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

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VA

AAN 2024 Annual Meeting

Disclosures

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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?

[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)

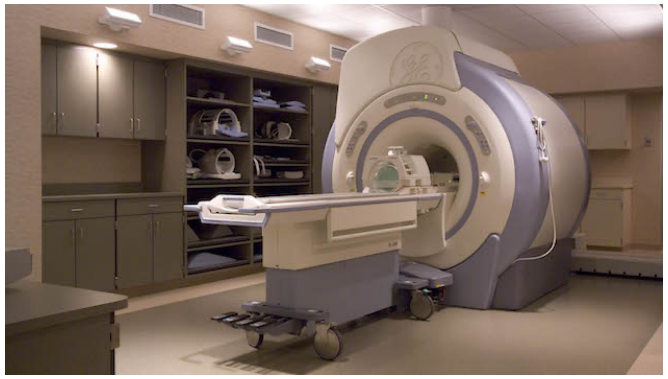
Can Imaging tell us anything?

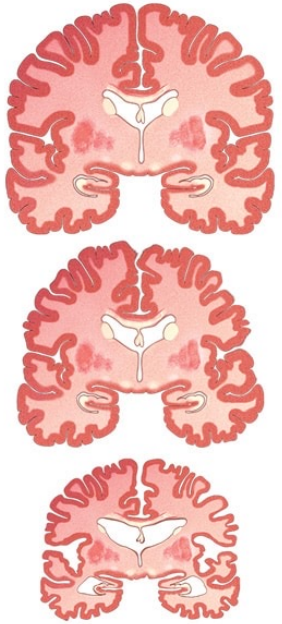
- T1weighted MRI scans provide insights into the brain region structures, volume of WM and GM,

  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

Trends in Pharmacological Sciences

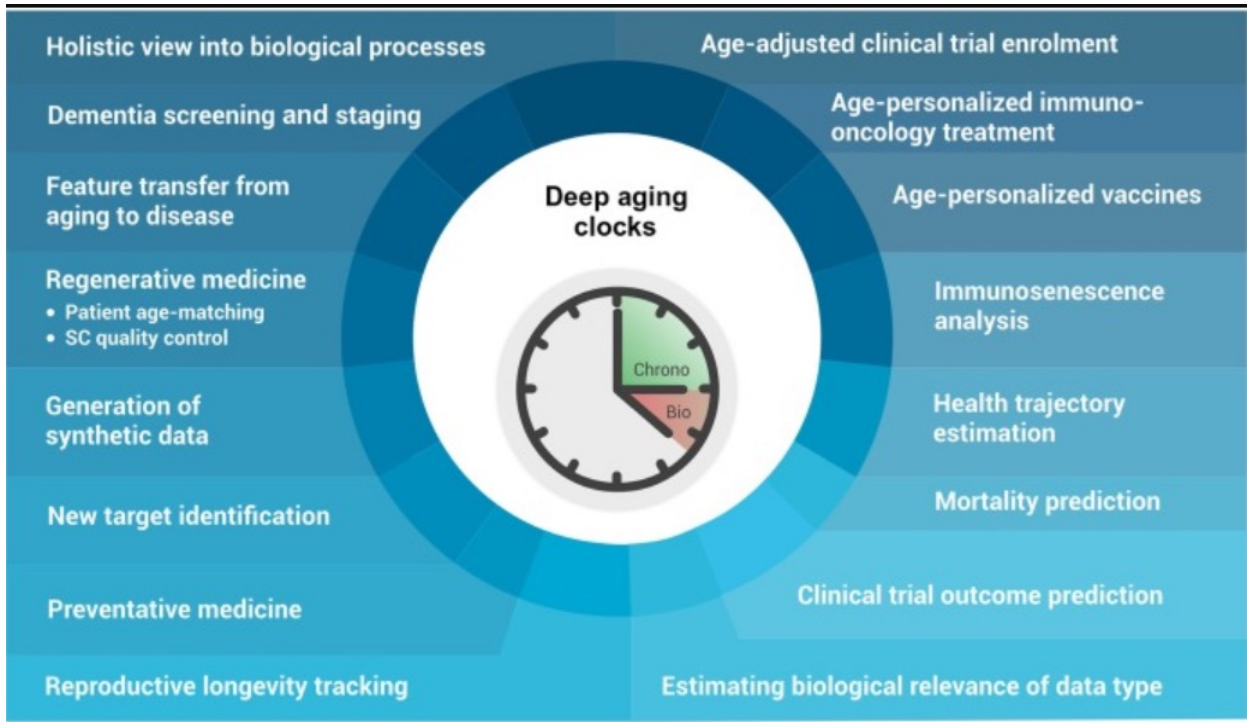
Volume 40, Issue 8, August 2019, Pages 546-549

