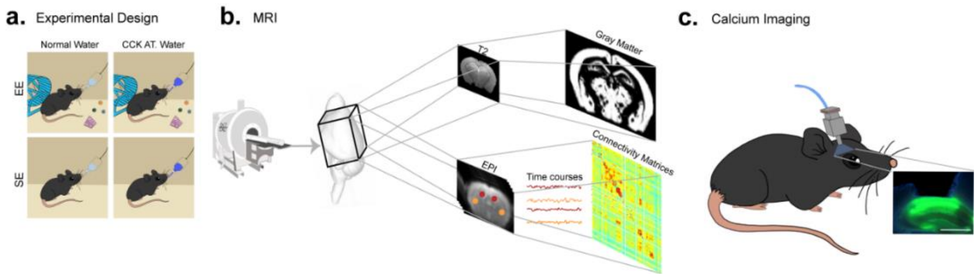
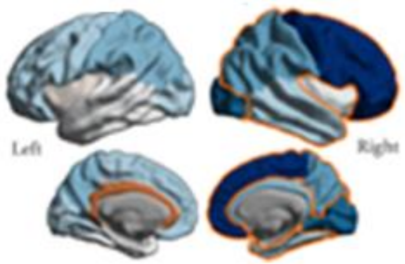
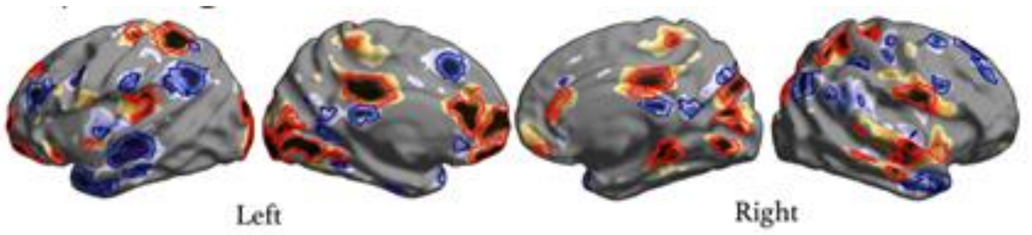






Neuroimaging models of human disease for better health: Neuronal connectomic fMRI approaches

---

Francis A. M. Manno, DPhil, PhD

Research & updates - sometimes surprises

Presentation

ORCID

Entire presentation link:
https://fmanno.com/research.pdf
https://francismanno.github.io/fmanno/research.pdf

My academic life (curriculum vitae visualized)

Virginia Beach USA

Lab Manager ODU

Virginia Wesleyan Uni

MSc Degree NYU

Centre for Neural Science

Cochlear Implant hospital work

SCUBA & Boating

Doctorate - DPhil Neuroimaging UNAM, Mexico ¡Defended In Spanish!

My wife Sina

Associate Lecturer Biomedical Engineering

Doctorate -PhD Physics & Materials Sciences Hong Kong

JHU Postdoctoral Fellow

Future?

Employment

NYU/CNS Center for Neural Science

SickKids

THE UNIVERSITY OF SYDNEY

VIRGINIA WESLEYAN UNIVERSITY

NYU

PADI

DAN

UNIVERSITY OF TORONTO

INSTITUTO DE NEUROBIOLOGÍA

CityU 香港城市大學 City University of Hong Kong

JOHNS HOPKINS BIOMEDICAL ENGINEERING

JOHNS HOPKINS WHITING SCHOOL of ENGINEERING

Master Captain Sailing

Backpacked Latin America (2 years)

Education: BA (hons), MSc, USCG Captain, DPhil, PhD

From|to …

Why does Rice play Texas? (nod to JFK)

- Moonshot speech: "We choose to go to the Moon"
- We do these things… “not because they are easy, but because they are hard”
- Hot topic discussed was the football rivalry

Overview – emphasized projects

- Alzheimer's
- Hearing Loss
- Environmental Enrichment

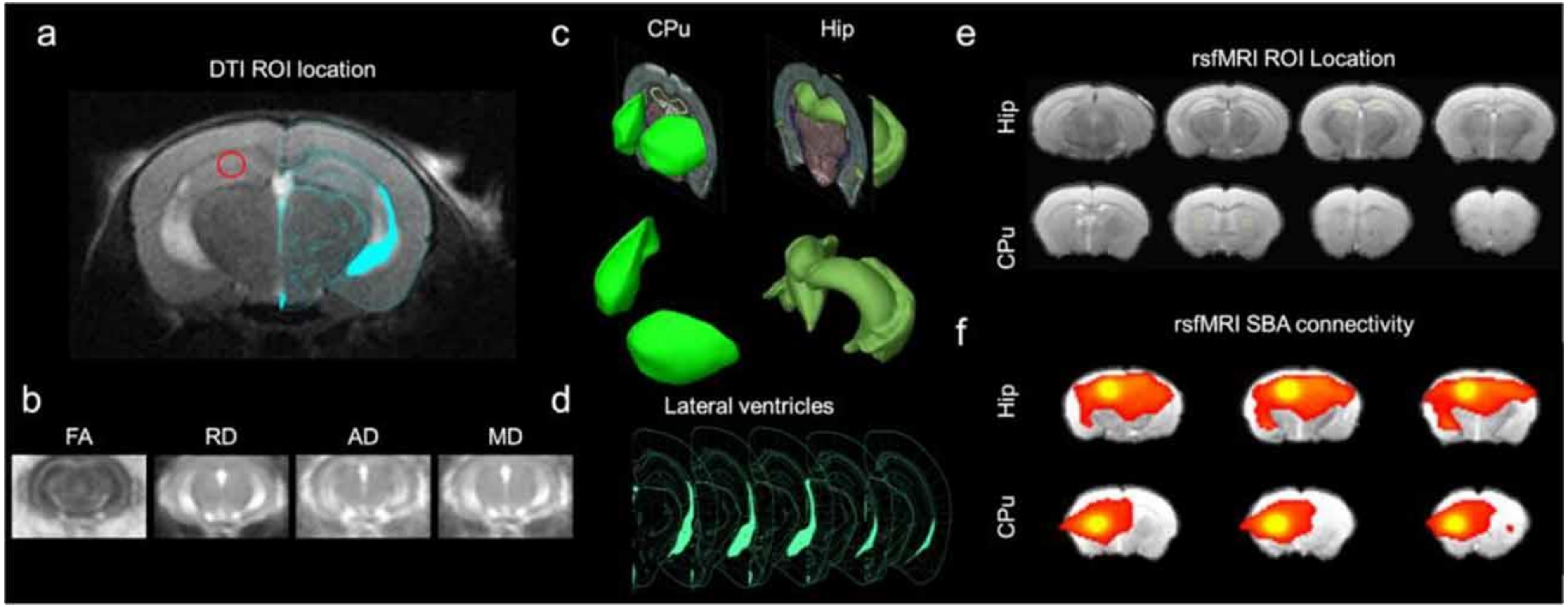
Introduction: What is Alzheimer's Disease?

- Alzheimer's disease is characterized by neurofibrillary tangles and amyloid plaques
  - -These proteins are normal in the human brain
  - -How these proteins become detrimental is currently unknown, but is thought to do with aggregation.

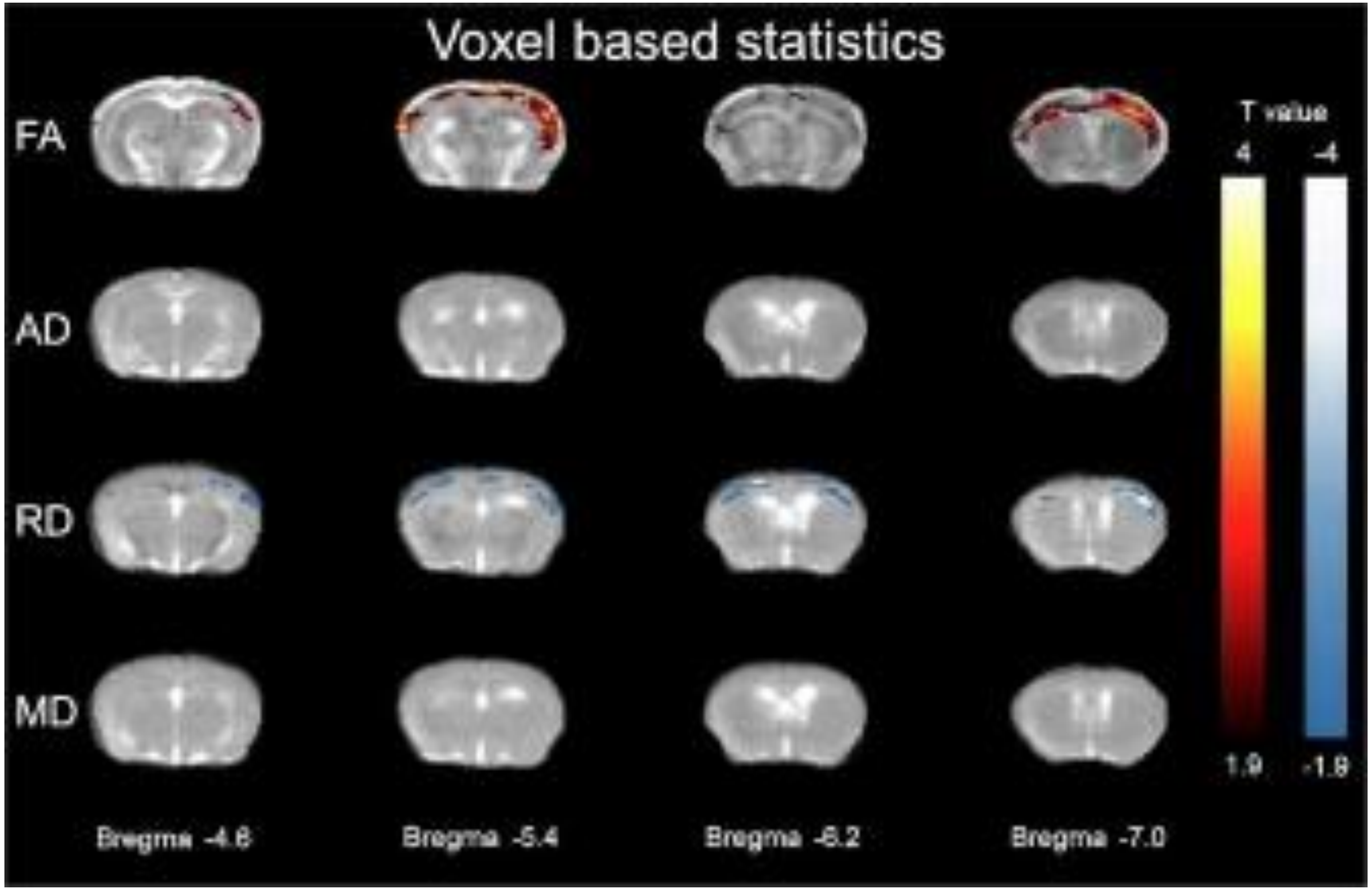
- Research questions: Does tissue state alter amyloidogenesis & tauopathy in human and mouse models of Alzheimer's Disease? Can we disrupt tissue-protein interactions to facilitate clearance?

