Review

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2025, Vol. 45(9) 1–18

DOI: 10.1177/03331024251368328
journals.sagepub.com/home/cep

Sage

Deciphering the mechanisms: Pathophysiology of migraine-related cognitive dysfunction

Catarina Fernandes[1] **and Raquel Gil-Gouveia**[2,3]

Abstract

Migraine is increasingly understood as a disorder of brain network dysfunction, where attack-related cognitive symptoms (attention deficits, slowed processing speed and executive dysfunction) can be as disabling as pain and may persist into the interictal period. Such symptoms are associated with functional and structural changes across the migraine cycle, involving the prefrontal cortex, thalamus, hypothalamus, hippocampus and cerebellum. Interictal deficits in working memory, visuospatial processing, verbal fluency and executive function are also documented. Rodent models show impairments in learning and memory, while humans studies suggest that cortical hyperresponsiveness and deficient sensory habituation contribute to altered attentional processing, reflecting thalamocortical dysfunction and abnormal synaptic plasticity as underlying mechanisms. Cognitive performance is modulated by disease severity, chronification, hormonal fluctuations, psychiatric comorbidities, sleep disturbances and medication use. Anxiety, depression and sleep disorders negatively affect working memory, executive function and attention, while medication overuse further impairs visuospatial skills and orientation. Dementia risk appears heightened in migraine patients with frequent and severe attacks, as clinic-based studies consistently report cognitive deficits in this cohorts, unlike population-based studies. While longitudinal cohorts find no increased dementia risk, meta-analyses suggest a modest risk elevation. Differences are likely due to methodological differences in cognitive testing and diagnostic approaches. Cognitive dysfunction in migraine is multidimensional, involving intrinsic neuronal mechanism and external modulators, supporting the need for rational management strategies and treatment interventions.

Keywords

cognition, cognitive impairment, functional brain imaging, headache, migraine, neuropsychology, neurophysiology

Date received: 7 June 2025; accepted: 28 July 2025

Introduction to cognitive dysfunction in migraine

Migraine is one of the most common chronic pain disorders affecting 5–20% of the population (1). Attack-related cognitive dysfunction ranks second only to pain in contributing to disability (2). Cognitive dysfunction in migraine is dynamic, peaking ictally but often persisting interictally. While attack-related cognitive dysfunction seems to be reversible and related to functional brain changes occurring during the attacks, interictal cognitive dysfunction seems to be persistent and influenced by attack frequency and disease complexity (3).

Whether the recurrence of cognitive symptoms or their underlying mechanisms contribute to long-term cognitive impairment or dementia risk remains debatable (4). Although there are studies (3,5–11) associating migraine with dementia, others found no evidence to consider migraine as a risk nor as a protective factor for cognitive decline (3,12,13).

[1]Neurology Department, Local Health Unit of Coimbra, Coimbra, Portugal
[2]Neurology Department, Hospital da Luz, Lisboa, Portugal
[3]Center for Interdisciplinary Research in Health, Universidade Católica Portuguesa, Lisboa, Portugal

Corresponding author:
Raquel Gil-Gouveia, Hospital da Luz Lisboa, Av Lusíada 100, 1500-650 Lisboa, Portugal.
Email: rgilgouveia@gmail.com

Children and adolescents with migraine face a higher risk of poor school performance, linked to the frequency and intensity of pain. This might not only be due to pain-related absenteeism, but also due to cognitive factors. A recent systematic review of interictal neuropsychological profiles in children shows deficits in verbal skills, memory, attention and processing speed. Non-verbal IQ is generally intact, but subclinical verbal impairments, especially in comprehension and semantic fluency, were identified. Visuospatial and verbal memory is also affected, including encoding, consolidation and recall. Processing speed is slower, with altered reaction times and impaired auditory selective attention. Data on visuomotor and visuospatial skills remain limited and inconsistent (14). An early study suggested that poorer verbal performance could relate to *in utero* developmental factors potentially limiting later academic success (15). This may be supported by findings that early migraine age of onset increases the risk of cognitive impairment (16) and that patients with familial hemiplegic migraine (FHM1, CACNA1A mutation) often exhibit intellectual deficits (17).

Migraine may be perceived as a brain "connectopathy", with ongoing debate about whether observed structural and functional dysconnectivity reflects an innate genetically imprinted migraine trait or whether it results from plastic remodeling induced by repeated attacks, in which case could potentially be reversible with appropriate treatment (18). As multiple cognitive networks seem to be involved, their dysfunction could explain cognitive complaints in migraine patients. However, the mechanisms driving these symptoms are likely multifactorial, involving altered nociceptive processing shaped by neuroanatomical, genetic, biochemical and neurovascular factors, along with cultural, psychological and pharmacological influences (4).

The study of cognitive function in migraine

The assessment of cognitive dysfunction in migraine is complex, involving both preclinical and clinical methods, each capturing different dimensions and levels of cognition. Preclinical research uses rodent models to replicate migraine-like states, either with electrical or chemical stimulation of the dura mater, systemic administration of nitroglycerin (NTG) or genetic strains mimicking FHM (19). Behavioural assays to study cognition are applied to these models, such as the Morris water maze for spatial learning and memory, the Novel Object Recognition (NOR) test for recognition memory and the Contextual and Cued Fear Conditioning test for associative fear learning and memory (20). In FHM1 mice, impaired spatial learning, recognition memory and contextual hippocampal learning were documented (19,20). NTG models identified learning and memory disruption using NOR and passive avoidance tests (a form of fear conditioning), which was suppressed by inhibiting the nitric oxide system (21). Repeated dural chemical stimulation in mice impaired non-spatial recognition memory and spatial memory retention, while spatial learning remained intact. Interestingly, pharmacological inhibition of the P2X7 receptor, an ATP-gated ion channel that mediates cytokine release, cell death and inflammasome activation, ameliorated cognitive deficits, particularly restoring recognition memory, suggesting that inflammation may be involved in migraine-associated cognitive impairment (22). Although these models are invaluable for identifying neurobiological pathways and testing pharmacological interventions under controlled conditions, the small number of animal studies focusing on cognition in migraine and the inherent challenge in interpreting and translating behavioral alterations in rodents as equivalents of human cognition limits the interpretation of such findings (20).

Neurophysiological techniques can be applied in humans offering high temporal resolution to investigate longitudinally the rapid neural dynamics associated with sensory and cognitive processing (23,24). Consistent differences in processing of visual, auditory and somatosensory stimuli are documented in migraine even during headache-free periods, characterized as a state of cortical hyperresponsiveness or a lack of habituation to repeated stimuli (24–27). Event-related potentials (ERP) studies focusing on cognitive tasks revealed enhanced cognitive potentials in migraineurs, particularly in paradigms related to attentional processing (26). This suggests that the sensory processing differences can impact higher-level cognitive function, aligning with anecdotal reports from migraineurs who feel overwhelmed by sensory input and experience difficulty ignoring background stimuli (24,28). Interestingly, these responses can fluctuate or normalize along the migraine cycle, depending on the time since the last attack. Potential underlying mechanisms include abnormal synaptic plasticity and thalamocortical dysfunction, which have shown correlations with genetic polymorphisms, suggesting their potential as endophenotypes for migraine vulnerability (24,29,30).

Neurophysiological methods also face limitations, such as lower spatial resolution (31,32) and different studies have shown inconsistent results, probably relating to migraine's variability, differing methodologies and confounding factors such as alertness, mood, sleep, time since last attack and external triggers (24,27,32). While advanced analysis techniques and quantitative methods exist, there is a need for larger, blinded, and confirmatory studies to establish reliable and validated neurophysiological biomarkers of cognitive dysfunction in migraine (33,34).

Functional neuroimaging, magnetic resonance imaging (fMRI) in particular, has been widely used to investigate cognition. Task-based studies show altered activity patterns in brain regions and networks involved in cognitive processes and pain modulation in migraine (35). Some

studies have shown less deactivation in pain modulation areas during attention tasks paired with pain, or reduced activation in ventral fronto-parietal attention networks during visual attention tasks, even when patients' behavioral performance is comparable to healthy controls, suggesting subtle, subclinical deficits (35). Resting state (RS)-fMRI has demonstrated disrupted functional connectivity (FC) within key cognitive networks, including the default mode network (DMN), executive control network (ECN), salience network (SN) and dorsal attention system (DAS) (35–37). These networks are crucial for stimulus detection, attention allocation, self-referential thought, and executive functioning (EF). Changes in FC within or between these networks have been linked to clinical features of migraine, such as pain severity and frequency, or disease duration (35,36). Functional changes are dynamic, depending on the migraine cycle phase (interictal versus ictal) or the chronicity (35,37). Structural gray matter (GM) density reduction in frontal and parietal lobes that correlated with slower response times on attention tasks, has also been identified (35,38).

However, the reproducibility of findings across different MRI studies has been a challenge, due to significant differences in study design, patient selection and analysis methods, although it remains a valuable tool in deciphering how migraine impacts cognition, and holds promise of serving as a future biomarker (35,37).

Objective assessment of the patients' subjective complaints requires neuropsychological testing, which uses standardized instruments to evaluate attention, memory and EF. Such studies identify subtle cognitive impairment in migraine, although the findings vary depending on the headache phase and patient characteristics. During attacks, studies consistently document reversible cognitive dysfunction, affecting processing speed, attention, verbal memory and EFs (39,40). In the interictal period, the results are less consistent; while many clinic-based studies report several impairments, population-based studies often find no differences, comparing to controls. Some research suggests deficits are more pronounced in specific subtypes, such as migraine with aura, higher attack frequency and/or chronification (4,40).

While these tests offer valuable quantitative data and could serve as endpoints in treatment trials, their utility in migraine research is again constrained by inconsistencies across studies. These discrepancies relate to variations in sample selection, methodology and the challenge of adequately controlling for confounding factors such as mood states, medication use, the impact of acute migraine symptoms (e.g. pain, nausea, photophobia) during testing and the learning effect of repeated testing (4,39,40).

