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Advanced Brain Aging Associated With Migraine and Posttraumatic Headache

A Deep Learning Study

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Page e000173

Abstract

Background and Objectives

Deep learning techniques can estimate "brain age" from MRI as a proxy for brain integrity. The difference between a person's brain and chronologic age (Δage) may reflect age-related structural changes. However, brain aging in headache disorders remains poorly understood. We investigated associations between Δage and headache phenotypes and its potential for predicting headache persistence.

Methods

We trained a predictive model of normal aging using a novel ORdinal Distance Encoded Regularization loss and T1-weighted brain MRI scans from public data sets of healthy controls ([HC]; age: 8–95 years). The model outperformed other brain-age methods on a held-out HC test set in our previous work. We then applied this model to an institutional data set including HCs, participants with acute posttraumatic headache (APTH), persistent posttraumatic headache (PPTH) attributed to mild traumatic brain injury (mTBI), and migraine. The primary outcome was baseline MRI-derived Δage, and its association with headache persistence at follow-up was evaluated.

Results

The study included 137 HC (39.5 ± 12.0 years; 53% female), 99 participants with APTH (42.2 ± 15.3 years; 56.6% female), 49 participants with PPTH (38.1 ± 10.6 years; 34.7% female), and 93 participants with migraine (39.6 ± 11.7 years; 74.2% female). Baseline imaging revealed significant differences in predicted Δage across headache phenotypes ($F = 3.53$, $\eta_p^2 = 0.03$, $p < 0.05$). The HC group showed the smallest predicted Δage (0.46 ± 0.87 years), followed by the APTH (1.25 ± 0.87 years), migraine (3.74 ± 1.03 years), and PPTH (4.65 ± 1.41 years) groups. Among APTH participants, those with headache recovery at 3 months post-mTBI had a Δage of 1.28 ± 0.22 years compared with 1.63 ± 0.73 years in those without recovery. Participants with headache persistence at 6-month follow-up had a Δage of 3.46 ± 0.75 years.

Discussion

Headache disorders are associated with accelerated brain aging. Patients with primary (migraine) and secondary (PPTH) headaches exhibit accelerated brain aging and structural decline related to headache persistence compared with HCs. APTH participants who later developed headache persistence at 3 and 6 months had older brain signatures at baseline compared with those who recovered. The results demonstrate the potential of Δage as an early neuroimaging marker for identifying individuals at a risk of PPTH. Limitations include sample size and lack of longitudinal imaging in all groups.

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Glossary

AD = Alzheimer disease; **APTH** = acute posttraumatic headache; **ctx** = cortical gray matter; **Grad-CAM** = gradient-weighted class activation mapping; **HC** = healthy control; **ICBM** = International Consortium for Brain Mapping; **IXI** = Information eXtraction from Image; **LDA** = linear discriminant analysis; **lh** = left hemisphere; **MAE** = mean absolute error; **mTBI** = mild traumatic brain injury; **NACC** = National Alzheimer's Coordinating Center; **OASIS** = Open Access Series of Imaging Study; **ORDER loss** = ORdinal Distance Encoded Regularization loss; **PPTH** = persistent posttraumatic headache; **PTH** = posttraumatic headache; **rh** = right hemisphere; **WM** = white matter; **Δage** = brain age delta (predicted chronological age).

Introduction

Normal aging has a significant effect in altering the structure and function of the human brain. Aging causes irreversible structural changes to the brain that are associated with an increased risk of neurologic and psychiatric disorders.[1-3] The rate at which the brain ages is governed by dynamic biological processes that can affect the timing of disease onset.[4] Identification of an advanced brain aging trajectory might reflect the sequelae of existing neurologic disease or be a risk factor for developing such diseases. Aging has been identified as a primary risk factor for most neurodegenerative disorders such as Alzheimer disease(AD) and Parkinson disease,[3] whereas its clinical relevance for nonneurodegenerative neurologic disorders is not as well understood.

Headache disorders rank among the top 3 most prevalent neurologic conditions, affecting approximately 40% of the global population, or 3.1 billion individuals, in 2021.[5] Migraine is a primary headache that affects about 14% of the global population, is a leading causes of disability,[5] and is among the most common conditions encountered in outpatient clinical settings.[6] Headache attributed to mild traumatic brain injury (mTBI) or concussion, is one of the more common secondary headache disorders. According to ICHD-3 criteria,[7] posttraumatic headache (PTH) must develop within 7 days following TBI. ICHD-3 defines acute PTH as headache lasting less than 3 months after onset of the headache following injury, whereas persistent PTH is defined as headache that endures for at least 3 months after onset.

