Capturing MRI signatures of Brain Age as a potential biomarker to predict persistence of Post Traumatic Headache

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Disclosures

This project received funding from
US Department of Defense & National Institutes of Health
Migraine & Post-Traumatic Headache (PTH)

- Common primary (migraine) and secondary (PTH) headache disorders

- PTH is a common symptom following mild traumatic brain injury (mTBI)
  
  Acute PTH (resolves within 3 months)
  Persistent PTH (persists more than 3 months)

- Migraine-like phenotype is common in PTH

  Significant long-term disability & health burden
Questions

- Pathophysiology of persistent PTH is poorly understood
  underlying mechanisms are likely multifactorial\(^1\)

- **Similarities** and **differences** are under study\(^2\)
  PTH symptoms often resemble Migraine
  Distinct findings in Migraine than PTH based on imaging characteristics

- Can we differentiate b/w Migraine and PTH phenotypes?

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\(^1\) Ashina, Håkan, et al. “Guidelines of the International Headache Society for controlled trials of pharmacological preventive treatment for persistent post-traumatic headache attributed to mild traumatic brain injury.” *Cephalalgia* 44.3 (2024)

\(^2\) Ihara, Keiko, and Todd J. Schwedt. “Posttraumatic headache is a distinct headache type from migraine.” *Current Opinion in Neurology* (2024)
Can Imaging tell us anything?

- T1 weighted MRI scans provide insights into the brain region structures, volume of WM and GM,
  
  Measure brain atrophy
  Neurodegeneration

- Brain shrinkage is associated with aging,
  
  Precursor to diseases such as dementia

https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/multimedia/img-20539583
First published in 2016, predictors of biological age using AI

- Multiple data can be used to predict age & associate it with mortality, disease, general wellbeing, & other biological processes
  - gene expression
  - microbiome
  - imaging data, ...
Brain Age gap ($\Delta_{\text{age}}$)

$\Delta_{\text{age}} = \text{predicted age} - \text{true age}$

Accelerated Aging (e.g., ADRD)

MRI signature for Aging

Monitoring Natural Aging
Alzheimer’s Disease (AD) early detection

5 clinical sub-groups of AD continuum from ADNI*

• Mild cognitive impairment (MCI), a pre-dementia stage, has greater cognitive decline than typical aging.

• $\Delta_{age}$ can detect and monitor this stage early\(^1\)

• $\Delta_{age}$ higher for higher disease severity (change order), bigger

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\*Alzheimer’s Disease Neuroimaging Initiative

\(^1\)Shah, Jay, et al. “Ordinal Classification with Distance Regularization for Robust Brain Age Prediction.” WACV. 2024.
Are there any **Brain Aging** signatures in Persistent Post-Traumatic Headache?

Can we detect them using AI?

Can we delineate similarities & differences in

- Migraine vs PTH vs Persistent PTH
- Better understand underlying pathophysiology
Datasets

Total 7,377 HC MRIs collected from public cohorts (age=53±22.3)

1. National Alzheimer’s Coordinating Center (NACC)
2. Open Access Series of Imaging Studies (OASIS)
3. International Consortium of Brain Mapping (ICBM)
4. Information eXtraction from Images (IXI)
5. Autism Brain Imaging Data Exchange (ABIDE)

Headache MRIs (from Mayo Clinic, Arizona)

1. Healthy Control (HC)
2. Acute PTH (APTH)
3. Migraineurs
4. Persistent PTH (PPTH)

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Count</th>
<th>Age Range(yrs)</th>
<th>mean±std</th>
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</thead>
<tbody>
<tr>
<td>NACC</td>
<td>4132</td>
<td>18 - 95</td>
<td>67.5±10.8</td>
</tr>
<tr>
<td>OASIS</td>
<td>1432</td>
<td>8 - 94</td>
<td>27.9±20.7</td>
</tr>
<tr>
<td>ICBM</td>
<td>1101</td>
<td>18 - 80</td>
<td>37.6±15.4</td>
</tr>
<tr>
<td>IXI</td>
<td>536</td>
<td>20 - 86</td>
<td>48.4±16.5</td>
</tr>
<tr>
<td>ABIDE</td>
<td>176</td>
<td>18 - 56</td>
<td>26.1±7.0</td>
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</table>

