NIH National Institute of Mental Health

Imaging Changes in Brain Anatomy

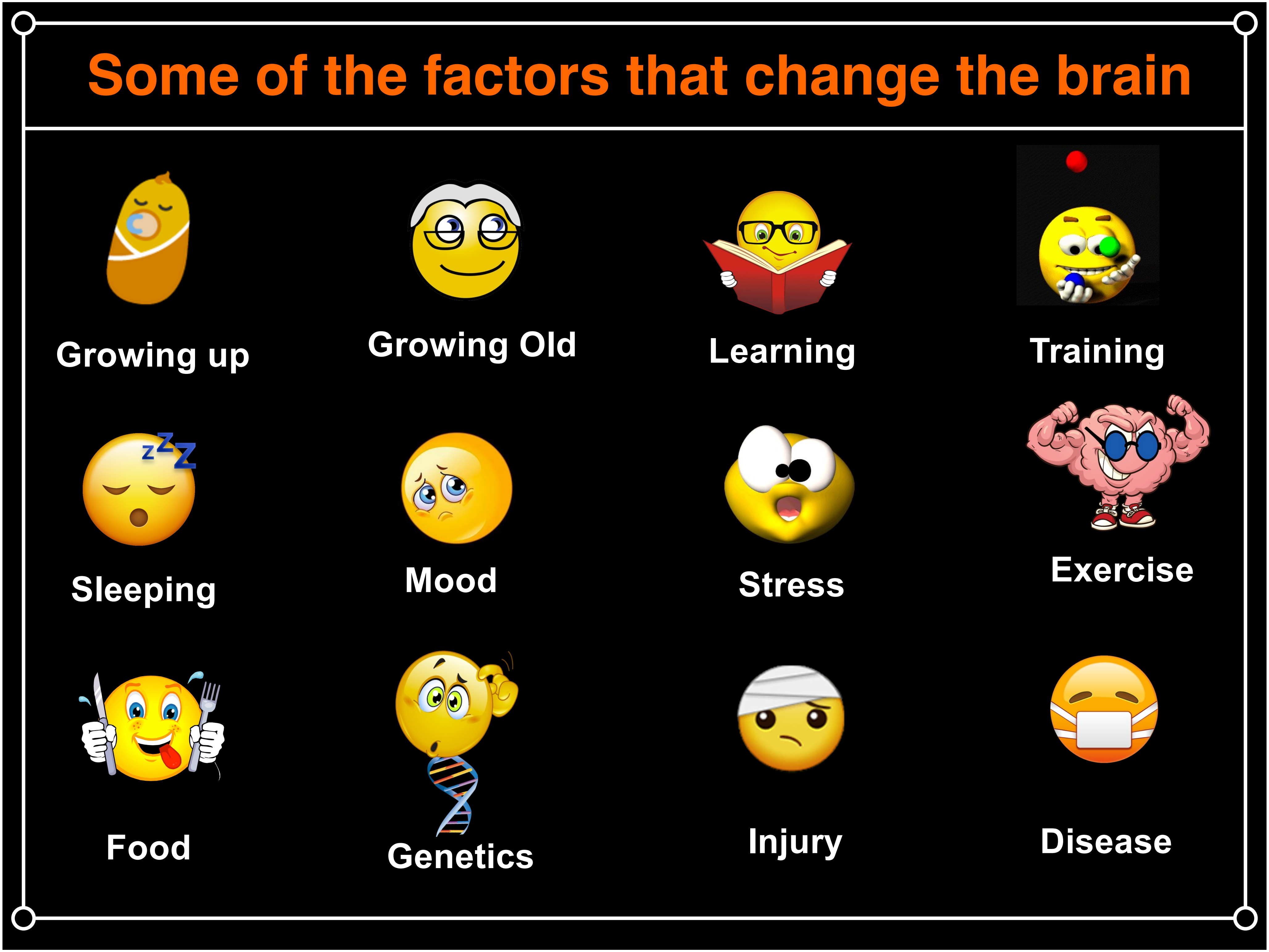
Cibu Thomas, PhD

Section on Learning and Plasticity

Laboratory of Brain and Cognition (LBC)

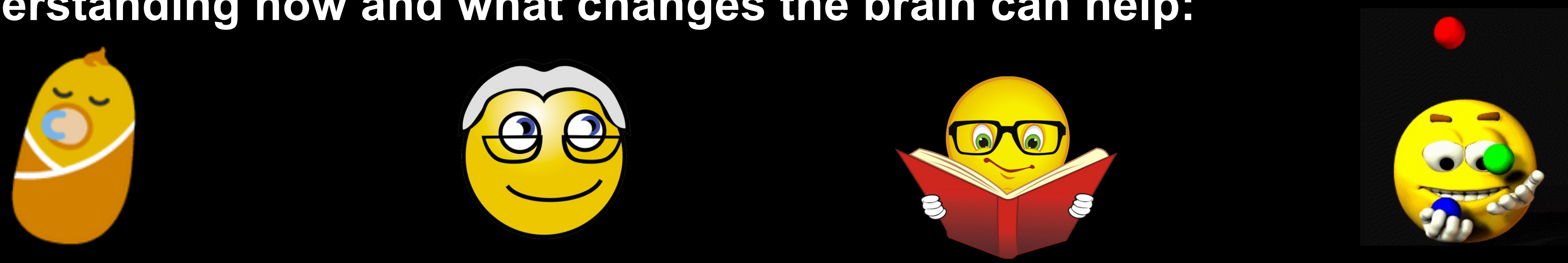
Scope of this lecture

- Cognitive Neuroscientist's perspective on imaging brain changes
- Starting or in the middle of a project looking at structural brain changes
- Ideas extend to functional brain changes also
- Some familiarity with MRI images and jargon

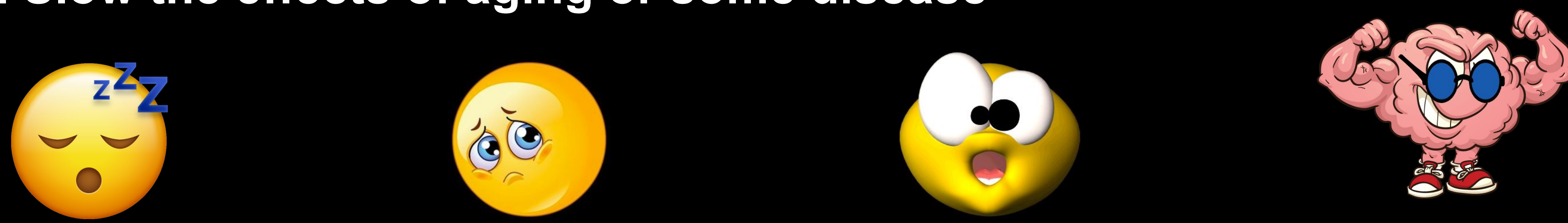

Some of the factors that change the brain
Growing up
Growing Old
Learning
Training
Sleeping
Mood
Stress
Exercise
Food
Genetics
Injury
Disease

Why imaging brain changes is important

Understanding how and what changes the brain can help:



1. Slow the effects of aging or some disease

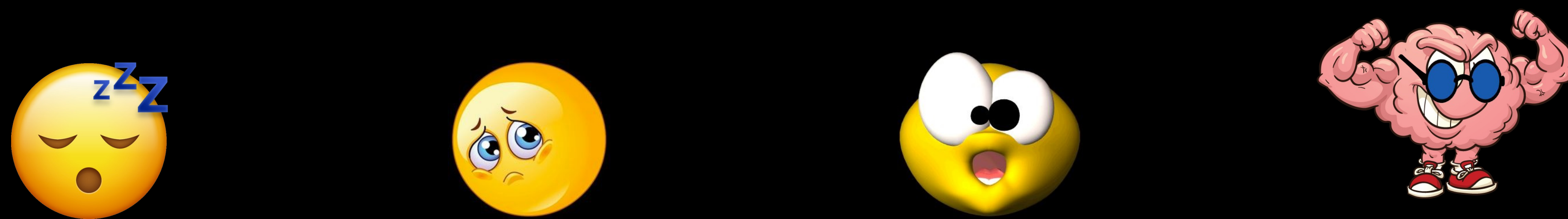


2. Measure the efficacy of a treatment strategy

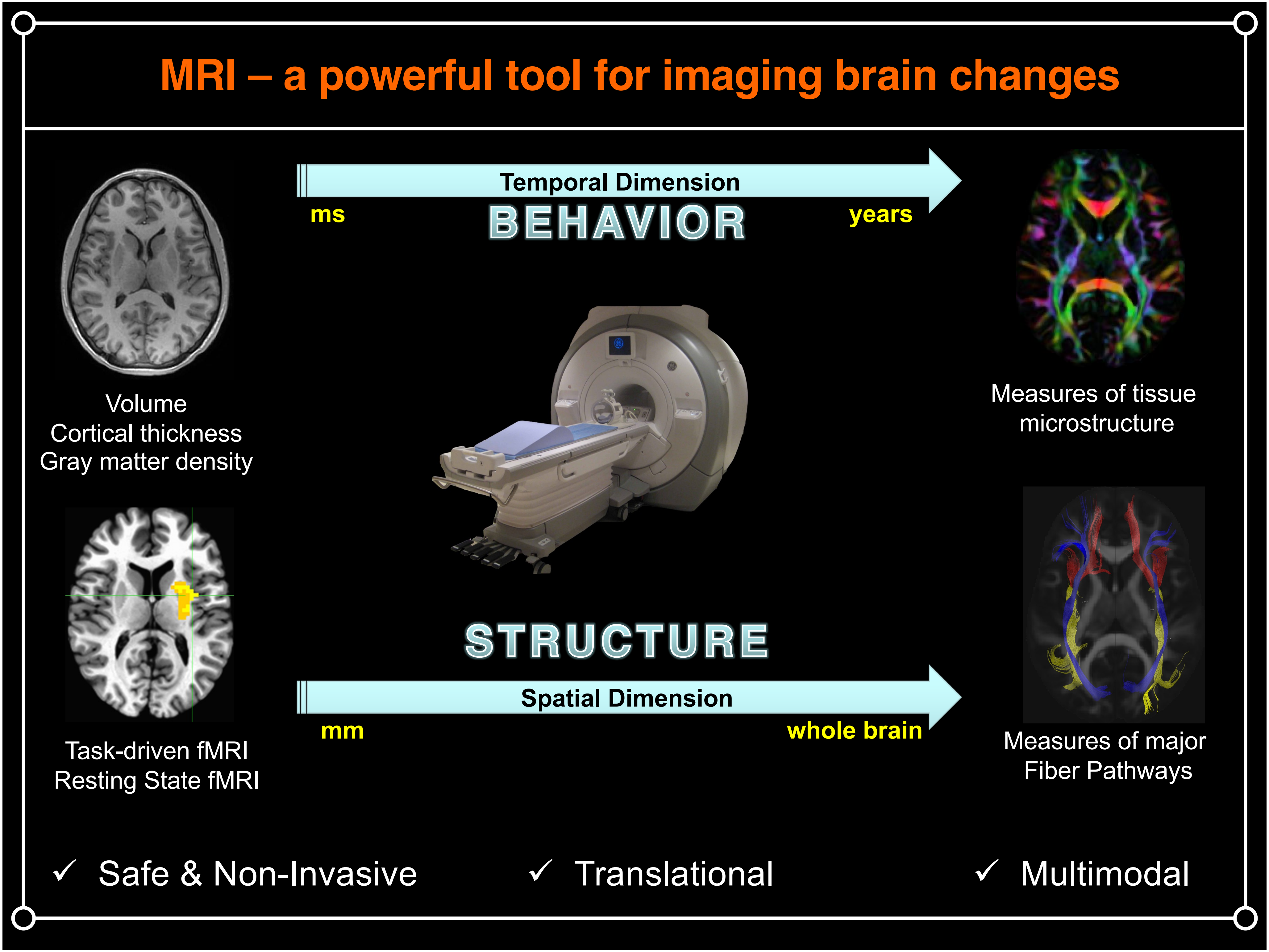
3. Guide public policy on promoting good mental health

How do we study the living human brain?

Temporal : Years, months, weeks, Days, Hours, minutes, seconds…

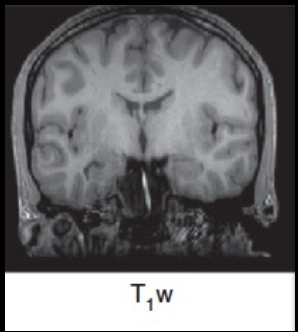


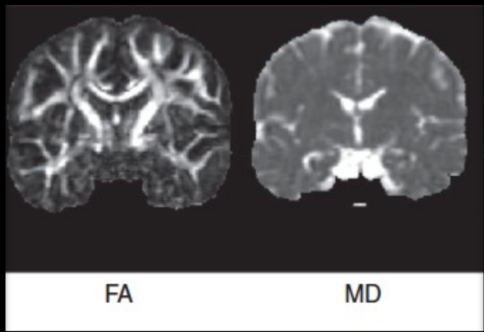
Spatial : Whole brain, cm, mm, microns


MRI – a powerful tool for imaging brain changes
Temporal Dimension
ms
years
BEHAVIOR
Volume
Cortical thickness
Gray matter density
Measures of tissue microstructure
STRUCTURE
Spatial Dimension
mm
whole brain
Task-driven fMRI
Resting State fMRI
Measures of major Fiber Pathways
✓ Safe & Non-Invasive
✓ Translational
✓ Multimodal

