# Generative AI and deep learning using NAIRR reveal brain aging trajectories before Alzheimer's disease

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& Quantitative/Computational Biology

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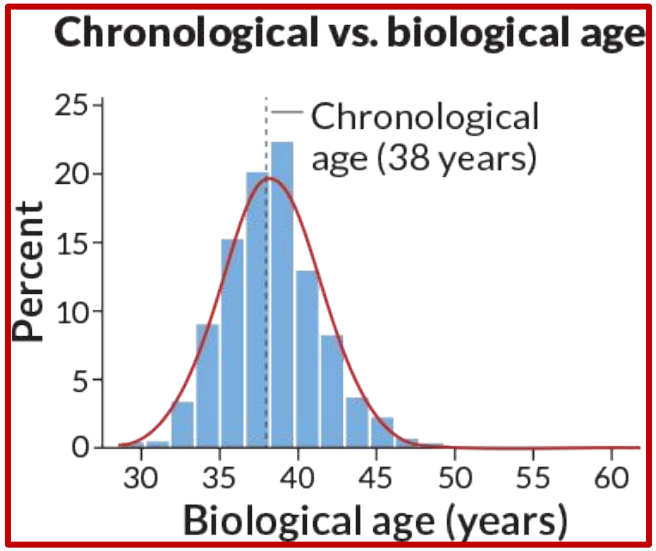
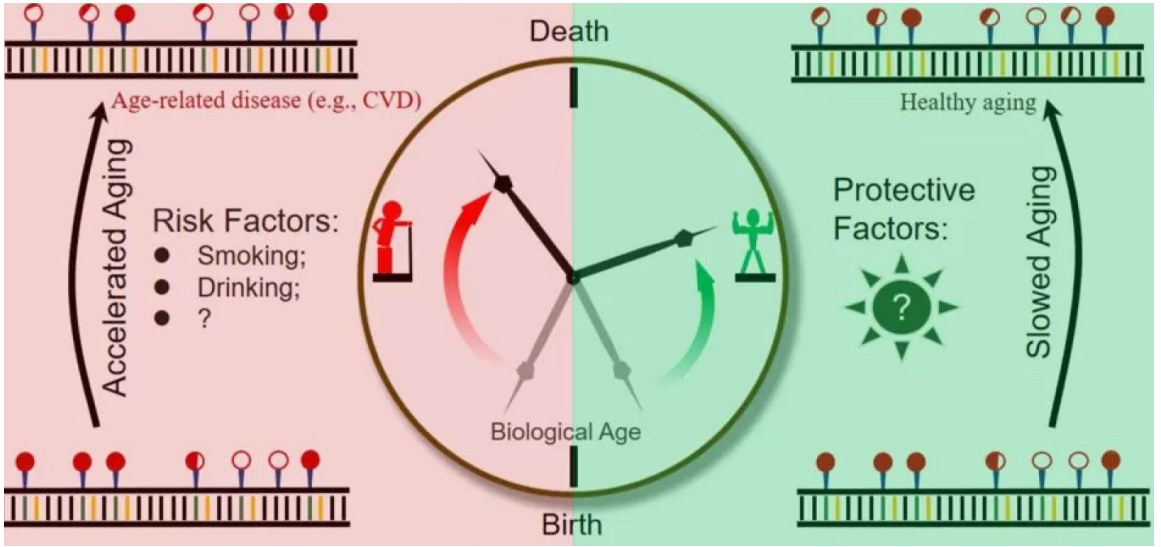
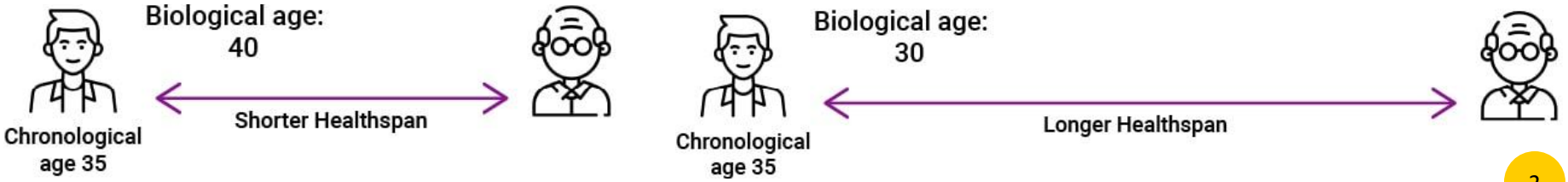
University of Southern California

