NIH National Institute of Mental Health

Imaging Changes in Brain Anatomy

Cibu Thomas, PhD

Section on Learning and Plasticity

LBC Laboratory of Brain and Cognition (LBC)

Scope of this lecture

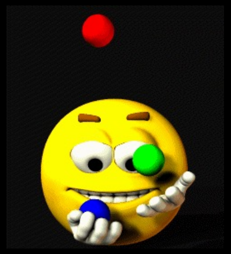
- Cognitive Neuroscientist's perspective on imaging brain changes
- Starting or in the middle of a project focused on studying structural brain changes
- Ideas extend to functional brain changes also
- Some familiarity with MRI images and jargon

Just about everything changes the brain

Growing up

Growing Old

Learning

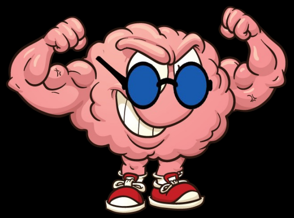


Training

Sleeping

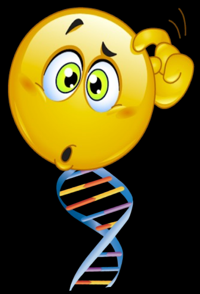
Mood

Stress



Exercise

Food



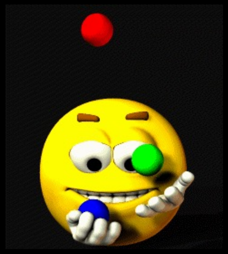
Genetics

Injury

Disease

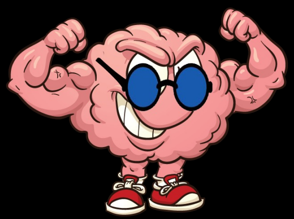
Why imaging/measuring brain changes is important



1. Slow the effects of aging or some disease



2. Measure the efficacy of a treatment strategy

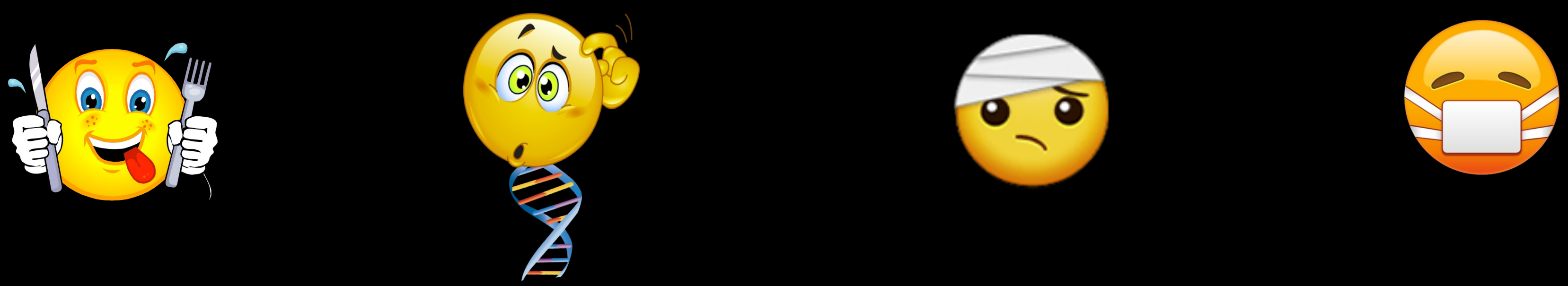



3. Guide public policy on promoting good mental health

How do we study the living human brain?

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

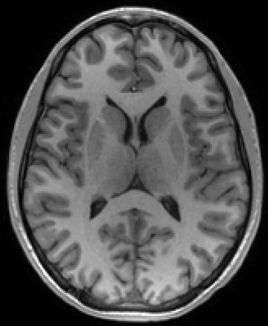
Spatial : Whole brain, cm, mm, microns



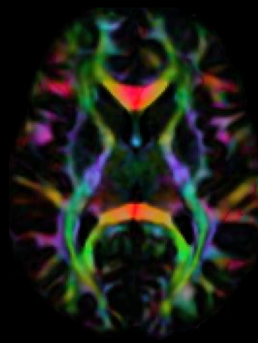
MRI – a powerful tool for imaging brain changes

Temporal Dimension

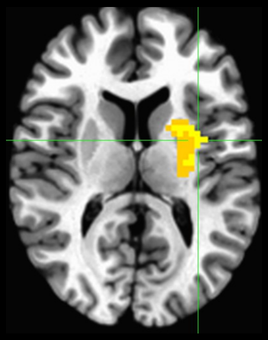
ms — **BEHAVIOR** — years



Volume
Cortical thickness
Gray matter density



Measures of tissue microstructure

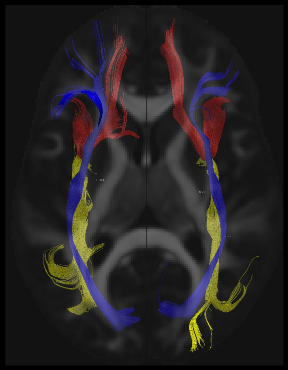


Task-driven fMRI
Resting State fMRI

STRUCTURE

Spatial Dimension

mm — whole brain



Measures of major Fiber Pathways

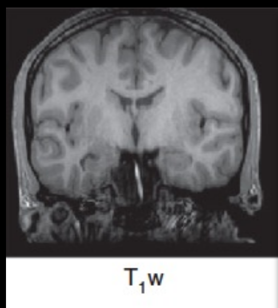
✓ Safe & Non-Invasive

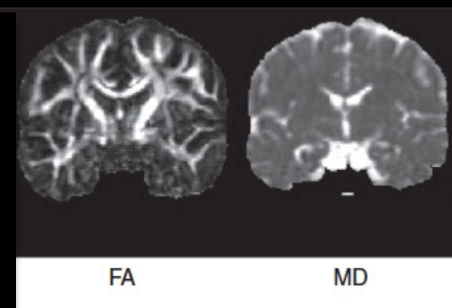
✓ Translational

✓ Multimodal

Outline

- Review popular MRI methods used for measuring brain changes



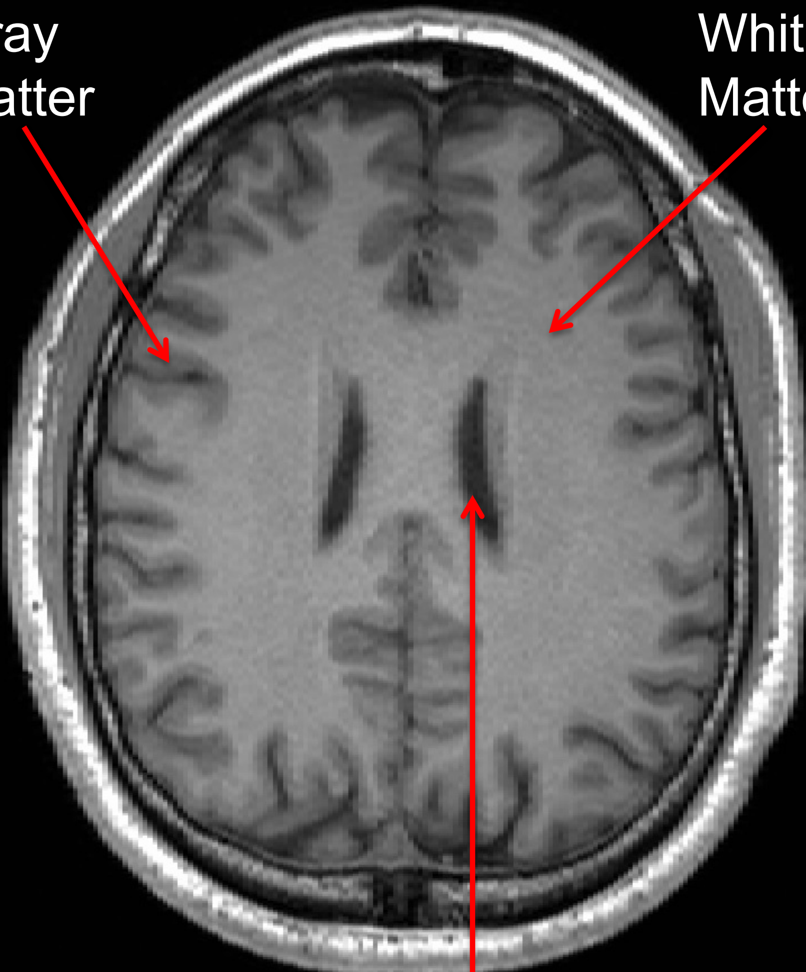


T_1W image - a powerful tool for Radiologists

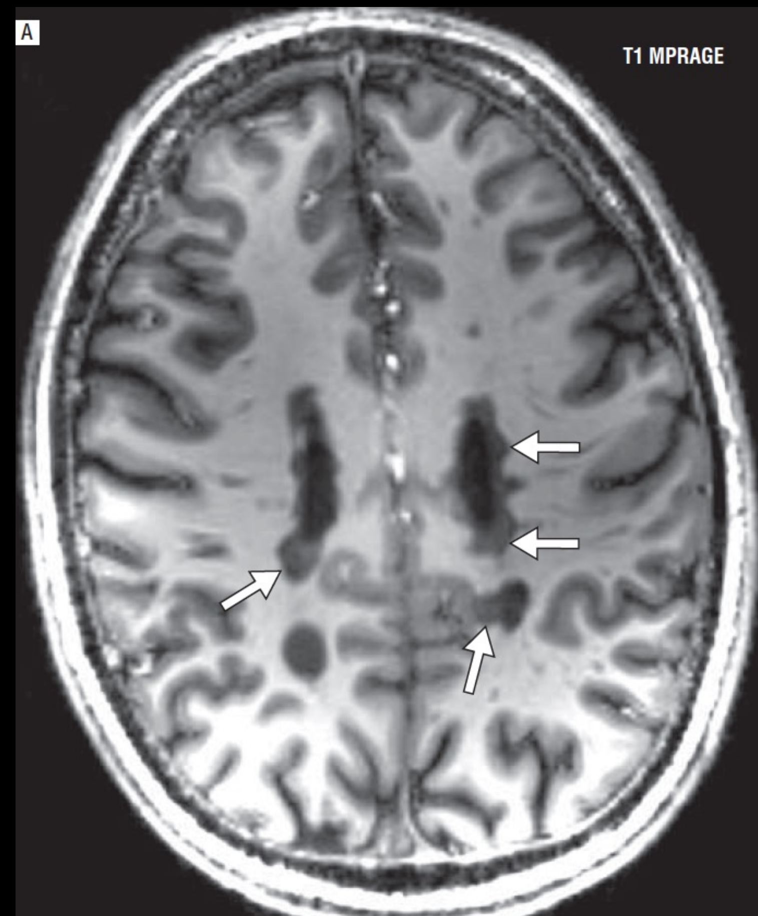
< 6 minutes

Gray Matter

White Matter



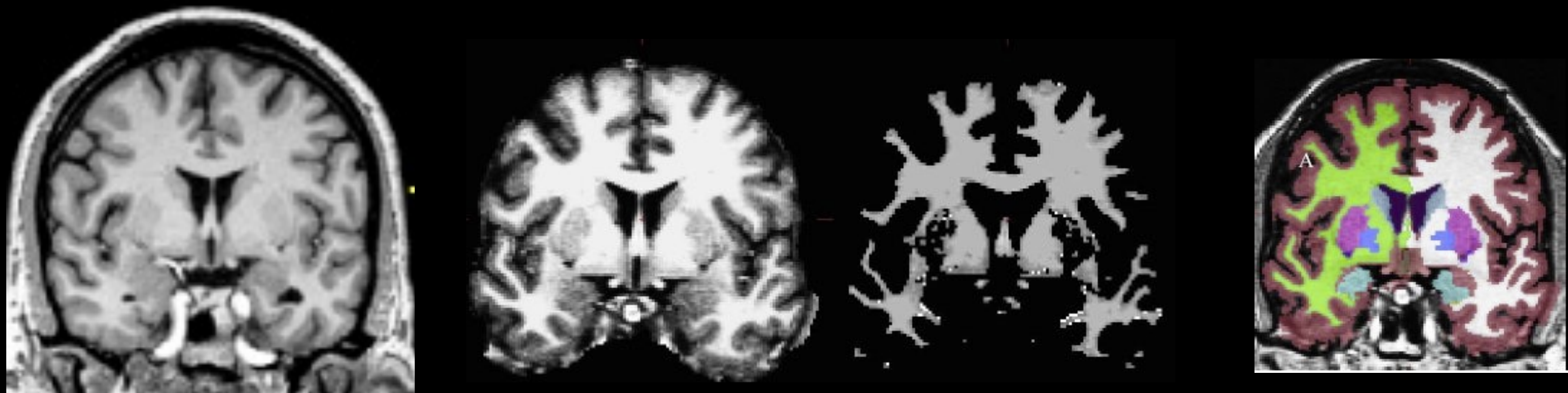
Cerebrospinal Fluid (CSF)



