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BOLD repetition enhancement in the orbitofrontal cortex during complex visuospatial processing in migraine without aura: a shift in periaqueductal gray - cortical coupling?

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Abstract

Background Visual discomfort and sensory overload are common complaints in migraine patients without aura (MwoA), even between attacks, yet their neural basis remains poorly understood. We aimed to explore brain activation patterns in response to complex visuospatial tasks with higher ecological validity by using functional magnetic resonance imaging in migraine patients without aura.

Methods Fifty-nine right-handed female participants (30 interictal MwoA and 29 non-headache controls, aged 18–46 years) were included in the study. Subjects completed visually demanding fMRI tasks, which were designed based on aversive visuals that are frequently encountered in daily routine. Participants were asked to locate a target presented within either a high-frequency grating or a crowded geometric array in two runs while undergoing an fMRI scan. Both behavioral, clinical, and neuroimaging data were analyzed to examine repetition-related neural dynamics.

Results A complex visual task induced higher BOLD activations in salience, executive control, and dorsal attention networks, particularly in visual areas, in migraine without aura patients compared to non-headache sufferers. Unlike controls, migraine patients exhibited repetition enhancement in the orbitofrontal cortex and the periaqueductal gray. Repetition suppression is impaired in higher-order visual areas of LOC, Pulvinar, and IPS compared to the control group. Reaction time and initial learning ability were comparable in the two groups; however, the accuracy rate decreased towards the end of the second run. Changes in the accuracy rate were positively correlated with changes in the OFC BOLD signal. Increased photophobia correlated with BOLD activation changes in the periaqueductal gray, the lateral occipital cortex, and the insula in migraine.

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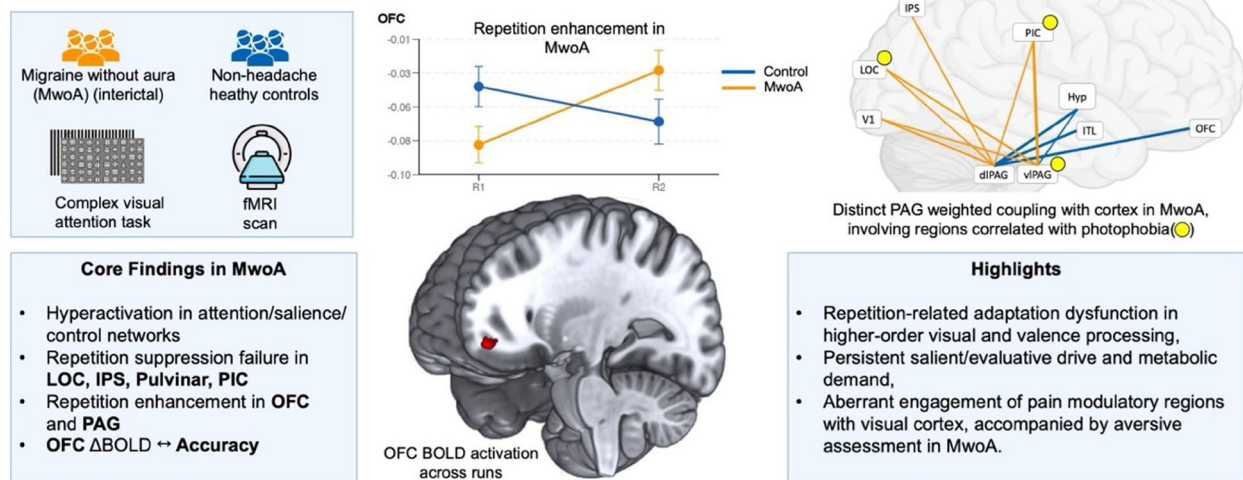
Conclusions Lack of repetition suppression in higher-order cortical and thalamic visual areas, and repetition enhancement in the OFC and PAG, are novel findings in migraine. Orbitofrontal activation correlated with task performance, indicating increased effortful top-down control to sustain accuracy, despite substantial metabolic demands, in migraine patients without aura. The enhanced BOLD activation in higher-order visual processing, along with reduced accuracy performance during repetition, may also reflect a prolonged reliance on aerobic glycolysis to meet neuronal energy demands. Abnormal engagement of pain-modulatory regions during visual processing suggests that sensory input is processed as aversive rather than neutral. These results provide a network-level explanation in which disrupted sensory gating and altered cortico-midbrain interactions impair predictive suppression, contributing to cognitive fatigue, sustained sensory gain, and visual hypersensitivity in migraine without aura.

Keywords Orbitofrontal cortex, Periaqueductal gray, Higher order-visual processing, Photophobia, Migraine, Repetition-suppression

Graphical Abstract

BOLD Repetition Enhancement in the Orbitofrontal Cortex During Complex Visuospatial Processing in Migraine without Aura: A Shift in Periaqueductal Gray-Cortical Coupling?

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Background

Migraine is a highly prevalent and disabling neurological disorder characterized not only by recurrent headache attacks but also by a broad array of sensory, cognitive, autonomic, and affective symptoms. Although headache remains the defining clinical feature, increasing evidence suggests that migraine is fundamentally a disorder of sensory regulation and large-scale brain network dysfunction rather than a condition restricted to pain processing alone [1]. Clinically, migraine attacks are frequently accompanied by sensory hypersensitivity, including photophobia, phonophobia, and osmophobia, as well as impairments in attention, executive control, autonomic regulation, and emotional processing [2, 3]. Importantly,

many of these abnormalities persist during the interictal period, indicating stable alterations in sensory gain control and cortical responsiveness outside the headache attack episode itself [4].

Functional neuroimaging studies have consistently demonstrated widespread alterations across cortical, subcortical, and brainstem regions involved in sensory processing, affective regulation, and cognitive control. These alterations are often conceptualized within the “pain matrix” framework, encompassing sensory-discriminative, affective-motivational, and cognitive-evaluative subsystems [5, 6]. However, this framework appears increasingly incomplete, as migraine-related abnormalities extend beyond classical nociceptive regions to

include visual, salience, and executive-control networks. This broader perspective aligns with contemporary views of migraine as a disorder of distributed brain systems rather than a localized pain condition. Migraine symptoms are proposed to be related to dysfunctional higher-order thalamic nuclei and cortical areas. As the visual system is the most affected sensory domain in migraine, the higher-order visual cortex, the lateral occipital cortex (LOC), and the higher-order thalamic nucleus pulvinar are of particular interest [7–9].

Within this broader network perspective, increasing attention has been directed toward subcortical and mid-brain structures that interact with cortical systems to shape sensory integration and modulation. Among these, the periaqueductal gray (PAG) occupies a pivotal position due to its broad reciprocal connections with thalamic, hypothalamic, limbic, and cortical regions. Beyond its traditional role as a descending pain modulatory center, the PAG is increasingly viewed as an interface linking sensory input with autonomic, affective, and behavioral responses [10]. Functional imaging studies in migraine have reported altered PAG activity and connectivity, including disrupted coupling between PAG subregions and cortical systems implicated in salience processing and cognitive control, such as the insula and prefrontal cortices [11, 12]. Notably, prefrontal areas such as the orbitofrontal cortex (OFC), which contribute to the contextual evaluation and top-down regulation of sensory information [13], are well-positioned to influence how visual input from early and higher-order visual regions is weighted and regulated via descending brainstem pathways [14]. Importantly, the functional heterogeneity of the PAG, with dorsal and ventrolateral subdivisions supporting distinct patterns of sensory facilitation and inhibition, motivates the hypothesis that migraine-related abnormalities may reflect disrupted coordination between cortical evaluative systems and midbrain pain regulatory mechanisms rather than dysfunction localized to a single structure [10, 11].

Altered responses to visual input represent one of the most prominent and disabling features of migraine. Patients frequently report discomfort, disorientation, or cognitive overload in visually complex environments where multiple stimuli compete for attentional resources [15]. Experimental studies have shown that visually demanding stimuli reliably provoke discomfort and exaggerated cortical responses in individuals with migraine [16, 17], indicating abnormal sensory gain and impaired filtering under conditions of increased perceptual load. A key mechanism proposed to underlie this altered visual responsiveness is deficient habituation, commonly assessed as reduced or absent repetition suppression. In healthy individuals, repeated stimulus exposure typically leads to attenuated neural responses, reflecting efficient

adaptation and inhibitory control. In contrast, migraine patients often exhibit impaired habituation or even paradoxical response enhancement, particularly within the visual cortex, even during the interictal period [18]. Within the dual-process framework of habituation and sensitization, migraine has been conceptualized as a state in which sensitization predominates over habituation [19], potentially due to reduced lateral inhibition within the visual cortical circuit [20].

Within predictive coding frameworks, the brain continuously generates top-down predictions about sensory input while propagating bottom-up prediction errors when expectations are violated. Repetition suppression is thought to index successful predictive updating and reduced prediction error [21]. Crucially, visual hypersensitivity in migraine is not confined to the early visual cortex. Behavioral and neuroimaging studies have demonstrated deficits in higher-order visual and attentional functions, implicating distributed networks that encompass the LOC, the intraparietal sulcus (IPS), the insula, and the prefrontal control region [22–24]. Despite these advances, it remains unclear how impaired habituation and visual hypersensitivity are implemented across interacting cortical, subcortical, and brainstem networks.

In the present study, we address this gap by using task-based functional MRI during ecologically valid, visually demanding stimulation to characterize network-level activation and adaptation in migraine without aura (MwoA), and to explore repetition suppression within a systems-level framework of visual sensory regulation.

Methods

Participants

A total of 138 female individuals were assessed for eligibility. Migraine patients were diagnosed with episodic migraine without aura (MwoA) according to ICHD-3 (1.1) by headache experts. Eligible participants were right-handed women aged 18–46 years. Only female participants were included due to the higher prevalence of migraine in women and documented sex-related differences in sensory hypersensitivity and neural processing, with the aim of reducing biological heterogeneity and increasing internal validity [25].

Individuals were not included in the study if they had chronic migraine, medication overuse headache, other primary or secondary headache disorders, any neurological or known psychiatric disorder, MRI contraindications, or claustrophobia. Following clinical assessment, 55 individuals were excluded (35 due to ineligibility for the migraine subtype and 20 due to claustrophobia), and 83 participants proceeded to MRI scanning.

