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Cognition and Cognitive Impairment in Migraine

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Abstract

Background Migraine is a complex neurological disorder that affects a significant percentage of the human species, from all geographic areas and cultures. Cognitive symptoms and dysfunctions are interim and disabling components of this disorder and may be related to the brain processes underlying the pathophysiology. Yet they are often undervalued by clinicians. In this review, we present the different types of cognitive dysfunctions associated with migraine and the mechanisms that are potentially causing them.

Findings While reversible attack-related cognitive dysfunction seems extremely consistent and likely related to functional cortical and subcortical brain changes occurring during attacks, interictal cognitive dysfunction is less consistent and might become more relevant as attack frequency and disease complexity increase. Migraine traits do not seem a predisposition to long-term cognitive decline.

Summary Cognitive dysfunction is a frequent manifestation of migraine attacks and may be specific to this disorder; it is important to understand if it could be useful in migraine diagnosis. Attack-related cognitive dysfunction is clinically relevant and contributes to disability, so it should be perceived as a therapeutic target. While there is no evidence to support that migraine increases the risk of long-term or persistent cognitive dysfunction, the fact that it occurs during the attacks and may persist in subjects with frequent or complicated attacks should prompt the understanding of the mechanisms related to its pathophysiology for it may also clarify the processes underlying migraine.

Keywords Migraine · Cognitive complaints · Brain imaging · Cognitive decline · Migraine attacks · Attention · Executive functions

Introduction

Migraine is nowadays widely recognized as a neurological disorder with pathophysiology that involves the whole brain, including several cortical and subcortical structures [1••, 2]. It is very frequently occurring—in 9 to 35% of the world population [3•, 4], and it seems that certain genetic traits increase the susceptibility of suffering from this disabling disorder [5].

Migraine impacts patients from all countries and all genetic backgrounds [3•] and is highly prevalent in the *Homo sapiens*, at least in their modern history [6] and likely since the Neolithic period [7].

Although debatable, it may be possible that other species may suffer from this disorder [8] and it is certainly consistent with studies which show that rodents can be experimentally driven to experience migraine-like behaviors. These studies have shown to be relevant to drug development and to the understanding of migraine pathophysiology [9]. For example, an inbred rat strain, spontaneous trigeminal allodynia (STA) rats, do exhibit a long-term cephalic hypersensitivity, and this shows promise for the study of chronic migraine [10]. A new experimental protocol has been successful in triggering migraine-like experiences in conscious rhesus monkeys, displayed by decreased motor behavior, reduced time spent on daily activities, reduced eating, unsettledness, and an

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increase in scratching behavior [11]. This data suggests that other mammal brains can experience migraine-like phenomena, implying that the brain structures, circuitries, and biochemical ambience needed to express migraine symptoms are well preserved through brain evolutionary changes, at least in mammals.

The migraine experience itself is very complex and difficult to decipher in humans; it is a syndrome involving different symptoms that occur cyclically with variable intensity and frequency and in numerous combinations. Even in-between pain-related cycles, migraine patients have been shown to process information differently [12]. Cognition is part of the human experience of migraine, not only because it is crucial for perception and consciousness—and maybe expression—of the process itself, but also because most patients experience cognitive dysfunction as part of the migraine syndrome, even without regard to cortical symptoms of the aura [13•, 14].

In this review, we aim to describe the cognitive aspects related to common migraine, whether those more strictly related to the cyclical nature of this disorder—covering cognitive symptomatology of the several phases of the attack, interictal cognitive processing, and the importance of frequent recurring attacks resulting in chronic migraine—but also the relation of migraine biology and physiological cognitive changes across the lifespan of migraine patients.

Cognitive Symptoms and Dysfunction During Migraine Attacks

A systematic review of the frequency and type of migraine non-core symptoms (i.e., clinical manifestations beyond pain, gastrointestinal, and aversive symptoms) [15] found that subjective cognitive complaints were amongst the most frequent symptoms reported in the premonitory (30%) and in the headache (38%) phases of the migraine cycle. Cognitive symptoms often persist after the resolution of pain, but the postdromal phase is mainly characterized by complaints of fatigue/tiredness (71%), reduced physical energy (34%), and depressive feelings (32%). Cognitive complaints were also reported during the aura, but data was insufficient to evaluate its frequency.