Outline

- Review popular MRI methods used for measuring brain changes



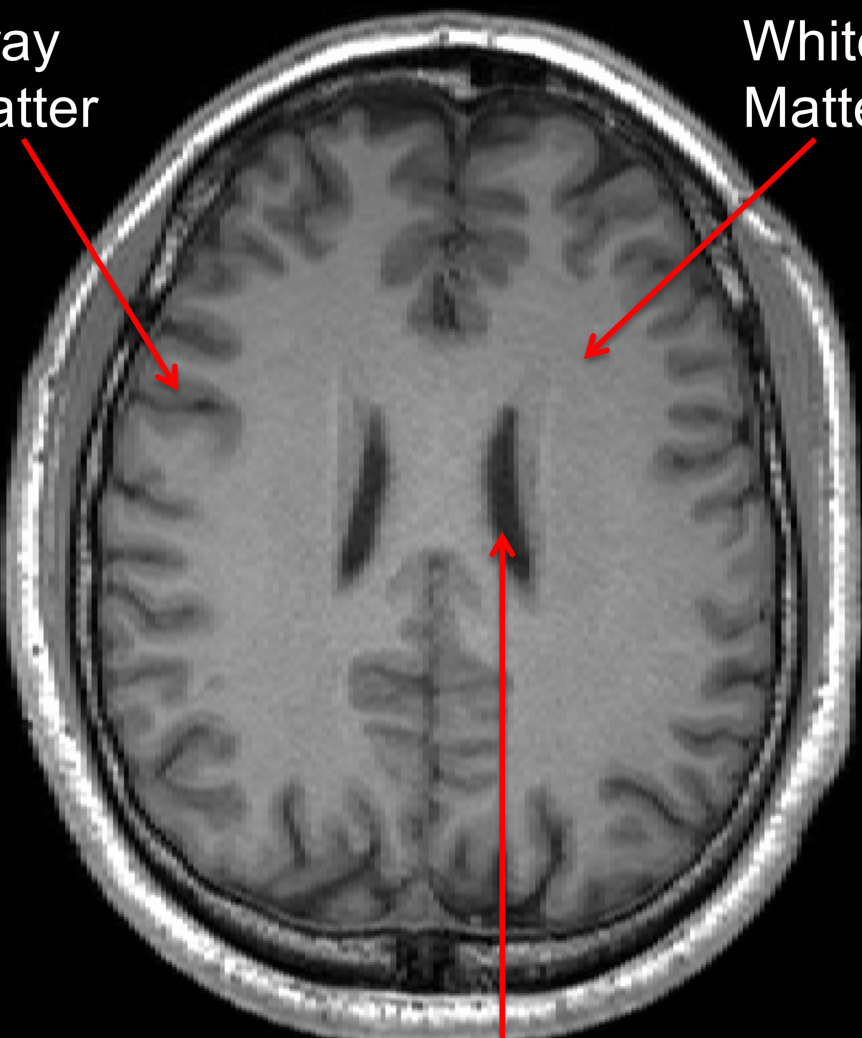


T_1W image - a powerful tool for Radiologists

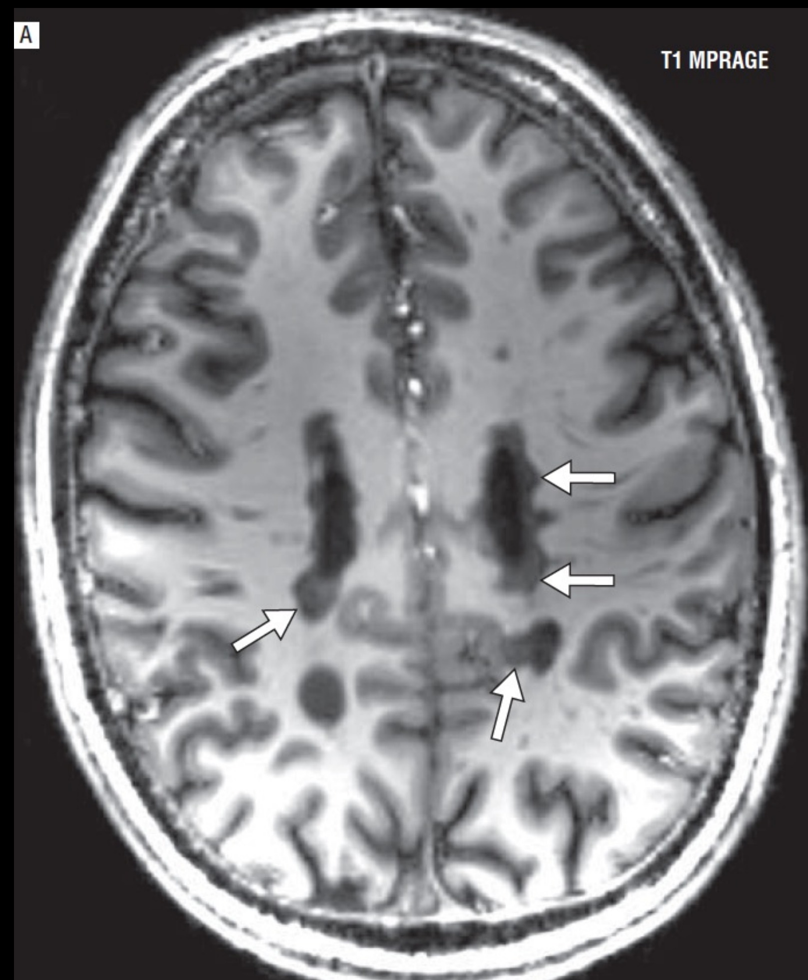
< 6 minutes

Gray Matter

White Matter



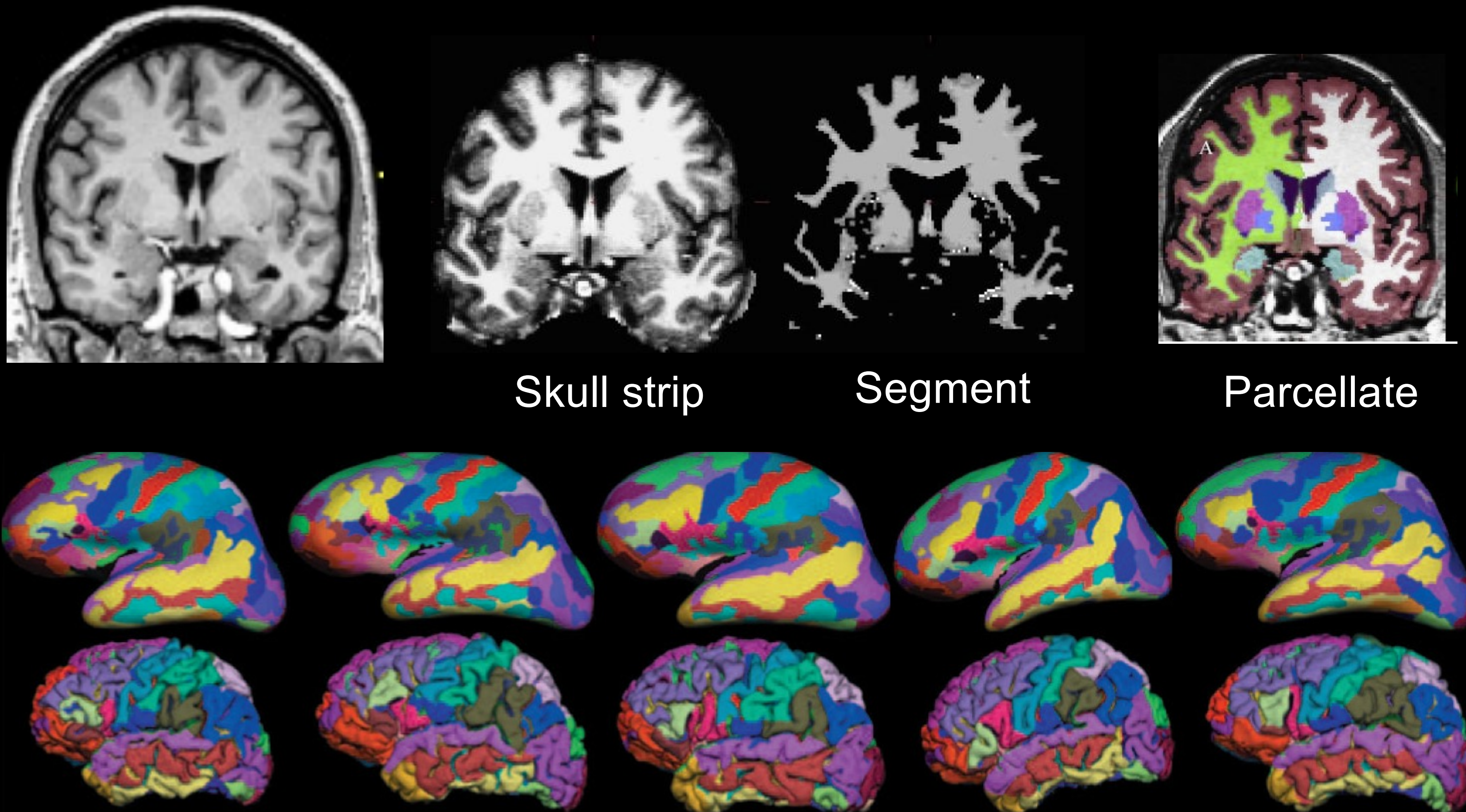
Cerebrospinal Fluid (CSF)



Neuroinflammatory Lesion

Sinnecker, et al., Arch, Neurol, 2012

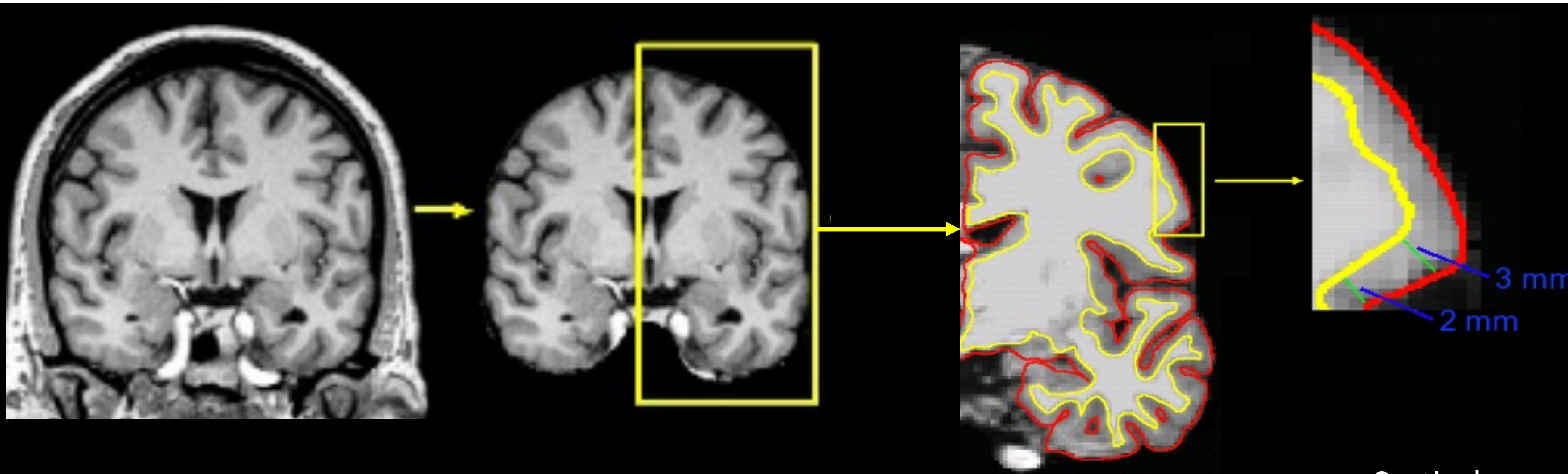
Automatically derive anatomically meaningful measures of Volume



Compute Subject – Specific Measure of volume of cortical areas

https://surfer.nmr.mgh.harvard.edu/fswiki

Automatically compute second-order measures like Cortical Thickness & Gray Matter Density



Surface Area

Gyral Height /Sulcal depth

Curvature Measures

Shape Measures

Cortical Thickness

Gray Matter Density

https://surfer.nmr.mgh.harvard.edu/fswiki

T_1W Morphometry - A powerful tool for Brain Research

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

Longitudinal changes in cortical thickness associated with normal aging

Aging

BRAIN

A JOURNAL OF NEUROLOGY

Longitudinal changes in cortical thickness in autism and typical development

Autism

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

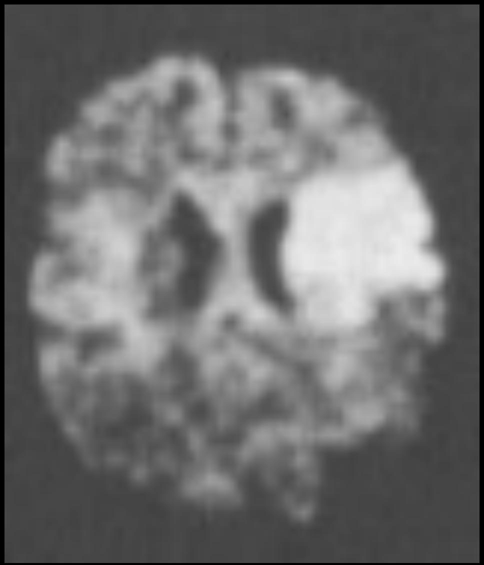
ELSEVIER

Effects of memory training on cortical thickness in the elderly

Brain Training

Diffusion MRI - a powerful tool for Radiologists

- T_2W image ~3 hrs post onset of stroke symptoms
- Shows a chronic infarct in subcortical WM



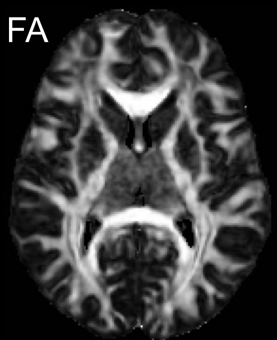
- DWI image ~3 hrs post onset of symptoms
- Decrease in water diffusion shows an acute infarct extending from temporal to frontal lobe

Warach et al., JoCBF&M_1996

Courtsey of Okan Irfanoglu

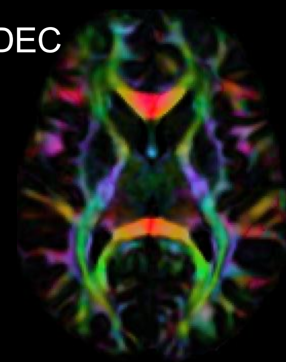
Maps from the Diffusion Tensor

FA

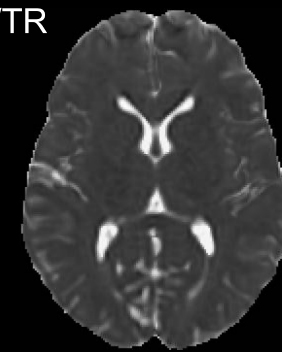


$$\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}}{\sqrt{(\lambda_1+\lambda_2+\lambda_3)^2}}$$

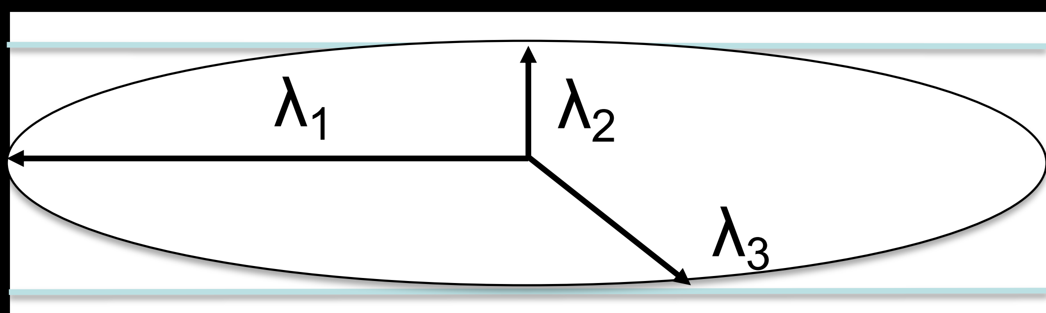
DEC



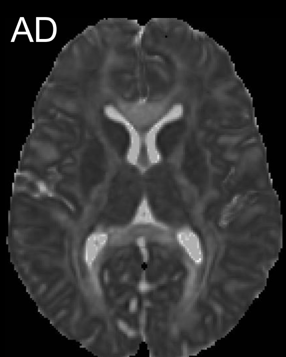
MD/TR



$$\lambda_1+\lambda_2+\lambda_3$$

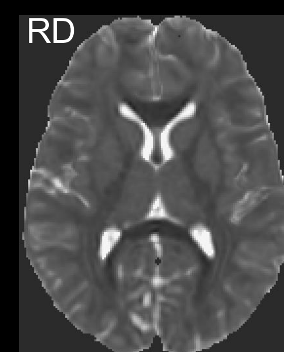


AD



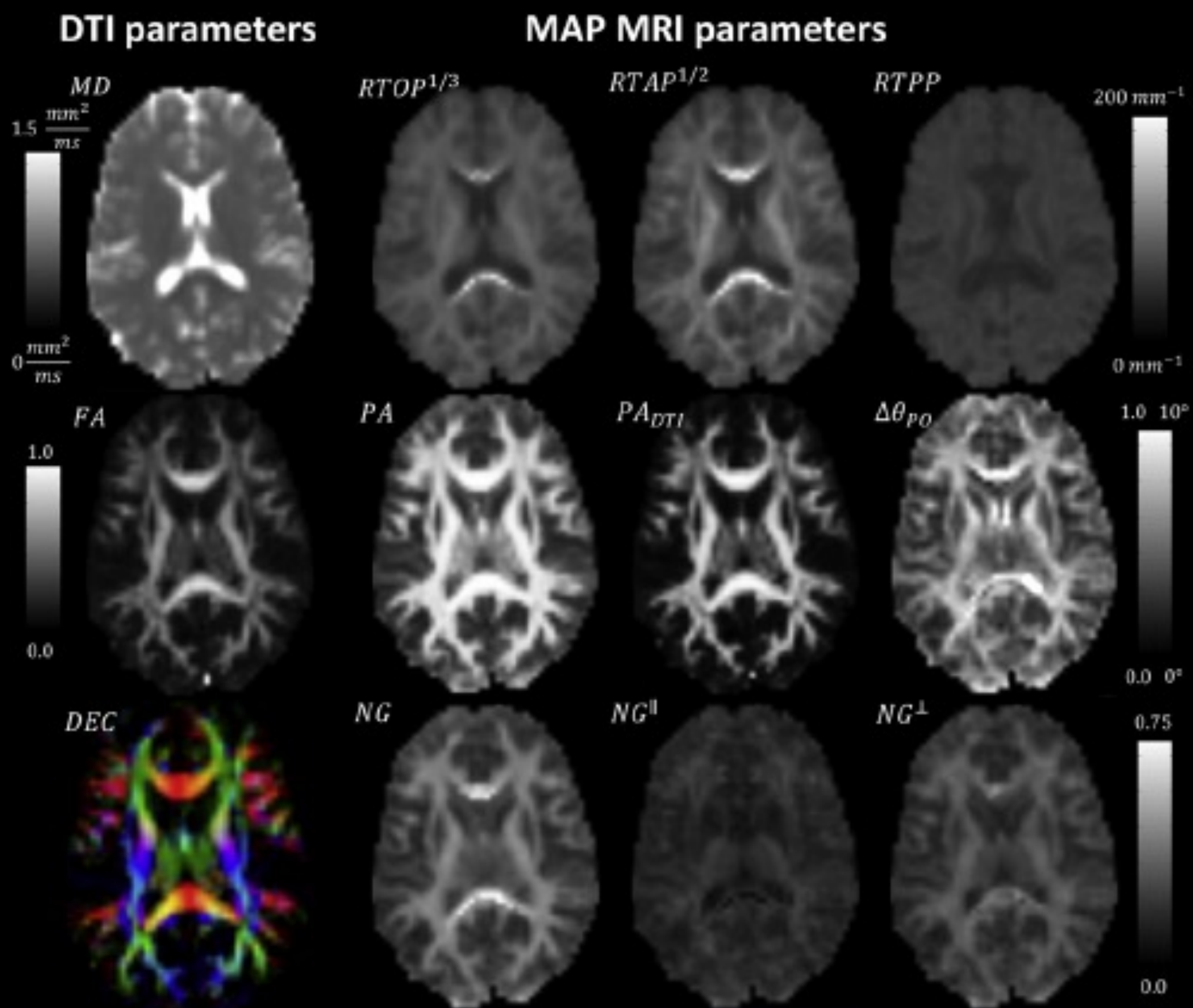
$$\lambda_1$$

RD



$$\frac{\lambda_2+\lambda_3}{2}$$

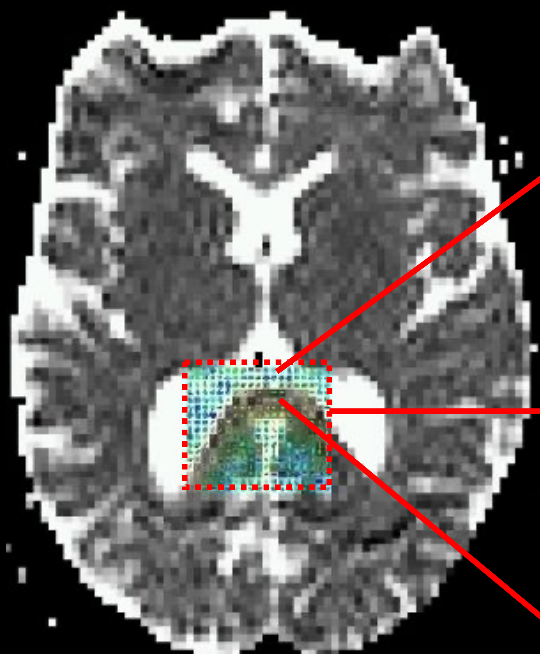
Maps from the Diffusion Propagator



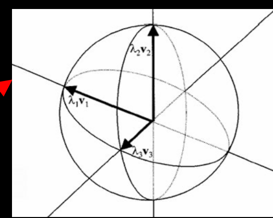
- A host of new diffusivity measures (See Avram 2016)
- Offers comprehensive characterization of tissue microstructure
- Other measures like diffusion kurtosis (Jensen et al 2005)
- Neurite orientation Dispersion and Density imaging (NODDI) (Zhang et al 2012)
- See Review by Hutchinson et al., J Neuro – Research 2017

