THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 7

REVIEW ARTICLE

Chronic Migraine and Accelerated Brain Ageing: A Focus on Hippocampal Atrophy

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OPEN ACCESS

PUBLISHED
31 July 2025

CITATION
Choudhary, AK., 2025. Chronic Migraine and Accelerated Brain Ageing: A Focus on Hippocampal Atrophy. Medical Research Archives, [online] 13(7). https://doi.org/10.18103/mra.v13i7.6728

DOI
https://doi.org/10.18103/mra.v13i7.6728

ISSN
2375-1924

ABSTRACT

Chronic migraine (CM) is increasingly recognized as more than just a recurring headache condition. It involves significant neurobiological changes that suggest accelerated aging of the brain, particularly affecting the hippocampus, which is essential for memory and cognitive functions. This overview examines the key findings linking CM to notable decreases in cortical thickness, increased white matter hyperintensities, and significant hippocampal atrophy. Research utilizing machine learning in neuroimaging has introduced the concept of the Brain Age Gap (BAG). This concept reveals that individuals with CM have an average brain age that is 4.16 years older than their chronological age, indicating premature aging of their neural structures. These structural changes are associated with difficulties in declarative memory, disruptions in memory-encoding processes, and higher rates of depression and anxiety. Factors such as neuroinflammation, ongoing pain signals, and related health conditions such as obesity and hypertension worsen this neurodegenerative trajectory. The growing body of evidence highlights the urgent need for early identification of at-risk individuals, validation of BAG as a potential cognitive health biomarker, and development of targeted interventions to prevent cognitive decline. To confirm these findings, prospective long-term studies are crucial to confirm the patterns of hippocampal atrophy and to establish effective imaging techniques for migraine management.

Keywords: Chronic Migraine, Brain Aging, Hippocampal Atrophy, Neuroimaging, and Cognitive Decline.

1. Introduction

Migraine affects approximately 12% of the global population, with 60% experiencing at least one attack annually[1]. Chronic migraine[2], defined as headaches[3] lasting over 72 hours or occurring at least 15 days per month for more than three months[4], is associated with accelerated brain aging, especially in the hippocampus[5]. The hippocampus is crucial for memory and cognitive function. Chronic migraine not only impairs the quality of life[6]. but it also increases the risk of memory loss[7], cognitive decline, and mood disorders[8]. Research indicates[9] that patients with chronic migraines[10] often exhibit[11]reduced hippocampal volume[12] and younger predicted brain age[13], suggesting early neurodegenerative changes[14,15]. This review examined the relationship[16] between chronic migraine and hippocampal atrophy[17] by reviewing neuroimaging evidence[18,19]. This review focuses on evaluating the neurological effects of migraines, identifying underlying neurobiological mechanisms, such as oxidative stress and neuroinflammation, and assessing structural brain changes. As individuals age, cognitive abilities and bodily functions gradually decline, particularly in brain regions such as the frontal and temporal lobes and hippocampus[20]. The Brain Age[21] framework provides a method for estimating an individual's brain health by comparing it to a healthy population baseline. When the predicted brain age exceeds the chronological age, referred to as the Brain Age Gap (BAG), it may serve as a biomarker for underlying health issues. Machine learning models can utilize neuroimaging data to predict brain age and identify the signs of accelerated aging. Studies have shown that chronic migraine patients exhibit significant BAGs, with MRI scans[22,23]revealing structural changes such as cortical thinning[24]. and reduced gray matter[25]. These alterations, influenced by genetic, environmental, and lifestyle factors, highlight the complex neurobiological nature of chronic migraine. The Brain Age framework not only sheds light on migraine-associated brain aging, but also helps differentiate between healthy and impaired brain states, paving the way for targeted interventions and further research.