All migraine patients were scanned during a strictly defined interictal phase. None were experiencing an acute migraine attack at the time of MRI, and no

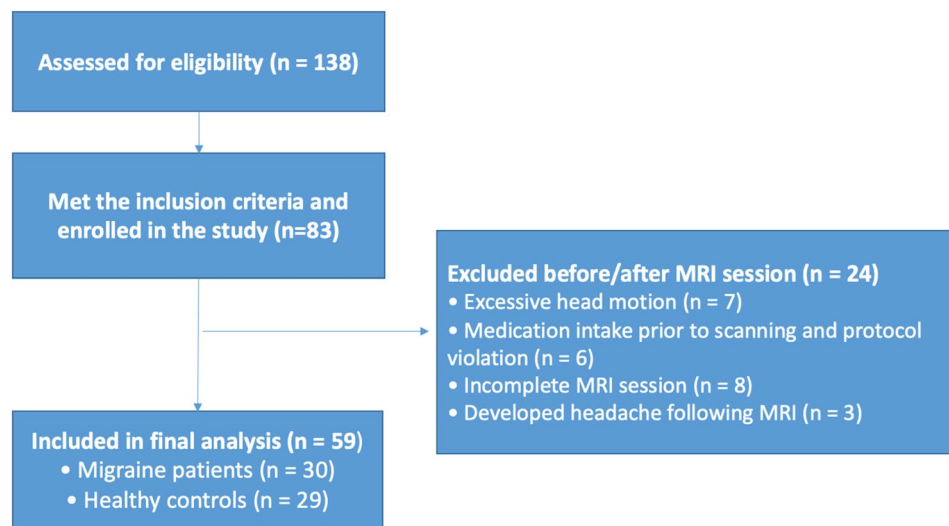


Fig. 1 Flow diagram of participant recruitment

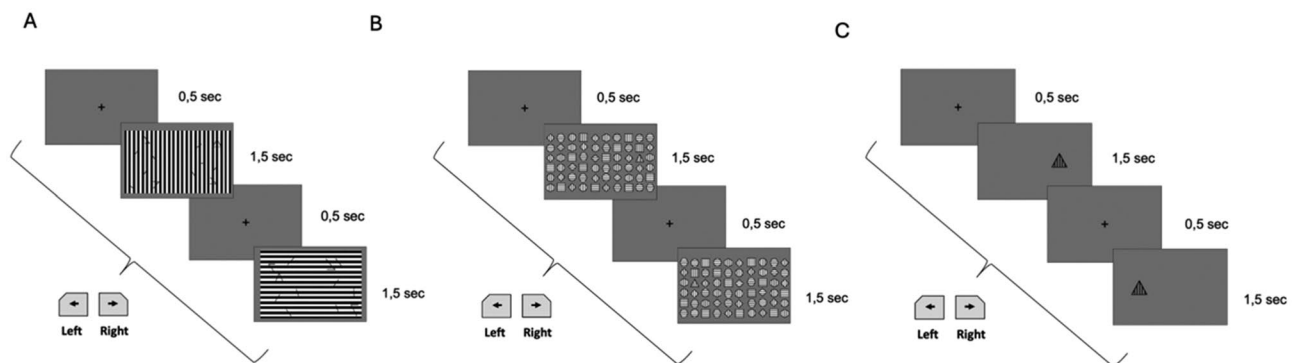


Fig. 2 Experimental paradigm. (A) High-frequency grating, (B) Crowded geometric arrays, and (C) Control condition. Each trial consisted of a 0.5 s fixation cross followed by 1.5 s stimulus presentation. Participants responded with left or right button presses depending on the target's spatial position (e.g., triangle). Trials were grouped into 30-second task blocks. Each run additionally included rest blocks, and task blocks were presented in a pseudo-randomized order within each run

migraine attack was reported within 72 hours before or after scanning. None of the patients were receiving prophylactic migraine treatment, and no participant had taken acute migraine medication on the day of scanning.

Before and after MRI acquisition, 24 additional participants were excluded due to excessive head motion ($n=7$), medication intake prior to scanning or protocol violation ($n=6$), inability to complete the MRI session ($n=8$), or development of headache within three days following scanning ($n=3$). The final sample consisted of 59 right-handed female participants, including 30 patients with MwoA and 29 headache-free healthy controls. Healthy controls met the same eligibility criteria except for the migraine diagnosis. The recruitment flow is presented in Fig. 1.

To minimize observer bias, different researchers were responsible for clinical assessment, MRI data acquisition, and statistical analysis. Investigators performing

preprocessing and statistical analyses remained blinded to group allocation until completion of the primary analyses.

All participants were scanned during morning hours within a consistent time window to reduce potential circadian variability. The study was approved by the Gazi University Clinical Research Ethics Committee. All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants prior to participation.

Experimental paradigm

To investigate sensory hypersensitivity in migraine patients, two experimental tasks were designed and presented during fMRI scanning (see Fig. 2). The tasks were implemented using PsychoPy (version 2022.2.5), a Python-based software, and each participant completed two experimental conditions in a block design.

In the first experimental condition, the High-frequency Grating, which displayed black-and-white striped patterns with varying spatial frequencies, was used. The stripes differed in terms of proximity (e.g., narrow versus wide), orientation (horizontal versus vertical), and thickness (thin versus thick), creating a complex visual environment. These patterns were designed to induce discomfort and cortical activation based on prior studies showing the effects of such patterns in migraine patients. Participants were asked to identify a target object (a triangle) that appeared among the stripes. If participants identified the triangle on the right side of the screen, they were instructed to press the right button; if they identified it on the left side, they pushed the left button.

The second experimental condition, Crowded Geometric Arrays, required participants to identify the position of a triangle within a dynamic, visually noisy environment. This task aimed to simulate real-world environments, where migraine patients often report discomfort in cluttered or moving visual scenes. The background was filled with various geometric shapes, including squares, circles, rhombuses, and hexagons, all of which were striped, alongside the target triangle. Participants were asked to press a button indicating whether the target triangle appeared on the left or right side of the screen.

In the control condition, participants were asked to identify the position of a triangle displayed on a plain gray background. This condition served as a baseline for comparison with the experimental conditions, where visual complexity and peripheral stimuli were manipulated. The triangle in this condition, like in the experimental conditions, was striped, ensuring participants were still engaged with visual processing, but in a less complex environment. We used striped patterns to maintain visual consistency across conditions, ensuring the control condition was neither overly simplistic nor less demanding than the experimental conditions.

In both experimental and control conditions, participants were instructed to fixate on the red fixation point at the center of the screen while also identifying a triangle. This dual-task design aimed to encourage participants to focus centrally on the screen while identifying the target triangle, while adding the challenge of presenting the visual stimuli (such as striped patterns) in the periphery. The intention was to ensure that participants were exposed to stimuli in their peripheral vision, which we hypothesized would increase discomfort while maintaining a central focus on the task. The fixation point also served as a way to encourage participants to minimize eye and head movements, which is crucial for reducing motion artifacts during fMRI analysis. The inclusion of a response requirement also allowed us to monitor whether participants were indeed visually attending to the stimulus, thereby ensuring they were exposed to the

stimulus with their eyes open. Behavioral responses were collected to ensure sustained attention to the task. These measures provided valuable data on both cognitive processing speed and response accuracy, which were crucial for assessing participants' performance under discomforting conditions.

In the study, four types of blocks were used: two experimental conditions, one control condition, and a rest block. The rest block was included to allow brain activation to return to baseline levels between task conditions, a standard approach in block design studies. During this block, participants were not required to perform any task but were instructed to maintain central fixation on the screen. This ensured that any observed brain activation in the task blocks could be attributed to the tasks themselves rather than residual activation from previous conditions.

The experiment consisted of two runs, each lasting 6 minutes. A block design was employed, where tasks were presented in 30-second blocks. During each block, participants completed 15 trials of the task, with each trial lasting 1500 ms. Between each trial, a fixation point was displayed for 500 ms. Therefore, each trial, including the fixation screen, lasted 2 s, and each 30-second block consisted of 15 trials. In total, participants performed each task 15 times per block. During these trials, the target triangle appeared on the left side of the screen in 7 trials and on the right in 8. The four block types were repeated three times within a run. fMRI scanning was conducted during the two 6-minute runs. The order of the tasks was pre-determined and randomized, and this order remained consistent across participants. Reaction times and accuracy were recorded during the tasks, enabling further analysis of cognitive processing under the experimental conditions.

Behavioral and clinical data analysis

The sample size of the study was determined a priori using G*Power (v3.1). Based on a recent study reporting functional abnormalities in the visual cortex of patients with migraine without aura [26] ($t = 3.62$, Cohen's $d = 1.067$), we calculated that a minimum of 24 subjects per group was required to achieve 95% power at $\alpha = 0.05$. Consequently, we recruited 30 patients and 29 healthy controls (total $N = 59$), ensuring the study was adequately powered to detect the expected effects.

To characterize the temporal dynamics of performance, raw behavioral data were preprocessed using a temporal binning approach. For each participant, consecutive trials were averaged into bins of 3, yielding a continuous time course. To compare the performance trajectories of the groups over time, Growth Curve Analysis was conducted using Linear Mixed models. This approach allowed for modeling both within-subject and between-subject

variability. The model included Accuracy as the dependent variable, with Time modeled using both a linear term (to test for monotonic trends) and a quadratic term (Time²; to test for non-linear, curvilinear adaptation or fatigue effects).

To examine changes in clinical symptoms during the experiment, digital visual analog scale (VAS) scores (on a 0-100 scale) for discomfort and photophobia were assessed before and after MRI scanning and analyzed using a 2 × 2 Mixed-Design Repeated Measures ANOVA. The model included Group (MwoA vs. Control) as the between-subjects factor and Time (Time 1 vs. Time 2) as the within-subjects factor. To robustly control for Type I error across multiple comparisons, significant main effects and interactions were investigated using Tukey's HSD post-hoc tests. The significance level was set at $p < 0.05$.

Image acquisition

Brain imaging was conducted using the Siemens 3 Tesla MAGNETOM Prisma magnetic resonance imaging (MRI) scanner at the Neuroscience and Neurotechnology Center of Excellence (NÖROM). The scanner was capable of both structural and functional brain imaging. Structural and functional images were collected from each participant throughout the study.

High-resolution T1-weighted anatomical imaging was performed to align each participant's brain anatomy with the functional data. The T1-weighted imaging parameters were as follows: TR = 2300 ms, TE = 3.01 ms, FOV = 240 mm, slice thickness = 0.9 mm, with a voxel size of $0.9 \times 0.9 \times 0.9$ mm³. These anatomical images were used for spatial normalization and co-registration with functional data.

Functional imaging was conducted during the execution of the tasks, as previously mentioned, using a block design. A multiband gradient-echo echo-planar imaging (EPI) sequence was employed with the following parameters: TR = 1000 ms, TE = 28.00 ms, FOV = 208 mm, 54 axial slices per volume, slice thickness = 2.5 mm, and isotropic voxel size = $2.5 \times 2.5 \times 2.5$ mm³. Acceleration was achieved through simultaneous multi-slice (SMS) acquisition (multiband factor = 3) combined with in-plane GRAPPA acceleration (factor = 3), allowing whole-brain coverage at $2.5 \times 2.5 \times 2.5$ mm³ isotropic resolution. Each functional run consisted of 360 volumes, resulting in 720 volumes analyzed across two runs.

