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Received: 7 March 2026

Accepted: 28 May 2026

Published online: 03 June 2026

Cite this article as: Ince M.S., Guzel I., Akgor M.C. *et al.* Kinematic analysis of multisensory integration and sensory load induced fatigue in migraine. *Sci Rep* (2026). <https://doi.org/10.1038/s41598-026-55972-1>

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Kinematic Analysis of Multisensory Integration and Sensory Load Induced Processing Fatigue in Migraine

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Acknowledgement: The authors thank the Neuroscience and Neurotechnology Center of Excellence (NÖROM) for providing data access and technical support. The study was partially supported by TÜBA.

Abstract

Individuals with migraine frequently experience performance deterioration during repetitive sensory tasks. This study aimed to investigate the

behavioral and temporal dynamics of this deterioration under multisensory load. We analyzed sensory profile assessment and kinematic data during a continuous sensorimotor tracking task with sequentially added visual, auditory, semantic-numeric, and somatosensory stimuli from 36 female participants (15 interictal migraine without aura (MwoA), mean age 21.6 ± 3.36 years; 21 healthy controls, mean age 20.81 ± 0.93 years). Kinematic data were analyzed using linear mixed-effects models, focusing on tracking error and temporal lag. During the unimodal visual baseline, sensorimotor skill acquisition was intact without any temporal lag in the MwoA group. Adding sensory cues reduced tracking error in the healthy group, indicating facilitated multisensory integration, while no change was observed in the MwoA group. Addition of sensory cues triggered a progressive phase lag; the final addition of continuous somatosensory input resulted in a significant temporal delay in the MwoA group. Cumulative temporal delay positively correlated with the patients' sensory sensitivity score. Collectively, these findings indicate that the interictal migraine brain struggles to temporally align and integrate complex, cross-modal information, suggesting a critical vulnerability to processing fatigue under continuous environmental load.

Keywords: Migraine without aura, Multisensory integration, Fatigue, Sensory overload, Sensorimotor control, Phase lag.

INTRODUCTION

Current perspectives in neuroscience conceptualize migraine not merely as an episodic headache syndrome, but as a complex brain network disorder [1]. A hallmark of this network-level dysfunction is altered processing of sensory information, manifested as pronounced hypersensitivity to visual, auditory, and somatosensory stimuli even during the symptom-free interictal phase [2,3]. Sensory processing disturbances affect temporal processing and multisensory integration across multiple domains. Patients exhibit prolonged temporal discrimination thresholds across both visual and somatosensory domains, indicating a reduced capacity to efficiently process successive

stimuli [4-6]. Furthermore, these widespread sensory deficits directly impair motor execution, with atypical short-latency afferent inhibition responses indicating a fundamental dysfunction in sensorimotor integration [7]. Crucially, this multisensory vulnerability persists interictally. Consecutive multisensory load during virtual gaming reduced performance in patients with migraine without aura [8].

In healthy individuals, repeated exposure to non-noxious sensory input typically results in repetition suppression. Conversely, individuals with migraine exhibit a fundamental and well-documented failure of this adaptation mechanism, and repetition enhancement is demonstrated by an fMRI study. Consequently, the migraine brain processes repetitive or continuous stimuli with high salience [9]. This inability to efficiently filter out irrelevant sensory "noise" imposes a sustained and cumulative neural load on thalamocortical networks, keeping them in a state of chronic hyperexcitability and dysrhythmia [10,11], and effectively acting as a continuous processing demand that leaves the interictal brain susceptible to processing fatigue [12]. Such repetition suppression failure reflects a broader disruption in top-down sensory regulation, contributing to the sustained neural load that renders the interictal brain susceptible to processing fatigue [9,13]. In neurotypical populations, multisensory integration serves as a powerful facilitatory mechanism. It enhances perceptual clarity, accelerates reaction times, and fundamentally optimizes the acquisition and execution of new sensorimotor skills [14,15]. However, for the migraine brain, this normally advantageous process can transform into a substantial cognitive load. Due to the underlying thalamic dysregulation and impaired sensory gating, the simultaneous influx of multisensory information brings the system toward its processing limits [16]. As environmental sensory load increases, the neural networks that integrate these varied inputs become saturated, leading to sensory overload. Recent electrophysiological and neuroimaging evidence strongly corroborates this vulnerability. During the interictal phase,

individuals with migraine without aura (MwoA) exhibit disrupted functional connectivity within thalamocortical and sensorimotor networks [17], alongside structural alterations in temporo-parietal multisensory regions [18]. Consequently, rather than facilitating performance, the convergence of cross-modal stimuli paradoxically heightens cortical sensitivity [19,20]. This global multisensory integration dysfunction implies that, as concurrent sensory loads accumulate, the limited thalamocortical capacity becomes overwhelmed, leading to a significant degradation in behavioral performance relative to unimodal processing [8].

The interictal migraine brain is recognized as operating under a state of cerebral energy deficit, driven by thalamocortical dysrhythmia and chronic cortical hyperresponsivity [21-24]. This elevated baseline metabolic demand, evidenced by reduced interictal ATP content relative to healthy individuals, may leave neural resources particularly vulnerable to depletion under sustained sensory loading [25,26]. We hypothesize that, in migraine, the metabolic cost of managing continuous multisensory inputs depletes already compromised neural resources required for sustained higher-order cognitive and motor control. Therefore, when individuals with migraine are forced to engage in a continuous, complex task, their primary challenge is not the initial acquisition of the skill (neuroplasticity), but rather the sustainability of their performance over time. Suppressing innate protective behaviors, such as sensory avoidance, to comply with task demands likely accelerates this neural exhaustion, leading to a rapid cycle of progressive cortical fatigue and a premature decline in performance. We propose the term “sustainability failure” as a theoretical framework to describe this hypothesized cycle, which we aimed to operationalize and test in the present study.

Despite the common sensory abnormalities in migraine, previous behavioral studies investigating sensorimotor performance have predominantly relied on static outcome metrics, such as overall error rates or binary

success/failure thresholds [8,27]. By evaluating performance solely based on spatial endpoint accuracy, these approaches inherently overlook the temporal dynamics, and the hidden processing demands of continuous task execution. Recent neuroimaging and metabolic profiling studies indicate that altered motor control during the interictal phase reflects a broader, energy-driven dysfunction of sensorimotor networks rather than a fundamental execution deficit. Specifically, individuals with migraine exhibit disrupted resting-state functional connectivity between the primary sensorimotor cortices, the thalamus, and cerebellar regions [17]. Furthermore, the aforementioned chronic cerebral energy deficiency, characterized by significantly reduced ATP levels [12,28], directly compromises the highly energy-dependent neural networks required for sustaining continuous motor tasks [24,29].

In cognitive neuroscience, the speed-accuracy trade-off (SAT) describes the fundamental behavioral mechanism by which the brain sacrifices response speed to maintain precision under cognitive load. Recent evidence indicates that this SAT regulation is altered in migraine. Driven by thalamocortical dysrhythmia and diminished intrinsic connectivity within the central executive network [30,31], the migraine brain struggles to adjust motor response thresholds dynamically. Consequently, when confronted with simultaneous multisensory demands, patients exhibit altered sensorimotor integration and must fundamentally shift their temporal processing strategies to avoid critical errors [7,20]. To accurately capture the neural burden of sensory processing, it is essential to decouple the spatial accuracy of a motor skill from its temporal execution. Advanced kinematic signal processing, such as phase locking (the ability to accurately replicate a target's spatial pattern) and phase lag (the processing delay required to execute that pattern), provides a precise measure of the trade-offs the brain makes as load accumulates.