Science & Society

Special Issue: Rise of Machines in Medicine

Deep Aging Clocks: The Emergence of AI-Based Biomarkers of Aging and Longevity

Alex Zhavoronkov [1 2 3], Polina Mamoshina [1 4]



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, …

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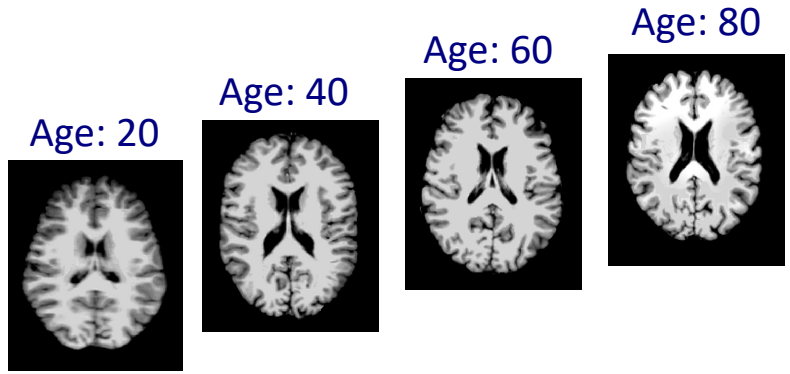
Brain Age gap (Δ_{age})

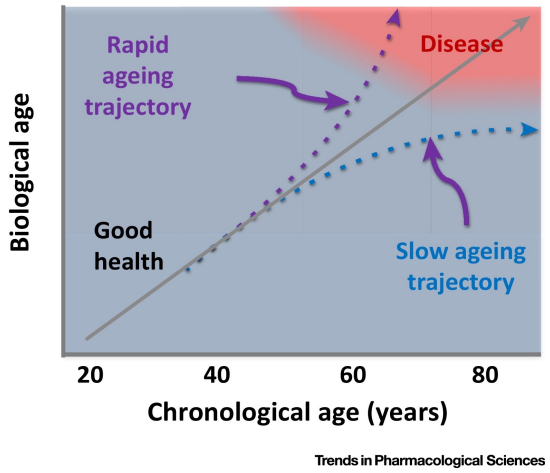
Δ_{age} = predicted age – true age



MRI signature for Aging

Accelerated Aging

(e.g., ADRD)