Avram et al., NeuroImage 2016

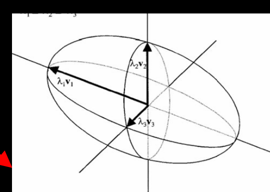
From Diffusion displacement profile to white matter pathways

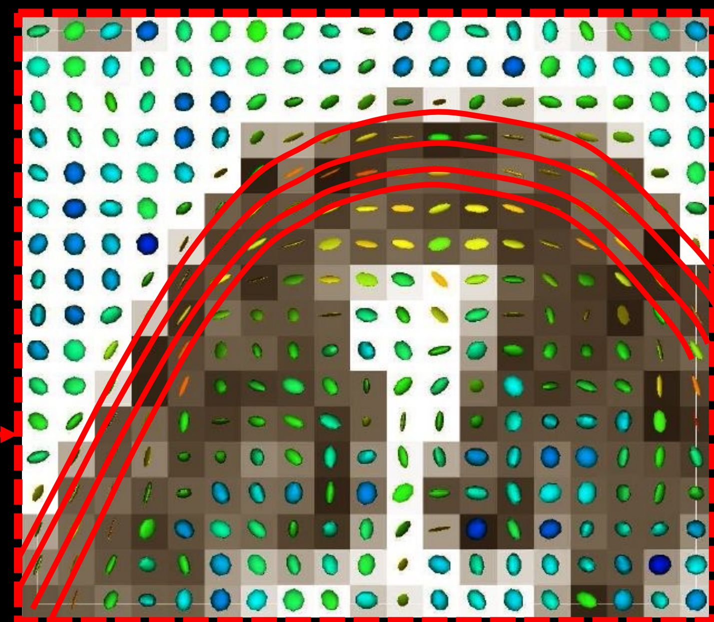


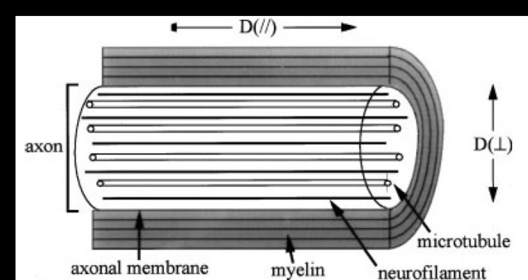
Isotropic



Anisotropic







Tract Volume, Fractional Anisotropy , Mean diffusivity, Radial Diffusivity,

Berenschot 2004

Catani et al., 2005

Diffusion MRI- A powerful tool for Brain Research

Longitudinal Development of Human Brain Wiring Continues from Childhood into Adulthood

Catherine Lebel and Christian Beaulieu

Brain Development

Longitudinal Changes in the Corpus Callosum following Pediatric Traumatic Brain Injury

Trevor C. Wu[a] Elisabeth A. Wilde[d, e] Erin D. Bigler[a–c] Xiaoqi Li[d]
Tricia L. Merkley[a] Ragini Yallampalli[d] Stephen R. McCauley[d, f]
Kathleen P. Schnelle[d] Ana C. Vasquez[d] Zili Chu[g, i] Gerri Hanten[d]
Jill V. Hunter[g, i] Harvey S. Levin[d, h]

TBI

Neuron
Article

Cell PRESS

Learning in the Fast Lane: New Insights into Neuroplasticity

Yaniv Sagi,[1,2] Ido Tavor,[1,2] Shir Hofstetter,[1] Shimrit Tzur-Moryosef,[1] Tamar Blumenfeld-Katzir,[1] and Yaniv Assaf[1,*]

Brain Training

Outline

Scanner related factors that impact MRI measures

Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer

Xiao Han,[a,b] Jorge Jovicich,[a,b] David Salat,[a,b] Andre van der Kouwe,[a,b] Brian Quinn,[a,b] Silvester Czanner,[a,b] Evelina Busa,[a,b] Jenni Pacheco,[a,b] Marilyn Albert,[d,e] Ronald Killiany,[f] Paul Maguire,[g] Diana Rosas,[a,b,c] Nikos Makris,[a,b,h] Anders Dale,[i] Bradford Dickerson,[a,c,d,j,1] and Bruce Fischl[a,b,k,*,1]

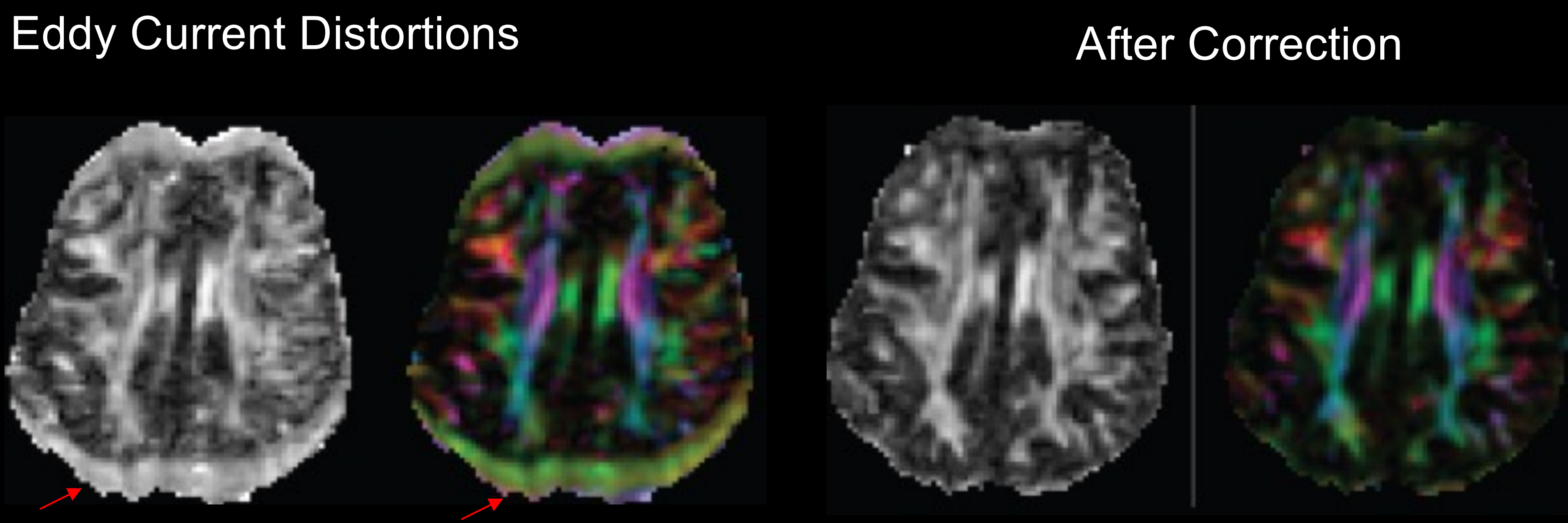
- MRI measures of brain structure can vary with
  - Scanner Type, Field Strength, Scanner OS platform, Coil …
  - Important to keep in mind when using MRI databanks

Sequence specific factors that impact T_1W-measures

- MPRAGE, MEMPRAGE, High field MP2RAGE
- Better SNR without parallel imaging, but risk of motion
- Impacts measures like cortical thickness etc (Wonderlick et al., Neuroimage 2009)
- Solution: Consider Subject demographics or 2 sets of accelerated T_1W images

Image from Jason Crutcher

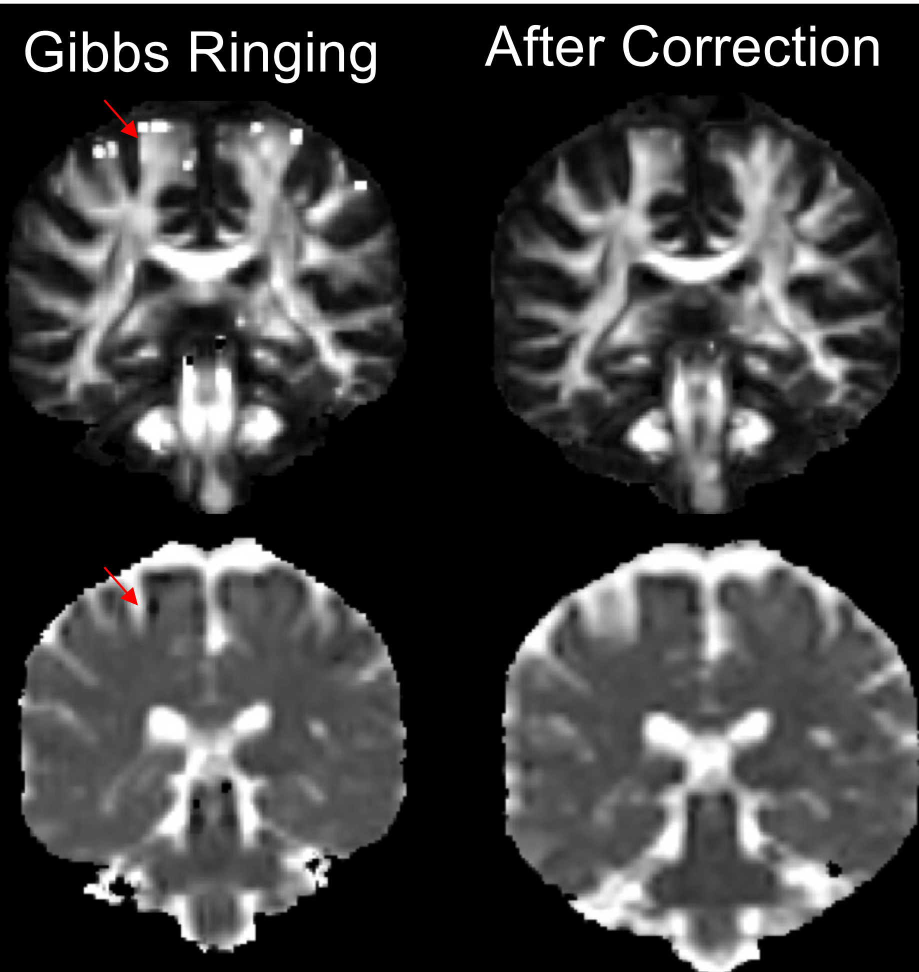
Sequence specific factors that impact DTI measures



- Caused by rapidly switching gradients
- Distorts images, alters actual diffusion sensitization
- Solution: Correctable in TORTOISE & latest version of FSL

From Carlo Pierpaoli 2011

Sequence specific factors that impact DTI measures

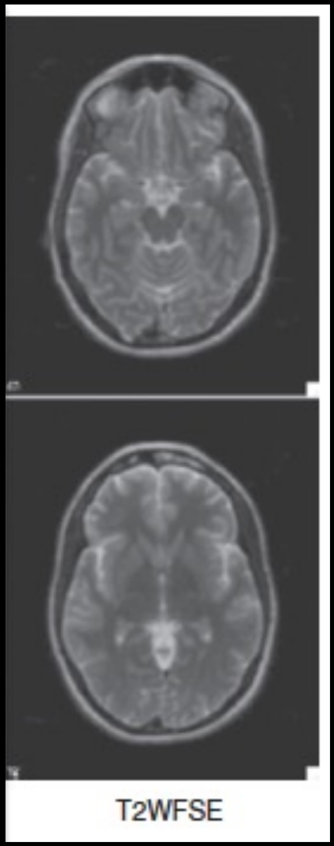


- Caused by sharp image transitions
- Distorts diffusivity measures
- Solution: Correctable if you use TORTOISE

Image from Amrita Nayak

Sequence specific factors that impact DTI measures

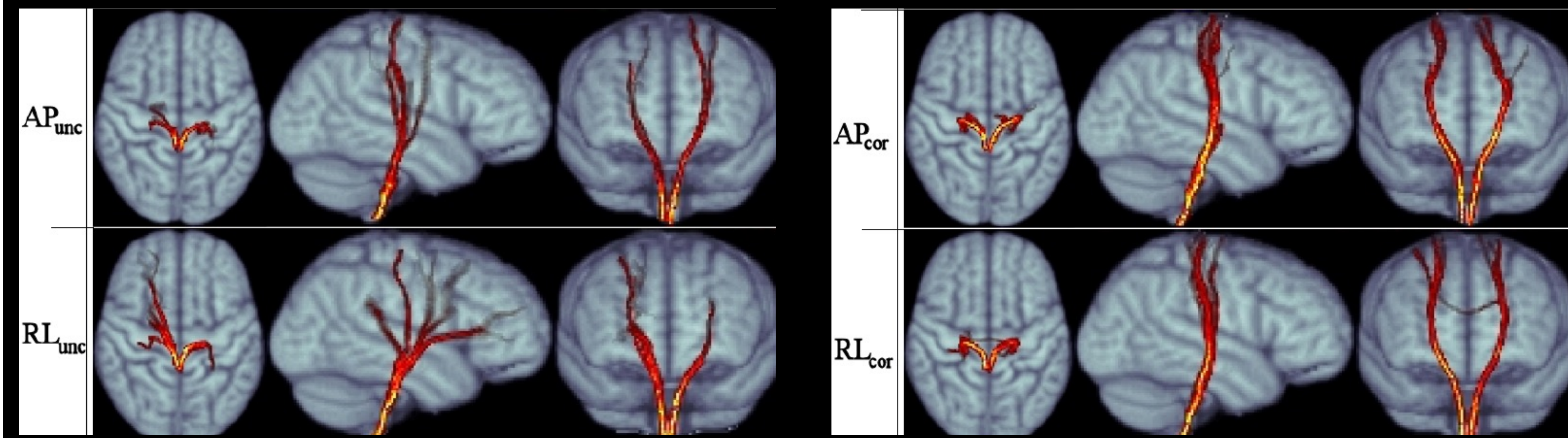
EPI Distortions



- Caused by B_0 field inhomogeneities (Jezzard and Balaban, 1995)
- Distorts images in phase encode direction in some brain regions
- Messes up tractography but not DTI measures, correctable

From Carlo Pierpaoli 2011

Sequence specific factors that impact DTI measures

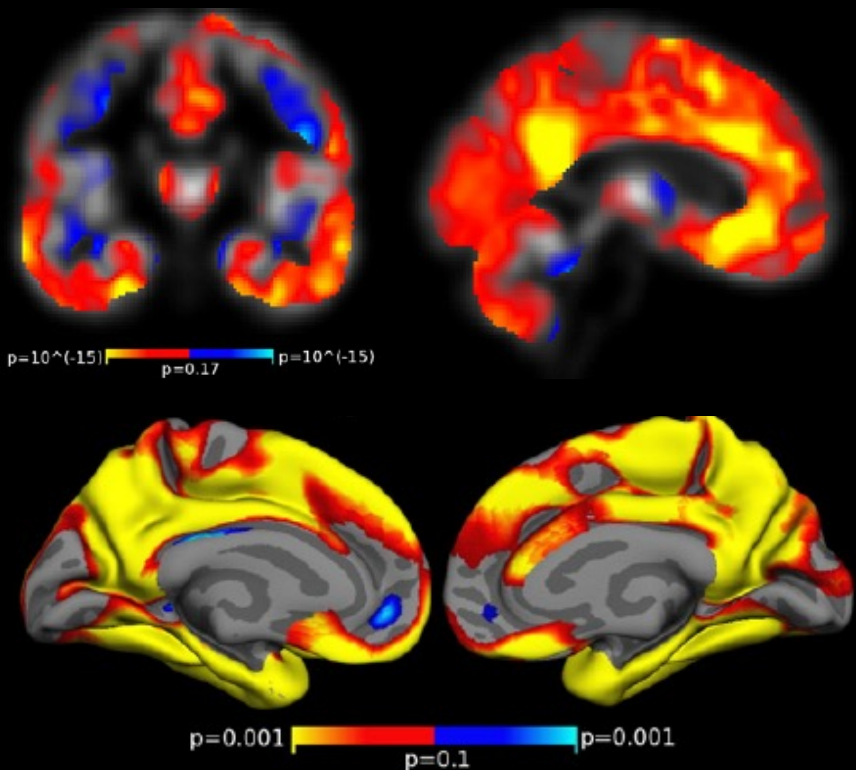


Irfanoglu et al, 2012

- Trajectory of the Corticospinal tracts heavily distorted without correction
- Solution: Acquire Blip up/Down, use TORTOISE

Subject factors that impact measures of T_1W Morphometry

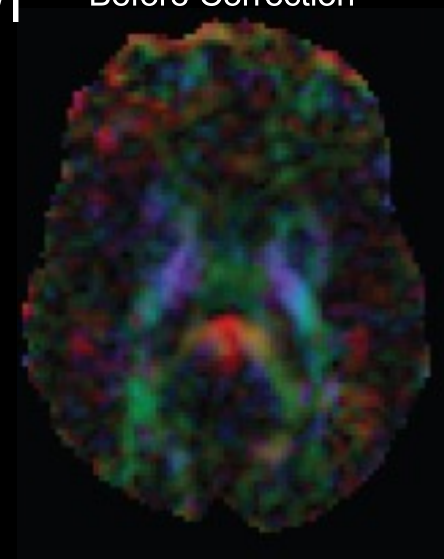
Subject head motion (T1W)



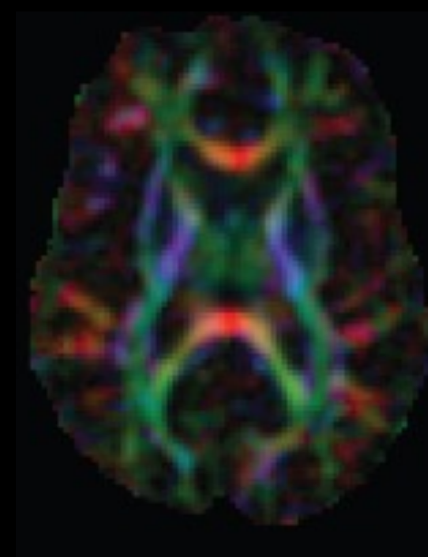
- Head motion impacts GMV and CT estimates
- 2mm/min motion -> ~1.4 – 2 % GMV loss
- Solution: Use PROMO, better padding etc

