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Migraine and cognitive dysfunction: a narrative review

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Abstract

The association between migraine and cognitive function has been studied during the last decade, however, this relationship is not well established. As migraine prevalence is highest between the ages of 30–40, aligning with some of our most productive years, we must understand cognitive changes within this disorder. Cognitive impairment potentially limits social and professional interactions, thus negatively impacting quality of life. Therefore, we will review the relationship between prevalent migraine and cognition. Cognitive dysfunction has been reported to be the second largest cause of disability, after pain, in migraine patients. While subjective patient reports on cognition consistently describe impairment, findings for objective neuropsychological assessments vary. Many studies report worse cognitive performance in the ictal phase compared to controls, which can persist into the postictal period, although whether this continues in the interictal period has been understudied. There is limited consensus as to whether cognition differs in migraine with aura versus migraine without aura, and while many studies do support cognitive impairment in chronic migraine, it remains uncertain as to whether this is more debilitating than the cognitive difficulties experienced by those with episodic migraine. To date, objective assessment of neurological abnormalities that may underlie cognitive impairment through neuroimaging has been underutilized. There is limited consensus as to whether cognitive impairment is a characteristic specific to migraine, whether it is driven by a combination of factors including co-morbidities such as anxiety, depression, or vascular dysfunction, treatment, or whether it is a more general characteristic of pain disorders. Overall, increasing numbers of studies support cognitive impairment in migraine patients. Future studies should consider longitudinal study designs to assess cognition across different migraine phases and subtypes of the disorder, including migraine with aura and chronic migraine, as well as controlling for important confounders such as treatment use.

Keywords Migraine, Cognition, Chronic migraine, Cognitive impairment

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Introduction

Migraine is one of the most prevalent disorders globally, affecting an estimated 14% of the population [1]. According to the Global Burden of Disease Study, migraine is the second-leading cause of years lost to disability [2] and the first in women [2]. Consequently, the socio-economic burden of migraine is large, costing the European Union an estimated €50 billion annually [3]. Productivity loss makes up 93% of the economic cost of migraine. Despite patients reporting cognitive symptoms to be the second-largest cause of attack-related disability after pain [4], the potential impact of migraine on cognitive performance remains controversial.

Migraine is a multifaceted disorder with symptoms extending beyond the headache phase. In the hours to days preceding the headache phase, patients may experience preictal symptoms, including mood changes and fatigue. Similarly, following headache resolution, postictal symptoms may be present. There are several subtypes of migraine; 30% of patients may experience a transient migraine aura consisting of sensory and, in some cases, motor disturbances lasting between 5 and 60 min (migraine with aura (MwA)) [5, 6], while the majority of patients have migraine without aura (MwoA). Furthermore, annually, 3% of migraine patients develop chronic migraine (CM) as they surpass 15 headache days per month, whereby 8 meet migraine headache criteria [7]. There is no current consensus on how cognition differs in different migraine phases or forms.

Cognitive performance can be assessed across various functional domains, including attention, concentration, memory, executive functioning, reasoning and problem-solving, processing speed, and language through neuropsychological evaluation. Furthermore, cognitive functioning can also include social cognition, such as the ability to understand social cues and interact with others [8].

These cognitive abilities are essential for daily life, underlying our capacity to perform routine tasks, make decisions, and adapt to changing environments.

Several studies have investigated the association between migraine and cognitive function, although the results are discordant [9]. Several authors have suggested that these inconsistencies regarding cognitive impairment and migraine in the literature may be due to methodologic issues such as sample size, unrepresentative samples, and lack of adequate comparison groups [10]. In contrast, other studies suggest that cognitive impairment is present compared to healthy controls (HCs) and that this impairment contributes to the worsening of quality of life alongside pain symptoms [9, 11, 12]. Additionally, the impact of frequent migraine attacks on cognition is a common source of concern for patients, as it is unclear whether attack repetition may have long-term consequences [13]. This highlights the importance of considering the complexity of migraine, focusing on broader impairment, beyond pain symptoms [14].

Consequently, in this review we evaluated the current consensus of cognitive performance in migraine patients during migraine episodes, focusing on cognitive impairment across different migraine phases, and different subtypes of the disorder. The influence of confounders, such as the presence of comorbidities including depression [15], and the use of prophylactic and acute treatments were considered [16].

To achieve this, we performed a non-systematic search on the PubMed/MEDLINE and EMBASE databases, and we used the following terms in our search strategy: "migraine" OR "chronic migraine" OR "episodic migraine" AND "cognition" OR "cognitive performance" OR "cognitive impairment". Studies followed the established inclusion criteria, peer-reviewed journal articles and only reported studies performed on living humans, and the exclusion criteria, reference lists, gray literature, and non-human studies.

Subjective cognitive impairment in migraine patients

Self-reported subjective cognitive impairment is most common in the elderly and correlates with age. There is a cumulative transformation rate to dementia of 10.7% over 5.2 years [17]. Similar subjective cognitive complaints have also been described in migraine patients [11]. A Taiwanese study, of 589 migraine patients and 80 healthy controls, showed that subjective memory complaint scores were similar in both groups. However, analysis of female MwA patients showed higher attack frequency correlated with higher scores on Ascertain Dementia 8 questionnaire [11]. Additionally, a Korean study reported a 44.7% prevalence of subjective cognitive decline in a cohort of 188 migraine patients, concerning patients with higher pain intensity and comorbid psychiatric disorders, such as anxiety and depression, and sleep disturbances [18]. Migraine patients often report cognitive impairment before it is evidenced by subjective and objective testing [see Additional file 1]. Subjective complaints are typically expressed through questionnaire and detail an individual's perception of cognitive impairment and difficulties. When assessing patient self-report of cognition, 89.7% report cognitive symptoms during the headache phase of the attack, most commonly in executive function and attention [19]. On an Ascertain Dementia 8 questionnaire, female MwA patients had higher scores than HCs, indicating a self-perceived decline in cognitive abilities [11]. Furthermore, a Korean study reported a 44.7% prevalence of subjective cognitive decline in a migraine cohort [18]. However, this subjective cognitive impairment has been shown to correlate with higher pain

intensity, and comorbid anxiety, depression, and sleep disturbances [8, 18].