- Manno FAM, et al., Front Aging Neurosci. 2019 Mar 22;11:39.

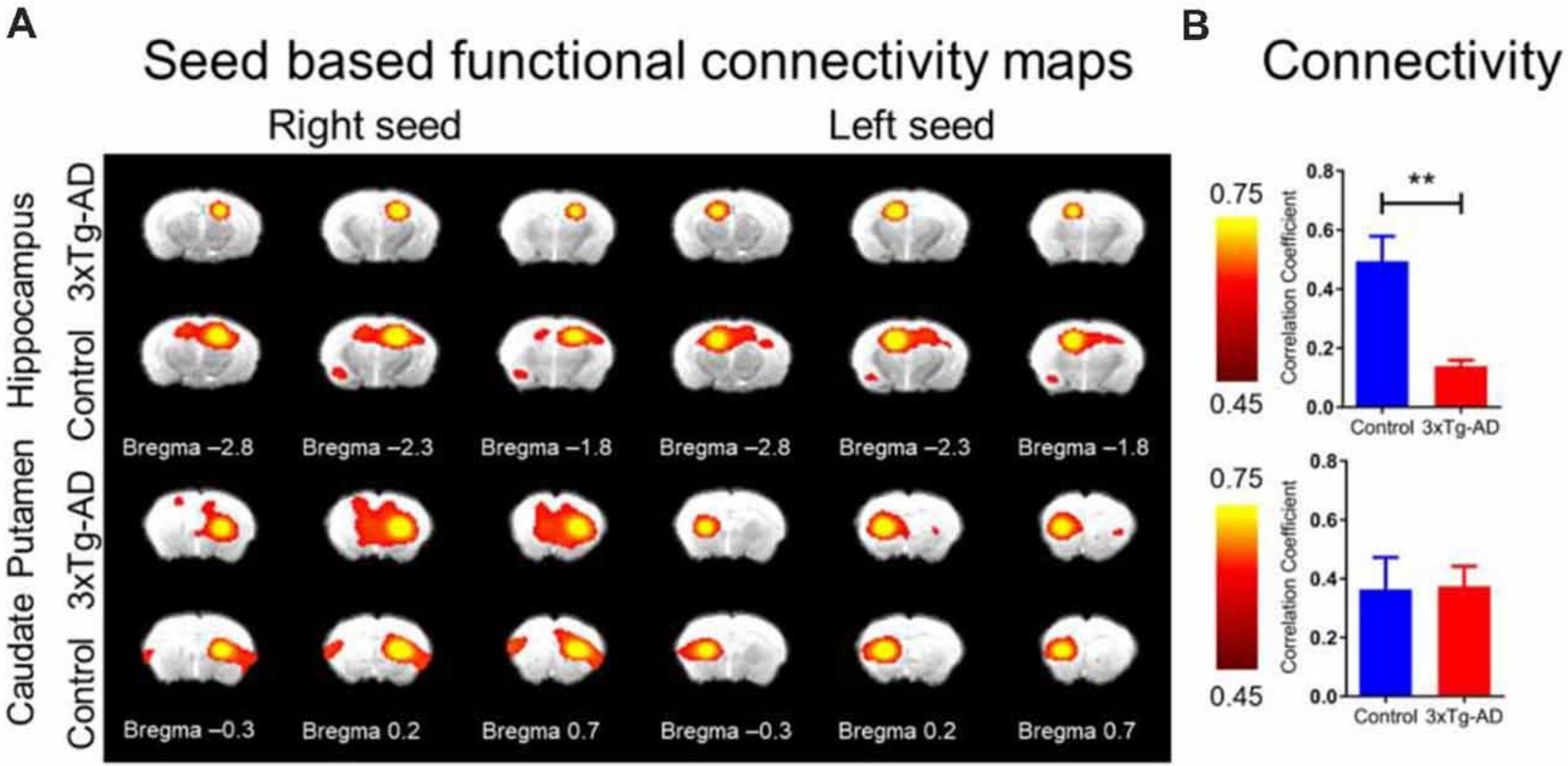
Neuroimaging the 3xTg AD mouse



DTI metrics in Alzheimers Disease

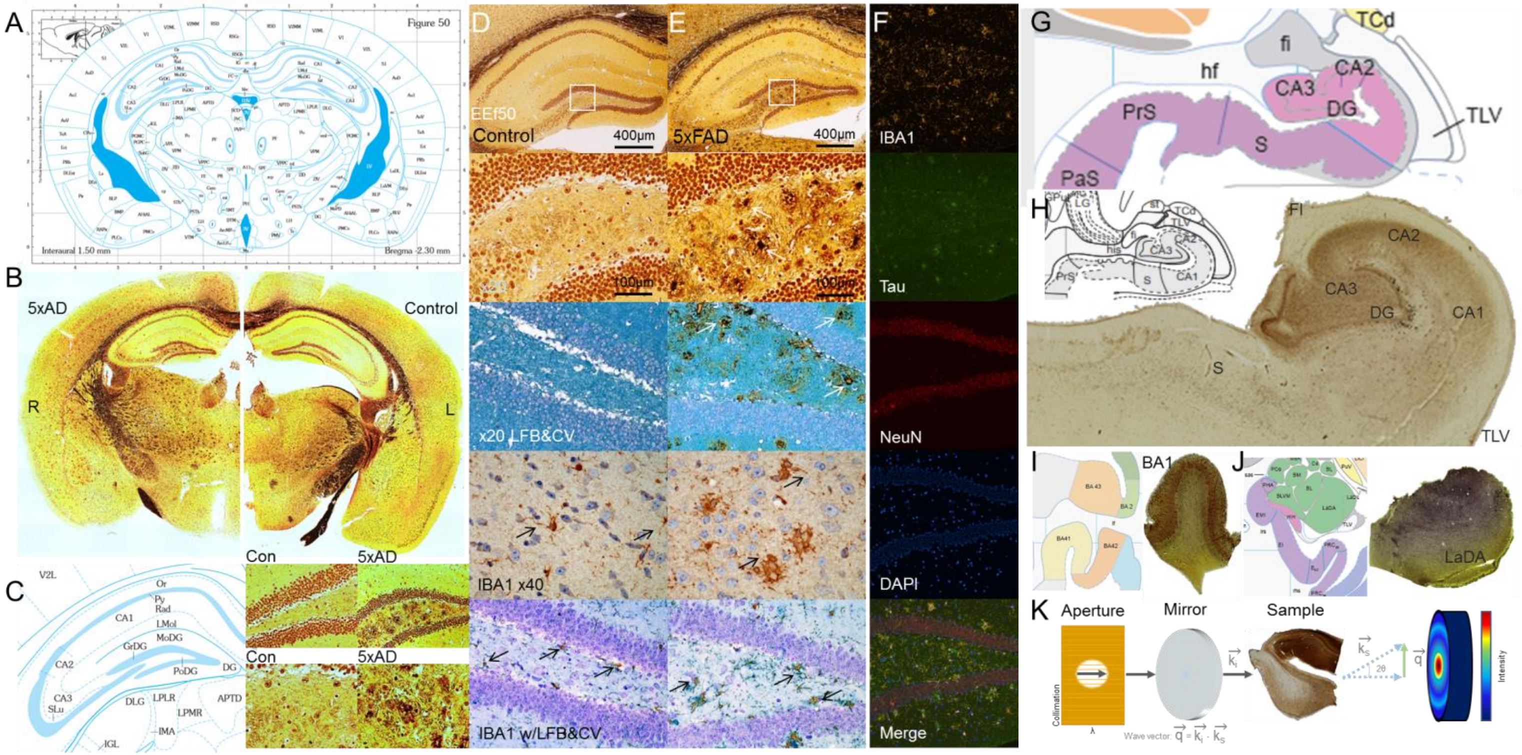


Decreased hippocampal functional connectivity



Future work

- Spectroscopic analysis of protein-tissue interactions in mouse model of Alzheimer's and in Human Alzheimer's Disease!