To address this critical gap in the literature, the present study investigated the temporal and performance-based costs of progressively increasing multisensory and cognitive load (visual, auditory, semantic-numeric, and somatosensory) during a continuous, 12-trial visuomotor tracking task in women with MwoA. An all-female cohort was intentionally selected to control for sex-specific differences in sensory processing and cortical excitability, given the substantially higher prevalence of migraine in women. We used Linear Mixed-Effects (LME) modeling of tracking error, along with dynamic signal analyses (specifically phase locking and phase lag) of raw kinematic data. We propose a novel conceptual framework and hypothesized that the continuous integration of accumulating multisensory and cognitive loads would disproportionately deplete the processing reserves of the migraine brain, forcing a compensatory processing delay to maintain spatial accuracy. We further hypothesized that this susceptibility to processing fatigue, termed 'sustainability failure', would be clinically associated with the patients' sensory profiles.

RESULTS

Data Integrity and Artifact Rejection

Following Z-score standardization ($Z > 3.0$) for artifact rejection, no participants were excluded from the analysis. At the block level, only one phase lag block (0.56%) was removed in the migraine group. In the healthy control group, five global tracking error (GTE) blocks (1.98%) and five phase lag blocks (1.98%) were removed. Data retention exceeded 98% across all block-level metrics, ensuring a robust dataset.

Baseline Capacity and Early Skill Acquisition

The final analytical cohort comprised 36 female participants: 15 with MwoA (mean age = 21.6 ± 3.36 years) and 21 healthy controls (mean age = 20.81

± 0.93 years). There was no significant difference in age between the two groups ($p = 0.265$), confirming a successfully age-matched baseline for the subsequent kinematic assessments. To evaluate baseline visuomotor capacity without multisensory interference, a LME model was applied exclusively to the Visual block (Trials 1-3). Both groups successfully reduced their tracking errors, indicated by a significant main effect of Trial ($\beta = -0.099$, $SE = 0.028$, $t(103) = -3.54$, $p < 0.001$). There was no significant main effect of Group ($\beta = 0.177$, $SE = 0.147$, $t(103) = 1.20$, $p = 0.232$) and no significant Group $\times$ Trial interaction ($\beta = 0.003$, $SE = 0.043$, $t(103) = 0.088$, $p = 0.929$). These results confirm that the initial visuomotor tracking capacity and early skill-acquisition trajectories were statistically equivalent across groups (Figure 1).

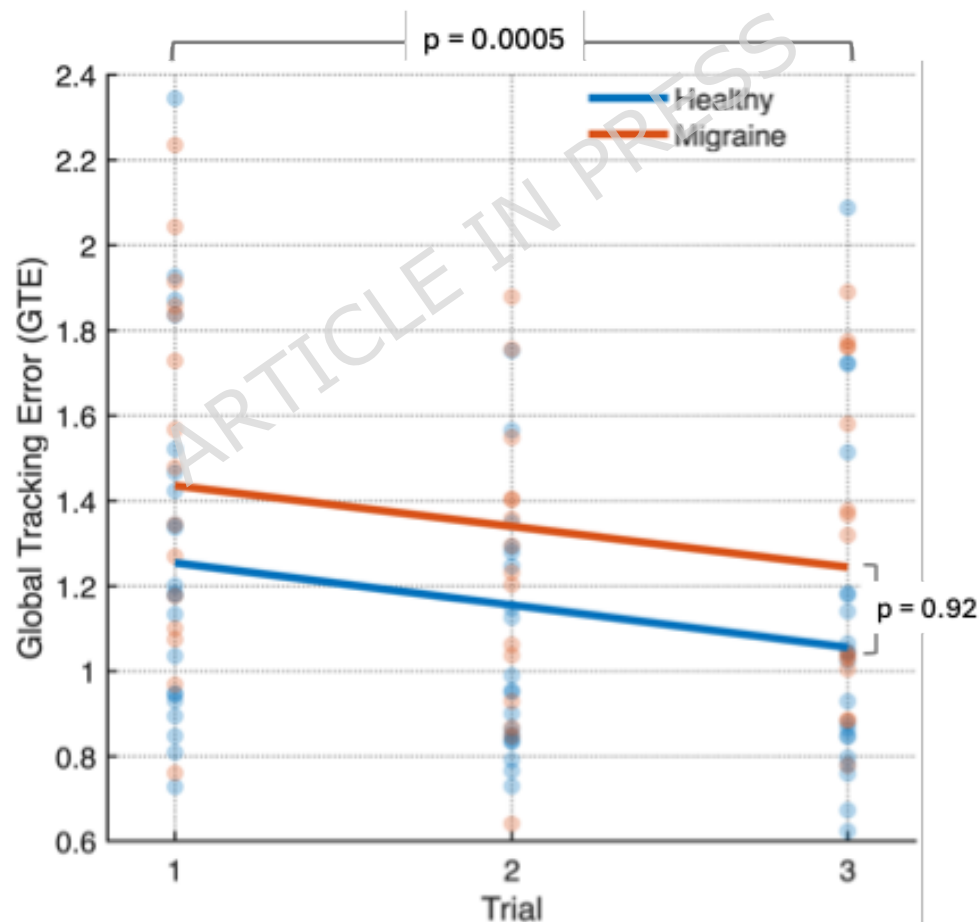


Figure 1. GTE trajectories during the initial unimodal Visual block. The scatter plot illustrates the Global Tracking Error (GTE) across Trials 1–

3. Individual data points (transparent markers) represent the single-trial tracking errors for healthy controls (blue) and individuals with MwoA (orange). Solid lines depict the performance trajectories modeled via LME analysis. The overarching horizontal bracket indicates that both cohorts demonstrated a significant reduction in GTE over time (main effect of Trial, $p = 0.0005$). The vertical bracket indicates that there is no significant difference in tracking performance between the groups ($p = 0.92$).

Behavioral Divergence Under Continuous Multisensory Load

When analyzed across the entire continuous tracking task (Trials 1-12), the LME model revealed a significant main effect of Trial ($\beta = -0.012$, $SE = 0.003$, $t(423) = -3.15$, $p = 0.0017$). Furthermore, a significant Group $\times$ Trial interaction was observed ($\beta = 0.014$, $SE = 0.006$, $t(423) = 2.42$, $p = 0.0158$). This significant interaction indicates a progressive behavioral divergence over time under accumulating task demands. Specifically, while the healthy control group demonstrated continuous adaptation and reduction in tracking error (maintaining a negative slope), the migraine group did not show equivalent performance improvement under progressive task demands. Mathematically, the net performance slope of the migraine group plateaued ($\beta_{net} \approx +0.002$), indicating a stagnation in kinematic accuracy optimization as task demands accumulated (Figure 2).