Patients have reported cognitive exertion as a potential migraine trigger. This may be the basis for the development of cogniphobia: the fear and avoidance of cognition exertion) [20]. A study of the associations between cogniphobia and key fear-avoidance constructs in migraine patients concluded that higher anxiety and pain-related fear is related to greater self-report of cognitive symptoms and lower neuropsychological functioning [20].

Summary: Subjective cognitive impairment, manly memory and attention complaints, are common in migraine patients with comorbidities such as depression, anxiety and/or sleep disturbances.

Objective cognitive performance in migraine patients

Migraine is a brain disorder accompanied by a risk of cognitive impairment [14, 21]. Evidence from neuropsychological measurements has suggested that cognitive functioning may differ during and between migraine attacks [21].

Cognitive symptoms, such as inattention, are reported throughout migraine phases, but there is a lack of knowledge about objective cognitive profiling. A meta-analysis, including 22 studies, showed a lower general cognitive function in the migraine group compared to HCs, especially in the language domain. However, no significant differences were found in visuospatial function, memory, or attention [18].

During migraine attacks, cognitive impairment is considered one of the most disabling manifestations [22]. As such, several studies have assessed cognition during migraine attacks, identifying transient declines in processing speed and working memory [23]. Meyer et al. showed that Mini-Mental State Examination (MMSE) scores decreased significantly during a migraine attack in patients who had normal scores during headache-free periods [24]. A home-based computerised cognitive test study examined the effect of cognition during migraine phases. During the headache and postdrome phase, migraine patients had a cognitive decline in working memory and simple and choice reaction time compared to the interictal period. Using a home-based computerised cognitive test, a decline in working memory and simple and choice reaction time has been identified in the headache and postdrome phase compared to the interictal period [23]. However, no consensus exists between different neuropsychological, clinical-based, and population-based studies on interictal cognitive dysfunction [20].

Beyond this, longitudinal studies evaluating the relationship between migraine and cognitive decline consistently fail to identify an increased risk of cognitive decline in migraine patients [25, 26]. A large population-based study of Danish twins investigated the cognitive functioning of migraine patients and healthy controls using a battery of tests, including Fluency, Forward and Backward Digit Span tests (DST), a Modified 12-Word Learning Test with immediate and delayed word recall, and a Symbol-Digit Substitution Task (SDST). Average scores did not differ between groups. The adjustment for possible confounders (age, sex, and schooling) suggested that a lifetime diagnosis of migraine was not associated with cognitive deficits [10]. Indeed, a Dutch population-based study of migraine patients found that middle-aged and elderly migraine patients, especially those with MwA, actually had higher MMSE scores and g-factor, a domain-independent general cognition indicator, than non-migraineurs [27].

Nevertheless, a significant association between migraine and dementia risk has been observed in an Asian subgroup [28]. Also, a Swedish population-based longitudinal study compared the cognitive performance of healthy controls and patients with migraine and non-migraine headaches. The authors found that migraine patients were younger and had a higher MMSE score at baseline [29]. Moreover, migraine has been associated with silent brain lesions, which are known risk factors for dementia. However, epidemiological studies have yielded inconsistent evidence with several population-based studies finding no association between migraine and cognitive decline. Conversely, several register-based studies did suggest an association of migraine with dementia [29]. Although the prevalence of dementia was around 0.49 (0.20–1.21) for migraine group, there was no evidence supporting the associations of migraine and its subtypes with cognitive decline and dementia among older adults [29].

Summary: Differences in cognitive functioning may differ during and between migraine but there still is more to know about cognitive profiling and the long-term effect of migraine on cognition.

Migraine and affected cognitive domains

The literature states that migraine patients complain primarily of deficits in attention and memory but also confusion during attacks, which compromises cognitive efficiency [30]. Clinic-based studies report worse cognitive performance on verbal and visuospatial memory, information processing speed, executive function, and attention, even during the interictal period [9, 14, 22, 31–35]. Migraineurs have trouble adjusting attention, requiring more time for automatic processes, and show cortical hyperexcitability and lack of habituation to repeated stimuli, known as one form of learning mechanism [32].

Summary: The cognitive domains that seem more affected in migraine patients are attention, memory and processing speed, but they can differ between the ictal or interictal phase.

Objective findings of cognitive impairment in migraine

Many measures of cognitive ability use subjective examination; however, the use of objective measures has the potential to identify possible biomarkers of cognitive impairment in migraine patients. Magnetic resonance imaging (MRI) and electroencephalography (EEG) are commonly used in clinical settings and research, especially when assessing neurological pathologies. A similar implementation may be beneficial for the migraine field.

MRI is widely used to examine structural and functional neurological changes. This can be utilised to identify changes associated with cognitive impairments. Some evidence suggests that migraine may be associated with white matter lesions (WML) [36]. However, studies in this regard are conflicting. While some studies theorise that the association between WML and migraine is purely incidental or caused by comorbidities, others identify no causal relationship between migraine and WML [37]. A significant limitation in this area is the lack of availability of MRI scans pre- and post-migraine diagnosis. WMLs are of substantial interest as a clear association between WML and cognitive impairment has been noted within the literature [38].

