUC = 0.86; independent testing: accuracy = 76.2%, AUC = 0.89) and patients with EM (training: accuracy = 77.5%, AUC = 0.84; independent testing: accuracy = 87%, AUC = 0.88) from HCs. Furthermore, the model effectively distinguished patients with CM from patients with EM (training: accuracy = 70.5%, AUC = 0.73; independent testing: accuracy = 72.7%, AUC = 0.74). Notably, even when only the characteristic features of SSEP responses and connectivity were included, the classification models performed well (with all accuracies > 71.2% and AUCs > 0.717) in identifying CM or EM. In summary, the neural signatures of early somatosensory processing may provide sufficient information for identifying CM or patients with EM.

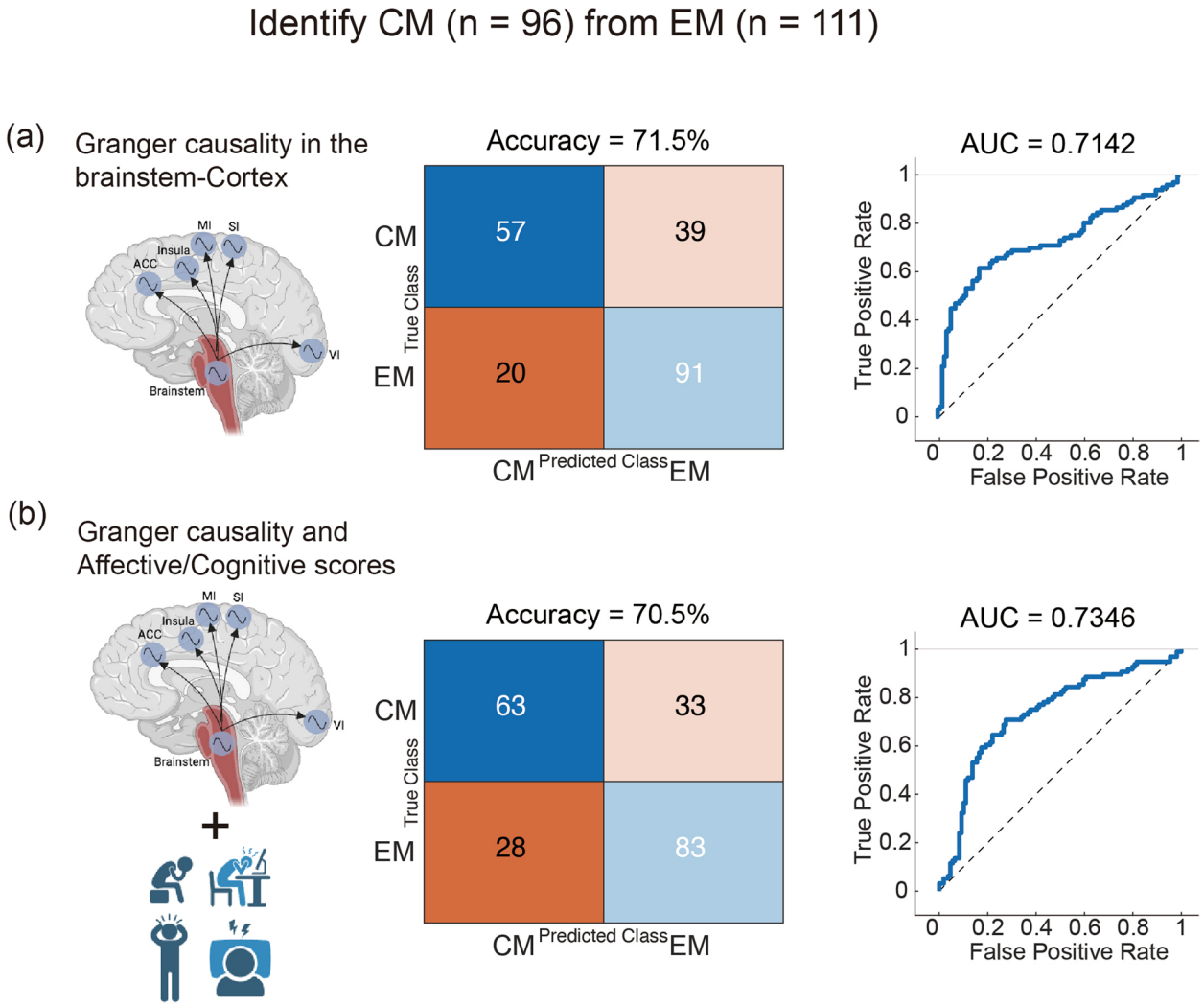

Fig. 6 Performance of classification models for CM vs. EM. (a) The accuracy and area under the curve (AUC) of the training model including the characteristic features of Granger causality values in identifying CM. (b) The accuracy and AUC of the training model including the characteristic features of Granger causality values and psychometric scores. CM, chronic migraine; EM, episodic migraine. V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex

Abnormalities of evoked responses in patients with migraine

In this study, patients with EM and CM exhibited equally altered evoked activities during early sensory processing in the brainstem, extending later on from the subcortical regions to cortical areas, particularly in the insula, SI, V1, and MI. These findings indicate the presence of sensory processing abnormalities in patients with migraine. These findings are consistent with those of previous neuroimaging studies, and they support the prevailing idea that patients affected by migraine have a different way to elaborate somatosensory inputs and to integrate them with other sensory modalities [4, 5, 10]. Prior studies identified abnormalities in cross-modal visual and sensorimotor integration in EM and CM [27, 28]. As for decreased brainstem activation during sensory processing, a positron emission tomography study reported reduced activity in the frontal and temporoparietal regions in conjunction with brainstem in response to olfactory stimulation during the pain-free interval compared with controls [29]. Similarly, an fMRI study found reduced brainstem activation, particularly during the interictal phase [30]. These results align with previous EEG findings, where patients with migraine exhibited significantly lower brainstem activation in response to median nerve stimulation, particularly in high-frequency oscillations [31]. Significant changes were also found in the insula, which plays a crucial role in autonomic regulation and