To correct for susceptibility-induced geometric distortions, gradient-echo field maps were acquired with the following parameters: TR = 400 ms, TE1 = 4.92 ms, TE2 = 7.38 ms, flip angle = 60°, voxel size = $3 \times 3 \times 3$ mm³, 40 slices, and FOV = 192 mm.

The MRI task was presented to participants using an MRI-compatible screen and mirror system, and

participants responded using an MRI-compatible response pad.

fMRI processing and data analysis

Image data were processed and analyzed using SPM12 (Wellcome Centre for Human Neuroimaging, London, United Kingdom) implemented in MATLAB.

Preprocessing included slice-timing correction (interleaved acquisition, middle slice as reference), realignment to correct for head motion, and fieldmap-based distortion correction using the acquired gradient-echo field-mapping sequence. The mean functional image was co-registered to the participant's high-resolution T1-weighted structural image. Structural images were segmented using the unified segmentation approach, and normalization parameters were applied to transform functional images into Montreal Neurological Institute (MNI) space. Spatial smoothing was performed using a 9-mm FWHM isotropic Gaussian kernel. This is within the range of commonly used Kernel widths in group-level fMRI analyses to balance signal-to-noise ratio and inter-subject anatomical variability and have been shown empirically to optimize sensitivity for corrected inference [27, 28].

Since fMRI data are often prone to motion-related artifacts, the six motion parameters obtained during realignment were included as covariates in the first-level statistical model. To further account for residual motion effects, volumes showing excessive frame-to-frame displacement (translation > 0.5 mm or rotation > 0.5°) were modeled using spike regressors.

Following preprocessing, neural responses evoked during experimental conditions were modeled using the general linear model. For each participant, first-level contrast images were generated and entered into group-level random-effects analyses. At the group level, a factorial analysis of variance (ANOVA) was conducted with three factors: Group (MwoA vs. healthy control), Task (High-frequency Grating, Crowded Geometric Arrays, Control), and Run (Run 1, Run 2), including all interaction terms. A full factorial ANOVA design allowed us to examine main effects and interactions across all conditions, groups and runs.

For group-level inference, implicit masking was disabled, and an explicit gray-matter mask derived from the SPM12 tissue probability map (threshold = 0.30) was applied. Statistical significance was assessed using family-wise error (FWE) correction at the voxel level ($p < 0.05$). For reporting purposes, a minimum cluster extent of 20 voxels was applied. All reported coordinates are provided in MNI space.

ROI data analysis

Our hypothesis is that “an ecologically valid complex visual task is associated with sensory hypersensitivity and noxious experience in female migraine patients without aura”. We have developed the visual paradigm specifically to test the noxious effects of repeated high-contrast visual input in migraine patients. This paradigm also included an ecologically relevant perceptual decision-making component that required sustained attention and repetition-related modulation across runs.

In addition to whole-brain analyses, region-of-interest (ROI) analyses with specific ROIs were conducted to test these hypotheses regarding repetition-related mechanisms, visual sensitivity, and its functional consequences of valence. And these ROIs were listed in Supplementary Table 4.

A priori neurosynth-based ROIs

Based on a priori hypotheses and to ensure independence from the present dataset, the majority of ROIs were defined using a meta-analytic approach implemented in the publicly available Neurosynth database. For each region, the anatomical name (e.g., “amygdala”, “pulvinar”, “intraparietal sulcus”) was used as a search term, and peak MNI coordinates corresponding to the most consistently reported activation site across studies were identified.

Using these coordinates, spherical ROIs (3–6 mm in radius, depending on the region size and prior literature) were constructed bilaterally. Neurosynth-derived ROIs included the LGN, pulvinar, V1, LOC, IPS, ITL, dlPFC, vlPAG, dlPAG, hypothalamus, amygdala, AIC, and PIC. The coordinates and sphere sizes for all Neurosynth-based ROIs are reported in Supplementary Table 4.

Functionally defined ROI and multivariate pattern analysis

In addition to a priori ROIs, the orbitofrontal cortex (OFC) was defined functionally based on a significant Group $\times$ Run interaction observed in the whole-brain analysis. The OFC ROI was determined using the cluster identified in this interaction contrast and was included to further characterize the observed effect. This functionally defined ROI was incorporated into the ROI framework but was not used to generate independent statistical inference beyond the whole-brain results.

All ROIs were implemented using the MarsBaR toolbox, registered within the SPM framework, and included in the ROI analysis pipeline. For each ROI, mean BOLD signal estimates were extracted from each participant's preprocessed functional data. Extracted values were used for visualization and hypothesis-driven analyses, as appropriate.

We employed a task-averaging approach to assess the general neural response to visual stress. For each

participant and each ROI, the mean BOLD activation values from the two visually demanding tasks (“High-frequency Grating” and “Crowded Geometric Arrays”) were averaged within each run. This procedure was applied to capture the generalized neural adaptation to visually stressful environments, independent of specific stimulus features.

Partial Least Squares Discriminant Analysis (PLS-DA) was conducted to characterize the multivariate neural patterns that best discriminate migraine patients from healthy controls based on their adaptation profiles [29]. The Δ BOLD values of all ROIs were entered as predictor variables (X matrix), while group membership served as the response variable (Y vector). Before modeling, an outlier detection procedure was applied using a Z-score threshold of ± 3 to minimize the impact of extreme values, and data were standardized (Z-score normalization). The model's classification performance was evaluated using R-squared and accuracy metrics. The loading weights on the first latent variable (LV1) were analyzed to identify the specific brain regions that contributed most to the separation between the migraine and control groups.

Averaged BOLD signal values were analyzed separately for each region of interest (ROI) using a 2×2 mixed-design repeated-measures analysis of variance (ANOVA). The model included Run (Run 1 vs. Run 2) as a within-subject factor to assess changes in neural responses across scanning runs, and Group (Migraine vs. Control) as a between-subject factor to examine overall group differences in activation. The Run $\times$ Group interaction was included to test whether migraine patients and healthy controls exhibited differential response patterns across runs. Post hoc comparisons were performed using Tukey's correction where appropriate. Statistical significance was set at $p < 0.05$.

Selected 23 areas for ROI ANOVA analysis, given in Supplementary Table 4, were determined through PLS-DA analysis and a hypothesis-driven approach. ANOVA results at the ROI level are adjusted using a permutation test (5,000 iterations), in which group labels are randomly permuted to derive empirical significance levels and obtain corrected p-values.

Correlation analysis

To elucidate the relationship between neural adaptation dynamics and clinical/behavioral outcomes, correlation analyses were performed using differential indices. For each participant and Region of Interest (ROI), neural adaptation was quantified as the change in BOLD signal intensity between the two runs (Δ BOLD = Run 2 mean - Run 1 mean). Within this framework, negative values indicate habituation (decreased response), while positive values reflect sensitization or response

maintenance. Clinical changes were calculated as the difference between post-scan and pre-scan photophobia scores ($\Delta\text{photophobia} = \text{Post-scan} - \text{Pre-scan}$). Behavioral performance was operationalized as the learning trajectory, indexed by the slope of accuracy across trials within Run 2. Given our main hypothesis regarding repetition-related changes, we focused particularly on Run 2. Spearman's rank correlation coefficients were computed to assess the coupling between these neural adaptation indices and behavioral/clinical measures separately for the migraine and control groups. To control for multiple comparisons, *p*-values were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) correction.

Because our primary aim was to characterize the cumulative neural effects of repeated visual stimulation and individual differences in response profiles, we focused on correlations of ROI activation changes rather than time-series-based connectivity measures. This approach allowed us to test whether individuals showing stronger run-to-run increases in one region also tended to show parallel increases in the other areas, thereby indicating shared responsivity across participants, rather than temporal or causal interactions between brain regions.

Results

Behavioral and clinical results

A total of 59 female participants (30 migraine patients without aura and 29 healthy non-headache controls) were included in the study. The mean age was 26.4 ± 5.9 years in the migraine group and 27.0 ± 6.8 years in the control group, with no significant difference between groups ($p = 0.70$). Disease duration was 5.58 ± 3.45 years and monthly attack frequency 2.37 ± 1.6 attacks/month in the migraine group. Migraine patients were not using any prophylactic medication.

Mean reaction time and mean accuracy did not differ significantly between groups or across tasks. Accuracy did not differ significantly between groups during either task in Run 1. These findings indicate that there are no initial learning ability differences between groups.

Regarding clinical measures, a repeated-measures ANOVA revealed significant Group $\times$ Time interactions for both discomfort ($F = 19.87$, $p < 0.001$) and photophobia ($F = 4.14$, $p = 0.047$). Post-hoc analyses confirmed that scores increased significantly over time exclusively in the migraine group. While discomfort was significantly higher in patients only at Time 2 ($p < 0.001$), photophobia was elevated at both Time 1 ($p = 0.018$) and Time 2 ($p < 0.001$) compared to the controls.

Functional imaging results

The main effect of group

The main effect of the group revealed significant differences across a distributed fronto-parietal, temporal,

limbic, and subcortical network (Table 1). Group-related effects were observed in parietal regions, including the supramarginal gyrus (SMG), superior parietal lobule (SPL), and IPS, predominantly in the right hemisphere, as well as in the dorsolateral prefrontal cortex (dlPFC), temporal and occipitotemporal cortices, and supplementary motor area (SMA). Additional effects were detected in limbic and subcortical regions, including the posterior cingulate cortex (PCC), posterior insula (PIC), entorhinal cortex, caudate nucleus, and cerebellum, indicating widespread group differences across higher-order cognitive, sensory-integrative, and limbic systems (Fig. 3).

To clarify the direction of the significant group effects identified in the ANOVA, pairwise comparisons were performed among the groups. These analyses revealed significant differences only in the Migraine > Control contrast. No significant activations were observed for the Control > Migraine contrast at the specified statistical threshold (Table S1, Fig. 3). The Migraine > Control contrast showed significant activations primarily within right-lateralized temporo-parietal regions, including the angular gyrus, superior temporal gyrus (STG), and SMG. These regions showed stronger BOLD responses in the migraine group than in healthy controls (Supplementary Table 1).

The main effect of the task

Brain activation differed significantly between task conditions. The task elicited robust, extensive activations primarily in the visual cortex (Table 1; Fig. 4). A large cluster encompassing the extrastriate and striate cortices was observed in the left hemisphere.

To evaluate whether the two visual paradigms engaged a common neural substrate, a conjunction analysis was performed across the High-Frequency Grating Task and Crowded Geometric Array tasks. The analysis revealed extensive overlapping activation across bilateral primary and extrastriate visual cortices, as well as the premotor and supplementary motor areas involved in task responses. Visual cortex activation, revealed by conjunction analysis, indicates that both tasks engaged a shared visual processing network (Supplementary Table 3).