The effective way to study cognitive dysfunction in migraine requires a multimodal approach (i.e. combining psychometrics, neurophysiology, functional imaging, and longitudinal tracking) to capture the neurocognitive

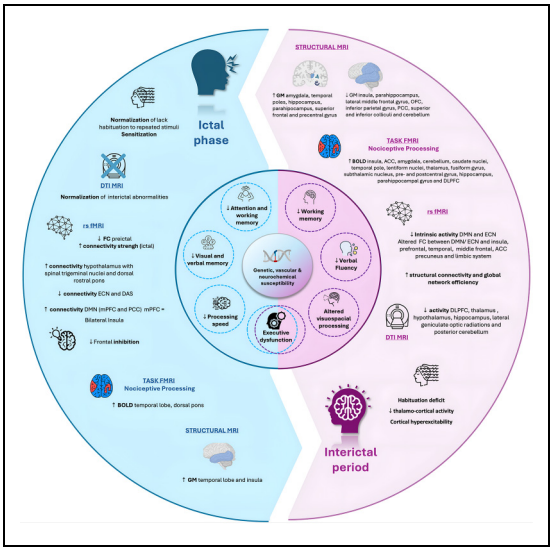

Figure 1. Pathophysiological mechanisms of migraine-related cognitive dysfunction. Cognitive dysfunction susceptibility in migraine is modulated by genetic, vascular and neurobiochemical factors. Surrounding this core, cognitive complaints may emerge across different migraine phases (i.e. ictal, periictal and interictal), each associated with distinct symptom profiles and the involvement of specific brain networks. Cognitive impairment during these phases can be explained by neurophysiological evidence of altered cortico-subcortical communication, as well as neuroimaging findings, particularly (magnetic resonance imaging (MRI), which highlight changes in network connectivity, dynamics, and plasticity. ACC = anterior cingulate cortex; CEN = central executive network; DMN = default mode network; DAS = dorsal attention system; DLPFC = dorsolateral prefrontal córtex; DTI = diffusion tensor imaging; FC = functional connectivity; GM = gray matter; mPFC = medial prefrontal córtex; PCC = posterior cingulate córtex; PFC = prefrontal córtex; RI = right inferior.

dynamics across migraine phases and brain states (e.g. treated versus untreated). However, this approach faces significant challenges, including logistical constraints, inconsistent baseline data, difficult control of confounder variables, lack of standardized protocols, and particularly the episodic, variable and heterogeneous nature of migraine-related cognitive changes. Integrating data across these modalities would require a robust big data analysis framework (Figure 1).

Factors shaping cognitive dysfunction in migraine

Migraine attacks frequency and chronification

Current evidence suggests that migraine attack frequency is associated with cognitive dysfunction, with chronic migraine (CM) patients at higher risk (41,42). Attack duration and intensity also appear to contribute, indicating that prolonged exposure to "migraine state" may contribute to cumulative cognitive dysfunction (5). Compared to

episodic patients, CM exhibit greater subjective and objective impairments in memory, attention, abstraction and language (43). These findings imply involvement of central sensitization and maladaptive neuroplasticity in brain regions responsible for nociception and cognition.

Camarda et al. (5) analyzed subjects with migraine without aura finding their performance to be lower in multifactorial EF tests. They noticed that the duration and intensity of attacks could predict cognitive impairment, suggesting a cumulative effect of attacks on pre-fronto-cerebellar networks. CM patients can present deficits in attention, EF and also social cognition; however, how chronification influences cognitive performance needs clarification (4,42).

A multimodal MRI study found that reduced GM volume in the dorsal anterior cingulate cortex (ACC) was inversely associated with disease duration. It also showed increased ACC functional connectivity with the bilateral middle temporal gyri, orbitofrontal cortex and left dorsolateral prefrontal cortex, suggesting that persistent nociceptive input may drive both structural and functional changes, particularly in regions involved in pain modulation and cognitive processing (44). Other studies identified distinct patterns of GM volume changes in temporoparietal regions that vary according to disease phases (ictal versus interictal); additionally, longitudinal analyses have revealed dynamic alterations in GM volume across multiple brain regions in migraine patients, suggesting that disease activity modulates brain structure (45).

The influence of hormones on cognitive performance

Migraine prevalence is higher in females. A previous study analyzing sex differences on cognition of migraine patients was negative (46), while a recent observational study reported higher levels of anxiety and greater impairment in processing of visual stimuli in females, during the interictal phase (47).

The hormonal fluctuations of the menstrual cycle in naturally cycling women influence brain function because sex hormone receptors are widely distributed throughout the brain, including key regions implicated in affective and cognitive processing, such as the hippocampus, amygdala, prefrontal cortex, insula, inferior parietal lobule and anterior cingulate cortex (48,49). Neuroimaging studies corroborate these effects, revealing cyclic changes such as increased hippocampal grey matter volume and white matter integrity during the late follicular phase, correlating with estradiol levels (48). Task-based and RS-fMRI show variations across the cycle in the amygdala, hippocampus, and prefrontal and parietal cortices (48,49). A study evaluating attention, memory and spatial ability found that behavioral changes correlate with cycle phase, suggesting subtle neural effects (50). The use of oral contraceptives, which maintain lower, more stable hormone levels, also alters brain activity patterns, compared to natural cycles (49,51).

A longitudinal case–control fMRI study in menstrual-related migraine, comparing migraineurs to perimenstrual controls, found that FC strength was increased during the ictal and postictal phases, particularly within and between networks including the sensorimotor network (SMN), Dorsal visual and ventral attention networks. Within the migraine group, comparisons of peri-ictal to interictal phases revealed a generalized decrease in FC. This pattern aligns with differences observed between perimenstrual (lower FC) and post-ovulation (higher FC) phases in healthy controls, demonstrating an interaction between the menstrual and migraine cycles and emphasizing the crucial importance of accounting for menstrual cycle phase when studying brain function, in women with migraine (52).

Medication overuse

Patients with CM are at more risk of developing medication-overuse headache (MOH). Changes in fronto-striatal networks were reported in CM patients, particularly in the orbitofrontal region, with impact on decision-making and possibly related to the risk of medication overuse (53). MOH patients present lower MoCA scores and involvement of the visuospatial and EFs, attention and orientation (54); coexisting CM with MOH has a higher risk of memory and executive dysfunction (42). Interestingly, poorer cognitive performance was associated with a higher burden of deep white matter hyperintensities (WMH) (54).

Preventive treatment

Preventive migraine treatments commonly involve drugs with known cognitive side effects, posing a potential confounding factor in the evaluation of cognitive function in migraine patients (4). The best example is topiramate, which causes attention deficits, memory impairment, psychomotor slowing and word finding difficulties (55,56) during treatment, with a dubious long-term effect. One study found that topiramate caused early attention and visual memory impairment, starting in the first month of treatment and improving over time (57). Conversely, a fMRI study identified differences during a phonemic task, associated with a "remapping" of the language cerebral network, which could explain the long-lasting word finding difficulties reported by patients (58). Memory, psychomotor slowing, word finding and decision-making problems were also described in patients taking tricyclic antidepressants, such as amitriptyline, and may be explained by its anticholinergic and antihistaminic negative effect on cognition (55).

Anti-dementia medications (memantine and donepezil) were tested in migraine prevention, on the basis of the

involvement of glutamatergic pathways in migraine chronification (59). First, a pilot study evaluated the efficacy of memantine for refractory patients (60), finding it to be effective and safe, while documenting improvement in trail making tests. The key question is whether the cognitive improvement was related to effects on migraine or on cognitive function. Another open-label study found a positive effect of donepezil in EM and CM prevention (61), suggesting that cholinergic dysfunction might underlie cognitive symptoms.

Interestingly, in one real-world study, treatment with onabotulinumtoxinA led to significant improvements in cognitive performance, anxiety and depression in chronic migraine patients. Cognitive gains were found to be independent of headache control but correlated with improved anxiety (62).

Psychiatric and sleep comorbidities

Migraine is often comorbid with anxiety and depression, which also influence cognitive performance (4). Anxiety impacts verbal and spatial working memory (WoM), supporting the theories of emotion-cognition interactions (63). Anxiety levels impact some cognitive domains in female migraine patients (47).

Depressive disorders are 2.5 times more prevalent among migraineurs and major depression is associated with attention and EF impairment (64). A RS-fMRI study showed that migraine patients with concomitant depression presented lower activation of the left cuneus, correlating with memory impairment (65).

Migraine often coexists with sleep disturbances, with each condition worsening the other (66). Patients with subjective cognitive decline have lower sleep quality and efficiency, greater sleep latency and higher arousal index (67). The severity of migraine is related with worst sleep quality and predicts cognitive difficulties (68). The effect of sleep disturbance on cognition is consistently well documented because sleep deprivation and insomnia primarily affect attention, working and non-verbal memory and EF such as problem-solving, and cognitive flexibility (69). A Nordic European longitudinal study reported that subjective sleep disturbances were associated with cognitive decline and diurnal hypersomnolence with poor episodic memory, verbal fluency and executive functioning (70). The link between sleep issues and cognitive dysfunction in migraine remains unclear because both are independently associated with cognitive complaints (71).

Cognition in migraine: what do we know?

Cognitive attack-related symptoms

Cognitive complaints are frequent during of attacks, being a main cause of attack-related disability and often rated as the most bothersome symptom, significantly impacting functional capacity and quality of life (3,72).

These transient symptoms often align with the migraine cycle, starting in the prodrome (30%) and persisting into the headache phase (38%), frequently mirrored by objective cognitive deficits (73,74). Most common symptoms relate to attention and concentration (up to 40%), cognitive efficiency, reasoning (up to 50%) and processing speed. Language disturbances and memory issues are less frequently reported (10,39,73,74).

Objective cognitive decline has been documented during the headache phase of migraine. A systematic review identified attention deficits as the most consistently reported cognitive impairment in migraine, followed by reduced processing speed, WoM dysfunction, visual memory, visuomotor ability and verbal learning (39). These findings point to executive dysfunction as central in migraine, although evidence was biased, at that point, toward ictal-phase studies focusing mainly on executive tasks (39). A subsequent randomized study employing an extensive neuropsychological battery demonstrated a general, reversible decline in cognitive performance during migraine attacks compared to headache-free periods, with significant impairments observed in processing speed, WoM, visuospatial abilities, attention and inhibitory control (39).

Complementing these findings, another study demonstrated slower and less accurate responses in simple and choice reaction times tasks, word reading speed, impaired WoM as well as significantly decreased verbal learning and recall during attacks (10,39). Postdromally, WoM deficits and reduced simple reaction time accuracy persist, although response times normalize. Yet, in another study, no changes in attentional domains (alerting, orienting, executive control) or WoM were found in the days following an attack (75).

Cognition involvement in migraine is not explained by pain intensity alone because similar pain levels in non-migraine headaches lack associated deficits (10,39). Cognitive findings suggest a reversible dysfunction involving both cortical and subcortical regions, including prefrontal and temporal cortices, hippocampus, medial temporal and dorsolateral prefrontal areas, along with thalamic–striatal circuits, the cingulate cortex and the insula,. Mechanisms may include cortical spreading depression and altered pain-cognition network dynamics, with regional hyperexcitability (e.g. anterior temporal pole) during attack (10,39,73,74).

Electrophysiological evidence supports disruptions in synaptic short- and long-term plasticity, marked by an imbalance between cortical inhibitory and excitatory circuits and persistent habituation deficits within the brainstem–thalamus–cortex axis. This fluctuating electrophysiological profile across migraine phases suggests a chronic, potentially genetically determined, thalamocortical dysrhythmia and an underlying "dysexcitatory ground" predisposing individuals to attacks (32).

Consistent with this electrophysiological profile, neuroimaging studies reveal widespread, phase-dependent alterations in structural and functional brain connectivity throughout the migraine cycle, particularly within networks subserving in cognitive processing, supporting the existence of dynamic network dysfunction in migraine.

