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Brain Age Prediction in Migraine and Posttraumatic Headache

Accelerated Aging or Biological Vulnerability?

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Advances in neuroimaging have expanded our understanding of headache disorders.[1] Structural MRI studies have identified morphometric alterations across brain regions involved in nociceptive processing, sensory, affective, and cognitive integration in both migraine and posttraumatic headache (PTH). Overlapping patterns of structural abnormalities across these conditions suggest shared neurobiological mechanisms, yet phenotype-specific findings indicate that common pathways coexist with disease-specific processes.[2] Despite this progress, the biological significance of observed alterations remains debated: whether they reflect preexisting traits, consequences of recurrent headache attacks, or manifestations of broader processes remains unclear.

A related, underexplored question concerns the interaction between headache disorders and brain ageing. While most neuroimaging studies have adjusted for age to disentangle disease-related from age-related effects,[3] few have directly investigated whether migraine or PTH influence brain ageing trajectories, and the available evidence remains inconsistent. Some studies suggest that migraine, particularly chronic migraine, is associated with patterns of cortical thinning and thickening that may reflect disease-related changes over time. Others have reported no meaningful structural differences between older individuals with and without migraine.[4,5]

Brain age prediction offers a promising approach to address this question. Unlike conventional morphometric analyses, these models use machine learning algorithms trained on large normative datasets to estimate an individual's brain age. The resulting brain age gap (Δage), defined as the difference between predicted and chronological age, reflects deviation from normative ageing trajectories: Positive values indicate an older-appearing brain, whereas negative values suggest relative preservation of brain integrity.[6]

In this issue of *Neurology® Open Access*, Shah and colleagues[7] applied a deep learning–based brain age prediction approach to investigate whether migraine and PTH are associated with deviations from normative ageing trajectories. The model, trained using an ordinal classification approach on a large lifespan dataset, was applied to an independent cohort of 378 participants (137 healthy controls, 93 migraine, 99 acute PTH, and 49 persistent PTH). A progressive increase in Δage was observed across headache phenotypes: Individuals with migraine and persistent PTH showed brains appearing approximately 3–5 years older than expected, and did not differ significantly from each other, while acute PTH patients displayed intermediate values, differing significantly from both groups but not from healthy controls. Notably, within the acute PTH group, higher baseline Δage predicted subsequent headache chronification. This is, in our view, the most clinically relevant finding of the study because it suggests that brain age estimation may help identify individuals at increased risk of persistent headache after mild traumatic brain injury. The anatomical substrate underlying these

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predictions preferentially involved frontal, parietal, occipital, and temporal white matter, the cingulum, and the basal ganglia.

Several explanations may account for the observed association between headache disorders and elevated Δage. One possibility is that recurrent headache attacks may contribute to structural alterations through mechanisms including neuronal hyperexcitability, neurogenic inflammation, oxidative stress, and metabolic dysfunction.[8] However, this hypothesis cannot be directly evaluated in the study by Shah and colleagues because the absence of clinical headache data precludes any correlation between Δage and disease activity metrics such as attack frequency or disease duration. Alternatively, elevated Δage may be a pre-existing trait rather than a disease consequence. This possibility is supported by the prognostic value of baseline Δage in acute PTH, where a structurally older-appearing brain predicts headache persistence before chronification. A third possibility is that both headache disorders and elevated Δage arise from a common underlying mechanism, such as impaired glymphatic function or altered cerebral energy metabolism.[8,9]

Addressing these possibilities will require longitudinal imaging studies. In the study by Shah and colleagues, imaging was acquired at a single time point; consequently, the observed Δage values are more accurately interpreted as evidence of structural deviation from normative trajectories rather than proof of accelerated ageing per se, and cross-sectional estimates cannot establish whether such deviations precede, accompany, or follow disease onset. Further uncertainty arises from the lack of information on whether participants were assessed during or outside a headache attack, given growing evidence that brain structure may vary across different disease phases and activity.[3,10] Additional caution stems from the absence of data on white matter hyperintensities, which accumulate with age, are common in headache populations and may independently influence brain age estimates. Unmeasured confounders, including cardiovascular risk factors, cognitive status, and medication exposure, may also have contributed to between-group differences.

These limitations should not obscure several important contributions of the work. The ordinal-learning approach was specifically designed to reduce biases inherent to conventional brain age prediction models. Its application to a lifespan normative dataset spanning multiple acquisition protocols further strengthens the robustness and generalizability of the findings. The inclusion of both primary and secondary headache disorders enables examination of shared and distinct neuroanatomical substrates. Most importantly, the prognostic analysis in acute PTH addresses a long-standing clinical challenge: identifying which individuals are most likely to develop persistent headache after mild traumatic brain injury.

The anatomical distribution of the observed changes is also noteworthy. Rather than involving regions typically affected in neurodegenerative disorders, the ageing signature was predominantly localized to white matter pathways and subcortical structures implicated in pain processing and sensory integration. Such topographic specificity suggests that the observed increase in brain age may capture disease-relevant neurobiological processes rather than generalized brain ageing. Elevated brain age may therefore be better viewed as a marker of biological vulnerability than as evidence of accelerated ageing itself. The directionality of this association remains uncertain: Does an older-appearing brain predispose individuals to chronic headache, emerge as a consequence of repeated attacks, or reflect a shared biological process underlying both phenomena? Longitudinal studies tracking brain age trajectories across different stages of disease will be essential to answer this question.

By providing a quantitative index of whole-brain structural status, brain age prediction offers a novel perspective on the relationship between headache disorders and brain ageing, one that regional morphometric analyses cannot easily capture. At present, however, it should be regarded as a research tool rather than a method for individual-level clinical decision making.

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