Overview

- Alzheimer's
- Hearing Loss
- Environmental Enrichment

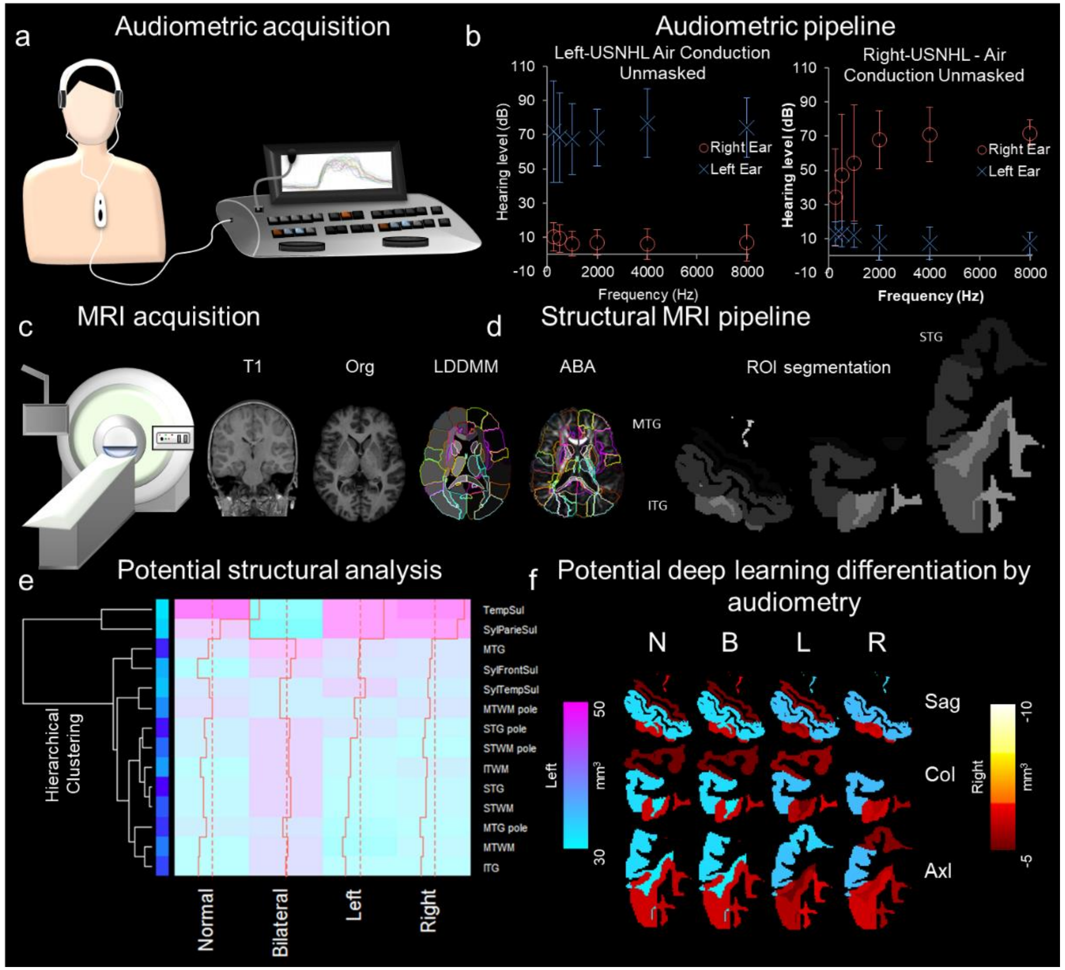
Introduction: Hearing loss

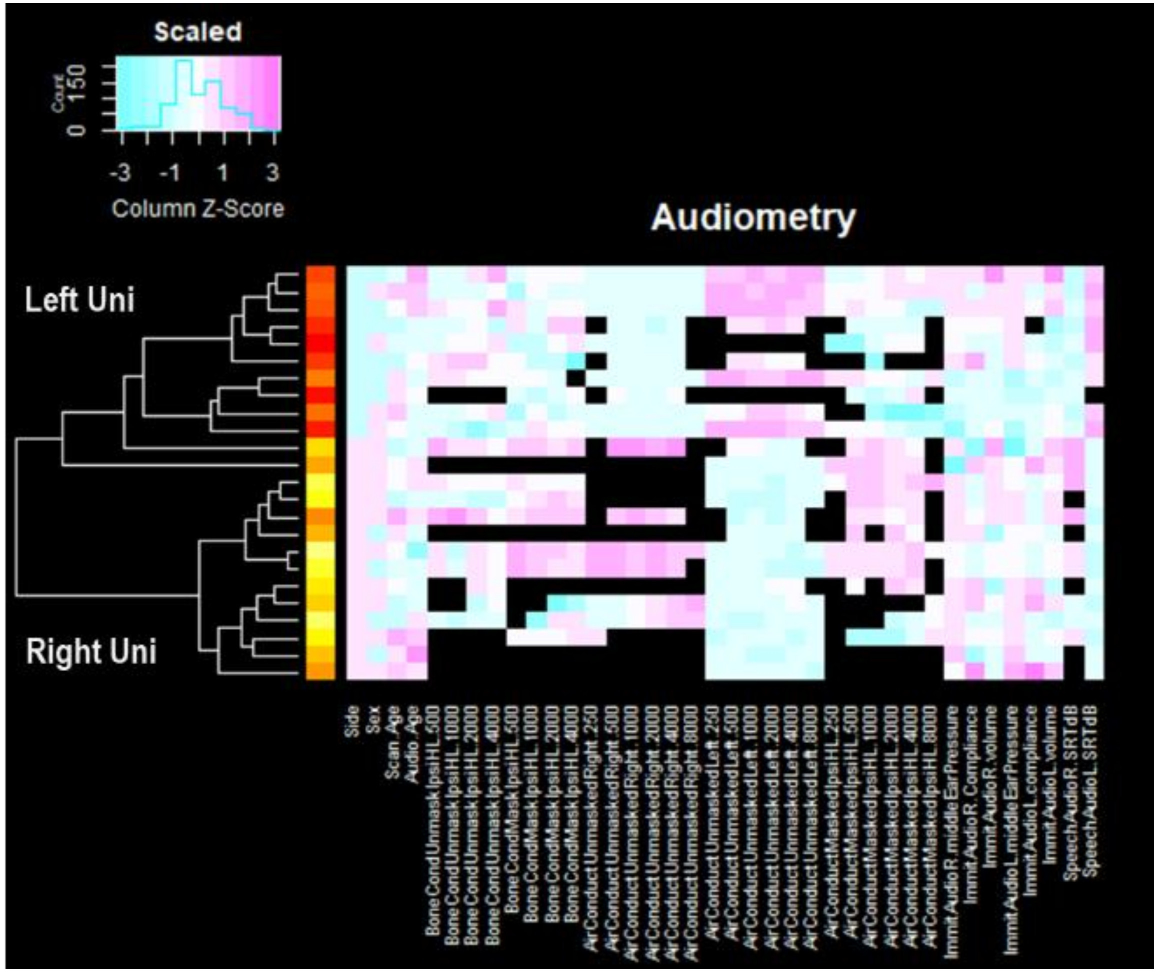
- Hearing Loss affects 1.5 Billion people worldwide (WHO)

- Research Questions: How does hearing loss across the lifespan affect the brain? How do gray matter and white matter change across the lifetime in hearing loss? Can we prevent changes?

- Manno FAM, et al. NeuroImage. 4 February 2021, 117826.