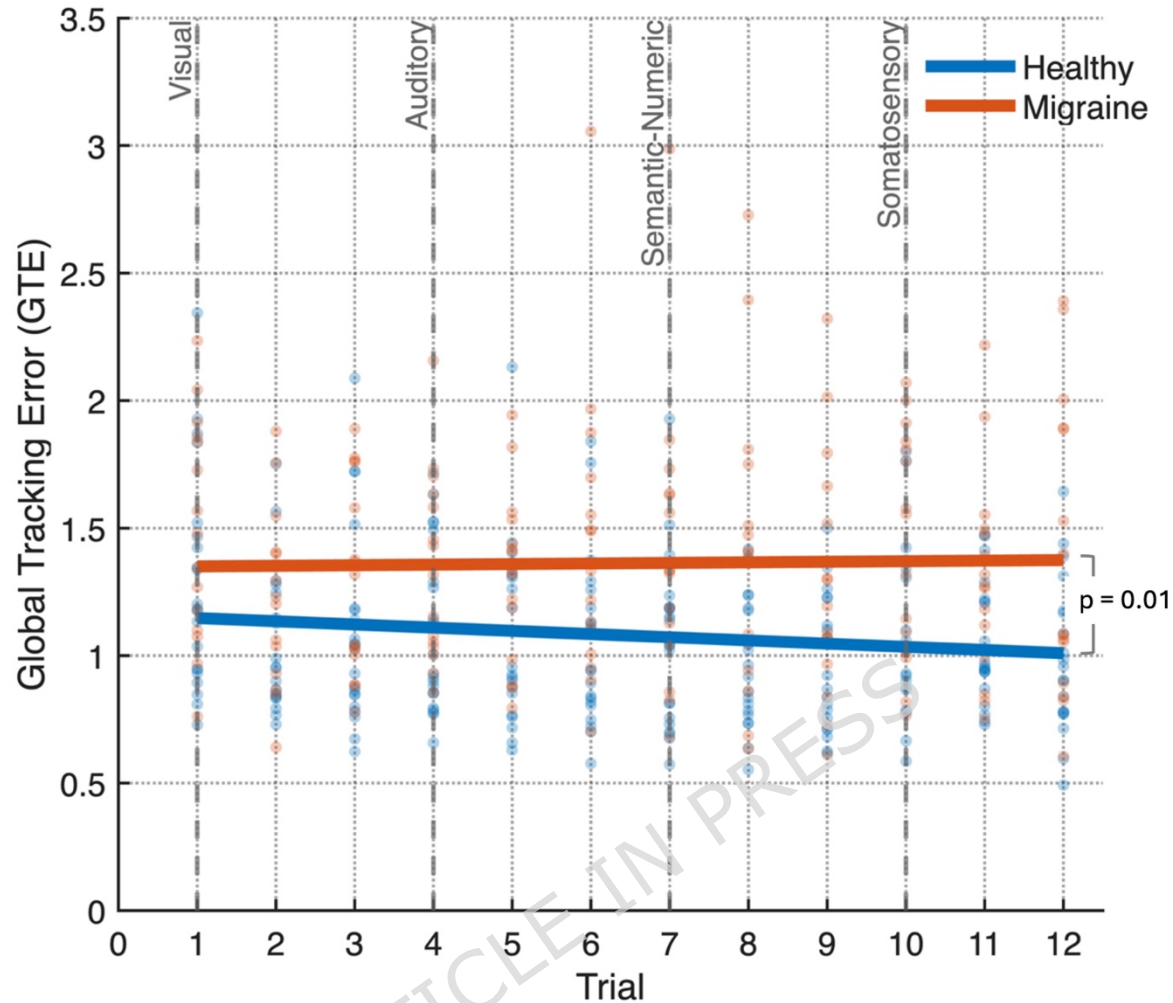


Figure 2. GTE across 12 consecutive trials of the continuous tracking task. The scatter plot visualizes the GTE under progressive sensory and cognitive loading for healthy controls (blue) and individuals with migraine without aura (orange). Individual transparent markers represent single-trial error scores per participant, while solid lines illustrate the overall performance trajectories modeled via LME analysis. Vertical dashed lines denote the sequential addition of cues to the unimodal visual baseline (Trials 1-3): Auditory (Trials 4-6), Semantic-Numeric (Trials 7-9), and Somatosensory (Trials 10-12). LME analysis indicates a significant Group $\times$ Trial interaction ($p = 0.0158$), reflecting differing GTE trajectories across task blocks between the cohorts. The LME models a single continuous trend

across all 12 trials, smoothing the initial rapid drop to reflect long-term performance sustainability.

Kinematic Phase Dynamics

Phase lag and phase locking values (PLV) were compared across the four experimental blocks using independent-samples t-tests, with p-values adjusted using the False Discovery Rate (FDR) procedure (p-adj).

In the unimodal Visual block, phase lag did not significantly differ between the migraine ($-18.47^\circ \pm 6.71^\circ$) and healthy control ($-13.85^\circ \pm 6.89^\circ$) groups ($t(34) = -2.00$, $p\text{-adj} = 0.0528$). A significant temporal delay emerged in the migraine group upon the introduction of the Auditory load ($-18.07^\circ \pm 5.23^\circ$ vs. $-12.51^\circ \pm 5.98^\circ$; $t(34) = -2.89$, $p\text{-adj} = 0.0132$, $d = 0.98$) and persisted during the Semantic-Numeric block ($-17.42^\circ \pm 7.64^\circ$ vs. $-12.13^\circ \pm 5.62^\circ$; $t(34) = -2.39$, $p\text{-adj} = 0.0297$, $d = 0.81$). The maximum absolute phase lag difference was observed during the Somatosensory block, with the migraine group exhibiting a delay of $-21.77^\circ \pm 8.55^\circ$ compared to $-14.07^\circ \pm 4.64^\circ$ in the healthy controls ($t(34) = -3.48$, $p\text{-adj} = 0.0055$, $d = 1.18$).

Despite the significant deviations in absolute phase lag, the temporal stability of the synchronization, measured by PLV, showed no statistically significant between-group differences across any of the blocks after FDR correction (all $p\text{-adj} > 0.05$) (Figure 3).

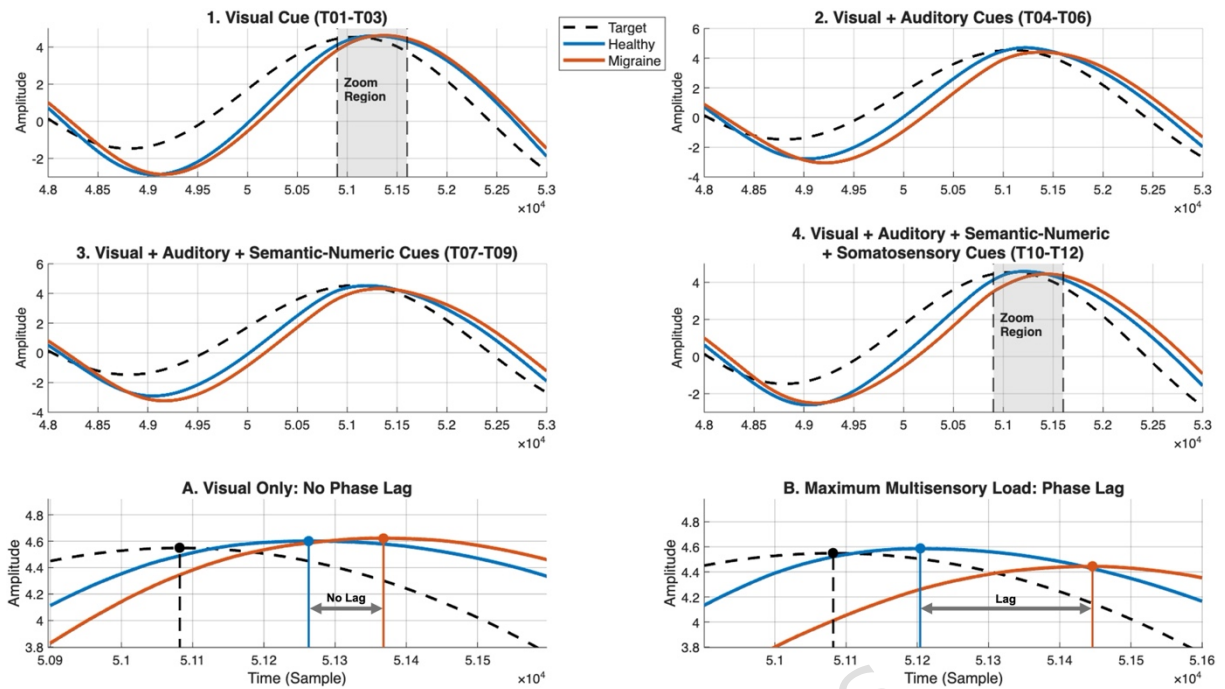


Figure 3. Kinematic waveforms and phase lag dynamics across progressive multisensory tracking conditions. Raw kinematic waveforms illustrating the temporal synchronization between the dynamic target stimulus (black dashed line) and the continuous motor execution of healthy controls (blue line) and individuals with migraine without aura (orange line). **(1-4)** The upper panels display representative macro-level tracking trajectories across the four experimental blocks: **(1)** unimodal visual baseline, **(2)** addition of auditory cues, **(3)** addition of semantic-numeric load, and **(4)** final multisensory block with somatosensory cues. **(A-B)** The lower panels provide magnified views of the shaded 'zoom regions' from panels 1 and 4, utilizing vertical stem lines at the wave peaks to illustrate the phase lag. Panel **(A)** shows the temporal delay during the unimodal visual baseline, where the phase lag in the migraine group is statistically comparable to that of healthy controls. Panel **(B)** shows the phase lag during the final multisensory block, with a significant difference between the groups (peak phase lag of -21.77° in the migraine cohort vs. -14.07° in healthy controls, $p_{\text{adj}} = 0.0055$).