The main effect of run

The main effect of the run revealed significant activations across bilateral premotor, prefrontal, insular, cingulate, and cerebellar regions (Table 1). Prominent clusters were observed in the premotor cortex extending into the SMA, along with activations in the dorsal ACC and insula, showing a modest left-hemisphere predominance. Additional run-related effects were detected in bilateral prefrontal regions, including the anterior prefrontal cortex (APFC) and dlPFC, as well as in the fusiform gyrus and cerebellum (Fig. 4).

Table 1 Activated brain regions across runs and tasks between groups

Cluster Size	Brain Region	Peak MNI Coordinates			Peak Statistic	Laterality
Voxels		x	y	z	Z- score	
Main Effect of Group						
119	Supramarginal gyrus	46	-44	28	5.36	R
92	Superior parietal lobule	-26	-62	44	5.51	L
89	Intraparietal sulcus	36	-60	50	6.12	R
80	Dorsolateral prefrontal cortex	34	18	24	6.23	R
76	Cerebellum	-36	-52	-34	5.84	L
68	Middle temporal gyrus	-48	10	-24	6.05	L
68	Extrastriate cortex	-34	-86	30	5.66	L
48	Fusiform / lateral occipitotemporal cortex	64	-54	0	6.69	R
36	Supplementary motor area / superior frontal gyrus	-18	10	50	6.25	L
34	Posterior cingulate cortex	6	-24	34	5.59	R
32	Entorhinal cortex	-32	0	-24	5.43	L
28	Dorsolateral prefrontal cortex	36	34	12	5.42	R
27	Caudate nucleus	-16	4	18	5.00	L
24	Posterior insula	38	-30	22	5.63	R
Main Effect of Task						
24,646	Extrastriate cortex	-22	-78	-12	Inf	L
	Striate cortex	-12	-94	2	Inf	L
1559	Anterior prefrontal cortex	-2	54	-8	6.99	L
	Dorsolateral prefrontal cortex	-20	22	44	5.97	L
1384	Angular gyrus	-56	-68	18	Inf	L
793	Premotor / supplementary motor area	44	6	30	Inf	R
	Superior frontal gyrus	20	14	68	6.03	
510	Anterior insula	32	24	2	Inf	R
411	Posterior cingulate cortex	-8	-50	34	5.94	L
349	Supplementary motor area	8	16	46	7.21	R
	Supplementary motor area	-2	12	50	5.34	L
307	Cerebellum	36	-84	-36	7.13	R
256	Anterior prefrontal cortex	42	50	22	6.39	R
229	Anterior insula	-30	24	0	7.33	L
192	Supplementary motor area	-42	0	32	6.60	L
165	Cerebellum	-28	-68	-52	7.28	L
89	Middle temporal gyrus	-60	-14	-20	5.28	L
47	Pars orbitalis	-34	34	-16	5.11	L
31	Hippocampus	24	-28	-6	7.55	R
27	Hippocampus	-22	-30	-6	Inf	L
23	Extrastriate cortex / precuneus	24	-66	24	6.45	R
Main Effect of Run						
3878	Premotor cortex	-60	8	10	Inf	L
	Insula	-50	-12	18	7.29	L
2153	Premotor / supplementary motor area	-8	6	62	7.70	L
	Dorsal anterior cingulate cortex	-10	24	32	7.25	L
1982	Premotor cortex	62	12	10	Inf	R
	Insula	48	12	-2	7.02	R
811	Anterior prefrontal cortex	-28	42	26	6.89	L
	Dorsolateral prefrontal cortex	-38	38	38	5.69	L
376	Dorsolateral prefrontal cortex	26	54	32	6.61	R
	Anterior prefrontal cortex	38	46	20	5.46	R
114	Cerebellum	-26	-54	-28	5.63	L
46	Supplementary motor area	44	-4	50	4.95	R
42	Supplementary motor area	24	10	58	5.02	R
25	Fusiform gyrus	50	-52	0	5.18	R

Table 1 (continued)

Cluster Size	Brain Region	Peak MNI Coordinates			Peak Statistic	Laterality
Group × run interaction						
22	Orbitofrontal cortex	-6	46	-18	5.02	L

All coordinates are reported in MNI space. Cluster size reflects the number of contiguous suprathreshold voxels. Multiple peaks are reported for clusters encompassing more than one local maximum. Inf indicates Z values exceeding the upper limit of numerical precision following statistical transformation. Laterality indicates the hemisphere of the peak voxel (L, left; R, right)

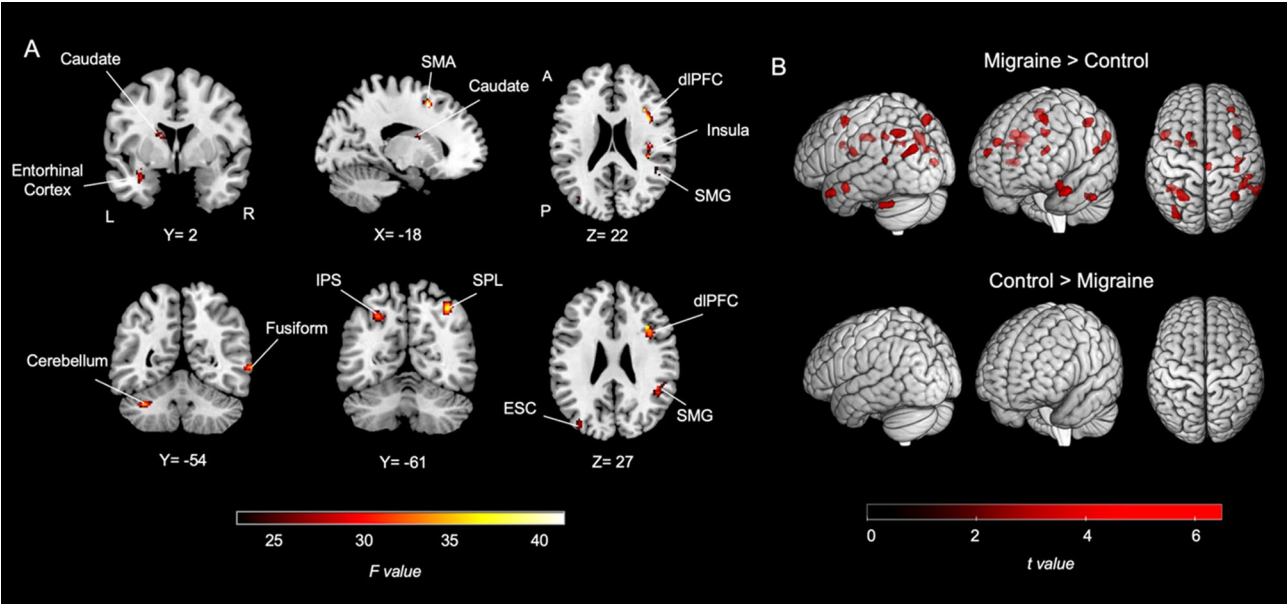


Fig. 3 Group differences between migraine patients and healthy controls. **(A)** Whole-brain maps illustrating brain regions that differed between migraine patients and healthy controls during task performance. Group-related differences were observed across a distributed network encompassing frontal, parietal, temporal, limbic, and subcortical regions, including the dorsolateral prefrontal cortex (dlPFC), insula, supramarginal gyrus (SMG), intraparietal sulcus (IPS), superior parietal lobule (SPL), supplementary motor area (SMA), caudate nucleus, entorhinal cortex, fusiform gyrus, and cerebellum. The color bar indicates F-values. **(B)** Direct group comparisons showed that these differences were driven exclusively by stronger activation in migraine patients, reflecting widespread hyperactivation of attention, executive-control, salience, and visual networks. No brain regions showed higher activation in healthy controls relative to migraine patients. n(Migraine) = 30, n(Control) = 29. Color bar indicates t-values. Results are family-wise error corrected (FWE, $p < 0.05$) and displayed on a standard anatomical template; slice locations are shown in MNI space. L, left; R, right; A, anterior; P, posterior

A comparison between Run 1 and Run 2 revealed distinct activation patterns between the groups. In controls, the Run 1 > Run 2 contrast showed activations in the premotor, fronto-parietal cortex, and ACC. Migraine patients exhibited bilateral activations encompassing prefrontal, motor, sensory, and limbic regions, including the APFC and dlPFC, premotor cortex, SMA, ACC, insula, and fusiform gyrus. No significant activations were observed in controls for the Run 2 > Run 1 contrast. In migraine patients, this contrast revealed significant bilateral dlPFC activation, indicating increased prefrontal engagement during the second run (Supplementary Table 2).

Group × run interaction and behavioral correlations

A significant interaction between group and run was observed in the orbitofrontal cortex (Table 1; Fig. 5). This interaction was localized to the left orbitofrontal cortex, indicating that run-related changes in activation differed

between groups within this region. There was no significant interaction in the Group × Task, Task × Run, or Group × Task × Run analyses. In other words, activation did not differ between the tasks within groups or across runs.

During the “High-frequency Grating” task, a significant quadratic Group × Time² interaction ($\beta < 0.001$, $z = 2.17$, $p = 0.030$) revealed distinct performance curvatures between groups across runs, reflecting different initial gain and fatigue/adaptation dynamics despite similar average accuracy (Fig. 5). In the migraine group, activation in the left OFC during Run 2 was significantly and positively correlated with task accuracy ($r = 0.64$, $p < 0.001$) ($n = 27$, due to corrupted behavioral response files of 3 in MwoA) (Fig. 5). No such correlation was observed in the control group ($r = -0.34$, $p = 0.087$).