# Biological age vs. chronological age



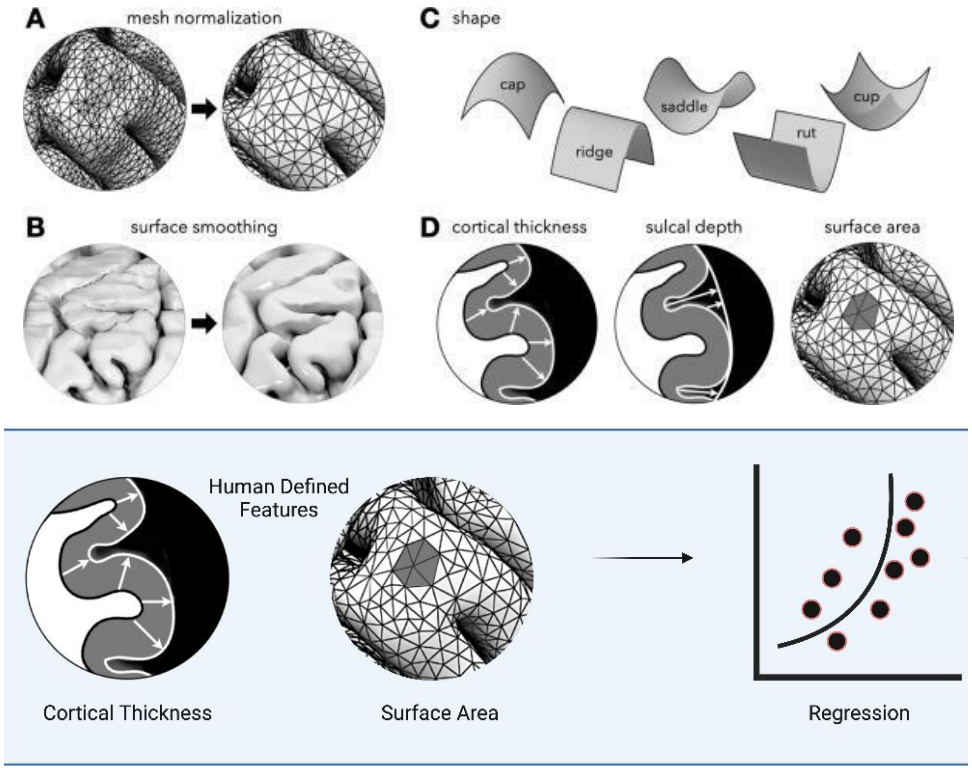






everlab.com.au (2025); Moffitt et al. (2020) Dunedin Study in

# First studies of brain age

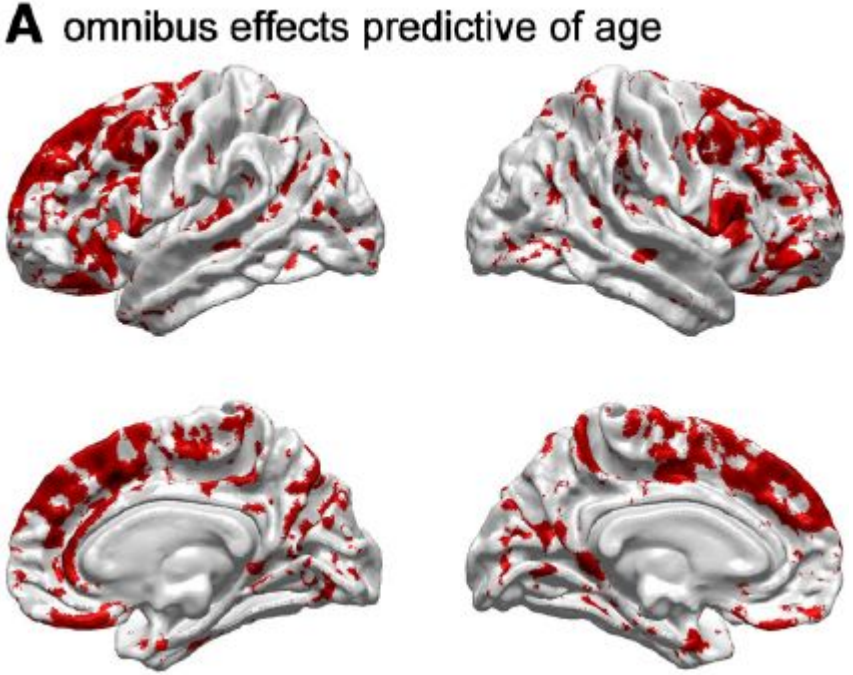



Brain Imaging and Behavior (2015) 9:678–689
DOI 10.1007/s11682-014-9321-0

ORIGINAL RESEARCH

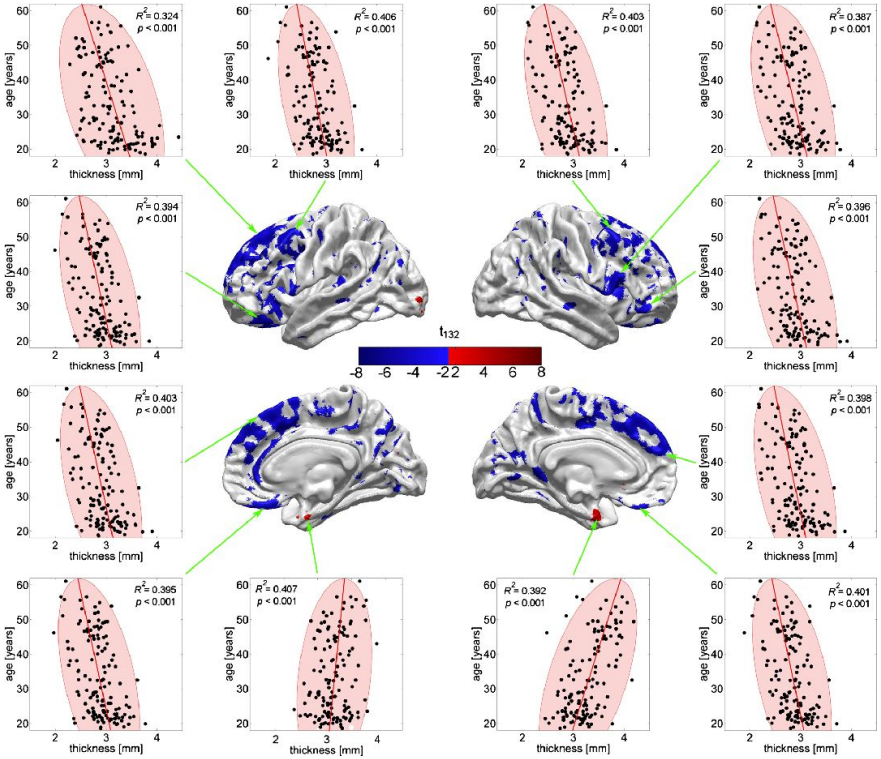
**Statistical estimation of physiological brain age as a descriptor of senescence rate during adulthood**

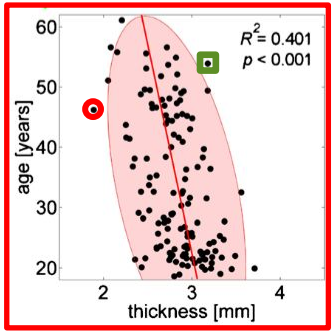
Andrei Irimia · Carinna M. Torgerson · S.-Y. Matthew Goh · John D. Van Horn