These findings align with some prior studies but highlight inconsistencies in the peri-ictal FC literature (52). In a longitudinal case–control multilevel connectome fingerprinting study, the interictal phase was characterized by increased structural connectivity and global network efficiency, prominently involving cerebellar regions such as the posterior lobe and crus, suggesting enhanced integration within pain processing and cognitive networks (76). Reduced FC is identified in the preictal phase relative to controls and is followed by increased connectivity strength during ictal and postictal phases, implicating the cerebellum and multiple large-scale brain networks, particularly in the dorsal and ventral attention networks, the visual network, and, during attacks, the SMN. Preictally, FC heterogeneity was elevated but diminished as the attack progressed. In symptom-free phases, patients' FC profiles resembled those of healthy controls (52). Although WoM performance remains largely intact in attacks, a distinct postictal hypoactivation of subcortical structures, particularly the hypothalamus, highlights its pivotal role in modulating cognition during attacks (11). WM microstructure also shows dynamic fluctuations, with axial diffusivity (AD) and fractional anisotropy varying across phases; notably, AD transiently normalizes in peri-ictal phases within projection and association fibers linked to limbic and salience networks (77).

Mathur et al. (78). investigated brain activity during cognitive task performance and its interaction with pain in migraine patients. Unlike controls, who showed typical pain-related modulation of task-induced deactivations, migraine patients lacked this modulation, instead exhibiting reduced task-related deactivations and altered pain-cognition interaction patterns in the left dorsolateral prefrontal cortex and dorsal anterior midcingulate cortex, comprising brain regions associated with cognitive processing.

Collectively, these data characterize migraine as a disorder of dynamic brain state transitions, impacting cognitive function, structural integrity, and network organization.

Interictal cognitive burden

The overall impact of the disease in-between attacks, referred to as the interictal burden, is increasingly recognized as a critical dimension of migraine related disability (2). Patients with frequent or poorly controlled attacks often experience anticipatory anxiety or "cephalalgiaphobia", which can worsen the course and burden of the disease (79,80), the interictal burden, in particular (81).

In addition, many patients report persistent cognitive difficulties even outside the attacks (82,83), raising the question of whether subtle cognitive impairment extends into the interictal period (4). Subjective cognitive complaints were shown to contribute meaningfully to the interictal burden (83).

Altered interictal neuropsychological functioning has been shown in pediatric migraine, despite normal general intelligence. Affected children often exhibit deficits in verbal comprehension, language reception, memory (verbal, visuospatial) and WoM, attention and processing speed. While core academic skills typically remain intact, reduced semantic verbal fluency has been reported (14,15). A recent meta-analysis confirms significantly poorer performance across multiple cognitive domains compared to headache-free peers and possibly those with tension-type headache (84).

Reduced verbal performance is detectable as early as age three years and remains stable throughout development, distinguishing migraineurs from both headache-free and tension-type headache controls. This pattern argues against a cumulative effect of migraine attacks and instead supports the involvement of underlying neurodevelopmental mechanisms or innate differences in brain function, potentially involving atypical left-hemispheric maturation and/or cerebral dominance or connectivity patterns (15). Pediatric migraine is consistently linked to increased risk of poorer academic outcomes, including lower grades, exam scores and reduced likelihood of completing secondary or tertiary education (14,15).

Interictal cognitive symptoms, particularly in language, memory and attention, are frequently reported by adults with migraine yet neuropsychological studies have produced inconsistent findings. Most cross-sectional population-based studies show no consistent deficits across domains (Table 1) such as general intelligence, EF, attention and processing speed, verbal and visual memory, language and fluency, visuospatial and constructional ability, and motor speed/coordination (38,85–93), with one study even reporting better performance in cognitive tests, more specifically in fine motor and EF in older adults with migraine (89). Only two small-sample studies and one from a cohort including chronic migraine patients have reported differences from controls (88).

In contrast, most clinic-based studies (5,7,12,38,41, 43,82,94–109) (Table 1) report impairments across multiple neuropsychological domains, including attention, EF, WoM, verbal and visual memory, language, visuospatial skills, psychomotor speed, and overall cognition. Only one study found no differences in intelligence, abstract reasoning, processing speed, sustained attention and visual-motor coordination, in older adults (12).

These discrepancies likely reflect bias of sampling in its clinical severity because the duration and severity of migraine attacks were found to be strong predictors of cognitive

Table 1. Cross-sectional controlled studies of neuropsychological evaluation in interictal migraine patients recruited from community and clinic-based settings.

Subtype	Study (first author, year)	Patients/controls	Neuropsychological testing	Conclusion
CROSS-SECTIONAL COMMUNITY-BASED STUDIES				
Recruitment by ADVERTISING	Schmitz, 2008 (38)	24/ 24	Maudsley attention and response suppression battery	↓
	McKendrick, 2006 (92)	29/ 27	Repeatable battery for assessment of NP Status	↓
	Leijdekkers, 1990 (91)	37/ 34 (MA 11)	Groninger Intelligence test; Cubes and Codes (WAIS-R); Letter Series Tests; Neurobehavioral Evaluation System	=
	Burker, 1989 (90)	47/ 24 (MA 20)	Halstead-Reitan NP test battery; Selective Reminding Test; Rey-Osterrieth Figure	=
	Rashidi, 2018 (93)	28 / 22 (MA 16)	Facial Expressions perception.	=
POPULATIONAL Studies	Jelicic, 2000 (86)	99/ 1753	Letter Digit Substitution Test; Verbal Learning Test	=
	Gaist, 2005 (85)	504/ 857 (MA 11) (twins)	Verbal fluency (animals); codes and digits (WAIS-R); delayed word recall test	=
	Wen, 2016 (89)	1021/ 5399 (+228 PM)	MMSE; 15- word learning test; letter–digit substitution test; stroop test; semantic fluency; Purdue pegboard test	↑
	Baena, 2018 (88)	1239/ 2969 (MA 435/ CM 257)	Alzheimer's Disease word list memory test; semantic fluency test and TMT B	↓
	Martins, 2012 (87)	478 /367 (50 NMH 61 MH)	MMSE (triage) + CVLT, WAIS-III; visual reproduction and faces I subtests TMT; semantic (foods and animals) and phonemic (letter "p") verbal fluency; stroop test, digit span; symbol search; WASI; vocabulary and matrix reasoning sub-tests; information; famous Faces Test	= Majority; ↓symbol search test (MH). ↓ semantic memory CVLT recognition discriminability)
CROSS-SECTIONAL CLINIC-BASED STUDIES				
	Study	Patients/ Controls	Neuropsychological testing	Conclusions
	Zeitlin, 1984 (94)	19/ 19	Stroop; TMT; Choice Reaction; PASAT; National Hospital Forced Choice Recognition Test for words and faces; Mill Hill Vocabulary	↓
	Hooker, 1986 (82)	31(MA16)/ 15	Assessing own functioning; Sensory perceptual Exam; Finger Tapping; Groove Pegboard; Aphasia Screening test; WMS; TMT; Wisconsin; WAIS-R; TPT	↓
	Wray, 1995 (95)	12 (MA 12) / 12	Computorized visual search paradigm testing with low-level (temporal-order discrimination, orientation dectection) and high level (picture naming and word priming) visual processing	↑ / =
	Palmer, 1998 (96)	24 (MA 12)/ 12	Computorized visual search paradigm testing with low-level (temporal-order discrimination, orientation dectection) and high level (picture naming and word priming) visual processing (replicating Wray et al., 1995 (95)	=
	Scherer, 1997 (97)	25/41	Alternating left-right finger tapping	↓
	Le Pira, 2000 (7)	30 (MA 14)/ 14	Boston Visual Exposition Test; Raven Matrices; Verbal Fluency; Rey Figure; Digits; WAIS; Corsi blocks; CVLT	↓
	Calandre, 2002 (98)	60 (MA 10)/ 30	WASI; Sroop; Black letters list; TMT; RAVLT; WMS; Rey Figure; Benton Visual Memory; Visual Reaction Time; Luria Sequence; Rhythm test; Poppelreuters; Benton Shape and Facial recognition	↓

(continued)

Table 1. (continued)

Subtype	Study (first author, year)	Patients/controls	Neuropsychological testing	Conclusion
	Le Pira, 2004 (99)	45 (MA21)/ NONE	Boston Visual Exposition Test; Raven Matrices; Verbal Fluency; Rey Figure; Digits WAIS; Corsi blocks; CVLT	↓
	Mongini, 2005 (100)	23/ 23	Gambling task; Hanoi Tower; Object alternating test	↓
	Pearson, 2006 (12)	74 (MA 45)/ 74	AH4 T; Mill Hill vocabulary; Digit substitution (>65 years old)	=
	Camarda, 2007 (5)	45 (MA 45)/ 90	MMSE; Token; Test d'intelligenza breve; TMT; Fonemic Fluency; Wisconsin	↓
	Schmitz, 2008 (38)	24 (MA 8) / 24	GO/NO-GO task; motor-STROOP task; visual-spatial SWITCH task	↓
	Le Pira, 2014 (101)	44/ 16	Frontal Assessment; Controlled Oral Word Association Test	↓
	Santangelo, 2016 (102)	72/ 72	MoCA	↓
	Huang, 2017 (41)	34/ 34	MoCA; Rey-Osterrieth Figure.	↓
	Tunç, 2018 (103)	100 (MA 47)/ 80	MoCA (controlled for depression and anxiety)	↓ MA
	Santangelo, 2018 (104)	97/ 84	MoCA; MIST (Prospective Memory) (controlled for depression and anxiety)	↓
	Lo Buono, 2019 (8)	100 (MA 50)/ 50	AT, TMT A and B, RAVLT, semantic and phonemic verbal fluencies (controlled for depression, anxiety, MIDAS)	↓
	Baschi, 2019 (105)	21 / 21	Corsi test (VSM and learning), Buschke Selective Reminding Test, TMT A and B (excluded depression and high migraine frequency)	↑VSM/ =
	Ferreira, 2018 (106)	30 (CM 30) /30	MoCA; Verbal Fluency Test; Stroop Test; Color Trails Test; WAIS-III; Digit Span, Vocabulary and Matrix Reasoning; RAVLT (controlled for depression, anxiety, medication)	↓
	Latysheva, 2020 (43)	144 CM / 44 LFEM	MoCA; DSST; RAVLT (controlled for depression)	↓ CM
	Migliore, 2022 (107)	42 (LFEM 13, HFEM 14, CM 20)/20	Task-switching paradigma	↓CM/HFEM > EM/HC
	Zucca, 2020 (108)	64 (CM + MOH 37) /29	WCST – executive and metacognition (controlled for depression, anxiety)	↓CM > EM

Legend: AH4 T = Alice Heim 4 test; AT = Attentive matrices; CM = Chronic migraine; CVLT = California verbal learning test; DSST = digit symbol substitution test; EM = episodic migraine; LFEM = Low frequency episodic migraine; HFEM = High frequency episodic migraine; MA = migraine with aura; MH = migraine headaches; MIDAS = Migraine Disability Assessment;
MIST = Memory for Intentions Screening Test; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MOH; medication overuse headache; NMH = non-migraine headaches;
NP = neuropsychological; PASAT = Paced Auditory Serial Addition Test; PM = probable migraineurs; RAVLT = Rey Auditory Verbal Learning Test; REF = references; TMT = Trail Making Test; TPT = Tactual Performance Test; VSM = visuospatial memory; WAIS-III = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WASI = Wechsler Abbreviated Scale of Intelligence;
WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.
↓ Indicates lower performance compared to controls.
↑ Indicates higher performance compared to controls.
= Indicates identical performance compared to controls.

impairment, so clinic-based studies are more likely to include such patients than populational (5). Supporting this, more pronounced cognitive dysfunction including global cognition, processing speed, attention, memory, EF and cognitive flexibility were described in clinical cohorts including chronic migraine patients, even after controlling for depression and anxiety (5,7,12,38,41,43,82,94–109).