Cumulative Sensory Fatigue and Clinical Correlations

The progressive temporal delay across the task blocks was measured using the CSFS. Calculated from the artifact-free kinematic phase lag magnitudes, a Mann-Whitney U test confirmed that the CSFS was significantly higher in the migraine group (median 4.21 [IQR: 1.66 - 6.86]°) compared to the healthy control group (median 1.50 [IQR: -1.65 - 3.17]°) ($U = 229.0$, $p = 0.0227$, rank-biserial $r = 0.45$). Although it is difficult to separate the effect of adding new sensory cues from general time-on-task fatigue, a higher CSFS in the migraine group shows a progressive shift in temporal synchronization under continuous load.

Within the migraine group, a Spearman rank-order correlation analysis was conducted between the individual CSFS and the Adolescent/Adult Sensory Profile (AASP) quadrants, with resulting p-values adjusted for multiple comparisons using the FDR procedure (p-adj). The analysis revealed a significant positive correlation between the CSFS and the Sensory Sensitivity quadrant ($r = 0.667$, p-adj = 0.028). No significant correlations were observed between the CSFS and low registration ($r = 0.119$, p-adj > 0.05), sensation seeking ($r = -0.137$, p-adj > 0.05), or sensation avoiding ($r = 0.395$, p-adj > 0.05). (Figure 4).

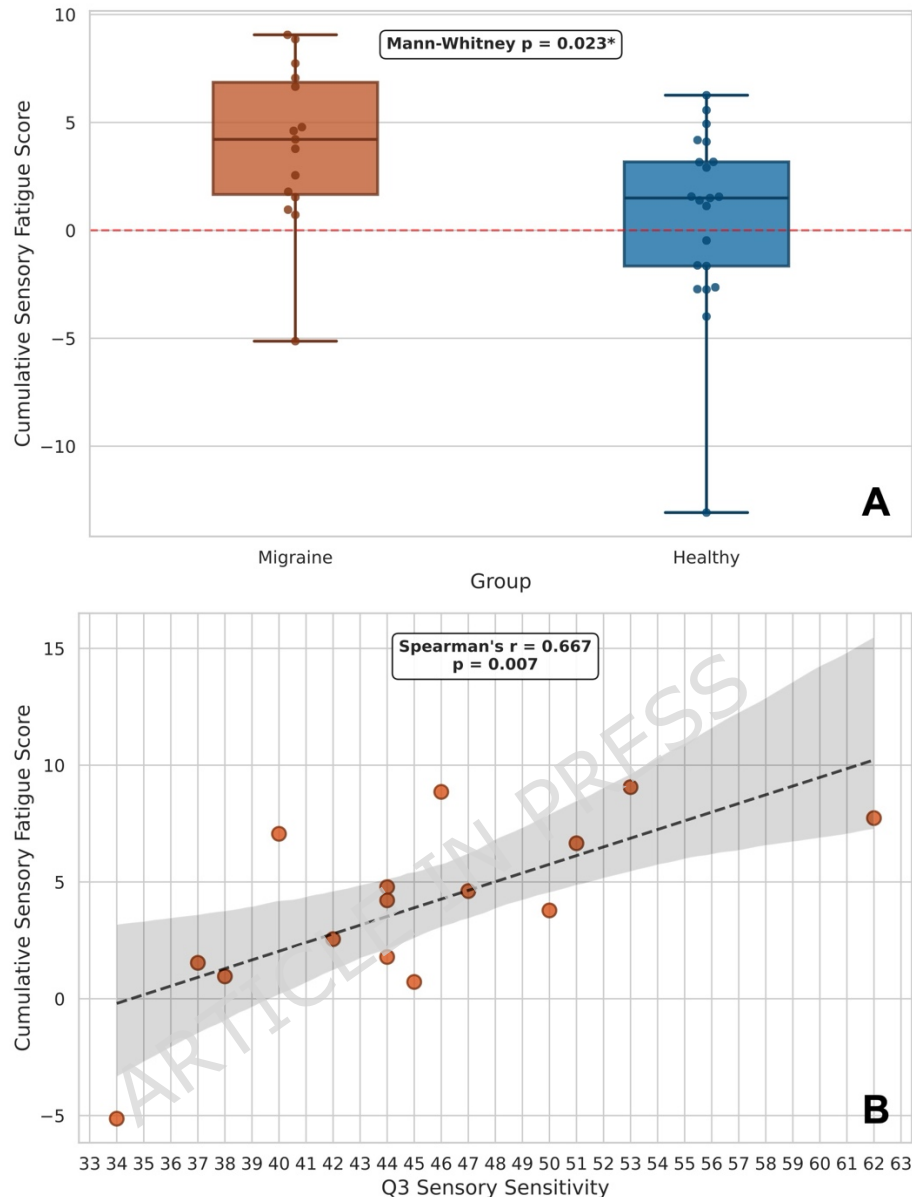


Figure 4. CSFS and its correlation with clinical sensory sensitivity. (A) Box plot comparing the CSFS between individuals with MwoA (orange) and healthy controls (blue). The CSFS is significantly higher in the migraine cohort compared to healthy controls ($U = 229.0$, $p = 0.023$, Mann-Whitney U test). The boxes represent the interquartile range (IQR, 25th to 75th percentiles), with the solid horizontal line inside indicating the median. The vertical lines extend to the minimum and maximum data points, illustrating the full range of the distribution, while individual data points are overlaid on

the plots. The horizontal red dashed line marks the zero-fatigue baseline. **(B)** Scatter plot illustrating the relationship between the CSFS and sensory sensitivity scores within the migraine group. A significant positive correlation is observed between the CSFS and Sensory Sensitivity scores (Q3 of the AASP) (Spearman's $r = 0.667$, $p = 0.007$). The dashed black line represents the linear trend, and the shaded gray area indicates the 95% confidence interval.

DISCUSSION

The present study provides a novel mechanistic framework for understanding the performance deterioration observed in individuals with episodic migraine without aura during continuous, demanding tasks. By decoupling spatial execution from temporal processing through dynamic kinematic analyses, our findings reveal that the continuous influx of task-related multisensory loads is associated with a progressive divergence in kinematic performance trajectories. This cumulative behavioral divergence may reflect underlying neural fatigue, and ultimately a processing limit [1,3]. Under escalating sensory and cognitive load, the migraine brain is forced into a compensatory state, sacrificing processing speed to maintain spatial accuracy. This processing limit precipitates a behavioral performance decline (sustainability failure) that is directly tied to patients' sensory sensitivity.

This perspective is explicitly supported by our initial baseline analyses, which demonstrate intact fundamental sensorimotor execution. During the continuous visuomotor tracking task's unimodal baseline, which relied exclusively on visual cues, there was no statistical difference in Global Tracking Error (GTE) or phase lag between the migraine group and healthy controls. The lack of a significant main effect for the migraine group in the LME models during this early stage is critical: it demonstrates the absence of a fundamental sensorimotor execution deficit at baseline. When the environment is simple and unimodal, sensorimotor skill acquisition and

execution in the migraine brain are just as effective as in a healthy brain [32,33]. In fact, under low or unimodal sensory demand, individuals with migraine can exhibit superior acquisition rates [34,35], a direct consequence of thalamocortical dysrhythmia and the resulting cortical hyperresponsivity [25,31].