In the premonitory phase, cognitive symptoms are reliable predictors of the incoming attacks. In a prospective study of the prodromal symptoms [16], speech and reading difficulties predicted 92% and 90% of the attacks, respectively, while in a controlled study [17], concentration difficulties, together with unhappiness, anxiety, and yawning, were the most common and consistent prodromal symptoms not present in the interictal period. During the headache phase, the most frequent cognitive complaints were "impaired thinking," "feeling distracted or slow," and "speech difficulties" [14, 18].

A detailed prospective cross-sectional study, conducted during the headache phase in 165 migraine patients without aura using an open-ended questionnaire and a 43-item checklist, confirmed that 89.7% of patients experienced cognitive symptoms at the time of headache, a frequency similar to migraine-defining symptoms (nausea, photophobia) and mood complaints [13•].

The most commonly reported symptoms suggest attentional or executive dysfunction, namely an impaired ability to concentrate (37%) and difficulty in reasoning (25%) and thinking (23%), a pattern confirmed with a symptom checklist. Interestingly, the least frequent complaints were related to spatial cognition, which is surprising since imaging studies show a consistent activation of the posterior cortical regions, which subserve visuospatial functions, during all stages of migraine attacks [19••]. The occurrence of cognitive symptoms was unrelated to measures of attack severity (frequency, intensity, duration, and impact), years of disease, age, or prophylactic medication. An analysis of patient symptoms led to the development of a 9-item questionnaire (MIG-sCOG) [20], for the evaluation of cognitive symptoms during attacks. Migraine patients scored significantly higher than patients with tension-type headaches in this questionnaire. Moreover, they scored higher during migraine attacks than during other types of pain or in the interictal period, suggesting a specificity of these complaints for migraine [21].

Studies performed during migraine attacks confirmed that symptoms reported by patients correspond to objective cognitive impairment [14, 18, 22–25]. Neuropsychological evaluations documented transient declines in tests targeting processing speed [14], working memory, visual-spatial processing [23–25], immediate and sustained attention, and verbal learning [14, 22]. Executive functions were the most consistently involved [18, 26], in line with the subjective complaints reported by patients. Functional studies in spontaneous or nitroglycerin-triggered migraine attacks have shown increased activation in cortical areas relevant to executive functions such as cingulate cortex, insula, prefrontal cortex, and temporal poles [2].

Cognitive impairment tends to correlate with attack severity. However, these studies are difficult to perform and they have some limitations in terms of sample size and the domains evaluated [18]. Most studies included small samples of subjects and used short or computerized batteries, to allow a repeated self-application. Five studies compared two evaluations of migraine in the ictal and interictal/postdromal phases, attempting to estimate the time course of cognitive impairment and recovery. While they measured intrasubject variability (during and in-between attacks), they did not control for the practice effect of repeated testing [27]. Possible confounding factors affecting cognition were not systematically controlled, such as anxiety, mood disorders, substance abuse, prophylactic drug treatment, or the presence of aura. Nonetheless, the studies provided some evidence of impairment, particularly of executive dysfunction, during attacks. This transient

decline agrees with the documentation of a reversible dysfunction of the prefrontal and temporal cortices during migraine attacks by functional imaging studies [28, 29]. This also agrees with neurophysiological studies documenting reversible changes in some basic cognitive processes, like somatosensory temporal discrimination and short latency afferent inhibition [26, 30].

A recent study indicates that this transient impairment may actually begin in the premonitory phase [31], supporting a continuum of changes occurring along all phases of the attack. This is in line with the cognitive complaints reported before the attacks and functional imaging data showing changes in interconnected regions, namely the hypothalamus, thalamus, brainstem, and the occipital cortex, before the attack [19••].