Although the potential relationship between neurodegeneration and headaches is complex and multifaceted, a meta-analysis found that headache disorders are associated with a 1.35-fold increased risk of all-cause dementia, a 1.49-fold increased risk of AD, and a 1.72-fold increased risk of vascular dementia.[8] Similar to that, another study reported that patients with migraine developed AD with a 1.32 hazard ratio compared with those without migraine history.[9] A previous research study[10] found unique age-related patterns of cortical thinning and thickening in migraine patients, suggesting an interaction between migraine and brain aging which was further confirmed by another study that found advanced brain aging patterns among those with chronic migraine.[11] However, a recent study found no significant structural brain differences between middle-aged and elderly people with migraine compared with those without migraine, challenging the notion of long-term structural changes because of migraine.[12] These contrasting findings underscore the complexity of headache's effects on the brain and necessitate further investigation into the role of headaches in developing accelerated aging patterns and predicting secondary headache persistence.[13] Advancements in imaging techniques, particularly MRI, have enabled direct quantification of such alterations in vivo[14] and at large scale. This has contributed significantly to headache research and search for data-driven imaging biomarkers.[15] However, identifying and understanding the alterations in brain structure linked to the onset, progression, and frequency of headache disorders remains an active area of research interest.[16]

Brain age prediction, which builds on the known relationship between age and neuroanatomy across the lifespan,[17] involves estimating an individual's "brain age," that is, the age at which their brain appears to function or resemble structurally using neuroimaging data. The difference between the predicted brain age and actual chronologic age (Δage) quantifies deviation from normal aging, with potential value for precision medicine and monitoring and predicting disease progression.[18] Deep learning methods outperform traditional machine learning approaches for brain age prediction, which can introduce bias and miss clinically relevant patterns.[19] End-to-end deep learning learns complex patterns directly from high-dimensional imaging.[1,2,20]

Previously, we developed a robust framework for brain age prediction using ordinal classification,[20] which models the ordinal nature of aging and mitigates regression-to-the-mean effect,[21] while capturing age-related structural patterns. The model was trained using a novel ORdinal Distance Encoded Regularization (ORDER) loss objective, and it showed improved sensitivity to subtle structural changes in the brain, which is key to early detection of AD and identifying at-risk individuals before symptom onset. In this research, we explore the applicability of the model to migraine and PTH studies. The primary objective of this study was to compare neuroimaging-derived brain aging patterns across migraine, acute posttraumatic headache (APTH), persistent posttraumatic headache (PPTH), and healthy controls (HC) using a deep learning–based brain age prediction model and to further investigate whether brain age deviation at baseline can serve as a prognostic biomarker for predicting PTH persistence.

The contribution of this study is twofold. First, we leveraged an in-house, state-of-the-art brain age prediction model[20] trained on a cohort of 7,377 T1-weighted brain MRI scans of HC ranging in age from 8 to 95 years. We employed a custom preprocessing pipeline to standardize images to train the model, which is known to increase the diversity of training data and improve model generalization. Second, we applied this model to an institutional data set of 378 individuals, including HC and those with migraine or PTH to investigate how these imaging-derived brain-aging biomarkers could potentially inform about the structural effects of these headaches and be useful for the prediction of PTH persistence.

Methods

Neuroimaging Data

The brain age model was developed using a cohort consisting of T1-weighted MRI scans of HC, aggregated from 5 different data sources available publicly for research: (1) National Alzheimer's Coordinating Center's (NACCs) Uniform Data Set[22] from 1999 to March 2021, (2) Open Access Series of Imaging Studies (OASISs),[23] (3) International Consortium for Brain Mapping[24] (ICBM), (4) Information eXtraction from Images (IXIs),[25] and (5) Autism Brain Imaging Data Exchange-I.[26] These cohorts included both 1.5T and 3T MRI brain scans with predominantly Caucasian participants but also included other race/ethnic groups. All 5 data sets applied clinical screening to exclude neurologic or cognitive disorders. In NACC, HC required a clinical dementia rating of 0 with no dementia, Parkinson, stroke, or other neurologic diagnoses per clinician-reviewed forms. OASIS cohorts similarly included only cognitively normal individuals (clinical dementia rating = 0) after neuropsychological testing and neurologic exams.[27] IXI and ICBM recruited healthy volunteers without structured protocols, but participants with evident brain abnormalities were excluded. In ABIDE-I, typically developing controls were screened to rule out autism and other major neurologic or psychiatric conditions.

The Mayo Clinic institutional data set consisted of T1-weighted MRI data from individuals diagnosed with migraine, APTH, and PPTH, in accordance with the diagnostic criteria of the International Classification of Headache Disorders available at the time the participant was enrolled (ICHD-3 beta or ICHD-3).[7,28] In addition, we included HC from the Mayo Clinic as the reference group.

All participants were imaged at the Mayo Clinic AZ. At enrollment, migraine cases met ICHD-3 (or beta) criteria for episodic or chronic migraine, with or without aura. APTH and PPTH groups had PTH attributed to mild TBI per ICHD-3; individuals with moderate or severe TBI were excluded. APTH participants were enrolled 0–59 days post-mTBI and PPTH participants after >3 months of PTH. Healthy controls were excluded if they had any headache other than infrequent tension-type or any TBI history. Enrollment occurred from 2013 to 2025.

Imaging was performed on 3T Siemens Magnetom Skyra scanners (Erlangen, Germany) with a 20-channel head/neck coil. T1-weighted magnetization-prepared rapid acquisition gradient echo images were acquired with repetition time (TR) = 2,400 ms, echo time (TE) = 3.03 ms, flip angle = 8°, and voxel size = 1 × 1 × 1.25 mm^3.

