

INTRODUCTION

- Plasma proteomics can estimate the biological aging of individual organs [1]
- Inferences from plasma are influenced by blood-brain barrier function
- Current approaches do not account for the cellular heterogeneity of the brain
- We developed brain cell-type clocks from CSF proteomics and investigated the link between cell-type age gap (CTAG) and dementia.

METHODS: Building cell clocks

- 357 cognitively normal (CN) participants from ADNI (N=174; SomaScan7k) and PPMI (N=183; SomaScan5k) with available CSF proteomics.
- Harmonized using ComBat [2]
- Tested for cell-type enrichment using single nucleus sequencing data of 76,533 total nuclei derived from two post-mortem human brain specimens obtained from the Allen Institute for Brain Science [3]
- LASSO regression models were trained to predict chronological age
- Full set of available proteins (~3,700), cell-type specific proteins (35-100), brain-enriched proteins (645), and non-brain enriched proteins (~3,000)

References:

- Oh (2023) *Nature*. doi: 10.1038/s41586-023-06802-1
- Johnson (2007) *Biostatistics*. doi: 10.1093/biostatistics/kxj037
- BICCN (2021) *Nature*. doi: 10.1038/s41586-021-03950-0

TL;DR: Neurons age faster than other brain cell-types in AD and FTD.