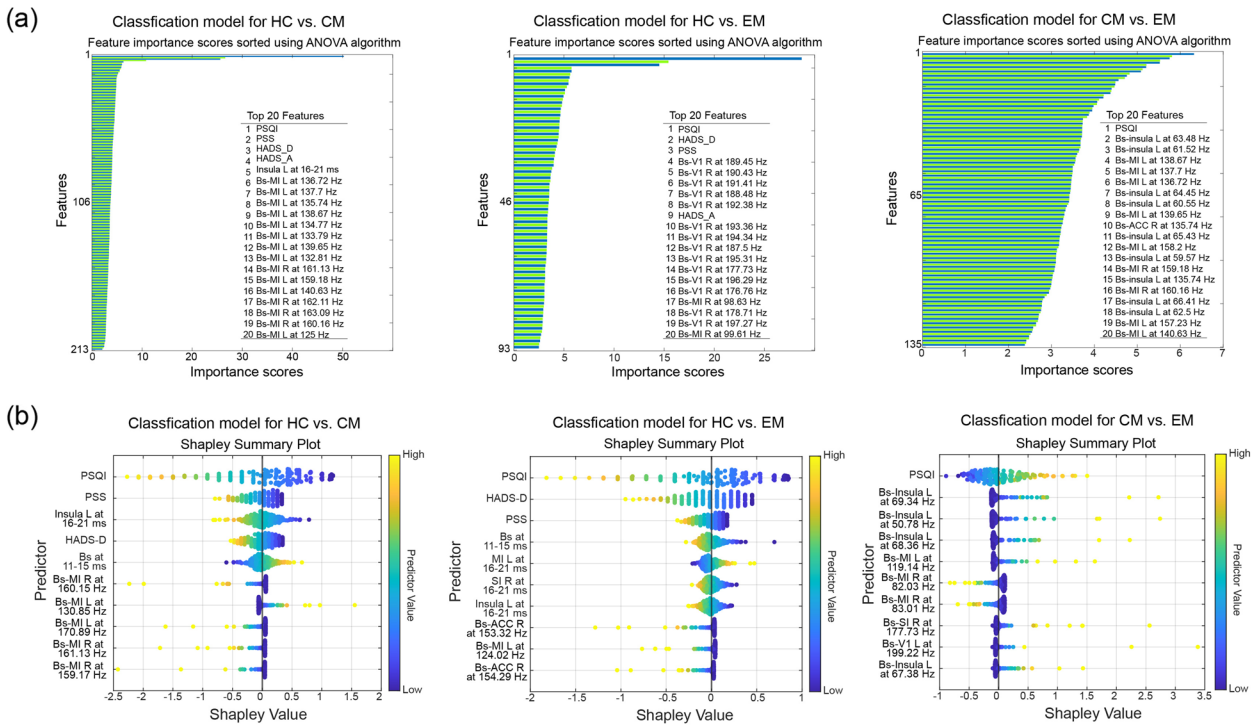

Fig. 7 Importance of features for classification models. (a) The importance scores of features for each model, calculated using analysis of variance (ANOVA) algorithm. (b) Shapley summary plots for each classification model. HC, healthy controls; CM, chronic migraine; EM, episodic migraine. Bs, brainstem, PSQI, Pittsburgh sleep quality index; PSS, Perceived stress scale; HADS, hospital anxiety and depression score; A, anxiety; D, depression; V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex. L, left; R, right

somatosensation (both of which are altered in patents with migraine) [32]. Patients with migraine exhibited a reduction in the cortical surface area in the left insula, with the most pronounced decrease observed in patients with CM [33]. Additionally, an fMRI study revealed the decreased dynamic amplitude of low-frequency fluctuations in the bilateral anterior insula among patients with migraine without aura [34]. These structural and functional changes in the insula suggest dysfunctional sensory processing in patients with migraine. In SI, reduced early neuronal activation was corroborated by the decreased amplitude of the high-frequency oscillation, reflecting more closely the subcortico-cortical network activity [35], and a reduced somatosensory evoked neuromagnetic field [14, 15] in patients with episodic migraine. Furthermore, there is much evidence in favour of hypofunctioning brainstem structures subserving conditioned pain modulation (CPM) of cortical activation in EM and CM. Reduced thermal pain-induced activation in this brainstem pain modulatory system and interconnected cortical areas like SI, V1, MI, and superior temporal gyrus was previously detected using fMRI and evoked EEG in patients with migraine [36–39]. These findings suggest a reduced preactivation excitability level for sensory cortices [40], which might be potentially linked to the thalamocortical dysrhythmia caused by brainstem dysfunction [6, 35].

Aberrant causal relationship of somatosensory processing in patients with migraine

Through spectral Granger causality analysis, we observed enhanced oscillatory effective connectivity from the brainstem to cortical regions in patients with migraine, particularly in the gamma and high-gamma frequencies. Notably, the experimental design of this study, which was specifically tailored for examining brainstem and cortical responses to sensory stimulation, enabled the first non-invasive electrophysiological recording for determining the causal relationships of brainstem–cortex interactions. An fMRI study revealed increased brainstem connectivity to the anterior insula and anterior midcingulate cortex during respiratory-gated auricular vagal afferent nerve stimulation in patients with migraine [41]. This observation suggests the involvement of the major serotonergic and noradrenergic nuclei and pathways located in the brainstem in pain modulation. In patients with EM, Liu et al. reported increased effective connectivity from the brainstem to the left ACC and right SI as well as from the brainstem to the left MI [42]. An abnormal deficiency in brainstem activity resulted in negative effects on