Brain Age Prediction

Data Preprocessing

All T1-weighted MRI scans underwent preprocessing using a fully automated pipeline. All T1-weighted MRI scans were first aligned to the Montreal Neurological Institute template through rigid transformation. Scans were then processed using FreeSurfer v7.3.2,[29] which performs internal bias field correction, intensity normalization, and image conformation, producing preprocessed images with 1-mm isotropic voxels and a 256 × 256 × 256 matrix. FreeSurfer was additionally used for anatomic parcellation to map Grad-CAM activations onto neuroanatomically defined brain regions. Importantly, the deep learning model takes the conformed T1-weighted images as direct voxel-level input and does not rely on FreeSurfer-extracted morphometric features.

Brain Age Prediction Model Training Using ORDER Loss

We used our previously described ORDER framework for brain age prediction.[20] ORDER treats age estimation as ordinal classification rather than direct regression, allowing the model to output a probability distribution over ages and reducing regression-to-the-mean bias.[1,20,21]

The approach combines cross-entropy with ordinal distance regularization so that latent representations from participants with similar ages are encouraged to cluster more closely than those with larger age differences.[20] The model was implemented with a 3D ResNet-18[30] trained on 7,377 T1-weighted scans from HC across the lifespan (Table 1). Additional details of the loss formulation, network architecture, training splits, and optimization are provided in the Supplemental File.

Table 1 Data Set Summary for Brain Age Model Training

Source	Number of participants	Sex	Age range (y)
ABIDE	176	163 M, 13 F	18–56 (26.1 ± 7.0)
ICBM	1,101	512 M, 589 F	18–80 (37.6 ± 15.4)
IXI	536	246 M, 290 F	20–86 (48.8 ± 16.5)
NACC	4,132	1409 M, 2723 F	18–95 (67.5 ± 10.8)
OASIS	1,432	508 M, 924 F	8–94 (27.9 ± 20.7)

Abbreviations: ABIDE = Autism Brain Imaging Data Exchange-I; ICBM = International Consortium for Brain Mapping; IXI = Information eXtraction from Image; NACC = National Alzheimer's Coordinating Center; OASIS = Open Access Series of Imaging Study.
Summary of age range with distribution and number of samples from each public data set used to train the brain age prediction model.

Brain Age Delta (Δage)

The model trained and validated on lifespan cohort data was applied to preprocessed MRI scans of individuals with headache from our institutional data set to predict brain age. The model outputs a probability distribution P (age = k) over integer ages k ∈ {8,…, 95}. The predicted brain age is derived as the expected value of this distribution: $predicted\ \ age\ = \sum_k k \times P\ (age\ = k\ )$. This expected-value approach leverages the full probability distribution and is more robust than taking the maximum a posteriori class, as it accounts for uncertainty and the ordinal nature of age. Brain age delta (Δage) is then computed as the difference between the predicted brain age and the individual's chronologic age and served as a quantitative measure of brain health: a positive Δage indicates aging-related aberrations, whereas a negative Δage reflects a younger or healthier-appearing brain.[31] A one-way analysis of variance assessed overall differences in Δage among the 3 headache phenotypes and HC, and pairwise *t* tests were performed for detailed group comparisons.

To further validate the neuroimaging-derived aging signatures, we used Gradient-weighted Class Activation Maps (GradCAMs)[32] to localize spatial contributions to predicted brain age across T1-weighted scans. GradCAM, widely used in medical imaging for model interpretation,[33] was computed for each subject and thresholded to retain the top 10% of salient voxels. We then mapped these activations to anatomically defined brain regions and aggregated the results across clinical groups: APTH, PPTH, and migraine. The regions are labeled according to the FreeSurfer neuroanatomical atlas. Cortical regions are prefixed with "ctx" (denoting cortical gray matter) and are further distinguished by hemisphere using the "lh" (left hemisphere) and "rh" (right hemisphere) prefixes. White matter regions are labeled with the "wm" prefix. Subcortical structures are named explicitly with "Left" or "Right" prefixes to indicate hemisphere. For each group, we calculated the proportion of subjects with nonzero activation in each region, highlighting regions salient in ≥50% of cases. This revealed phenotype-specific patterns of consistently engaged regions, offering interpretable, group-level insights into structural aging signatures. The results were summarized as regional occurrence percentages for cross-condition comparison. These thresholding choices were selected to identify consistently activated regions and should be considered exploratory; different thresholds may yield different regional profiles.

To test whether the model learned clinically meaningful representations, we examined whether latent features distinguished headache phenotypes. The goal was to assess shared vs divergent patterns of accelerated brain aging. We extracted 512-dimensional features from the penultimate ResNet-18 layer and applied linear discriminant analysis (LDA) using phenotype labels. Clustering quality was evaluated using Silhouette score, Calinski-Harabasz Index, and Davies-Bouldin Index. It should be noted that LDA is a supervised method that uses phenotype labels to derive projections. The resulting cluster separation should therefore be interpreted as confirmatory of label-driven differences rather than unsupervised discovery of natural groups.