The degree of disability and reduction of work productivity has been estimated to be around 54% during a migraine attack [32]. While pain is the main determinant of disability, cognitive dysfunction also contributes to attack-related impairment. In a prospective study of 229 attacks, which were recorded by 100 consecutive patients from a headache outpatient clinic, cognitive symptoms ranked second, after pain, in attack-related intensity and disability, followed by aversive symptoms [33]. Therefore, cognitive dysfunction should be considered a therapeutic target, together with pain, to evaluate the efficacy of acute attack treatment in order to reduce migraine disability and costs. It is possible that cognitive difficulties during the attack may interfere with a patient's ability to make the right decisions regarding acute medication choice, timing, dose, and route. This issue has not been explored but is relevant in a disorder that is acutely managed by the patient.

Interictal Cognitive Processing in Migraineurs

In episodic migraine, by definition [34], attack-related symptoms disappear in-between attacks, the so-called interictal period, during which patients' brains are supposed to function normally and no symptoms should persist.

Neurophysiological evidence argues otherwise, as data from the late 1990s revealed that even in the interictal period, migraine brains process sensory information differently. Visual phosphene generation after transcranial magnetic stimulation of the occipital cortex was elicited with lower thresholds in migraine patients than in controls, even in patients without aura [35], suggesting cortical hyperexcitability. This phenomenon was documented for all sensory modalities, such as sound, smell, and taste, and could have a clinical correlation to some interictal symptoms. In fact, interictally, migraine patients are more sensitive to light, have more stripe-induced visual discomfort [35], have increased sound aversion [36], and are more sensitive to painful thermal stimulation [37] than controls.

Initial neurophysiological studies produced conflicting results that were later perceived to be influenced by the moment, within the migraine cycle, in which stimulation was delivered and also with response modifications following repeated stimulations [38]. Habituation [12] deficit for migraine patients seems to have an initial weaker response, but then fails to ignore repeated sensory (visual, auditory, olfactory, somatosensitive, and nociceptive) stimuli, building up a higher response with each repetition of the stimulus. Surprisingly, its ability to increase the response with repeated stimuli actually decreases to levels of healthy controls near or within an attack, and also during treatment with migraine prophylactic drugs, such as valproic acid, beta-blockers, and fluoxetine [38]. These neurophysiological differences are not completely replicable, nor are they specific for migraine, so it is debatable if they can be acknowledged as a biomarker of the migraine pathology or are an epiphenomenon [39].

The mechanism by which this dysexcitability occurs is still elusive, but it likely depends on the influence of subcortical serotoninergic and noradrenergic neurons in setting low pre-activation excitability levels of sensory cortices, thus requiring stimuli repetition for obtaining adequate responses [38]. Studies of high-frequency oscillations performed outside the attacks suggest the occurrence of functional thalamocortical disconnection, leading to the increased gamma band oscillations in the cortex and to reduced cortical habituation [40]. Gamma activity increase is noradrenaline-mediated, while its decrease is serotonin-related, so low serotonin levels demonstrated in-between attacks could relate to reduced habituation, which normalizes towards an attack as serotonin levels rise [41•]. Neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) were able to enhance cortical excitability and normalize the abnormal interictal information processing in migraine [42].

Functional magnetic resonance (fMRI) studies have revealed interictal differences in pain processing from controls, with several cortical and subcortical areas including the anterior and middle cingulate, temporal pole, and parahippocampal gyrus showing increased activity while there was decreased activity in the secondary somatosensory cortex, precentral gyrus, superior temporal gyrus, and brainstem. During an attack, increased activity in the temporal pole, parahippocampal gyrus, and thalamus is documented [43]. The habituation deficit was also studied in pain processing with fMRI, in which subjects with migraine outside the attacks showed increased activation as compared to controls in the anterior insula, middle cingulate, and thalamus with repeated intranasal nociceptive stimulation with ammonia [43]. Functional connectivity studies have consistently shown differences in migraine patients in several areas, such as those involved in pain processing and modulation, but also areas related to affective, emotional, and cognitive processing, such as the hippocampus, parahippocampal gyrus, and orbitofrontal cortex [43].