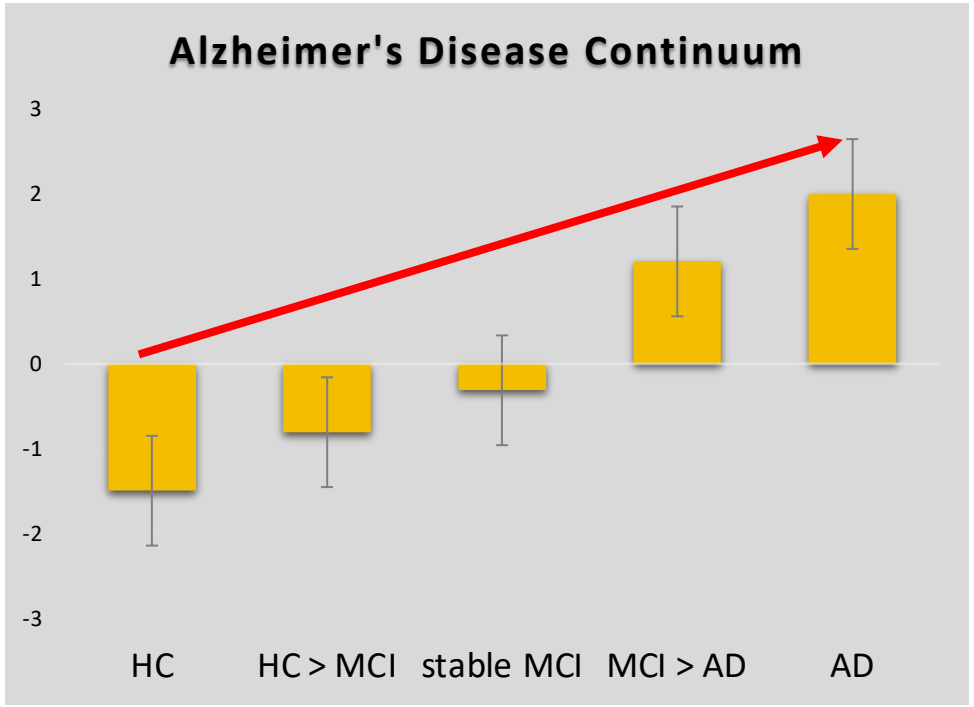
Monitoring Natural Aging

Alzheimer's Disease (AD)
early detection

5 clinical sub-groups of AD continuum from ADNI*

Severity
Healthy Control (HC)
HC conv MCI (HC>MCI)
Stable MCI
MCI conv AD (MCI>AD)
AD

- Mild cognitive impairment (MCI), a pre-dementia stage, has greater cognitive decline than typical aging.
- Δ_{age} can detect and monitor this stage early[1]
- Δ_{age} higher for higher disease severity (chamge order), bigger



*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**)

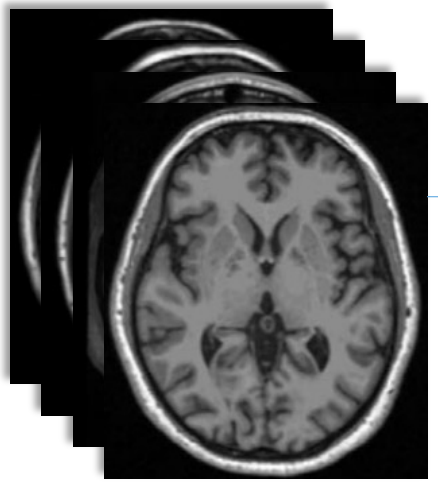
Dataset	Count	Age Range(yrs)	mean±std
NACC	4132	18 - 95	67.5±10.8
OASIS	1432	8 - 94	27.9±20.7
ICBM	1101	18 - 80	37.6±15.4
IXI	536	20 - 86	48.4±16.5
ABIDE	176	18 - 56	26.1±7.0

Headache MRIs (from Mayo Clinic, Arizona)

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

Dataset	Count	Age Range(yrs)	mean±std
HC	111	18 - 64	39.1±11.4
APTH	52	19 - 63	44.4±13.9
Migraine	93	22 - 66	39.6±11.7
PPTH	49	19 - 63	38.1±10.6

Regression



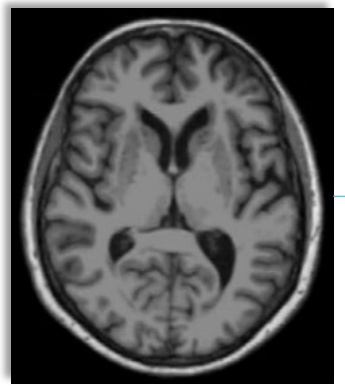
Healthy subjects

training[2]

Deep Learning Model

ResNet-18[1]