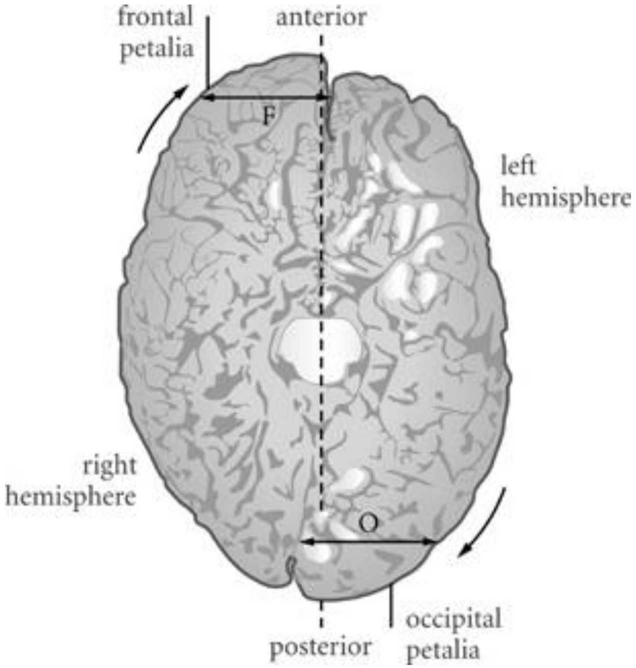
Experimental design of an MRI study

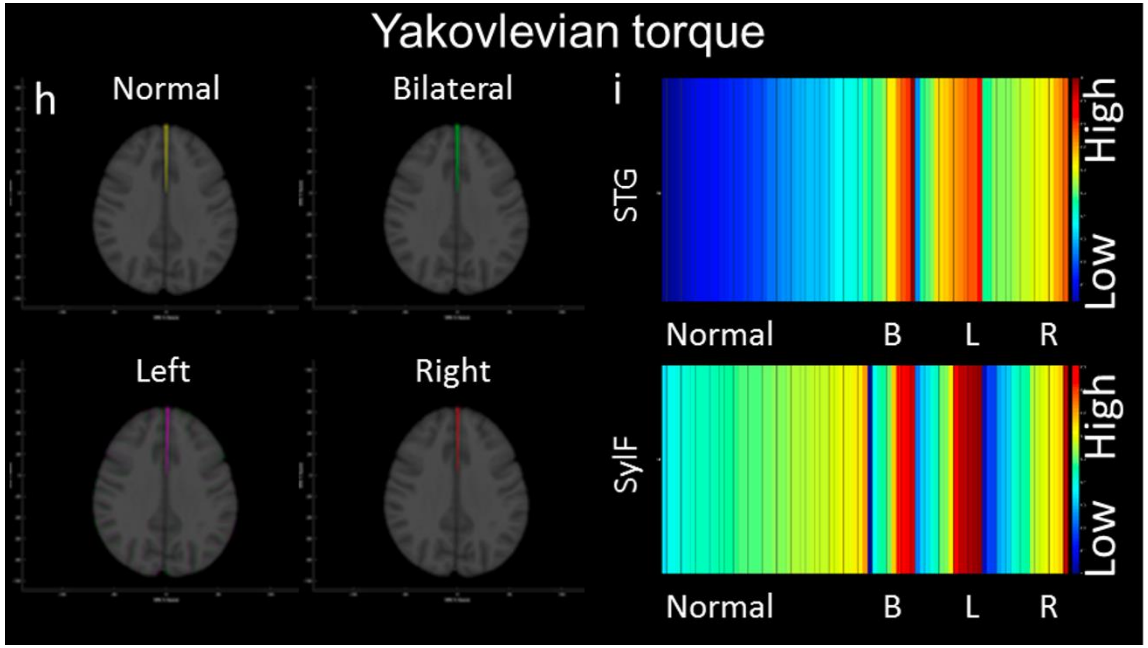




What do MRI studies Measure

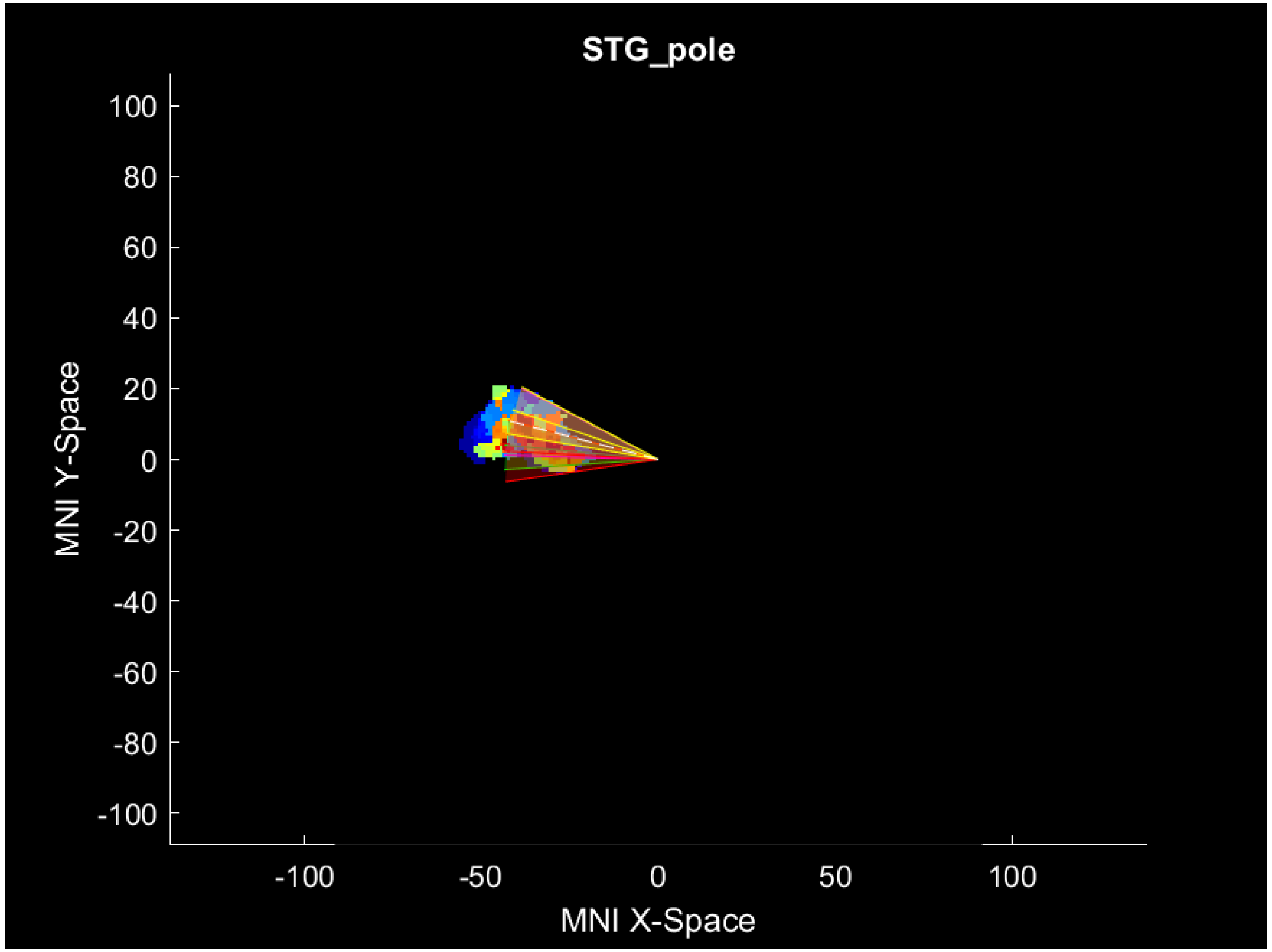
- GM, WM Volume and DTI metrics
- Fancy aspects like twist