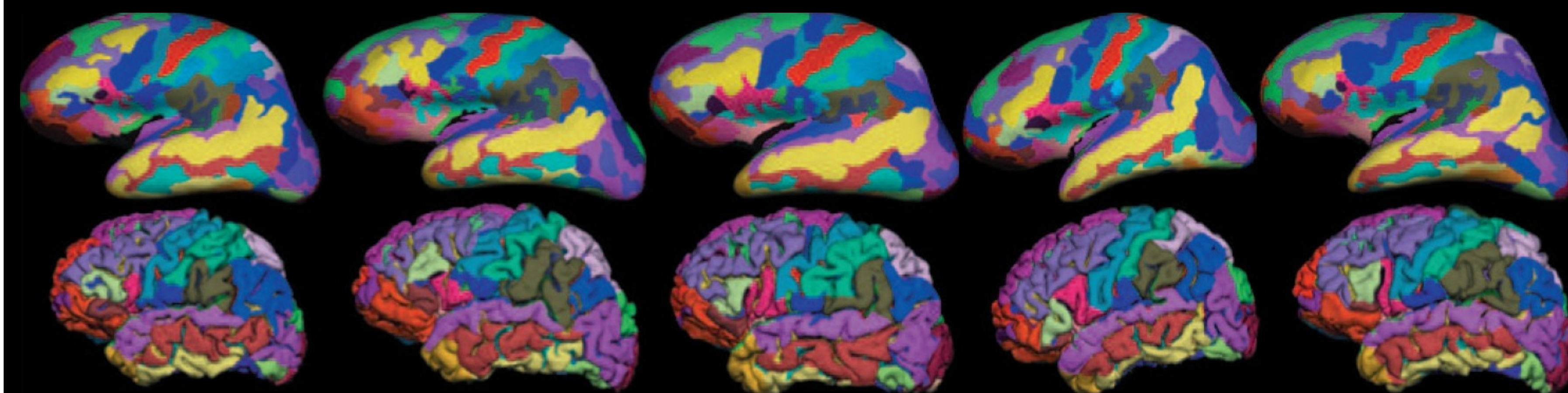
Neuroinflammatory Lesion

Sinnecker, et al., Arch, Neurol, 2012

Automatically derive anatomically meaningful measures of Volume



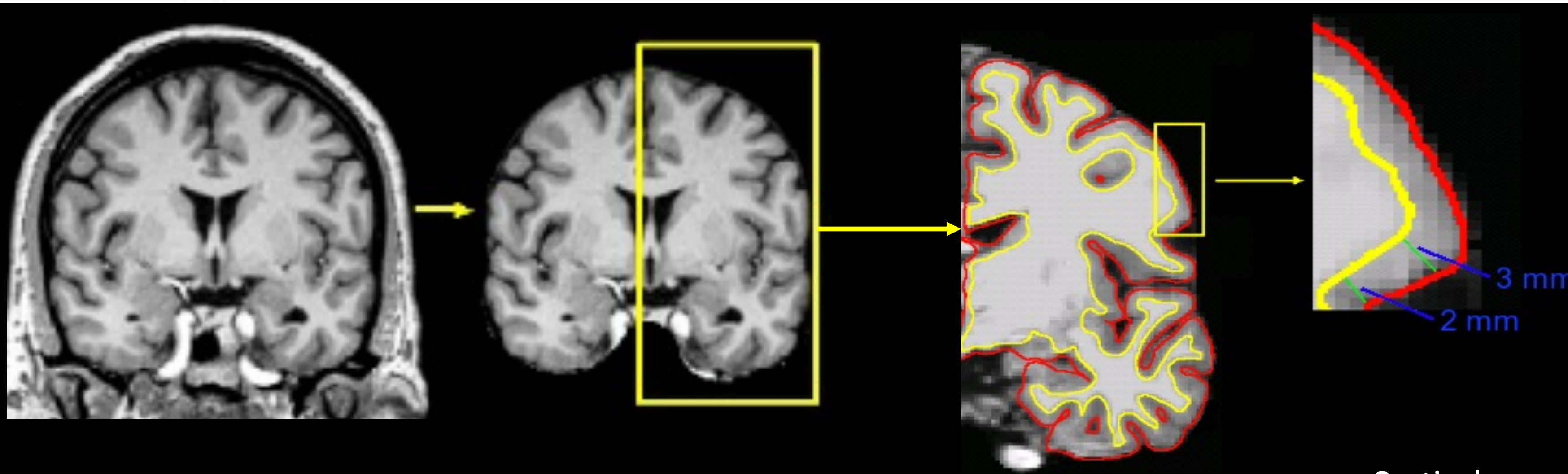
Skull strip   Segment   Parcellate



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 Volume

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

T_1W Morphometry - A powerful tool for Brain Research

ELSEVIER
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

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

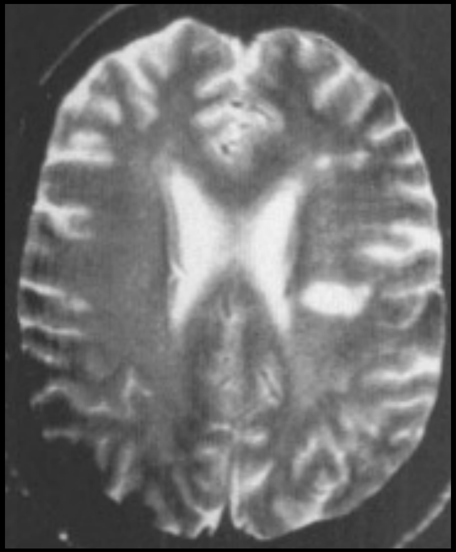
Autism

ELSEVIER
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

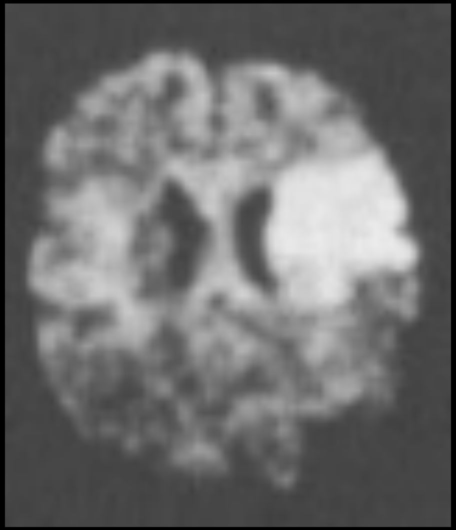
Effects of memory training on cortical thickness in the elderly

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



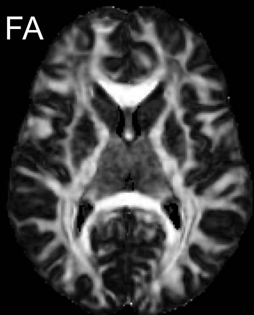
- DWI image ~3 hrs post onset of symptoms
- Decrease in water diffusion shows an acute infarct extending from temporal to frontal lobe

Warach et al., JoCBF&M_1996

Courtsey of Okan Irfanoglu

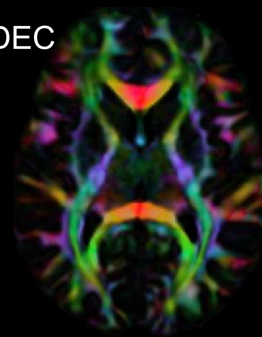
Maps from the Diffusion Tensor

FA

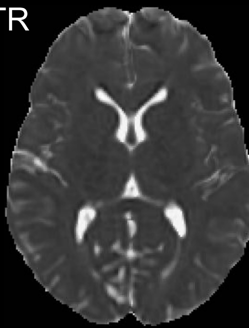


$$\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}}{\sqrt{(\lambda_1+\lambda_2+\lambda_3)^2}}$$

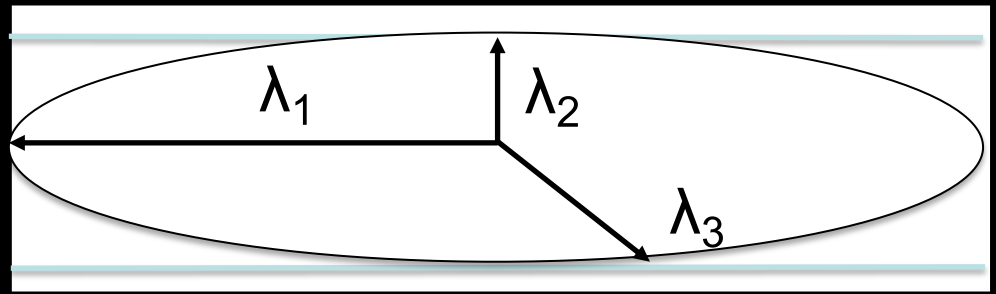
DEC



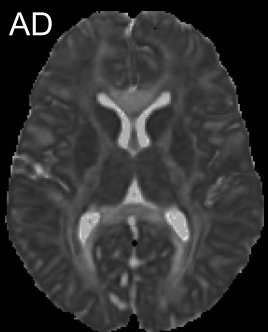
MD/TR



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

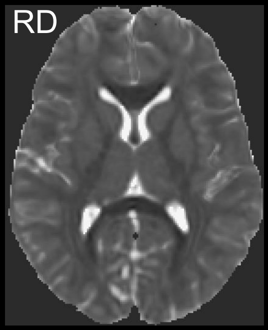


AD



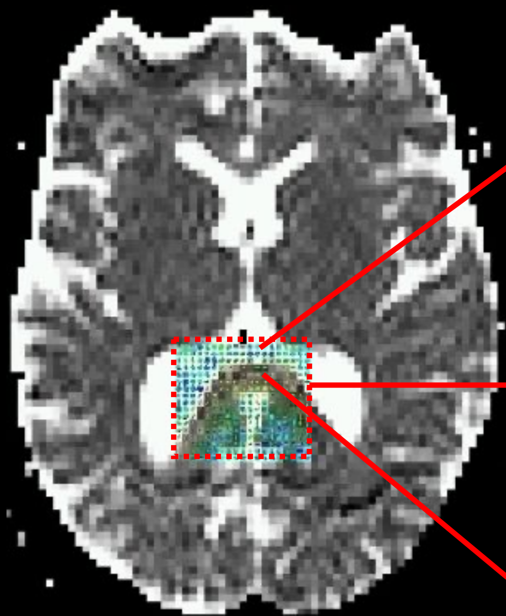
$$\lambda_1$$

RD

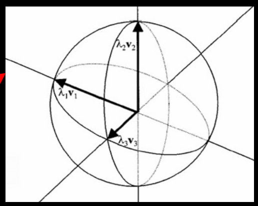


$$\frac{\lambda_2+\lambda_3}{2}$$

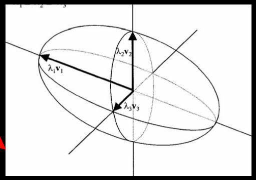
From Diffusion displacement profile to imaging white matter pathways