However, as the task progressed and the environment became more complex, the first signs of processing fatigue emerged. When supplementary task-related sensory cues were superimposed on the visual baseline, healthy controls successfully integrated these streams to optimize performance, drastically reducing tracking errors. This phenomenon, known as "multisensory facilitation," enables a healthy neurocognitive system to reinforce the target pattern (9, 10) dynamically. In contrast, the migraine group failed to exhibit equivalent performance improvement under increasing load, a pattern consistent with impaired multisensory facilitation, stagnating at a premature performance plateau. This behavioral failure aligns with structurally compromised multisensory convergence hubs [36] and reduced brain entropy [37], both of which severely limit their capacity to dynamically reconfigure neural resources. This inability to capture multisensory facilitation marks the initial processing limit and the onset of network-level processing fatigue, resulting in a substantial discrepancy in cumulative performance improvement.

The kinematic dynamics underlying this behavioral divergence reveal a complex, progressive pattern. Upon introduction of auditory sensory load, healthy controls accelerated their motor networks, whereas migraineurs plateaued and fell significantly behind in temporal processing (phase lag). This temporal delay is consistent with psychophysical studies demonstrating abnormally broad audiovisual temporal integration windows and weakened cross-modal suppression in migraine [20,38], which overloads, rather than suppresses, thalamocortical circuits [19]. Strikingly, when the task

transitioned to include a secondary dual-task paradigm (specifically, the introduction of a semantic-numeric cognitive load via continuous on-screen performance feedback), a unique compensatory mechanism was triggered. We speculate that the migraine group may have utilized these on-screen semantic-numeric cues, potentially engaging their prefrontal cognitive networks to actively reduce their phase lag, demonstrating a theoretical top-down "catch-up" trend. This reveals a critical mechanistic dichotomy: while the superimposition of supplementary sensory cues degraded sensorimotor execution, the interpolation of a non-sensory, semantic-numeric cognitive load temporarily stabilized the network (Figure 5).

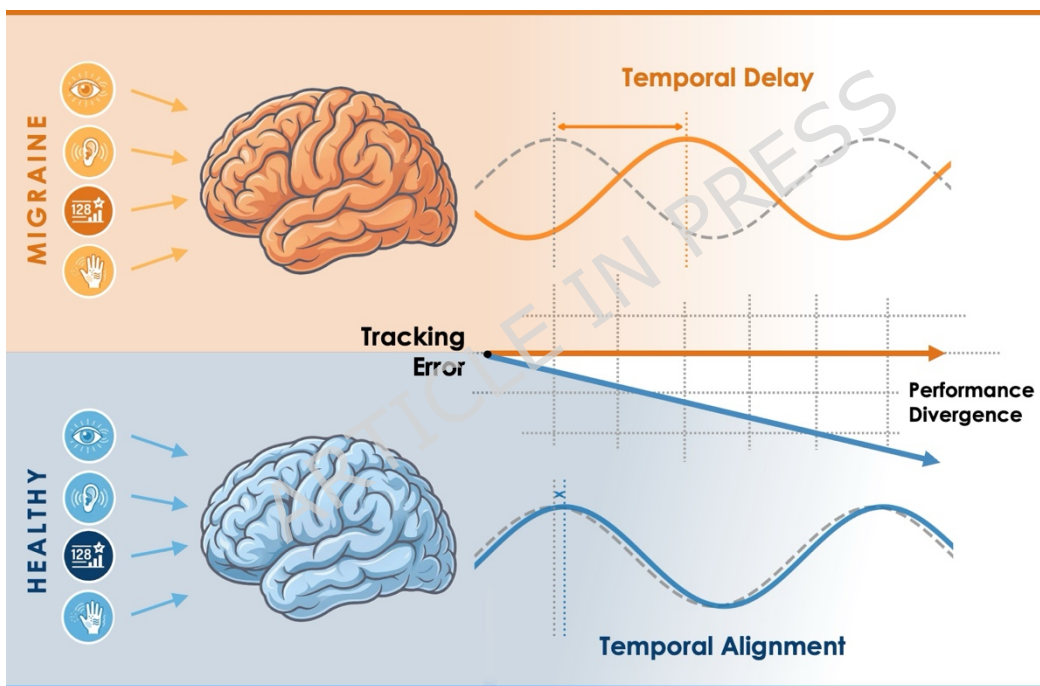


Figure 5. Illustration of temporal dynamics and performance divergence in multisensory processing. The figure summarizes the study's conceptual framework by comparing the responses of the interictal migraine brain (orange panel) and the healthy control brain (blue panel) to continuous, concurrent multisensory and cognitive inputs (icons). In migraine, the accumulation of these additive inputs leads to a marked temporal delay in the motor execution waveform (orange line) relative to the

target stimulus (dashed gray line), as indicated by “Temporal Delay”. Under identical input conditions, the healthy control waveform (blue line) remains synchronized with the target stimulus, as indicated by “Temporal Alignment”. The central section labeled “Performance Divergence” schematically depicts the differing tracking-error (GTE) trajectories between the cohorts, illustrating the progressive separation in tracking performance observed as sensory and cognitive loads are sequentially added.

However, from a fatigue perspective, this cognitive compensation is not a sustainable solution. Instead, it indicates that the brain is heavily utilizing its remaining executive reserves to overcome the underlying sensory deficit. Sustaining this effort requires the progressively increasing involvement of the prefrontal cortex, specifically the orbitofrontal cortex [39-41]. Functional neuroimaging indicates that such continuous demand forces an over-recruitment of cortical resources, leading to abnormally heightened neural synchrony across widespread cortical networks [42,43]. An already fatigued neural system may struggle to sustain such high-level attention allocation over time.

This top-down cognitive resistance appeared unsustainable, which may be attributed to the high metabolic and neurophysiological demands placed on the migraine brain. The critical shift occurred during the final block with the introduction of the somatosensory cue. This addition demanded maximum bottom-up continuous sensory influx, which overwhelmed the migraine brain's compensatory cognitive capacity, resulting in a generalized sensory overload. Under this combined multisensory and cognitive load, phase lag increased significantly in the migraine group. From a fatigue perspective, this represents the paradigm's peak processing demand. Sustaining widespread top-down hyperactivation requires a disproportionately high processing demand [12]. Prior spectroscopic and neuroimaging evidence suggests that the interictal migraine brain may operate under elevated metabolic demands,

potentially with reduced energy reserves relative to healthy controls [21,23,44,45]. The progressive phase lag escalation observed in our data under continuous sensory loading may reflect the behavioral correlate of these resource constraints. Consequently, top-down compensatory mechanisms may no longer be sustainable under such conditions, a pattern consistent with a progressive saturation of multisensory integration capacity.

The sustainability failure and progressive cortical fatigue observed in our dynamic kinematic models are reflected in the patients' sensory sensitivity traits. Our correlation analyses revealed that this objective motor-tracking failure was highly specific to individuals with elevated Sensory Sensitivity (AASP, Quadrant 3), with a strong positive correlation. Individuals with migraine continuously allocate cognitive resources to filter routine environmental stimuli. Consequently, these patients enter the laboratory setting with their processing networks already partially allocated. When subjected to continuous multisensory task loads, they reach their integration limits earlier than healthy controls, precipitating a sustainability failure. This kinematic deterioration serves as the behavioral analog to the loss of neural adaptability, directly linking sensory overload to the significant cognitive fatigue clinically reported by patients [46,47].

This proposed mechanism explains macro-level behavioral adaptations seen in daily life, most notably driving cessation or reduction. Driving is a complex, continuous task requiring concurrent visual, auditory, semantic-numeric, and somatosensory integration, which induced processing failure in our cohort. The continuous integration of spatial orientation and inertial signals is also critical; vestibular-multisensory mismatches in migraine substantially compound this environmental vulnerability [48]. Recent large-scale epidemiological data indicate that a significant proportion of individuals with migraine alter their driving habits, often reducing their driving frequency or ceasing the activity entirely [49]. These individuals do not avoid such complex

environments due to a lack of baseline motor skills; instead, their hyperexcitable thalamocortical networks reach their processing limits, leading to significant temporal delays and subsequent processing fatigue. This sensory overload is clinically reflected in the real-world coping strategies employed by drivers with migraine, who frequently report turning off the music or wearing sunglasses to reduce the continuous multimodal load deliberately [49]. Ultimately, these behavioral adaptations represent a direct, real-world manifestation of the sustainability failure observed in our cohort [50,51]. Furthermore, the underlying abnormal amplification of sensory signals is positively associated with worse clinical impact scores (e.g., MIDAS, HIT-6) and longer disease duration [49].