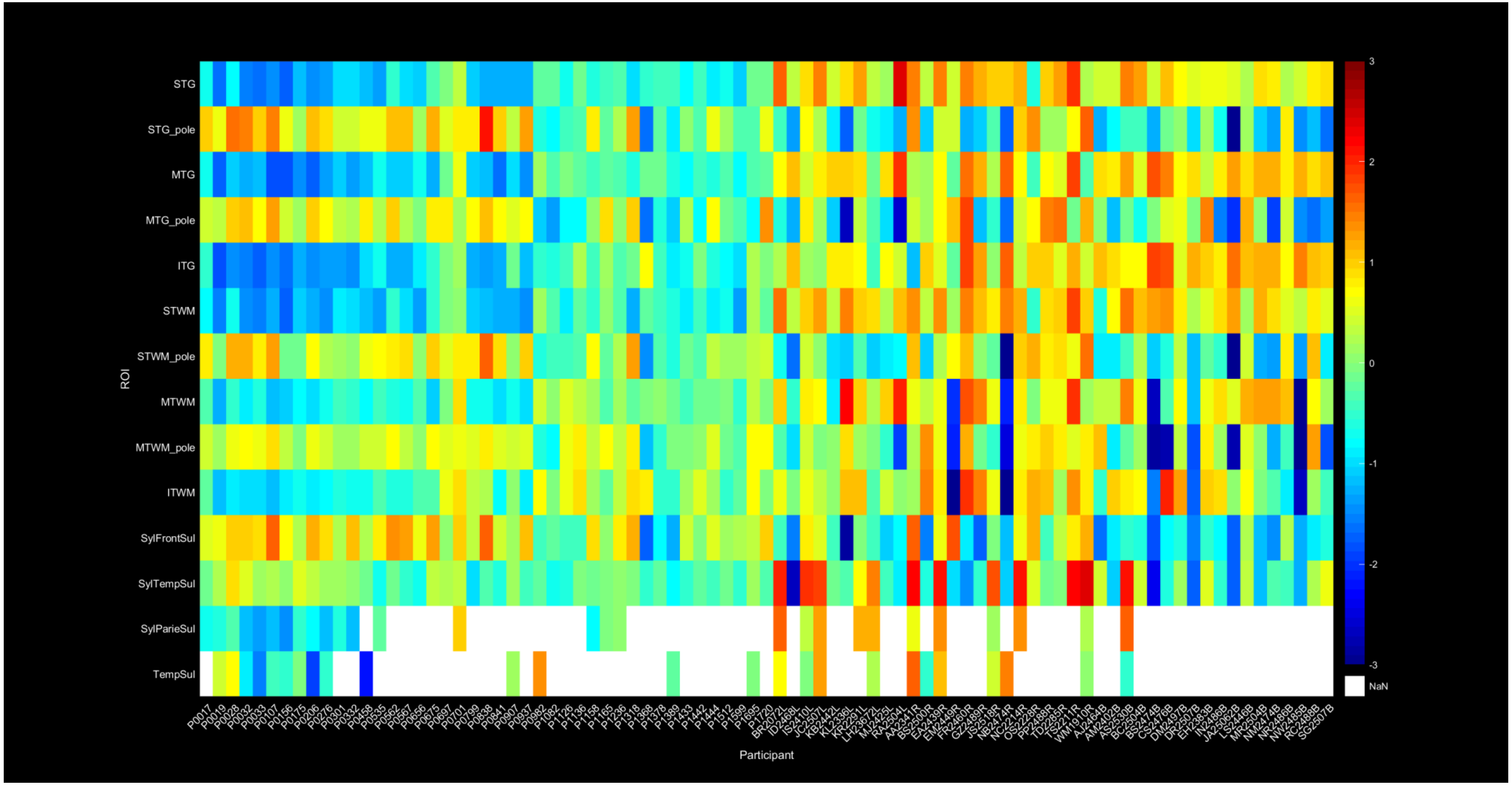


- Figure left – Toga and Thompson (2003)
- My figure is to the right

Brain shifts

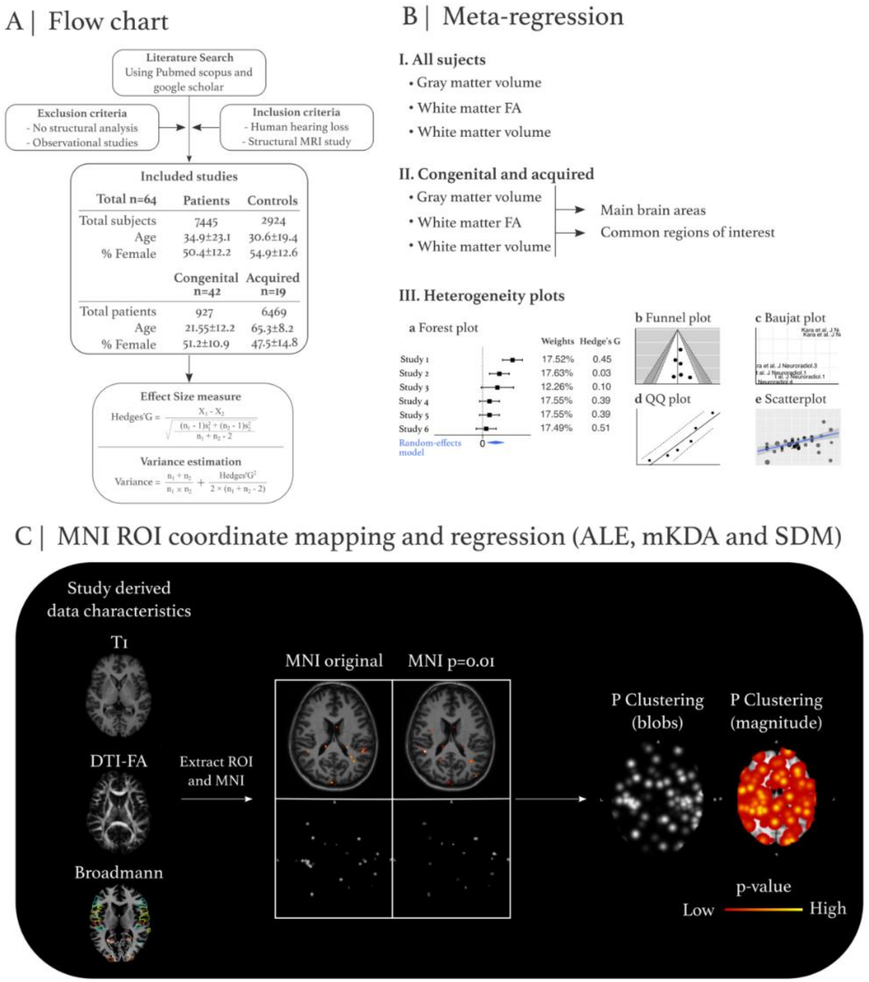


Auditory Structural Brain shifts

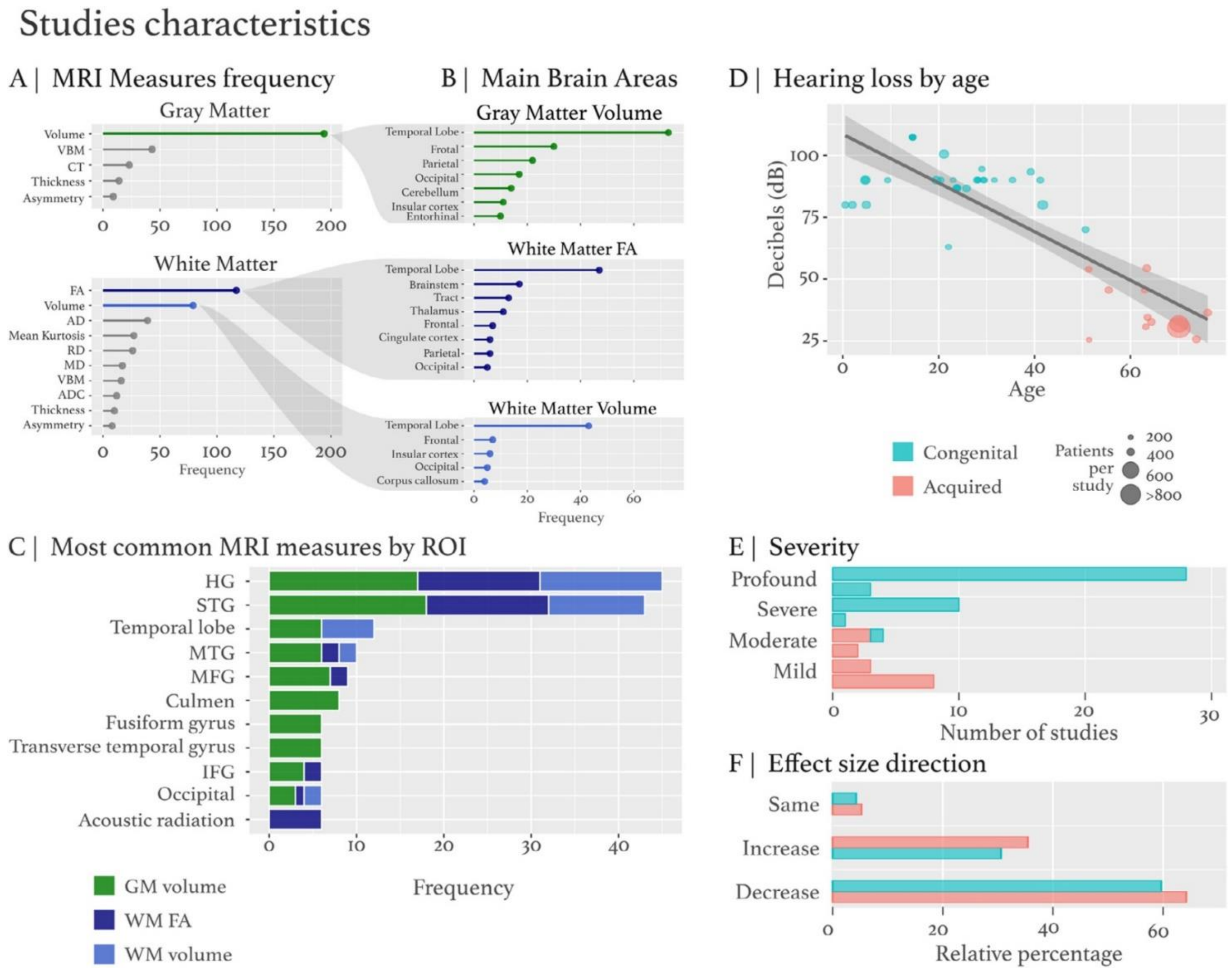


Experimental Design

- We extract these variables from m = 80 studies
- Outcome measure
- Volume, DTI metrics
- VBM and thickness
- Congenital & acquired cases
    - n = 7445
    - Control n = 2924
- >68000 datapoint metrics