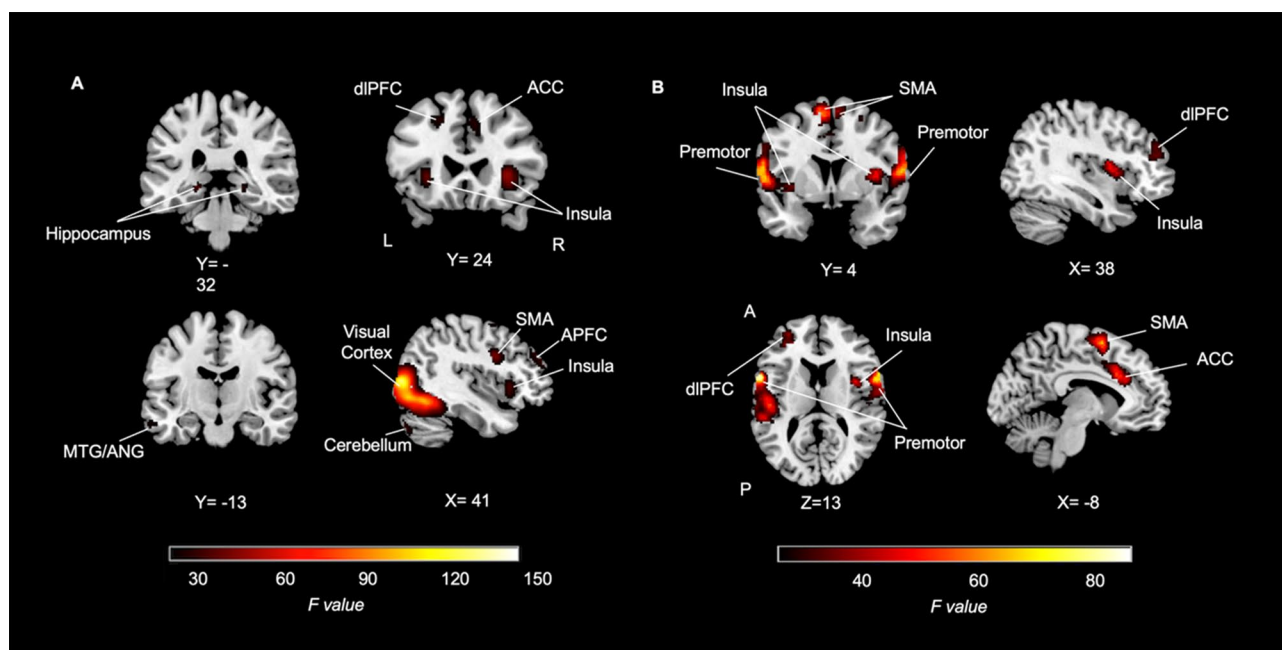


Fig. 4 Brain activation differed across tasks (A) and runs (B). (A) Whole-brain statistical parametric maps illustrating regions significantly engaged during task performance. Robust activations were observed across visual, frontal, parietal, limbic, and cerebellar regions, including the dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), insula, supplementary motor area (SMA), anterior prefrontal cortex (APFC), middle temporal/angular gyri (MTG/ANG), hippocampus, visual cortex, and cerebellum. (B) Statistical parametric maps showing run-related differences in brain activation across scanning runs. Significant clusters were detected in premotor cortex, supplementary motor area (SMA), insula, and dorsolateral prefrontal cortex (dlPFC), indicating widespread run-dependent modulation of motor and control-related regions. $n(\text{Migraine})=30$, $n(\text{Control})=29$. Results are FWE corrected ($p < 0.05$) and displayed on a standard anatomical template, with coronal, sagittal, and axial slices shown at the indicated MNI coordinates. The color scale represents F-values. L: Left, R: Right, A: Anterior, P: Posterior

ROI results (visual network)

All reported p -values have been adjusted for multiple comparisons. Analyses of the LOC revealed a significant main effect of Run specifically in the left hemisphere ($F=5.03$, $p=0.031$). The right LOC and bilateral V1 regions did not yield any significant main effects or interactions. In the left IPS and Pulvinar demonstrated significant main effects of Run ($F=9.80$, $p=0.003$ and $F=4.60$, $p=0.045$, respectively). Corresponding right-hemisphere ROIs and the bilateral LGN were non-significant. The Amygdala exhibited bilateral main effects of Group (Left: $F=6.24$, $p=0.015$; Right: $F=5.29$, $p=0.025$), reflecting hyperactivation in patients. In the midbrain, the Dorsolateral PAG (dlPAG) showed a significant Run $\times$ Group interaction ($F=4.21$, $p=0.046$), indicating differential adaptation trajectories. No significant effects were observed in the ventrolateral PAG (vlPAG) or the Inferior Temporal Lobe (ITL) (see Fig. 6).

Correlation and multivariate pattern analysis results

To investigate the relationship between repetition-related neural changes (Delta: Run 2 - Run 1), we calculated difference scores for the parameter estimates of each ROI. These Delta values reflect the magnitude of neural adaptation (e.g., habituation or sensitization) across the runs.

Analysis of functional coupling revealed positive correlations between activity changes in visual cortical areas and the midbrain in patients, specifically between left V1 and dlPAG ($r=0.56$, $p=0.014$). The right V1 with both the dlPAG ($r=0.47$, $p=0.039$) and vlPAG ($r=0.47$, $p=0.039$). LOC exhibited significant coupling with the PAG in the migraine group for specific connections (Left LOC-dlPAG: $r=0.56$, $p=0.015$; Right LOC-vlPAG: $r=0.52$, $p=0.021$), whereas the Right LOC-dlPAG association was not significant ($r=0.40$, $p=0.085$). In the control group, V1-PAG and LOC-PAG correlations were generally non-significant ($p > 0.05$). Regarding clinical symptoms, changes in photophobia score in migraine patients were positively correlated with changes in vlPAG activity ($r=0.38$, $p=0.042$), right LOC ($r=0.39$, $p=0.035$), and left PIC ($r=0.38$, $p=0.039$). No significant associations between photophobia and these regions were found in the control group (all $p > 0.5$) (see Fig. 7).

Complementing the univariate correlations, the PLS-DA analysis demonstrated that the distributed pattern of repetition-related neural changes (Δ BOLD) could robustly distinguish migraine patients without aura from healthy controls (MwoA $n=29$, Control $n=27$, 3 outliers). The multivariate model achieved a classification accuracy of 76.8% and an R^2 of 0.426, indicating that

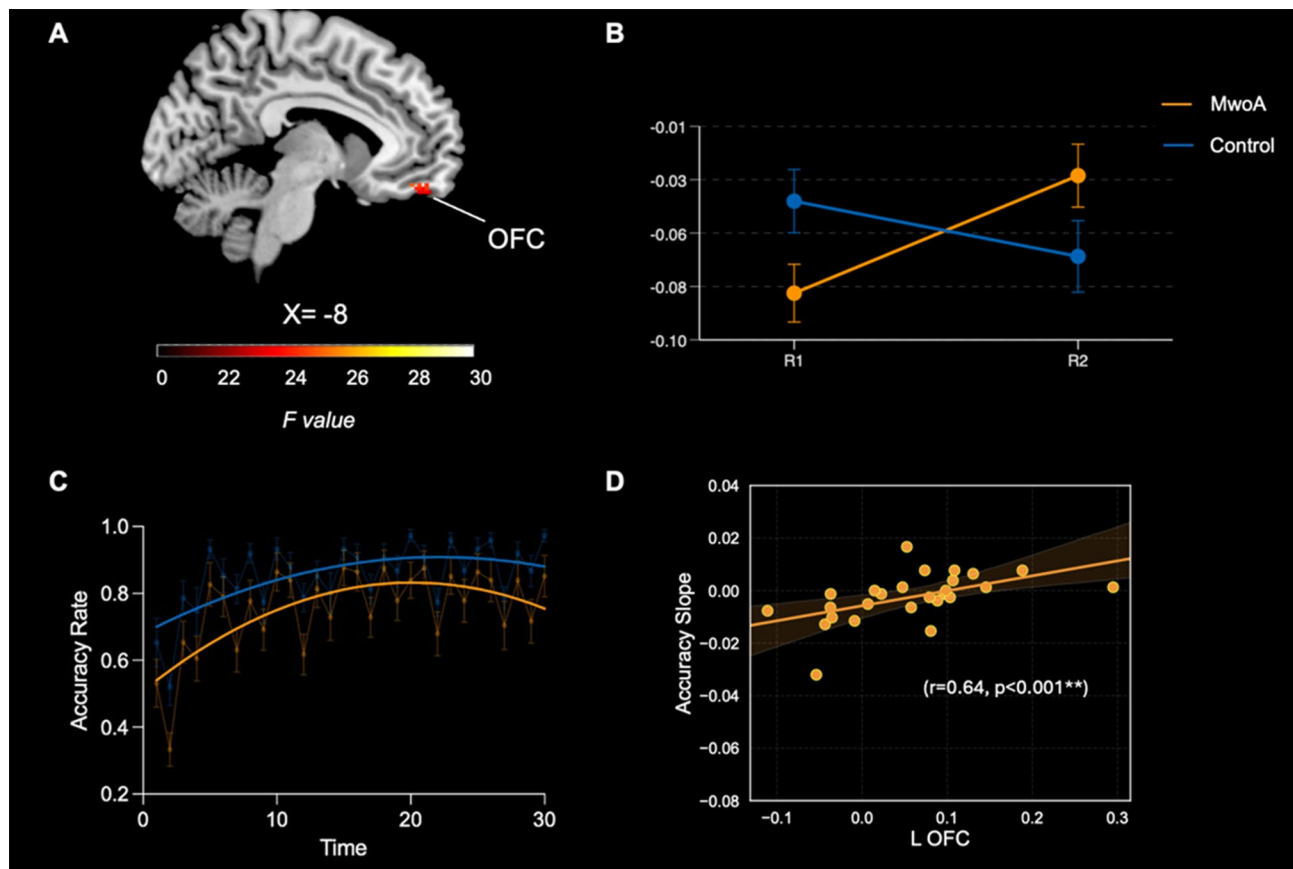


Fig. 5 The orbitofrontal cortex emerged as the key region differentiating the groups across runs. **(A)** Whole-brain statistical parametric map illustrating a significant Group $\times$ Run interaction localized to the left orbitofrontal cortex (OFC). The interaction effect is displayed on a sagittal slice at the indicated MNI coordinate ($X=-8$), with the color scale representing F-values. $n(\text{Migraine})=30$, $n(\text{Control})=29$. Results are FWE corrected ($p<0.05$). **(B)** ROI-based analysis extracted from the left OFC. Mean BOLD signal values are plotted separately for the groups across Run 1 (R1) and Run 2 (R2). BOLD repetitive enhancement in the left OFC is detected in patients with migraine without aura (orange), while repetitive suppression is seen in the healthy controls (blue). Error bars represent the standard error of the mean. **(C)** Accuracy rate analysis revealed an improved task performance in both groups. Compared to controls (blue trajectory), migraine patients exhibit a faster initial gain in accuracy, followed by a significant decline in performance (orange trajectory) towards the end of the task. **(D)** Correlation analyses demonstrate that higher OFC activation is associated with the ability to maintain performance in migraine patients ($n=27$)

approximately 42.6% of the variance in group membership is explained by the shared variance in neural adaptation profiles. Analysis of the loading weights on the first latent variable (LV1) revealed the specific regional contributions driving this separation. The migraine group showed high positive loading weights, most prominently in the Right PIC, Left OFC, and dlPAG, with contributions from the Right V1 and LOC. In contrast, the control group showed negative loadings driven primarily by the Left Hypothalamus, Right ITL, and Right dlPFC (see Fig. 8).