While this study provides a novel perspective on multisensory integration in migraine without aura, certain methodological considerations should be acknowledged. First, the sequential, non-randomized structure of the experimental blocks introduces an inherent confound between sensory condition and time-on-task effects, including general fatigue, practice, and adaptation. Changes in kinematic performance across blocks, therefore, cannot be uniquely attributed to modality-specific multisensory integration processes but rather represent the behavioral cost of continuous, cumulative sensory and cognitive loading over time. Future studies employing randomized or counterbalanced block orders, while acknowledging that such designs may not capture cumulative load dynamics, would provide stronger causal evidence for modality-specific contributions. However, evaluating data from a deliberate cumulative design was methodologically necessary to accurately capture the progressive onset of sustainability failure. Second, although our statistical models were sufficiently powered to detect significant kinematic deviations in this homogeneous, medication-free interictal cohort, future prospective studies encompassing broader demographics, such as male patients or individuals with chronic migraine, will be beneficial to determine the wider generalizability of the sustainability failure hypothesis.

In conclusion, this study fundamentally reframes the understanding of sensorimotor performance deficits in MwoA. By employing dynamic signal processing, we demonstrate that these deficits stem not from a fundamental unimodal visuomotor execution impairment, but rather from an increased susceptibility to processing fatigue under accumulating multisensory load. When sensory demands are low, patients acquire and execute complex spatial patterns as accurately as healthy controls. However, the continuous integration of multisensory inputs imposes substantial temporal and metabolic demands, triggering a progressive cycle of cortical fatigue. To maintain spatial accuracy under multisensory overload, the migraine brain sacrifices processing speed, resulting in significant phase lag. We propose that this temporal delay may act as a regulatory adaptation against sensory overload, potentially reflecting increasing kinematic processing costs that may involve limitations in top-down compensatory capacity. Ultimately, this high neural cost results in a "sustainability failure", a state of pronounced neural fatigue that limits the continuous execution of an acquired skill. These findings highlight that cognitive and motor challenges in migraine must be evaluated not merely by the capacity for sensorimotor execution, but also by cognitive endurance and, likely, the underlying metabolic capacity required to resist cortical fatigue in a demanding multisensory world. Continuous multisensory loading rapidly exhausts the migraine brain, forcing a compensatory delay in motor execution to avoid inaccuracies and inducing an inevitable progressive neural fatigue and sustainability failure.

METHODS

Study Design and Data Source

This study was designed as a retrospective, cross-sectional, and observational analysis. The dataset was obtained from the electronic archives of the Neuroscience and Neurotechnology Center of Excellence (NÖROM). The database search targeted the computerized visuomotor tracking task records

and clinical questionnaire data of female patients clinically diagnosed with episodic migraine without aura (according to the International Classification of Headache Disorders [ICHD-3] criteria) and healthy female control volunteers with no prior history of neurological, psychiatric, or chronic pain disorders. All archival data used in this study were strictly anonymized prior to extraction. The visuomotor tracking paradigm employed in this study was originally developed and validated by our group and was utilized in a prior publication [8]. However, the dataset analyzed in the current study is independent: it was assembled from additional data collection sessions conducted after that publication, using an expanded and more stringently filtered archival database. The participant cohorts do not overlap.

Participants

Primary Inclusion and A Priori Exclusion Criteria

- **Interictal Verification:** For the migraine cohort, the original data collection protocol mandated a verified interictal state. To ensure that testing did not occur during a premonitory or postdrome phase, participants were longitudinally monitored via telephone follow-ups. Any patient who reported a migraine attack within 72 hours prior to or following the kinematic assessment was directly excluded from the primary study cohort.
- **Sex-Specific Cohort and Hormonal Control:** The original dataset intentionally comprised an all-female cohort to align with the high epidemiological prevalence of migraine in women, where the female-to-male ratio is approximately 3:1 [52]. Furthermore, since fluctuations in ovarian hormones are well-known to modulate cortical excitability, pain pathways, and potentially sensorimotor integration, restricting the enrollment to a female-only cohort, while strictly excluding those in their menses or using oral contraceptives, was methodologically critical to minimize sex-driven variance and maximize sample homogeneity.

- **Medication-Free Status:** To ensure that the observed kinematic phase lag and processing delays were not confounded by medication, the archival database was constructed exclusively from medication-free patients. Individuals using prophylactic migraine medications or those who had consumed acute abortive drugs (e.g., triptans, simple analgesics) prior to testing were excluded during the primary data collection phase.

Retrospective Exclusions and Archival Data Filtering

- **Age-Matching:** To control for the potential confounding effects of age-related cognitive and motor slowing, participants whose ages deviated significantly from the young-adult target demographic (defined as 35 years of age and older) were systematically excluded from the archival dataset prior to the current analysis.
- **Headache-Free Baseline:** To preserve the behavioral baseline of the healthy control group, archival clinical survey data were thoroughly screened. Healthy control participants who scored clinically significant on the six-item Headache Impact Test (HIT-6 > 65) were excluded from the dataset due to suspicion of subclinical, undiagnosed, or tension-type recurrent headaches.

Following the implementation of these exclusion criteria, the final analyses were conducted on a final sample comprising 15 women with episodic migraine without aura and 21 healthy control women.

Experimental Paradigm: Continuous Sensorimotor Tracking Task

The behavioral and kinematic data extracted from the archives were generated using a continuous sensorimotor tracking task. During the experiment, participants were instructed to continuously track a dynamic

target stimulus moving along a vertical axis on a computer screen using a controller.

To precisely isolate the effects of multisensory integration and processing capacity, the motor task's kinematic difficulty was strictly controlled. The trajectory, speed, and overall pattern of the target stimulus remained constant across all 12 consecutive trials of the experiment. Therefore, any observed fluctuation in motor performance was attributed to the capacity to process and integrate the concurrent external stimuli, rather than an increase in primary motor demand.

While the motor difficulty was kept constant, the paradigm was designed to evaluate cortical adaptation through progressive sensory and cognitive loading. Unlike traditional sensory integration paradigms that randomize stimulus presentation to isolate modality-specific effects, the archival dataset utilized in this study was originally generated using a strictly sequential, non-randomized loading design. Analyzing data derived from this cumulative approach was methodologically essential for our objective, as it experimentally models 'sustainability failure' and simulates the continuous sensory accumulation experienced in real-world environments. No practice trials were administered prior to the experimental session. Participants received a standardized verbal explanation of the task instructions and a brief visual demonstration of the target trajectory before commencing the first trial. An initial, unimodal visual block served as a fundamental baseline to verify intact sensorimotor execution before the induction of processing fatigue. As the task progressed, task-relevant cues (intended to provide real-time performance feedback) were systematically introduced in four distinct blocks:

- **Block 1: Unimodal Visual Baseline (Sensory Cue, Trials 1-3):** A unimodal sensory block where participants tracked the target relying

exclusively on visual input. This phase established the baseline visuomotor tracking capacity.

- **Block 2: Additive Auditory Load (Sensory Cue, Trials 4-6):** A multisensory block where a continuous, task-relevant auditory signal was added to the visual input. The pitch of this tone varied dynamically and proportionally to the participant's real-time spatial distance from the target. This design ensured that the auditory cue carried ecologically valid, task-congruent information rather than serving as neutral background noise.
- **Block 3: Additive Semantic-Numeric Load (Cognitive Cue, Trials 7-9):** A cognitive cue block where a real-time numerical performance scoreboard was displayed in the upper-left corner of the screen. The score was computed continuously based on the participant's instantaneous tracking accuracy and updated at each simulation timestep, providing ongoing semantic-numeric feedback in parallel with the ongoing visuomotor and auditory streams.
- **Block 4: Additive Somatosensory Load (Sensory Cue, Trials 10-12):** The final multisensory load block incorporates vibrotactile feedback delivered through the game controller's built-in vibration motors. The vibration intensity varied continuously and proportionally to the participant's real-time deviation from the target trajectory. This somatosensory cue was spatially and temporally congruent with the task goal.