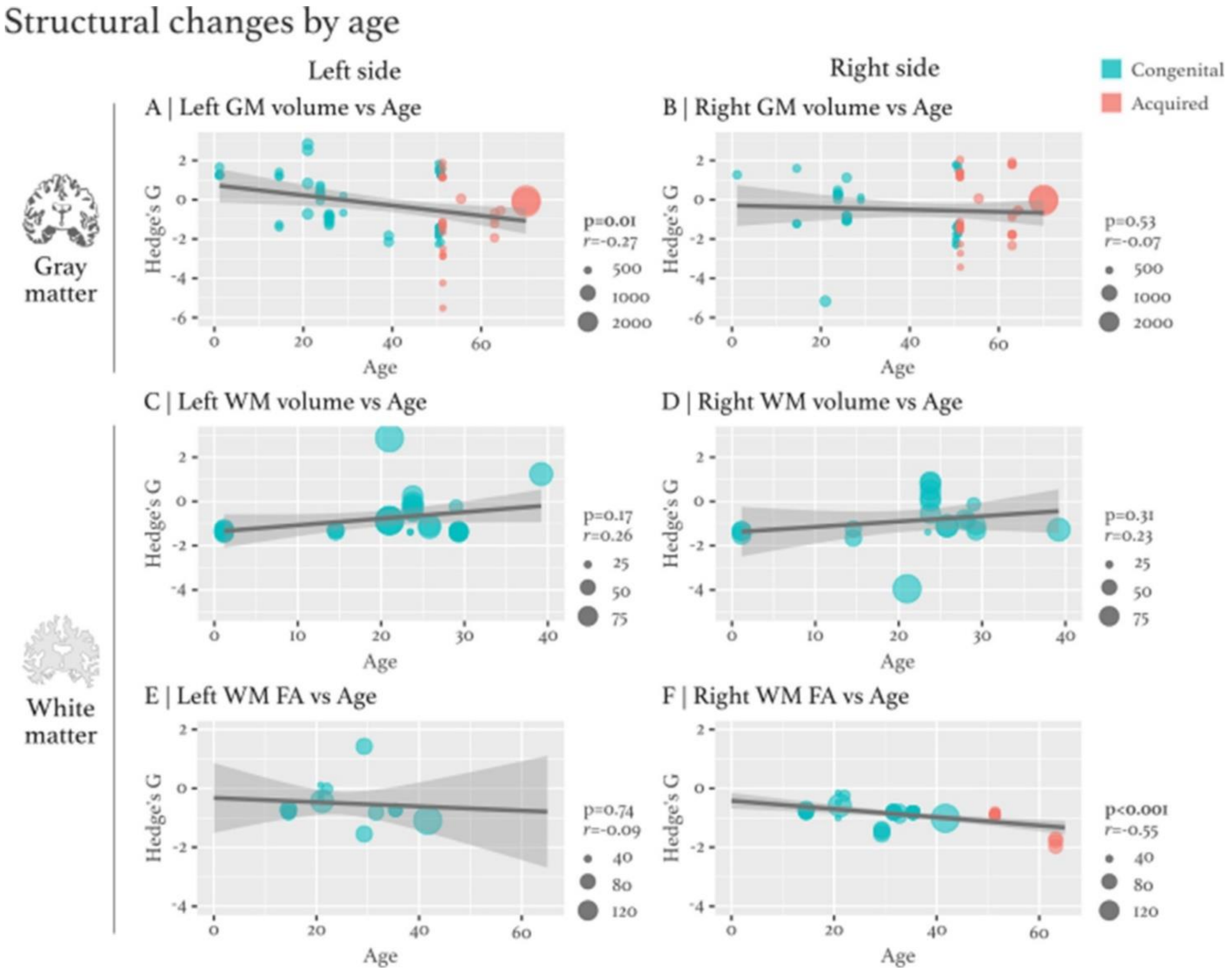
Study Characteristics



Meta-regression of hearing loss

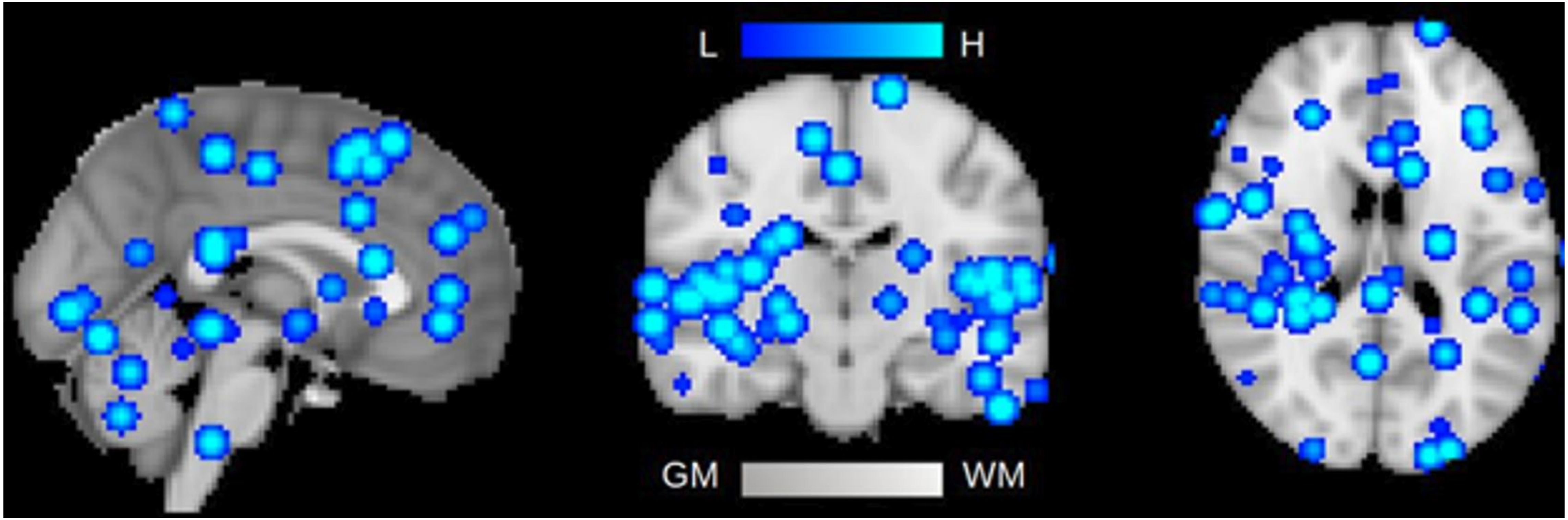
- Left and right hemisphere Grey matter (GM) and White Matter (WM) compared to controls

- Significant regressions were left GM volume by age and right WM FA by age.

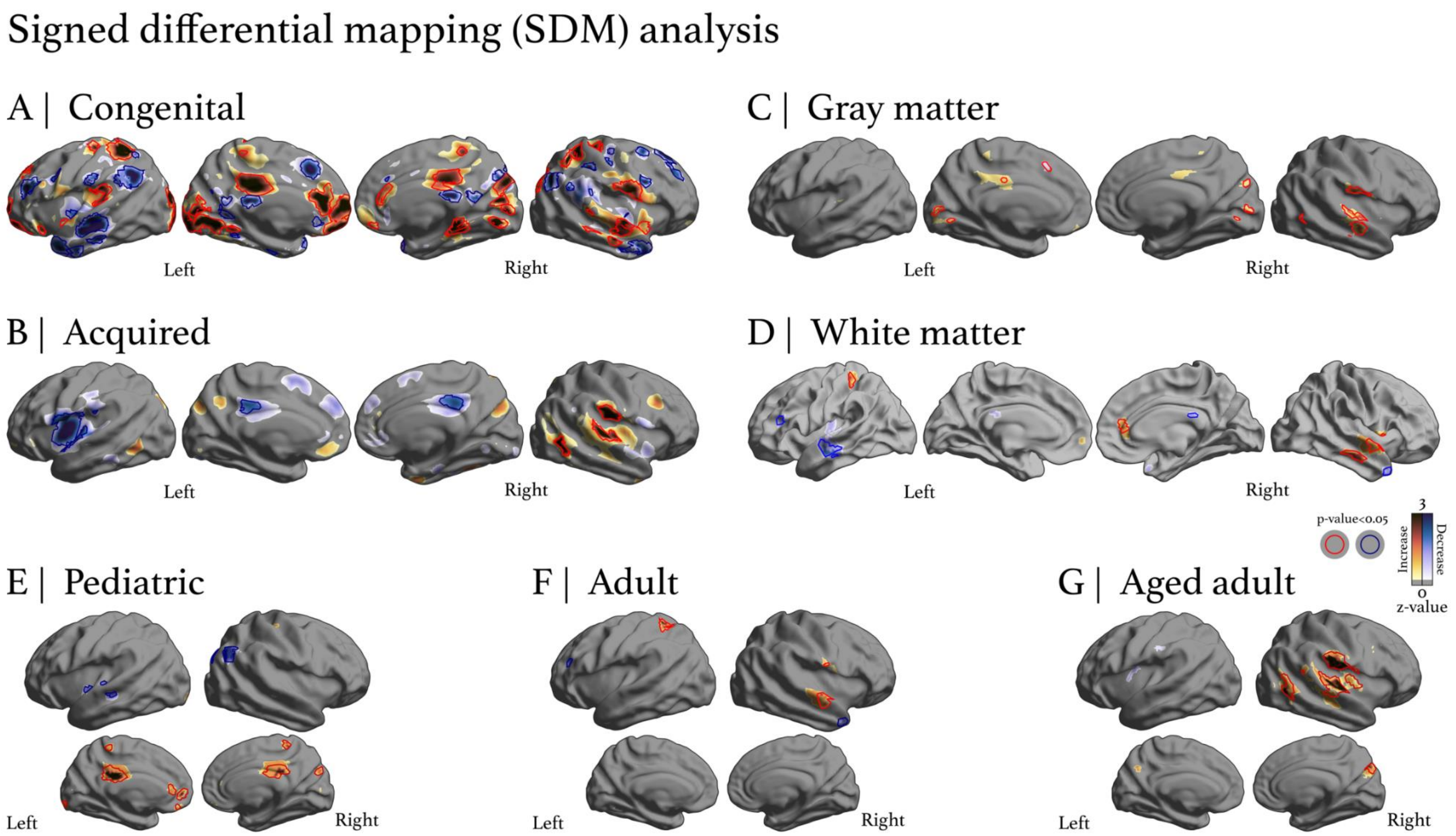


Coordinate mapping to determine loci of hearing loss

- Blue dots are region of interest (ROI) found in hearing loss studies
- Our meta-analytical review indicates hearing loss is widespread

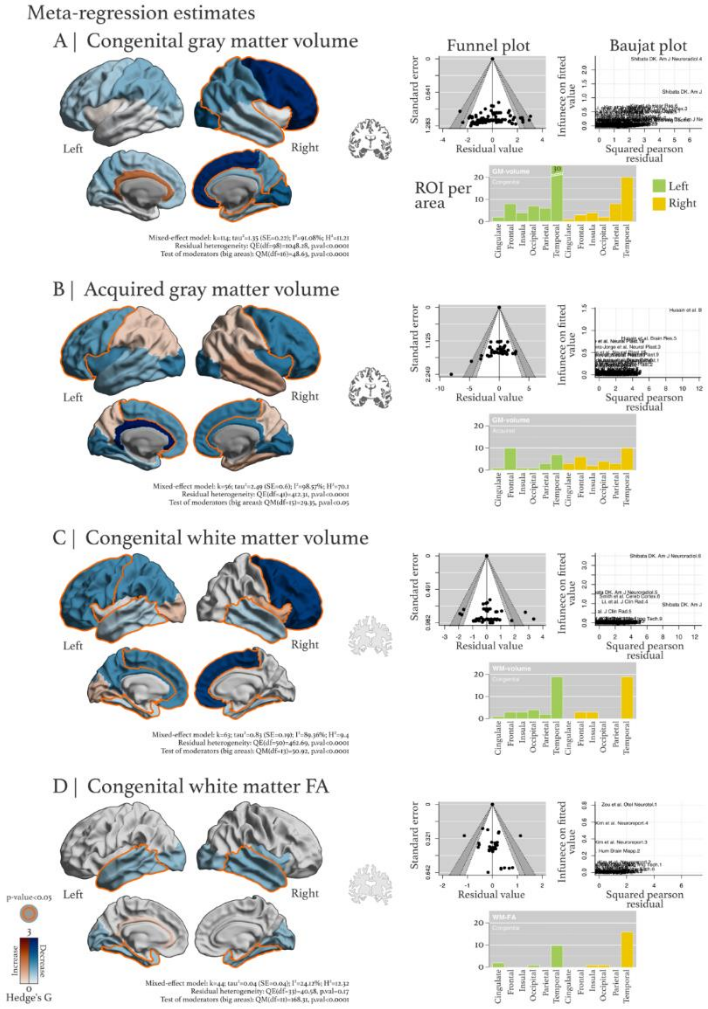


Signed (positive or negative) impact



Endophenotype of Hearing Loss

- We take all data to make a composite
- Congenital gray matter
- Acquired gray matter
- Congenital white matter
  - Volume
  - Fractional Anisotropy



Overview of human hearing loss

- In congenital hearing loss, GM decreased most in the frontal lobe.
- Acquired hearing loss similarly had a decrease in frontal lobe GM, albeit the insula was most decreased.
- Congenital white matter underlying the frontal lobe GM was most decreased.
- The temporal lobe had different GM alterations in congenital and acquired.
- The WM alterations most frequently underlined GM alterations in congenital hearing loss, while acquired hearing loss studies did not assess the WM metric frequently.