2. Hippocampal Atrophy in Chronic Migraine

Chronic migraine[26] is a debilitating neurological disorder defined by headaches occurring five or more days per month for over three consecutive months[27], with at least eight fitting migraine-specific criteria[28]. This condition significantly affects the quality of life[29] and poses a serious global health concern[30]. Chronic migraines increase the risk of cerebrovascular events such as stroke as well as psychiatric issues such as depression and anxiety[31]. Neuroimaging studies have indicated accelerated brain aging in patients with chronic migraine, with limited research on hippocampal atrophy[32-34]. Evidence shows altered gray matter volume and disrupted functional connectivity, with patients exhibiting a higher prevalence of white matter hyperintensities (WMH)[35]. The hippocampus, vital for memory processing, is located in the medial temporal lobes and includes subregions such as the dentate gyrus (DG) and the CornuAmmonis (CA) fields[36]. It plays a key role in encoding episodic memory by interacting with the neocortex. Studies in animals, especially rats, have revealed its circuitry and how the DG processes incoming signals[37]. Hippocampal volume is often reduced by approximately 15% in chronic migraine patients compared to those with other headache disorders, indicating accelerated aging and its link to chronic pain and neurodegeneration[33]. Structural MRI studies have shown significant volume reductions in the hippocampus and related areas (e.g., the left temporal pole) in patients with chronic migraine[38]. Functional MRIs indicate altered connectivity, including reduced gray matter density in the anterior cingulate cortex, suggesting compensatory changes in neural organization[39]. These findings challenge traditional models and highlight the need for a reevaluation of the roles of various brain regions in chronic migraine.

Particular focus on the atrophy of the hippocampus specifically permits an even more detailed investigation of the susceptibility of this part of the brain. Although changes in other brain areas may be also observed, hippocampus should be considered as an object of study since it gives more insights into how these structures are related to cognitive and affective sequelae of chronic migraine.

3. Cognitive Implications of Hippocampal Atrophy

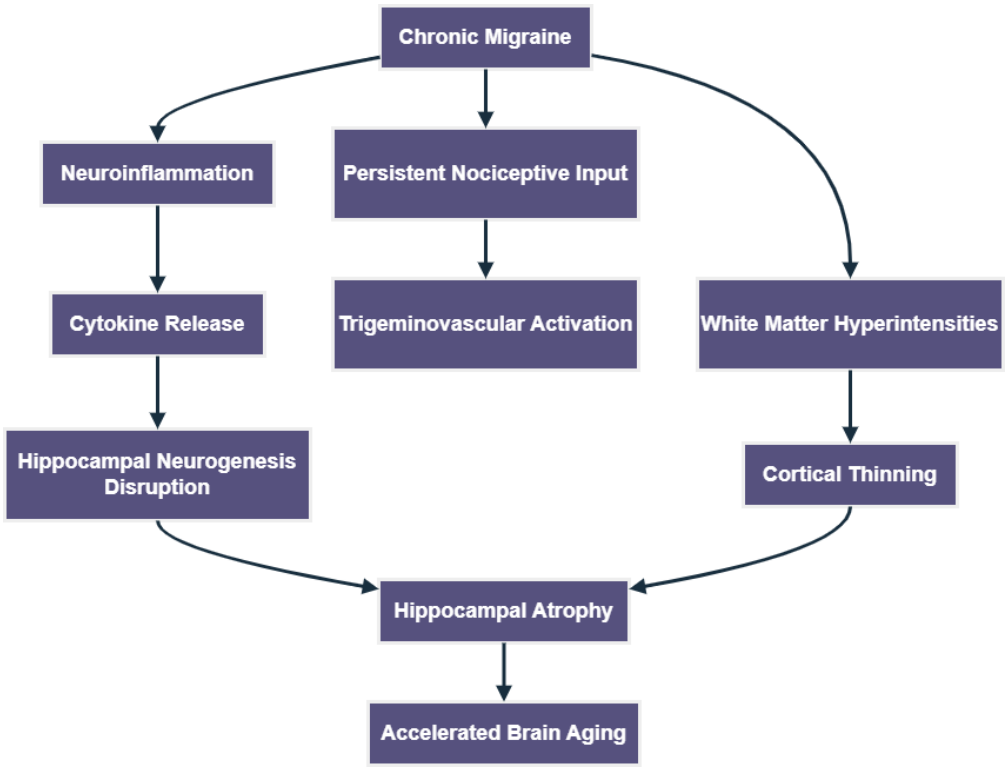
The hippocampus is essential for episodic memory, spatial navigation, and various cognitive functions[40]. Recent studies have emphasized its role in processing speed, working memory, and executive functions[39]. However, it is vulnerable to age-related shrinkage, particularly in the early stages of Alzheimer's disease, contributing to cognitive decline and linked to elevated Alzheimer's biomarkers, even in cognitively healthy individuals[41]. Accelerated brain aging in older adults is often reflected in a discrepancy between chronological and brain-predicted age, correlating with neurodegenerative conditions[42]. Additionally, hippocampal atrophy affects cognitive performance in children, leading to deficits in verbal memory and contextual learning[43]. Patients with chronic migraine often experience memory and learning impairments due to hippocampal atrophy[44]. They tend to perform poorly in declarative memory tasks because of inefficient mnemonic strategies and altered information encoding[45]. Compensatory reconsolidation mechanisms emerge as a response to initial learning deficits, and differences in cognitive processing are evident when comparing patients with migraine to healthy controls[46]. Chronic migraine presents a significant burden in terms of disability and is often accompanied by psychiatric comorbidities such as mood disorders[7]. This can lead to hippocampal degeneration, emotional dysregulation, and increased vulnerability to psychological issues. Furthermore, altered connectivity between the hippocampus and surrounding brain regions contributes to cognitive and emotional impairments. Migraines, once considered episodic, are now recognized for their potential to become chronic, especially after menopause[47]. Increased pain sensitization and cognitive impairment contribute to this progression. Patients frequently report cognitive deficits and reduced quality of life due to stress, anxiety, and depression[48]. Understanding the progression of migrainesfrom episodic to chronicrequires a comprehensive approach that considers headache duration, emotional well-being, and cognitive decline, which is crucial for effective interventions and improving patient outcomes.