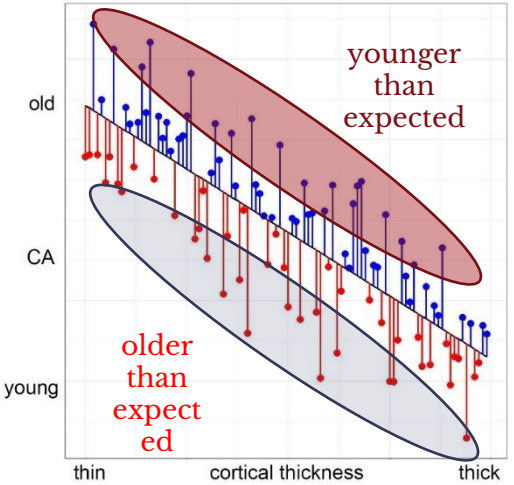



Irimia et al. (2015) Brain

# Local aging of frontal cortex revealed by linear models




$$Y = X \times \beta + \varepsilon$$

responses = [predictors] x β + residuals

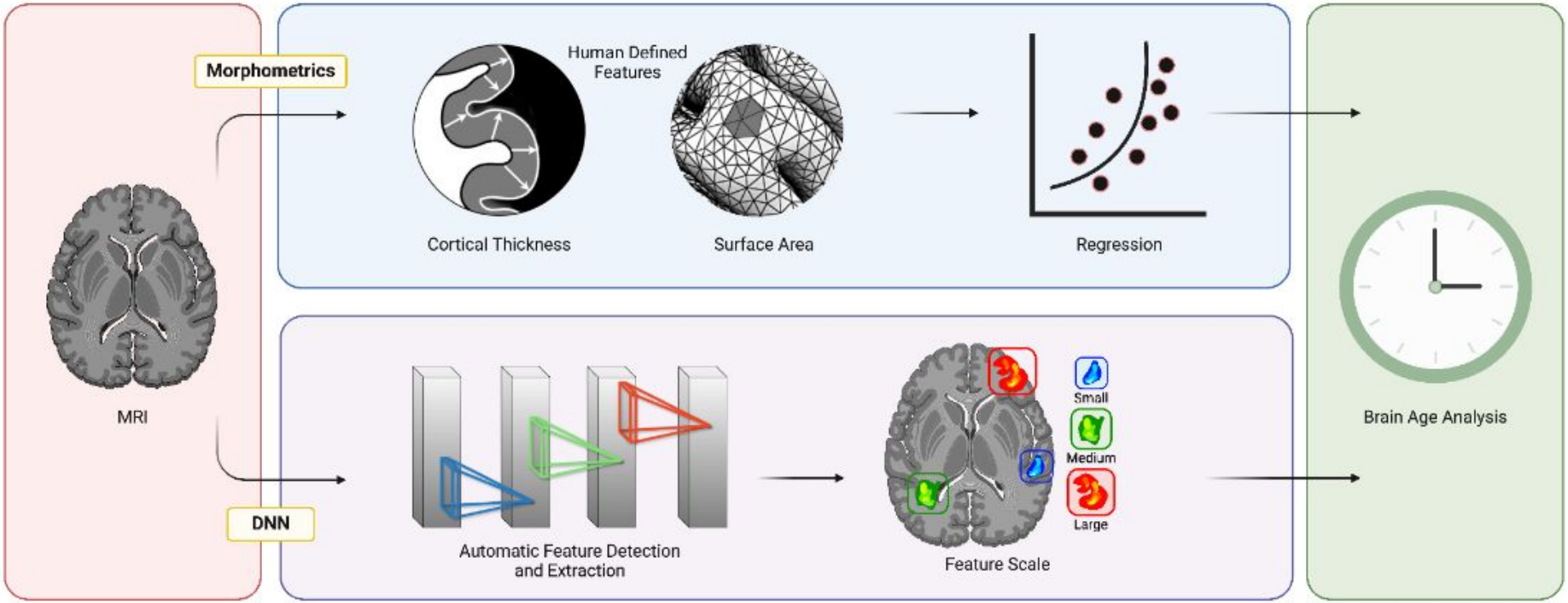
thickness = [ CA ] x β + residuals

CA = [ thickness ] x β + residuals



Irimia et al. (2015) Brain Imaging &

# Estimating brain age: from regression to deep learning



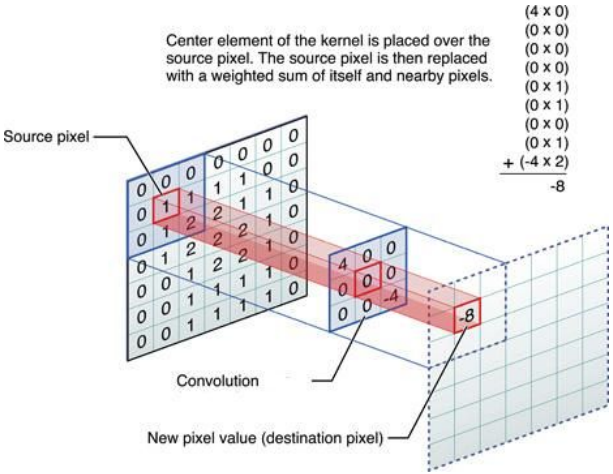


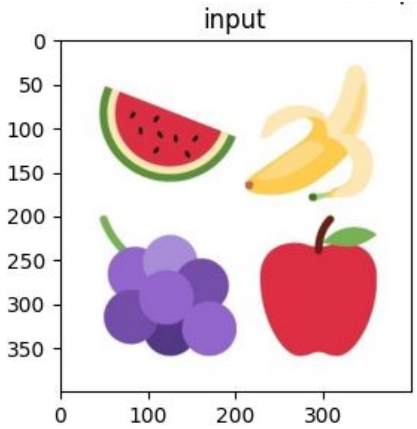

Chaudhari et al. (2025) to be

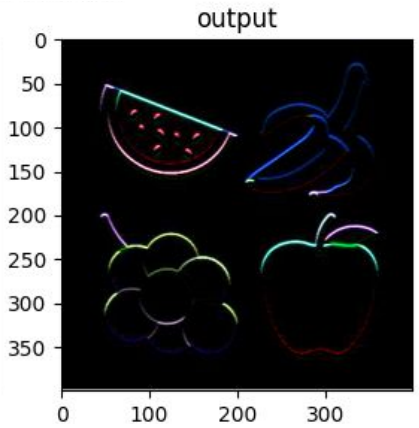
# Convolution can examine anatomy across spatial scales

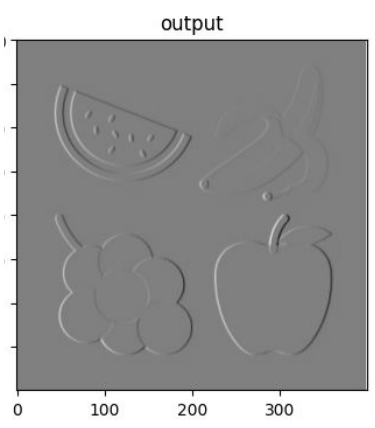
$$(f * g)(t) \overset{\text{def}}{=} \int_{-\infty}^{\infty} f(\tau) g(t - \tau)\, d\tau$$

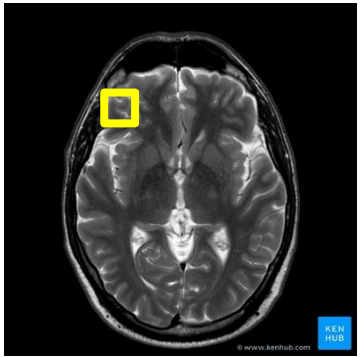
To convolve a kernel with an input signal:
flip the signal, move to the desired time,
and accumulate every interaction with the kernel

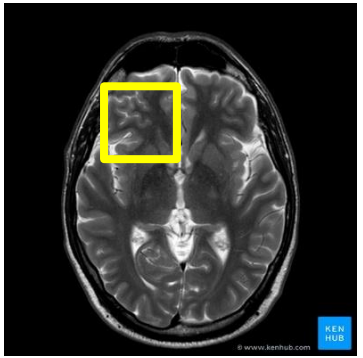


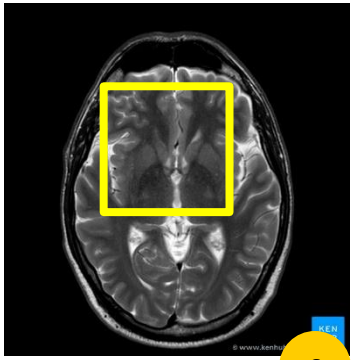







# Brain age recapitulates stages of amyloid and tau propagation

PNAS RESEARCH ARTICLE | NEUROSCIENCE

**Anatomically interpretable deep learning of brain age captures domain-specific cognitive impairment**

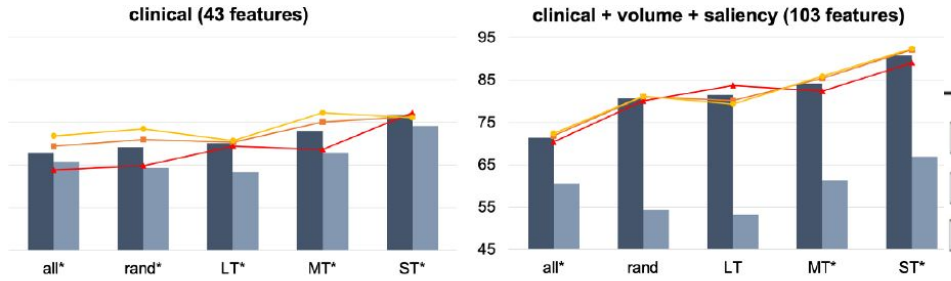
Chenzhong Yin[a,1], Phoebe Imms[b,1], Mingxi Cheng[a,1], Anar Amgalan[b,1], Nahian F. Chowdhury[b,1], Roy J. Massett[b], Nikhil N. Chaudhari[b,c], Xinghe Chen[a], Paul M. Thompson[c,d,e,f,g,h,i], Paul Bogdan[a,1], Andrei Irimia[b,c,e,1,2], and the Alzheimer's Disease Neuroimaging Initiative[3]

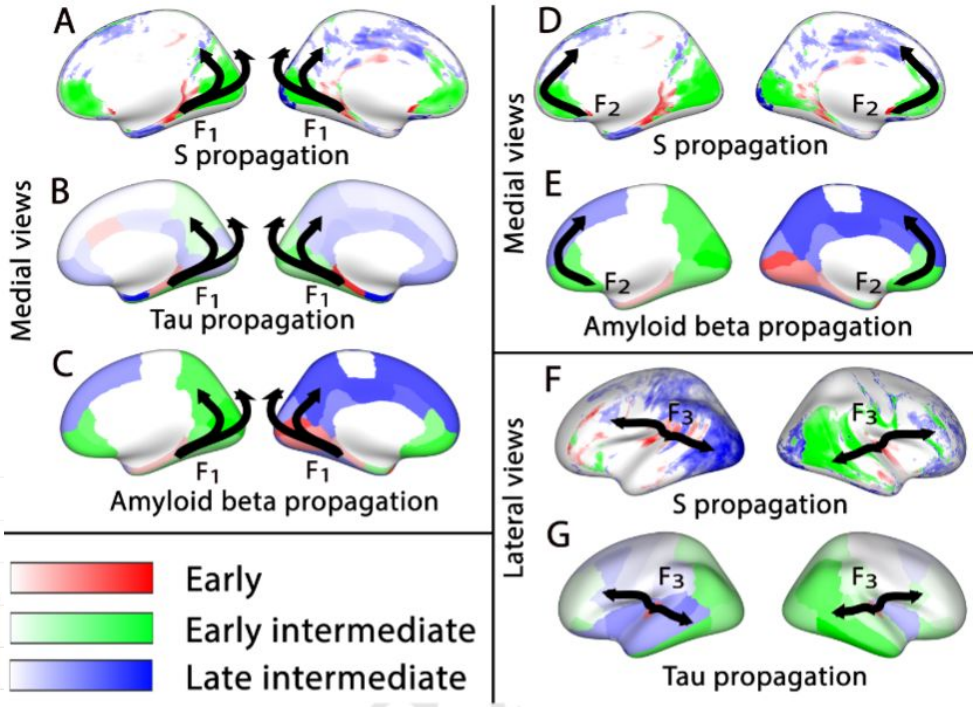
Edited by Brian Wandell, Stanford University, Stanford, CA; received August 26, 2022; accepted November 10, 2022