APTH Recovery vs Persistence

In addition to determining predicted brain age associated with migraine, APTH, and PPTH, we aimed to predict which participants with APTH would go on to develop PPTH. Resolution vs persistence of PTH was determined using prospectively collected headache frequency data provided by participants with APTH. For participants who did not experience headaches before developing PTH, a participant was considered to have "recovered" if they had zero headache days in the third month following PTH onset. For participants who experienced headaches before PTH onset (e.g., they might have had migraine or tension-type headache before developing PTH), they were considered "recovered" if the number of headache days in the third month was no more than twice the baseline number of headache days.[34]

Standard Protocol Approvals, Registrations, and Patient Consents

This was an observational neuroimaging study and not a clinical trial. The institutional study was approved by the Mayo Clinic Institutional Review Board and the United States Department of Defense Human Research Protection Office. All participants in the institutional cohort provided written informed consent before enrollment. Publicly available data sets used for model development were accessed and analyzed in accordance with the terms, approvals, and data-use conditions described in the original publications and source repositories. Details on enrollment, demographics, and other characteristics of the public data sets are available in their original publications and documentation.[22,24-27] Readers are referred there for full descriptions of study populations and methodologies.

Data Availability

Deidentified participant data from the institutional cohort, including demographic and clinical variables and derived imaging measures underlying the findings reported in this article, will be considered for sharing with qualified investigators for methodologically sound research on reasonable request to the corresponding author, subject to approval by the Mayo Clinic Institutional Review Board, the United States Department of Defense Human Research Protection Office, and execution of any required data use agreements. Because the institutional data set includes potentially identifiable neuroimaging data, sharing of raw MRI data and related study documents may be restricted for legal and ethical reasons. Publicly available training data sets can be obtained from their original sources.[22-27] The analysis code and pretrained model weights are publicly available.[35]

Results

A total of 378 participants were included in the final analysis, comprising 93 individuals with migraine, 99 with APTH, and 49 with PPTH and 137 were HC. For each data cohort and headache disorder, the information of participants is summarized in Tables 1 and 2. Participants with migraine (mean age 39.6 ± 11.7 years; 74.2% female) reported 13 ± 8.4 headache days/month and a migraine history of 21.8 ± 12.9 years; 49 experienced auras with at least some migraine attacks. The PTH cohort (onset within 7 days of mTBI) included 99 participants with APTH and 49 participants with PPTH. APTH cases (mean age 42.2 ± 15.3; 56.6% female) had PTH for 30 ± 14 days before imaging, with headaches on 86.3% of days since onset. Headache phenotypes in this cohort were classified as follows: 55 (56%) migraine-like, 16 (16%) probable migraine-like, 21 (21%) tension-type, 5 (5%) probable tension-type, and 1 (1%) was not classifiable to a primary headache type. Their mTBI resulted from falls (n = 39), motor vehicle accidents (n = 28), other causes (n = 13), direct head impacts (n = 11), sports injuries (n = 5), and fights (n = 3). PPTH cases (mean age 38.1 ± 10.6; 34.7% female) reported 15.3 ± 7.4 headache days/month and had PTH for 11.3 years on average. Among the 49 PPTH cases, headache phenotype classification was 37 (76%) migraine-like, 10 (20%) probable migraine-like, and 2 (4%) tension-type. Their mTBIs arose from blast injuries (n = 22), falls (n = 12), sports (n = 8), and motor vehicle accidents (n = 7).

Brain Age Delta

Figure 1 summarizes the trend of the neuroimaging-derived aging biomarker and its association with different headache types. The model predicted Δage using baseline imaging was significantly higher for those with migraine (3.74 ± 1.03 years, $p = 0.03$) and PPTH (4.65 ± 1.41 years, $p = 0.01$) compared with HC (0.46 ± 0.87 years). For participants with APTH, Δage was higher compared with HC (1.25 ± 0.87 years) with statistically significant differences compared with the PPTH ($p = 0.04$) and migraine ($p = 0.08$) groups. One-way analysis of variance analysis revealed a statistically significant effect of group on Δage (F value = 3.53, $p < 0.05$), indicating that the model-predicted Δage varied significantly across the groups. However, the differences between APTH and HC ($p = 0.55$) and PPTH and migraine ($p = 0.67$) groups were not significant with pair-wise t tests.

Brain Regions

As an exploratory analysis, we examined Grad-CAM activations to identify brain regions associated with the model's age predictions in each headache group. Grad-CAM revealed a set of brain regions that consistently influenced the age prediction in each group. Table 3 lists these regions for APTH, PPTH, and migraine, along with the percentage of participants in each group for whom that region contributed substantially to their brain aging signature. In APTH, 21 regions met the ≥50% criterion, indicating a widespread pattern of model attention. Participants with migraine showed a similar breadth with 20 regions, whereas PPTH had a more restricted set of 12 regions (notably all of which overlapped with the APTH/migraine sets, see next section). The highlighted regions spanned frontal, parietal, temporal, occipital, and subcortical areas. For example, the rostral middle frontal gyrus white matter (bilateral prefrontal region) was prominently highlighted in all 3 groups (appearing in ~65%–73% of participants per group as the top feature). Other common regions included the postcentral gyrus (primary somatosensory cortex region, particularly its subcortical white matter), lingual gyrus (WM) in the occipital lobe, precuneus (WM) in the parietal lobe, superior temporal gyrus (WM), and parts of the anterior cingulate (rostral ACC white matter), and posterior cingulate (isthmus cingulate gyrus white matter). In addition, subcortical structures of the basal ganglia: the pallidum, putamen, and caudate (left hemisphere), were frequently highlighted, suggesting these deep gray matter nuclei contributed to the model's age predictions in patients with headache.