4. Mechanisms Linking Chronic Migraine and Brain Ageing

Accelerated brain aging has emerged as a significant concern, especially with regard to chronic migraine. This condition is linked to reduced cortical thickness and increased brain age, particularly in the frontal, insular, and temporal lobes[5]. Chronic migraines are associated with early signs of microstructural injury[49] and neuroinflammation, which may arise in preclinical stages[50]. Continuous nociceptive input activates trigeminovascular pathways, leading to a cycle of hyperexcitability and discomfort[51]. Additionally, white matter lesions[52]can worsen this dysfunction, further affecting the brain structure and function[53]. The proposed neurobiological pathways connect chronic migraine to accelerated brain aging, highlighting persistent nociceptive signalling, neuroinflammation, and hippocampal degeneration (Figure 1). Chronic migraine is associated with neuroinflammation, alterations in the white matter, and dysfunction of the hippocampus, resulting in cortical thinning and atrophy of the hippocampus, all of which contribute to accelerated aging of the brain. Neuroinflammation plays a critical role in chronic migraines, contributing not only to migraine pathology but also to mechanisms of brain aging[54]. Shared risk factors for other neurodegenerative disorders include depression, anxiety, obesity, and hypertension, which may interact synergistically through neuroinflammation[55]. The

association between chronic migraine and hippocampal atrophy complicates this issue because inflammatory mediators may disrupt hippocampal integrity[56]. Evidence suggests[57-61] that increased brain age and hippocampal atrophy often co-occur, highlighting the need for further research on these interactions. With over one billion people affected by migraines, approximately one-third experience chronic forms, and the implications for brain health are profound[62].

Figure 1. Pathways that connect chronic migraine and faster ageing of the brain: Chronic migraine is associated with neuroinflammation, alteration in white matter, and hippocampal impairment, which factors mediate cortical thinning and hippocampal atrophy.