Future Work

- T32 to K99/R00 (kangaroo grant in preparation)
  - If accepted: 250K/Year transferable!
  - Collaboration with Johns Hopkins University and University of Maryland, College Park
  - -UK BioBank (213,424 Screens | 17,649 HL)
  - -NIH all of US (18,040 MRIs | 14,460 Screens)
  - -CHOP (4,000 MRIs)
- MRI-transcriptomic analysis using Machine Learning

Overview – emphasized projects

- Alzheimer's
- Hearing Loss
- Environmental Enrichment

Introduction: Environmental Enrichment

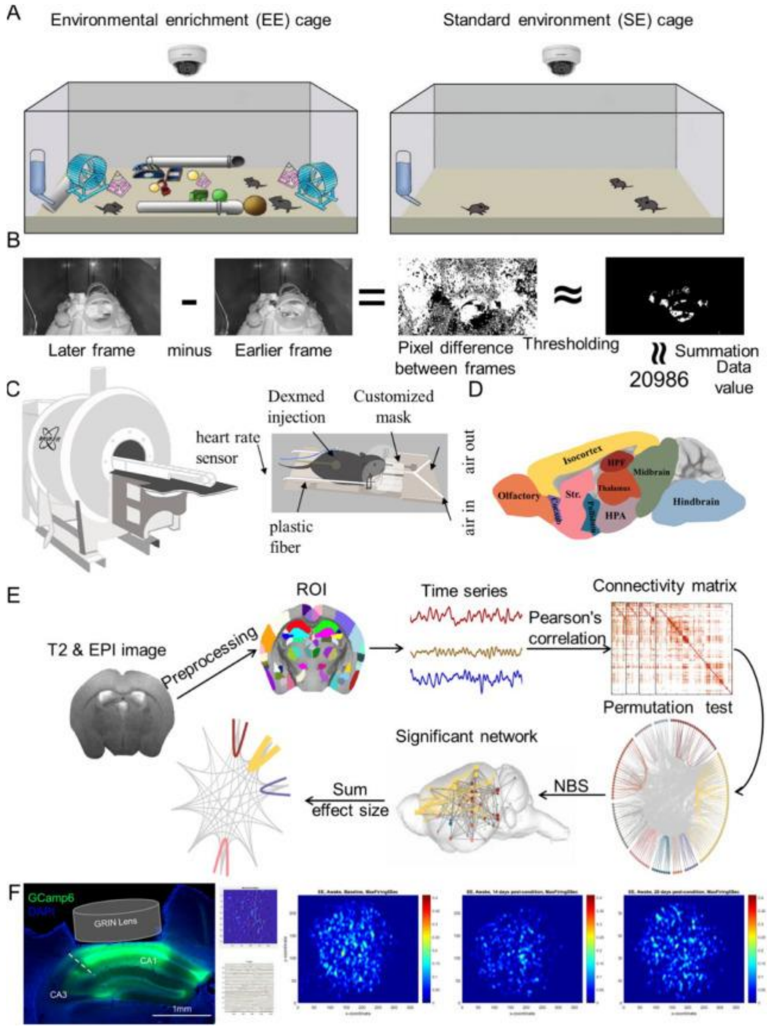
- Environmental enrichment induces widespread neuronal changes, but the initiation of the cascade is unknown.

- Research questions: What in the environment initiates the divergence between environmental enriched (EE) and standard environment (SE) mice. What is the critical period and what do the neuronal changes look like?

- Manno FAM, et al., Neuroimage. 2022 Feb 18;252:119016.

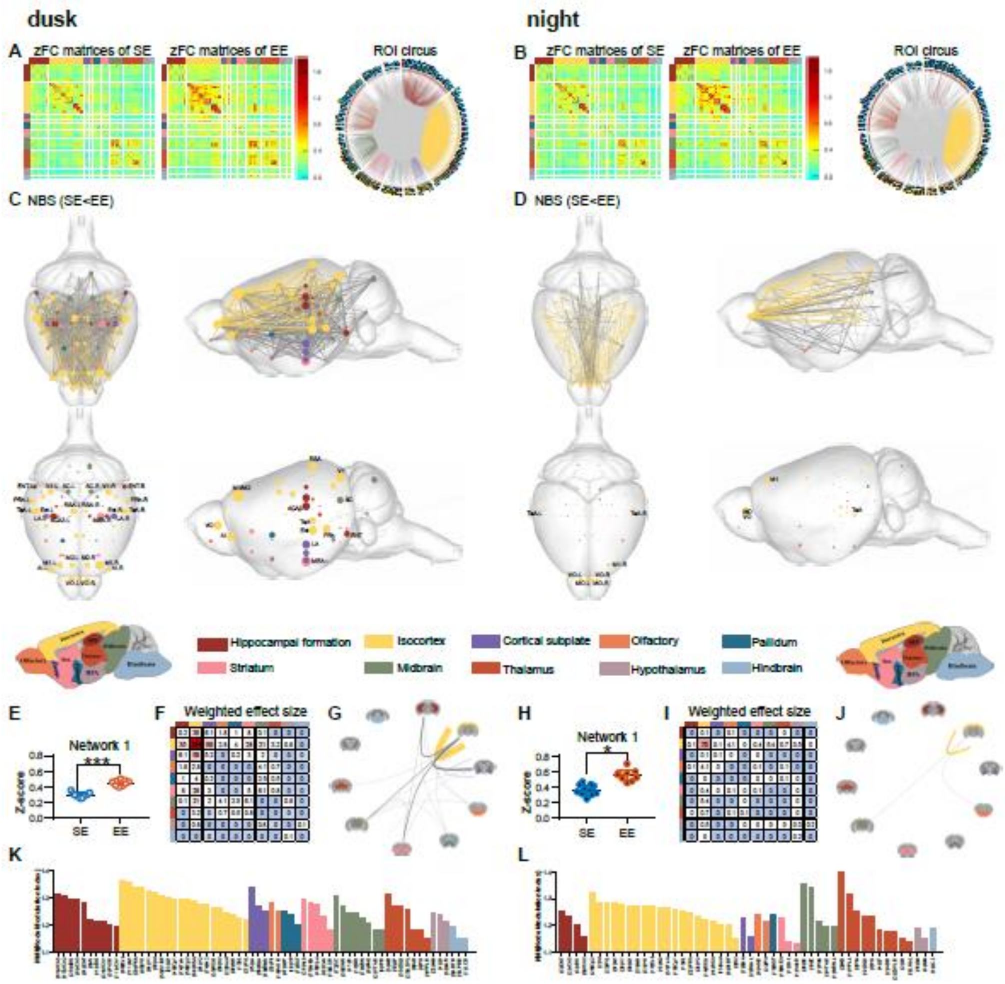
Experimental design

- fMRI and Ca2+ imaging based on circadian features
- Connectome analysis using network based stats
- The timepoints of interest were the baseline prior to the experiment, 14-day after EE and 1-month after EE compared to SE control during awake recordings.



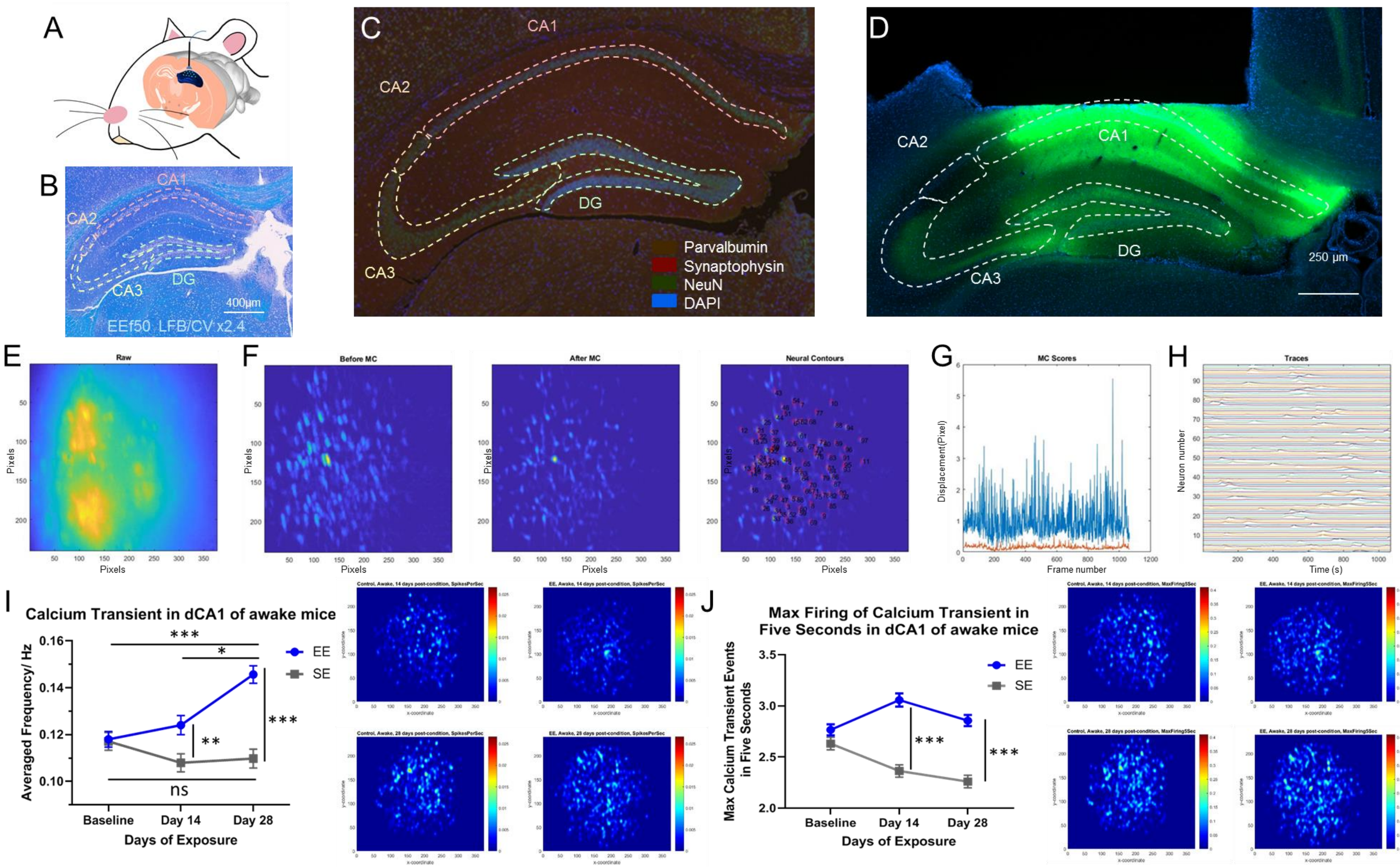
Functional connectome enhancement during dusk and night