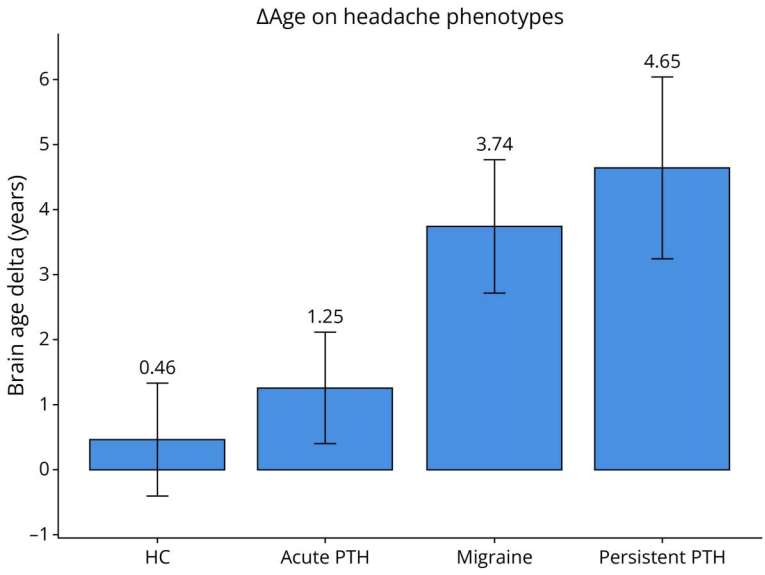
In Figure 2, LDA applied to the model's latent representations demonstrated a clear separation among the headache phenotypes along with HCs. The LDA projection revealed 4 distinct clusters corresponding to the clinical labels. This visual separation suggests that the model captures meaningful latent patterns reflective of phenotype-specific brain aging signatures. To validate this observation quantitatively, the Silhouette Score was 0.602, indicating that patients were more similar to others within their own phenotype cluster than to

Table 2 Data Set Summary for Headache Phenotypes and Controls

Number of participants	Diagnostic status	Sex	Age range (y)
99	Acute PTH	43 M, 56 F	18–70 (42.2 ± 15.3)
49	Persistent PTH	32 M, 17 F	19–63 (38.1 ± 10.6)
93	Migraine	24 M, 69 F	22–66 (39.6 ± 11.7)
137	HC	65 M, 72 F	18–66 (39.5 ± 12.0)

Abbreviations: HC = healthy control; PTH = posttraumatic headache.
Summary of age range with distribution and number of samples for each headache phenotype along with healthy controls collected from the institutional data set (Mayo Clinic, AZ).

Figure 1 Brain Age Delta (Predicted—Chronological Age) Across Different Headache Types



Those with persistent posttraumatic headache (PTH) had the oldest brain age, followed by those with migraine, acute PTH, and healthy controls (HC).

those in neighboring clusters. The Calinski-Harabasz Index was 645.986, highlighting compact, well-differentiated clusters. And the Davies-Bouldin Index was 0.542, further confirms low intracluster similarity and overall separation. Collectively, these metrics suggest that the model's latent space encodes distinct patterns associated with each phenotype.

APTH Recovery vs Persistence

As a secondary analysis, we examined Δage in relation to PTH recovery trajectories among participants with APTH. Δage, using baseline MRI data, for participants with APTH who went on to have PTH recovery before 3 months was 1.28 ± 0.22 years, whereas it was 1.63 ± 0.73 years for those with APTH who did not recover by 3 months. Notably, participants who continued to have PTH persistence at 6 months exhibited a substantially higher baseline Δage of 3.46 ± 0.75 years.

Discussion

The findings from this study suggests that APTH, PPTH, and migraine are associated with advanced brain aging and that greater Δage in APTH is associated with later headache persistence. Participants in the APTH cohort whose headaches persisted at 3 and 6 months had more advanced brain aging at baseline compared with those who recovered. These findings support the possibility that neuroimaging-derived brain age signatures capture clinically meaningful structural abnormalities in headache disorders and may have prognostic relevance for PTH.

The predominance of white matter regions among the top Grad-CAM features (Table 3) is notable and consistent with age-related structural change.[36] Common regions across groups included frontal and temporal white matter, postcentral and parietal association regions, cingulate areas, and basal ganglia. Many of these regions are implicated in pain modulation, sensory integration, and executive control.[37-39] Thus, the model may be capturing structural features that lie at the intersection of normal aging and headache-related brain alteration. Because the model was trained on structural T1 MRI to predict age, the highlighted regions should be interpreted as features contributing to older-appearing brains rather than as direct markers of headache pathophysiology. Figure 3 shows a visual illustration of model-predicted activations identified using Grad-CAM of sample participants chosen randomly across headache disorders. Alterations in the hypothalamus, pons, thalamus, insula, and limbic structures are commonly noted in prior migraine and PTH literature, particularly in fMRI studies assessing altered connectivity and activation. In contrast, our study used structural T1-weighted MRI sequences to estimate brain age using a deep learning model trained to detect age-related structural patterns. The Grad-CAM analysis also prioritized structural features that contributed most strongly to brain age predictions, which may differ from regions typically identified in brain functional or structural imaging studies.