Chronological Age



Healthy/Diseased subjects

Trained Model

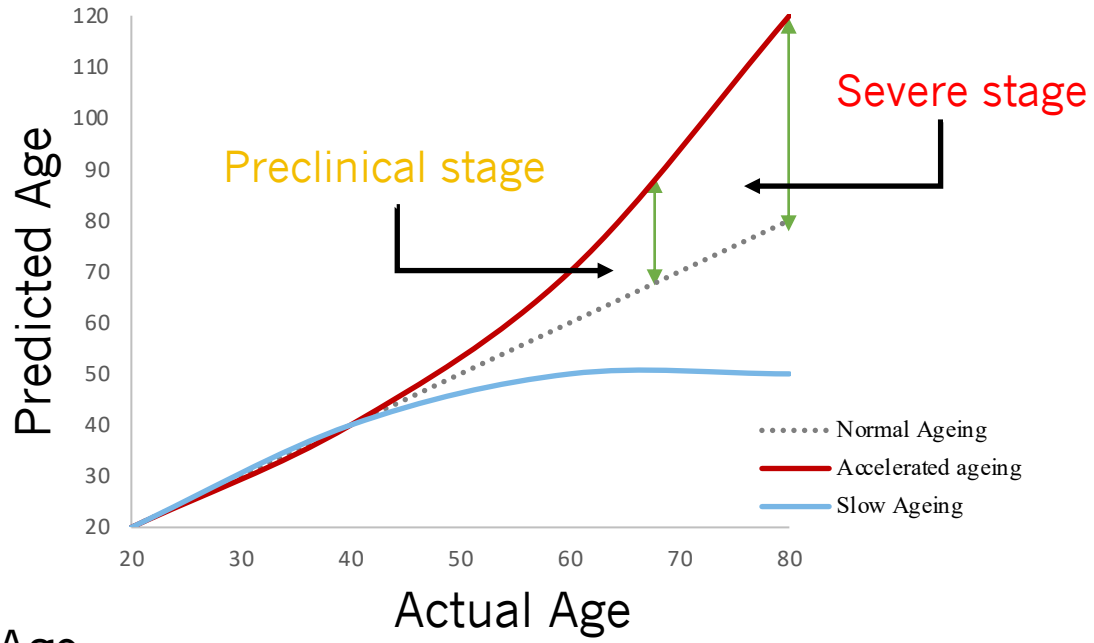
ResNet-18[1]

Predicted Age

Δ_{age} = (predicted – actual) age

[1]He, Kaiming, et al. "Deep residual learning for image recognition." CVPR. 2016.
[2]Shah, Jay, et al. "Ordinal Classification with Distance Regularization for Robust Brain Age Prediction." WACV. 2024.

Disease detection



Regression to Mean bias

RTM effect

Using **MSE** loss,

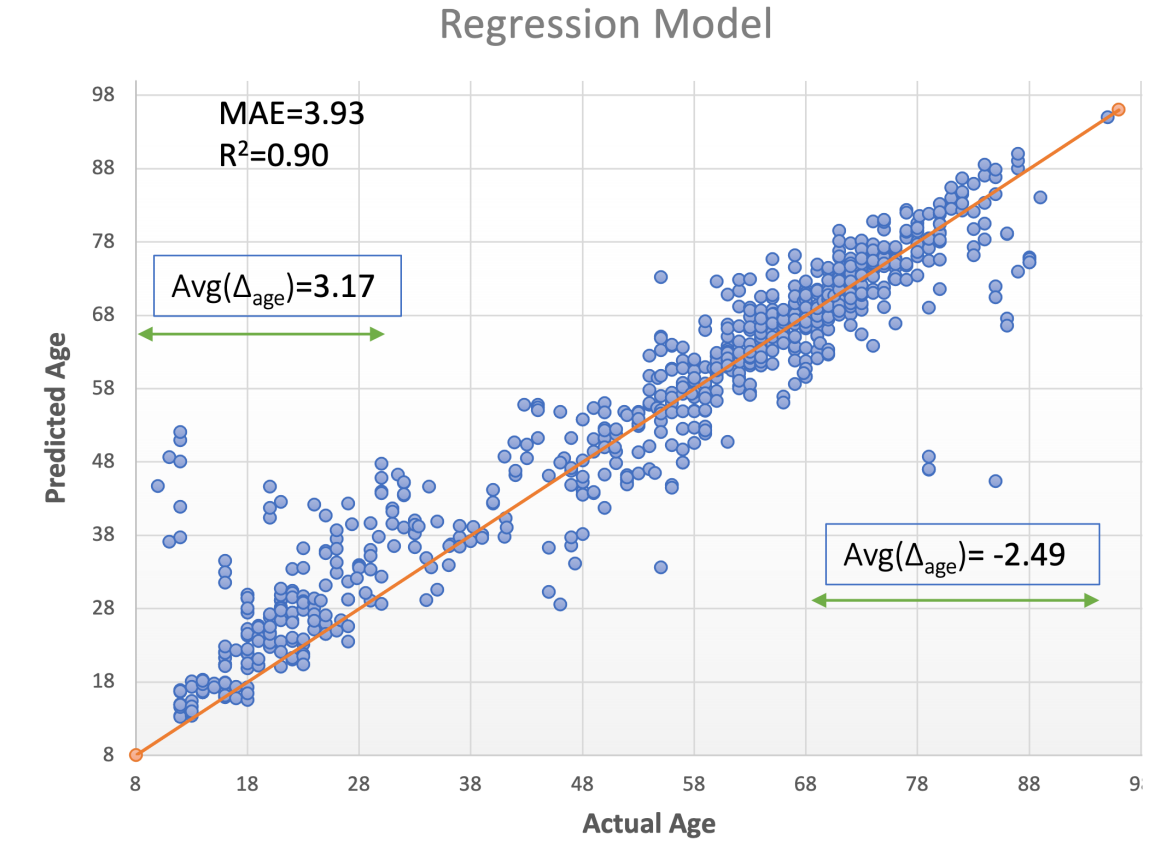
- Young subjects predicted older
- Old subjects predicted younger