- A and B) Mean functional connectivity matrices
- C and D) Anatomical visualization of a network calculated by NBS
  - size of the node represents the degree of the node
- E and H) Barplots displaying the defined networks
- F and I) The weighted effect size from the defined networks and G and J) The schematic illustration
- K and L) The node modulation index (NMI)



Increased calcium spiking of dCA1 during dusk session

- A) Schematic representation of calcium imaging of hippocampus and B) histology and C) immunihistology demonstrating our region of interest for D) calcium imaging
- E) pipeline for calcium imaging,
- F) taking neural traces and correcting for motion and feature F) and denoising H)
- J) Max firing



Overview of environmental enrichment

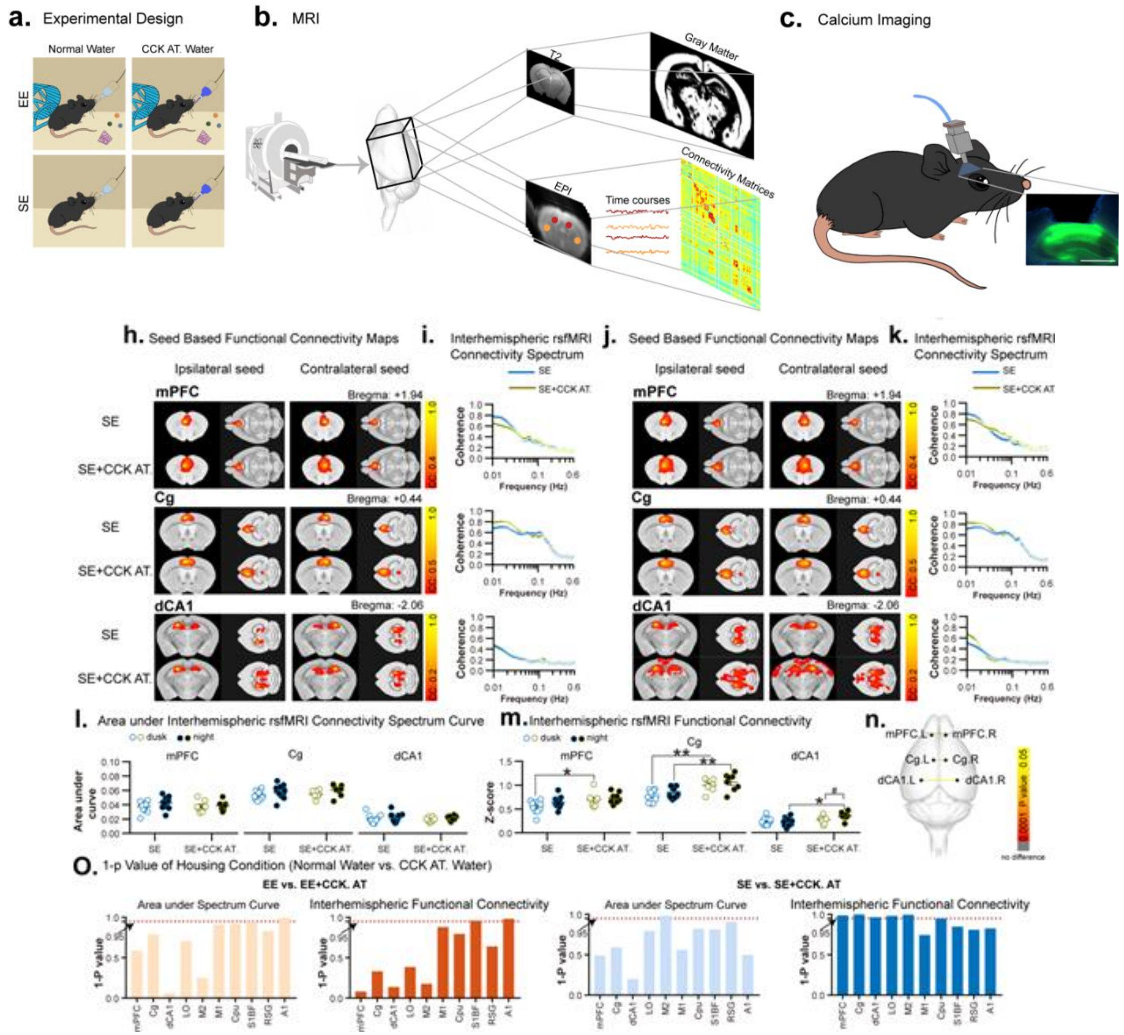
- Seed-based analysis: Increased functional connectivity in the visual cortex, motor cortex, retrosplenial granular cortex, and cingulate cortex
- Network based statistics: modulated functional connectome in EE concentrated in two hubs: the hippocampal formation and isocortical network.
  - Hubs experienced a higher node degree and significant enhanced edge connectivity.
- Calcium imaging revealed increased spikes per second and maximum firing rate in the dorsal CA1 pyramidal layer, in addition to location (anterior-posterior and medial-lateral) effect size differences between EE and SE.

Future Work

- We have another…NeuroImage (Revisions)

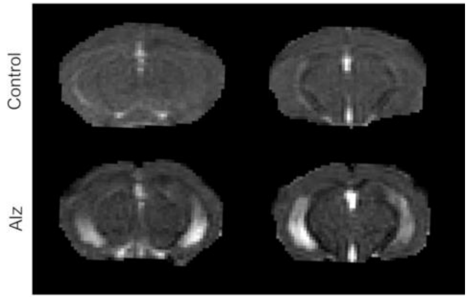
- Cholecystokinin receptor antagonist challenge elicits brain-wide functional connectome modulation with micro-network increased hippocampal neuronal calcium transients and firing rate: CCKergic environmental enrichment resistance to remodulation

- CCK is a gut peptide hormone

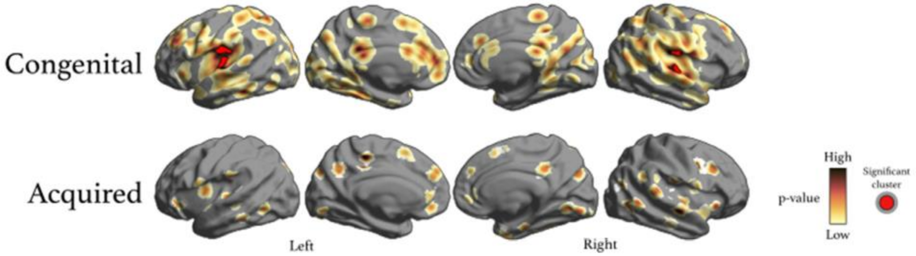


Main Summary

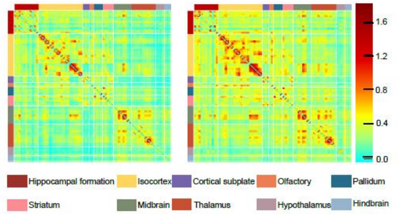
- Alzheimer's: Human tissue and mouse models to discern spectroscopically protein tissue interactions – can we disrupt bad protein formations?



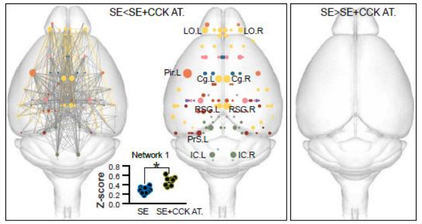
- Hearing Loss: Implement machine learning algorithms to discern template patterns of hearing loss



- Environmental Enrichment: Why do certain environments elicit detrimental neuronal alterations- can we inhibit these changes?



- Models of human disease to determine improved health outcomes – future work employs machine learning algorithms to model pattern



Thank you







Collaborators

Alzheimer's: Yubin KE, Xuelian WU, Muhammad S. KHAN, Vincent MOTTO-ROS, Xun-Li WANG, Condon LAU

Hearing Loss Mouse: Ziqi AN, Vardhan BASNET, Rachit KUMAR, Junfeng SU, Martin PIENKOWSKI, Shuk Han CHENG, Ed X. WU, Jufang HE, Yanqiu FENG, Condon LAU

Hearing Loss Human: Rachit KUMAR, Raul Rodríguez-CRUCES, J. Tilak RATNANATHER, Condon LAU

Environmental enrichment: Ziqi AN, Rachit KUMAR, Junfeng SU, Ed X. WU, Jufang HE, Yanqiu FENG, Condon LAU

Universities

Perelman School of Medicine
University of Pennsylvania

Johns Hopkins
Whiting School of Engineering

CityU
Department of Physics
香港城市大學
City University of Hong Kong

neuro
Institut-Hôpital neurologique de Montréal
Montreal Neurological Institute-Hospital

Johns Hopkins
Biomedical Engineering

Boston Children's
F.M. Kirby Neurobiology Center

Faculty of Engineering
The University of Hong Kong

Center for Imaging Science
Johns Hopkins University

Main Funding - Thank you!

≈1.5 million through 2025

NIH National Institute on Deafness and Other Communication Disorders

NIH National Institutes of Health

UGC 大學教育資助委員會 University Grants Committee

NSFC 国家自然科学基金委员会 National Natural Science Foundation of China

Equipment – segue

- Electrophysiology and calcium imaging equipment.

- Everything I have described to complete the experiments, except the MRI scanner!
  - Experiments I have not described: hearing loss transcriptomics and optogenetics fMRI

Thank you for your time

Presentation

ORCID