Neurophysiological studies of interictal migraine patients show distinct brain activity patterns compared to healthy controls. Transcranial magnetic stimulation findings suggest reduced cortical inhibition, especially in GABAergic and cholinergic circuits (32), while electroencephalogram (EEG) data show abnormal resting-state rhythms and reduced interhemispheric coherence (24,32). One of the most consistent findings is a deficit in sensory habituation, in which responses to repeated stimuli fail to decrease as expected, suggesting impaired sensory gating (24). Evoked potential studies further support this, with visual, auditory and somatosensory responses showing abnormal patterns, often normalizing during attacks or after treatment (24,32).

A meta-analysis of ERP findings, particularly changes in P300, point to subtle impairments in attention and information processing (with decreased P300 amplitude and prolonged latency) although some studies failed to find significant differences from controls. The inconsistency may reflect the episodic nature of migraine and methodological variability across studies (110). In one positive study, slower and less efficient cognitive responses also correlated with the frequency and duration of migraine attacks (6).

Functional connectivity studies in interictal migraine support the hypothesis of disrupted thalamo-cortical network dynamics, with consistent evidence of reduced activation in the ventral fronto-parietal attention network and weaker connectivity within the executive control network compared to healthy controls (25,37). These functional abnormalities are paralleled by structural deficits because decreased GM density in frontal and parietal cortices correlates with slower response times during attention-shifting tasks, suggesting a neuroanatomical basis for subtle cognitive inefficiencies (35,37). Additionally, aberrant connectivity patterns have been reported within the SN, along with reduced coupling between salience and visual networks, particularly in migraine patients with aura, implicating impaired top-down sensory integration and attentional control mechanisms (35,37).

Interictal phases are also marked by increased structural connectivity and global network efficiency, particularly involving cerebellar regions such as the posterior lobe and crus, indicating a possible compensatory reorganization within pain-cognitive processing systems (76). However, during cognitive tasks with concurrent nociceptive input, migraineurs show reduced deactivation in key pain modulation regions, such as the dorsolateral prefrontal cortex, middle cingulate cortex and cerebellum, highlighting impaired dynamic switching between pain processing and executive networks (25,35,37). Collectively, these findings point to a dysfunctional interplay between sensory, cognitive and modulatory systems in migraine, likely supported by altered thalamo-cortical and cortico-cerebellar communication.

Progression of cognitive dysfunction

Several longitudinal studies (summarized in Table 2) investigated the relationship between migraine and cognitive decline over follow-up periods ranging from 3.4 to 12 years. Across diverse cohorts, including general population samples, aging studies and well-characterized migraine cohorts, cognitive function was extensively assessed using standardized neuropsychological tests and batteries. Importantly, none of the studies found evidence of increased risk of dementia or accelerated global cognitive decline in migraineurs compared to controls, regardless of migraine type (with or without aura, episodic or chronic) (13,111–116).

One study noted more subjective cognitive complaints among migraineurs, but objective measures did not show greater decline (113). Similarly, the CAMERA study found structural brain differences on MRI, but these did not translate into measurable cognitive deficits (114). Overall, these findings suggest that while migraine may involve altered brain structure or function, it does not appear to significantly increase the risk of dementia or age-related cognitive decline. This aligns with the view that migraine is not a neurodegenerative condition.

These findings seem inconsistent with several recent meta-analysis suggesting that migraine is associated with an increased risk of all-cause dementia (acD), as well as Alzheimer's disease (AD) and, to a lesser extent, vascular dementia (VaD) (Table 3) (117–121).

Across meta-analyses, the increased risk of acD in migraineurs ranged from relative risk (RR) 1.26 to 1.35, with elevated risks also reported for AD (RR/hazard ratio (HR) up to 2.49) and VaD (RR/HR up to 1.85) (118,119,122,123). While Wang et al. (120) and Gu et al. (117) found increased risk for acDa and AD and no significant associations with VaD, Jiang et al. (118) and Zhu et al. (123) found significantly elevated risks for both AD and VaD, with the study by Zhu et al. (123) also identifying higher risk in migraine with aura. Qu et al.,(119) analysing broader headache disorders, confirmed similar increased risks, particularly in females.

This divergence in findings between longitudinal cohort studies and meta-analyses may relate to key methodological differences: longitudinal cohort studies directly track cognitive change over time using repeated neuropsychological assessments, always concluding that migraine does not increase the risk of cognitive decline or dementia (13,111–116). In contrast, meta-analyses synthesize data from observational and registry-based studies, which may

Table 2. Longitudinal cohort studies with sequential neuropsychological evaluations assessing cognitive decline and dementia risk in migraine patients.

Study (first author, year, location)	Patients/controls	Headache diagnosis/neuropsychological test/follow-up	Risk of dementia
Kalaydjian, 2007, Baltimore, USA (111)	204 (MA 95) / 1244	Self-report questionnaire / MMSE; immediate and delayed Recall /12 years	=
Baars, 2010, Masstricht, NED (13)	99/ 1724	Self-report of doctor diagnosis / MMSE; immediate and delayed word recall; Stroop interference; Letter digit substituition / 6 years	=
Rist, 2011 EVA study, FRA (115)	167 (MA 24, NMH 65) / 938	Telephone interview with neurologist /MMSE Digit-symbol substituition; TMT A and B; Rey, Raven; Benton;Finger Tapping, Word Fluency / 4–5 years	=
Rist, 2012 WHS study, FRA (116)	443 (MA 195, PM 410) / 5496	Self-report questionnaire / TICS; East Boston Memory test; category Fluency, TICS 10 word list/ 3.4 years	=
Palm-Meinders, 2012 CAMERA, NED (114)	203 / 83	Sample of CAMERA – 1 (Well-characterized) / Verbal Learning Test; Stroop, verbal fluency; Letter Digit Substitution; Purdue pegboard, Block Design Test and MRI Scan/ 9 years	=
Martins, 2020, Lisboa Cohort (113)	59 (NMH 24)/ 219	Follow up of Lisboa cohort / MMSE; Verbal-Paired Associates, immediate and delayed Logical Memory; Visual Reproduction from WMS-III; 9-item CVLT; Vocabulary subtest from WASI; Symbol search; WAIS-III; TMT-A and TMT-B; Stroop Test; Digit Span backwards; semantic (Food and Animals) and phonemic verbal fluency; IADL / 5 Years	=
Liang, 2022, Swedish National study (112)	657 (85 MA, 305 NMH) / 2412 (352 MH	MMSE and Dementia Diagnosis (by DSM-IV) mean follow-up of 7.20 years (SD 3.09).	=

Abbreviations: CVLT = California Verbal Learning Test; DSM = diagnostic and statistical manual of mental disorders; IADL = Instrumental Activities of Daily Living Scale; MA = migraine with aura; MH = migraine without aura; MMSE = Mini Mental State Examination; N = number; NMH = non-migraine headaches; PM = probable migraine; REF = references; WAIS-III = Wechsler Adult Intelligence Scale-III; WASI = Wechsler Abbreviated Scale of Intelligence; WMS-III = Wechsler Memory Scale– III; TICS = Telephone Interview for Cognitive Status; TMT = Trail Making Test.
= risk is identical in migraine and controls

rely on administrative coding or self-reported dementia diagnoses without detailed cognitive testing. These retrospective designs are more susceptible to selection bias, diagnostic misclassification and confounding factors, but can detect broad population-level associations over larger sample sizes. Moreover, while cohort studies typically assess cognitive performance trajectories, meta-analyses often focus on diagnostic endpoints, such as clinical dementia diagnoses, which may reflect later stages of cognitive pathology. Thus, the apparent discrepancy may reflect differences in sensitivity to early cognitive change versus later-stage neurodegeneration, implying the need for harmonized definitions and combined methodologies in future research.

Pathophysiology overview of cognitive dysfunction: why does it happen?

Genetic and epigenetic mechanisms

There is a lack of knowledge regarding genetic and epigenetic mechanisms involved in cognitive complaints of migraine patients. Studying genetic forms of migraine can be important to fill this gap. A study conducted *in vivo* examined hippocampal neurotransmission and plasticity in knock-in mice expressing with FHM type 1 R192Q gain-of-function mutation in the *CACNA1A* gene (124). That mutation enhanced hippocampal excitatory transmission and led to impaired learning and memory, highlighting that genetically enhanced neuronal excitability may impact cognitive function, providing a possible explanation for cognitive changes detected in FHM patients.

Affected CACNA1A individuals can show diverse cognitive profiles, including normal function, developmental delay, episodic encephalopathy and persistent executive or visuospatial deficits, often with cerebellar atrophy (125). When comparing FHM1 with other types of migraine, FHM1 patients have cerebellar motor and cognitive dysfunction (126). A seven-year follow-up study of FHM1 patients found language and verbal memory to remaining intact, while memory, attention and EF showed impairment (127). Overlapping phenotypes and intrafamilial variability suggest the influence of modifier genes and environmental factors (125).

Migraine is also a feature of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Table 3. Meta-analyses of studies assessing dementia risk in individuals with migraine.

Study (first author, year)	N total; inclusion window	Main findings
Wang, 2022 (120)	249,303 individuals; up to 1 April 2021	Increased risk of all-cause dementia (RR = **1.35**; 95% CI = 1.13–1.59). Increased risk of AD (RR = **2.49**; 95% CI = 1.16–5.32); No increase risk of VaD (RR = 1.51; 95% CI = 0.77–2.96)
Gu, 2022 (117)	306,752 individuals; up to June 22	Increased risk of dementia (RR = **1.30**; 95% CI = 1.11 to 1.52).
Jiang, 2022 (118)	291,549 individuals; up to 1 May 2021	Increased risk of all-cause dementia (RR = **1.33;** 95% CI = 1.16–1.53) Increased risk of VaD (RR = **1.85**; 95% CI = 1.22–2.81)
Zhu, 2025 (123)	6,964,353 individuals; up to 2024	Increased the risk of all-cause dementia (HR = **1.26**; 95% CI = 1.09–1.46) Increased risk of AD (HR = **1.32**; 95% CI = 1.26–1.38). Increased risk of VaD (HR = **1.28**; 95% CI = 1.24–1.32) Subgroup analyses: • MA had increased risk of all-cause dementia compared MH
Qu, 2022 (119)	465,358 individual; from 2001 to 2020	Increased risk of all-cause dementia (OR = **1.35**; 95% CI = 1.21–1.50) Increased risk of AD (OR = **1.49**; 95% CI = 1.08–2.05;) Increased risk of VaD (OR = **1.72**; 95% CI = 1.32–2.25) Subgroup analysis: • Females slightly higher risk than males (OR = 1.32; 95% CI = 1.16–1.51) • Retrospective cohort slightly higher than prospective cohort (OR = 1.38; 95% CI = 1.22–1.56)

AD = Alzheimer's disease; CI = confidence interval; HZ = hazard ratio; I2 = inconsistency; MA = migraine with aura; MH = migraine without aura; N = number; OR = odds ratio;
REF = references; RR = relative risk; VaD = vascular dementia.