Daglas et al. investigated the potential causality between genetic liability to migraine and Alzheimer's disease through assessment of brain volume. The possible association between interictal migraine cognitive function and dementia risk remains controversial; identification of silent WML and regional brain volumes could provide evidence to support this link. Nevertheless, in the above study, genetic liability to migraine was not associated with Alzheimer's disease or any brain volume measures [39]. These null findings are consistent with multiple cohort studies, which did not identify an effect of migraine on rates of cognitive decline [39].

Functional MRI (fMRI) can be used to characterise regions of altered activity in migraine, thus making the relationship between migraine and cognitive functioning better understood [40, 41]. One study identified altered frontoparietal network connectivity [42] involved in executive functioning and mental flexibility. A reRt systematic review of neuroimaging of memory function in migraine highlighted nine studies that showed altered activity in memory-related structures, including the hippocampus, insula, and temporal cortices, providing objective evidence supporting memory alterations in migraine patients. Furthermore, patients with MwoA showed abnormal intrinsic connectivity within the bilateral central executive network (CEN) and salience network (SN) and more excellent connectivity between the default mode network (DMN) and right CERN and the insula, angular and supramarginal gyrus. These networks have been associated with cognition, such as working, semantic, and episodic memory, attention, social cognition, and executive function. These studies underlie a possible neurobiological mechanism of pain-related reorganization of connectivity and the impact on cognitive performance [42]. Further studies are required to fully understand the neurological changes that may underlie cognitive alterations in migraine, covering a broader range of cognitive domains. Studies have identified overlap between regions of altered activity and areas that are associated with a role in pain processing, highlighting a need for additional studies across a variety of pain disorders to identify migraine-specific and pain-related functional changes that impact cognition [43].

Other functional imaging studies, such as positron emission tomography, support a prefrontal and temporal cortical dysfunction during migraine attacks that can be clinically associated with a predominant involvement of processing speed, attention, and memory [44].

Electroencephalography (EEG) can also be used to assess altered neurological functioning which may underlie cognitive changes in migraine. While EEG studies have been under-utilised to date, one study has identified changes in beta event-related desynchronisation during sensorimotor processing across different migraine phases [45], thus highlighting the potential for this approach to be expanded to assess cognition, both across different migraine phases and compared to HCs.

Objective assessment of neurophysiological changes in cognitive processing has been underutilised to date. Broader utilisation of such approaches would enable a clearer understanding of which cognitive domains are affected and which migraine phases, allowing a better understanding of migraine prognosis and betterment of patient QoL.

Summary: Although there is evidence of a connection between cognitive functioning and objective findings during or between migraine episodes, there is still not enough data to have a solid conclusion on this matter.

Cognitive performance across migraine phases

Though headache is the predominant migraine symptom, other symptoms, including cognitive symptoms, develop over the migraine episode [46]. Thus, researchers have tried to establish whether objective cognitive impairments are present during the ictal or peri-ictal phases in migraine patients [23, 24, 34, 41, 47–56].

A systematic review assessing decreased cognitive functions during a migraine attack compared to headache-free performance [53]. Five studies were included.

They all showed a performance reduction in cognitive tests during the ictal phase of the migraine episode compared to the pain-free period [24, 47, 48, 50]. These findings were later confirmed by three original studies published after 2014, which showed decreased cognitive functions in the ictal phase compared to the interictal phase [23, 34, 41].

An impairment in global cognition during the ictal phase, compared to a headache-free period, was found in one study [24]. The most affected cognitive domains were memory, attention, and processing speed, present in six [4, 23, 34, 47, 48, 50] out of the seven [4, 23, 34, 41, 48, 50, 52] studies that assessed them. The remaining impaired domains were in executive function, found in three [41, 48, 50] out of four [34, 41, 48, 50] studies, and in motor function, found in two [41, 47, 50] out of three [34, 41, 47] studies. Language impairment was found in one [34] of the two [34, 41] studies that assessed it, while impairment in the visuospatial domain was only found in the study that assessed it [4]. However, the studies that assessed memory, attention, processing speed, executive function, and language using a comprehensive battery of tests for each cognitive function [34, 41] found impairments in only one test among the two to four used. Thus, not all cognitive tests are sensible in detecting ictal impairment in mental performance.

While there is consistent evidence supporting the presence of cognitive impairments in migraine patients during the ictal phase, data regarding the presence of a decline in mental performance during the preictal and postictal phases are less conclusive. Four studies assessed cognitive impairments during the postictal phase with conflicting results. Two showed no differences in cognitive function between migraine patients during the postictal and the interictal phase [52, 57]. Conversely, the other two studies showed worse performance in cognitive tests in the post-ictal phase compared to the interictal phase, specifically in attention [23, 51], processing speed [23, 51], and memory domains [23]. However, among those four studies, only one did not allow acute medication use before the evaluation [52]. One study assessed postictal migraine patients following the utilisation of acute migraine drugs [23], while the other two did not specify if patients took acute medication before the assessment [51, 57].

Only one study assessed the presence of cognitive impairments during the preictal phase [23]. In this study, migraine patients performed one month of daily testing with a computerised cognitive battery assessing memory, attention, and processing speed [23]. Then, the performance of each test in the preictal, ictal, and postictal phases was compared with the performance in the interictal days. The authors showed reduced cognitive performance during the ictal and postictal phases, with the latter being less pronounced. Conversely, no significant differences were observed between the pre and interictal phases [23].