Habituation abnormalities were also found to occur consistently in cortical potentials related to higher mental functions, such as in the early component of contingent negative variation (CNV), mediated by noradrenergic drive and serving as a measure of expectancy and attention [44]. Lack of habituation of the P300 response, which relates to information processing and cognitive workload, was found to be inversely related to platelet 5HT content [38, 44]. All these lines of evidence support that interictal cognitive and sensorial processing of migraine patients differs from that of controls.

Cognition and pain processing have several overlapping networks, so concurrent activation of both systems could be expected to compete for resources. In healthy individuals, both these systems can be active simultaneously, but while cognitive tasks have the ability to mildly reduce brain activity in response to pain, acute pain has shown little ability to interfere with cognitive activity [45]. Migraine patients, on the contrary, show decreased cognitive task-related brain activity during painful stimulation, suggesting abnormal cognitive-related activity involving the insula, dorsolateral prefrontal, and dorsal anterior midcingulate cortices [46].

From a clinical perspective, cognitive complaints in the interictal phase in episodic migraine patients without aura are not as frequent nor as disturbing as they are during attacks, and symptoms reported interictally tend to relate to name-finding difficulties rather than processing speed and attention [21].

The majority of clinic-based cross-sectional controlled studies evaluating interictal cognitive performance in young adults with episodic migraine were *positive*, demonstrating lower performance of migraine patients (either with or without aura) than controls in several different cognitive domains (executive functions, processing speed, visual-spatial memory, attention, motion perception, language, and memory) [47–56]. Clinic-based studies had small samples (from 24 to 72 patients) and different designs, test batteries, and data analysis techniques; half failed to control for confounding factors (medication, proximity of the attack, anxiety) [47–54]. Some of the differences found were independent [50, 55–57] of clinical variables while others were dependent on attack intensity [53, 56] or headache frequency [51, 55]. Only one clinical-based study was negative and included patients over 65 years old [58].

Four studies recruited patients with advertising in the community [54, 57, 59] or in college students [60], again with small samples (from 24 to 47 patients) and the same type of limitations. Two of the studies were positive, demonstrating global motion [57] and attention deficits [54] while the other two were negative, one using rather extensive battery, which allowed patients to continue their baseline medication [59].

Two out of the three studies performed in community-based settings with large samples (99 to 1021 patients) were *negative* [61, 62]. One study favored migraine patients who showed *better* executive function, inhibitory control, and verbal fluency, more evident amongst subjects with aura and those who had improved their migraine over the years. It is unclear if this was a confounding factor [63].

From these data sets, it seems that the most severely affected episodic migraineurs (clinical-based samples) seem to experience interictal cognitive difficulties. Self-referrals through advertising have conflicting results, while scarcely affected community-indwelling subjects (populational studies) are no different or even better than the controls. This suggests that the impact of the disease is the strongest predictor of interictal cognitive function in migraine.

Cognition in Chronic Migraine

Increasing attack frequency narrows the impairment-recovery cycle in migraine brains, which has been shown to influence cortical responsivity. It also has shown an influence in the risk of developing chronic migraine [64], which is defined as having a headache more than 15 days per month, in which at least eight are migraine days [34]. Electrophysiological studies on chronic migraine patients show an increase in cortical excitability, translated by an increase in amplitude of response to somatosensory, nociceptive, and visual-evoked potentials, sometimes with increased habituation, which may show increased central sensitization [65].

In a fMRI resting-state study, the periaqueductal gray (PAG), a modulator of somatic pain transmission, has been shown to increase its connectivity to brain regions involved in pain and nociception processing. It has also been shown to decrease it with pain modulation areas (such as the prefrontal cortex, anterior cingulate, amygdala) with increasing attack frequency [66] with consequent hyperexcitability or sensitization of trigemino-vascular neurons [67].

Chronic trigeminal sensitization may mediate ongoing headache that occurs in-between migraine attacks and also interictal cutaneous allodynia, a clinical marker of chronic migraine, of lower pain thresholds to mechanical and thermal skin stimulation [68] and of resistance to triptan treatment [69, 70]. Migraineurs with allodynia were shown to have stronger resting-state functional connectivity of the PAG to brain regions, which are involved in pain and nociception processing, and weaker with middle and superior frontal regions [71].