DWI

Before Correction



After Correction using TORTOISE



Reuter et al., NeuroImage 2015

From Carlo Pierpaoli, 2011

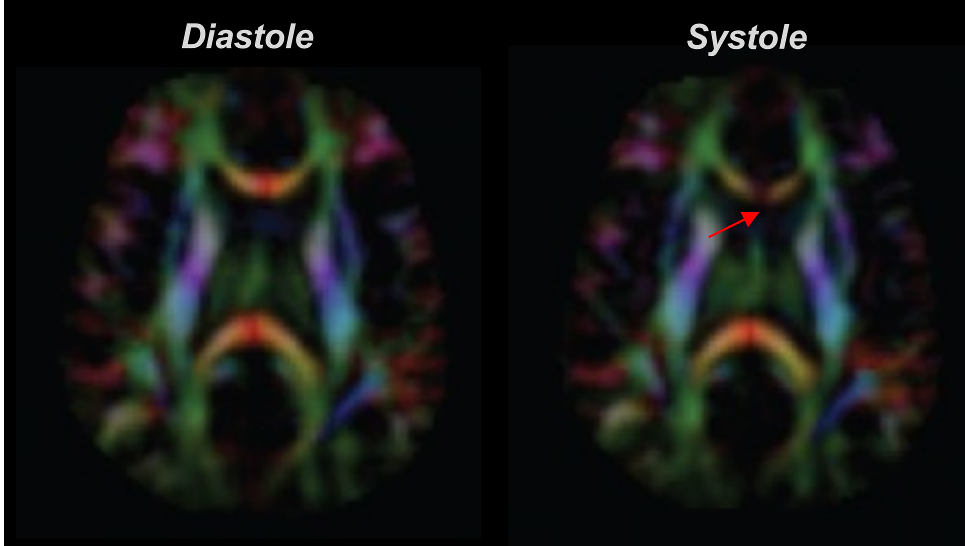
Subject factors that impact measures of T_1W Morphometry

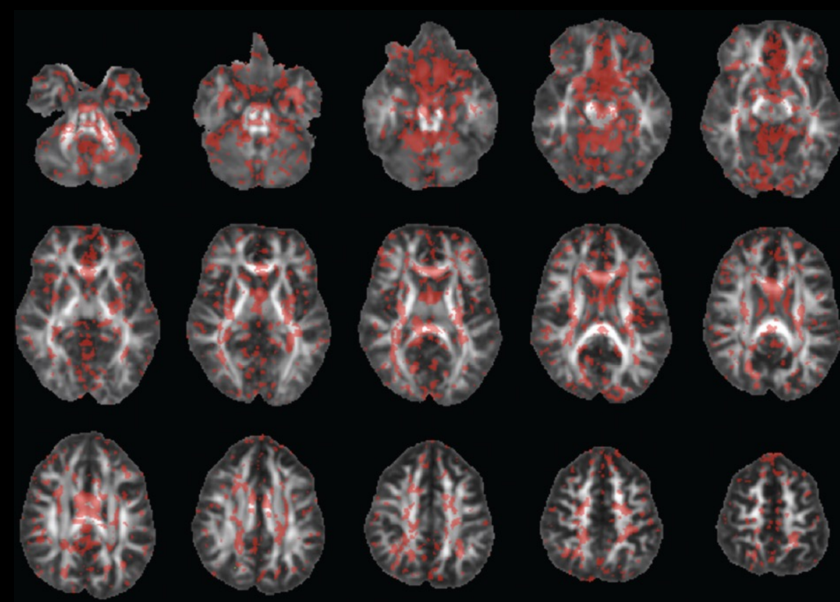
Blood Pressure on T_1W imaging

Schaare et al., HBM 2017

- GMD/GMV /CT estimates may be spurious in specific brain regions

Cardiac Pulsation on DWI





- Solution: identify outlier voxels and remove using TORTOISE

From Carlo Pierpaoli, 2011

Data processing factors that impact MRI measures

OPEN ACCESS Freely available online

PLoS one

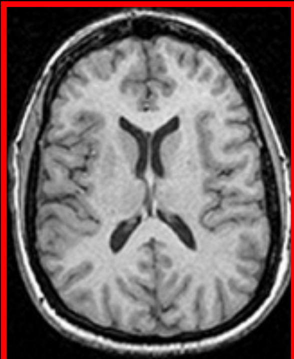
The Effects of FreeSurfer Version, Workstation Type, and Macintosh Operating System Version on Anatomical Volume and Cortical Thickness Measurements

Ed H. B. M. Gronenschild[1,2*], Petra Habets[1,2], Heidi I. L. Jacobs[1,2,3], Ron Mengelers[1,2], Nico Rozendaal[1,2], Jim van Os[1,2,4], Machteld Marcelis[1,2]

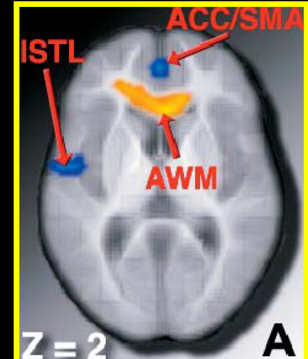
- MRI measures of brain structure can vary with Computer OS, Software Version
- Solution: Pick a stable version and stick to it

Data processing factors that impact MRI measures

From Raw data to statistical maps data undergoes several transformations



Raw Data



Result

From Nicola Hobbs & Marianne Novak

Several biases can be introduced

ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 26 (2005) 546–554

The effect of filter size on VBM analyses of DT-MRI data

Derek K. Jones,[a,b,*] Mark R. Symms,[c] Mara Cercignani,[d] and Robert J. Howard[e]

Results and inferences differ with smoothing levels

Same data – different software – different results

Subject trained in a visuo-motor task

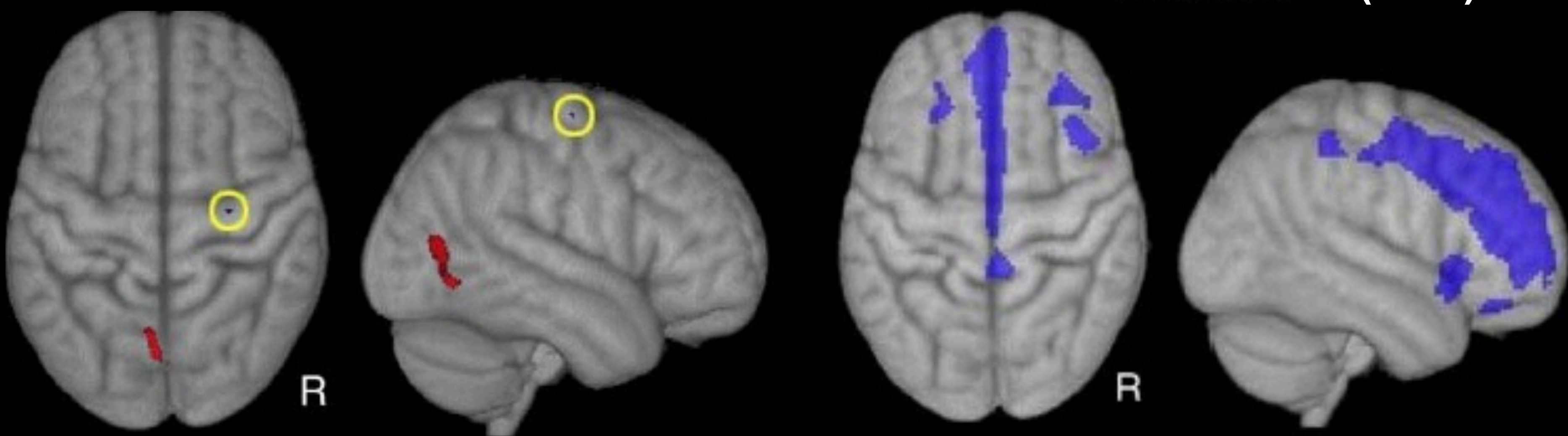
Behavioral evidence for training effect

fMRI evidence for training effect

Structural changes following training?

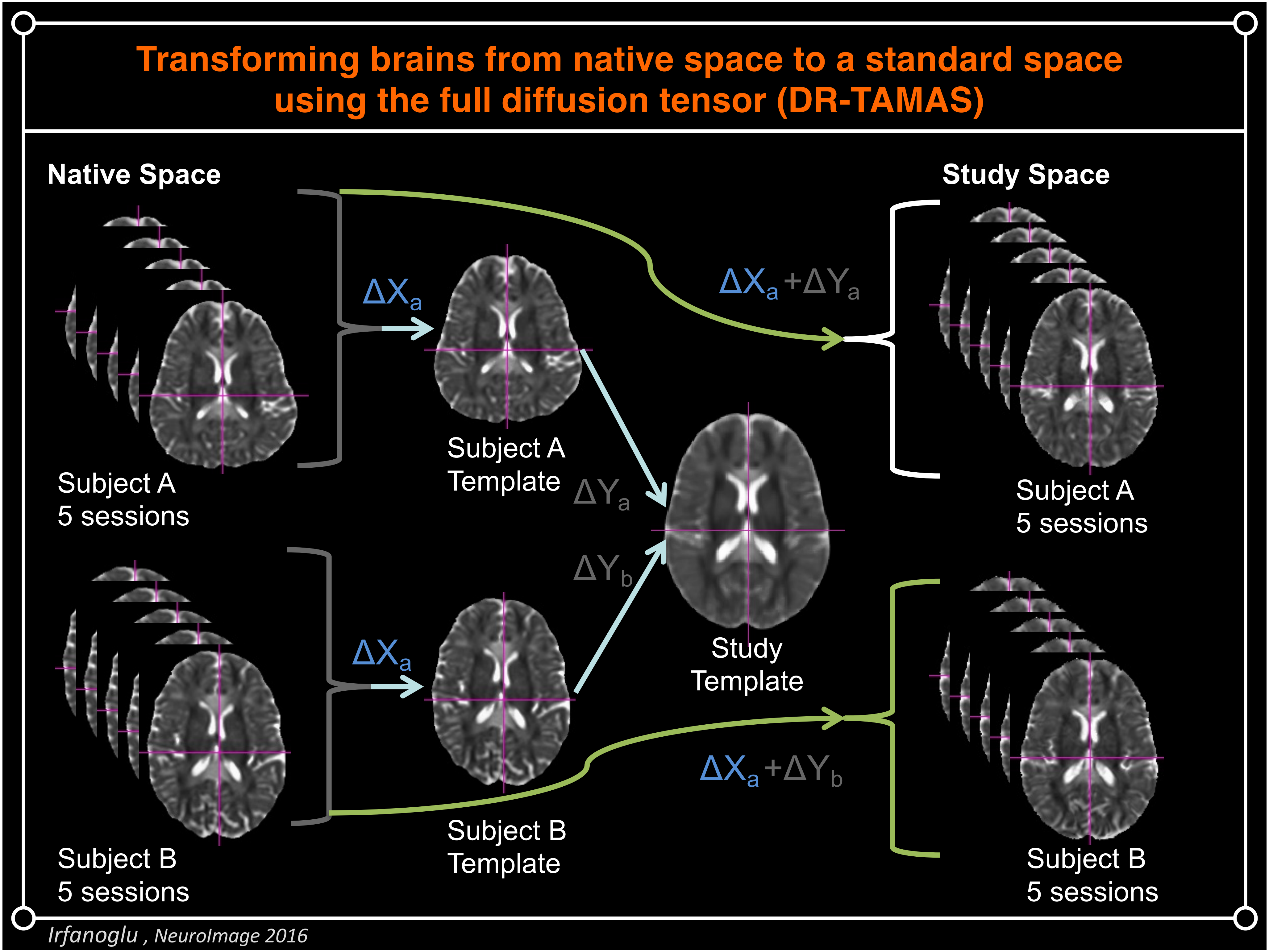
Method A (SPM2)

Method B (FSL)



- Solution: Be aware of these issues, test reproducibility with different packages
- Talk to your local statistics guru

Adam Thomas et al., Neuroimage, 2009


Transforming brains from native space to a standard space
using the full diffusion tensor (DR-TAMAS)
Native Space
Study Space
ΔXa
ΔXa +ΔYa
Subject A
5 sessions
Subject A
Template
ΔYa
ΔYb
Study
Template
Subject A
5 sessions
ΔXa
Subject B
Template
ΔXa +ΔYb
Subject B
5 sessions
Subject B
5 sessions
Irfanoglu , NeuroImage 2016

Some Practical recommendations

- Pick a stable scanner – Stick to it
- Pick a robust MRI sequence
  - Talk to an MRI physicist about the study goals
  - Better data comes at a cost
- Pick a stable pipeline for data processing – Stick to it
  - Freesurfer for surface based analysis
  - FSL/SPM – VBM pipeline
  - TORTOISE - Diffusion MRI processing (Corrects for Eddy, Gibbs ringing, motion, EPI)
- QC images as you collect them at the scanner, QC after!
- Be consistent with your instructions to the subject

Some reading recommendations

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Full Length Articles

Advanced MRI techniques to improve our understanding of experience-induced neuroplasticity

Christine Lucas Tardif [a,*,1], Claudine Joëlle Gauthier [a,b,**,1], Christopher John Steele [a], Pierre-Louis Bazin [a], Andreas Schäfer [c], Alexander Schaefer [d], Robert Turner [c], Arno Villringer [a]

REVIEW

FOCUS ON HUMAN BRAIN MAPPING

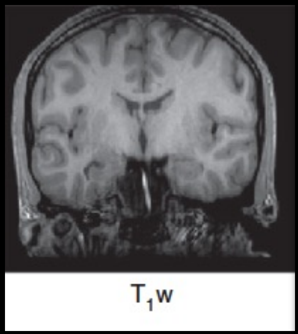
nature neuroscience

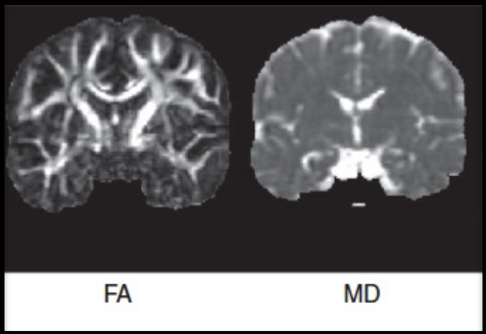
Studying neuroanatomy using MRI

Jason P Lerch[1,2], André J W van der Kouwe[3,4], Armin Raznahan[5], Tomáš Paus[6–8], Heidi Johansen-Berg[9], Karla L Miller[9], Stephen M Smith[9], Bruce Fischl[3,4,10] & Stamatios N Sotiropoulos[9,11]