PNAS RESEARCH ARTICLE | NEUROSCIENCE COMPUTER SCIENCES

**Deep learning to quantify the pace of brain aging in relation to neurocognitive changes**

Chenzhong Yin[a], Phoebe Imms[b], Nahian F. Chowdhury[b], Nikhil N. Chaudhari[b,c], Heng Ping[a], Haoqing Wang[b], Paul Bogdan[a], Andrei Irimia[b,c,d,e,1], and the Alzheimer's Disease Neuroimaging Initiative[2]

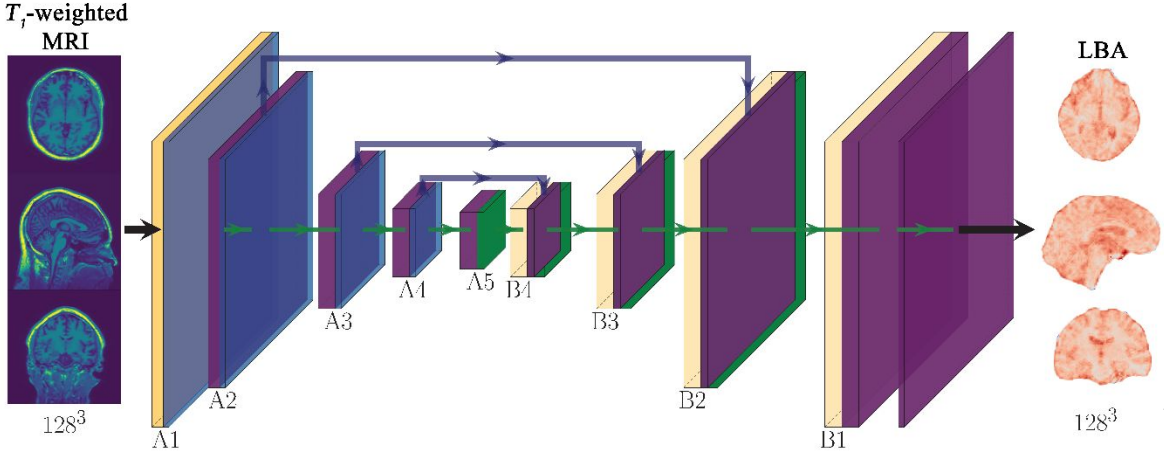


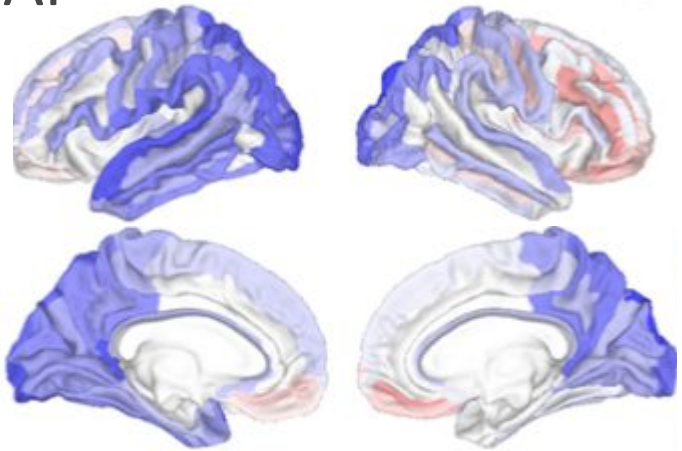






Chaudhari et al. (2026)

# From global to local brain age using AI



Brain aging patterns suggest older sulci and younger gyri, consistent with amyloid and tau deposition

al lobe is the 'last to [illegible] and first to go'

THE WALL STREET JOURNAL.

**Is Your Brain Aging Faster Than You? New Science Offers Clues**

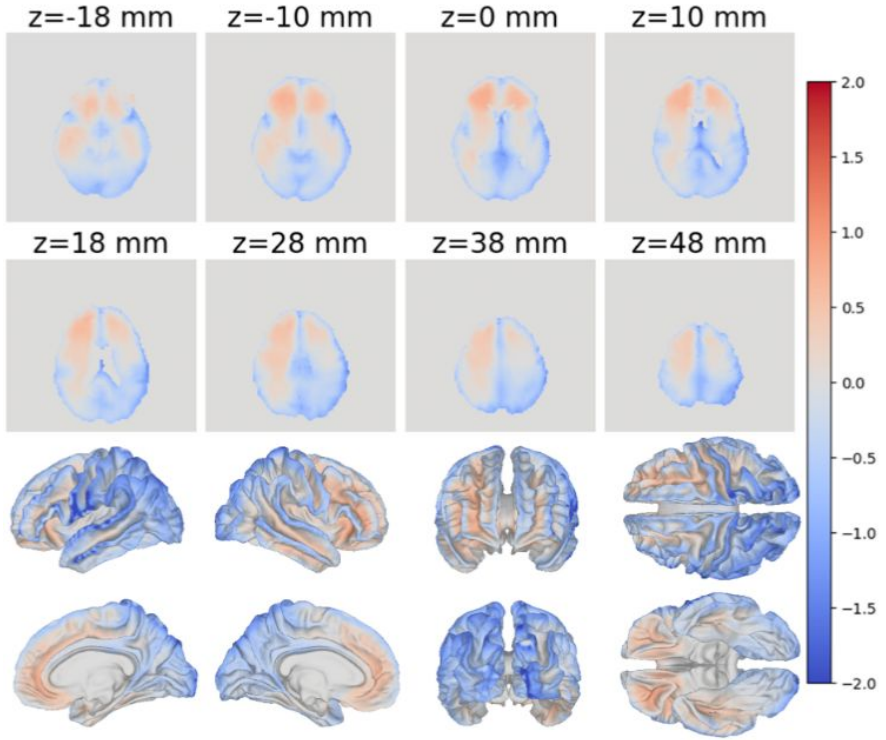
BBC

**Can we change how our brains age? These scientists think it's possible**

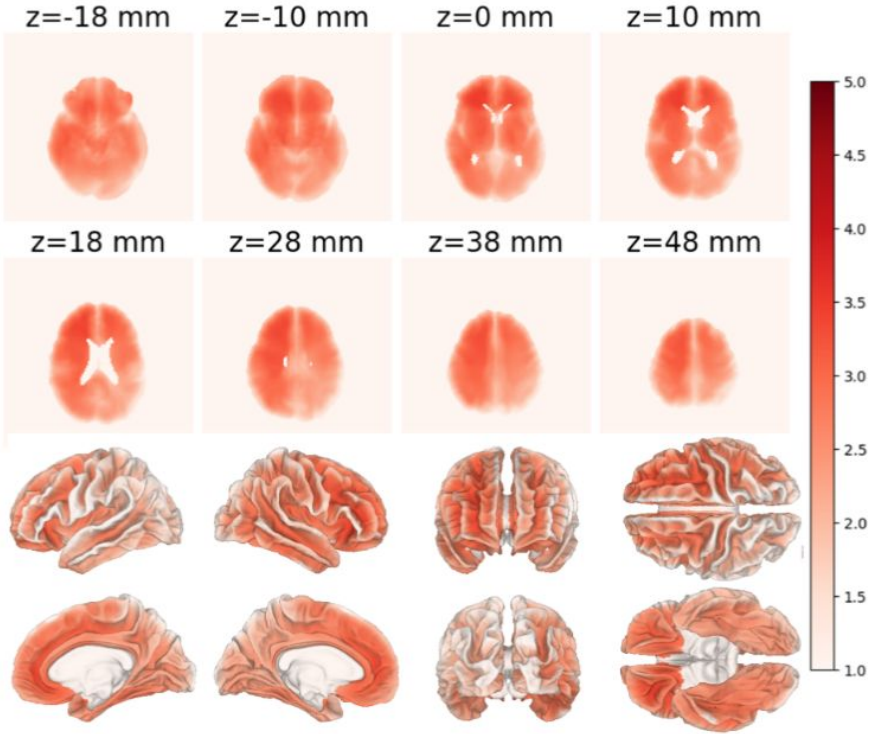



Chaudhari et al. (2025) and Kim et al.