Discussion

In this study, we characterized how interictal MwoA alters behavioral sustainability and distributed neural dynamics during repeated exposure to visually demanding, high-contrast, ecologically relevant stimuli. Across two runs, migraine participants demonstrated preserved

initial task acquisition but reduced performance stability over time, along with marked differences in BOLD recruitment and repetition-related adaptation. At the systems level, the results converge on a framework in which migraine is associated with an amplified engagement of the attention-salience-control circuitry during visual processing, coupled with impaired repetition suppression in higher-order cortical and thalamic nodes, and atypical recruitment of midbrain modulatory structures. Together, these findings suggest that migraine-related visual hypersensitivity reflects disrupted network-level sensory regulation, rather than an abnormality confined to the early visual cortex.

Behavioral profile: intact learning with reduced sustained performance

Behaviorally, reaction time and the linear component of learning trajectories were comparable between groups,

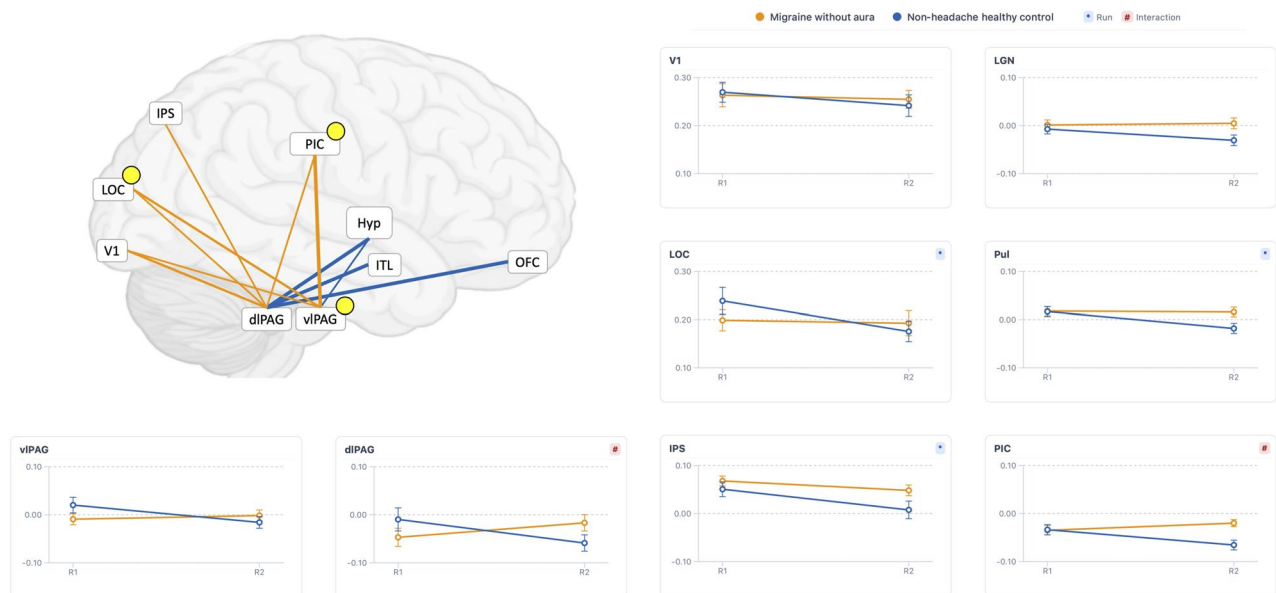


Fig. 6 Schematic illustration of the main visuospatial task-induced areas correlated with PAG activity, based on Spearman correlation analyses. The distinct association pattern in the two groups is striking. During the task, PAG activity change was mainly associated with OFC, ITL, and Hyp in the non-headache controls (blue lines). PAG activity changes across runs show correlated changes in V1, LOC, IPS, and the Posterior insula in patients with MwoA (orange lines). The top three significant associations of dlPAG and vlPAG are shown. Different line thickness reflects the strength and consistency of functional associations. Yellow circles identify ROIs in which task-induced neural activity was significantly correlated with changes in photophobia in MwoA. **Impaired repetition suppression in higher-order visual areas, insula, and PAG in Migraine.** Percent Signal Change extracted from selected regions of interest (ROI) was analyzed using a 2×2 Mixed-Design Repeated Measures ANOVA in which a two-level Run factor (Run1 vs. Run2), a two-level group factor (Migraine ($n = 30$) vs. Control ($n = 29$)), and their interaction were investigated. Post hoc comparisons were conducted using Tukey's correction to further explore significant main effects or interactions. Statistical significance was set at an adjusted $p < 0.05$. (*) used to show significant changes between runs, and (#) used to show significant interaction. **Abbreviations:** dlPAG, dorsolateral periaqueductal gray; Hyp, hypothalamus; IPS, intraparietal sulcus; ITL, inferior temporal lobe; LGN, lateral geniculate nucleus; LOC, lateral occipital complex; OFC, orbitofrontal cortex; PIC, posterior insular cortex; Pul, pulvinar; V1, primary visual cortex; vlPAG, ventrolateral periaqueductal gray

indicating that basic task comprehension and early learning were preserved in migraine. However, accuracy declined toward the end of the run in migraine, implying a deficit in sustaining performance under repeated visual load. This pattern is consistent with difficulty maintaining sustained attention under conditions that engage with sensory filtering and executive control, a domain frequently affected in migraine [2, 30]. Importantly, photophobia and discomfort were higher in migraine at the end of the task without concomitant headache escalation, suggesting that repeated exposure to aversive visuospatial input can elicit interictal sensory distress and performance costs even in the absence of an acute attack [31, 32].

Network-level hyperactivation during complex visual processing

At the whole-brain level, both tasks robustly engaged visual, dorsal attention, salience/interoceptive, and motor-control networks, demonstrating effective task manipulation. Expected activation of visual cortices was accompanied by dorsal attention regions (e.g., SPL/IPS and parietal association cortex) and frontal executive areas (dlPFC/APFC), consistent with target monitoring

and stimulus-driven attentional shifts. The engagement of the premotor cortex, SMA, and cerebellum likely reflects visuomotor coordination and response preparation.

Critically, direct group contrasts revealed widespread Migraine > Control activation encompassing frontoparietal, temporal, and limbic regions, including angular and supramarginal gyrus, dlPFC, ACC, insula, and amygdala, with no regions showing the reverse contrast. Given broadly similar early behavioral performance, this pattern is most consistent with increased neural recruitment for sensory regulation and control rather than simply greater task difficulty [18]. Such distributed hyperactivation is consistent with prior reports of visual hypersensitivity and heightened salience processing in migraine, supporting that interictal hyper-responsivity can be detected outside the attack period [4, 33]. It also aligns with the literature, which emphasizes the hyperactivation of extrastriate and higher-order visual areas during visually provocative patterns, such as stripes or checkerboards [20, 34]. Notably, posterior insula involvement is compatible with its central role in coding aversive bodily states and nociceptive salience, providing a plausible interface through which visual stress is translated into discomfort [35].

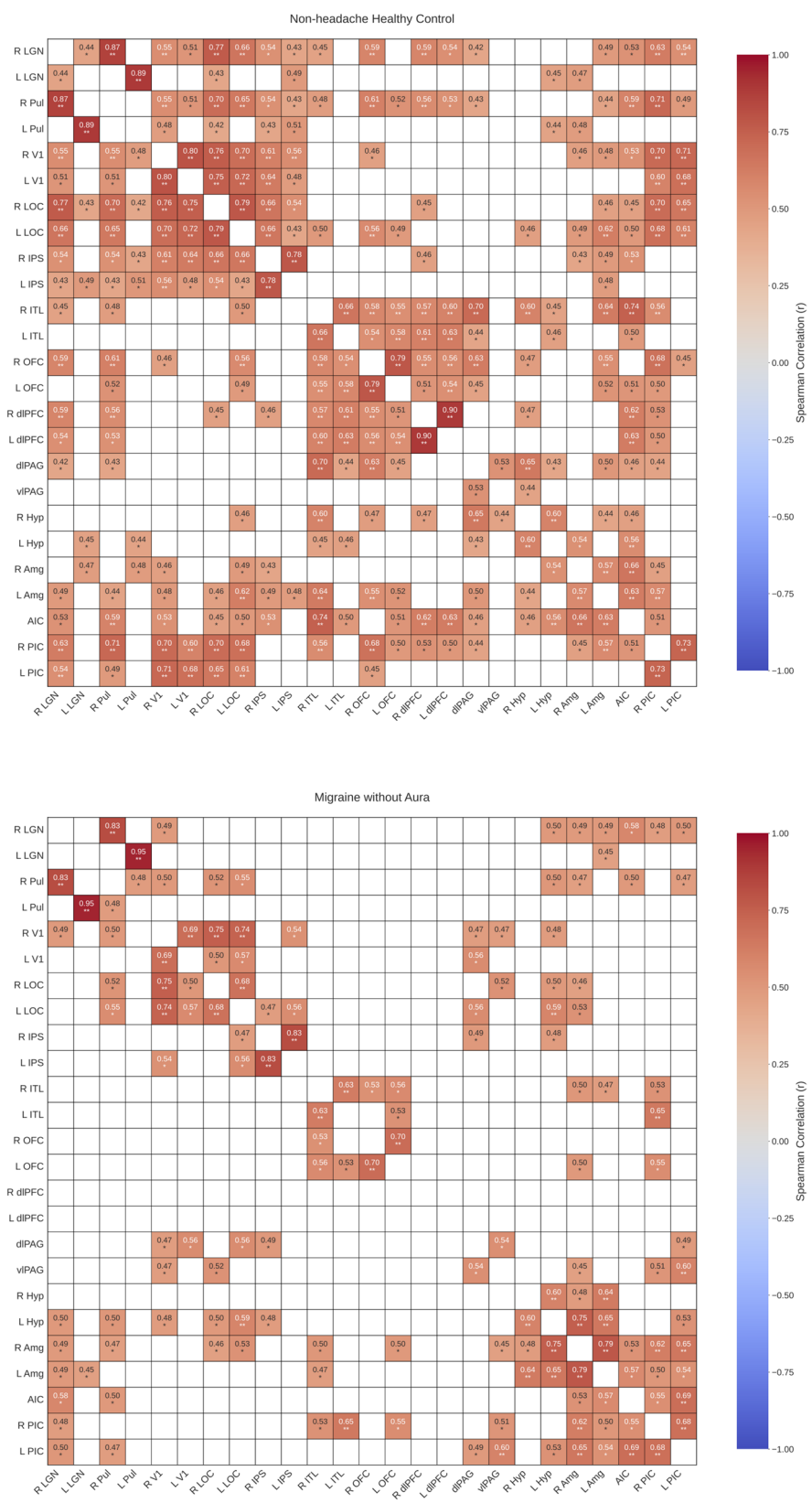


Fig. 7 (See legend on next page.)

(See figure on previous page.)