Neuroimaging studies have revealed that up to 50% of chronic migraine sufferers exhibit white matter hyperintensities compared to less than 20% of those with episodic migraines[63,64]. Chronic migraine is also linked to a decline in cognitive performance, suggesting that vascular dysregulation may contribute to brain aging[65]. Advanced neuroimaging techniques, especially brain age estimation algorithms, have provided evidence of accelerated brain aging in chronic migraine patients[66]. These tools link higher predicted brain age with poorer neurological outcomes. Recent studies have shown an inverse relationship between hippocampal volume[67] and headache frequency[68], suggesting that chronic migraine contributes to structural degeneration[69], particularly in the right hippocampus[70]. Further studies are needed to assess these effects bilaterally and confirm their similarities to neurodegenerative diseases. Morphometric analyses[71] have revealed significant structural changes in the hippocampus[72] of chronic migraine patients[73] compared with those with episodic migraines[74]. While hippocampal atrophy[75] is commonly associated with dementia, its role in primary headache disorders remains underexplored. The entorhinal cortex-hippocampal axis[76], which is important for memory and mood regulation, may be specially vulnerable to the effects of chronic headaches[77]. Conducting longitudinal studies using serial imaging is essential to understand the long-term impact of chronic migraine on the brain.

5. Clinical Correlations

Persistent and severe headaches are often associated with thinking difficulties, such as memory problems, trouble concentrating, and task management[78]. The convergence of neuroimaging

and clinical findings reinforces the link between hippocampal atrophy and cognitive-psychiatric manifestations in individuals suffering from chronic migraine, as illustrated (Figure 2). Neuroimaging indicates a reduction in hippocampal volume and an increased brain age gap in individuals with chronic migraine, which is associated with cognitive deficits and psychiatric comorbidities, ultimately leading to a decline in neurocognitive function. The clinical, cognitive, and neuroimaging aspects of chronic migraine linked to hippocampal atrophy and brain aging were compiled (Table 1). Studies have shown a direct link between shrinkage of the hippocampus, a part of the brain, and the level of cognitive difficulty[79]. People with significant shrinkage of the hippocampus often have trouble remembering and retrieving memories, indicating that hippocampal shrinkage plays a role in the decline of thinking abilities in individuals with severe and frequent headache[14]. Moreover, research has found that the frequency and duration of headaches are directly related to shrinkage of the hippocampus, demonstrating the long-term impact of these headaches on brain structure and function[56]. Mental health issues often observed in individuals with severe headaches, such as sadness and anxiety, are also associated with the condition of the hippocampus[79]. Brain scans have revealed that individuals experiencing severe headaches and sadness tend to have more hippocampal shrinkage than those who only experience headaches, indicating a possible relationship between feelings of sadness and the condition of the hippocampus and its impact on thinking ability[14]. Furthermore, changes in the hippocampus of individual with severe and frequent headaches can also affect the perception and management of pain[76,80]. Researchers have noted that the hippocampus can influence the body's response to pain, and any changes to its structure might affect an individual's pain perception and lead to long-term pain in those with severe headaches[81]. Understanding these connections can help in developing specific treatments aimed at reducing the impact of severe headaches on brain health and the overall quality of life. Hippocampal atrophy is present in both patients with chronic migraine with and without aura. Chronic migraine, which is defined as 15 or more headache days per month along with new-onset drug misuse, is more severe than episodic migraine and can lead to brain shrinkage. However, controlled studies have shown that medications for migraine do not affect brain atrophy. A higher prevalence of migraine is linked to lower educational attainment, which is associated with more significant brain atrophy[82].Furthermore, hippocampal metabolic dysfunction in chronic migraine has been documented and societal-level changes in the chronic migraine population are related to brain development[83]. A problem in the medial temporal lobe can make it difficult to learn new things and impede neocortical synthesis of theta, which is essential for long-term potentiation-inducing stimulation[84]. Further research is required to understand the accelerated aging associated with chronic migraine and enhance management strategies. Chronic migraine affects intellectual abilities and emotions and has a greater burden than episodic migraine and traumatic brain injury[85]. Notably, accelerated brain aging was observed in chronic migraine, and the increased number of years of brain aging is comparable to the burden of mild traumatic brain injury[86]. Greater hippocampal and temporal lobe atrophy in chronic migraine corresponds to a greater burden of cognitive decline and Alzheimer's disease dementia[14]. Even after accounting for white matter hyperintensities, brain age in chronic migraine remains elevated due to the contribution of white matter hyperintensities in underestimating chronological age. This implies that white matter hyper intensity has the effect of downgrading chronological age in brain age estimation, thereby making true impact of brain aging in these individuals unknown.