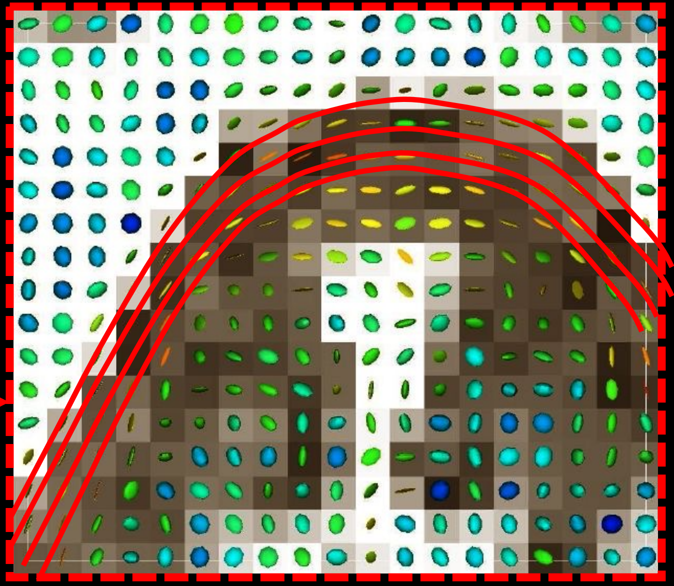


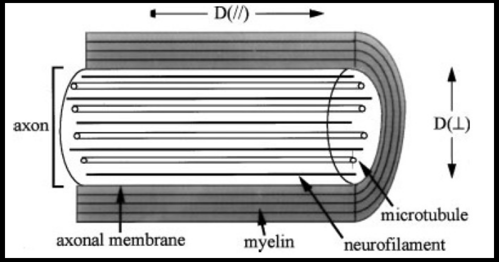
Isotropic



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

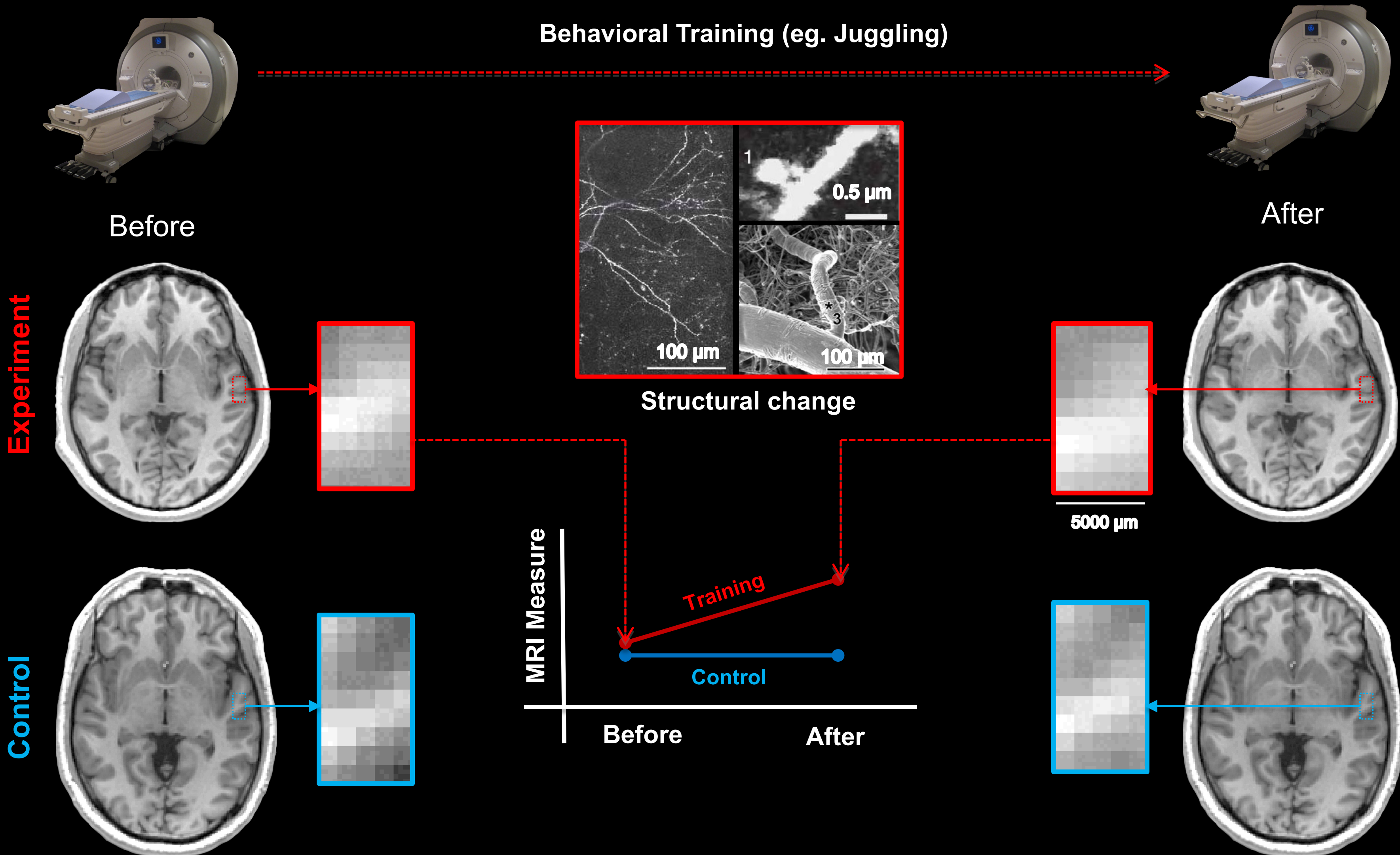
Learning in the Fast Lane: New Insights into Neuroplasticity

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

Longitudinal design – a strong argument for a causal link



Test for a Group X Timepoint interaction

How robust is the evidence from MRI based studies of Brain Plasticity?

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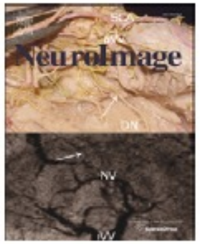
Contents lists available at SciVerse ScienceDirect

NeuroImage

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



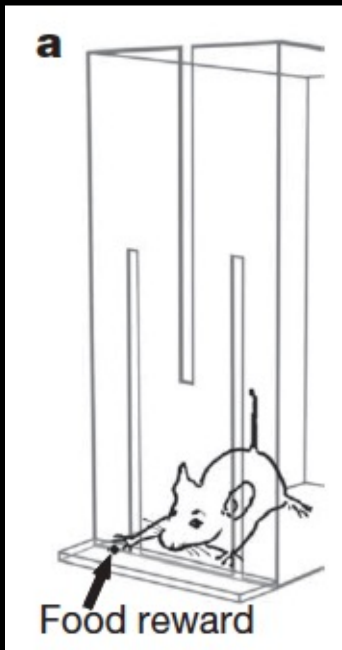
Review

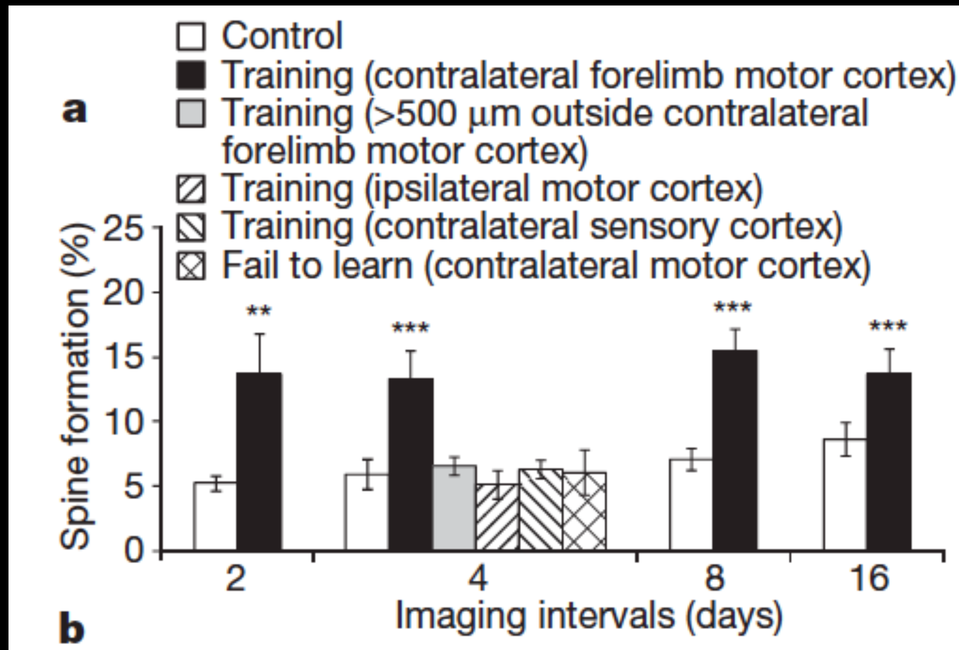
Teaching an adult brain new tricks: A critical review of evidence for training-dependent structural plasticity in humans☆

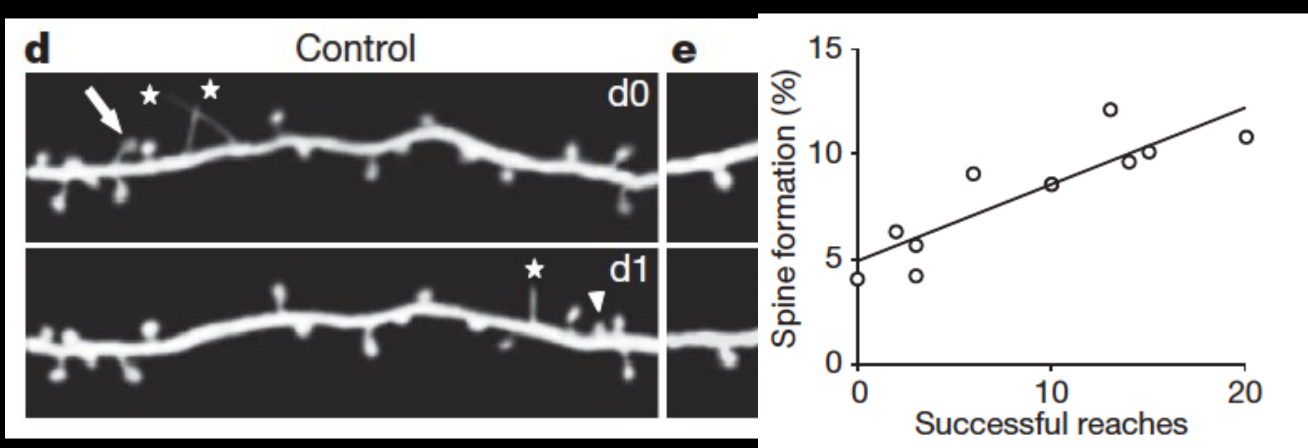
Cibu Thomas*, Chris I. Baker

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

Compelling evidence for training-specific changes







- Specificity to training group
- Specificity to brain region
- Specificity to task
- Correlation with behavior

Xu et al ., 2009

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

Contents lists available at SciVerse ScienceDirect

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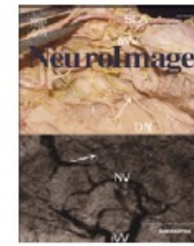
journal homepage: www.elsevier.com/locate/ynimg



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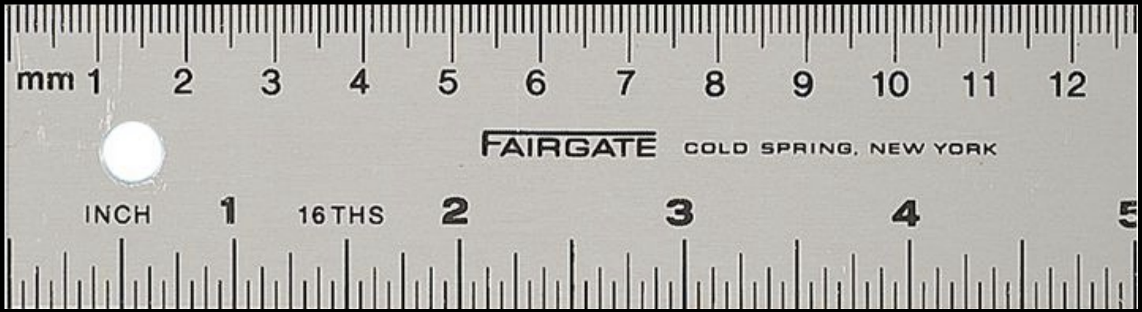
Bulk of the evidence from human sMRI studies – Not very compelling

The challenge with MRI

1. Scanner
2. Sequence
3. Subject
4. Analysis
5. Interpretation
6. Know the limits/details
7. Know how to overcoming some of the limits