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

Note: all are Healthy Controls

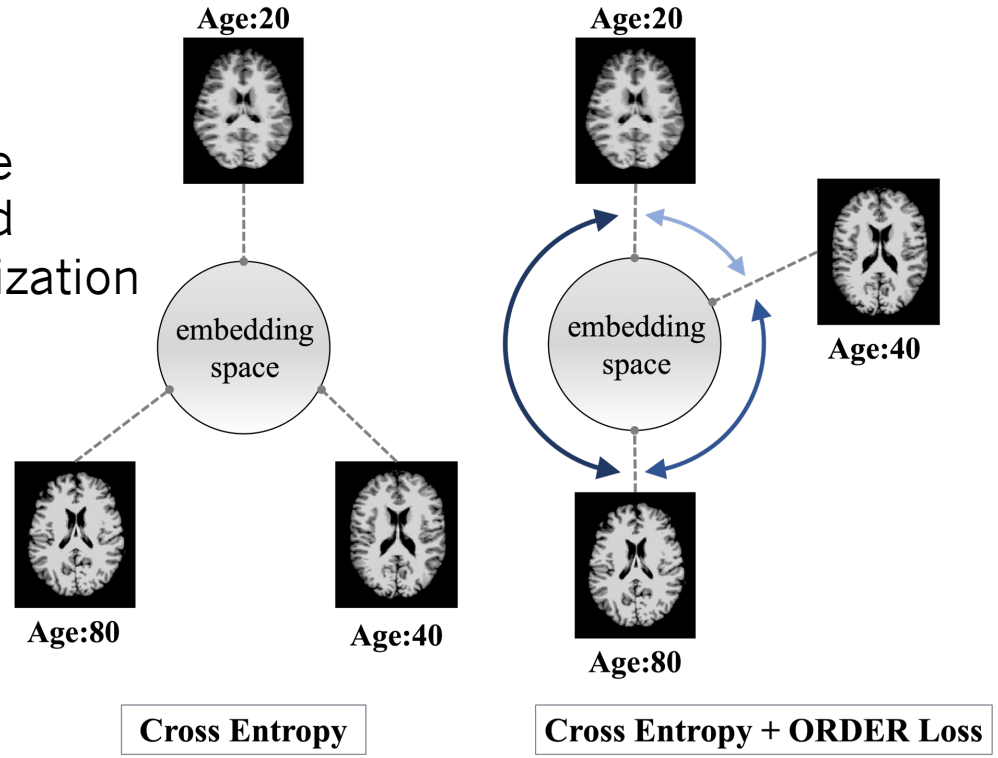


[1]Liang, Hualou, et al. Investigating systematic bias in brain age estimation with application to post-traumatic stress disorders. (2019)