Overall, these results confirm that objective cognitive impairments occur in migraine patients during the ictal phase and could persist in the postictal phase in a subgroup of patients. Alternatively, no reduction in cognitive performance has been shown in the preictal phase. However, whether these cognitive impairments could be considered an epiphenomenon due to the ongoing pain processing in the brain [58] or a migraine-specific phenotype is still a point of debate. Studies that fail to find significant differences in ictal cognitive performance between migraine and cluster headache patients or patients with other pain conditions support the first hypothesis of ongoing pain processing [49]. This may explain why cognitive impairment is most commonly observed in the ictal but not the preictal phase [23] when, conversely, activation of cortical and subcortical brain regions associated with a migraine episode is already in place [59, 60]. In contrast to this hypothesis, a recent study found that the reduction in cognitive performance occurred only on "migraine days" but not on "non-migraine days," suggesting that cognitive impairments could be considered a characteristic of migraine [23]. Whilst evidence does indicate a reduction in cognitive performance during the migraine attack, more research is needed to conclusively determine the presence of cognitive impairment during the preictal and postictal phases.

Summary: Migraine patients had objective cognitive impairments during the ictal phase, especially in memory, attention, processing speed, and executive functions, and during the postictal phase, in attention, processing speed, and memory domains (See Fig. 1).

Cognition in episodic migraine with aura vs. migraine without aura

Few studies have detailed the discrepancies between cognition in MwA compared to MwoA. Le Pira et al. conducted two studies using tests, including the California Verbal Learning test (CVLT) and the Rey Complex Figure test (ROCF-m), which assesses verbal memory and learning strategies, to compare MwA and MwoA patients. The initial study found no significant differences in CVLT, but the subsequent study showed that MwA patients performed significantly worse [61, 62]. Additionally, ROCF-m showed no significant differences in short- and long-term verbal memory between the groups, although MwA individuals with bilateral or right-sided pain performed worse than MwoA patients, although not significantly [61, 62]. Further assessments using the DST and Corsi Block-Tapping Test found no differences in working memory between MwA and MwoA [61, 62]. Despite some evidence of significant verbal memory impairment

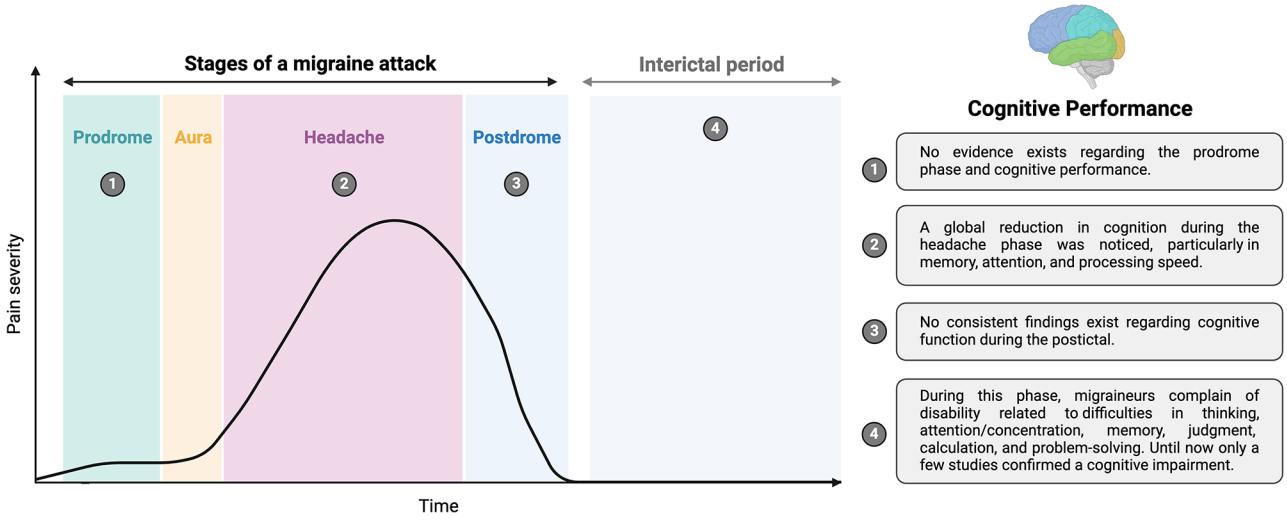

Fig. 1 Migraine episode and cognitive function - a representation of "the cycle of migraine" and the findings in the cognitive function according to our review. (Created with BioRender.com)

in MwA, it is inconsistent, and the impact of aura on memory remains inconclusive.

The Trail-Making Test (TMT) assesses attention and processing speed. It comprises two parts: Part A involves sequentially connecting numbers, while Part B alternates between numbers and letters. In a Latin American cohort, MwoA patients performed significantly worse on TMT B; however, the MwA cohort was underpowered, limiting the generalisability of these findings [63]. Conversely, other studies have not identified significant differences in TMT performance between MwA and MwoA patients [64, 65].

Additional tests assessing attention and processing speed, such as the Continuous Performance test, the Colour Word Task, the Checkerboard Attention test, and the SDST, revealed significantly slower reaction times in MwA compared to MwoA patients [57, 66, 67]. Le Pira et al. demonstrated impaired selective attention in MwoA patients, but subsequent studies did not corroborate this finding [61, 62, 65]. Furthermore, the Pattern Perception test, evaluating visual perception, spatial processing, and attention, showed no differences in reaction times between the two migraine subsets [57]. Despite some studies indicating differential impacts on attention and processing speed between MwA and MwoA, these findings are inconsistent, underscoring the need for further powered studies to be able to conclude attention and processing speed discrepancies between MwA and MwoA.