Fig. 7 Heatmaps reveal a significant decrease in the number of regions correlated with the activation of visual areas and the OFC, as well as a shift in PAG activation coupling from the OFC to the visual cortex in patients with migraine without aura. The matrices display Spearman's rank correlation coefficients (r) between the inter-run change in BOLD signal ($\Delta\text{BOLD} = \text{Run 2} - \text{Run 1}$). Warmer colors (red) indicate stronger positive correlations, while cooler colors (blue) indicate negative correlations. Heatmaps display only statistically significant correlations; non-significant cells are masked and rendered in white to improve visual interpretability. $n(\text{Migraine}) = 30$, $n(\text{Control}) = 29$. Spearman analysis was conducted. **Abbreviations:** AIC, anterior insular cortex; Amg, amygdala; dlPAG, dorsolateral periaqueductal gray; dlPFC, dorsolateral prefrontal cortex; Hyp, hypothalamus; IPS, intraparietal sulcus; ITL, inferior temporal lobe; LGN, lateral geniculate nucleus; LOC, lateral occipital complex; OFC, orbitofrontal cortex; PIC, posterior insular cortex; Pul, pulvinar; V1, primary visual cortex; vlPAG, ventrolateral periaqueductal gray; L, left; R, right

Accordingly, PIC and OFC, PAG, LOC, and V1 can discriminate migraine patients from healthy controls with a higher weight of activity changes across two runs (Fig. 8). It may indicate BOLD changes in these ROIs during the task performance that can be used to predict migraine features. We can speculate that our task with a high cognitive and visual load unmask underlying pathophysiological dysfunction that is more prominent with repetition and can be used to develop a disease marker for migraine.

Repetition suppression: group differences in adaptive downregulation

Repetition suppression is typically interpreted as an adaptive reduction in neural response to repeated stimulation, reflecting a decrease in salience, reduced prediction error, and decreased attentional and motor demands [21]. Consistent with this, the main effect of the run revealed reduced activation from the first to the second run across motor, executive, and salience networks (premotor/SMA/cerebellum; dlPFC/APFC; insula/ACC). However, group-specific contrasts revealed an apparent dissociation: controls showed strong and spatially extensive downregulation with no regions exhibiting run-related increases, suggesting efficient habituation and clean disengagement of control and salience circuitry on repetition. Migraine participants also showed decreases in overlapping areas, indicating that some run-wise adaptation is preserved. Yet the magnitude of suppression was reduced, and localized increases emerged in dorsolateral prefrontal regions, suggesting sustained or compensatory executive engagement on repetition. This profile is consistent with impaired habituation to visually aversive input, a phenomenon frequently reported in migraine and commonly discussed in terms of altered adaptation and inhibitory balance [18].

Orbitofrontal cortex: repetition enhancement and compensatory control

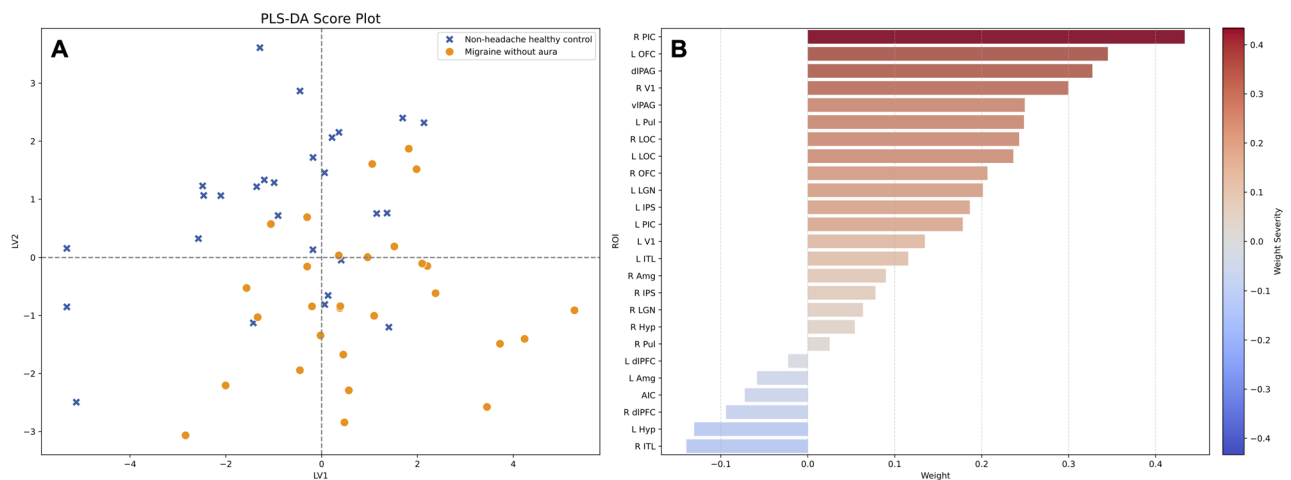
A key finding was a significant interaction between run and group in the left OFC. ROI analyses showed that OFC activation decreased across runs in controls but increased in migraine, indicating repetition enhancement rather than suppression. This divergence suggests that repeated exposure does not become “less behaviorally relevant” in migraine; instead, evaluative and control

processes may remain engaged or intensify, consistent with persistent salience attribution in interictal states.

The OFC is positioned to support multisensory integration, valuation, outcome monitoring, and predictive updating, and to modulate sensory processing through interactions with the insula/ACC, thalamus, and basal ganglia [36, 37]. In vision, the OFC has been implicated in rapid top-down facilitation during object recognition; OFC activity can arise early relative to temporal recognition regions and is thought to convey coarse predictions that bias processing in occipito-temporal cortex [38, 39]. The observed OFC enhancement with repetition in migraine is therefore compatible with altered predictive control, where repeated stimuli continue to evoke evaluative processing rather than being efficiently suppressed.

Notably, OFC BOLD changes were positively correlated with task accuracy in migraine, suggesting a compensatory role: greater OFC engagement may help sustain goal-directed behavior in the face of increasing sensory discomfort or fatigue. In controls, accuracy did not correlate with any single ROI, consistent with the idea that maintaining stable performance is more automatic and distributed in the healthy system. In migraine, sustaining performance requires stronger top-down drive, potentially reflecting reduced efficiency of downstream filtering and adaptation mechanisms.

Although repetition-related increases were interpreted within a predictive suppression framework, non-specific factors such as fatigue or increasing discomfort may also contribute to these effects. The observed behavioral decline across runs, together with the reported increase in discomfort and photophobia, raises the possibility that non-specific factors such as fatigue, affective load, or reduced task engagement may have contributed to the observed repetition-related effects, particularly in the orbitofrontal cortex. However, several observations argue against a purely global fatigue account. The enhancement effects were anatomically selective rather than diffusely distributed, prominently involving orbitofrontal and higher-order visual regions instead of showing a generalized reduction in activation. Moreover, behavioral decline was modest and did not indicate task disengagement, and the enhancement pattern was condition-specific rather than uniform across stimuli. Nonetheless, the present design does not allow complete dissociation of predictive suppression failure from fatigue-related or



affective mechanisms. Future paradigms explicitly separating perceptual repetition from task demand will be required to clarify these processes.

Higher-order visual cortex and thalamus: disrupted thalamocortical gating

Complementary ROI analyses of visual streams clarify where adaptation diverges most strongly. In the V1 and LGN, both groups showed comparable changes across runs, implying that early sensory habituation is relatively intact. However, this pattern did not generalize to higher-order visual and thalamic regions. The LOC and pulvinar both showed reduced suppression (or run-related increases) in migraine relative to controls. This convergence across OFC, LOC, and pulvinar suggests an impairment not at the level of primary encoding but rather at higher-order integration and thalamocortical gating.

The pulvinar is a major thalamic hub with widespread cortical connectivity spanning primary and secondary visual cortices, as well as temporal, prefrontal, and cingulate areas [40]. It has been implicated in coordinating visuospatial attention and context-dependent modulation [41, 42] and may contribute to selection and suppression processes via oscillatory gain control in thalamocortical circuits [43]. Reduced repetition suppression in pulvinar and LOC, therefore, supports a model in which migraine

involves deficient filtering of repeated visual input, maintaining high sensory gain and prolonging control demands across runs. A related loss of habituation in the pulvinar and insula has also been reported in migraine following repeated nociceptive trigeminal stimulation, highlighting the potential role of thalamic and trigemino-cervical pathways in modulating habituation/sensitization dynamics [44].

PAG involvement and visual-midbrain coupling: toward a cortico-midbrain mechanism

Another primary dissociation was observed in the PAG. Controls showed repetition suppression in PAG alongside cortical and thalamic ROIs, whereas migraine showed repetition enhancement, and this enhancement scaled with worse photophobia. This pattern suggests that repeated visual stress in migraine recruits midbrain modulatory circuitry, amplifying rather than dampening the response profile. Functional imaging studies have previously reported altered PAG connectivity with prefrontal and temporal regions, as well as associations with disease duration involving the vIPAG, thalamus, putamen, and OFC, supporting PAG involvement in migraine network organization [11]. OFC projections to the parvalbumin-expressing GABAergic nucleus in the hypothalamus and overlapping projections in the PAG are recognized [45]. OFC neuronal electrophysiological

recordings from OFC neurons in patients with post-stroke pain or phantom limb pain predicted chronic neuropathic pain states in humans [46].

Most strikingly, V1 activity was strongly correlated with PAG activity in migraine but not in controls. In a normative setting, early visual processing is typically embedded within visual networks and functionally segregated from midbrain pain nuclei. The observed V1-PAG coupling in migraine suggests a failure of decoupling between early sensory encoding and midbrain pain- and arousal-related systems, providing a plausible systems-level route by which visual inputs gain immediate access to nociceptive-modulatory circuitry. In this framework, high-contrast or perceptually loaded stimuli may bypass higher-level filtering and engage autonomic/aversive response programs via PAG coupling, contributing to photophobia and discomfort even interictally.

Cortical ROIs include early and higher-order visual regions (V1, LOC), dorsal attention areas (IPS), salience/interoceptive regions (posterior and anterior insula), and executive-control regions (orbitofrontal cortex, inferior temporal lobe). Subcortical and midbrain ROIs include the pulvinar, hypothalamus, and periaqueductal gray, highlighting pathways that support sensory modulation and affective–autonomic integration. Correlated activations in the ventral and dorsal visual streams, as well as the OFC, are altered in the presence of PAG in migraine. Photophobia is correlated with vl-PAG, LOC, and posterior insular BOLD activity change in migraine. Aberrant visuospatial processing in MwoA involves OFC, higher-order cortical and thalamic visual areas, and PAG.