(CADASIL), a small-vessel genetic disease with ischemic progressive WM damage, leading to dementia (128). A familiar study showed that the presence of migraine associates with worse cognition and correlates with frontal, temporal and basal ganglia hypoperfusion on single-photon emission computed tomography (129).

Meta-analytic evidence identified a genetic relationship between migraine and depression, as well as genetic susceptibility to AD (121). In another large, controlled genotyping cohort study (130), a single nucleotide polymorphism (SNP) (*rs144191744* in *TGFBR3* genes) was associated with subjective cognitive symptoms in migraineurs, particularly EM, migraine without aura and females. Additionally, three SNPs (rs112400385 in ST18, rs4488224 and rs17111203 in ARHGAP29) are linked to subjective cognitive decline in migraineurs but not in non-migraine controls; these genes are implicated in inflammation, cell growth, differentiation and apoptosis, and cytoskeletal dynamics (130).

Vascular mechanisms

A key factor in migraine pathophysiology is the trigeminovascular system's central role in regulating cerebrovascular tone (131,132). Chronic pain has been associated with neurovascular coupling dysfunction, which occurs in migraineurs in parietal or occipital lobes, comprising areas related to sensory and visual information processing, respectively (133). Cerebral hypoperfusion correlated with lower performance in verbal and visual memory tests in the interictal period (98).

WMHs are small lesions, typically in deep or periventricular WM, linked to small vessel damage. Their prevalence increases with age and is two to four times higher in migraine patients, being correlated with executive dysfunction (134). Migraine is also an independent risk factor for WMH in individuals under 50 years without cardiovascular risk, in brain regions associated with pain modulation, emotion, cognition and cognitive reserve (135). Although the exact mechanism remains unclear, proposed contributors include hypercoagulability, endothelial dysfunction, neuroinflammation and cortical spreading depolarization because patients with aura present with a higher burden of WMHs (136).

Neurochemical and neurophysiological mechanism

The thalamus filters sensory input to the cortex and is modulated by serotonergic and dopaminergic systems, both implicated in migraine. Serotonin from the raphe nuclei and dopamine from the periaqueductal gray and hypothalamus influence the trigeminovascular system. These systems affect arousal, attention and mood, helping explain cognitive symptoms such as "brain fog" and difficulty concentrating during migraine (137).

Electrophysiological studies associate migraine with disrupted cortical excitatory–inhibitory balance, impaired modulation of cortical circuits, and altered brain rhythms;

specifically, a dominance of slower theta and delta waves. These changes reflect a malfunction in thalamocortical control and dynamic changes in cortical excitability, background rhythmicity and habituation processes, which fluctuate throughout the migraine cycle, suggesting an ongoing maladaptive brainstem–thalamus–cortex network (138).

During the interictal phase, individuals with migraine exhibit fluctuating levels of motor and visual cortex excitability as assessed by transcranial magnetic stimulation, alongside an unbalance between inhibitory and excitatory cortical activity. Also in that phase, EEG shows a diffuse slowing of background activity and EPs demonstrate a habituation deficit and decreased thalamocortical activity. As patients transition into the preictal phase, EEG activity tends to normalize closer to the attacks, and the normalization of the habituation deficit (139) is observed with EPs. The ictal phase itself shows less consistent data for EEG, while EPs reveal sensitization and normal thalamocortical activity (32). A longer reaction time as well as larger variability in arousal was documented in migraine patients, demonstrating attentional deficits (138).

A study examining interictal cognitive habituation during exposure to visually complex images with a ERP paradigm, showed that migraineurs had abnormal cognitive processing of complex visual stimuli beyond sensory-level deficits (140). Interestingly, these neurophysiological characteristics were associated with familial predisposition (141).

The P300 event-related potential evaluates cognitive processes such as encoding, stimulus identification and categorization, and reflects the efficiency and dynamics of information processing. Typically elicited using an "oddball" paradigm, the amplitude of the P300 is modulated by attention, task complexity and stimulus significance, while its latency indicates the time needed for stimulus evaluation. Its sensitivity to both neurological dysfunction makes it especially suitable for detecting subtle cognitive alterations in migraine (110), although study findings vary, likely due to migraine's episodic nature and methodological differences (110).

The neurophysiological findings in migraine, particularly the persistent cortical hyperresponsivity and impaired habituation between attacks, suggests a disrupted information filtering, possibly related to reduced serotonergic input and thalamocortical dysfunction. This implies that the migraine brain is in a constant state of sensory overload and inefficient information filtering, likely contributing to the subtle cognitive impairments reported by migraineurs, including attentional deficits and slower processing. As P300 reflects activity across a broad neural network, it may serve as a useful biomarker for monitoring cognitive effects with better standardized protocols (6,24,32,142).

Brain network dynamics and plasticity

Functional neuroimaging studies showed network changes in different brain areas associated with a reduced pain threshold (36) that relate to cognitive symptomatology. Frontal and parietal GM density deficits with malfunction of the fronto–striatal–parietal network could explain the executive dysfunction in migraine patients (38).

Hippocampus structural abnormalities and network changes have been reported in patients with subjective cognitive decline and migraine, suggesting a shared mechanism in the anterior hippocampus and inferior temporal gyri and between the posterior hippocampus and precentral gyrus in both conditions (143). A fMRI study identified lower hippocampal volume and connectivity to be associated with poor cognitive performance, highlighting the possible hippocampus's role as a cognitive biomarker for cognitive risk in migraine (144).

The role of cerebellum in migraine is not well understood, yet migraineurs have functional and structural changes in the posterior cerebellum, namely the crus, modulated by pain intensity (145). The crus connects to higher cognitive areas, with increased interaction seen between the crus and posterior lobe, regions involved in cognitive and emotional processing (76).

Furthermore, CM has been linked to glymphatic system dysfunction, while it remains unknown whether repetitive attacks impair glymphatic system function over time (146). As glymphatic dysfunction has been linked to many neurodegenerative disorders, it can have a role in cognitive impairment in migraine.

Beyond functional changes, structural imaging revealed regional volume changes in brain areas involved in pain modulation and visual/affective/cognitive processing, such as the frontal lobe, visual processing system, basal ganglia and thalamus (147). Particularly, fronto-orbital volumes were negatively correlated with headache frequency (CM had lower frontal lobe volume than EM). These might be influenced by age, migraine phenotype and cognitive complaints (35). Longitudinal imaging in pediatric patients also showed changes in brain structure and function, over time (148).

Pain processing mechanisms

It is yet to be determined whether cognitive impairment is part of the migraine-specific phenotype or an effect of brain modulation by chronic recurrent pain episodes (4). The claustrum is a subcortical nucleus with a major role in cognitive network modulation and evidence of its pathological activity, as well as of the right dorsolateral prefrontal cortex during attacks, does support the hypothesis of a possible cognitive network dysfunction (149).

A study comparing CM with EM patients found poor performance in the Rey Auditory Verbal Learning Test and the Montreal Cognitive Assessment (MoCA), with impairments

in memory and attention in CM (138). The presence of chronic pain was an independent predictor of cognitive decline and was related to aberrant cognitive network activity (43).

Clinical and preclinical studies consistently document cognitive impairments in other chronic pain syndromes, including fibromyalgia, diabetic neuropathy, chronic lower back pain and whiplash-associated disorder (150,151). Cognitive domains commonly affected include attention deficits, spatial and verbal working memory, recall and recognition memory, slower reaction times, impaired psychomotor ability, and higher-order executive processes, including planning, organization, control of conflicting thoughts, goal-directed behaviour and emotional decision-making (150,151).

Cognitive dysfunction in other chronic pain syndromes is also thought to relate to multiple interacting mechanisms, one being the competition for limited cognitive resources, as pain captures attention via "bottom-up" processes and requires effortful "top-down" control to redirect focus (150). Additionally, structural brain changes, including grey matter loss and synaptic alterations in the anterior cingulate cortex, insular cortex, prefrontal cortex and amygdala, may contribute to deficits in WoM and EF (150,151).

Neurochemical imbalances also play a role, with dysregulation of glutamate, GABA, monoamines, acetylcholine and endocannabinoids affecting both pain processing and cognitive functions, such as attention and memory (150). Finally, inflammatory processes, including glial activation and elevated pro-inflammatory cytokines, further impair synaptic function, while reduced levels of brain-derived neurotrophic factor in the hippocampus hinder memory and neuroplasticity (150).

It remains unclear to what extent these mechanisms apply to migraine. Although cognitive symptoms may overlap, migraine's episodic nature (with variable attack frequency) leads to transient but repeated activation of pain and cognitive networks. Moreover, evidence indicates that the migraine brain differs from that of healthy controls even during interictal periods. This suggests that, despite some shared pathways, migraine likely involves distinct patterns of brain modulation compared to continuous pain conditions (3,18,25,35,122,150,151).

Evolutionary perspective of migraine related cognitive dysfunction

Despite its high prevalence and disabling nature, migraine has persisted through evolutionary history, suggesting that the underlying genetic traits may have conferred selective advantages in ancestral environments (152,153). Migraine attacks may represent an evolutionarily conserved, adaptive neurobehavioral response to internal or external stressors, aimed at restoring energy balance and protecting neural integrity. The systemic physiological responses during attacks (pain, fatigue, sensory and cognitive withdrawal, hypotension) resemble tonic immobility, a primitive defence behaviour that reduces energy expenditure and sensory overload in the face of overwhelming stimuli. Taking this view, attack related cognitive dysfunction can be seen as a form of functional disconnection, encouraging behavioural withdrawal, limiting further stimulation and potentially protecting a metabolically vulnerable brain (25,152,154–156).

Migraine-related sensory hypersensitivity (153), a genetically driven hyperresponsiveness of sensory systems in migraineurs, might have been useful by improving detection of environmental threats or improving foraging, in the past. Enhanced visual, auditory and olfactory sensitivity could increase vigilance, facilitate early detection of predators or toxins, and improve attentional focus (3,32,152,153,155). From an evolutionary game theory perspective, these traits may also benefit social groups, through reciprocal altruism. Hypersensitive individuals detect threats early, providing warnings to others. In return, support during their own periods of vulnerability (migraine attacks) would promote survival and social cohesion; mutual benefit could explain the evolutionary stability and global distribution of migraine-associated genes (152).