The Frontal Assessment Battery Test, which evaluates motor programming, mental flexibility, and sensitivity to interference, revealed significantly poorer performance in MwA compared to MwoA patients [65]. However, this finding was based on a single study, necessitating further research to draw reliable conclusions. Conversely, investigations into language functions using the Phonemic Fluency Word Generation test, Verbal Fluency test, and the Controlled Oral Word Association test reported equal performance between the two migraine subsets and HCs [61, 63, 65]. Similarly, no differences were observed in social cognition, assessed by the Raven Progressive Matrices 47 Test, which evaluated comparative reasoning and analogical thinking [62, 63].

Current evidence indicates that MwA and MwoA patients exhibit cognitive impairments, with MwA patients experiencing more pronounced deficits [62]. Specifically, in multiple studies, MwA patients showed significantly poorer attention and processing speed performance, particularly under conditions requiring sustained focus and rapid processing. This suggests that aura, despite causing temporary sensory disturbances, may have lasting effects on attentional and processing capacities. The evidence suggests these deficits are confined to higher-order cognitive functions, as no significant differences were observed in primary sensory processing, perception, and recognition tests. Additionally, no language and social cognition differences were found, although the research was limited. Findings are further limited by potential selection bias as studies recruited patients from their neurological department and commonly had underpowered MwA populations. Moreover, the variability in neuropsychological assessments across studies hinders the ability to draw reliable comparisons. Further research is needed to clarify these cognitive differences and their underlying mechanisms.

Summary: Evidence indicates that MwA and MwoA patients exhibit cognitive impairments, specifically, MwA patients showed poorer attention and processing speed performance, this suggests that aura may have lasting effects on cognition.

Cognition in chronic migraine

As mentioned before, migraine attack frequency has been shown to correlate with cognitive performance in EM, particularly in executive functioning, visual short-term memory, and attention [68, 69]. Since cognitive impairment is the second largest cause of episode-related disability after pain, understanding how it evolves with migraine chronification is crucial [13].

While global cognitive assessments suggest that some CM patients show cognitive deficits, findings are inconsistent [35, 70, 71]. Nevertheless, CM patients have demonstrated poor performance on individual components compared to healthy controls and EM patients [71], suggesting that a more nuanced view of assessing individual cognitive domains may provide a more detailed understanding of how cognition differs in CM.

Interest in decision-making and reward prediction in CM has partially stemmed from the prevalence of medication overuse headache (MOH) among this population [72]. Despite hypotheses of impaired performance in CM-MOH patients, studies utilising the Iowa Gambling Task, which simulates risk-taking during decision-making, found no significant differences when comparing HCs and EM patients [73, 74]. While one more extensive study did identify a substantial deficit in decision-making versus HCs, following MOH treatment with detoxification (protocol not specified), scores remained significantly lower despite Migraine Disability Assessment questionnaire (MIDAS) improvement [75, 76]. Thus, impaired decision-making in CM appears unrelated to the presence of MOH, although studies are limited. There is greater consistency of evidence for impaired cognitive flexibility in CM. CM patient performance is worse than that of HCs and EM in the Wisconsin Card Sorting Task [73, 77, 78], most commonly in the number of categories completed. A second task-switching paradigm complements these findings, indicating worse performance than HCs and low-frequency EM [79], suggesting executive functioning is impaired in CM, more so than in EM patients. Evidence does not support a more significant impairment in CM with MOH versus without [73], although sample sizes are small. Additionally, the Tower of London test provides evidence of impaired planning compared to HCs [74, 80, 81], although contradictory findings exist [74, 80, 81].

Inconsistency in cognitive assessment and continued medication use, as preventives and abortive drugs, limits the coherence of findings. Working memory deficits identified in the forward DST [35, 81] are influenced by medication use [35], which may contribute to contradictory findings [79, 82]. Similarly, performance deficits have been identified in the Rey-Auditory Verbal Learning test; however, they only occur in the number of words learned [70]. When reporting only an overall score, no significant difference was found when comparing CM to HCs [35]. Further assessments of memory in CM patients have reported deficits in delayed recall compared to HCs. However, there is no additional evidence assessing performance relative to EM patients [80, 81, 83]. Thus, while some evidence supports impaired memory in CM, variability in studies conducted to date precludes definitive conclusions.

As mentioned above, evidence supporting the deficit in selective attention and processing speed in CM is discrepant. While four studies identify significantly worse performance in either TMT A and/or B compared to HCs [71, 73, 78, 83], many show no difference [35, 80–82]. Comparisons between CM and EM are equally as varied [35, 71, 76, 81]. Nevertheless, performance in the Stroop test is consistently poor compared to HCs [35, 81], suggesting a potential selective attention impairment in CM individuals.

Few studies have assessed visuospatial processing and language, with two demonstrating visuospatial impairments [35, 80] despite inconsistency across individual tasks. One study documented reduced verbal fluency in CM vs. HCs [35], but this has not been replicated. Further studies across a broader range of cognitive domains are required to provide a complete understanding of cognition in CM.

Social cognitive assessments indicate CM patients may have difficulty recognising or describing emotions. Three studies reveal greater alexithymia in CM versus HCs in the Toronto Alexithymia Scale, in both total score and factor 1, which assesses difficulty identifying feelings [84–86]. Despite consistently higher CM scores, there are no firm conclusions when comparing CM to EM [84, 85]. Further emotional cognition deficits were seen in various tests compared to HCs [78, 81, 85, 87] and, in some cases, versus EM. Social cognition is impaired in CM, potentially impacting social interactions and QoL [83, 85].