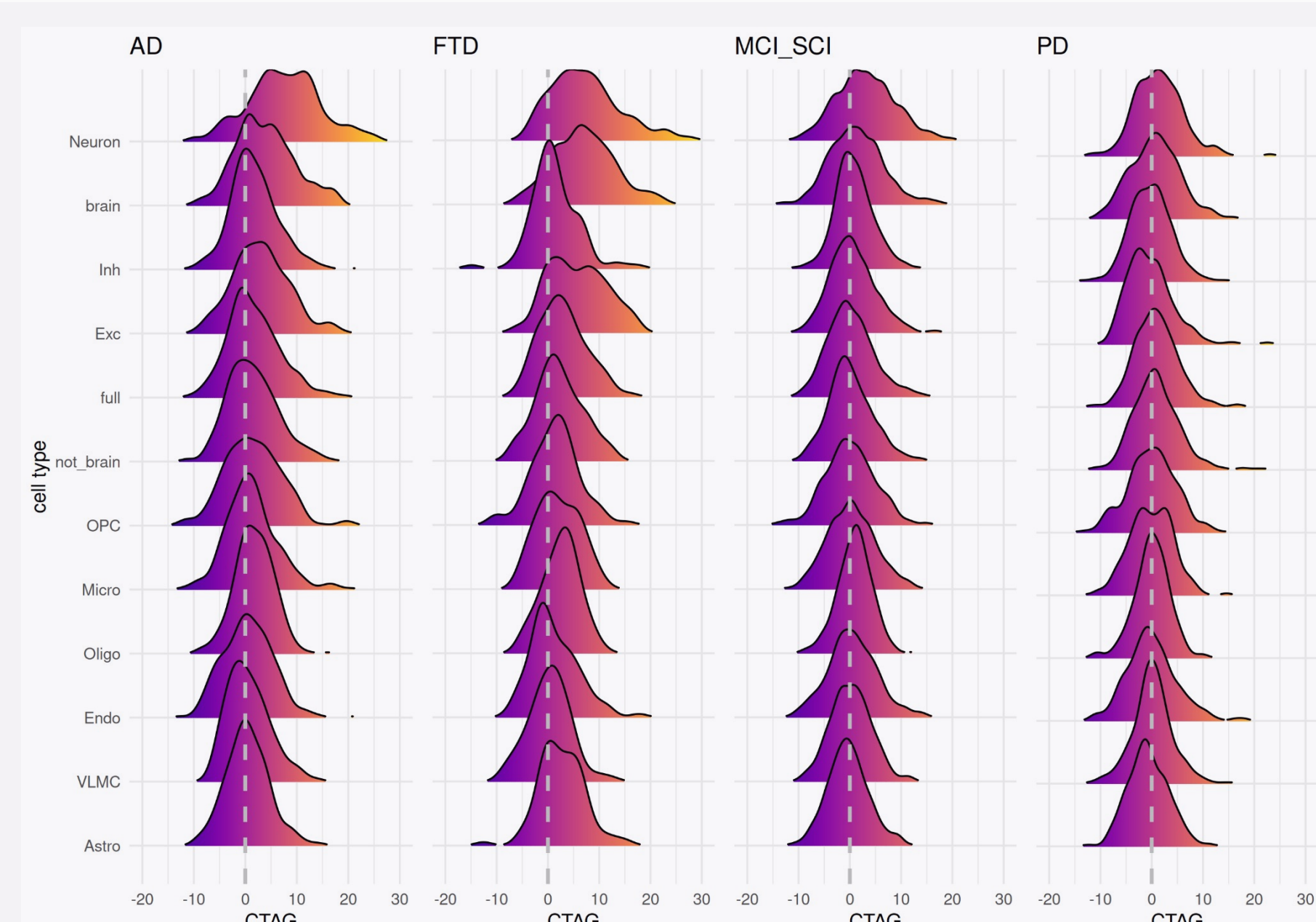


Figure 2: Ridge plot of CTAG in the GNPC cohort. Corrected cell-type age gap (CTAG) distribution for different CSF proteomic clocks (rows) in people with different diagnoses (columns). AD=Alzheimer's disease (N=284); FTD=Frontotemporal Dementia (N=83); MCI_SCI=mild cognitive impairment and subjective cognitive impairment (N=844); PD=Parkinson's disease (N=355).

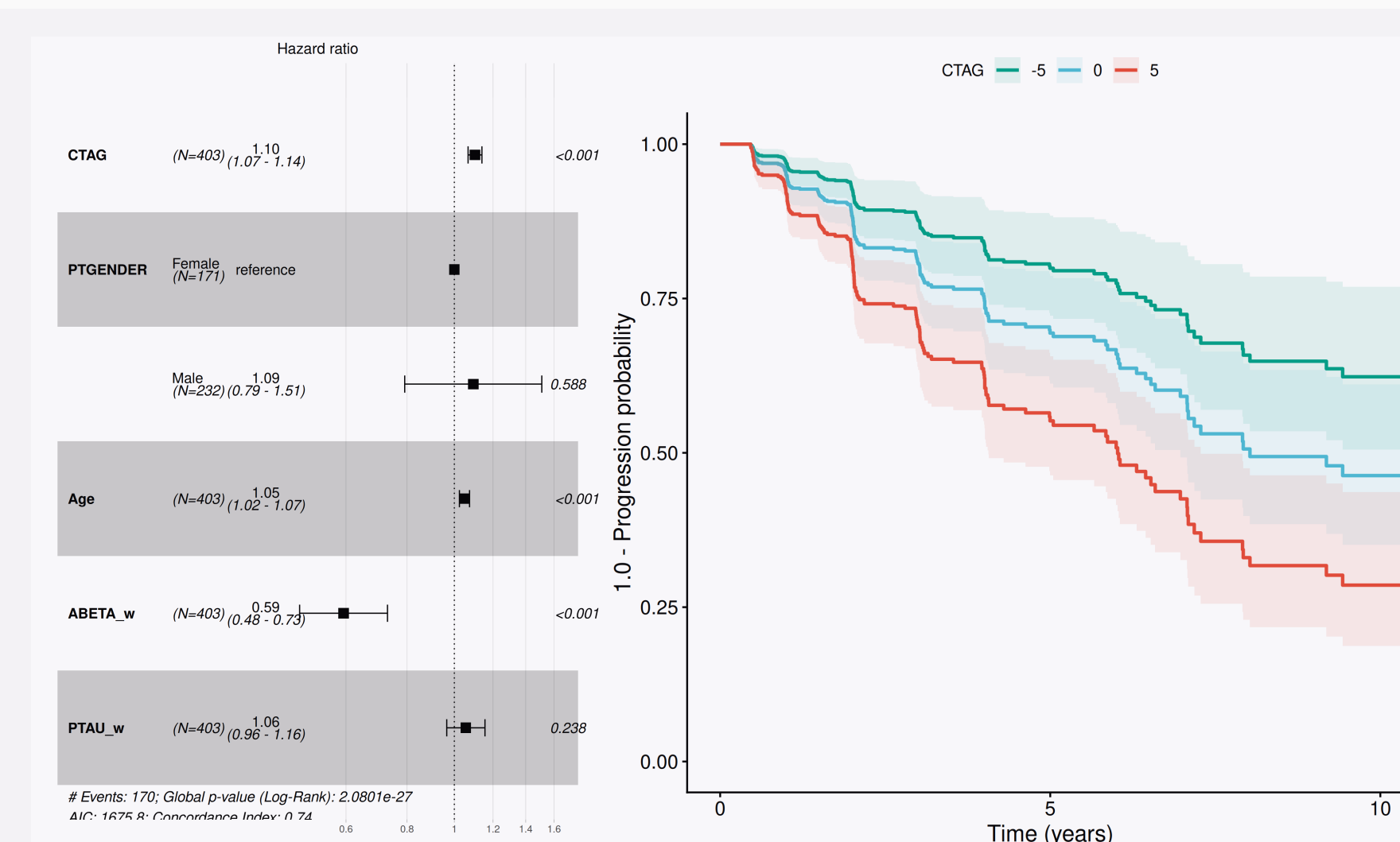


Figure 3: Older neurons are linked to quicker progression from MCI to AD. (Left) Cox proportional hazards model for N=403 MCI participants in ADNI. Model adjusted for age, sex, CSF Abeta (w-scored), and CSF p-TAU (w-scored). CTAG=Cell type age gap. (Right) Exemplary survival curves for an MCI participant with different CTAG (-5 years, 0 years and +5 years).