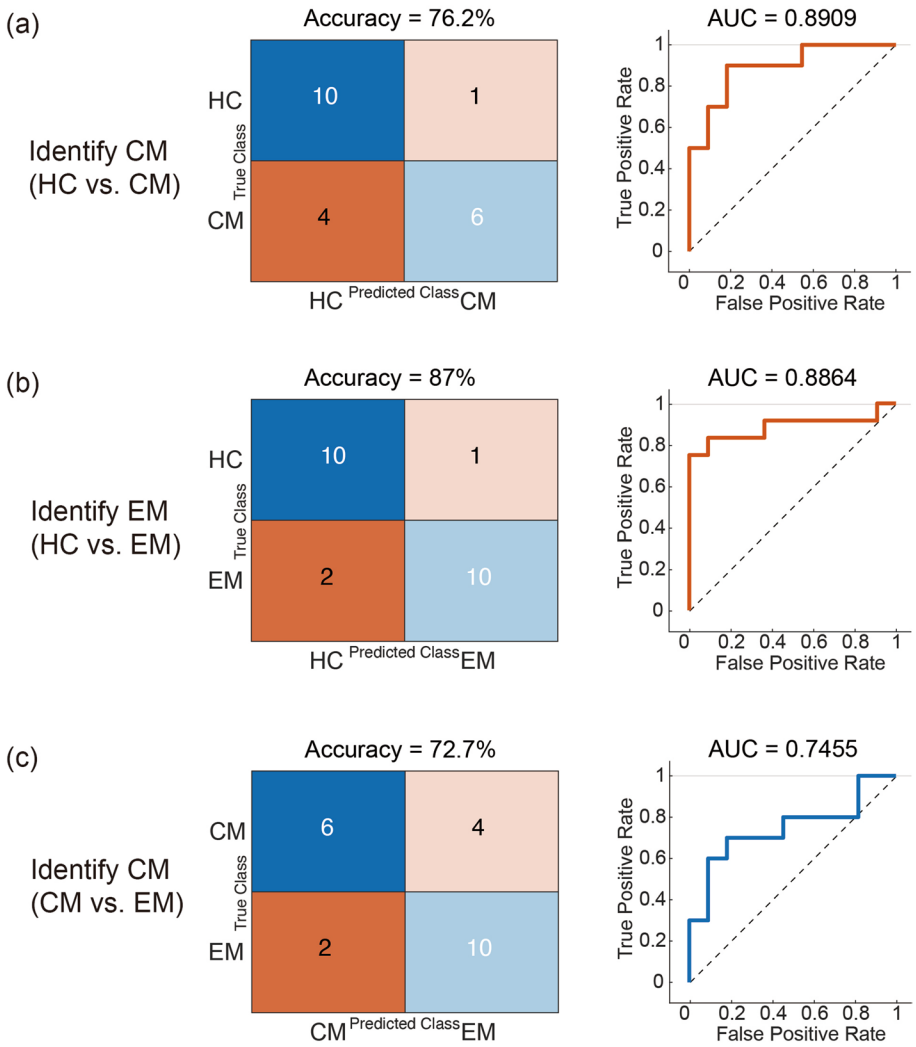

Fig. 8 Performance of classification models including independent testing data set. (a) The accuracy and area under the curve (AUC) of the model in identifying CM. (b) The accuracy and AUC of the model in identifying EM. (b) The accuracy and AUC of the model in identifying CM. HCs, healthy controls; CM, chronic migraine; EM, episodic migraine

the plasticity of the visual cortex, as shown in migraine patients recording visual evoked responses during CPM [39]. These findings highlight the potential role of abnormal brainstem–to–cortical connectivity in the neuropathology of migraine. Additionally, a significant increase in connectivity between the brainstem and left SI was observed during migraine attacks [43]. Leveraging the fine temporal resolution of EEG recordings, this study analysed EEG signals during the latency period of 10–30 ms, which likely represents the sequential activation of subcortical and cortical neurons through thalamo-cortical and cortico-cortical connections [44]. Regarding the characteristic frequency of connectivity, increased responses in the sensory cortex in the gamma band are linked to abnormalities in sensory processing in patients with migraine [45]. Notably, thalamocortical connections in pain disorders are believed to be abnormally engaged in the gamma band, inducing an 'edge effect' that is likely due to lateral disinhibition resulting from the asymmetrical inhibitory activity of interneurons at the cortical level [46]. Collectively, these findings support the neuropathological role of thalamocortical dysrhythmia in migraine; this dysrhythmia may be induced by decreased regulation from monoaminergic nuclei in the brainstem of cortical areas at low frequency oscillatory activity bands [6, 35]. These dysfunctional subcortical-to-cortical activation can induce the emergence of abnormal high level of gamma band oscillatory activity in the thalamo-cortical loop generating high-frequency, phase locked coherent increased activation of cortical areas [47]. All this complex pattern