ORDER Loss

with L1 Distance Regularization

ORDER
ORdinal
Distance
Encoded
Regularization



Objectives

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

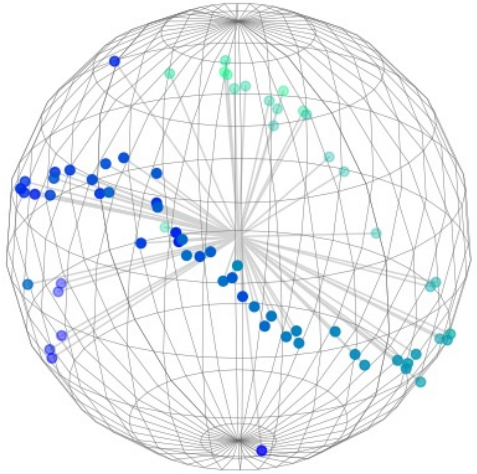
Model

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

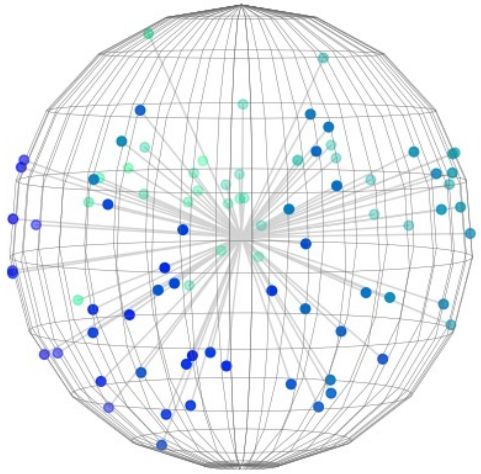
[1]Shah, Jay, et al. "Ordinal Classification with Distance Regularization for Robust Brain Age Prediction." WACV. 2024.

Age ordering

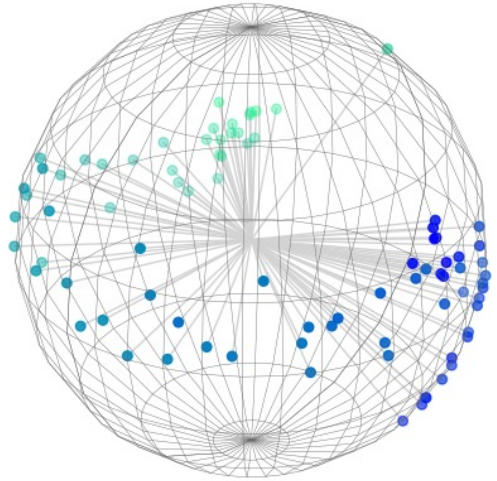
high-dimensional embedding of model



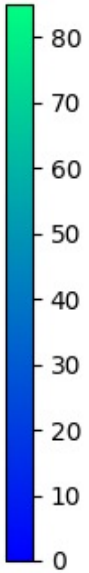
MSE



Cross Entropy



Cross Entropy
+ ORDER



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

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

	Method (Loss)	MAE	RTM Bias	
			SB-L	SB-R
Regression	MSE	3.93	3.4	-4.2
	MSE + Euclidean norm[1]	4.57	4.8	-4.1
Classification	CE	3.33	1.1	-3.6
	CE + mean-variance[2]	2.65	0.4	-4.2
Ours	CE + ORDER	**2.56**	**0.1**	**-2.5**