Atypical resting-state functional connectivity has been demonstrated in chronic migraine [72]; these functional changes may contribute to structural changes observed in a chronic migraine patient's visual (V5) areas [2] and also in areas involved in cognitive aspects of pain processing, such as the anterior cingulate cortex (affective and cognitive pain processing, pain anticipation, identification of relevant environmental stimuli), the orbital frontal cortex (affective response to pain and emotion-based decision-making), entorhinal cortex (modulating expectations), and pars triangularis

(empathy) [73]. Such structural changes can already be noticed in patients with more than nine migraine days per month [73].

In two studies evaluating response to noxious stimulation, high-frequency (8 to 14 days) migraine patients were found to have a thicker cortex with increased activity in the post-central gyrus (sensory processing) and a thinner cortex with decreased activity in the inferior insula and anterior and posterior midcingulate (affective and cognitive processing) [74]. This group was also found to have decreased activation of all the basal ganglia structures, with increased functional connectivity of the putamen and pallidum to the anterior insula, temporal pole, hippocampus, and decreased functional connectivity of the caudate to the temporal pole, anterior insula, pallidum, and middle frontal cortex [75]. Pain-cognition interactions also seem to depend on headache frequency in episodic migraineurs [46]. These findings suggest that repeated attacks induce adaptive brain changes in areas that are relevant to cognitive processing, and support the clinical impression that patients with high-frequency episodic migraines have a profile in which migraine disability measures, comorbidities (such as sleep disturbance, anxiety, and mood disorders), and medication use seem to resemble chronic, rather than episodic, migraine patients [76].

Only two clinic-based controlled studies of interictal cognitive performance in migraineurs found that cognitive performance was dependent on headache frequency [51, 55]. One used a very extensive battery and found that all test scores results declined with increasing headache frequency, yet only attention, memory, and visuomotor speed processing were significantly affected in high-frequency migraineurs. Motor coordination, visual perception, abstract reasoning, mental calculation, and praxis were not affected in high-frequency migraineurs [51]. In another study that related cognitive performance in MOCA and event-related potentials, migraineurs performed worse on language, verbal and visual memory, executive functions, calculus, and orientation but only executive dysfunction was related to headache frequency [55]. Both of these studies had small samples, but did exclude patients with psychiatric disorders and with current psychoactive medication (including migraine prophylactics and medication overuse) [51, 55]. Executive measures (processing speed, attention) seem more likely to be affected, which is in accordance with areas that have shown to be involved in adaptive brain changes to a high frequency of attacks (insula, cingulate, and frontal cortices) [73–75] and affected by pain-cognition interactions [46].

Cortical excitability is also influenced by the presence of analgesics, which modulate the habituation response but somewhat differently, according to the drug. NSAID overuse induced sensitization with lack of habituation, while triptan overuse seems to reduce both sensitization and habituation [65]. Different drugs show different profiles and likelihood of contributing to the development of medication overuse headache (MOH). Drugs that target pain receptors (such as opiates and analgesics) have the highest risk as compared to those directed to the serotoninergic system (such as triptans and ergotamine). NSAIDs were found to be protective in patients with less than ten monthly days of use [77]. Interestingly, the length of exposure also contributes to MOH, but triptans need a lower exposure length (an average of 1.7 years) than ergotamine (an average of 2.7 years) and analgesics take longer (an average of 4.8 years), suggesting that modulation of the serotoninergic system has faster influence on central sensitization and headache chronification [78].

MOH induces changes in brain structure and metabolism in regions related to pain processing (PAG, hippocampus, thalamus, posterior parietal cortex, cerebellar vermis, and insula) and in the mesolimbic dopaminergic circuit (putamen, nucleus accumbens, tegmental ventral area, and orbitofrontal cortex). This represents the reward (ventral striatum) and habit (dorsal striatum) systems [79]; most of these changes are reverted with medication withdrawal, except for the decreased volume of the orbitofrontal cortex, which seems to be a specific marker of risk of addition [80].

Chronic migraine complicated by MOH is also associated with a myriad of comorbidities that may impact a patient's cognitive profile, such as psychiatric disorders (anxiety, depression, obsessive-compulsive disorder, and drug addiction) and regular use of tranquilizers. It is also associated with smoking habits, physical inactivity, obesity, and the presence of chronic musculoskeletal and gastrointestinal complaints [77].