CM is associated with increased co-morbidities such as depression and anxiety [15, 88–90], which are also linked to cognitive dysfunction [15, 88–90] and, therefore, may contribute to the cognitive deficits seen in CM. One study stratified CM patients and showed those with normal mood still performed worse than HCs in ROCF-m but not TMT-A or B [83]. Similarly, several studies showed no significant effect of depression and anxiety on cognitive performance [35, 70, 85]. Thus, while the increasing prevalence of co-morbidities may be a contributing factor to cognitive impairment, it is not the sole factor.

Overall, evidence of worsening cognitive performance with CM is mixed, although there are indications of deficits in executive function, social cognition and potentially in selective attention and delayed recall compared to HCs. Comparisons between CM and EM are limited

and incongruous, often confounded by contradictory evidence on whether EM patients differ from HCs. Migraine frequency and severity likely contribute to this discrepancy. Hypotheses of worsening cognitive performance with migraine chronification [35, 71, 76, 81] are supported by studies that find significantly poorer cognitive performance in CM patients compared to EM [79, 84, 85], which is particularly highlighted by a single study which reports significant differences between CM and low-frequency, but not high-frequency EM [79, 84, 85], however, greater scrutiny in this area is required [59, 61, 66, 69, 71, 74, 75] (Fig. 3). Recruitment of participants exclusively from neurology clinics may generate selection bias towards more severe cases, limiting generalisability. Low sample sizes, varying treatment regimes, and inconsistency in test batteries further constrain reproducibility. Consequently, further research, including longitudinal studies, is required to clarify the impact of CM on cognition and assess cognition during migraine chronification.

Summary: Chronic migraine patients seem to show deficits in executive function, social cognition, and attention; however, longitudinal studies are missing to clarify the impact of CM and how chronification influences cognitive performance (See Fig. 2).

Preventive migraine treatment and its impact on Cognition

Migraine treatment can be divided into acute and preventive treatment. Topiramate, a preventative treatment, is known to cause dose-dependent cognitive side effects, including attention deficits, psychomotor slowing, and language and comprehension difficulties [91]. While migraine patients tend to have fewer cognitive complaints than epilepsy patients, drop-out complaints in topiramate trials mainly surround memory and concentration deficits [92].

Pregabalin, another preventative treatment, negatively affects cognition, especially visuospatial memory, processing speed, and attention [83]. Tricyclic antidepressants, such as amitriptyline, show an overall detrimental effect on cognition due to their anticholinergic and antihistaminic properties, which primarily affect attention, decision-making, and psychomotor speed [91]. A prospective study concerning the cognitive effects of onabotulinum toxin A treatment that included 60 patients noticed an improved cognitive score at 3 and 6 months, independent of improvement in headache frequency or intensity [93].

Regarding more recent migraine treatments, no cognitive side effects have been reported for anti-CGRP monoclonal antibodies and "gepants", and a possible neuroprotective role is being debated [91]. Torrisi and colleagues studied the efficacy of erenumab, an anti-CGRP treatment, on cognitive performance and psychological well-being in migraine patients, comparing MoCA and Short Form Health Survey 36 (SF-36) scores at baseline and follow-up. Improvement in both cognitive performance and QoL was seen, postulating that effective preventive treatment could improve cognitive performance [31]. Additionally, lamotrigine, duloxetine and venlafaxine show a possible neuroprotective effect with improvement of cognitive performance [91].

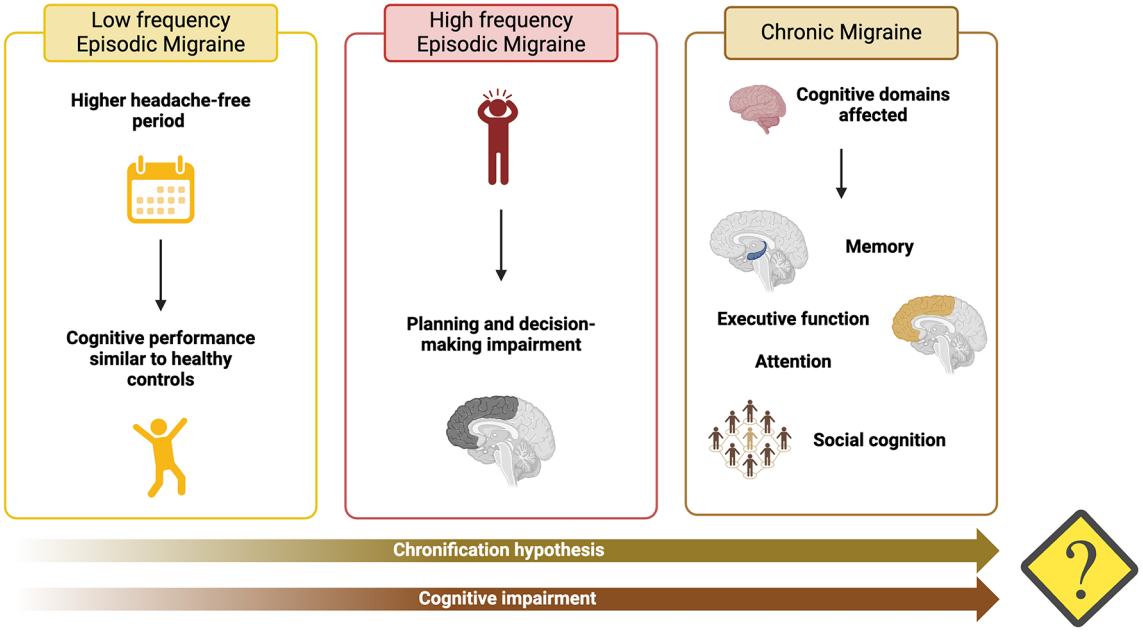

Fig. 2 Migraine subtypes and cognition model - a relationship between "chronification" and cognitive performance seems to exist, but still no evidence supports it. (Created with BioRender.com)