1. Scanner related factors that impact MRI measures

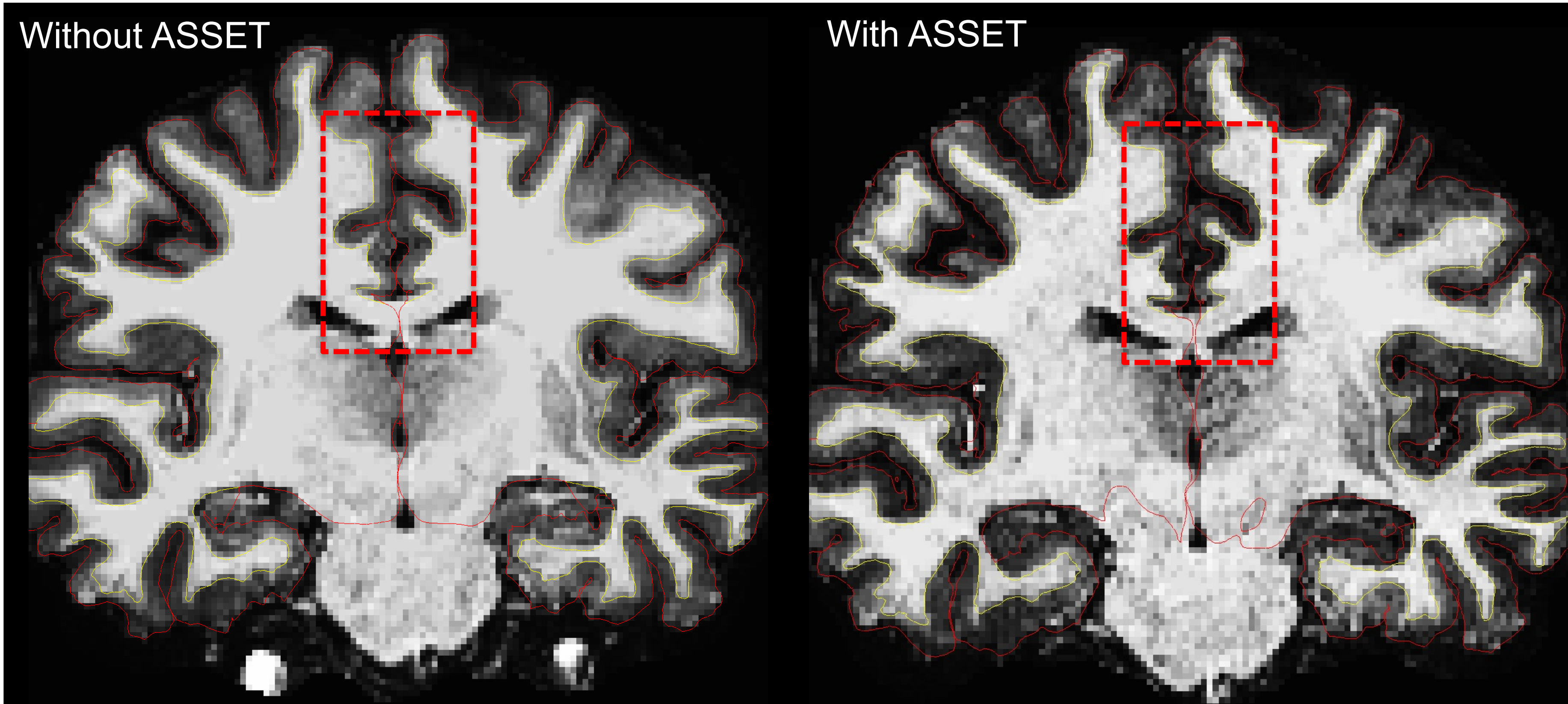


Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer

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

2. Sequence specific factors that impact T_1W-measures

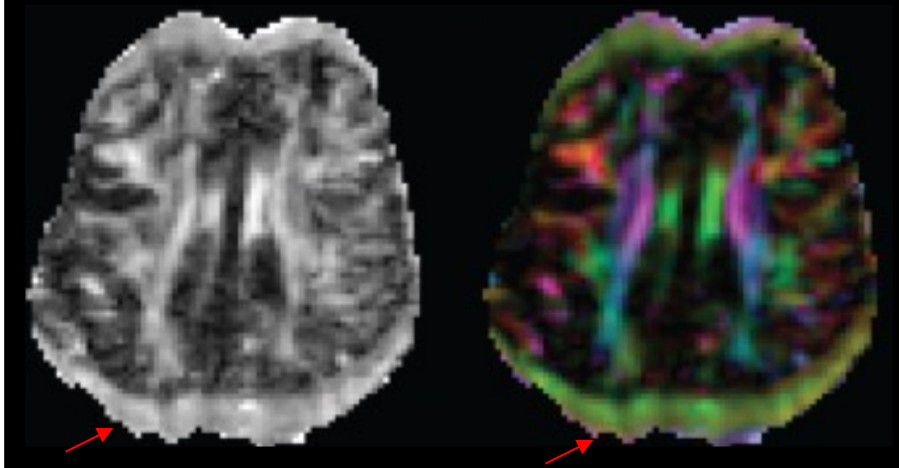


- MPRAGE, MEMPRAGE, High field MP2RAGE
- Better SNR without parallel imaging, but risk of motion
- Impacts measures like cortical thickness etc (Wonderlick et al., Neuroimage 2009)
- Solution: Consider Subject demographics or 2 sets of accelerated T_1W images

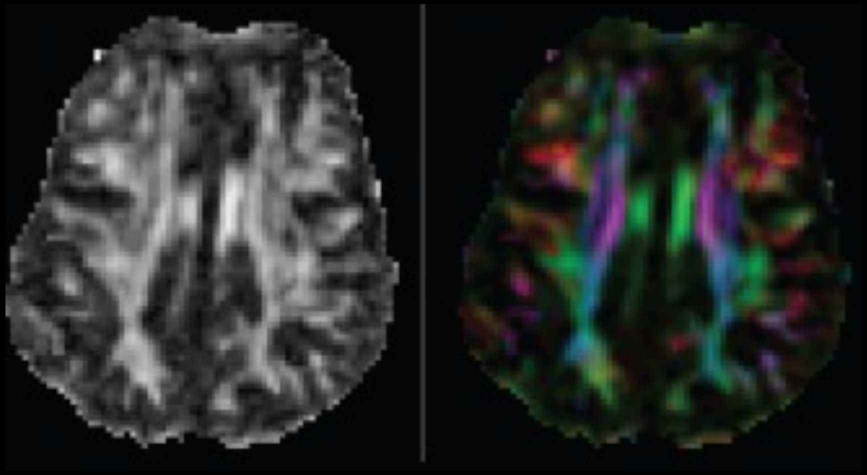
Image from Jason Crutcher

2. Sequence specific factors that impact DTI measures

Eddy Current Distortions



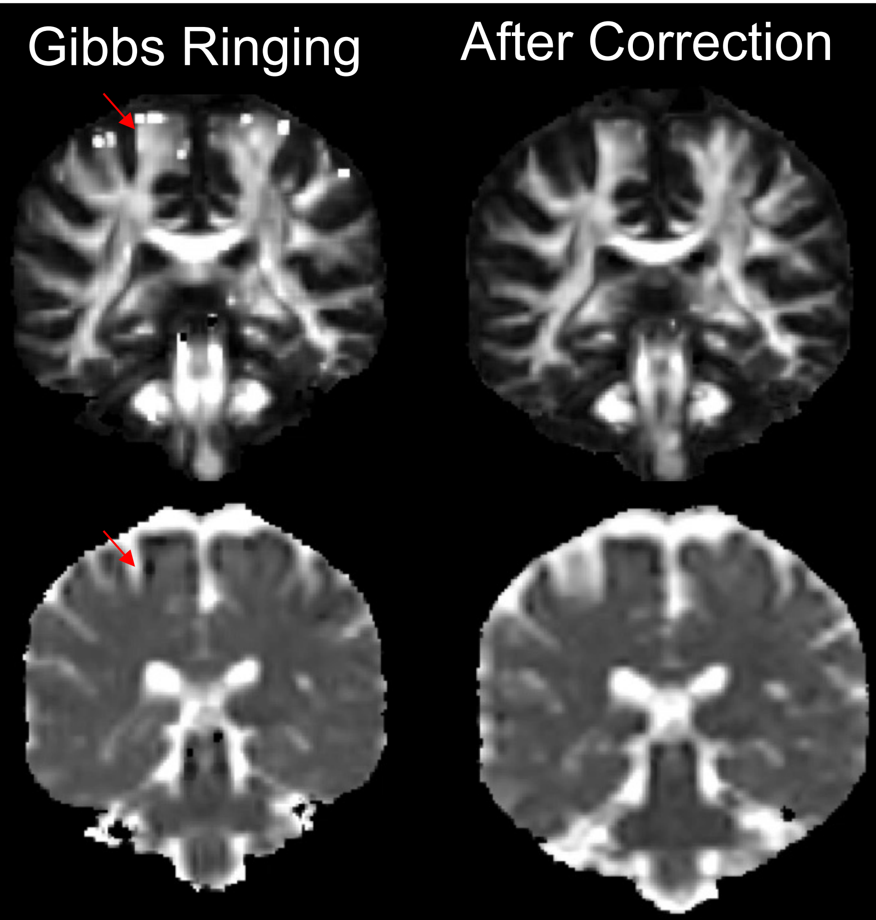
After Correction



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

From Carlo Pierpaoli 2011

2. Sequence specific factors that impact DTI measures

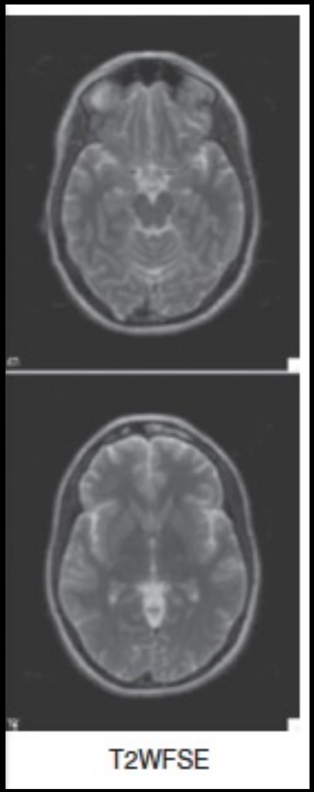


- Caused by sharp image transitions
- Distorts diffusivity measures
- Solution: Correctable if you use TORTOISE

Image from Amrita Nayak

2. Sequence specific factors that impact DTI measures

EPI Distortions



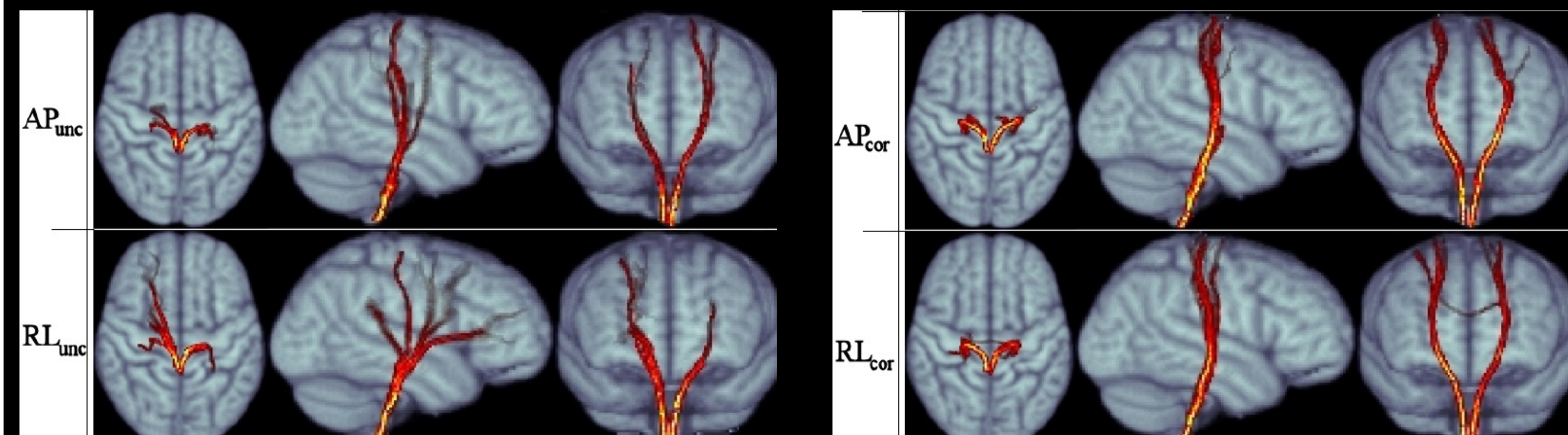
- Caused by B_0 field inhomogeneities (Jezzard and Balaban, 1995)
- Distorts images in phase encode direction in some brain regions
- Messes up tractography but not DTI measures, correctable