The comparison between APTH and PPTH suggests that brain age deviation may also have prognostic value. Participants who later remained symptomatic had older-appearing brains at baseline, raising the possibility that Δage could help identify people at a risk of persistent PTH and support earlier, more individualized management. However, APTH imaging occurred within weeks of mTBI, whereas PPTH imaging occurred roughly a decade after injury, so this study cannot

Table 3 Brain Regions Predictive of Headache Type Identified by GradCAM

Region	APTH (%)	Migraine (%)	PPTH (%)
Right rostral middle frontal gyrus, WM	67.3	64.9	73.5
Left globus pallidus	61.2	59.6	69.4
Right postcentral gyrus, WM	61.2	59.6	63.3
Left lingual gyrus, WM	60.2	62.8	65.3
Right precentral gyrus, WM	58.2	64.9	53.1
Left isthmus cingulate gyrus, WM	58.2	62.8	51.0
Left precuneus, WM	56.1	60.6	51.0
Left superior temporal gyrus, WM	55.1	52.1	59.2
Left putamen	53.1	61.7	51.0
Right rostral anterior cingulate, WM	52.0	62.8	51.0
Left lateral orbitofrontal cortex, WM	51.0	60.6	51.0
Left inferior parietal lobule, WM	51.0	57.4	57.1
Left caudate nucleus	57.1	59.6	—
Right pars orbitalis, WM	53.1	53.2	—
Left banks of superior temporal sulcus, WM	53.1	60.6	—
Right paracentral lobule, WM	52.0	60.6	—
Right supramarginal gyrus, WM	51.0	50.0	—
Left rostral anterior cingulate, WM	51.0	61.7	—
Left cuneus, WM	50.0	52.1	—
Right postcentral gyrus, cortex	51.0	—	—
Left paracentral lobule, WM	50.0	—	—
Right banks of superior temporal sulcus, WM	—	53.2	—

Abbreviations: APTH = acute posttraumatic headache; GradCAM = Gradient-weighted Class Activation Map; PPTH = persistent posttraumatic headache; WM = white matter.
Total 22 brain regions identified by GradCAM as predictive and present in the majority of participants (e.g., >50% in this study) within each headache group. A dash ("–") indicates the region was not highlighted in that group at the 50% threshold.

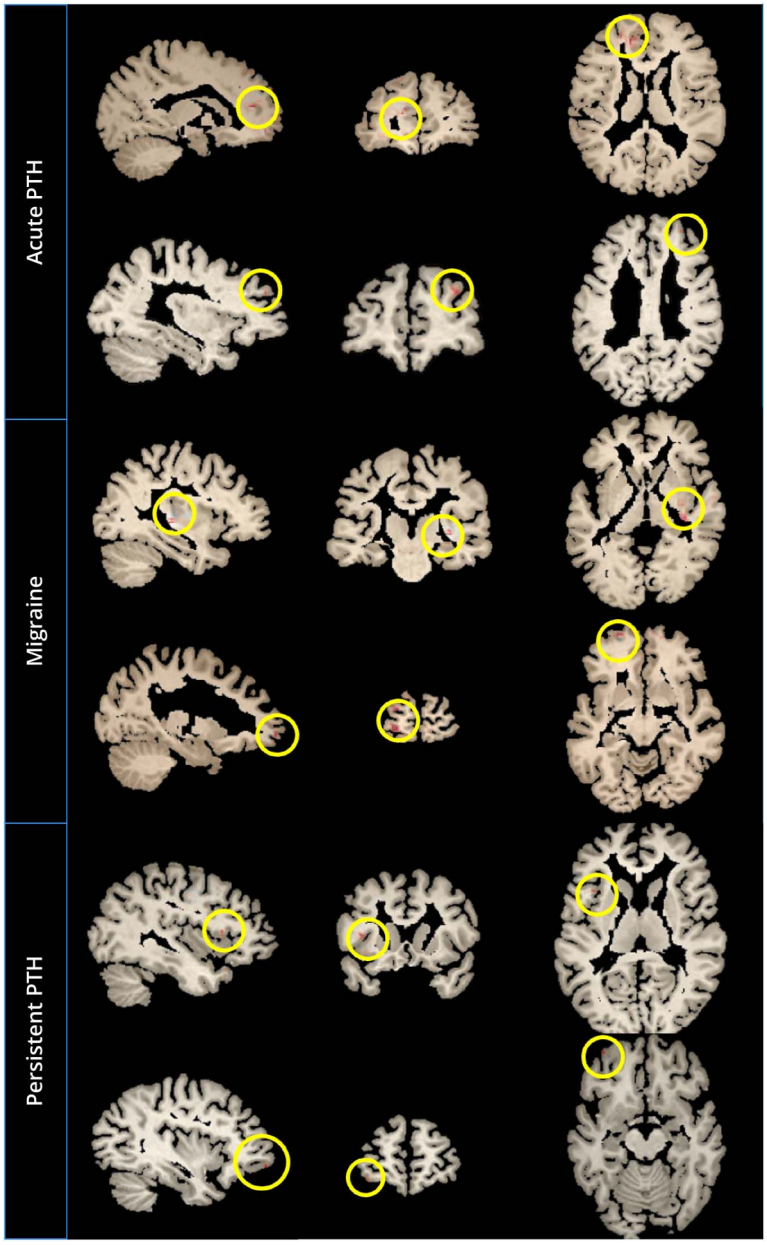
disentangle effects of headache persistence from effects of time since injury.