Figure 2. The neuroimaging correlates of hippocampal atrophy in chronic migraine: a reduced hippocampal volume and a large brain age difference have been found in a self-reporting clinical and imaging study of patients with chronic migraine and are linked to cognitive impairment and mental disorders, resulting in neurocognitive deterioration.

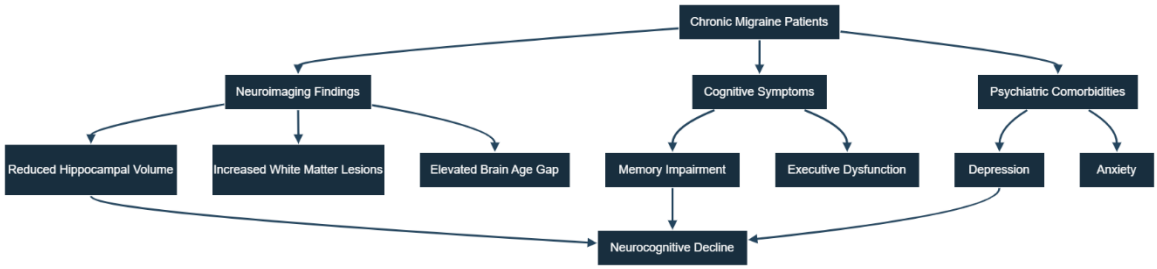


Table 1: Cognitive, and Neuroimaging Characteristics in Chronic Migraine and Their Implications for Brain Aging.

Category	Observations in Chronic Migraine	Implications for Brain Aging	References
Neuroimaging	Decreased volume of the hippocampus. Elevated levels of white matter hyperintensities (WMHs). Thinning of the cortex in the frontal and temporal lobes.	These changes are indicators of rapid brain aging and initial neurodegenerative processes.	(87-91)
Cognitive Function	The dysfunction observed in episodic and declarative memory among chronic migraine patients significantly impacts their overall cognitive abilities Additionally, impaired executive functioning and reduced processing speed	This suggests active involvement of the hippocampus and prefrontal cortex in these cognitive processes	(92-94)
Emotional and Psychiatric Aspects	Increased rates of depression and anxiety Heightened sensitivity to stress and challenges in emotional regulation	Disruption of the hippocampal stress response can accelerate emotional aging.	(95-97)
Brain Age Gap (BAG	Increased rates of depression and anxiety Heightened sensitivity to stress and challenges in emotional regulation	Disruption of the hippocampal stress response can accelerate emotional aging.	(66, 98-100)
Discomfort and Long-term Persistence	Regular nociceptive input and central sensitization Altered sensory processing pathways	Continuous activation may lead to neuroinflammation and stress within the hippocampus.	(101-103)

6. Implications and Future Directions

Recent research has revealed a link between chronic migraines and accelerated brain aging. List (table 2) of the main research gaps and suggest future investigations to improve knowledge and control of brain activity linked to persistent migraines.

A study utilizing MRI-based machine learning models found that individuals suffering from chronic migraine exhibited an increased brain age gap (BAG), indicating accelerated brain aging. This BAG correlates with self-reported cognitive decline and performance on cognitive tests. However,

these findings must be approached with caution as they originate from a single-center study with a relatively small sample size, highlighting the need for further validation and careful interpretation of the results. Further analysis showed that patients with chronic migraine experienced significant reduction in gray matter volume. This reduction was especially noticeable in the brain regions associated with pain processing and crucial cognitive functions, such as the anterior cingulate cortex, insula, and hippocampus. Notably, changes in hippocampal volume have been linked to the frequency of headaches, suggesting a potential biomarker for predicting migraine prognosis and offering hope for future diagnostic tools. There is a clear need for further investigation that focuses on longitudinal studies. They should utilize neuroimaging methods to investigate the intricacies of ageing in the brains of people with chronic migraines and analyze any possible targeted treatment to impede any worsening symptoms and/or slow down the deterioration of the mind. This strategy has the potential to open up the possibilities of better managing and preventing migraines and avoiding long-term deterioration of the neurological condition.