Outline

• Review popular MRI methods used for measuring brain changes

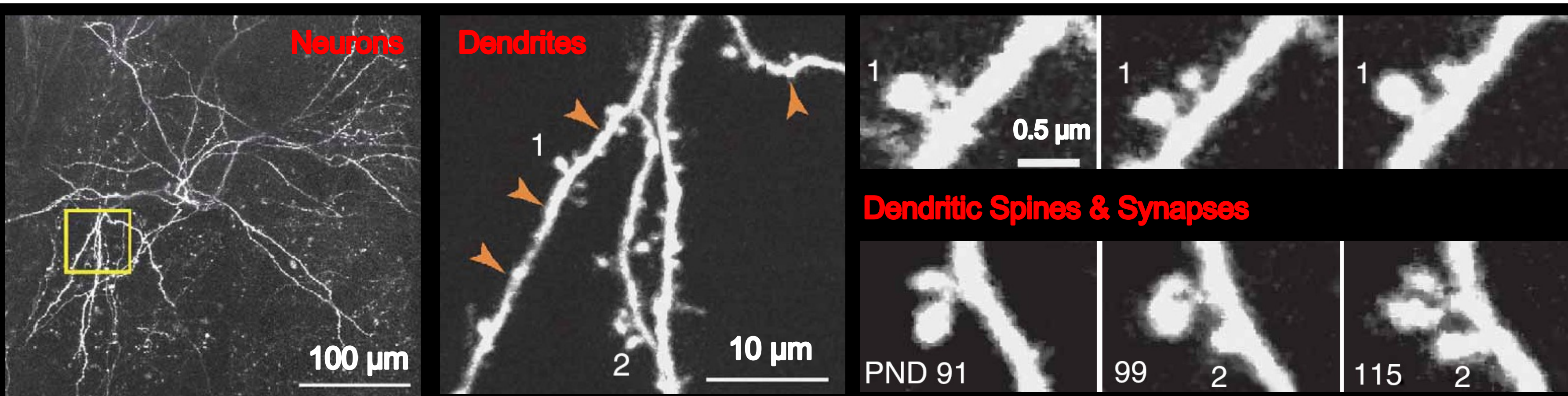




• The most important tool for imaging brain changes

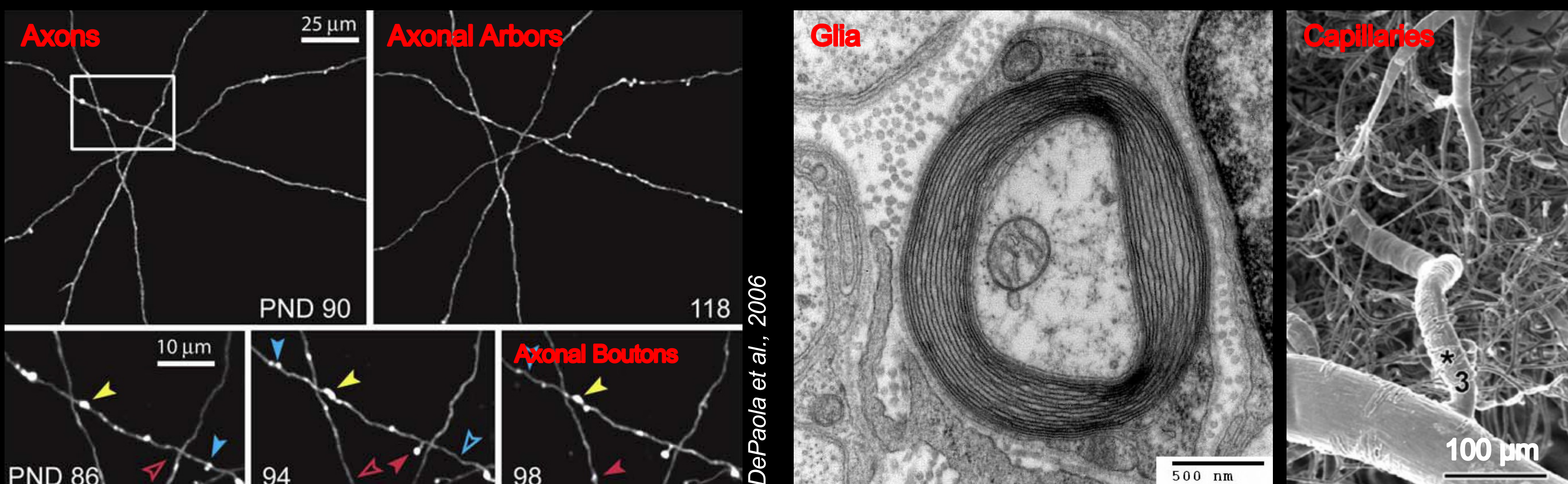
• Good Experiment Design

Some candidate brain structures that are likely to change



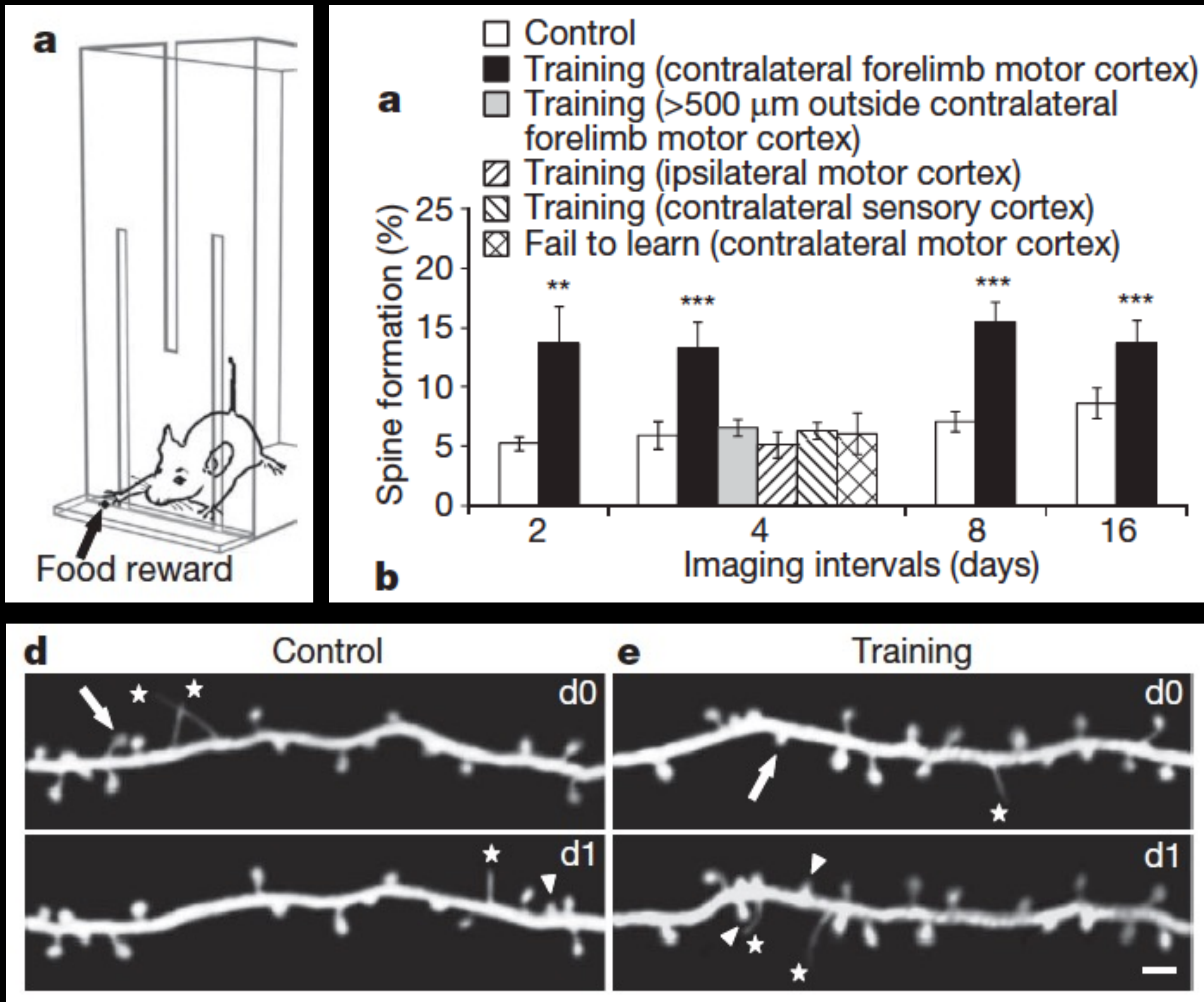
Knott et al., 2006

Challenge: Is MRI robust enough to detect subtle structural changes given what we know of its limitations?



DePaola et al., 2006

Lessons from animal models



- Motor learning in the adult brain is mediated by changes in dendritic spines
- Specificity to the trained group, task and brain region
- Human MRI – lower spatial resolution poor biological specificity
- Is there an experiment specific change?
- Where in the brain are the changes?
- “What” is changing is difficult

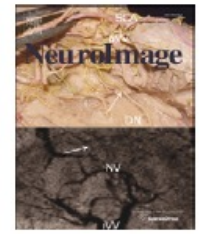
Xu et al ., 2009

A framework for assessing the robustness of training-dependent structural changes

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Review

Teaching an adult brain new tricks: A critical review of evidence for training-dependent structural plasticity in humans ☆

Cibu Thomas*, Chris I. Baker

Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA
Center for Neuroscience and Regenerative Medicine at the Uniformed Services University of the Health Sciences, Bethesda, MD, USA

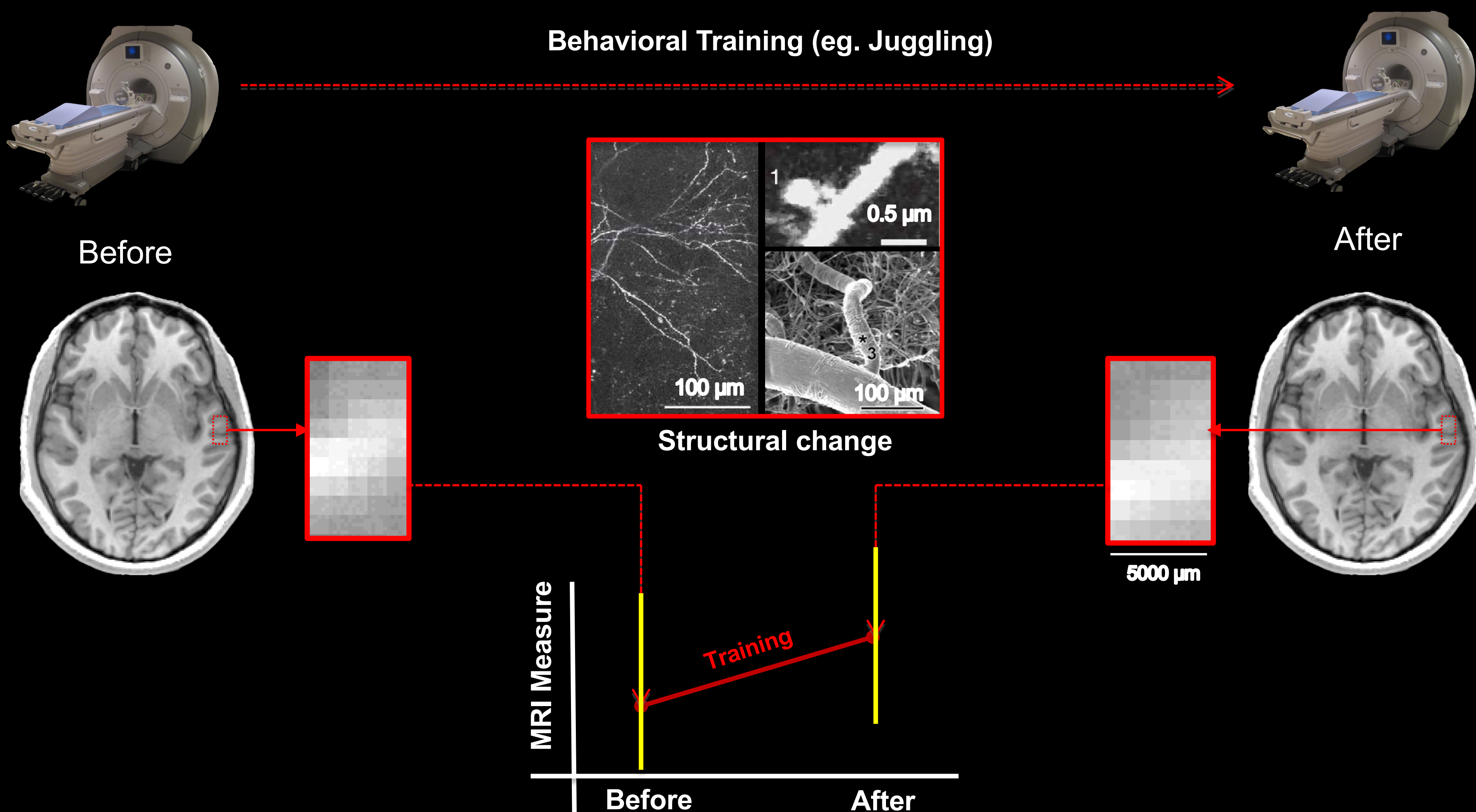
1. How specific are the changes?

   a. Training group

   b. Task

   c. Brain region

Longitudinal Design - to demonstrate causality

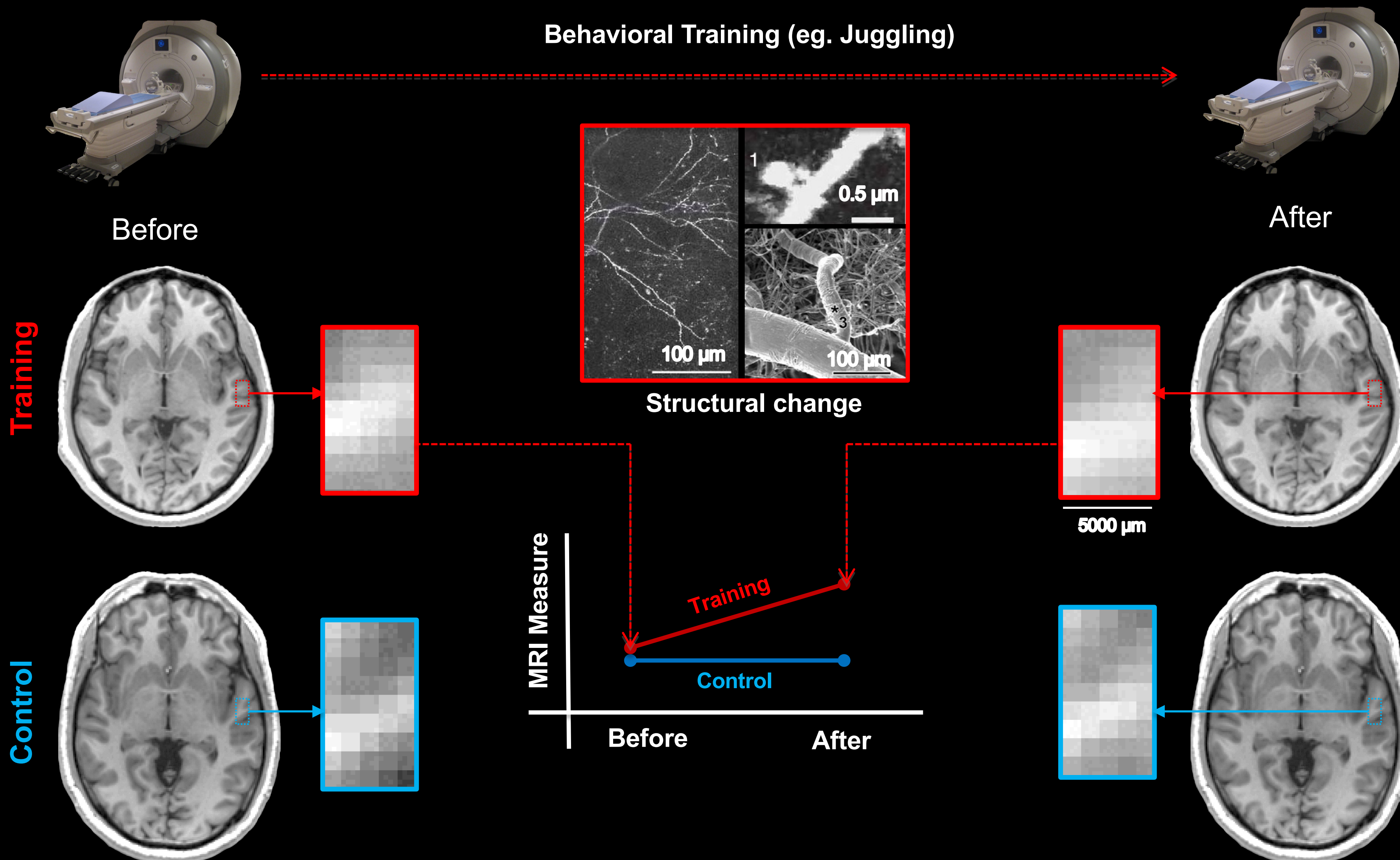


Training induced change in gray matter concentration/volume?

Difference could be due to measurement error or some other confound

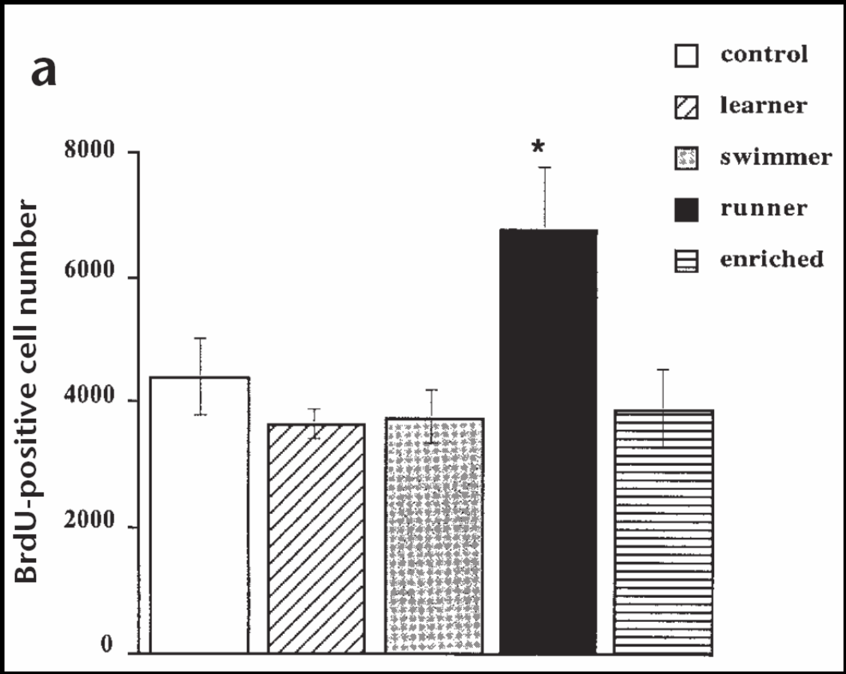
Need to show specificity to group.