of dysrhythmic thalamo-cortico-thalamic activation can easily explain the results of the present study, namely a co-occurrence of reduced low-frequency evoked activity and increased effective brainstem connectivity with different cortical areas devoted to high-frequency multisensory processing. Furthermore, we discovered that this atypical effective connection pattern between the brainstem and cortical regions is more evident in patients with CM. These findings were corroborated by resting-state fMRI studies, which revealed a significant reconfiguration of large-scale functional cortical networks in CM patients, likely due to a central sensitization-induced reorganization process [48]. This process of sensitisation boosts the level of effective connectivity with the cortical mantle (insula, SI and V1) not only in relation to healthy subjects, but also to episodic migraineurs. This was not the case for the right motor cortex, which showed reduced connectivity in CM patients compared to EM patients. This finding can be interpreted by acknowledging the significant antinociceptive role of the motor cortex, which is impaired due to the chronic manifestation of migraine, similar to other forms of chronic pain [49].

Performance of classification models including multimodal data

In this study, with the combination of the characteristic features of SSEP amplitude and connectivity during sensory processing along with the scores of psychometric assessments, classification models performed well in distinguishing CM and patients with EM from HCs (all accuracy values > 76%, all AUC values > 0.84) and in identifying migraine subtypes (all accuracy values > 70%, all AUC values > 0.73). Our previous studies have revealed that somatosensory-related oscillations reflect altered central processing involving excitability and habituation [14, 15, 25]. The classification model including these characteristic sensory features performed well in identifying patients with CM [25]. Furthermore, Zhu and colleagues [50] effectively distinguished HCs from patients with migraine during interictal or ictal periods by utilising classification models including latency, amplitude, and high-frequency power of somatosensory-evoked potentials. Notably, even when only the characteristic features of SSEP amplitude and connectivity were included, the classification models still performed well (with all accuracies > 71.2% and AUCs > 0.717) in identifying CM or patients with EM. Given that migraine is linked to altered central sensory processing, involving neuronal excitability, inhibition, or synchronisation [5, 6, 8, 10, 51], these dysfunctional central responses to sensory stimulation may serve as crucial biomarkers for migraine diagnosis. Notably, incorporating the scores of key psychometric assessments into the classification models significantly enhanced their accuracy and AUC, particularly in identifying patients with CM. This finding aligns with the prevailing understanding that migraine is a complex disorder with sensory, affective, and cognitive components [4–6, 8, 10, 51]. Moreover, these results are consistent with the excellent performance obtained in ML studies that leverage neuroimaging resting-state data for identifying patients with CM, which involves multiple brain networks including sensory, affective, and cognitive domains [9, 24]. Collectively, these results indicate that altered brainstem–cortex activities in combination with the scores of key psychometric assessments can be effectively used to develop clinical decision-support tools based on ML algorithms.

Notably, in clinical practice, accurately assessing the migraine phase in patients diagnosed with migraine is challenging. Moreover, dynamic changes in neural excitability were noted across migraine phases [11]. For addressing this challenge, in this study, we identified common alterations in sensory processing, regardless of the migraine phase, and used these features to develop diagnostic classification models. By contrast, in previous studies, magnetoencephalography (MEG) resting-state connectivity in the interictal period within or among networks had > 90% of accuracy in identifying CM [9]. Similarly, a functional MRI study demonstrated excellent performance, with an accuracy of > 84% in distinguishing patients with migraine from HCs during headache-free periods [52]. Although our approach may lead to slightly reduced model performance, it enhances the practical applicability and utility of the models in routine clinical settings.