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Count</th>
<th>Age Range(yrs)</th>
<th>mean±std</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>111</td>
<td>18 - 64</td>
<td>39.1±11.4</td>
</tr>
<tr>
<td>APTH</td>
<td>52</td>
<td>19 - 63</td>
<td>44.4±13.9</td>
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<tr>
<td>Migraine</td>
<td>93</td>
<td>22 - 66</td>
<td>39.6±11.7</td>
</tr>
<tr>
<td>PPTH</td>
<td>49</td>
<td>19 - 63</td>
<td>38.1±10.6</td>
</tr>
</tbody>
</table>

Regression to Mean bias

RTM effect

Using **MSE** loss,

- Young subjects predicted older
- Old subjects predicted younger

Not due to model choice, data imbalance, or cohort diversity$^1$

Why it matters?

- Diseased subjects are often old (Alzheimer's, Parkinson's, etc.)
- Post-hoc correction can bias findings

**ORDER Loss**

with L1 Distance Regularization

**Objectives**
1. Reduce RTM Bias
2. Learn natural Age ordering
3. Improve Brain age prediction

**Model**

a. Transform Regression → Classification task
b. Models learns ordinal information from Age using **ORDER** loss
c. More details in our published work\(^1\)

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\(^1\)Shah, Jay, et al. "Ordinal Classification with Distance Regularization for Robust Brain Age Prediction." WACV. 2024.
**Observations:**

1. Mean-squared Error (MSE) – traditional **regression** loss
   - suffers from RTM bias
2. Cross Entropy – traditional **classification** loss
   - does not preserve Age order
## Results on Lifespan (Healthy) cohort

<table>
<thead>
<tr>
<th>Method (Loss)</th>
<th>MAE</th>
<th>RTM Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SB-L</td>
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<tr>
<td>Regression</td>
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<tr>
<td>MSE</td>
<td>3.93</td>
<td>3.4</td>
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<tr>
<td>MSE + Euclidean norm</td>
<td>4.57</td>
<td>4.8</td>
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<tr>
<td>Classification</td>
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<tr>
<td>CE</td>
<td>3.33</td>
<td>1.1</td>
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<tr>
<td>CE + mean-variance</td>
<td>2.65</td>
<td>0.4</td>
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<tr>
<td>Ours</td>
<td>2.56</td>
<td>0.1</td>
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</tbody>
</table>

CE = cross entropy; MSE = mean squared error


Systematic bias left (SB-L) – Young subjects
Systematic bias right (SB-R) – Old subjects

Reduced RTM Bias
Improved brain age prediction
Results on Headache cohorts

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>$\Delta_{age} \pm SE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC (Mayo)</td>
<td>0.38 ± 0.99</td>
</tr>
<tr>
<td>Acute PTH</td>
<td>1.54 ± 1.19</td>
</tr>
<tr>
<td>Migraine</td>
<td>3.74 ± 1.03</td>
</tr>
<tr>
<td>Persistent PTH</td>
<td>4.65 ± 1.41</td>
</tr>
</tbody>
</table>

Observations

1. Persistent PTH & Migraine had significant aging signatures
2. Cumulative effect of headaches – headaches >3 months had more aging effects
3. Acute PTH show early but subtle aging signatures
Results

t-test among $\Delta_{age}$ of headache groups

<table>
<thead>
<tr>
<th></th>
<th>APTH</th>
<th>Migraine</th>
<th>PPTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>0.15</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>APTH</td>
<td>0.24</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

P-values among $\Delta_{age}$ of headache groups

Observations

1. Migraine & PPTH had ~similar (severe) accelerated aging patterns
2. APTH phenotype had different structural differences compared to Migraine or PPTH
Takeaways

• **Persistent PTH** showed effects of accelerated brain aging with significant differences from Acute PTH.

• Headache frequency had a *cumulative effect*; headache persistence >3 months had severe aging effects.

• **Migraine** also had brain aging signatures; less severe than Persistent PTH, more severe than Acute PTH.

• **Relevance**: Brain age gap ($\Delta_{\text{age}}$) can be used as a potential biomarker in predicting persistence of PTH.
Thank You

Questions?

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