METHODS: Applying cell clocks

- Applied to N=2072 independent CSF proteomics samples from the Global Neurodegeneration Proteomics Consortium (GNPC) with cognitive or neurodegenerative diagnoses
- Applied to N=403 people with mild cognitive impairment (MCI) in ADNI.
- Cox proportional hazards models were used to test for the association between CTAG and time-to-conversion while covarying for age, sex, CSF pTau and Abeta.

Model	Selected proteins	MAE
Full	94	4.58
Astro	14	7.88
Endo	21	6.78
Exc	19	7.25
Inh	17	7.82
Neuron	41	6.82
Micro	23	6.85
Oligo	30	7.58
OPC	30	6.10
VLMC	13	8.17
Brain	67	5.29
Not Brain	114	4.53

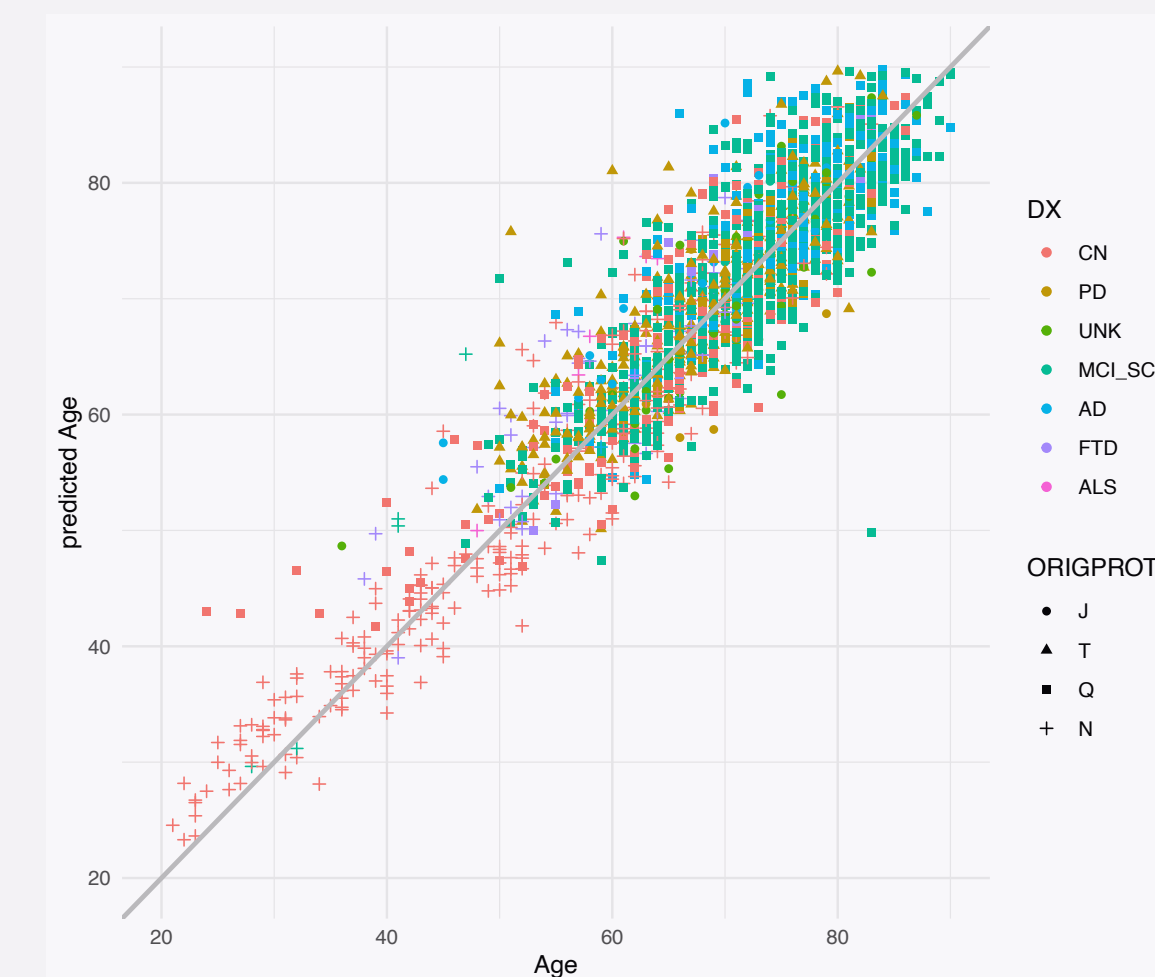
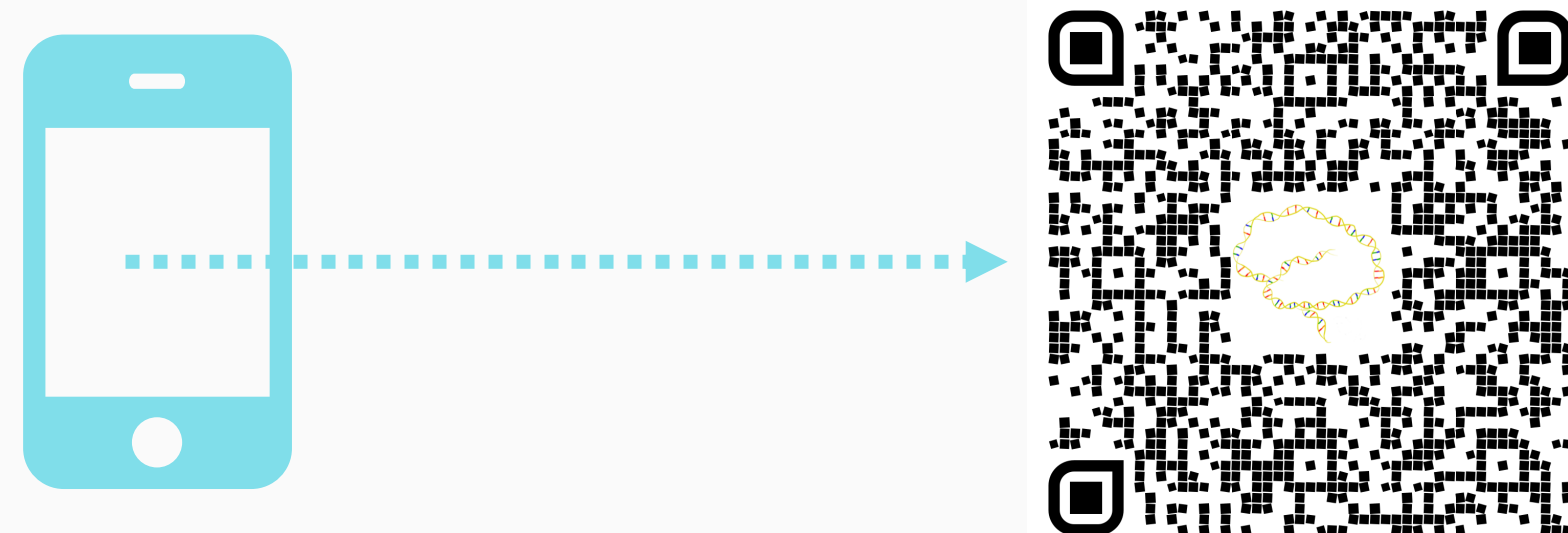