# Local brain aging in CN adults and patients with AD



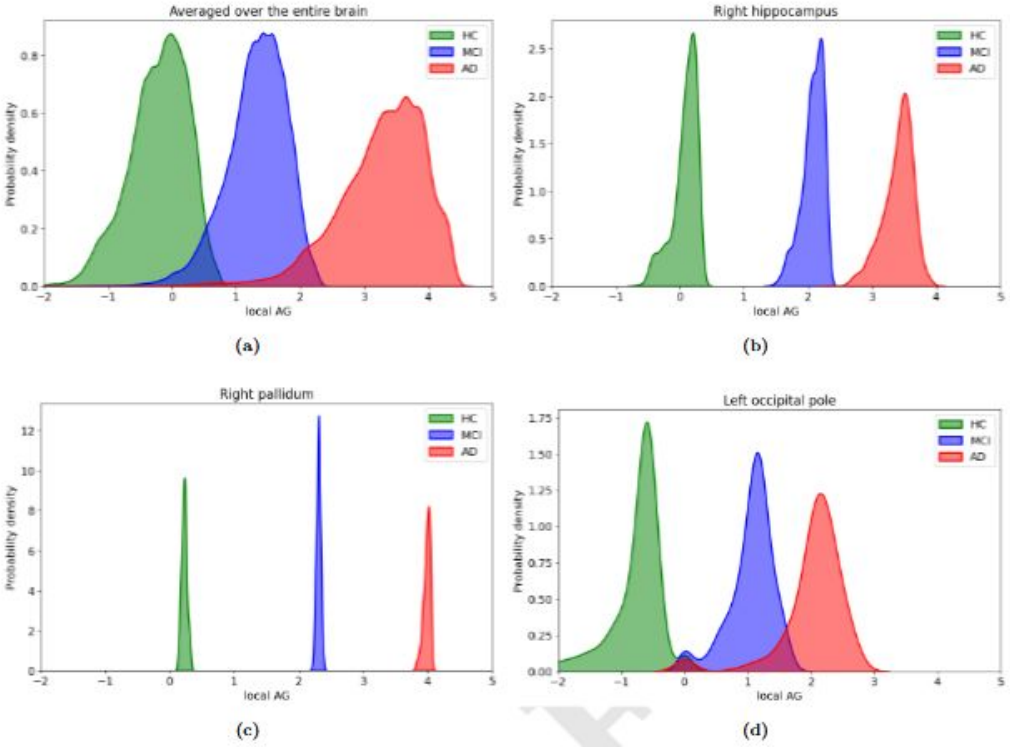

Cognitively normal adults

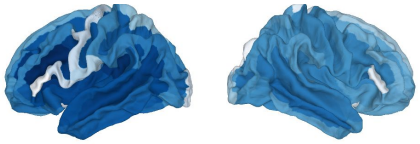



Alzheimer's disease

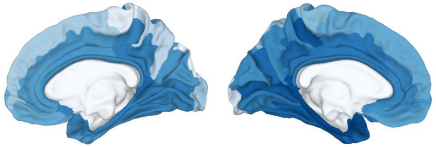
Chaudhari et al. (2025) *to*

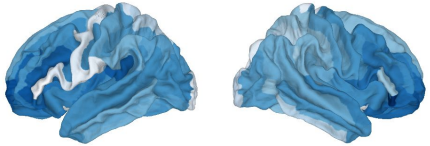
# Brain aging differs by region and cognitive status



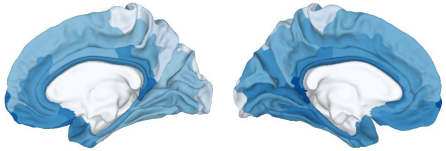



Age at menopause is associated with younger local brain ages in the left temporal lobe ($p<0.01$).





Reproductive span is associated with younger brains in the orbitofrontal regions ($p<0.05$)



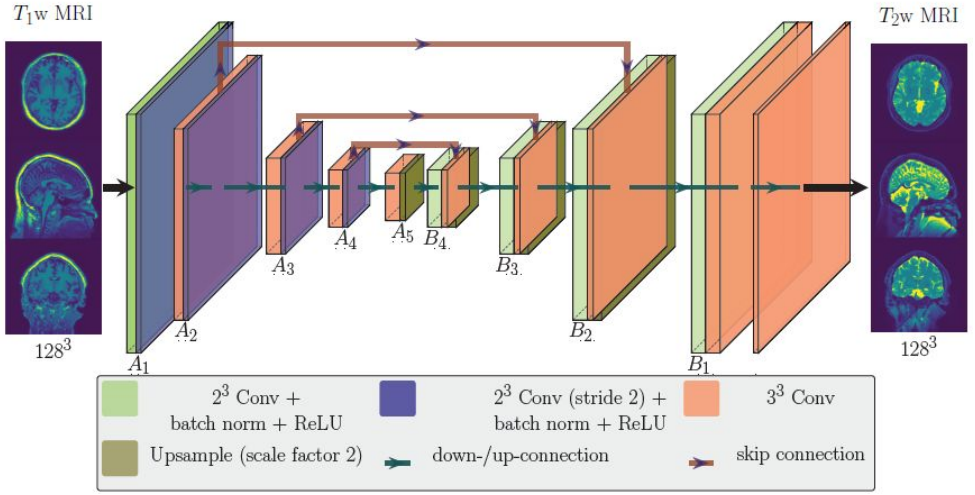
**Adverse effects**:
hysterectomy
oophorectomy
HRT
young CA at menopause

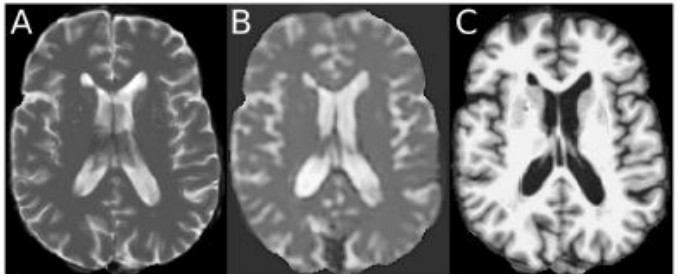
**Neutral effects**:
Reproductive period
Contraceptive use
Age HRT started
Years taking HRT

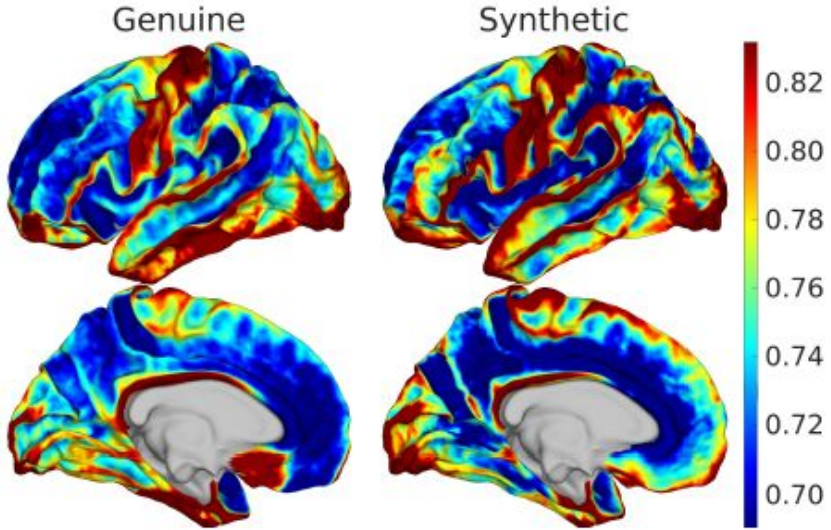
**Favorable effects**:
Older age at menopause
Number of births
w/o HRT (but only 1.75 on avg)