In terms of acute treatment, triptans can impair cognition with known global amnesia-like symptoms due to vasoconstriction and transient ischemia [91]. However, two small studies evaluated cognitive symptoms during an acute attack and following sumatriptan administration. No restored cognitive performance after sumatriptan administration was seen [22]. Regarding ditans, selectively 5-hydroxytryptamine receptor 1 F (5-HT1F) receptor agonists, a study enrolled in healthy volunteers showed that lasmiditan impaired simulated driving performance around 1 h after administration, showing a possible central effect of this drug [94]. Less specific, acute treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), may have a neuroprotective role due to their mechanism of action as an anti-inflammatory drug [91].

An open-label clinical study of the impact of donepezil as a migraine preventive treatment showed that donepezil was effective in both EM and CM. This may be due to a possible cholinergic dysfunction in migraine. This supports that cognitive performance could be impaired because of dysfunctional cholinergic activity in the cortex [22].

As it has been evidenced that migraine medication can affect cognition, this is a key confounding factor that should be considered when assessing cognitive performance in migraine patients. Many studies fail to control for this, potentially contributing to the lack of consistency in findings.

Summary: We need to be aware that preventive treatment could influence cognitive performance and this fact is a confounding factor when assessing cognitive function in migraine patients.

Migraine comorbidities and cognition

While cognitive impairment is evident in migraine, it should be considered that several of the most common migraine co-morbidities include multiple disorders known to be associated with cognitive dysfunction. These include certain psychiatric, neurological, vascular, and metabolic disorders.

Epilepsy has well-documented links with both migraine [95] and cognitive dysfunction [96]. The frequency of migraine among epileptic patients is at least two-fold higher than in the general population (1–17% vs. 0.5-1%) [93]. Cognitive impairment can occur in nearly 70–80% of epileptic patients throughout their lifetime [97]. Although the clear mechanism is unknown, cognitive impairment in epilepsy is likely due to a combination of factors, such as treatment side effects, psychosocial consequences, and structural brain deficits [97]. Although the literature on the topic is scarce, one study specifically explored cognitive performance in focal epilepsy patients with and without migraine. Memory scores were found to be significantly lower in patients with co-morbid migraine. However, higher depression and anxiety scores among these patients may also contribute to this relationship [96].

Depression is 2.5 times more prevalent among migraine patients than in the general population [98]. Major depressive disorder has an established link with cognitive dysfunction, with diminished ability to think and concentrate being one of the core symptoms [99]. It was found that cognitive deficits in patients with depression can persist after effective treatment, which is especially concerning migraine patients because depressive symptoms have been reported in around 40% of the patients during their lifetime [99, 100]. Although a direct link has not yet been established, psychiatric conditions such as depression and anxiety are highly prominent in migraine patients [101]. They are also known to be associated with worse cognitive performance as well as worse pain severity, and poor sleep quality [22].

Cognitive impairment is frequently discussed in other chronic pain conditions, such as fibromyalgia [102]. One of its characteristics is a so-called 'fibro-fog,' described as forgetfulness, concentration difficulties, and mental slowness [102, 103]. Cognitive dysfunction has been linked to pain intensity [102, 103], suggesting pain-symptomatology, rather than migraine directly, may underlie the cognitive impairment seen in patients and across other chronic pain disorders [102, 103]. However, psychiatric comorbidities such as depression and anxiety, also prominent in migraine, are widely recognised as impactful in cognitive impairment, based on previous studies where the cognitive function was worse in fibromyalgia patients exhibiting more severe depression and anxiety symptoms [104]. This is also supported by meta-analysis data on cognitive impairment in fibromyalgia, where cognitive function was statistically significantly associated with depression and anxiety scores [105]. Future studies should assess if a similar relationship exists for migraine.

Migraine as a neurovascular disorder [106] has an established link to other cardiovascular diseases, such as ischemic stroke, with a 2-fold higher risk among migraine patients [107]. In addition, as previously described in this review, WMLs of presumed vascular origin [108] are often found in migraine patients' brain MRIs. As WMLs are themselves associated with cognitive impairment, it is important to consider vascular comorbidity as a possible explanation for decreased cognitive function in migraine patients. Risk factors for all-etiology dementia include multiple cardiovascular factors, including type 2 diabetes, hypercholesterolemia, and obesity [109]. Migraine has been reported to even further exacerbate the risk for cerebrovascular diseases [110], suggesting a potential mechanism of cognitive decline in individuals with migraine via increased prevalence of cerebrovascular

events that are known to perturb cognitive performance [111].

Additionally, migraine has been associated with various metabolic disorders [98], such as hypothyroidism, which is more prevalent in CM than in EM patients. Even at subclinical levels, this condition is associated with mild cognitive impairments in memory and executive function [112]. Insulin resistance has also been described as more prevalent in CM patients than in EM patients [113]. Insulin resistance is recognised as one of the risk factors for dementia, with a significant association between cognitive function and baseline hyperinsulinemia, as well as metabolic syndrome and insulin resistance [113–115]. However, the effect of metabolic irregularities on migraineurs in the scope of cognitive performance has not been widely studied. Thus, to fully understand the relationship between migraine and cognitive impairment, it is necessary to consider co-morbidities as potential confounders that may contribute to cognitive test scores.