Numerous EEG and MEG studies have investigated resting-state activities, focusing on oscillatory power and connectivity parameters, to explore the underlying neuropathological mechanisms of migraine and to develop models for migraine identification [9, 24]. Although these studies have reported strong performance by their models, their findings on resting-state alterations in migraine remain inconclusive. By contrast, altered sensory processing has been consistently established as a crucial hallmark of migraine neuropathology [6, 8, 11, 14, 15, 40, 51], suggesting that sensory responses are key features for developing classification models for migraine identification. Given the complexity of sensory, affective, and cognitive disorders in migraine [4–6, 8, 10, 51], integrating multimodal data—sensory responses, psychometric scores, and resting-state activities—represents a promising next step for developing highly effective diagnostic tools for migraine.

Limitations

Our study has several limitations. First, further research is needed to determine whether the classification models

developed in this study can effectively differentiate other pain disorders, such as tension-type headache, fibromyalgia, or lower back pain, from migraine. Although distinct alterations in sensory processing have been observed in various pain disorders [14], the present findings do not establish that the aberrant brainstem–cortex activation and interactions are specific to patients with migraine. Second, due to the limited spatial resolution of the EEG approach, the activation of specific brainstem subregions, which play distinct roles in the neuropathology of migraine, could not be detected. Third, the selected latency period (11–30 ms) and the direction of effective connectivity (from the brainstem to cortex) in this analysis limit the exploration of sensory processing. Further investigation is warranted to assess the effects of higher-order functional integration and downstream sensory modulation in patients with migraine. Fourth, the differences in gender ratios across groups may have influenced the performance of the classification models and require further exploration. Finally, since dynamic changes in neural excitability have been observed across different migraine phases [6, 8, 11, 51], caution is warranted when interpreting electrophysiological findings in this study that were examined without accounting for migraine phase.

Conclusion

Decreased activation in brainstem and cortical regions and increased brainstem-to-cortex effective connectivity are characteristic of the abnormal sensory processing in migraine. This enhanced connectivity in the gamma is indicative of the progression toward migraine chronification. In this study, multimodal data incorporating EEG features and psychometric assessment scores were used to develop reliable and generalisable models for identifying patients with migraine and for differentiating between CM and patients with EM. With its advantages in terms of affordability, wide availability, and potential for mobile use, evoked EEG recording combined with ML algorithms can serve as a rapid clinical decision-support tool for diagnosing headache disorders.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-024-01892-2.

Supplementary Material 1.

Supplementary Material 2. Fig. 1 Difference of effective connectivity from the brainstem to cortex regions between groups. The analysis of variance on the spectral Granger causality values was visualised in a *F*-value matrix for the factor of group, where the *x*-axis represents frequency, and the *y*-axis corresponds to distinct brainstem–cortex connections. The plots display the F value that exceed the statistical threshold with colour coding. HCs, healthy controls; EM, episodic migraine; CM, chronic migraine; Ins, insula; V1, primary visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex; ACC, anterior cingulate cortex. L, left; R, right.

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Authors' contributions

F.J. Hsiao and W.T. Chen contributed to the study design. W.T. Chen, H.Y. Liu, Y.F. Wang, K.L. Lai, S.P. Chen, and S.J. Wang recruited patients and collected data. F.J. Hsiao, W.T. Chen, Y.T. Wu, L.L.H. Pan, and S.J. Wang performed data analysis and interpretation. F.J. Hsiao, W.T. Chen, and G. Coppola wrote the manuscript. F.J. Hsiao, W.T. Chen, G. Coppola, and S.J. Wang critically reviewed the article. All authors interpreted the data, reviewed the manuscript, and approved the final version.

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Data availability

Derived data supporting the findings of this study are available on request from the corresponding authors.

Declarations

Competing interests

FJ Hsiao, WT Chen, HY Liu, YT Wu, YF Wang, LLH Pan, KL Lai, SP Chen, and G Coppola declare no potential conflicts of interest. SJ Wang reports grants and personal fees from Norvatis Taiwan, personal fees from Daiichi-Sankyo, grants and personal fees from Eli-Lilly, personal fees from AbbVie/Allergan, personal fees from Pfizer Taiwan, personal fees from Biogen, Taiwan, outside the submitted work.

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