Data Pre-processing and Metric Extraction

To ensure the integrity of behavioral and kinematic signals, an artifact-rejection protocol at the data-point level was implemented before metric extraction. Transitory hardware disconnections or sudden, reflexive motor jumps were identified and filtered out using Z-score standardization. Within each block, individual data points that deviated by more than 3 standard

deviations (Z-score > 3.0) from the group mean were classified as artifacts and replaced with Not-a-Number (NaN) values. This group-level threshold was specifically chosen to identify transient technical artifacts, such as sudden motor impulses or brief hardware disconnections, that are qualitatively distinct from genuine inter-individual performance variability.

Following artifact rejection, the following primary metrics were calculated to quantify motor accuracy and kinematic adaptation:

- **Global Tracking Error (GTE):** The behavioral motor accuracy was quantified by calculating the root mean square error between the kinematics of the target stimulus and the participant's motor trajectory.
- **Phase Lag and Phase Locking Value (PLV):** The kinematic synchronization between the target stimulus trajectory and the participant's motor response was analyzed using the Hilbert Transform. The target moves along a quasi-periodic sinusoidal trajectory (sum of three sinusoids), producing a narrow-band signal suitable for instantaneous phase estimation via this method. The instantaneous phase of both the target and follower signals was extracted, and the phase lag was calculated as the mean angular delay (in degrees) between the two signals across the trial. The PLV was computed as the circular mean of the phase difference vector, providing an index of the temporal stability of this synchronization. The stability of this synchronization across the continuous task was indexed by the PLV, ranging from 0 (completely desynchronized) to 1 (perfectly phase-locked).
- **Cumulative Sensory Fatigue Score (CSFS):** A novel kinematic index was developed to quantify the cumulative processing cost or integration cost of additive bottom-up sensory streams. To ensure directional consistency, all phase lags were first converted to absolute magnitudes ($|\text{Lag}|$), representing the magnitude of the temporal delay.

The CSFS was calculated by summing the incremental delay costs introduced during the two critical sensory transitions: (1) the initial auditory integration cost ($|\text{AuditoryLag}| - |\text{VisualLag}|$), and (2) the terminal somatosensory integration cost relative to the immediately preceding cognitive state ($|\text{SomatosensoryLag}| - |\text{SemanticLag}|$). This composite score reflects the accumulated temporal delay of processing continuous sensory additions.

Statistical Analysis

All statistical analyses and mathematical modeling were performed using MATLAB (MathWorks, Natick, MA) and Python (SciPy and Statsmodels libraries).

To investigate the temporal dynamics of motor performance and the hypothesized behavioral divergence between the groups, a LME model was constructed ($\text{GTE} \sim \text{Group} * \text{Trial} + (1|\text{ID})$). In this model, 'Group' and 'Trial' were assigned as fixed effects, while participant 'ID' was modeled as a random intercept to account for individual baseline variances. The interaction term ($\text{Group} \times \text{Trial}$) was specifically utilized to test for differential performance trajectories and the progressive linear divergence in sensorimotor tracking accuracy under continuous multisensory loading.

Before group comparisons, the normality of all primary outcome variables was evaluated using the Shapiro-Wilk test. For the block-wise phase lag comparisons, normal distribution was confirmed in both groups (all $p > 0.05$), supporting the use of parametric independent-samples t-tests. For the CSFS, the Shapiro-Wilk test indicated a violation of normality; therefore, a non-parametric Mann-Whitney U test was employed for the group comparison. Results are reported as median (IQR).

To evaluate the clinical correlates of the observed processing fatigue, a Spearman rank-order correlation analysis was conducted within the migraine group. This analysis tested the relationship between the objective CSFS and AASP questionnaire scores.

To control for Type I error inflation arising from multiple comparisons (specifically in the block-wise neurophysiological t-tests and the multi-scale AASP clinical correlations), all resulting raw p-values were systematically adjusted using the Benjamini-Hochberg FDR procedure. Statistical significance was defined as $p < 0.05$ for primary models (LME, CSFS Mann-Whitney U test) and as $q < 0.05$ for multiple comparisons, adjusted for FDR.

Due to the study's retrospective design and the absence of prior literature utilizing equivalent phase analysis in migraine cohorts to provide an a priori effect size, a post hoc power analysis was calculated using G*Power based on the observed maximum multisensory phase lag (Somatosensory block, Cohen's $d = 1.18$). For a two-tailed independent-samples t-test with $\alpha = 0.05$, the estimated sample size to achieve 90% statistical power was $N = 34$. However, we acknowledge the inherent circularity of conducting post hoc power analyses based on observed effect sizes from the same dataset. Therefore, these post hoc estimates are provided solely as retrospective descriptive context.

DECLARATIONS

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to institutional privacy regulations and participant confidentiality but are available from the corresponding author on reasonable request.

Author contributions

MSI and IG contributed equally to this work. HB, MB, KBA designed the study. MSI and IG analyzed the data. MSI, IG and MCA curated the data. HB, MSI and IG wrote the manuscript. All authors reviewed, contributed to, and edited the final draft. All authors approved the final version.

Competing interests

The authors declare no competing interests.

Ethical approval and informed consent

The retrospective use of the archival data was approved by the Gazi University Ethics Committee (Decision No: 2025-2054). The requirement for informed consent was waived by the Gazi University Ethics Committee (Decision No: 2025-2054) due to the retrospective and anonymized nature of the dataset. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Funding

Turkish Academy of Sciences (TÜBA) partially supported the study.

REFERENCES

- 1 Goadsby, P. J. *et al.* Pathophysiology of migraine: a disorder of sensory processing. *Physiological reviews* (2017).
- 2 Meylakh, N. & Henderson, L. A. Exploring alterations in sensory pathways in migraine. *The journal of headache and pain* **23**, 5 (2022).
- 3 Schwedt, T. J. Multisensory integration in migraine. *Current opinion in neurology* **26**, 248-253 (2013).
- 4 Vuralli, D., Evren Boran, H., Cengiz, B., Coskun, O. & Bolay, H. Chronic migraine is associated with sustained elevation of somatosensory temporal discrimination thresholds. *Headache: The Journal of Head and Face Pain* **56**, 1439-1447 (2016).
- 5 Vuralli, D., Boran, H. E., Cengiz, B., Coskun, O. & Bolay, H. Somatosensory temporal discrimination remains intact in tension-type headache whereas it is disrupted in migraine attacks. *Cephalalgia* **37**, 1241-1247 (2017).