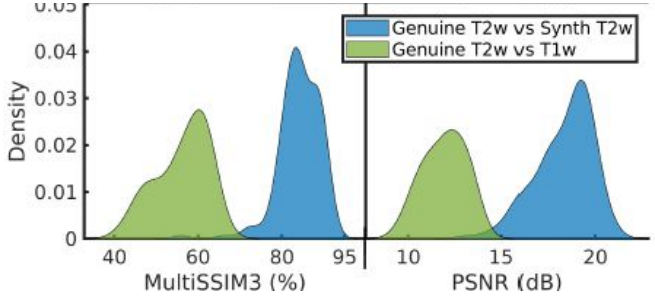
Chaudhari et al. (2025)

# MRI synthesis by generative AI reveals myeloarchitecture



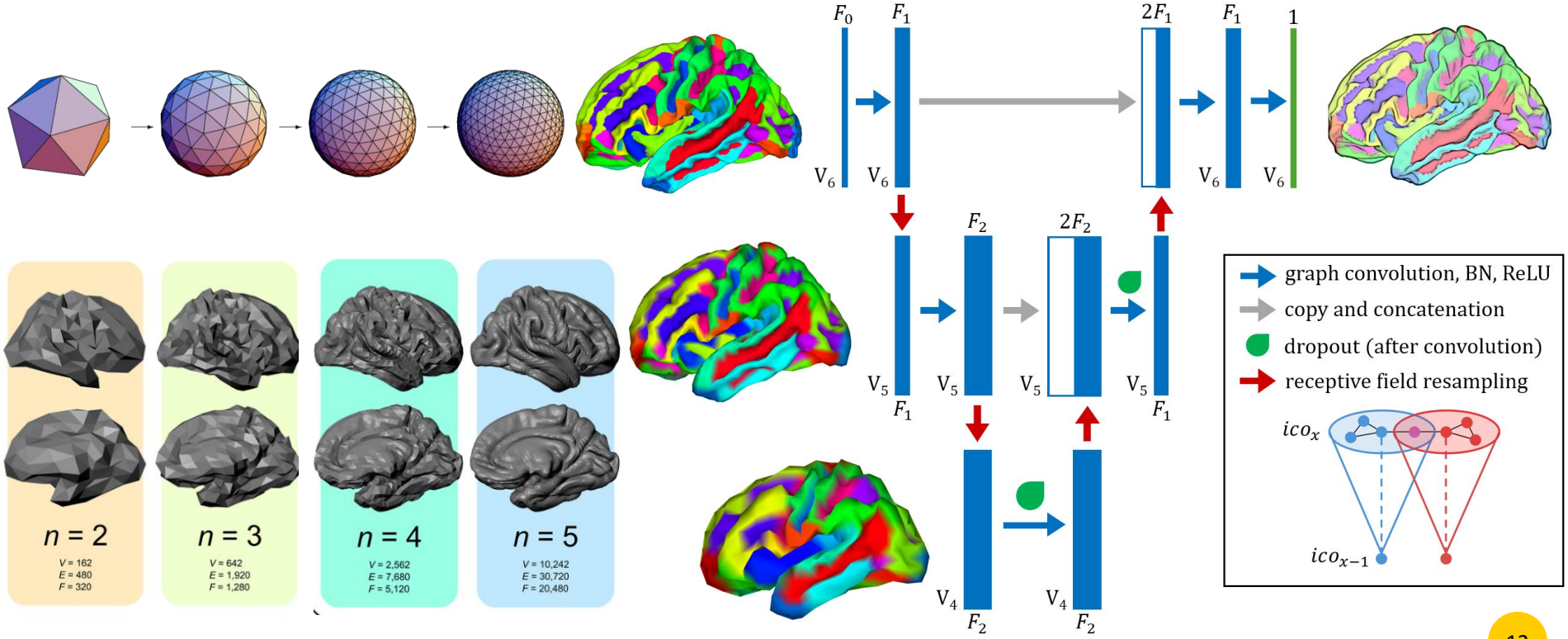




Liu et al. (2025)

Chaudhari et al.

# Graph neural networks reveal the aging of cortical morphology

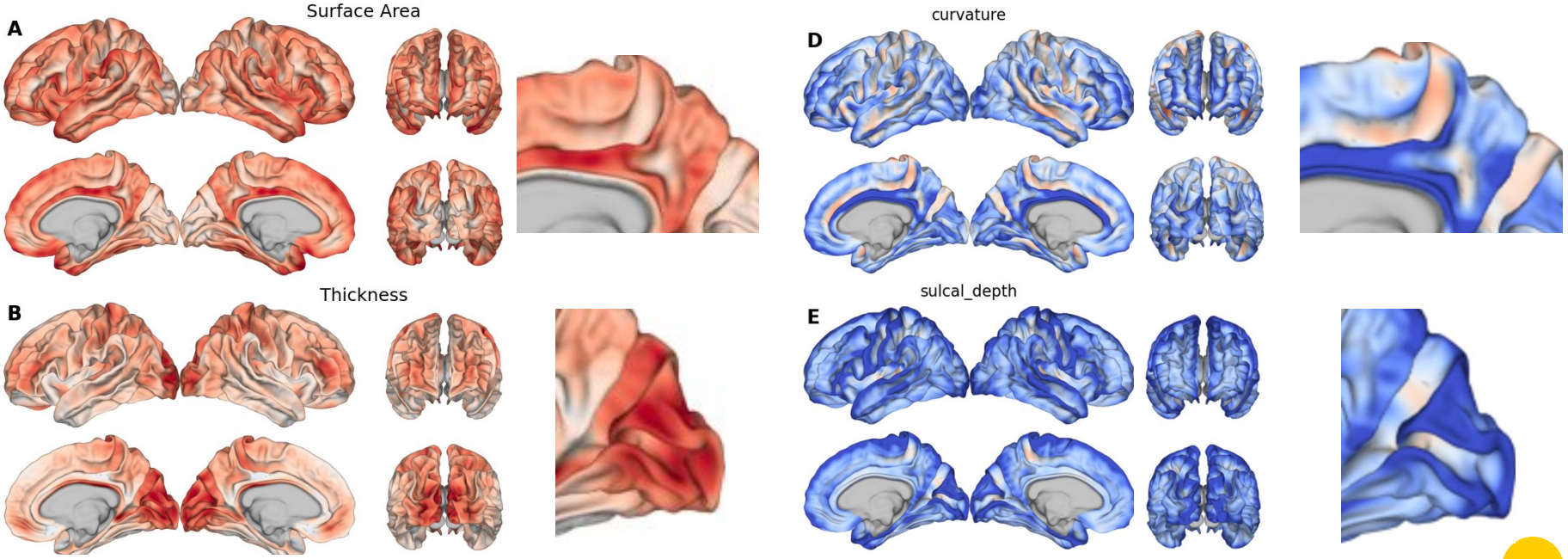





Anderson et al. (2025) *to be submitted*; Zugman et al. (2020) HBM;