Summary: Migraine is often linked to other neurological and psychiatric disorders, such as Depression and anxiety, that have a well-documented association with cognitive impairment.

Cognitive impairment and disability in migraine

Estave et al. conducted interviews with migraine patients to assess how migraine affects daily life. Over 90% of patients reported a negative overall impact on daily life, whereas only 14% described cognitive impairment regarding concentration and communication difficulties [116].

Gil-Gouveia et al. [4] assessed how cognitive symptoms affect patients during migraine attacks. Each reported attack-related symptom was evaluated using the Visual-Analog Scale (VAS) to estimate two factors: symptoms' intensity and perceived disability. Besides typical migraine features, patients also evaluated cognitive symptoms, such as thinking difficulties and overall worsening of cognitive symptoms with mental effort. Additionally, each patient was assessed by the SCI scale for migraine (Mig-SCog) and HIT-6. The final analysis showed that the occurrence of cognitive symptoms was highly correlated with attack-related disability. Furthermore, pain was the only symptom that proved to be more burdensome than cognitive dysfunctions [4].

Gómez-Beldarrain et al. assessed cognitive reserve in EM, CM-MOH, and HCs [117]. Cognitive reserve can be considered as the brain's capacity for problem-solving and adaptation. Using multiple questionnaires, migraine patients were found to have a lower cognitive reserve than HCs, with the lowest cognitive reserve found in the CM-MOH group. Furthermore, lower CR scores were correlated with worse QoL outcomes [117].

Conversely, Qin et al., assessed headache disability and cognitive functions using MIDAS, HIT-6, and the MoCA test [33]. The results showed a higher prevalence of cognitive impairment in the migraine patient population compared to HCs. However, no correlation between cognitive impairment and the QoL was found [33].

Nevertheless, it was suggested in several studies that cognitive symptom relief should be implemented as one of the endpoints in future clinical trials for anti-migraine drugs [4, 33, 118]. A pilot study was conducted to assess erenumab's ability to improve cognitive and psychological functions in CM patients [31]. Subjects were examined with several diagnostic tools such as MoCA, MIDAS, SF-36, Beck's Depression Inventory, and the Hamilton Anxiety Rating Scale [31]. Daily erenumab dosing resulted in higher MoCA scores in the three subscales of SF-36 (pain, general health, energy/fatigue) [31]. An improvement in MIDAS was also observed; nonetheless, the change was not statistically significant [31]. Thus, cognition should be considered as a potential metric for treatment efficacy due to the potential detrimental impact of cognitive impairment on QoL and the potential for appropriate treatment to reduce cognitive symptoms.

Summary: Not only do headaches impact daily life, but cognitive symptoms related to migraine attacks also have a negative effect, especially in patients with lower cognitive reserve. These findings indicate that cognition should be considered a potential outcome metric for treatment efficacy.

Conclusion

Cognitive impairment appears predominantly in the headache phase itself. However, there remains a lack of certainty as to whether cognitive impairment extends into the interictal period in EM patients. In CM, evidence supports cognitive impairment on both migraine and non-migraine days, suggesting that cognitive impacts may be more persistent as migraine frequency increases and interictal days decrease, with considerable impacts on social cognitive domains. Further research to assess whether poor cognitive performance persists throughout migraine phases or worsens with migraine chronification is required. Such insight may be instrumental in defining cognitive symptoms as a key factor that should be considered in patient care.

It is yet to be determined whether cognitive impairment is a phenotype specific to migraine or an effect seen in broader pain-related disorders. Furthermore, there is evidence that specific co-morbidities, such as anxiety and depression or treatments, may influence worsening cognition. Thus, it is likely that a combination of factors contributes to poor cognitive performance in migraine patients. To address these remaining questions, future studies should consider a longitudinal study design to

assess cognitive function across different migraine phases and across periods of migraine chronification. Use of acute and preventative therapies should be considered an important confound in such studies. Additionally, comparison of migraine patients to patients with other primary headache or pain disorders would be informative to determine which cognitive changes may be directly associated with migraine, and which may be triggered more broadly due to pain.

Abbreviations

HCs	Healthy controls
CEN	Central executive network
CVLT	California Verbal Learning Test
DMN	Default mode network
DST	Digit span tests
EEG	Electroencephalography
fMRI	Functional MRI
HIT-6	Headache Impact Test-6
MIDAS	Migraine Disability Assessment questionnaire
Mig	SCog-SCI scale for migraine
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment test
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MSQoL	Migraine-Specific Quality of Life
MwA	Migraine with aura
MwoA	Migraine without aura
QoL	Quality of life
CERN	Right CEN
ROCF	m-Rey Complex Figure test
SCI	Subjective cognitive impairment
SDST	Symbol Digit Substitution Task
SF-36	Short Form Health Survey 36
SN	Salience network
TMT	Trail Making Test
WML	White matter lesions
5-HT1F	5-hydroxytryptamine receptor 1 F

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors on behalf of the European Headache Federation contributed equally to the drafting and critical revisions of the manuscript. C.F. took the lead in conceptualising, writing, drafting and revising the manuscript. A.M and C.L. review the main manuscript text, figures and additional material. All authors reviewed the last version of the manuscript and have agreed to be personally accountable for their own contributions.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

Intellectual Christian Lampl is the Director of the School of Advanced Studies of the European Headache Federation and associate editor for The Journal of Headache and Pain. Antoinette Maassen van den Brink is the President of the European Headache Federation. The other authors declare no competing interests.

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