Cognition in Migraine Across the Lifespan

The possible impact of migraine attacks on brain health is a common source of concern to patients who fear that attack repetition might have long-term consequences and/or increase risk of another brain disorder. Structural brain imaging studies performed in the last decade seem to support these fears by showing that migraine is associated with increased risk of stroke [81], with silent brain lesions [82–84], progressing deep white matter hyperintensities [85], and anatomic alterations in the visual cortex [86]. These findings suggest that migraine can be a progressing disorder and eventually impact cognitive functions. So far, the evidence on long-term effects of migraine in cognition does not support this hypothesis.

Studies targeting the long-term effect of migraine on cognition are large cross-sectional or longitudinal studies on cognitive aging. These studies were performed in the community or in a primary care setting, all in adult and aging populations [26, 61, 63, 83, 87–92]. Migraine is diagnosed by self-report [61], screening tools [91], or interviews aiming to confirm ICHD criteria. Some studies compare participants with migraine to subjects without headaches or with non-migraine

headaches, and a few [63, 83] include a subgroup of participants with migraine aura. The majority do control possible confounding factors, such as age, education, gender, depressive symptoms, and vascular risk factors. Longitudinal studies compare the age-related decline in the different groups, after a follow-up time of 4, 6, and 12 years [87–90]. Cognitive assessment varies, including screening tools (such as the Mini Mental state evaluation) to measures of processing speed, executive functions (set shifting, inhibitory control, monitoring, working memory), episodic memory, naming, visuospatial functions, and intelligence [see [26] for a detailed review of tests]. Some studies include neuroimaging data and control for white matter hyperintensities [83]. No studies evaluated the impact of attack severity on cognition. Apart from two exceptions, all studies were negative—they failed to show significantly worse performance between participants with migraine and controls. On the contrary, three longitudinal studies showed that individuals with migraine presented *less cognitive decline* in the follow-up [87, 89, 92] compared to controls in a number of measures. In one analysis, the benefit affected subjects with aura who are over 50 years of age. This is reassuring for the long-term effects of migraine in the general population, including individuals with less severe forms of migraine than those observed in clinic-based studies.

The eventual benefit of migraine on cognition may have different explanations. One of them is the impact of migraine on lifestyle [26, 93]. As migraine attacks are often triggered by all types of homeostatic changes, migraine sufferers tend to avoid lack or excess of sleep, missing meals, excessive meals, or alcohol and tobacco consumption. These positive lifestyle features are clearly observed in the migraine group in some of these epidemiological studies [26]. Moreover, individuals with migraine may seek medical advice early in life, leading to early detection and prevention of risk factors.

The only exceptions among these results are two cross-sectional studies that, interestingly, include individuals with low literacy. One included older subjects with a mean of 6 years of literacy, and found that participants with migraine had lower scores in a test of attention, but also that subjects with non-migraine headaches had low scores in other tests [90]. In the other study [92], 20% of participants had chronic migraine. This factor may have biased the results. Subjects with migraine, particularly with aura, had a lower percentage of college education, compared to controls, which may have impacted test results, since education is the single most important determinant of cognitive performance. This data could eventually indicate that literacy could mitigate the subtle effects of this brain disorder.

A single study evaluated a large sample of twins from a registry in Denmark [62]. It included 157 participants with migraine aura and 347 without aura. Diagnosis was confirmed by a neurologist, and subjects were evaluated with tests of working memory, delayed recall, verbal fluency, and processing speed. No differences were found between migraine groups and controls.

The third type of study is directed to migraine in children and focuses on the early effects of migraine in cognition, as well as the impact of migraine in development and academic achievement. Interictal studies of children with migraine from headache clinics have consistently demonstrated lower performance in cognitive tests, especially in attention and reaction times but also in other domains. This finding correlated with attack frequency, suggesting some effect of repeated attacks on cognition [26], just like in adults.