However, in modern environments, the same traits might have become maladaptive, particularly to where constant sensory overload from persistent artificial stimuli, chronic stress and sustained cognitive demands, prevail. The mismatch between evolutionary adaptations and modern life may lead to chronic activation of the trigeminovascular system, exacerbating migraine susceptibility and impact (152,153).

Conclusions

The relationship between migraine, cognitive function and brain connectivity is multifaceted and there is growing recognition of migraine impact on brain function, beyond pain. Migraine sufferers, especially during attacks and in CM, experience measurable cognitive dysfunction with functional impact, which also raise concerns about dementia risk. Cognitive symptoms may arise from disruptions in structure and function of brain networks, including cortical hyperexcitability, impaired sensory habituation and abnormal connectivity in regions responsible for cognition and pain processing. Such features support the emerging view of migraine as a "connectopathy" (3,18,25,35,122). Neuroimaging reveals that the brain of migraine sufferers exhibits altered organization, with increased local and global efficiency and heightened clustering coefficients. These indicate a potential imbalance between the brain's capacity for effective information transfer and the metabolic burden required to sustain these connections, reinforcing the concept of an "energetically inefficient migraine brain" (18,155,156).

Functional neuroimaging further demonstrates abnormal activity and connectivity in regions critical for cognition, including the dorsolateral prefrontal and parietal cortices, changes associated with reduced GM density

and slower response times in attention-shifting tasks. Moreover, migraine patients exhibit diminished brain activation during cognitively demanding tasks under painful stimulation and intrinsic connectivity abnormalities within core cognitive networks (central executive network, SN and DMN), suggesting a pain-induced network reorganization that may underlie cognitive dysfunction (3,25,35,37,52,117).

The relationship between migraine and cognition is modulated by confounding factors, such as psychiatric comorbidities, sleep disturbances, vascular risk factors, hormonal fluctuations and pharmacological treatments (3,4,20).

Future research should explore how shifting environmental pressures interact with inherited neural traits to alleviate all migraine experience and guide more targeted therapies, which tackle all migraine symptoms.

Key findings

- Migraine attacks involve reversible dysfunction of cognitive and pain-processing networks, marked by disrupted connectivity, impaired synaptic plasticity and altered thalamo-cortical dynamics, and leading to significant, transient cognitive deficits that affect attention, processing speed and executive function, independently of pain intensity, and are major contributors to disability.
- In the interictal phase, migraine is associated with disrupted thalamo-cortical and cortico-cerebellar connectivity, impaired sensory habituation and reduced cortical inhibition, comprising mechanisms that may underlie subtle, persistent cognitive dysfunction specially in individuals with higher attack frequencies.
- This reversible episodic and possible chronic cognitive dysfunction raise concerns about the potential impact of migraine on long-term cognitive health.

Author contributions

CF and RGG contributed to the concept of the review, and both drafted the manuscript. Both authors reviewed, edited and provided final approval of the manuscript content, and had final responsibility for the decision to submit for publication.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the contents of this article. CF reports support to atten meetings from Allergan-AbbVie, Lundbeck, Novartis, Teva, Organon, Pfizer and Sanofi; RGG reports honoraria for consultant and/or advisory boards from Allergan/Abbvie, Astra Zeneca, Almirall, Bial, Biogen, Bristol-Myers Squibb, CMBE, FLOAT, Lilly, Lundbeck, Merk, Novartis, Novo Nordisk, Organon, Pfizer, Roche, Sanofi, Tecnifar and Teva; research funding from Fundação Ciência Tecnologia (Project 29675, MigN2Treat, 02/SAICT/2017); Learning-Health, Luz Saúde (LiON, Luz Innovation on Neurosciences); Novartis-Sociedade Portuguesa de Cefaleias; Bolsa –Projecto Centro de Investigação Interdisciplinar em Saúde and UCP.

Funding

The authors received no financial support for the authorship of this article. RGG has received research funds for a project evaluating cognitive function across the migraine cicle in woman with migraine (MigN2Treat) and some papers cited in this manuscript-were result of this project.

ORCID iDs

Catarina Fernandes https://orcid.org/0000-0002-9556-3134
Raquel Gil-Gouveia https://orcid.org/0000-0002-4256-4256

References

1. Lipton RB and Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache* 2005; 45: S3–s13.
2. Gil-Gouveia R, Oliveira AG and Martins IP. The impact of cognitive symptoms on migraine attack-related disability. *Cephalalgia* 2016; 36: 422–430.
3. Gil-Gouveia R and Martins IP. Cognition and cognitive impairment in migraine. *Curr Pain Headache Rep* 2019; 23: 84.
4. Fernandes C, Dapkute A, Watson E, et al. Migraine and cognitive dysfunction: a narrative review. *J Headache Pain* 2024; 25: 221.
5. Camarda C, Monastero R, Pipia C, et al. Interictal executive dysfunction in migraineurs without aura: relationship with duration and intensity of attacks. *Cephalalgia* 2007; 27: 1094–1100.
6. Guo Y, Tian Q, Xu S, et al. The impact of attack frequency and duration on neurocognitive processing in migraine sufferers: evidence from event-related potentials using a modified oddball paradigm. *BMC Neurol* 2019; 19: 73.
7. Le Pira F, Zappalà G, Giuffrida S, et al. Memory disturbances in migraine with and without aura: a strategy problem? *Cephalalgia* 2000; 20: 475–478.
8. Lo Buono V, Bonanno L, Corallo F, et al. Cognitive functions and psychological symptoms in migraine: a study on patients with and without aura. *Int J Neurosci* 2019; 129: 588–592.
9. Mulder EJ, Linssen WH, Passchier J, et al. Interictal and postictal cognitive changes in migraine. *Cephalalgia* 1999; 19: 557–565. discussion 41.
10. Ray JC, Darby D, Butzkueven H, et al. Cognitive assessment during the phases of a spontaneous migraine: a prospective cohort study. *Neurol Sci* 2024; 45: 4445–4449.

11. Ruiz-Tagle A, Caetano G, Fouto A, et al. Preserved working memory performance along with subcortical modulation during peri-ictal phases in spontaneous migraine attacks. *Headache* 2025; 65: 407–419.
12. Pearson AJ, Chronicle EP, Maylor EA, et al. Cognitive function is not impaired in people with a long history of migraine: a blinded study. *Cephalalgia* 2006; 26: 74–80.
13. Baars MA, van Boxtel MP and Jolles J. Migraine does not affect cognitive decline: results from the Maastricht aging study. *Headache* 2010; 50: 176–184.
14. Tarantino S, Proietti Checchi M, Papetti L, et al. Interictal cognitive performance in children and adolescents with primary headache: a narrative review. *Front Neurol* 2022; 13: 898626.
15. Waldie KE, Hausmann M, Milne BJ, et al. Migraine and cognitive function: a life-course study. *Neurology* 2002; 59: 904–908.
16. Parisi P, Verrotti A, Paolino MC, et al. Headache and cognitive profile in children: a cross-sectional controlled study. *J Headache Pain* 2010; 11: 45–51.
17. Humbertclaude V, Riant F, Krams B, et al. Cognitive impairment in children with CACNA1A mutations. *Dev Med Child Neurol* 2020; 62: 330–337.
18. Silvestro M, Tessitore A, Caiazzo G, et al. Disconnectome of the migraine brain: a "connectopathy" model. *J Headache Pain* 2021; 22: 102.
19. Spekker E, Fejes-Szabó A and Nagy-Grócz G. Models of trigeminal activation: Is there an animal model of migraine? *Brain Sci* 2024; 14: 317.
20. Vuralli D, Wattiez AS, Russo AF, et al. Behavioral and cognitive animal models in headache research. *J Headache Pain* 2019; 20: 11.
21. Taheri P, Mohammadi F, Nazeri M, et al. Nitric oxide role in anxiety-like behavior, memory and cognitive impairments in animal model of chronic migraine. *Heliyon* 2020; 6: e05654.
22. Wang Y, Shan Z, Zhang L, et al. P2x7r/NLRP3 signaling pathway-mediated pyroptosis and neuroinflammation contributed to cognitive impairment in a mouse model of migraine. *J Headache Pain* 2022; 23: 75.
23. Lisicki M and Chen W-T. Neuroimaging correlates of neurophysiological findings. In: Coppola G and Chen W-T (eds) *Neurophysiology of the migraine brain*. Cham: Springer International Publishing, 2021, pp.211–221.
24. Coppola G and Ambrosini A. Chapter 9 – what has neurophysiology revealed about migraine and chronic migraine? In: Swanson JW and Matharu M (eds) *Handbook of clinical neurology*. 198: Elsevier, 2023, pp.117–133.
25. Bonavita V, De Simone R and Ranieri A. Pain cognition in migraine: from basic neurophysiology to a behavioral paradigm. *Neurol Sci* 2018; 39: 3–9.
26. Coppola G and Magis D. *Neurophysiology of the migraine brain – Evoked Potentials*. Cham, Switzerland: Springer, 2021.
27. Cosentino G, Fierro B and Brighina F. From different neurophysiological methods to conflicting pathophysiological views in migraine: a critical review of literature. *Clin Neurophysiol* 2014; 125: 1721–1730.
28. Mickleborough Marla JS, Sun G, Moss D, et al. *Neurophysiology of the migraine brain – Cognitive Potentials*. Cham, Switzerland: Springer, 2021.
29. Vollono C. *Neurophysiology of the migraine brain – Brainstem Reflexes*. Coppola G and Chen W-T (eds). Cham, Switzerland: Springer, 2021.
30. Lisicki M and Chen W-T. *Neurophysiology of the migraine brain - Neuroimaging correlates of neurophysiological findings*. Coppola G and Chen W-T (eds). Cham, Switzerland: Springer, 2021, pp.211–221.
31. Coppola G and Pierelli F. *Neurophysiology of the migraine brain - Brain oscillations and migraine*. Coppola G and Chen W-T (eds). Cham, Switzerland: Springer, 2021.
32. Puledda F, Viganò A, Sebastianelli G, et al. Electrophysiological findings in migraine may reflect abnormal synaptic plasticity mechanisms: a narrative review. *Cephalalgia* 2023; 43: 3331024231195780.
33. Hsiao F-J, Xiang J and Chen W-T. *Neurophysiology of the migraine brain – Magnetoencephalography*. Coppola G and Chen W-T (eds). Cham, Switzerland: Springer, 2021.
34. Sand T, Omland Petter M and Wang S-J. *Neurophysiology of the migraine brain – Electroencephalography*. Coppola G and Chen W-T (eds). Cham, Switzerland: Springer, 2021.
35. Chong CD, Schwedt TJ and Dodick DW. Migraine: what imaging reveals. *Curr Neurol Neurosci Rep* 2016; 16: 64.
36. Russo A, Silvestro M, Tedeschi G, et al. Physiopathology of migraine: what have we learned from functional imaging? *Curr Neurol Neurosci Rep* 2017; 17: 95.
37. Skorobogatykh K, van Hoogstraten WS, Degan D, et al. Functional connectivity studies in migraine: what have we learned? *J Headache Pain* 2019; 20: 108.
38. Schmitz N, Arkink EB, Mulder M, et al. Frontal lobe structure and executive function in migraine patients. *Neurosci Lett* 2008; 440: 92–96.
39. Gil-Gouveia R, Oliveira AG and Martins IP. Cognitive dysfunction during migraine attacks: a study on migraine without aura. *Cephalalgia* 2015; 35: 662–674.
40. Vuralli D, Ayata C and Bolay H. Cognitive dysfunction and migraine. *J Headache Pain* 2018; 19: 109.
41. Huang L, juan Dong H, Wang X, et al. Duration and frequency of migraines affect cognitive function: evidence from neuropsychological tests and event-related potentials. *J Headache Pain* 2017; 18: 54.
42. Cai X, Xu X, Zhang A, et al. Cognitive decline in chronic migraine with nonsteroid anti-inflammation drug overuse: a cross-sectional study. *Pain Res Manag* 2019; 2019: 7307198.
43. Latysheva N, Filatova E, Osipova D, et al. Cognitive impairment in chronic migraine: a cross-sectional study in a clinic-based sample. *Arq Neuropsiquiatr* 2020; 78: 133–138.
44. Jin C, Yuan K, Zhao L, et al. Structural and functional abnormalities in migraine patients without aura. *NMR Biomed* 2013; 26: 58–64.
45. Coppola G, Casillo F, Sebastianelli G, et al. *Chapter 5 - Neuroimaging studies of migraine without aura neuroimaging of headache disorders*. Martelletti P (ed.). Springer Nature, 2025.
46. Wang R, Dong Z, Chen X, et al. Gender differences of cognitive function in migraine patients: evidence from event-related potentials using the oddball paradigm. *J Headache Pain* 2014; 15: 6.