CE=cross entropy; MSE=mean squared error

Reduced RTM Bias

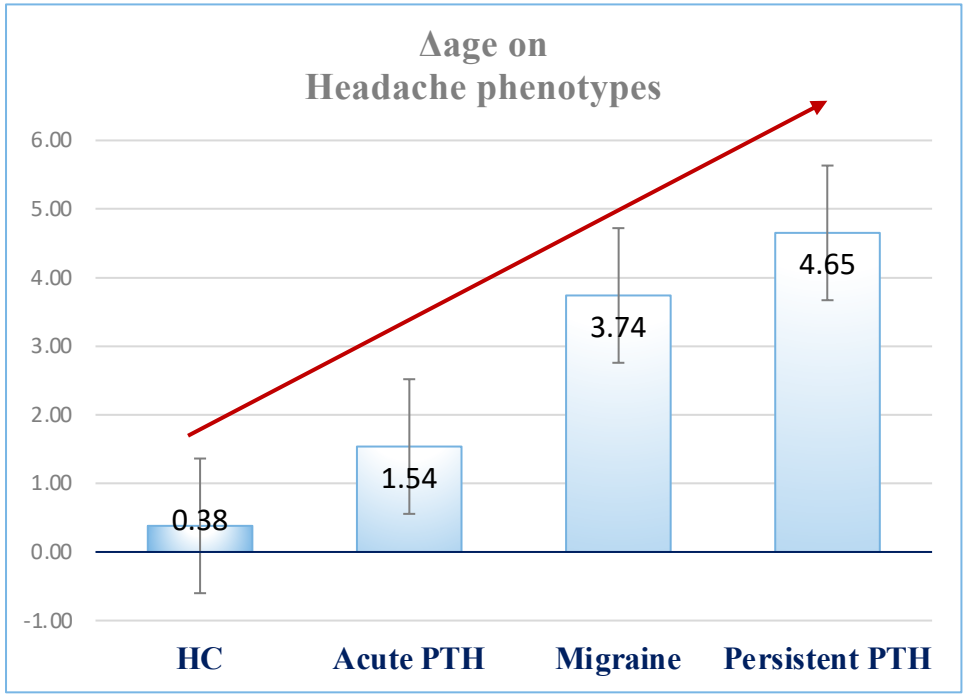
Improved
brain age prediction

[1]Zhang, Shihao, et al. "Improving Deep Regression with Ordinal Entropy." ICLR (2023).
[2]Pan, Hongyu, et al. "Mean-variance loss for deep age estimation from a face." CVPR (2018).

Results

on Headache cohorts

Phenotype	Δ_{age} ± SE
HC (Mayo)	0.38 ± 0.99
Acute PTH	1.54 ± 1.19
Migraine	3.74 ± 1.03
Persistent PTH	4.65 ± 1.41



Observations

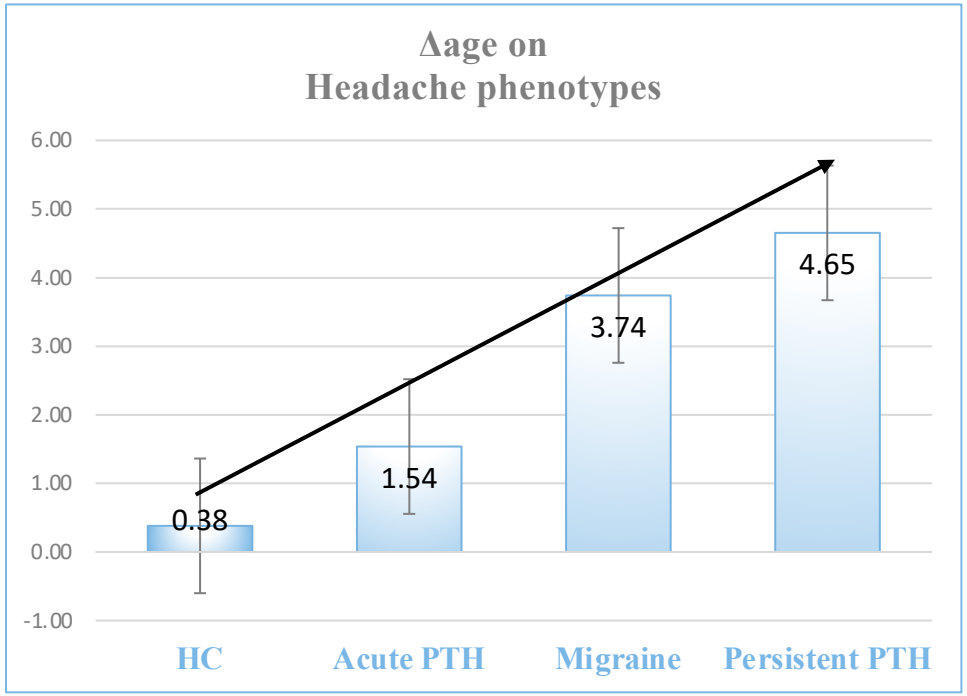
1. Persistent PTH & Migraine had significant aging singatures
2. Cumulative effect of headaches – headaches >3 months had more aging effects
3. Acute PTH show early but subtle aging signatures

Results

t-test among Δ_{age} of headache groups

	APTH	Migraine	PPTH
HC	0.15	0.03	0.01
APTH		0.24	0.04
Migraine			0.67

P-values among Δ_{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 (Δ_{age}) can be used as a potential biomarker in predicting persistence of PTH

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Thank You

Questions?

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