From Carlo Pierpaoli 2011

2. Sequence specific factors that impact DTI measures

Before EPI Distortion Correction

After EPI Distortion Correction

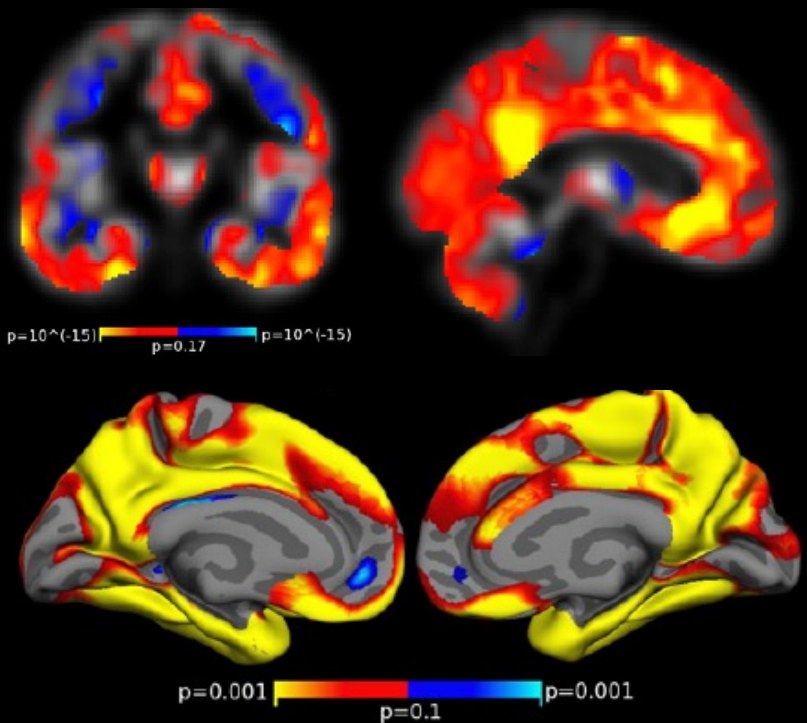


Irfanoglu et al, 2012

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

3. Subject factors that impact measures of brain structure

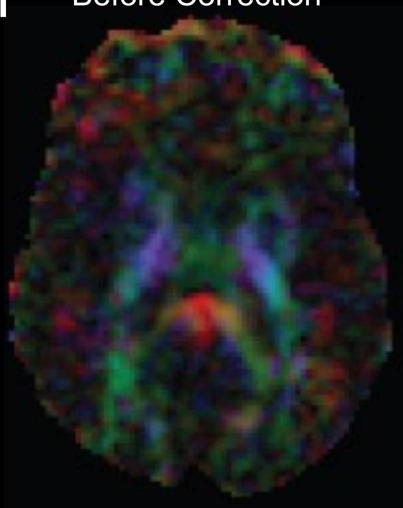
Subject head motion (T_1W)



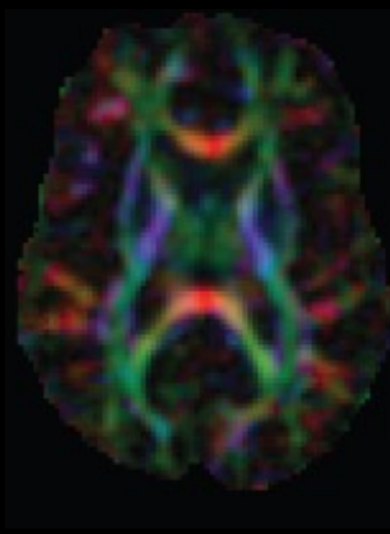
- Head motion impacts GMV and CT estimates
- 2mm/min motion -> ~1.4 – 2 % GMV loss
- Solution: Use PROMO, better padding etc

DWI

Before Correction



After Correction using TORTOISE



Reuter et al., NeuroImage 2015

From Carlo Pierpaoli, 2011

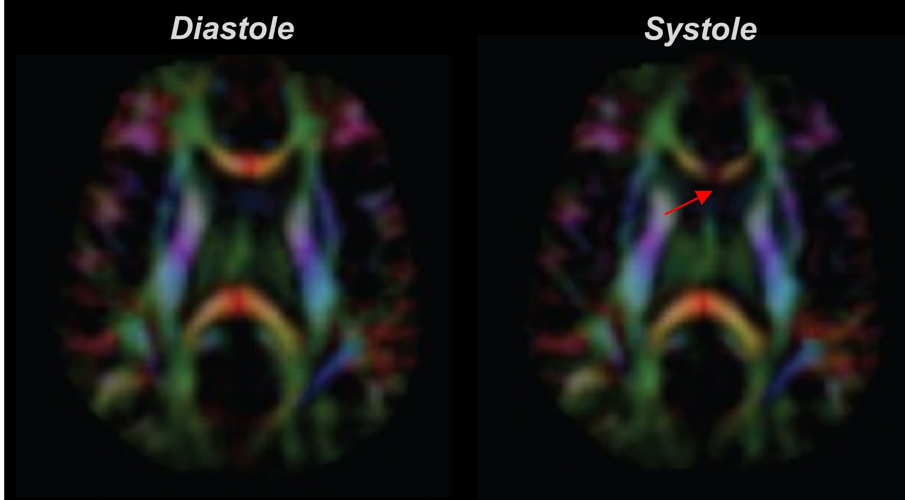
3. Subject factors that impact measures of brain structure

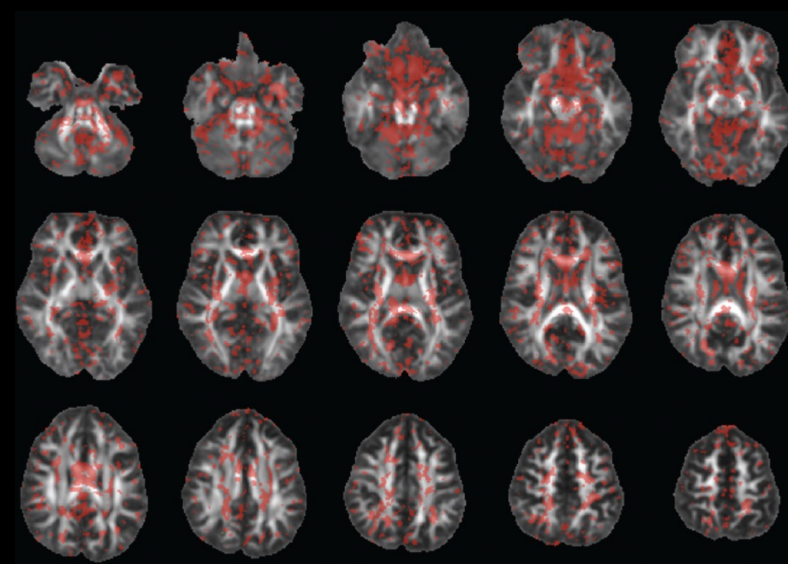
Blood Pressure on T_1W imaging

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

Schaare et al., HBM 2017

Cardiac Pulsation on DWI





- Solution: identify outlier voxels and remove using TORTOISE

From Carlo Pierpaoli, 2011

4. Data processing factors that impact MRI measures

OPEN ACCESS Freely available online

PLoS one

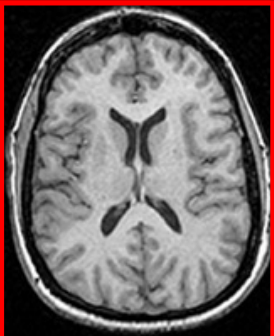
The Effects of FreeSurfer Version, Workstation Type, and Macintosh Operating System Version on Anatomical Volume and Cortical Thickness Measurements

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]

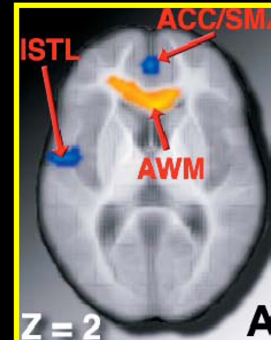
- MRI measures of brain structure can vary with Computer OS, Software Version
- Solution: Pick a stable version and stick to it

4. 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

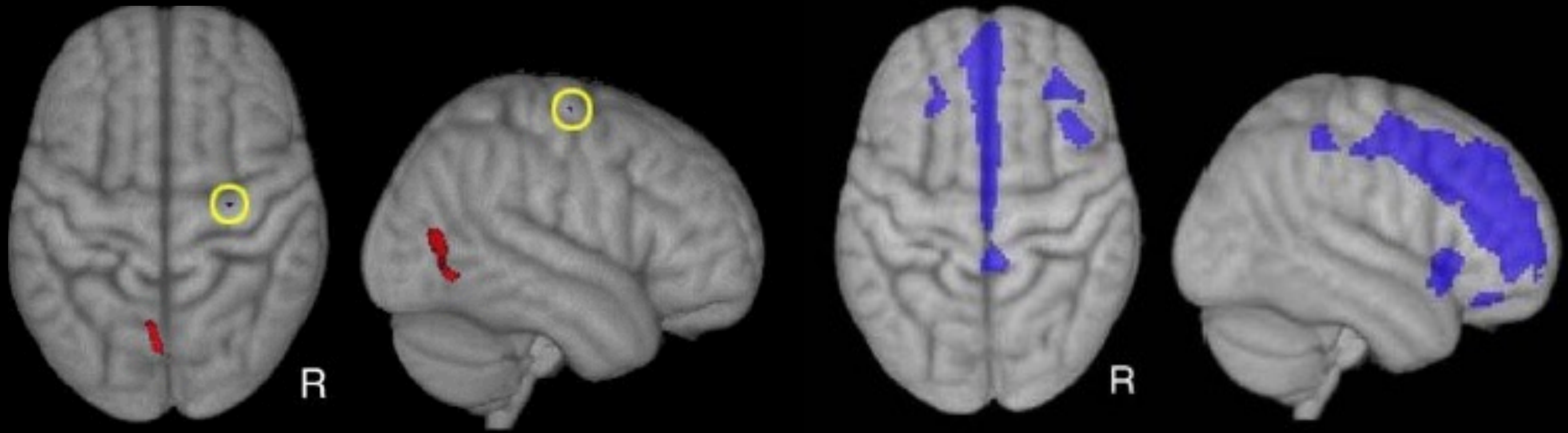
Subject trained in a visuo-motor task

Behavioral evidence for training effect

fMRI evidence for training effect

Structural changes following training?

Method A (SPM) **Method B (FSL)**



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

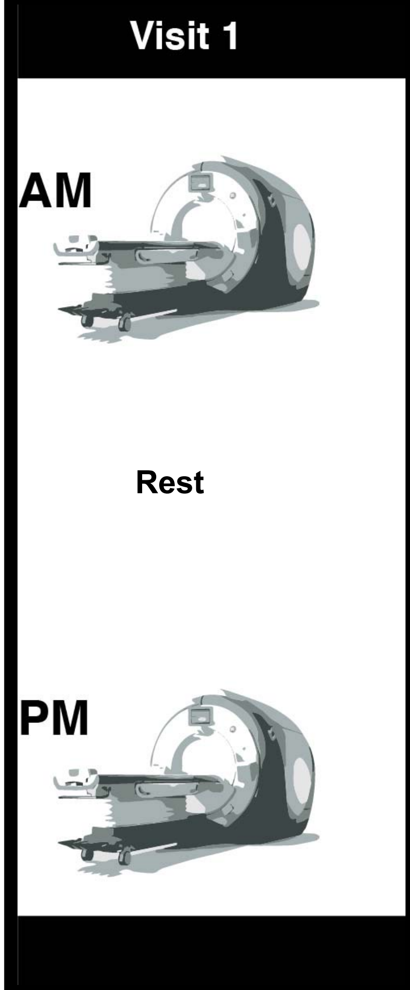
Adam Thomas et al., Neuroimage, 2009

Some Practical recommendations

- Pick a stable scanner – Stick to it
- Pick a robust MRI sequence
  - Talk to an MRI physicist about the study goals / hypothesis
  - Brain regions that matter
  - Better data comes at a cost
- Be mindful of potential confounds
  - Head motion, Physiology,
- 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