47. Guo Y, Xu S, Nie S, et al. Female versus male migraine: an event-related potential study of visual neurocognitive processing. *J Headache Pain* 2019; 20: 38.
48. Dubol M, Epperson CN, Sacher J, et al. Neuroimaging the menstrual cycle: a multimodal systematic review. *Front Neuroendocrinol* 2021; 60: 100878.
49. Toffoletto S, Lanzenberger R, Gingnell M, et al. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: a systematic review. *Psychoneuroendocrinology* 2014; 50: 28–52.
50. Jang D, Zhang J and Elfenbein HA. Menstrual cycle effects on cognitive performance: a meta-analysis. *PLoS One* 2025; 20: e0318576.
51. Ronca F, Blodgett JM, Bruinvels G, et al. Attentional, anticipatory and spatial cognition fluctuate throughout the menstrual cycle: potential implications for female sport. *Neuropsychologia* 2025; 206: 108909.
52. Esteves I, Fouto AR, Ruiz-Tagle A, et al. Uncovering longitudinal changes in the brain functional connectome along the migraine cycle: a multilevel clinical connectome fingerprinting framework. *J Headache Pain* 2025; 26: 29.
53. Biagianti B, Grazzi L, Gambini O, et al. Decision-making deficit in chronic migraine patients with medication overuse. *Neurol Sci* 2012; 33: 151–155.
54. Xiang Y, Chen S, Lin H, et al. Cognitive function and white matter lesions in medication-overuse headache. *J Pain Res* 2021; 14: 1845–1853.
55. Russo M, De Rosa MA, Calisi D, et al. Migraine pharmacological treatment and cognitive impairment: risks and benefits. *Int J Mol Sci* 2022; 23: 11418.
56. Sommer BR, Mitchell EL and Wroolie TE. Topiramate: effects on cognition in patients with epilepsy, migraine headache and obesity. *Ther Adv Neurol Disord* 2013; 6: 211–227.
57. Kececi H and Atakay S. Effects of topiramate on neurophysiological and neuropsychological tests in migraine patients. *J Clin Neurosci* 2009; 16: 1588–1591.
58. De Ciantis A, Muti M, Piccolini C, et al. A functional MRI study of language disturbances in subjects with migraine headache during treatment with topiramate. *Neurol Sci* 2008; 29: 141–143.
59. Ramadan NM. The link between glutamate and migraine. *CNS Spectr* 2003; 8: 446–449.
60. Bigal M, Rapoport A, Sheftell F, et al. Memantine in the preventive treatment of refractory migraine. *Headache* 2008; 48: 1337–1342.
61. Nicolodi M, Galeotti N, Ghelardini C, et al. Central cholinergic challenging of migraine by testing second-generation anticholinesterase drugs. *Headache* 2002; 42: 596–602.
62. Ho S, Darby D and Bear N. Cognitive effects of onabotulinumtoxinA in chronic migraine. *BMJ Neurol Open* 2020; 2: e000014.
63. Vytal KE, Cornwell BR, Letkiewicz AM, et al. The complex interaction between anxiety and cognition: insight from spatial and verbal working memory. *Front Hum Neurosci* 2013; 7: 93.
64. Altamura C, Corbelli I, de Tommaso M, et al. Pathophysiological bases of comorbidity in migraine. *Front Hum Neurosci* 2021; 15: 640574.
65. Chen W, Xie G, Xu C, et al. The relationship between regional homogeneity in resting-state functional magnetic resonance imaging and cognitive function in depressive disorders with migraine. *Sci Rep* 2025; 15: 11810.
66. Tiseo C, Vacca A, Felbush A, et al. Migraine and sleep disorders: a systematic review. *J Headache Pain* 2020; 21: 126.
67. Esmael A, Abdelsalam M, Shoukri A, et al. Subjective cognitive impairment in patients with transformed migraine and the associated psychological and sleep disturbances. *Sleep Breath* 2021; 25: 2119–2126.
68. Ikechukwu O, Khan M, Khan S, et al. Association between sleep quality and cognitive complaints among young adults with migraine. *Cureus* 2025; 17: e83649.
69. Kong J, Zhou L, Li X, et al. Sleep disorders affect cognitive function in adults: an overview of systematic reviews and meta-analyses. *Sleep Biol Rhythms* 2023; 21: 133–142.
70. Overton M, Skoog J, Laukka EJ, et al. Sleep disturbances and change in multiple cognitive domains among older adults: a multicenter study of five Nordic cohorts. *Sleep* 2024; 47: zsad244.
71. Huang X, Zhang Z, Lan X, et al. The association between hypoxic burden and the risk of cognitive impairment in patients with obstructive sleep apnea. *Sleep* 2025; 48: zsae269.
72. Schwedt TJ, Digre K, Tepper SJ, et al. The American registry for migraine research: research methods and baseline data for an initial patient cohort. *Headache* 2020; 60: 337–347.
73. Gil-Gouveia R and Martins IP. Clinical description of attack-related cognitive symptoms in migraine: a systematic review. *Cephalalgia* 2018; 38: 1335–1350.
74. Gil-Gouveia R, Oliveira AG and Martins IP. Subjective cognitive symptoms during a migraine attack: a prospective study of a clinic-based sample. *Pain Physician* 2016; 19: E137–E150.
75. Koppen H, Palm-Meinders I, Kruit M, et al. The impact of a migraine attack and its after-effects on perceptual organization, attention, and working memory. *Cephalalgia* 2011; 31: 1419–1427.
76. Matoso A, Fouto AR, Esteves I, et al. Involvement of the cerebellum in structural connectivity enhancement in episodic migraine. *J Headache Pain* 2024; 25: 154.
77. Fouto AR, Nunes RG, Guadilla I, et al. Alterations of white matter microstructure in migraine patients vary in the perictal phases. *eNeuro* 2025; 12: Patrícia ENEURO.0300–24.2024.
78. Mathur VA, Khan SA, Keaser ML, et al. Altered cognition-related brain activity and interactions with acute pain in migraine. *Neuroimage Clin* 2015; 7: 347–358.
79. Giannini G, Zanigni S, Grimaldi D, et al. Cephalalgiaphobia as a feature of high-frequency migraine: a pilot study. *J Headache Pain* 2013; 14: 49.
80. Klan T, Diezemann-Prößdorf A, Guth AL, et al. Fear of migraine attacks: diagnosis and treatment. *Schmerz* 2025; 39: 177–184.
81. Kaske E, Pradela J, Otto M, et al. Factors affecting fear of attacks in patients with episodic migraine – a cross-sectional study. *Cephalalgia Reports* 2025; 8: 25158163251345140.
82. Hooker WD and Raskin NH. Neuropsychologic alterations in classic and common migraine. *Arch Neurol* 1986; 43: 709–712.
83. Sotero FD, Nobre J, Vicente BN, et al. Predictors of migraine interictal burden: the hidden role of subjective memory complaints. *Headache* 2025; 65: 54–60.