- 6 Boran, H. E., Cengiz, B. & Bolay, H. Somatosensory temporal discrimination is prolonged during migraine attacks. *Headache: The Journal of Head and Face Pain* **56**, 104-112 (2016).
- 7 Alaydin, H. C. *et al.* Reduced short-latency afferent inhibition indicates impaired sensorimotor integrity during migraine attacks. *Headache: The Journal of Head and Face Pain* **59**, 906-914 (2019).
- 8 Ince, M. S. *et al.* Virtual dynamic interaction games reveal impaired multisensory integration in women with migraine. *Headache: The Journal of Head and Face Pain* **64**, 482-493 (2024).
- 9 Onlat, Z. C. *et al.* BOLD Repetition Enhancement in the Orbitofrontal Cortex During Complex Visuospatial Processing in Migraine without Aura: A Shift in Periaqueductal Gray - Cortical Coupling? *The Journal of Headache and Pain* (2026).
- 10 Hodkinson, D. J. *et al.* Increased amplitude of thalamocortical low-frequency oscillations in patients with migraine. *Journal of Neuroscience* **36**, 8026-8036 (2016).
- 11 Tu, Y. *et al.* Abnormal thalamocortical network dynamics in migraine. *Neurology* **92**, e2706-e2716 (2019).
- 12 Gross, E. C., Lisicki, M., Fischer, D., Sándor, P. S. & Schoenen, J. The metabolic face of migraine—from pathophysiology to treatment. *Nature Reviews Neurology* **15**, 627-643 (2019).
- 13 Başarı, A., Boran, H. E., Vuralli, D., Cengiz, B. & Bolay, H. Visual temporal discrimination is impaired in patients with migraine without aura. *Headache: The Journal of Head and Face Pain* **63**, 202-210 (2023).
- 14 Effenberg, A. O., Fehse, U., Schmitz, G., Krueger, B. & Mechling, H. Movement sonification: Effects on motor learning beyond rhythmic adjustments. *Frontiers in neuroscience* **10**, 219 (2016).
- 15 Stein, B. E. & Stanford, T. R. Multisensory integration: current issues from the perspective of the single neuron. *Nature reviews neuroscience* **9**, 255-266 (2008).
- 16 Bouilloche, N. *et al.* Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. *Journal of Neurology, Neurosurgery & Psychiatry* **81**, 978-984 (2010).
- 17 Qin, Z. *et al.* Disrupted functional connectivity between sub-regions in the sensorimotor areas and cortex in migraine without aura. *The journal of headache and pain* **21**, 47 (2020).
- 18 Coppola, G. *et al.* Thalamo-cortical network activity between migraine attacks: insights from MRI-based microstructural and functional resting-state network correlation analysis. *The Journal of Headache and Pain* **17**, 100 (2016).
- 19 Sebastianelli, G. *et al.* Bimodal sensory integration in migraine: a study of the effect of visual stimulation on somatosensory evoked cortical responses. *Cephalalgia* **42**, 654-662 (2022).
- 20 Yang, W. *et al.* Elevated audiovisual temporal interaction in patients with migraine without aura. *The Journal of Headache and Pain* **15**, 44 (2014).

- 21 Saberi, M. *et al.* The brain selectively allocates energy to functional brain networks under cognitive control. *Scientific Reports* **14**, 32032 (2024).
- 22 BELEN, H. B. Thalamocortical network interruption: A fresh view for migraine symptoms. *Turkish journal of medical sciences* **50**, 1651-1654 (2020).
- 23 Cho, L. Y. *et al.* Region-specific changes in brain glutamate and gamma-aminobutyric acid across the migraine attack in children and adolescents. *Pain* **165**, 2749-2761 (2024).
- 24 Puleda, F. *et al.* Electrophysiological findings in migraine may reflect abnormal synaptic plasticity mechanisms: a narrative review. *Cephalalgia* **43**, 03331024231195780 (2023).
- 25 De Tommaso, M. *et al.* Altered processing of sensory stimuli in patients with migraine. *Nature Reviews Neurology* **10**, 144-155 (2014).
- 26 Sprenger, T. & Borsook, D. Migraine changes the brain: neuroimaging makes its mark. *Current opinion in neurology* **25**, 252-262 (2012).
- 27 Deodato, M. *et al.* Neurophysiological and clinical outcomes in episodic migraine without aura: a cross-sectional study. *Journal of Clinical Neurophysiology* **41**, 388-395 (2024).
- 28 Reyngoudt, H., Achten, E. & Paemeleire, K. Magnetic resonance spectroscopy in migraine: what have we learned so far? *Cephalalgia* **32**, 845-859 (2012).
- 29 Grimaldi, D. *et al.* Clinical and neuroimaging evidence of interictal cerebellar dysfunction in FHM2. *Cephalalgia* **30**, 552-559 (2010).
- 30 Porcaro, C. *et al.* Impaired brainstem and thalamic high-frequency oscillatory EEG activity in migraine between attacks. *Cephalalgia* **37**, 915-926 (2017).
- 31 Barbanti, P. *et al.* Migraine as a cortical brain disorder. *Headache: The Journal of Head and Face Pain* **60**, 2103-2114 (2020).
- 32 Theriault, J. E. *et al.* A functional account of stimulation-based aerobic glycolysis and its role in interpreting BOLD signal intensity increases in neuroimaging experiments. *Neuroscience & Biobehavioral Reviews* **153**, 105373 (2023).
- 33 Mykland, M. S., Bjørk, M. H., Stjern, M. & Sand, T. Alterations in post-movement beta event related synchronization throughout the migraine cycle: a controlled, longitudinal study. *Cephalalgia* **38**, 718-729 (2018).
- 34 Tót, K. *et al.* Enhanced audiovisual associative pair learning in migraine without aura in adult patients: an unexpected finding. *Cephalalgia* **44**, 03331024241258722 (2024).
- 35 Fernandes, C. & Gil-Gouveia, R. Deciphering the mechanisms: Pathophysiology of migraine-related cognitive dysfunction. *Cephalalgia* **45**, 03331024251368328 (2025).
- 36 Coppola, G. *et al.* Evidence for brain morphometric changes during the migraine cycle: a magnetic resonance-based morphometry study. *Cephalalgia* **35**, 783-791 (2015).

- 37 Majid, S., Kim, D. J., Hu, X.-S. & DaSilva, A. F. Reduced brain entropy in migraine with partial restoration during attacks: A resting-state fMRI study. *medRxiv*, 2025.2010. 2029.25339059 (2025).
- 38 O'Hare, L. Multisensory integration in migraine: recent developments. *Multisensory Research* **30**, 549-563 (2017).
- 39 Stankewitz, A. & Schulz, E. Intrinsic network connectivity reflects the cyclic trajectory of migraine attacks. *Neurobiology of Pain* **11**, 100085 (2022).
- 40 Kringelbach, M. L. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature reviews neuroscience* **6**, 691-702 (2005).
- 41 Bogdanov, V. B. *et al.* Increased cerebral responses to salient transitions between alternating stimuli in chronic migraine with medication overuse headache and during migraine attacks. *Cephalalgia* **39**, 988-999 (2019).
- 42 Mehnert, J., Bader, D., Nolte, G. & May, A. Visual input drives increased occipital responsiveness and harmonized oscillations in multiple cortical areas in migraineurs. *NeuroImage: Clinical* **23**, 101815 (2019).
- 43 Klammer, K. *et al.* Differential fMRI neural synchrony associated with migraine during naturalistic stimuli with negative emotional valence. *The Journal of Headache and Pain* **26**, 62 (2025).
- 44 Brennan, K. & Pietrobon, D. A systems neuroscience approach to migraine. *Neuron* **97**, 1004-1021 (2018).
- 45 Bathel, A. *et al.* Increased thalamic glutamate/glutamine levels in migraineurs. *The journal of headache and pain* **19**, 55 (2018).
- 46 Suzuki, K. *et al.* Investigating the relationships between the burden of multiple sensory hypersensitivity symptoms and headache-related disability in patients with migraine. *The Journal of Headache and Pain* **22**, 77 (2021).
- 47 Chong, C. D., Schwedt, T. J. & Hougaard, A. Brain functional connectivity in headache disorders: a narrative review of MRI investigations. *Journal of Cerebral Blood Flow & Metabolism* **39**, 650-669 (2019).
- 48 Balaban, C. D., Black, R. D. & Silberstein, S. D. Vestibular neuroscience for the headache specialist. *Headache: The Journal of Head and Face Pain* **59**, 1109-1127 (2019).
- 49 Peng, K.-P., May, A. & Basedau, H. Cycling multisensory changes in migraine: more than a headache. *Current opinion in neurology* **35**, 367-372 (2022).
- 50 GENÇ, H. *et al.* Driving with Migraine: Challenges, Risks, and Coping Strategies.
- 51 Lipton, R. *et al.* Migraine and functional impairment associated with driving: results of the OVERCOME study (1638). *Neurology* **94**, 1638 (2020).
- 52 Bolay, H. *et al.* Gender influences headache characteristics with increasing age in migraine patients. *Cephalalgia* **35**, 792-800 (2015).