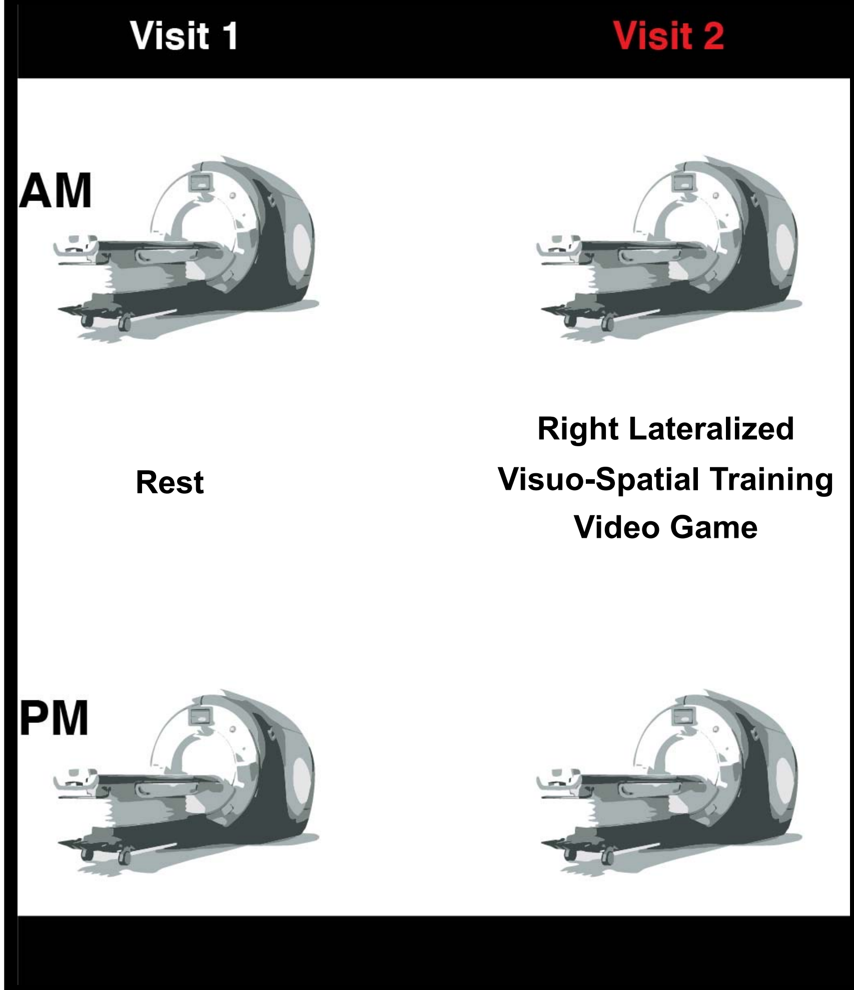
How does learning vs mastering a motor skill change the human brain?

N = 21, 11 F, Age Range: 20-38



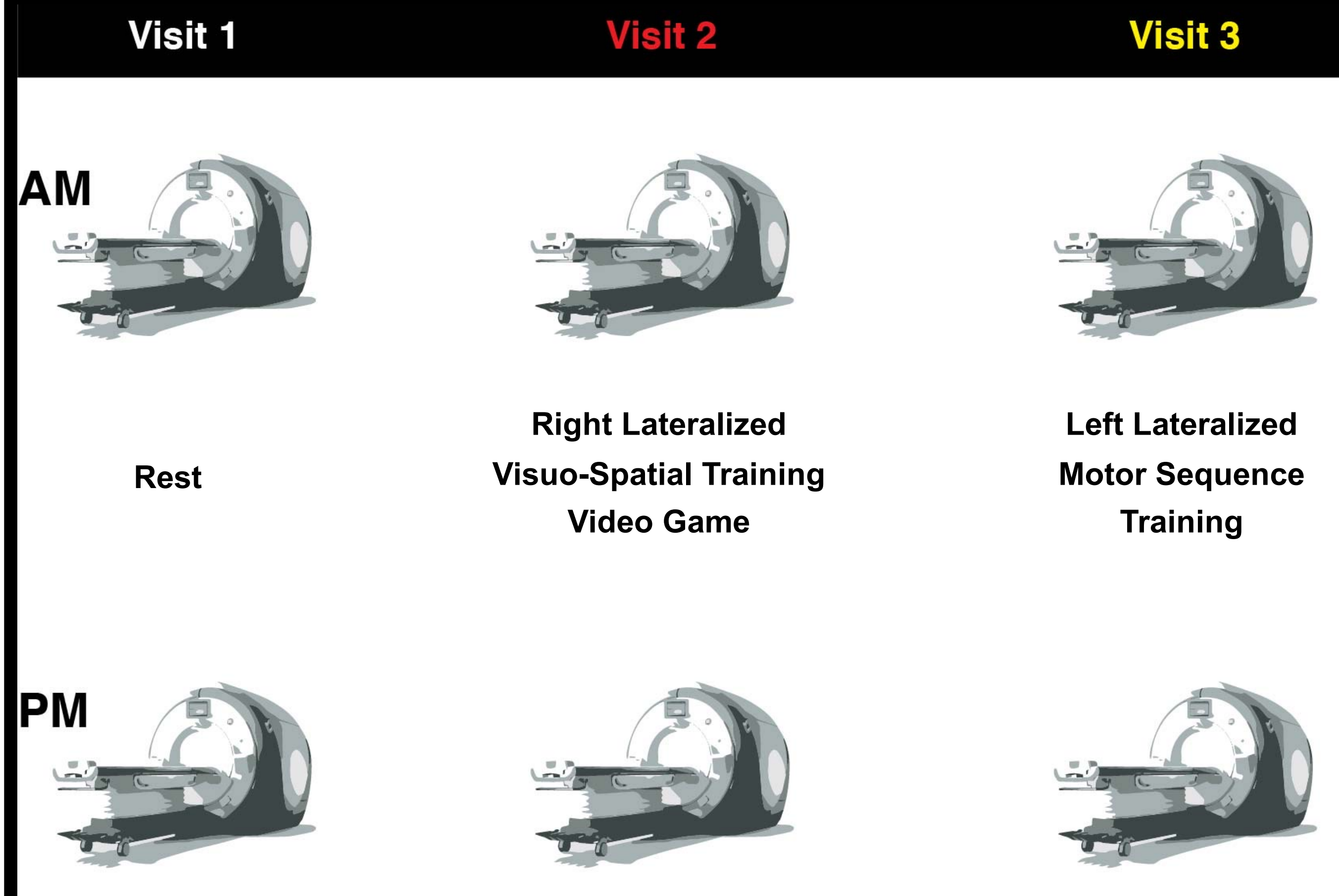
Thomas et al., *In preparation*

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



Thomas et al., In preparation

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



Thomas et al., In preparation

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

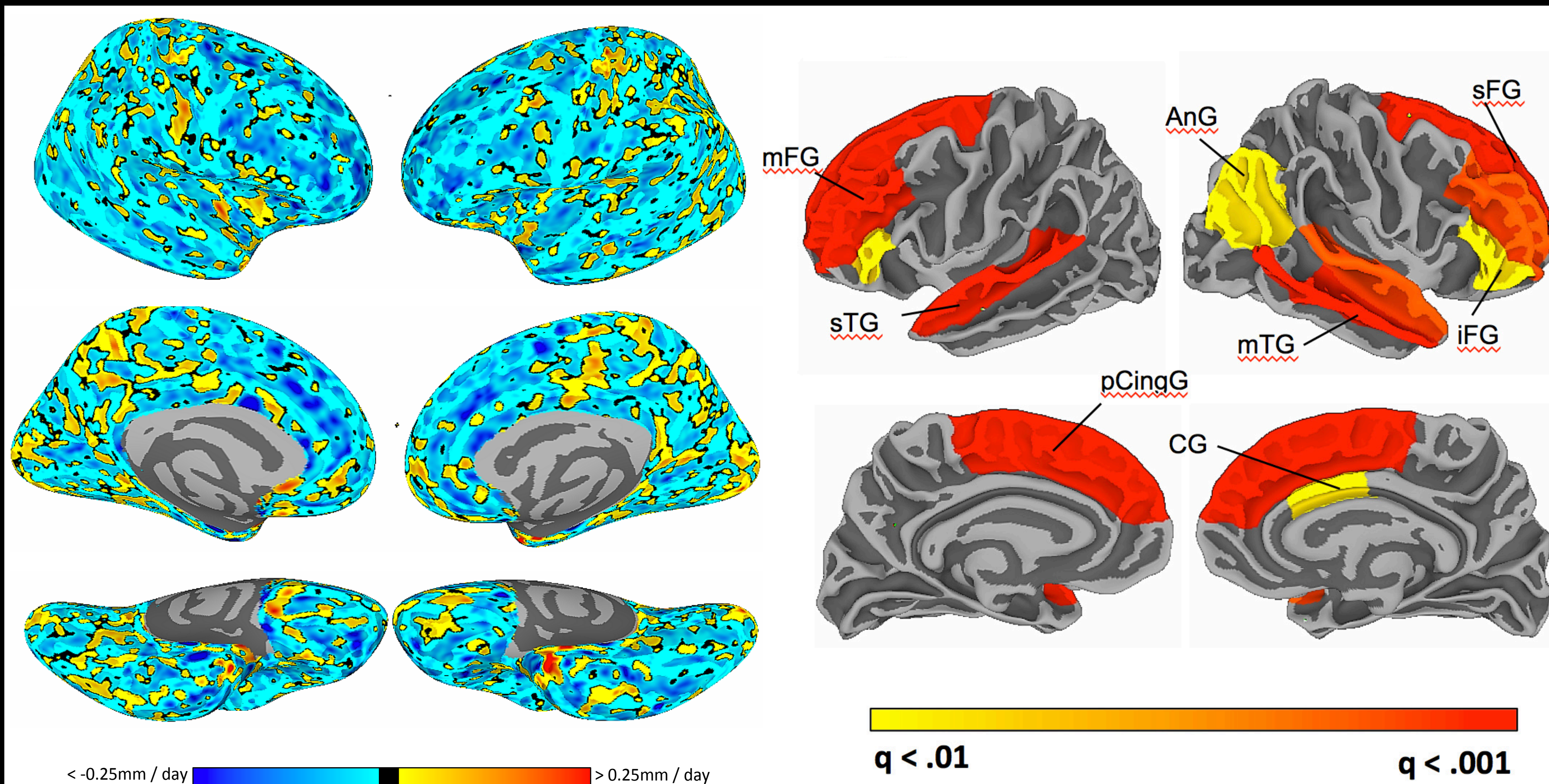
Multimodal MRI: T1W images, advanced DWI, Resting State fMRI (Two Datasets each)

Thomas et al., In preparation

Time-of-day (TOD) impacts surface based morphometric measures: cortical thickness, and surface area