Demonstrate specificity to the training group



Test for a Group X Timepoint interaction

Demonstrate specificity to the training task



Van Praag et al 1999

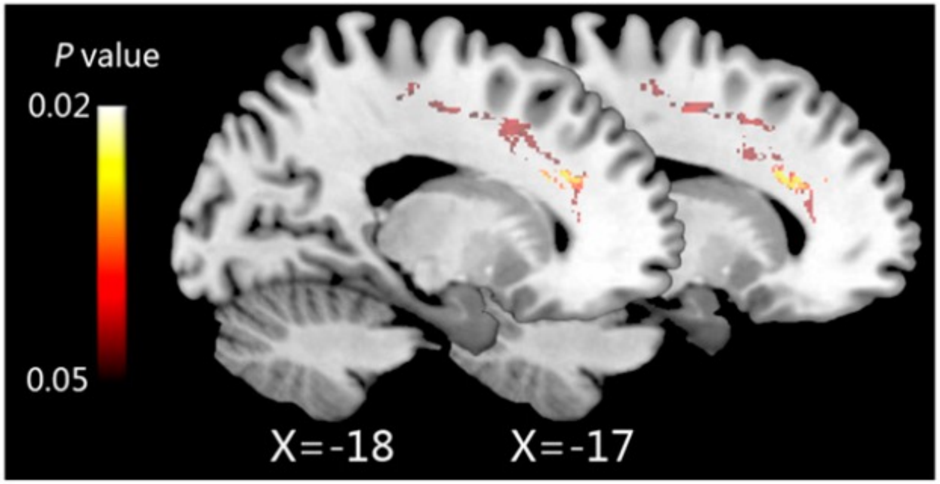


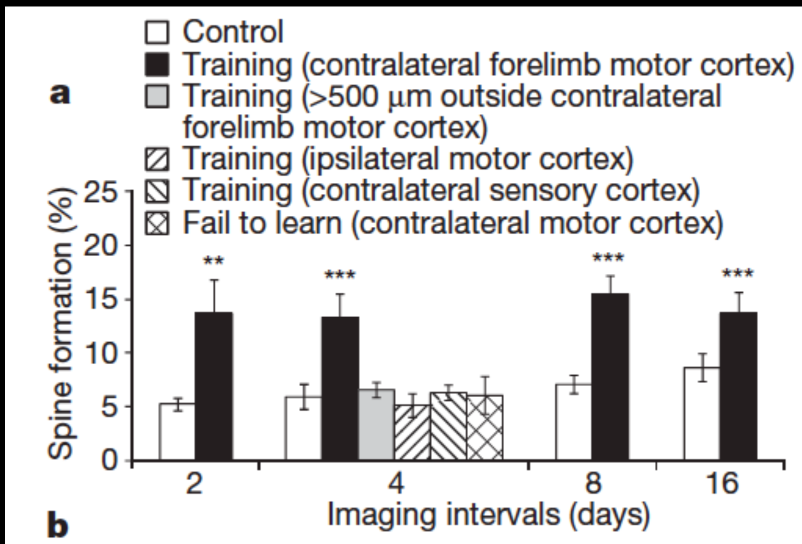
Fig. 1. Eleven hours of IBMT increases fiber integrity in the left anterior corona radiata (after versus before training, two sagittal sections, *x* = −17 and −18).

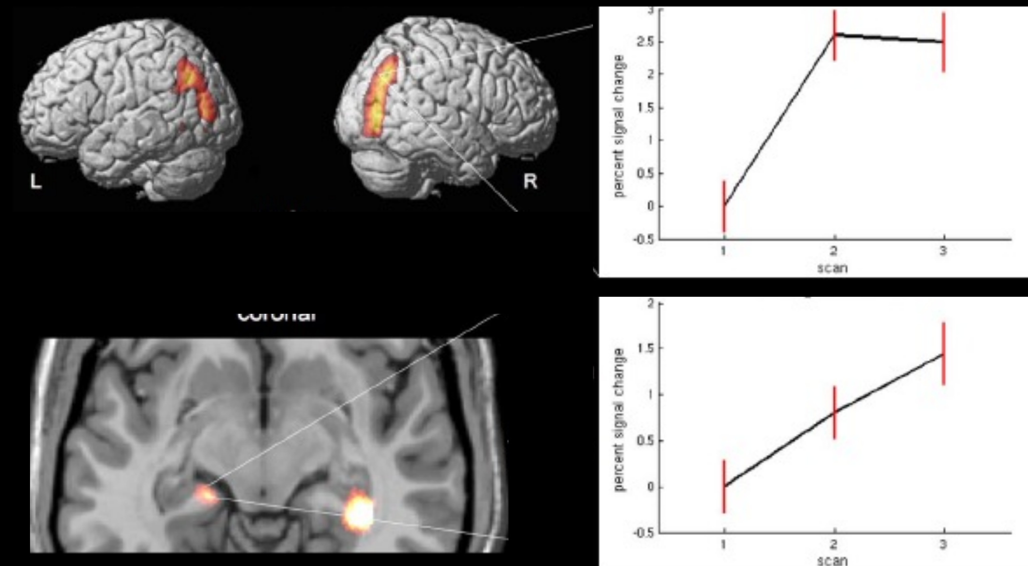
Tang et al 2010

Increase in neurogenesis specific to running

- Two groups should be equated in terms of overall experience
- Control group more anxious, more head motion?
- Other confounds: difference in BP, respiration etc…

Directly test if effect of training is specific to a brain region





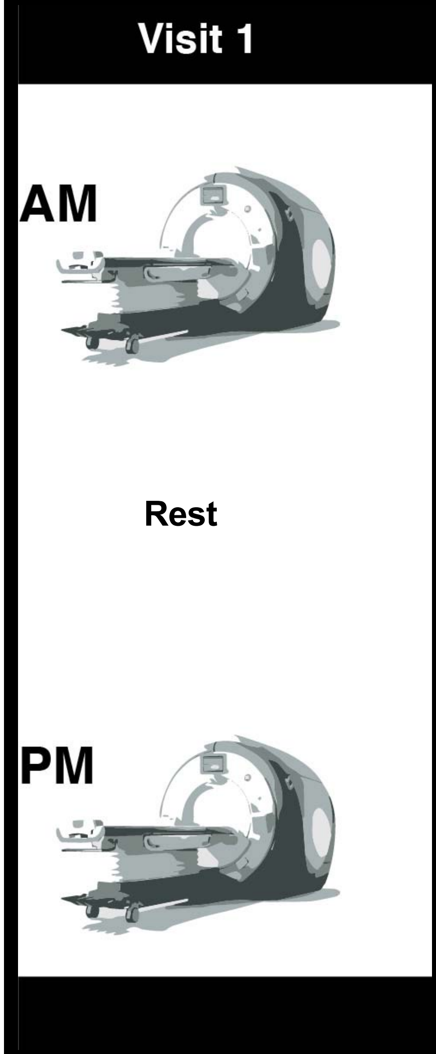
Draganski et al., J of Neuroscience, 2006

Training effects specific to brain region.

- Maps only show change relative to baseline
- Claim: Profile of structural change different across brain regions
- Test using Group x time x region interaction

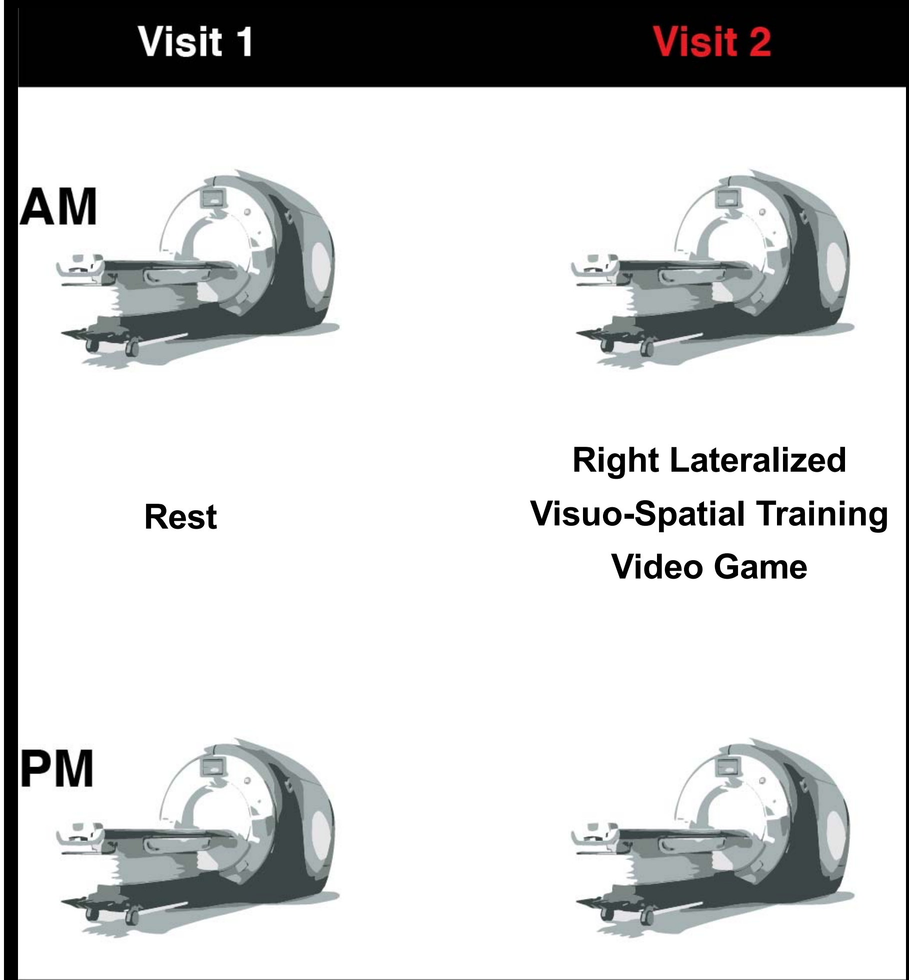
How does learning vs mastering a motor skill change the human brain?

N = 20, 11 F, Age Range: 20-38



Thomas et al., In preparation

How does learning vs mastering a motor skill change the human brain?



Thomas et al., In preparation

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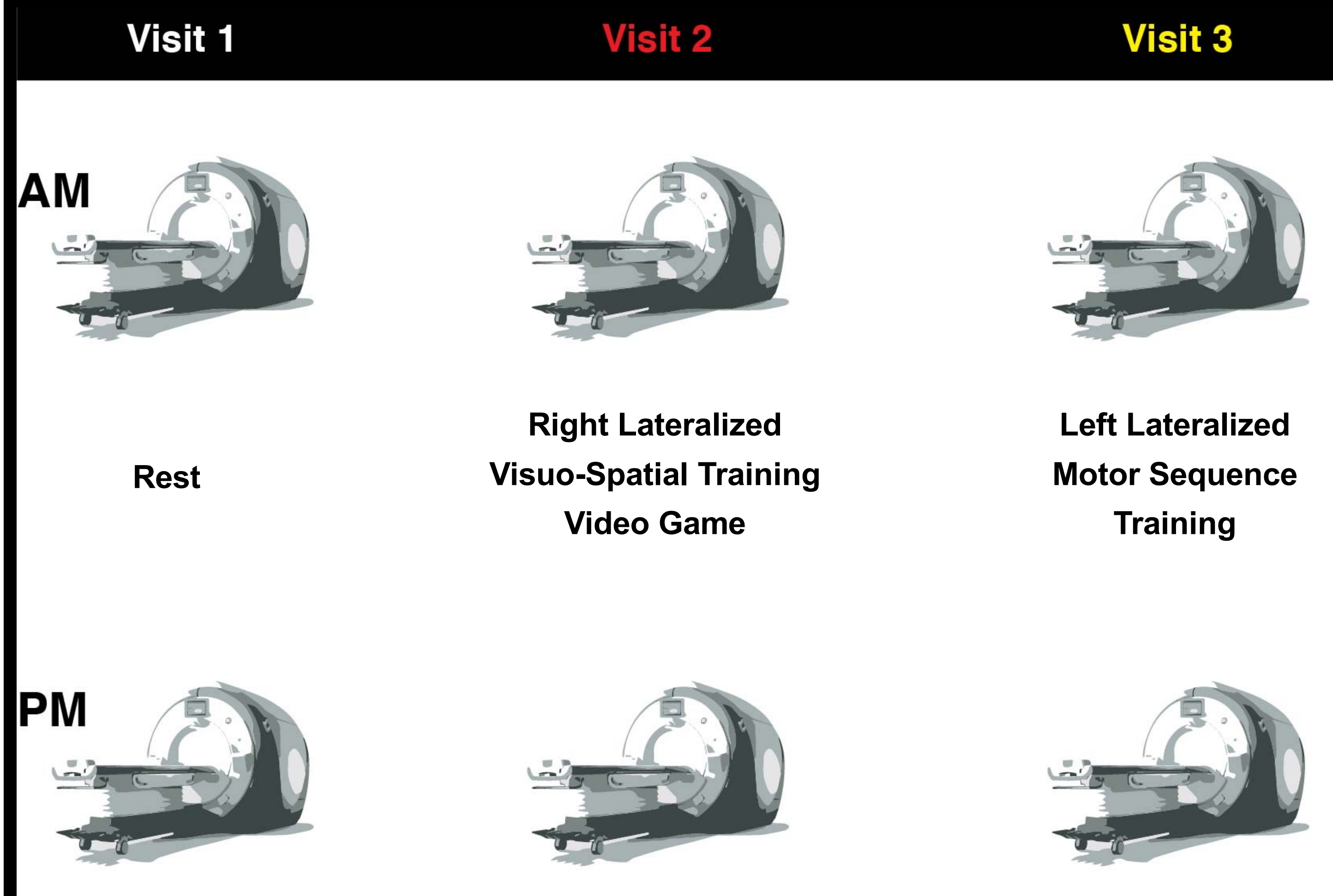
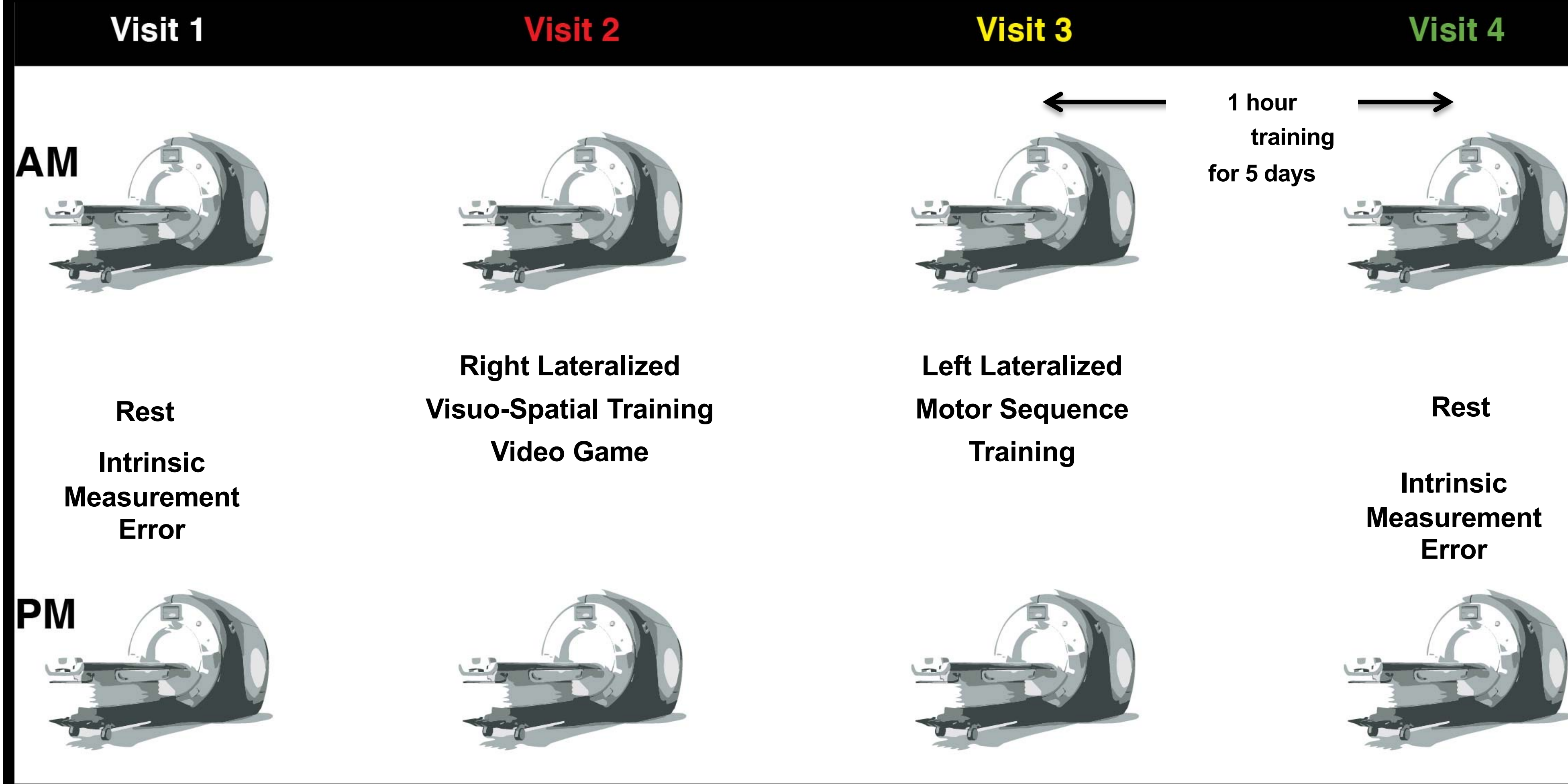


Thomas et al., In preparation

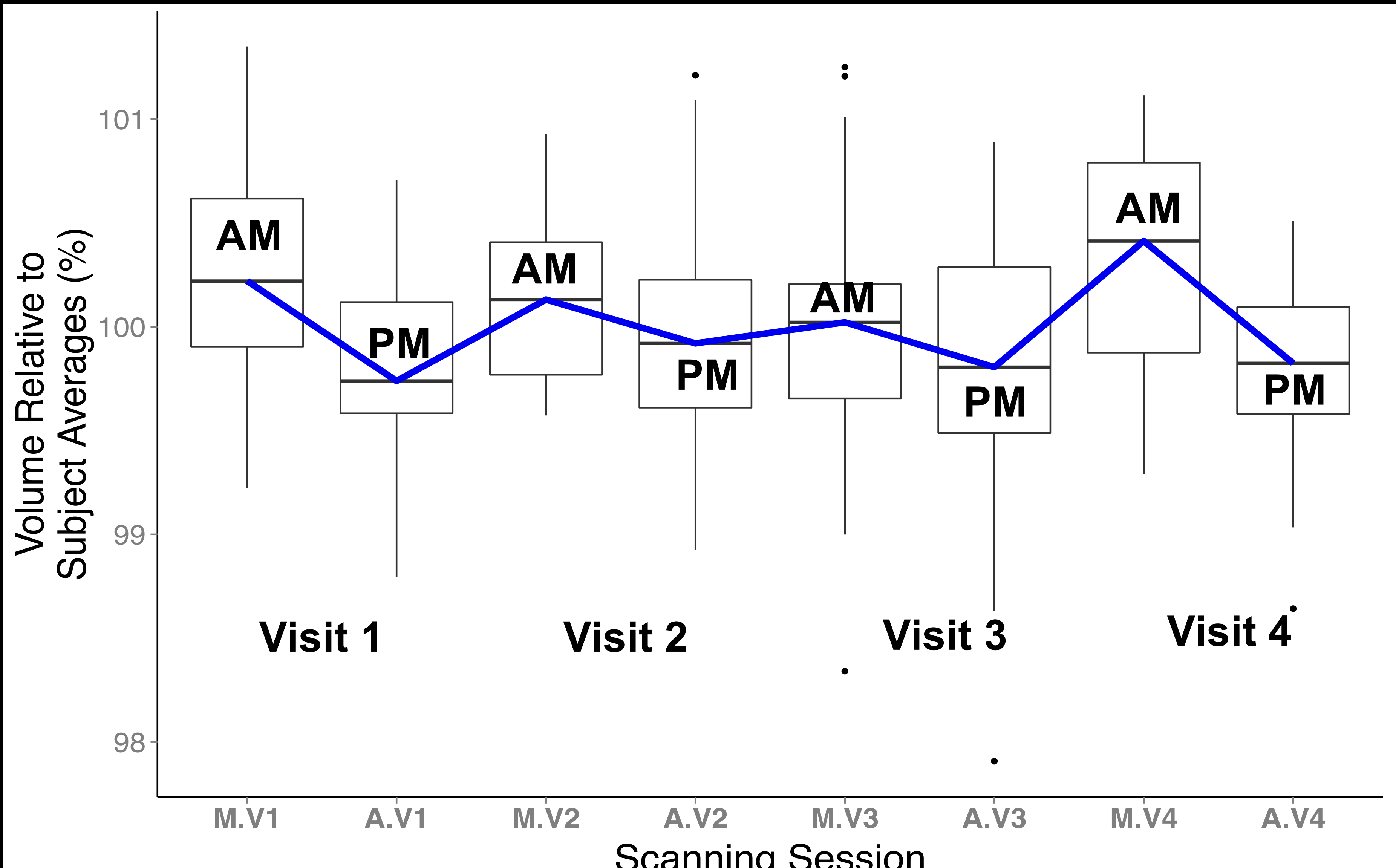
How does learning vs mastering a motor skill change the human brain?