Although APTH, PPTH, and migraine shared a core set of regions, there were phenotype-specific differences. All PPTH regions were also present in APTH and migraine, whereas APTH and migraine showed additional frontal, sensorimotor, and temporal regions. This pattern is consistent with the clinical overlap between migraine and PTH[40] and suggests that persistent PTH may reflect a partly migraine-like structural signature superimposed on trauma-related brain change. Our findings also align with previous studies reporting accelerated brain age after traumatic brain injury[41] and in chronic migraine,[11] as well as structural abnormalities in frontal, cingulate, and parietal regions in migraine and PTH.[42-44]

The gradient in Δage across APTH recovery groups suggests potential clinical relevance. If validated, baseline brain age deviation could complement clinical assessment by identifying patients who may benefit from closer monitoring or earlier intervention.[45]

Grad-CAM identified regions that have been implicated in normal aging and neurodegeneration, which is expected given the model is trained for brain age prediction. For instance, the prominence of frontal white matter aligns with known age-related volume loss in frontal lobes.[36] Subcortical GM like the caudate and putamen are among the fastest declining brain volumes in aging, often showing pronounced atrophy in older adults. It is therefore notable that participants with migraine and PTH show changes in those areas sufficient to register on an age prediction model. In patients with mild TBI, Cole et al.[41] found that brain-predicted age exceeded chronologic age by about 5 years on average, signifying accelerated atrophy postinjury. Patients with chronic migraine likewise exhibit accelerated aging effect (on the order of +4 years in chronic

Figure 2 Brain Age Model Predicted Peak Activation Regions in T1 MRI Scans

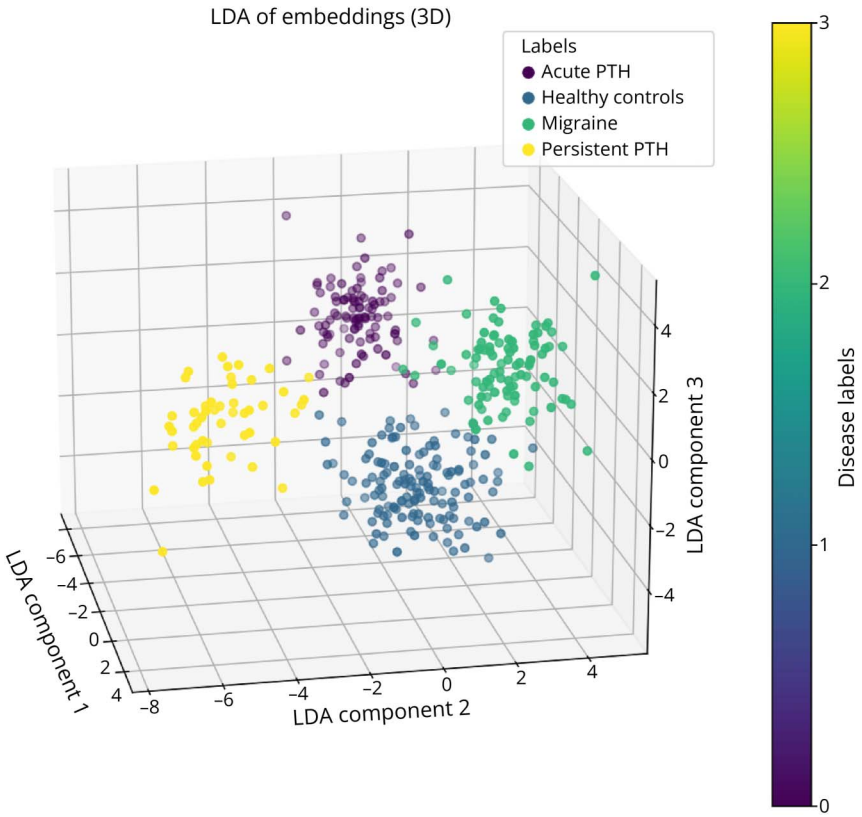


Axial, coronal, and sagittal snapshots of the patient's T1-weighted MRI overlaid with the voxels of highest model-predicted normalized activation (≥50% of the within-brain maximum). Note that these images show only the topmost activation; the full set of suprathreshold regions and their statistics are reported in Table 3.

migraine vs ~0 in HC).[11] Our Grad-CAM analysis suggests that this "aging acceleration" in headache disorders is not diffuse but rather concentrated in specific regions, particularly frontal lobe white matter, cingulate, temporal and parietal association areas, and basal ganglia. These regions may undergo subtle atrophy degradation in patients (because of chronic pain, vascular risk, or injury effects), making the brain appear older. Our findings support the idea that both acute and persistent PTH not only share migraine-like brain alterations in key regions but also underscore the role of diffuse white matter aging-like changes after trauma. Headache phenotype (migraine-like vs tension-type) could also influence the observed brain aging patterns and regional findings. Also, the majority of participants with PTH having migraine-like or probable migraine-like phenotype, which may partly explain the overlap in regions identified between PTH and migraine groups.