A single epidemiological study from New Zealand followed a large sample of children for 23 years [94]. Headache diagnosis was made when the population reached 26 years of age, and 114 participants were classified as having migraine, 109 with tension-type headache, and 739 as without headache. Cognition was evaluated with IQ-batteries and school achievement by students' national exams. The results showed that children with migraine had lower verbal-IQs, compared to controls, in all four assessment periods (without decline), but only those with childhood history of tension-type headache had worse scores in cognition in adulthood. Individuals with migraine and a childhood history of headache were identical to controls in verbal expression, mathematical skills, and reading but worse on verbal comprehension, and had lower scores on national exams (predicted by their low performance in verbal comprehension). This study shows that a childhood history of migraine does not have an impact on cognitive development but, instead, that migraine can be associated with a lower verbal performance that does not decline as a function of migraine attacks.

Another study comparing children with migraine to their unaffected siblings found no evidence of impact of migraine in cognitive performance [95].

While it is clear that migraine attacks include some degree of cognitive impairment, in the long run, migraine is not associated with any significant impact in cognitive performance, nor in age-associated cognitive decline in the general population, despite association with white matter hyperintensities, silent brain lesions, and increased risk of stroke. This suggests that acute cognitive dysfunction is reversible. However, individuals with more severe and frequent migraine attacks, followed in specialized clinics, and subjects with chronic migraine tend to maintain cognitive difficulties between attacks. This indicates that they do not fully recover between attacks or that their apparent interictal period is either a premonitory or postdromal phase. In addition, they develop or sustain other risk factors, such as depression, anxiety, poor sleep, and medication abuse, conditions that are associated with poor cognitive performance (Fig. 1). Of concern is the fact that repeated attacks may change brain network organization and the activations and deactivations related to normal cognitive activity [46, 52, 96].