Change in magnitude of cortical thickness

Statistically significant differences

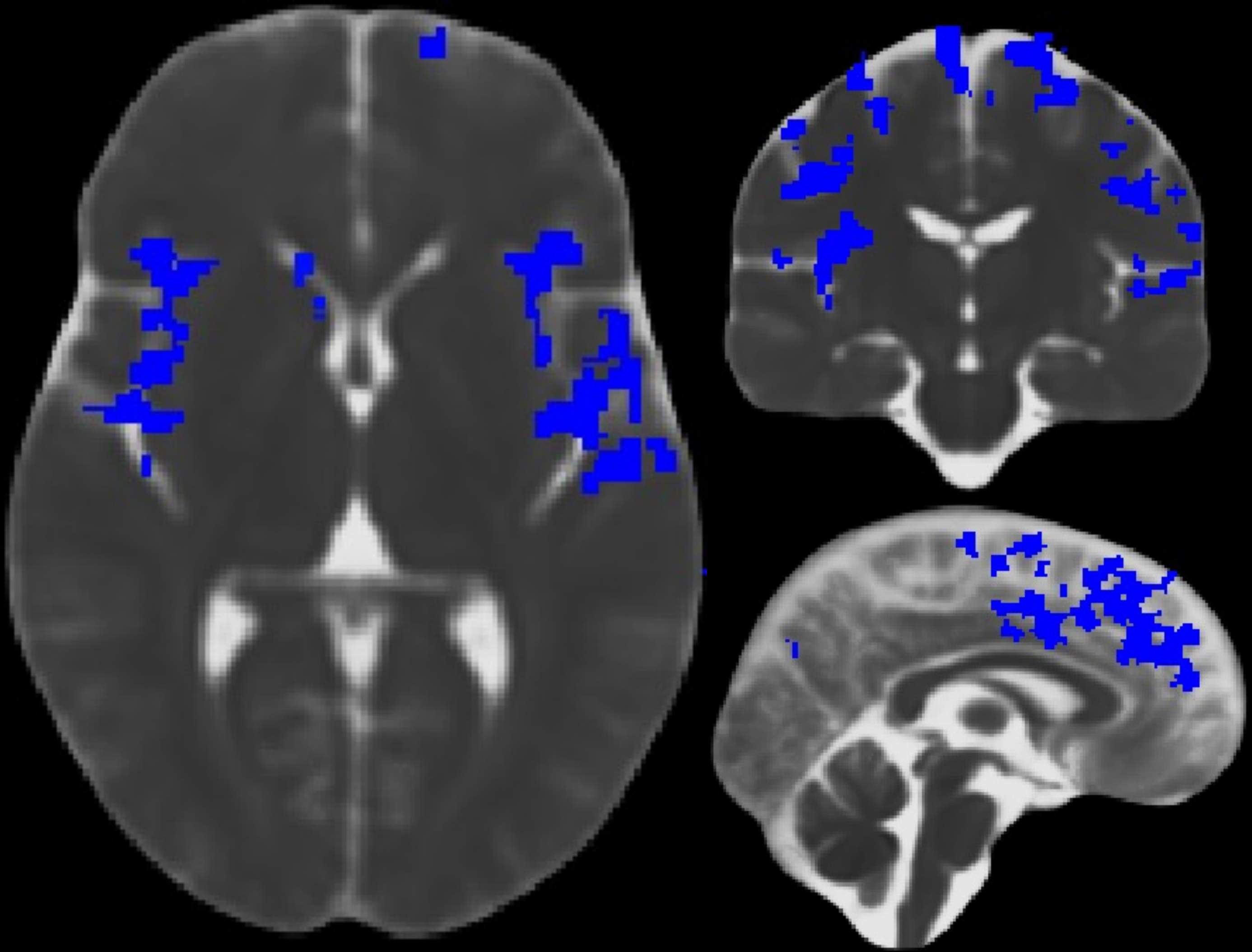


No significant impact on apparent gyrification index, sulcal depth

Trefler, et al., NeuroImage, 2016

Time of day impacts gray matter volume

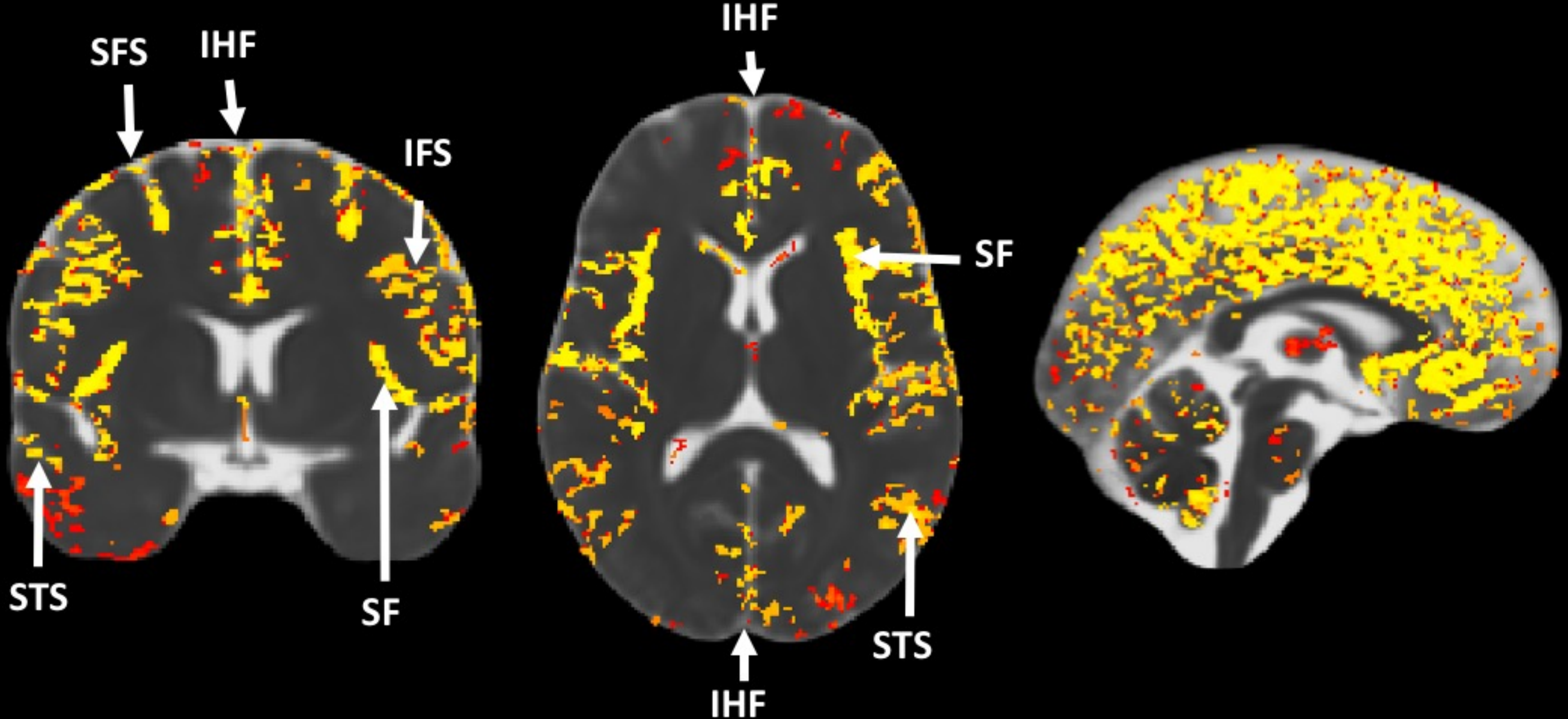
Regions that show a significant decrease in Gray matter volume from AM to PM



Trefler, et al., NeuroImage, 2016

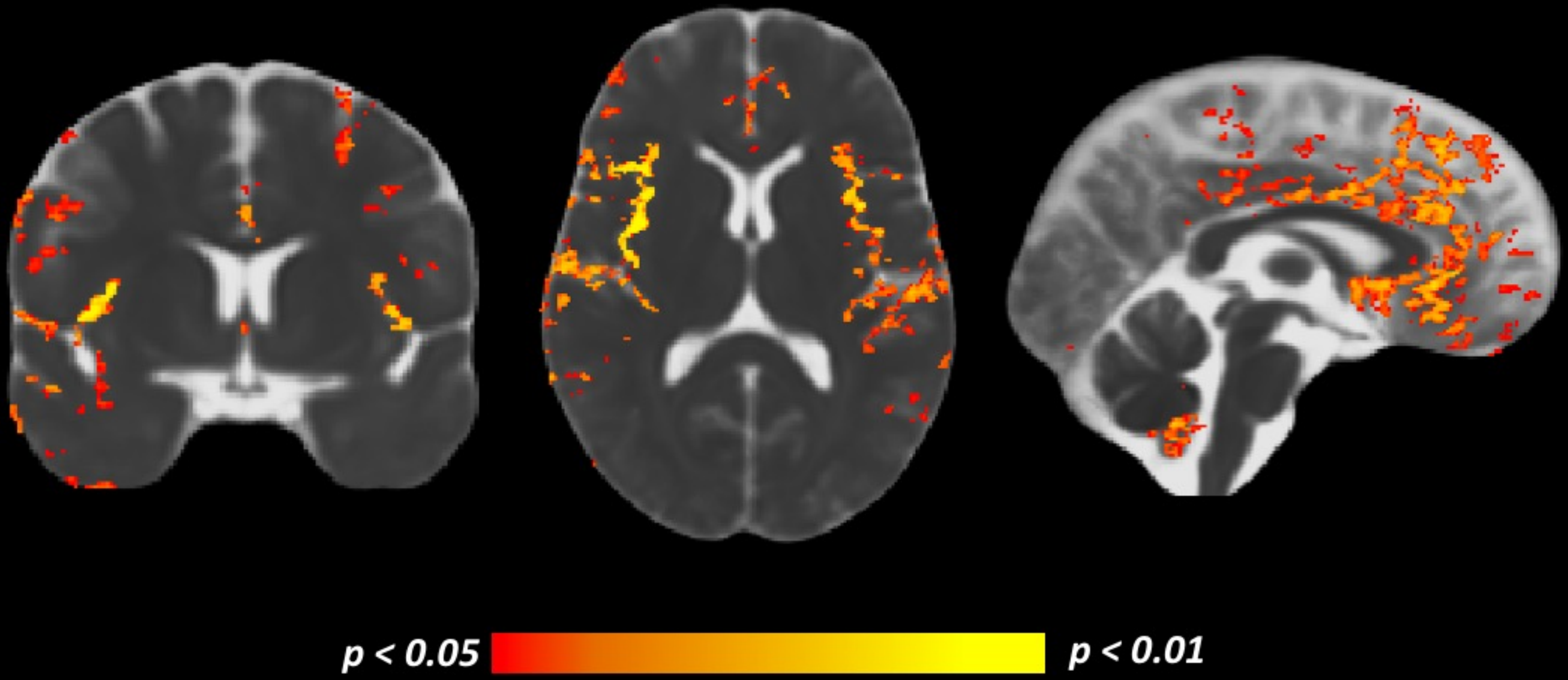
Time of day impacts DTI measures of brain structure

Regions that show a significant increase in Trace/ Mean diffusivity from AM to PM



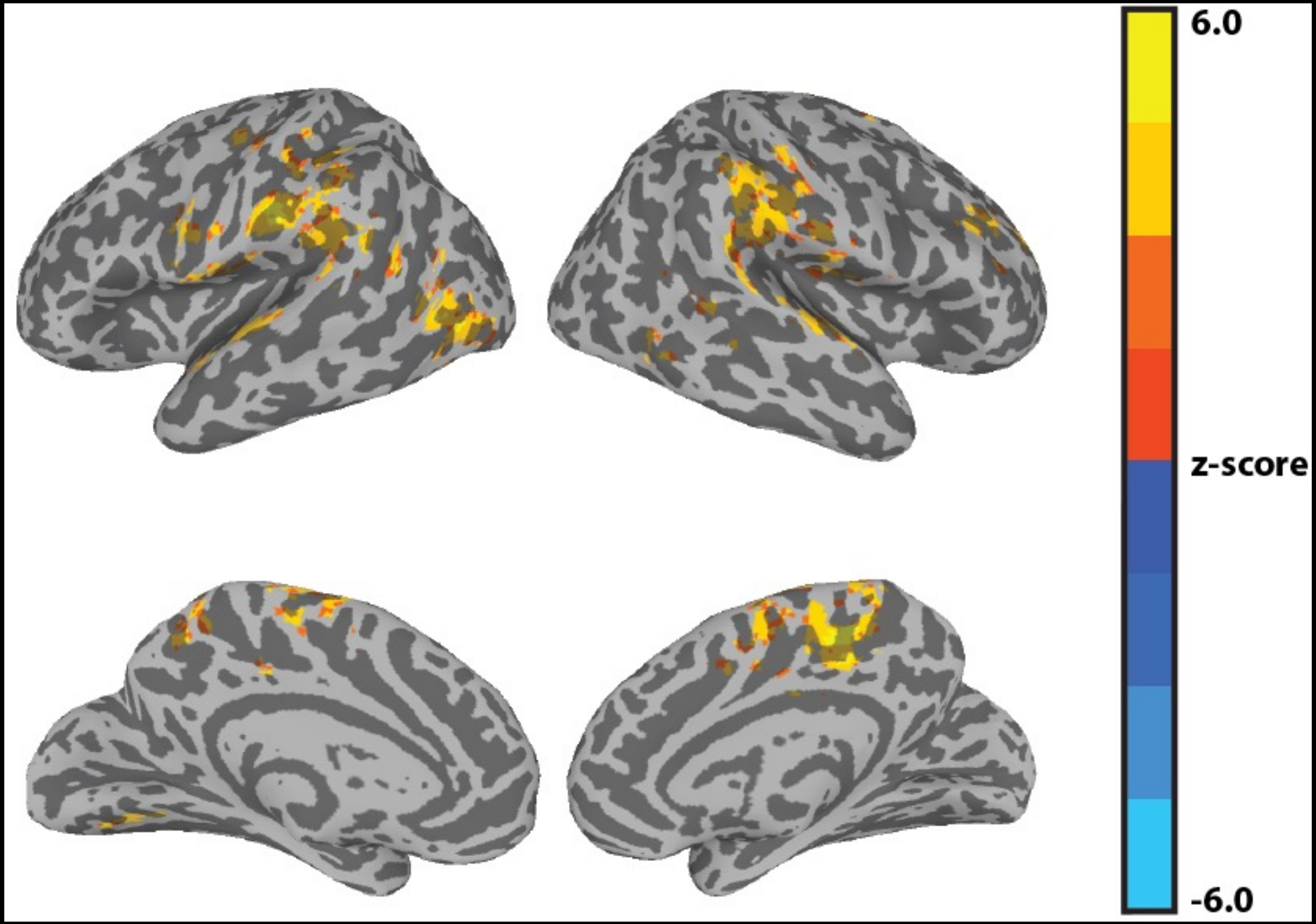
TOD impact on DTI measures of brain structure is driven by changes in freewater volume fraction