There are only a few previous studies directly listing the specific regions discovered in this study, but existing neuroimaging literature does corroborate many individual findings. For instance, a voxel-based morphometry study of migraine reported GM density decreases in the ACC, insula, and inferior frontal cortex, as well as in the posterior parietal (including precuneus) and orbitofrontal cortex.[42] These match several of our Grad-CAM regions (frontal, ACC, and

Figure 3 Visualization of Headache Phenotype Clustering in a 3 days LDA-Reduced Feature Space



The plot demonstrates 3 discernible clusters, effectively separating migraine, persistent PTH, acute PTH, and healthy control groups based on model-extracted neuroimaging features. Each dot represents an individual patient. LDA = linear discriminant analysis; PTH = posttraumatic headache.

precuneus). In the posttraumatic cohort, gray matter volume loss in the frontal lobes and cingulate has been noted in those with persistent post-TBI headaches.[43]

Several limitations should be noted. The study was cross-sectional, so causality and temporal ordering cannot be inferred. The PPTH sample was modest. Larger samples would improve statistical power and the reliability of subgroup comparisons. Although ORDER reduces regression-to-the-mean bias, explicit post hoc bias correction[46] was not performed. This residual bias, if present, could influence group comparisons, particularly if groups differ in age distribution, and should be addressed in future work. Training data were aggregated across public data sets and scanner settings, which likely improved generalizability but may also have introduced residual site effects. Grad-CAM analyses are exploratory and do not establish causality. Saliency maps, including Grad-CAM, are known to be susceptible to false positives and negatives in medical imaging settings, and their reliability can be affected when multiple regions contribute simultaneously to the model's output. Future work should validate these regional findings using complementary and fundamentally different interpretability methods (e.g., occlusion sensitivity,[47] Integrated Gradients,[48] Shapley Additive Explanations[49]-based approaches). In addition, group comparisons of Δage were not adjusted for covariates such as age and sex. Although the groups were similar in mean age, differences in sex distribution (e.g., PPTH: 34.7% female; migraine: 74.2% female) could confound the results. Our study lacks data on cardiovascular risks such as smoking or diabetes, white matter hyperintensities, and cognitive status, which likely contribute to Δage variance. Clinical states during scanning (active headache, medication) were not captured. Regarding training data, although public data sets lacked headache screening, the potential inclusion of undiagnosed migraineurs likely biased the normative model toward more advanced aging, making our reported group difference more conservative.

Future research is needed to determine the clinical relevance of the accelerated brain aging signatures found in this study. Although our findings suggest that neuroimaging-derived brain age deviations may serve as a biomarker associated with headache persistence, longitudinal studies with repeated neuroimaging and detailed clinical follow-up will be critical to determine whether the observed structural changes represent transient changes following injury or progressive neuropathologic processes related to headache chronification. Future studies should also examine anatomic-cognitive relationships by incorporating comprehensive neurocognitive and behavioral assessments because several of the brain regions implicated in our analyses (e.g., prefrontal cortex, cingulate cortex,

and parietal association regions) are involved in executive function, attention, and pain modulation. Understanding whether advanced brain aging signatures correlate with cognitive performance, symptom burden, or functional outcomes will help to clarify and interpret the clinical significance of these imaging findings. Finally, validation in larger, multicenter cohorts with standardized imaging protocols will be critical to confirm the robustness and generalizability of these findings and determine whether brain age biomarkers may be of utility for clinical risk stratification or treatment monitoring in migraine and PTH.

Using a deep learning-based brain age prediction model, we identified set of brain regions associated with accelerated brain aging patterns in APTH, PPTH, and migraine. The highlighted regions included frontal and parietal white matter, cingulate gyrus, temporal association areas, and basal ganglia that were common to all 3 headache phenotypes, suggesting a shared neuroanatomical pattern underlying headache chronification and brain aging. APTH and migraine showed involvement of sensorimotor and temporal regions, differentiating them slightly from PPTH. These results are supported by and extend previous neuroimaging studies, which have reported structural and functional changes in frontal, cingulate, and parietal regions in both posttraumatic and primary headaches. Moreover, our findings reinforce the concept of accelerated brain aging in persistent headache conditions, pinpointing where in the brain such aging may be most pronounced. Future studies should investigate whether effective headache treatments can prevent and reverse accelerated brain aging. Although deep learning models hold promise for automated diagnosis, subtype classification, and biomarker discovery in headache disorders, it is important to emphasize that these tools remain investigational. The brain age predictions and regional findings reported here are not yet validated for guiding clinical therapy. Clinicians should interpret these results within the context of established clinical evaluation frameworks.

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Author Contributions

J. Shah: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Dumkrieger: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. C.D. Chong: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. Todd J.J. Schwedt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. T. Wu: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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