Multimodal MRI: T1W images, advanced DWI, Resting State fMRI (Two Datasets each)

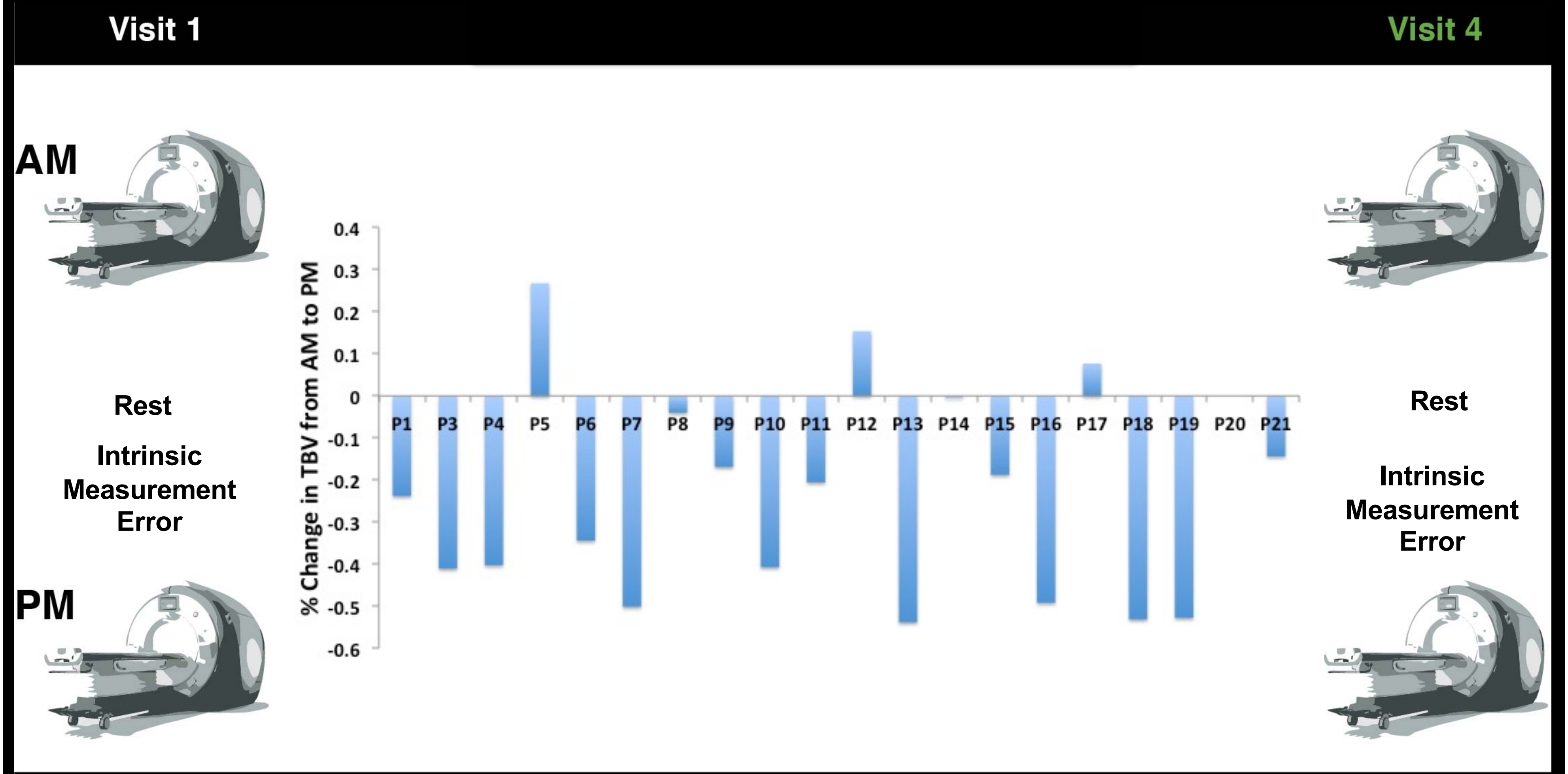
Thomas et al., In preparation

Significant changes in total brain volume from AM to PM



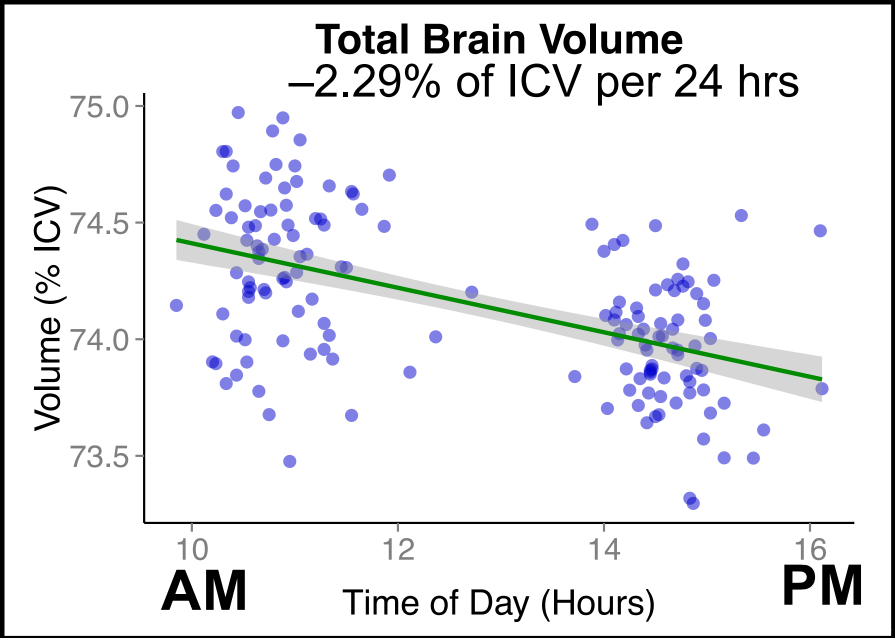
Trefler, et al., NeuroImage, 2016

16/19 participants shows a reduction in total brain parenchymal volume



Trefler, et al., NeuroImage, 2016

TOD impacts the apparent volume of GM, WM, and CSF

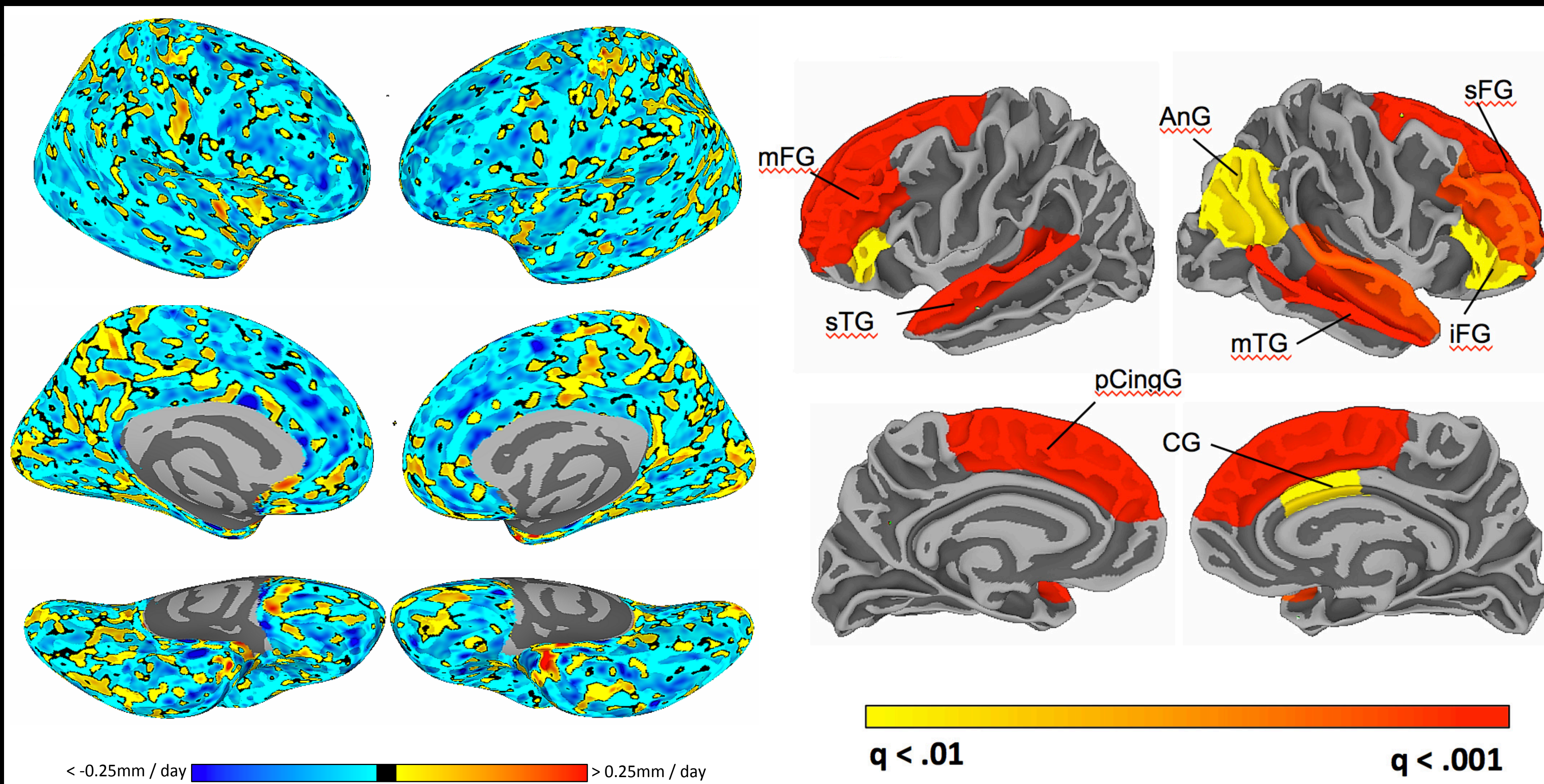


Trefler, et al., NeuroImage, 2016

TOD impacts surface based morphometric measures: cortical thickness, and surface area

Change in magnitude of cortical thickness

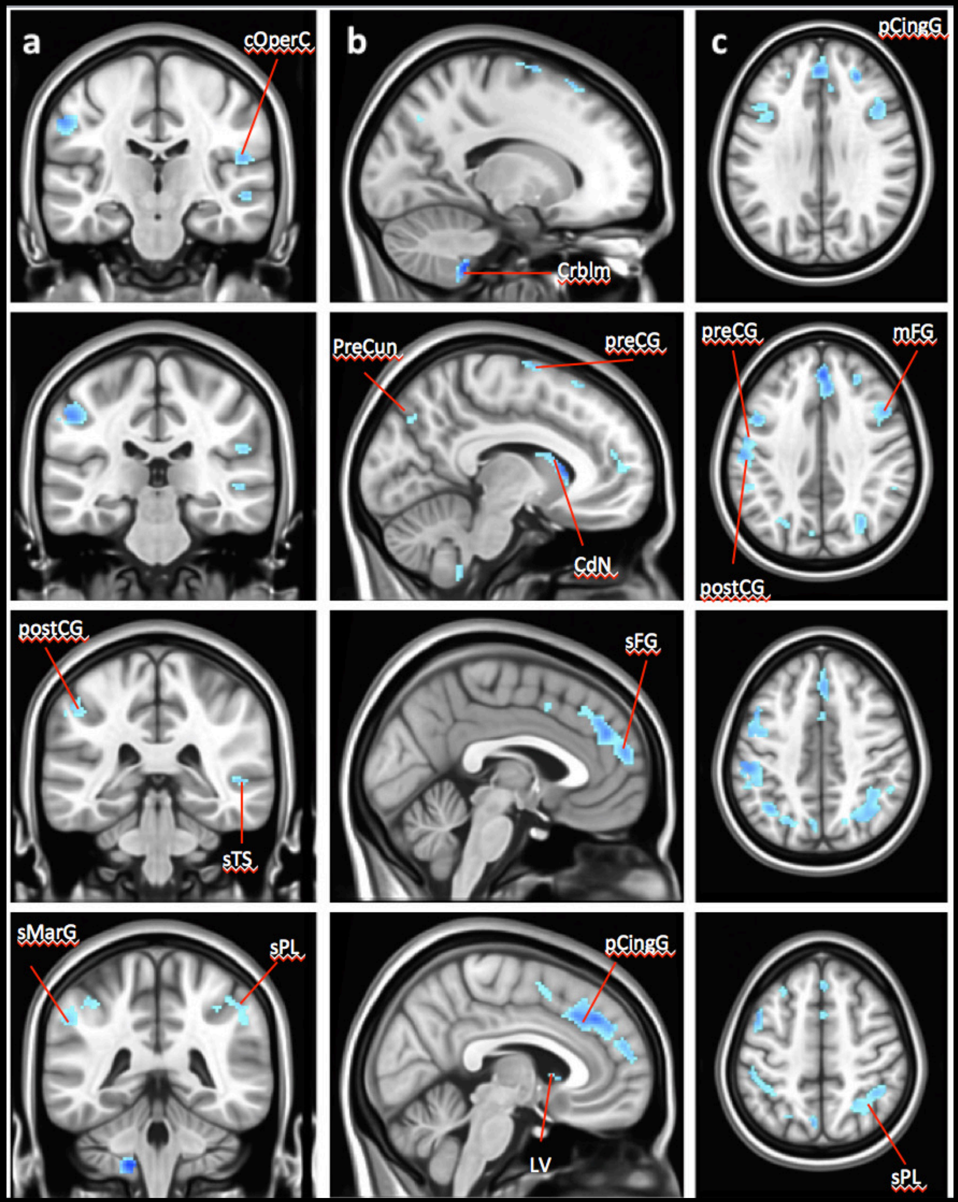
Statistically significant differences



No significant impact on apparent gyrification index, sulcal depth

Trefler, et al., NeuroImage, 2016

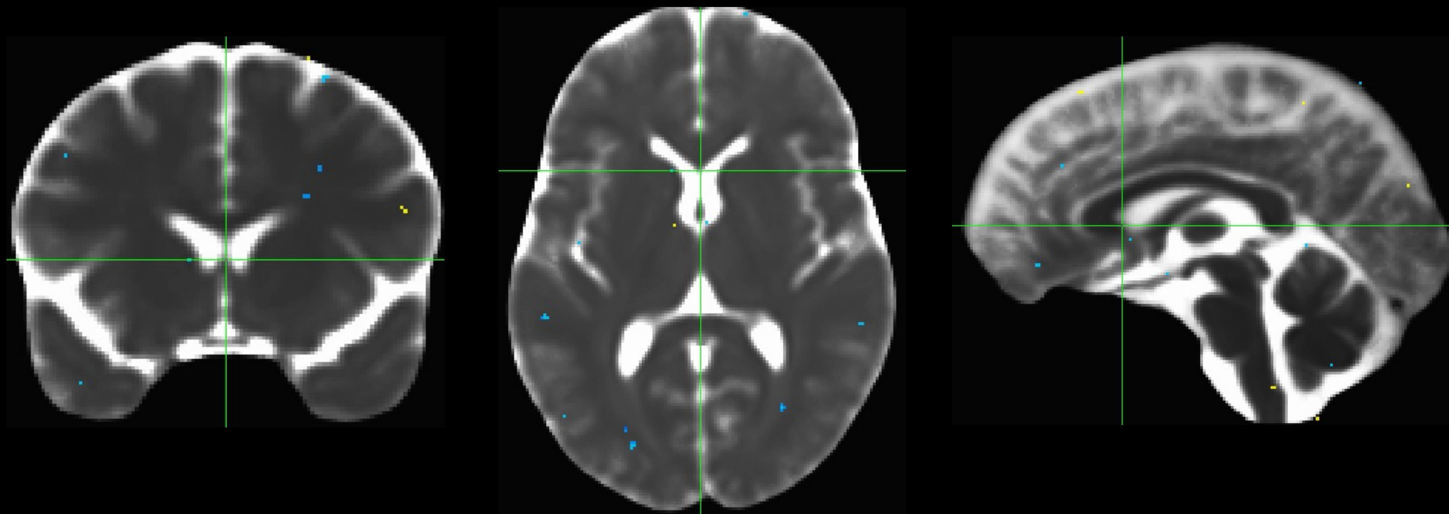
TOD impact Volume based morphometric measures of apparent gray matter density