84. Pizer JH, Hernandez KA, Aita SL, et al. Neuropsychological functioning in pediatric primary headache disorders: A meta-analysis. *Pediatrics* 2025; 155: e2024067838.
85. Gaist D, Pedersen L, Madsen C, et al. Long-term effects of migraine on cognitive function: a population-based study of danish twins. *Neurology* 2005; 64: 600–607.
86. Jelicic M, van Boxtel MP, Houx PJ, et al. Does migraine headache affect cognitive function in the elderly? Report from the Maastricht Aging Study (MAAS). *Headache* 2000; 40: 715–719.
87. Martins IP, Gil-Gouveia R, Silva C, et al. Migraine, headaches, and cognition. *Headache* 2012; 52: 1471–1482.
88. Pellegrino Baena C, Goulart AC, Santos IS, et al. Migraine and cognitive function: baseline findings from the Brazilian Longitudinal Study of Adult Health: ELSA-Brasil. *Cephalalgia* 2018; 38: 1525–1534.
89. Wen K, Nguyen NT, Hofman A, et al. Migraine is associated with better cognition in the middle-aged and elderly: the rotterdam study. *Eur J Neurol* 2016; 23: 1510–1516.
90. Burker E, Hannay HJ and Halsey JH. Neuropsychological functioning and personality characteristics of migrainous and nonmigrainous female college students. *Neuropsychology* 1989; 3: 61–73.
91. Leijdekkers ML, Passchier J, Goudswaard P, et al. Migraine patients cognitively impaired? *Headache* 1990; 30: 352–358.
92. McKendrick AM, Badcock DR, Badcock JC, et al. Motion perception in migraineurs: abnormalities are not related to attention. *Cephalalgia* 2006; 26: 1131–1136.
93. Rashidi M, Oelkers-Ax R, Sharma A, et al. Perception of facial expressions of emotion in migraine. *Brain Res* 2018; 1686: 42–47.
94. Zeitlin C and Oddy M. Cognitive impairment in patients with severe migraine. *Br J Clin Psychol* 1984; 23: 27–35.
95. Wray SH, Mijović-Prelec D and Kosslyn SM. Visual processing in migraineurs. *Brain* 1995; 118: 25–35.
96. Palmer JE and Chronicle EP. Cognitive processing in migraine: a failure to find facilitation in patients with aura. *Cephalalgia* 1998; 18: 125–132.
97. Scherer P, Bauer H and Baum K. Alternate finger tapping test in patients with migraine. *Acta Neurol Scand* 1997; 96: 392–396.
98. Calandre EP, Bembibre J, Arnedo ML, et al. Cognitive disturbances and regional cerebral blood flow abnormalities in migraine patients: their relationship with the clinical manifestations of the illness. *Cephalalgia* 2002; 22: 291–302.
99. Le Pira F, Lanaia F, Zappalà G, et al. Relationship between clinical variables and cognitive performances in migraineurs with and without aura. *Funct Neurol* 2004; 19: 101–105.
100. Mongini F, Keller R, Deregibus A, et al. Frontal lobe dysfunction in patients with chronic migraine: a clinical-neuropsychological study. *Psychiatry Res* 2005; 133: 101–106.
101. Le Pira F, Reggio E, Quattrocchi G, et al. Executive dysfunctions in migraine with and without aura: what is the role of white matter lesions? *Headache* 2014; 54: 125–130.
102. Santangelo G, Russo A, Trojano L, et al. Cognitive dysfunctions and psychological symptoms in migraine without aura: a cross-sectional study. *J Headache Pain* 2016; 17: 76.
103. Tunç A, Tekeşin AK, Güngen BD, et al. Cognitive performance in young and middle-aged adults with migraine: investigating the correlation with white matter hyperintensities and psychological symptoms. *Neurol Neurochir Pol* 2018; 52: 470–476.
104. Santangelo G, Russo A, Tessitore A, et al. Prospective memory is dysfunctional in migraine without aura. *Cephalalgia* 2018; 38: 1825–1832.
105. Baschi R, Monastero R, Cosentino G, et al. Visuospatial learning is fostered in migraine: evidence by a neuropsychological study. *Neurol Sci* 2019; 40: 2343–2348.
106. Ferreira KS, Teixeira CT, Cáfaro C, et al. Chronic migraine patients show cognitive impairment in an extended neuropsychological assessment. *Arq Neuropsiquiatr* 2018; 76: 582–587.
107. Migliore S, D'Aurizio G, Altamura C, et al. Task-switching abilities in episodic and chronic migraine. *Neurol Sci* 2022; 43: 3803–3810.
108. Zucca M, Rubino E, Vacca A, et al. Metacognitive impairment in patients with episodic and chronic migraine. *J Clin Neurosci* 2020; 72: 119–123.
109. Lo Buono V, Bonanno L, Corallo F, et al. Functional connectivity and cognitive impairment in migraine with and without aura. *J Headache Pain* 2017; 18: 72.
110. Raggi A and Ferri R. Information processing in migraine: a review of studies on P300. *Appl Psychophysiol Biofeedback* 2020; 45: 131–144.
111. Kalaydjian A, Zandi PP, Swartz KL, et al. How migraines impact cognitive function: findings from the Baltimore ECA. *Neurology* 2007; 68: 1417–1424.
112. Liang Y, Gao Y, Wang R, et al. Migraine, cognitive decline, and dementia in older adults: a population-based study. *J Alzheimers Dis* 2022; 88: 263–271.
113. Martins IP, Maruta C, Alves PN, et al. Cognitive aging in migraine sufferers is associated with more subjective complaints but similar age-related decline: a 5-year longitudinal study. *J Headache Pain* 2020; 21: 31.
114. Palm-Meinders IH, Koppen H, Terwindt GM, et al. Structural brain changes in migraine. *Jama* 2012; 308: 1889–1897.
115. Rist PM, Dufouil C, Glymour MM, et al. Migraine and cognitive decline in the population-based EVA study. *Cephalalgia* 2011; 31: 1291–1300.
116. Rist PM, Kang JH, Buring JE, et al. Migraine and cognitive decline among women: prospective cohort study. *Br Med J* 2012; 345: e5027.
117. Gu L, Wang Y and Shu H. Association between migraine and cognitive impairment. *J Headache Pain* 2022; 23: 88.
118. Jiang W, Liang GH, Li JA, et al. Migraine and the risk of dementia: a meta-analysis and systematic review. *Aging Clin Exp Res* 2022; 34: 1237–1246.
119. Qu H, Yang S, Yao Z, et al. Association of headache disorders and the risk of dementia: meta-analysis of cohort studies. *Front Aging Neurosci* 2022; 14: 804341.
120. Wang L, Wu JC, Wang FY, et al. Meta-analysis of association between migraine and risk of dementia. *Acta Neurol Scand* 2022; 145: 87–93.
121. Zhu H, Ni H, Yang Q, et al. Evaluating the bidirectional causal effects of Alzheimer's disease across multiple conditions: a systematic review and meta-analysis of mendelian randomization studies. *Int J Mol Sci* 2025; 26; 3589.

122. Akerman S, Romero-Reyes M and Holland PR. Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. *Pharmacol Ther* 2017; 172: 151–170.
123. Zhu W, Zhan Y, Pei J, et al. Migraine is a risk factor for dementia: a systematic review and meta-analysis of cohort studies. *J Headache Pain* 2025; 26: 136.
124. Dilekoz E, Houben T, Eikermann-Haerter K, et al. Migraine mutations impair hippocampal learning despite enhanced long-term potentiation. *J Neurosci* 2015; 35: 3397–3402.
125. Bozkaya-Yilmaz S, Olgac-Dundar N, Aliyeva N, et al. Phenotypic variability in cases with CACNA1A mutation. *Eur J Pediatr* 2025; 184: 261.
126. Koppen H, Boele HJ, Palm-Meinders IH, et al. Cerebellar function and ischemic brain lesions in migraine patients from the general population. *Cephalalgia* 2017; 37: 177–190.
127. Karner E, Nachbauer W, Bodner T, et al. Long-term outcome of cognitive functions, emotional behavior, and quality of life in a family with familial hemiplegic migraine. *Cogn Behav Neurol* 2012; 25: 85–92.
128. Kalimo H, Viitanen M, Amberla K, et al. CADASIL: hereditary disease of arteries causing brain infarcts and dementia. *Neuropathol Appl Neurobiol* 1999; 25: 257–265.
129. Mellies JK, Bäumer T, Müller JA, et al. SPECT Study of a German CADASIL family: a phenotype with migraine and progressive dementia only. *Neurology* 1998; 50: 1715–1721.
130. Yeh PK, Liang CS, Tsai CL, et al. Genetic variants associated with subjective cognitive decline in patients with migraine. *Front Aging Neurosci* 2022; 14: 860604.
131. Goadsby PJ. The vascular theory of migraine—a great story wrecked by the facts. *Brain* 2009; 132: 6–7.
132. Hoffmann J, Baca SM and Akerman S. Neurovascular mechanisms of migraine and cluster headache. *J Cereb Blood Flow Metab* 2019; 39: 573–594.
133. Hu B, Yu Y, Dai YJ, et al. Multi-modal MRI reveals the neurovascular coupling dysfunction in chronic migraine. *Neuroscience* 2019; 419: 72–82.
134. Swartz RH and Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol* 2004; 61: 1366–1368.
135. Gomez-Beldarrain M, Oroz I, Zapirain BG, et al. Right fronto-insular white matter tracts link cognitive reserve and pain in migraine patients. *J Headache Pain* 2016; 17: 4.
136. Eikermann-Haerter K and Huang SY. White matter lesions in migraine. *Am J Pathol* 2021; 191: 1955–1962.
137. Noseda R, Borsook D and Burstein R. Neuropeptides and neurotransmitters that modulate thalamo-cortical pathways relevant to migraine headache. *Headache* 2017; 57: 97–111.
138. Chen Y, Xie S, Zhang L, et al. Attentional network deficits in patients with migraine: behavioral and electrophysiological evidence. *J Headache Pain* 2024; 25: 195.
139. Schoenen J, Wang W, Albert A, et al. Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. *Eur J Neurol* 1995; 2: 115–122.
140. Mickleborough MJ, Chapman CM, Toma AS, et al. Interictal neurocognitive processing of visual stimuli in migraine: evidence from event-related potentials. *PLoS One* 2013; 8: e80920.
141. Schoenen J, Ambrosini A, Sándor PS, et al. Evoked potentials and transcranial magnetic stimulation in migraine: published data and viewpoint on their pathophysiologic significance. *Clin Neurophysiol* 2003; 114: 955–972.
142. Coppola G, Pierelli F, Schoenen J, et al. *Neurophysiology of the migraine brain - Neurophysiological model of migraine pathophysiology: bringing the past into the future*. Springer Cham, 2021.
143. Tsai CL, Chou KH, Lee PL, et al. Shared alterations in hippocampal structural covariance in subjective cognitive decline and migraine. *Front Aging Neurosci* 2023; 15: 1191991.
144. Cankaya S, Ayyildiz B, Sayman D, et al. Hippocampal connectivity dynamics and volumetric alterations predict cognitive status in migraine: a resting-state fMRI study. *NeuroImage* 2025; 305: 120961.
145. Mehnert J and May A. Functional and structural alterations in the migraine cerebellum. *J Cereb Blood Flow Metab* 2019; 39: 730–739.
146. Burgos AF, Olson PA and Vgontzas A. The glymphatic system and its relationship to migraine. *Curr Neurol Neurosci Rep* 2024; 24: 517–525.
147. Chen XY, Chen ZY, Dong Z, et al. Regional volume changes of the brain in migraine chronification. *Neural Regen Res* 2020; 15: 1701–1708.
148. Liu J, Lan L, Li G, et al. Migraine-related gray matter and white matter changes at a 1-year follow-up evaluation. *J Pain* 2013; 14: 1703–1708.
149. Stewart BW, Keaser ML, Lee H, et al. Pathological claustrum activity drives aberrant cognitive network processing in human chronic pain. *bioRxiv* 2023: Nov 2:2023.11.01.564054. doi: 10.1101/2023.11.01.564054.
150. Moriarty O, McGuire BE and Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol* 2011; 93: 385–404.
151. Phelps CE, Navratilova E and Porreca F. Cognition in the chronic pain experience: preclinical insights. *Trends Cogn Sci* 2021; 25: 365–376.
152. Han DG. Evolutionary game model of migraine based on the human brain hypersensitivity. *Front Neurol* 2023; 14: 1123978.
153. Lisicki M and Schoenen J. What is the evolutionary disadvantage of migraine? *Cephalalgia* 2025; 45: 3331024251327361.
154. Cortelli P, Pierangeli G and Montagna P. Is migraine a disease? *Neurol Sci*. 2010; 31: S29–S31.
155. Pensato U, Cevoli S, Pierangeli G, et al. The evolutionary meaning of migraine. *Cephalalgia* 2023; 43: 333102423 1209303.
156. Rispoli MG, De Angelis MV, Melchionda D, et al. High-risk area for migraine attacks - a new concept in migraine pathophysiology. *Front Neurol* 2025; 16: 1569361.