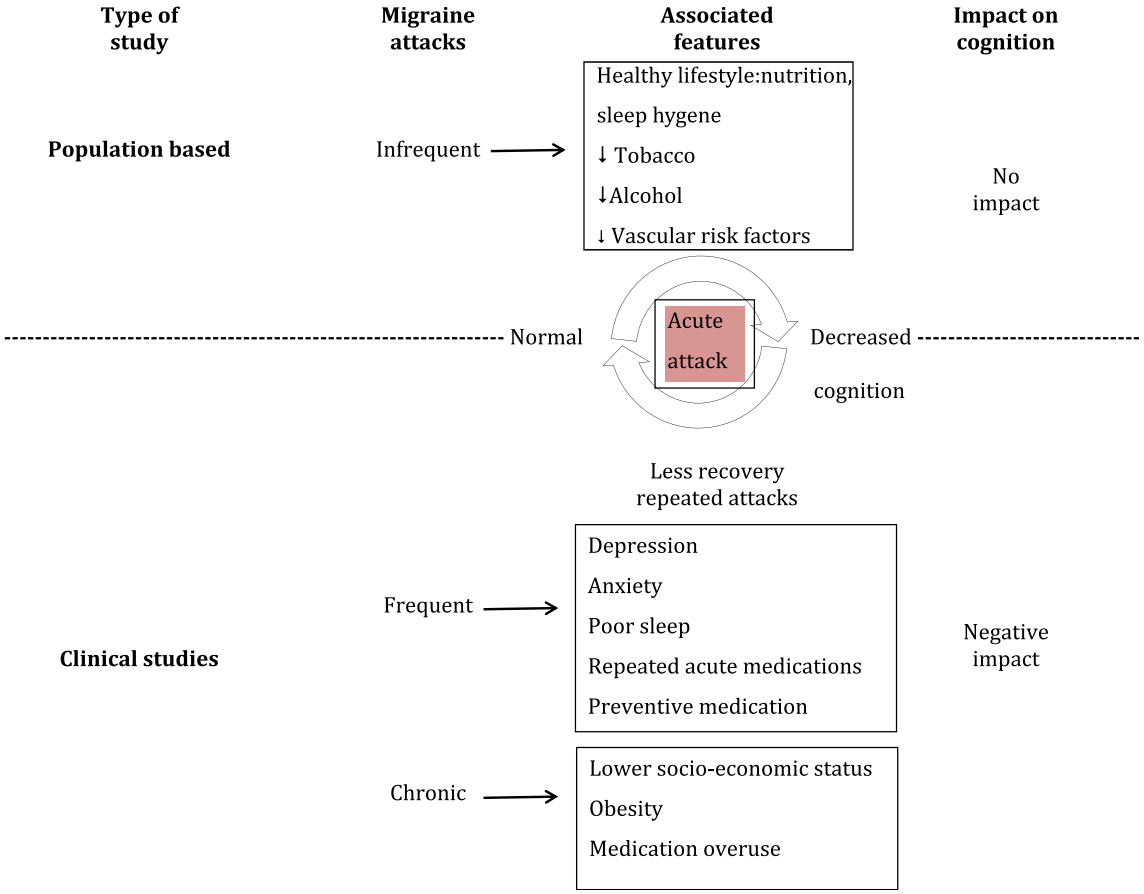

Fig. 1 Context of poor cognitive performance in Migraine Patients

Conclusions

The relation between migraine and cognition is complex. Cognitive symptoms are part of the subjective experience of migraine attacks and contribute to attack-related disability, being likely to interfere with performance at work, family, and social life, and also with self-management of the attacks. Intricate neurophysiological and neuroplastic changes seem to underlie the migraine brain cycle, involving both cortical and subcortical structures which are vital in cognitive processing [2, 40, 43]. Evidence suggests that the existence of this pathological process in a given individual, over the lifespan, is not the main inducer of disability, as there are no long-term cognitive effects (or survival issues) attributable to migraine [92, 97]. Yet, at any given time, a migraineur's brain might become dysfunctional in association with a rapid cycling of attacks, which translates to an increase or persistence of cognitive dysfunction, anxiety and mood disorders, weight and sleep changes, immobility and bodily pain, gastrointestinal complaints, social unfitness, and medication overuse [98]—as if attack-related symptoms evolve to persistent symptom-related disorders (Fig. 1).

Migraine expression depends not only on a robust genetic predisposition but also on exposure to several biological and environmental factors, seemingly inseparable from normal brain function. Its high frequency and evolutionary persistence raise the issue of its potential adaptive value/evolutionary advantage, at least in primates and humans [11, 99].

One of the proposed explanations for high prevalence of migraine postulates that the migraine trait may offer a protective advantage as a defense mechanism depending on the environment or particular situation. Migraineurs' brains do seem to be sensitive to external stimuli and process sensory information differently. This could serve as an evolutionary advantage by itself, as they are able to process visual stimuli with higher intensity and for longer, have higher attentional activation, and have deeper problem-solving strategies [100].

Migraine could be understood as a set of disseminated genetic traits with different effects and strengths that confer some survival advantage or benefit. When several of these traits (or some more severe) are inherited together, a patient will develop a more severe disease state or phenotype [99]. This explains the differences found in community and clinical-based samples of migraine patients.

Another perspective could be that migraine is an alarm system that monitors the brain state itself—the pain system of the brain—and may serve as a neuroprotective response for

example to brain oxidative stress [101]. On the other hand, this brain state could serve as maladaptive, increasing the brain's autonomic nervous and neuroendocrine responses—raising the allostatic load in response to everyday stressful events [102•].

Migraine might be a different expression of the whole organism's defense system (the defense cascade), activated by changes in homeostatic or physiological states beyond conscious control. Its activation results in a coordinated whole-body response—traditionally defined by arousal, freezing, flight or fight, tonic immobility, collapsed immobility, or quiescent immobility. Migraine could therefore be considered a whole-body stress response to homeostatic stressors. Traditional threat responses are mediated by neural circuits also involved in migraine, such as the amygdala, hypothalamus, periaqueductal gray (PAG), ventral pontine tegmentum, ventral and dorsal medulla, and spinal cord [103].

It is undeniable that migraine influences brain areas involved in more widespread cognitive processing—whether this influence is responsible for the cognitive symptomatology of migraine patients or, on the contrary, cognitive difficulties are a consequence of genetic, physiological, or functional differences in migraine patients' brains that serve an evolutionary function remains to be accessed.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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