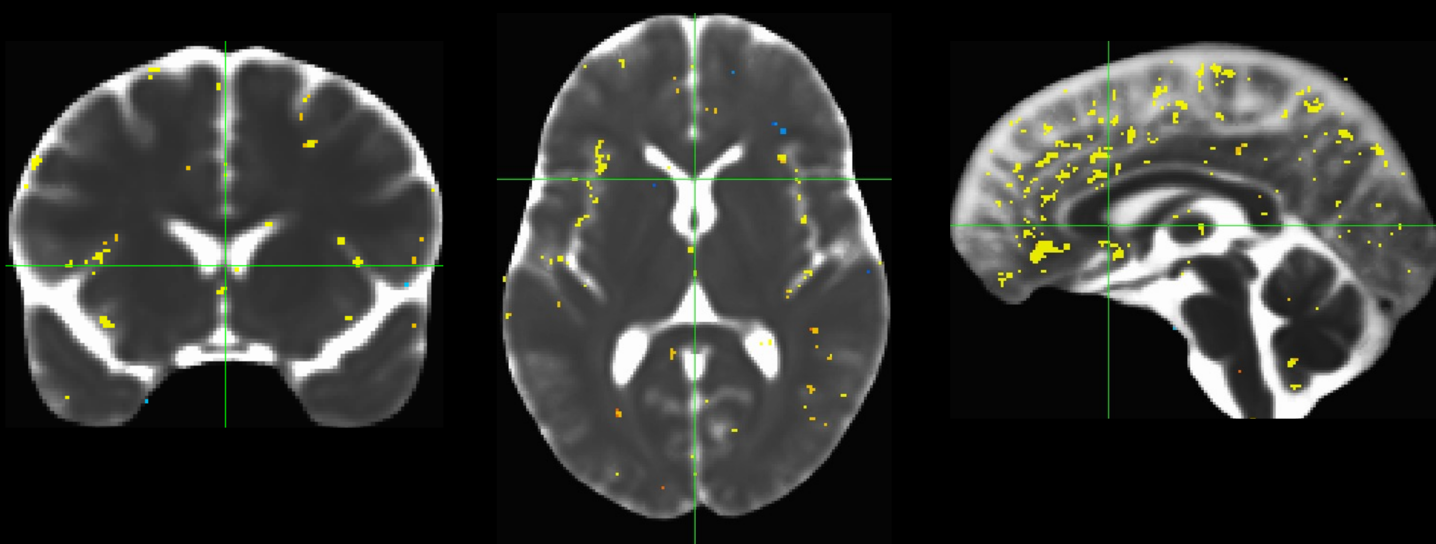
Trefler, et al., NeuroImage, 2016

TOD impacts DTI measures of brain structure

Visit 4 AM – Visit 1 AM (3 weeks apart)

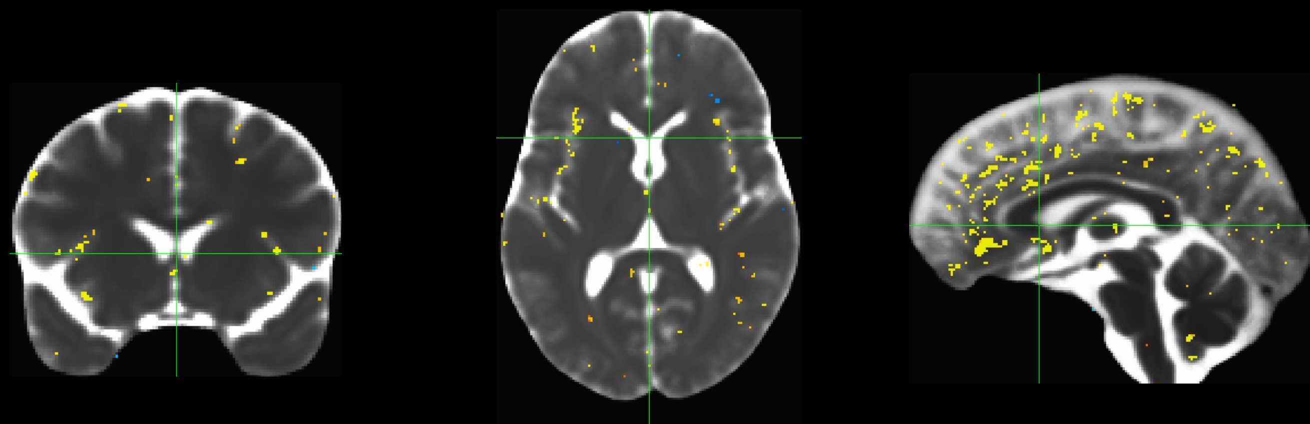


Visits 4 & 1 PM – AM (3 hours apart)

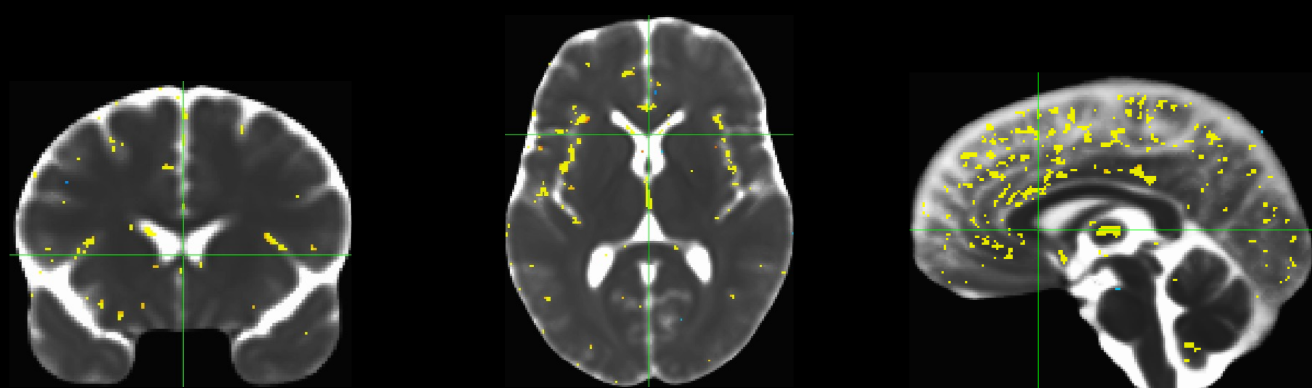


TOD impact on DTI measures of brain structure is reproducible

Trace - Visits 4 & 1 : PM – AM (Blip-Up Dataset)



Trace - Visits 4 & 1 : PM – AM (Blip-Down Dataset)



Study Summary

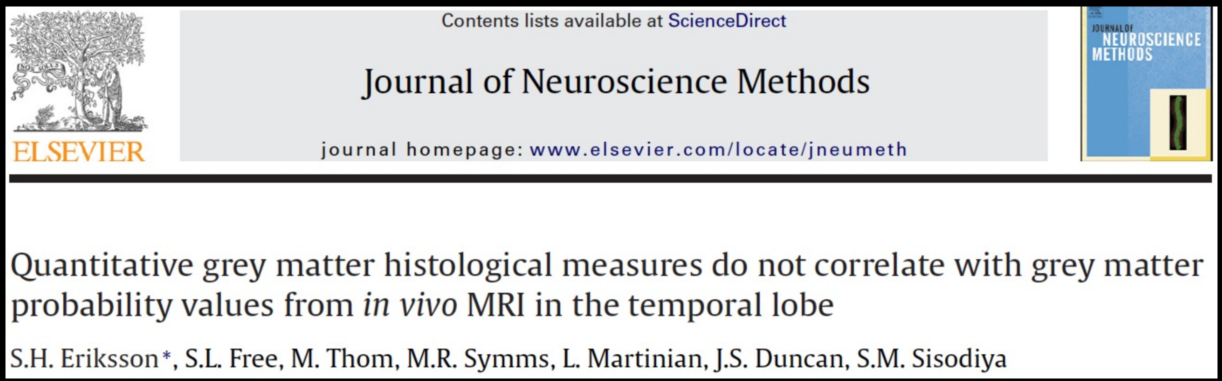
- The rest controls helped identify time-of-day as a significant confound
- Important to keep in mind for longitudinal and cross-sectional designs
- Time-of-day impacts T_1W, DTI, and Resting state measures
- Multimodal data helps understand possible mechanism
- It’s not just a confound – physiological phenomenon
- Data replicates help test reproducibility
- To test impact of training: Time of day x Visit interaction

Some Experimental Design recommendations

- Well matched control group
- Give the control group a effort-matched task
- Use multimodal MRI
- Collect 2 sets of data if possible
- Consider the potential confounds
    - Biological rhythms: Circadian, post lunch dip, infradian, Seasonal….
    - Chronotype, Hydration level, Caffeine, Sleep Quality, Medication, Body temperature, cortisol levels,
- If you can’t screen/control for it measure it or be mindful of it
- Report the methods you use, in as much detail as possible

Some “Inference” recommendations

- Second-order measures of brain structure are only estimates derived from the MR signal
- Cortical Thickness vs Apparent cortical thickness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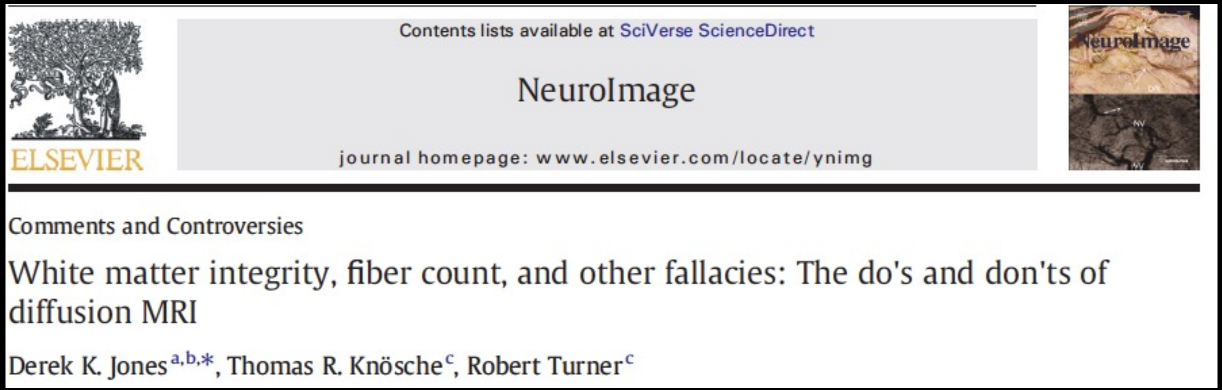
Quantitative grey matter histological measures do not correlate with grey matter probability values from *in vivo* MRI in the temporal lobe

S.H. Eriksson*, S.L. Free, M. Thom, M.R. Symms, L. Martinian, J.S. Duncan, S.M. Sisodiya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Comments and Controversies

White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI

Derek K. Jones[a,b,*], Thomas R. Knösche[c], Robert Turner[c]

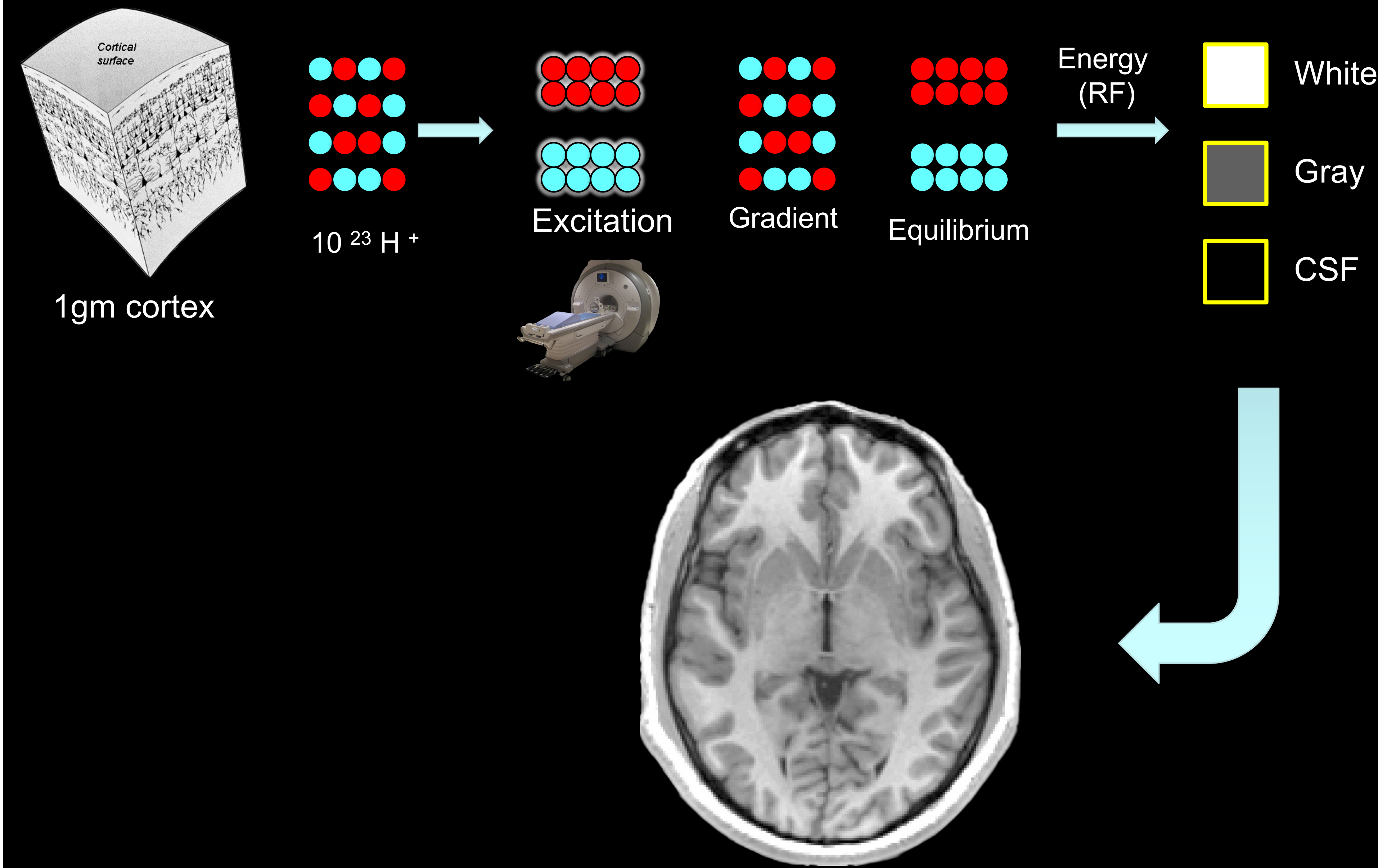
Thank you for your attention!

Thanks also to members of the
Baker lab and Pierpaoli lab

Image brain changes boldly, but cautiously

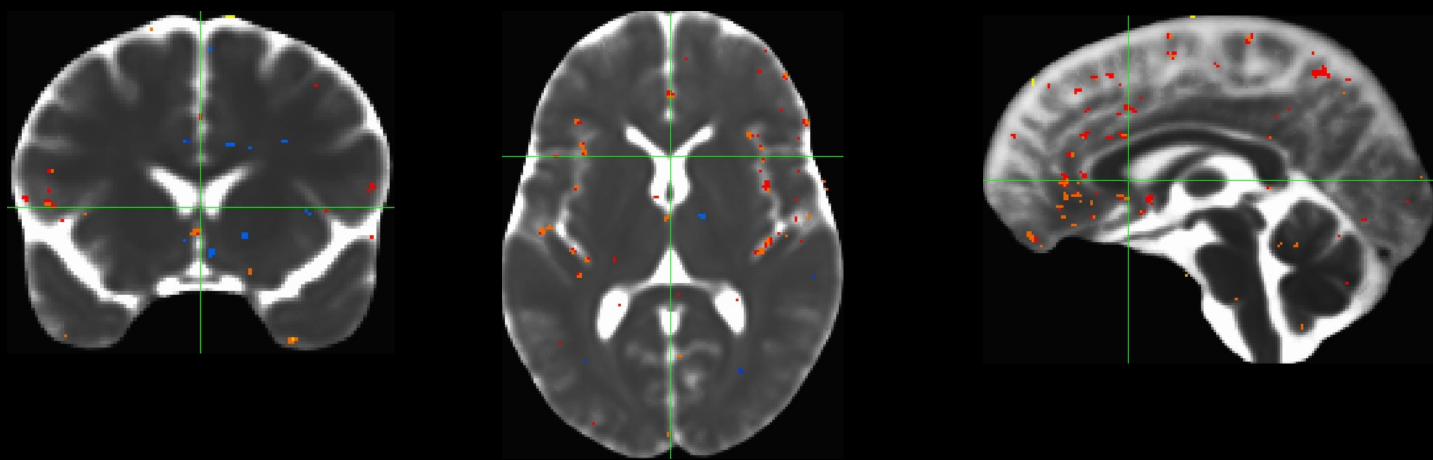
Questions/ Comments?

From molecules to gray matter volume/concentration



Increase in CSF-like Freewater accounts for diurnal fluctuations in DTI measures

Free Water Volume Fraction- Visits 4 & 1 : PM - AM



Trace Without Free Water Contamination - Visits 4 & 1 : PM - AM