Energetic and inhibitory constraints: sustained recruitment and metabolic demand

The combination of widespread hyperactivation, reduced repetition suppression in higher-order sensory-thalamic-prefrontal circuitry, and compensatory OFC engagement is consistent with a state of reduced processing efficiency under repeated visual demand. One mechanistic account suggests that impaired inhibitory regulation compromises adaptation, leading to the sustained recruitment of control systems and an increased energetic cost. The transition from rest to task involves disproportionate increases in glucose metabolism relative to oxygen metabolism, a phenomenon linked to positive BOLD responses and stimulation-based aerobic glycolysis [47]. BOLD changes have been linked to neuronal lactate shuttling via MCT2, indicating a metabolic coupling between neural activity and lactate dynamics during sensory activation [48]. From this perspective, repeated visually aversive stimulation in migraine may impose higher metabolic requirements, particularly if inhibitory circuitry fails to reduce prediction error and sensory gain across repetitions.

This interpretation is consistent with models linking gamma-band activity and fast-spiking parvalbumin-positive interneurons to high energetic demand [47, 49]. Also, thalamocortical gating structures, such as the TRN, can influence sensory filtering via inhibitory mechanisms [8]. While our data do not directly measure metabolism or inhibitory neurotransmission, the late accuracy decline, the positive correlation between accuracy slope and OFC activation, repetition enhancement in the OFC, and persistent evaluative/salient network recruitment are compatible with an efficiency constraint that emerges under repeated load.

Broader sensory dysfunction and implications

Our results align with a broader literature that frames migraine as a disorder of central sensory processing and multisensory integration, with prominent involvement of the visual pathways [50–53]. Deficits in visual temporal discrimination and multisensory integration implicate higher-order thalamic and cortical hubs, supporting a network-level account of sensory dysregulation. Within this context, diminished repetition suppression, also reported in autistic traits [54], may reflect partially shared constraints on predictive suppression and sensory filtering, which is of potential relevance given the higher rates of autistic traits reported in migraine [55].

Overall, the present findings suggest that interictal MwoA is characterized by (i) distributed hyperactivation of visual–attention–salience–control networks during ecologically valid visual stress, (ii) reduced repetition suppression in higher-order visual cortex and thalamus with preserved early visual adaptation, (iii) repetition enhancement in OFC and PAG, consistent with persistent salience evaluation and altered modulatory signaling, and (iv) abnormal coupling between early visual cortex and PAG, providing a candidate circuit mechanism linking visual input to aversive midbrain responses. These results advance a systems neuroscience account in which visual hypersensitivity in migraine arises from disrupted coordination among thalamocortical gating, prefrontal evaluative control, and midbrain modulation, rather than from a single locus of cortical hyperexcitability. This network-level adaptation framework is schematically illustrated in Fig. 9.

Methodological strengths: homogeneity, interictal state, and ecological validity

Several design features strengthen the interpretability of the neural findings. Rigorous clinical ascertainment and exclusion criteria resulted in a highly homogeneous migraine sample, diagnosed by neurologists using established criteria, thereby reducing heterogeneity in symptom profiles and diagnostic ambiguity. Testing was conducted in a headache-free interictal state with

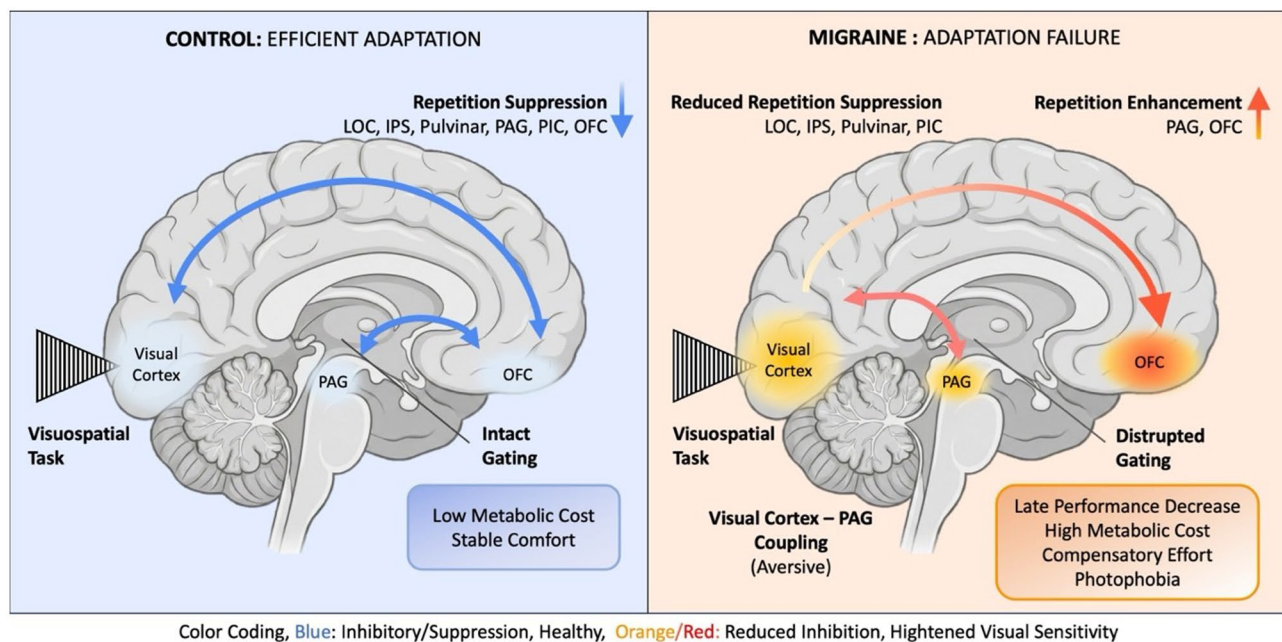


Fig. 9 Infographic summary of the key findings of non-headache healthy controls and patients with migraine without aura in response to a complex visuospatial attention task. Abbreviations: IPS, intraparietal sulcus; LOC, lateral occipital complex; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PIC, posterior insular cortex

no medication use, limiting confounds related to acute pain, analgesics, or attack-related physiological fluctuations. Importantly, none of the participants were receiving prophylactic treatment (e.g., beta-blockers, SNRIs, or antiepileptic medications) at the time of scanning. These medications are known to influence neural adaptation processes, modulate prefrontal functions such as decision-making, and alter sensory sensitivity. To minimize these potential confounding effects, only medication-free participants were included in the present study. Their absence reduces pharmacological confounding and strengthens the interpretation that the observed repetition-related alterations reflect intrinsic network characteristics of migraine rather than medication effects. Parallel symptom sampling (VAS pain and photophobia ratings pre- and post-task) provided an internal check that participants remained outside attack-level intensity and that light sensitivity did not escalate markedly during scanning. These procedures support the interpretation that the observed neural differences reflect trait-like alterations in sensory regulation rather than transient ictal effects.

The paradigm was also designed for ecological validity. The high-contrast striped stimulus models common real-world triggers (e.g., blinds, curtains, patterned surfaces). At the same time, the crowded geometric array introduces perceptual load and decision demands reminiscent of those in visually complex environments, such as supermarket aisles. By combining visually aversive features with sustained attentional demands, the task probes the

conditions under which migraine patients often report overload in daily life, providing a bridge between laboratory measures and clinical phenomenology.

Limitations

First, although we observed systematic covariation of BOLD signals across cortical, thalamic, and midbrain regions, the analyses were intentionally restricted to activation and adaptation-based measures. As such, the study cannot make formal inferences about the connectivity of areas, and terms such as coupling or correlation should be interpreted descriptively. Future work using functional and effective connectivity approaches could test explicit hypotheses about changes within the visual-midbrain circuitry implicated in this study. Although we discuss the potential metabolic implications of sustained BOLD activation, fMRI provides only an indirect hemodynamic measure of neuronal energetics and lacks the temporal resolution to capture rapid oscillatory dynamics implicated in sensory gating. The pattern of sustained recruitment and reduced repetition suppression is consistent with altered metabolic demand and inhibitory regulation, but no direct measures of neurochemistry or metabolism were obtained. Multimodal studies incorporating magnetic resonance spectroscopy are necessary to directly link BOLD dynamics to metabolic explanations. Lastly, the sample consisted exclusively of women, reflecting the higher prevalence of migraine in females and facilitating clinical homogeneity, but limiting generalizability to male patients. Given known sex-related

differences in migraine prevalence, sensory hypersensitivity, and neurobiology, the present findings primarily reflect female migraine populations.

Conclusion

In summary, interictal migraine without aura is characterized by impaired higher-order visual processing in response to repeated stimuli. Migraine patients showed widespread hyperactivation, reduced repetition suppression across visual, prefrontal, and thalamic systems, and repetition enhancement in the orbitofrontal cortex and PAG. Abnormal V1-PAG correlation suggests repeated visuals are engaged as aversive stimuli even at earlier visual stages. Our findings demonstrate that a failure of repetition suppression in higher-order nodes of visual processing, along with the functions of evaluation and valence, and the maladaptive recruitment of the PAG, could reinforce visual hypersensitivity in migraine without aura. Rather than a localized deficit in early visual processing, this altered neural dynamic reflects a systems-level disruption in top-down sensory regulation and midbrain–cortical coupling, leading to sustained metabolic demand and inefficient filtering of repetitive stimuli. These findings support a network-level account in which visual hypersensitivity arises from disrupted adaptive downregulation and midbrain engagement, rather than from cortical hyperexcitability.

Abbreviations

ACC	Anterior cingulate cortex
AIC	Anterior insular cortex
ANOVA	Analysis of variance
APFC	Anterior prefrontal cortex
BOLD	Blood-oxygen-level-dependent
dIPAG	Dorsolateral periaqueductal gray
dIPFC	Dorsolateral prefrontal cortex
FDR	False discovery rate
FOV	Field of view
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
IPS	Intraparietal sulcus
ITL	Inferior temporal lobe
LGN	Lateral geniculate nucleus
LOC	Lateral occipital complex
LV	Latent variable
MAGNETOM Prisma	Siemens MAGNETOM Prisma MRI system
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MwoA	Migraine without aura
OFC	Orbitofrontal cortex
PAG	Periaqueductal gray
PCC	Posterior cingulate cortex
PIC	Posterior insular cortex
PLS-DA	Partial least squares discriminant analysis
Pul	Pulvinar
ROI	Region of interest
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SPM	Statistical Parametric Mapping
SPL	Superior parietal lobule
STG	Superior temporal gyrus
TE	Echo time

TR
VAS
V1
vIPAG

Repetition time
Visual analog scale
Primary visual cortex
Ventrolateral periaqueductal gray

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s10194-026-02327-w>.

Supplementary Material 1

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Author contributions

HB, DV and SU designed the study. ZCO, HK, MCA, DV collected the data. IG, SU, MC, SA, and HB analyzed the data. ZCO, SU, IG and HB wrote the manuscript. All authors reviewed, contributed to, and edited the final draft. All authors approved the final version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Gazi University Clinical Research Ethics Committee (decision date: 19 December 2022). All procedures were conducted in accordance with the Declaration of Helsinki and relevant national and institutional ethical guidelines. Written informed consent was obtained from all participants prior to participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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