Figure 1: Scatter plot between chronological age and corrected cell-type age in the GNPC cohort.

Table 1: Model performance. Neuron=neuron enriched; brain=brain enriched; Inh=Inhibitory neuron enriched; Exc=Excitatory neuron enriched; full=all available proteins; not_brain=not brain enriched; OPC=oligodendrocyte progenitor cell enriched; Micro=microglia enriched; Oligo=oligodendrocyte enriched; Endo=endothelial enriched; VLMC=vascular leptomeningeal cells enriched; Astro=astrocyte enriched

CONCLUSION

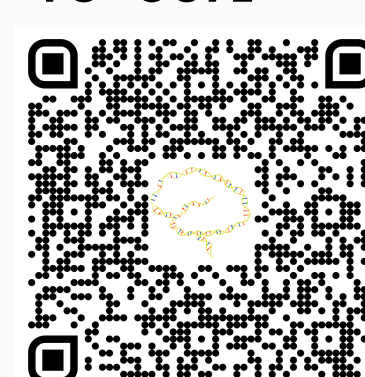
- Neurons age faster in AD and FTD
- Increased neuron-age-gap is linked to faster progression from MCI to AD



Contact

Andre Altmann
email: a.altmann@ucl.ac.uk
web: <http://combine-lab.science/>

TU-0371



Parkinson's
Precision
Medicine
Initiative