Table 2: Identified Gaps in Knowledge and Suggested Areas for Future Investigation in Chronic Migraine and Brain Aging

Recognized Deficiency	Justification	Suggested Research/Initiative
Insufficient longitudinal imaging data	Cross-sectional studies are limited in determining causality or the progression of phenomena	Conduct prospective cohort studies involving multiple MRI scans and cognitive evaluations
Lack of emphasis on hippocampal atrophy in migraine research	Most studies focus on global brain aging or white matter hyperintensities, neglecting hippocampal atrophy	Utilize high-resolution structural MRI to assess hippocampal subfields in individuals with chronic migraine
Unverified application of the Brain Age Gap (BAG) as a clinical indicator	While BAG shows potential, it has not yet achieved standardization or widespread validation	Evaluate the BAG concerning ongoing cognitive decline and the effectiveness of treatments.
Ambiguity surrounding the effects of migraine treatments on brain structure	The impact of prophylactic treatments on slowing brain atrophy remains uncertain	Investigate brain structure changes before and after therapies (e.g., CGRP inhibitors)
Insufficient studies on migraine-related brain aging in younger populations	Need to explore how early life exposures affect long-term brain health	Analyze hippocampal and cognitive changes in younger population

The rationalized description of the research gaps, shown in Table 2, makes abstracted demands to conduct more research into specific research questions, since it introduces a focus in research, which is the hypothesis. As an example, the acknowledged lack of the element of insufficient longitudinal imaging data is explained by the fact that the cross-sectional study does not allow defining causality or development of alteration of the brain. The proposed study, the idea of which is to conduct prospective cohort studies with repeated MRI scans and cognitive assessments, efficiently eliminates this weakness since it offers a study approach that can ascertain whether a causal relationship exists and monitor individual progress on a longitudinal scale. Likewise, the problem of the unverified clinical usefulness of Brain Age Gap (BAG) metric also needs a spot to develop. The Mention that BAG is not standardized or validated as a clinical indicator is a direct cause of the proposed study to find out BAG as against cognitive decline and treatment outcome. Such design is a very strong point, as BAG is elevated to an interesting finding to potentially validated clinical biomarker, which makes the paper even more significant, as it actively informs future research directions and possible clinical translation.

7. Conclusion

Chronic migraines linked to a decline in brain health, particularly involving shrinkage of the hippocampus, which is crucial for memory. Advanced neuroimaging has revealed structural changes similar to early neurodegeneration in patients with chronic migraine. Machine learning analyses indicate that they have a Brain Age Gap of over four years older than their actual age, highlighting the difference between predicted brain age and chronological age. MRI studies consistently show reduced hippocampal volume, correlating migraine with cognitive decline. This cognitive deterioration is compounded by emotional challenges; even during headache-free periods, individuals may struggle with episodic memory and executive function. Anxiety and depression often accompany chronic pain, which complicates the patient experience. The factors driving accelerated brain aging in chronic migraineurs include continuous pain signaling and neurogenic inflammation. Additionally, comorbidities, such as obesity and hypertension, can trigger systemic inflammation, further exacerbating brain aging. Future studies ought to build on monitoring of the Brain Age Gap volume loss as a meaningful biomarker of cognitive deterioration in migraine with long-term aims of assessing ways of reducing or inhibiting them. The new method of focusing on the hippocampal atrophy and the fact of such an approach has been biblical is a good base to base further and higher-evidence research. This study forms a basis of specific testable hypothesis of longitudinal studies on bigger scale i.e., monitoring of hippocampal loss in volume as biomarker thus making the study one of the significant contributions to the long-term scientific direction in the field.

Conflict of Interest Statement:

The authors had identified no conflicts of interest.

Funding Statement:

None.

Acknowledgements:

The authors had no acknowledgement.

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