# Gero-morphology: cortical thinning, sulcal widening & deepening

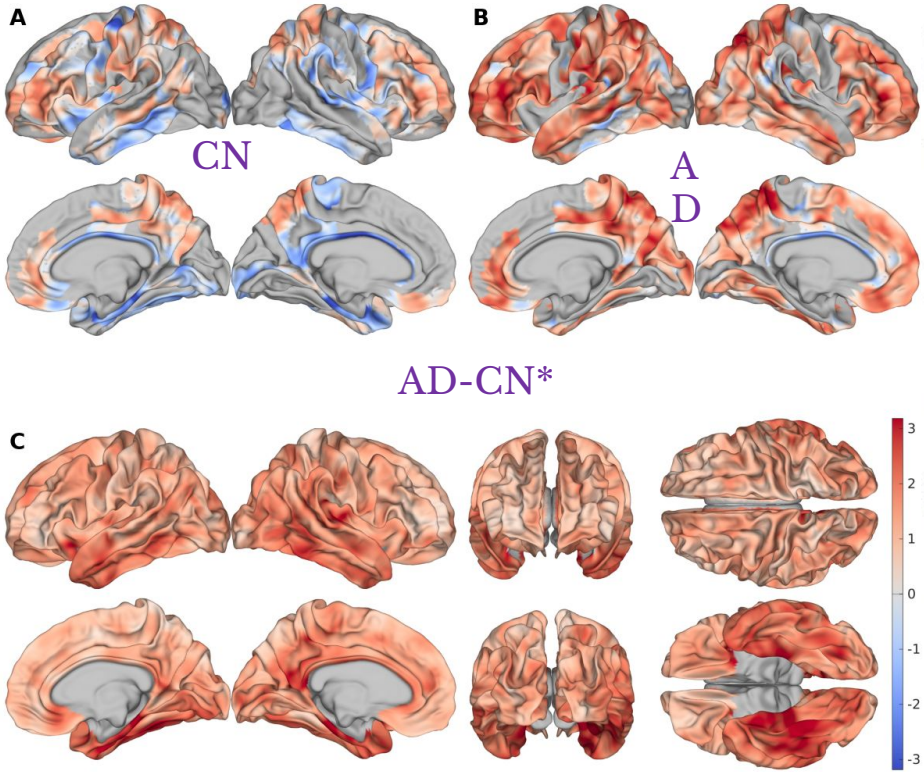
- Morphological aging involves known anatomic features (thinning, sulcal changes) but also novel patterns in AD- and PD-vulnerable regions

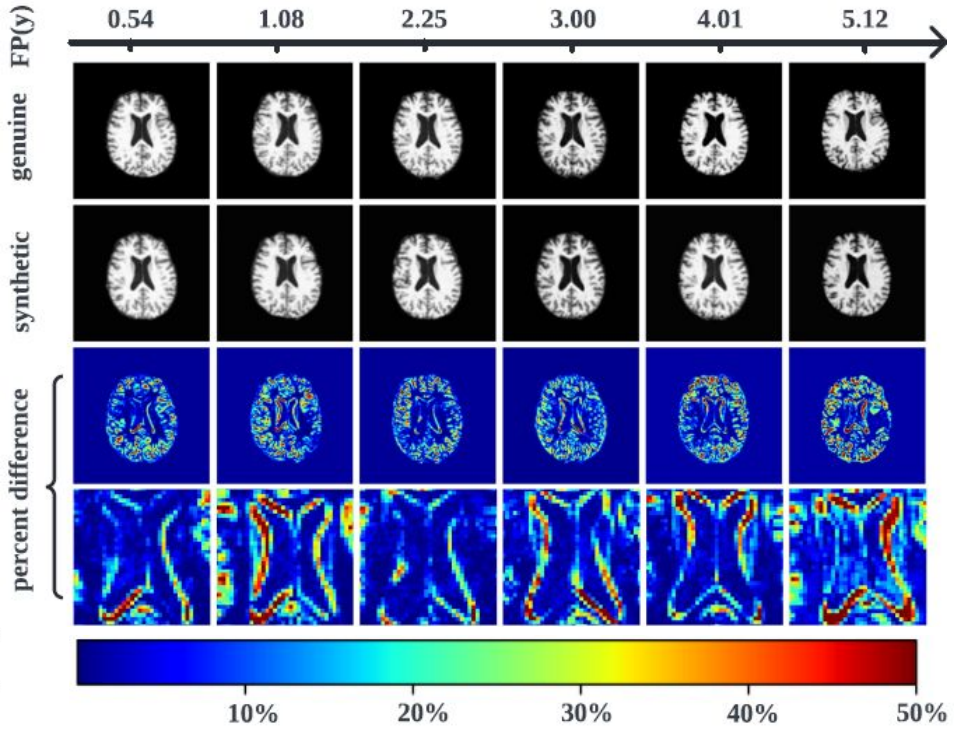





Anderson et al. (2025) *to*

# The aging of cortical morphology reflects cognitive impairment



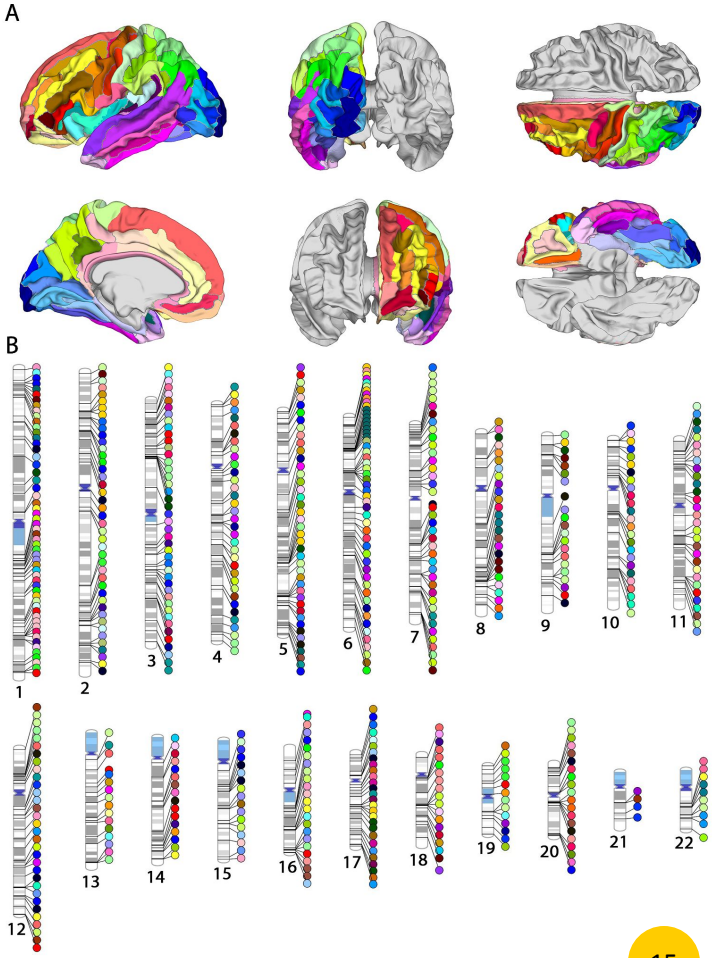




Anderson et al. (2025) *to*

Liu et al. (2025)

# GWAS of local brain age

- In 41,708 UKB adults, 1212 SNPs are associated with LBA across cortex
- Genes involved in developmental, metabolic, immune, and cytoskeletal pathway are in three clusters linked to morphogenetic, cytoskeletal, and immune-epigenetic processes
- Coordinated genetic programs (developmental, metabolic, cytoskeletal, immuno-epigenetic) choreograph brain aging over the life course




NATURE METHODS

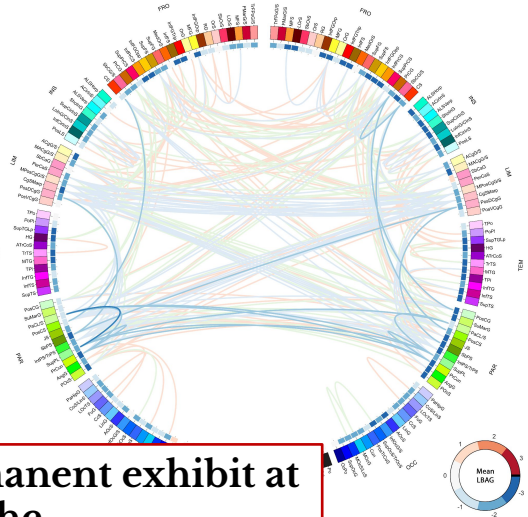
**Imaging human connectomes at the macroscale**

R Cameron Craddock[1,2], Saad Jbabdi[3,9], Chao-Gan Yan[1,2,4,9], Joshua T Vogel
F Xavier Castellanos[2,4], Adriana Di Martino[4], Clare Kelly[4], Keith Heberlein[8],
Stan Colcombe[2] & Michael P Milham[1,2]

REVIEW NATURE (2015)

**Progress and challenges in probing the human brain**

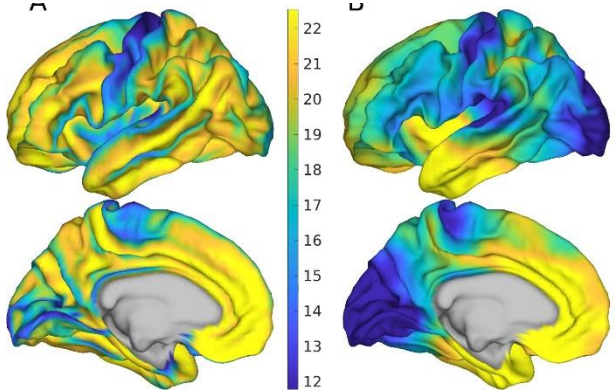
Russell A. Poldrack[1] & Martha J. Farah[2]



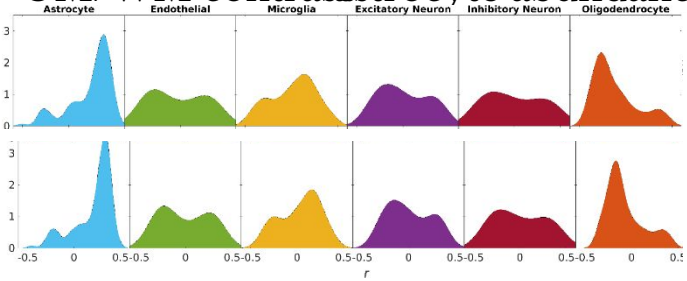

**Now in a permanent exhibit at the Francis Crick Institute in**

Kim et al. (2025)

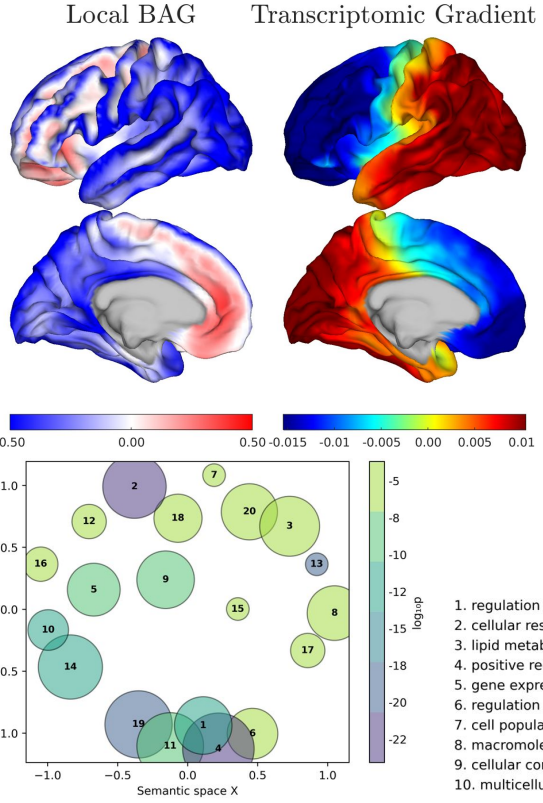
# Spatial transcriptomics of brain aging



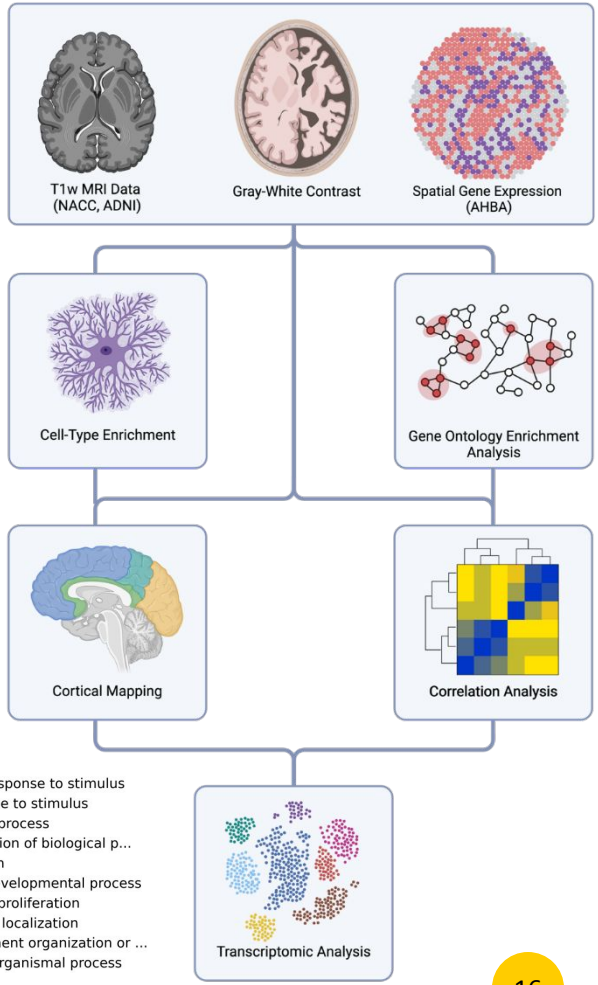

GM/WM contrast




Astrocyte abundance




1. regulation of response to stimulus
2. cellular response to stimulus
3. lipid metabolic process
4. positive regulation of biological p...
5. gene expression
6. regulation of developmental process
7. cell population proliferation
8. macromolecule localization
9. cellular component organization or ...
10. multicellular organismal process

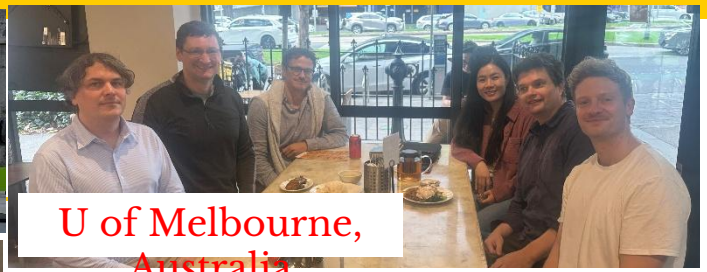



Cortical distributions of correlations between cell type marker gene expressions and GM/WM contrast

Chowdhury et al. (2025) under review; Jafar et al.

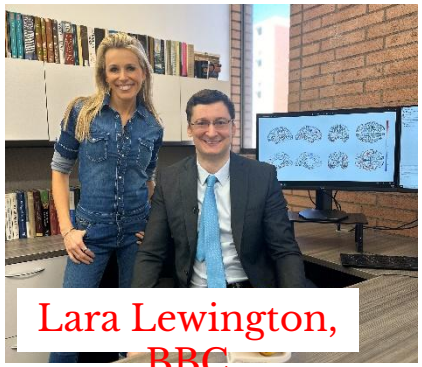

NVIDIA, San Jose

GeroScience Board, UWisconsin



U of Melbourne, Australia

King's College London



Lara Lewington, BBC

Queen's College, U of Cambridge

ISBI '24, Cartagena, Colombia

USC Imaging Genetics Center, Los Angeles

U of Edinburgh, UK

OHBM '23, Montreal