Regions that show a significant increase in freewater/ CSF volume fraction from AM to PM



Time of day impacts resting state functional connectivity

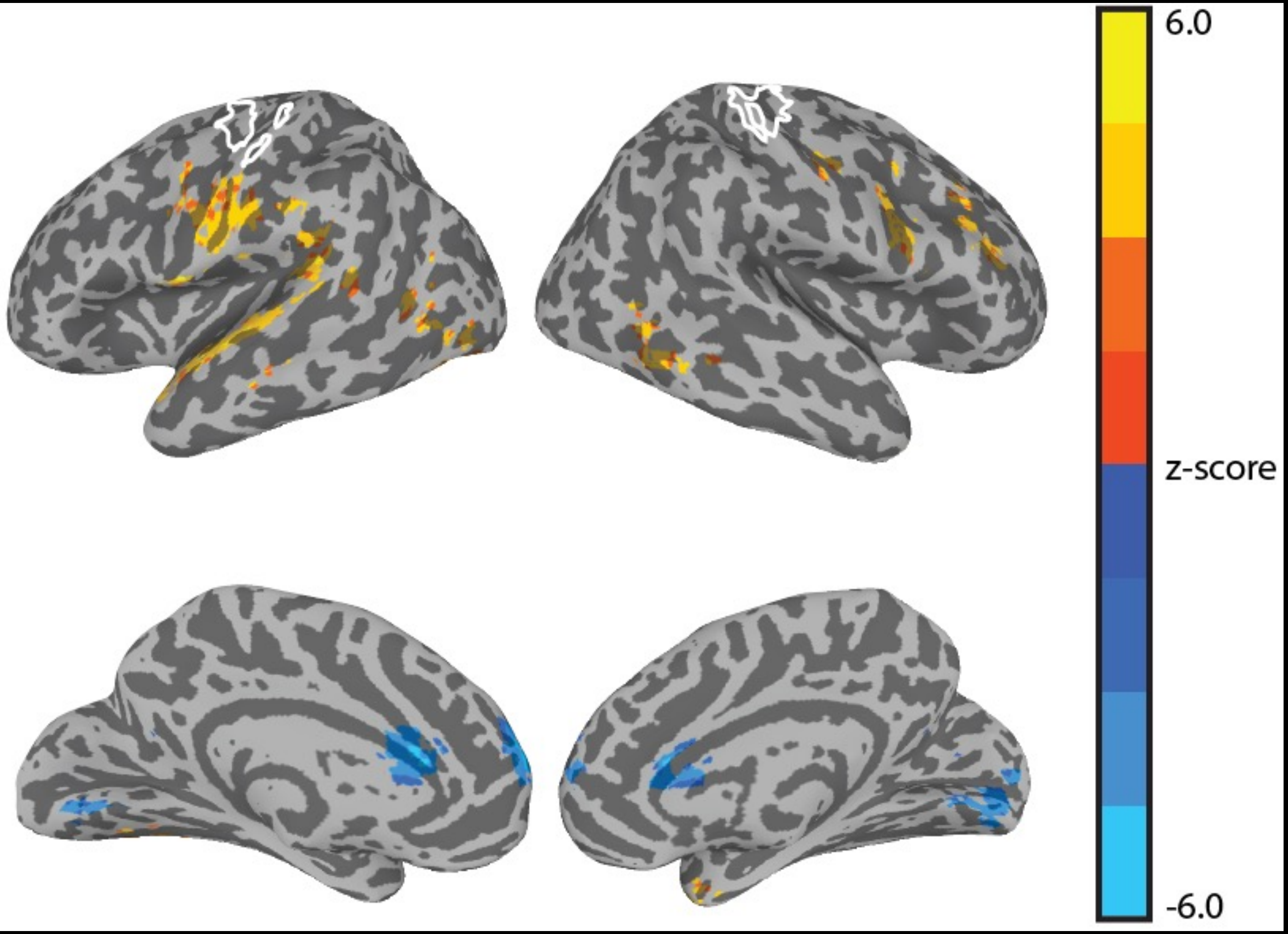
rsFC of the Hippocampus increases from AM to PM



Steel, et al., NeuroImage, Under Review

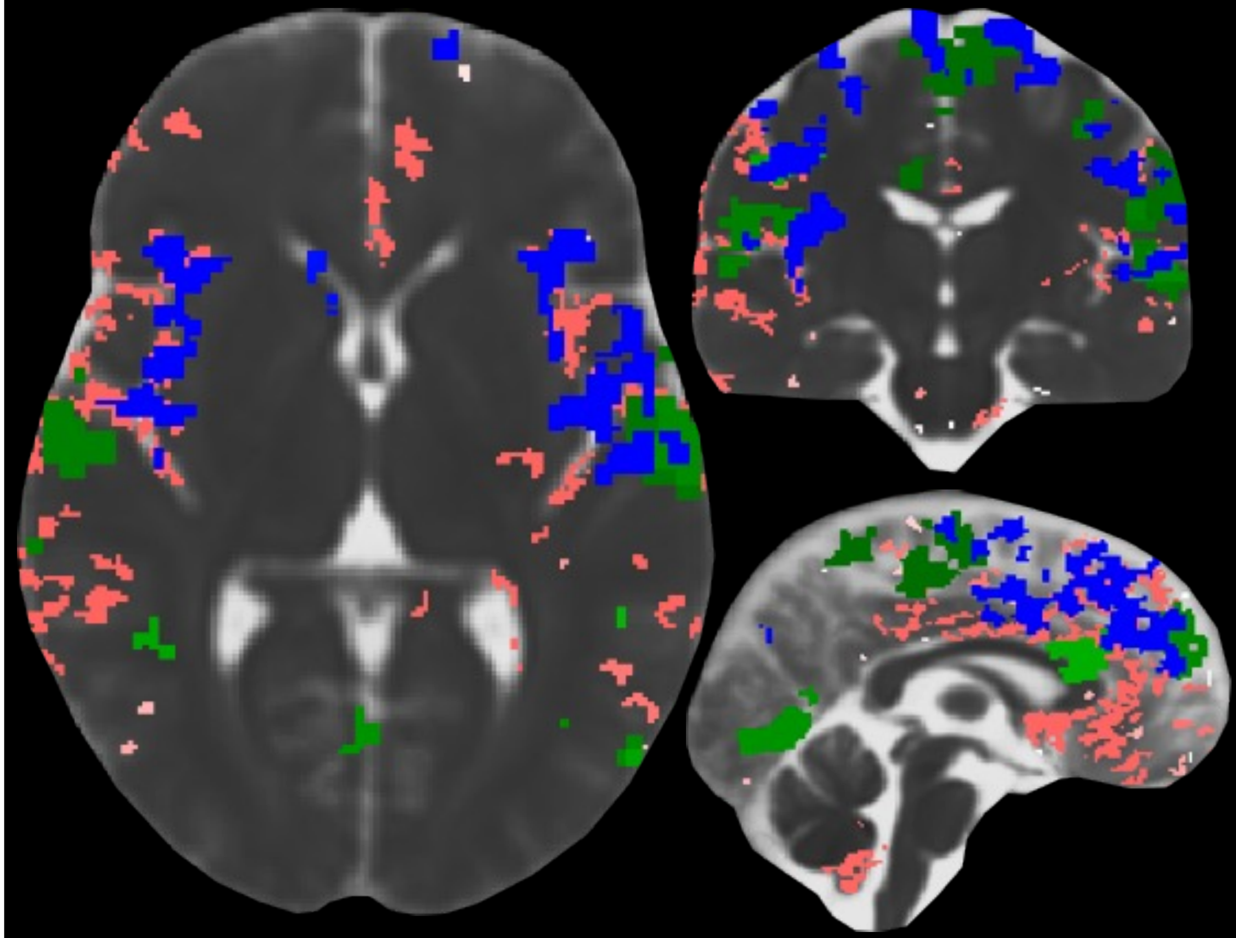
Time of day impacts resting state functional connectivity

rsFC of the Sensorimotor cortex increases & decreases from AM to PM



Steel, et al., NeuroImage, Under Review

Time of day impacts functional and structural MRI measures



Impact of time of day on:

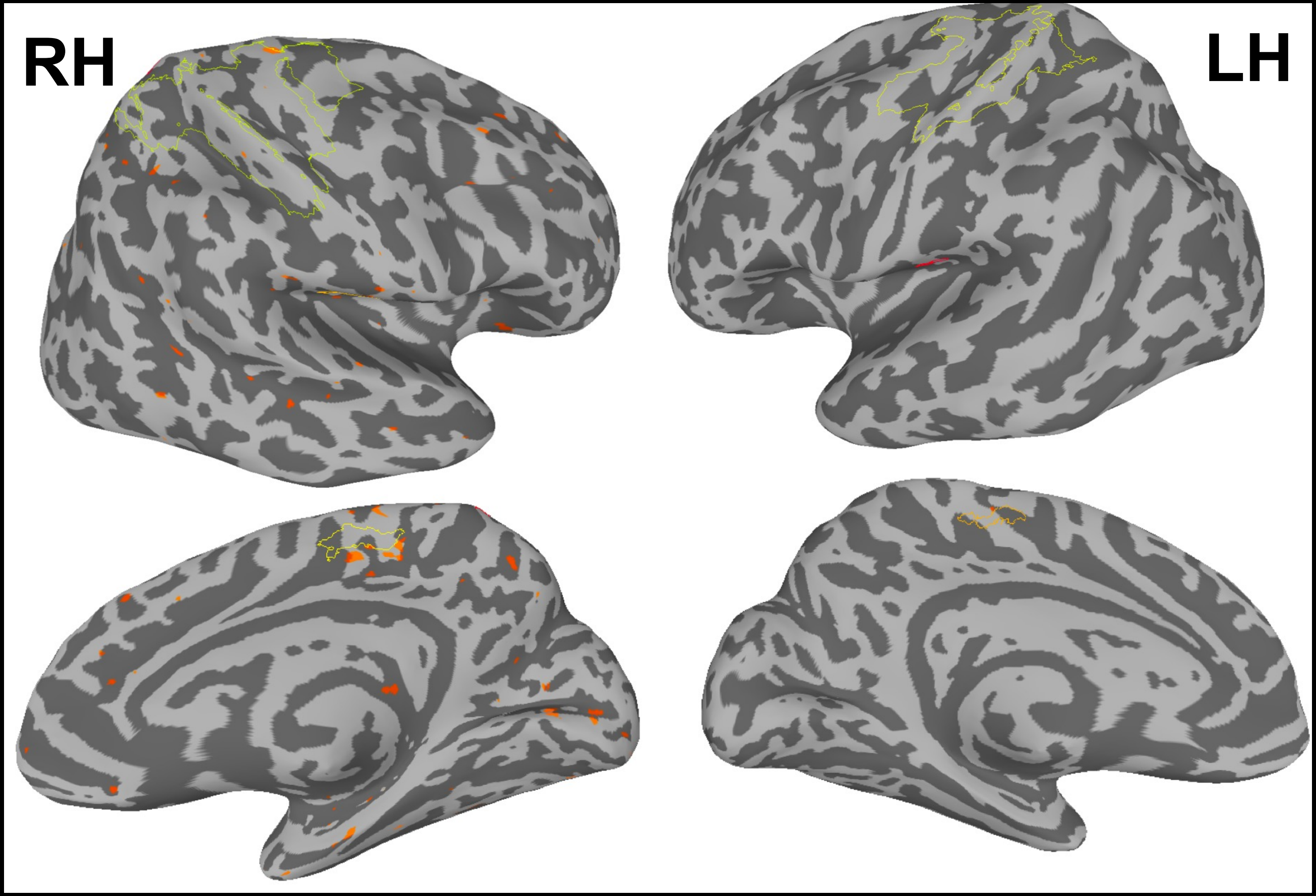
Gray matter volume Decrease (T_1w Data) (Trefler et al, 2016)

Free water volume fraction Increase (DWI Data) (Thomas et al., 2018)

Resting State functional connectivity

Impact of training on brain function (Cortical Thickness)

Timepoint x Visit interaction



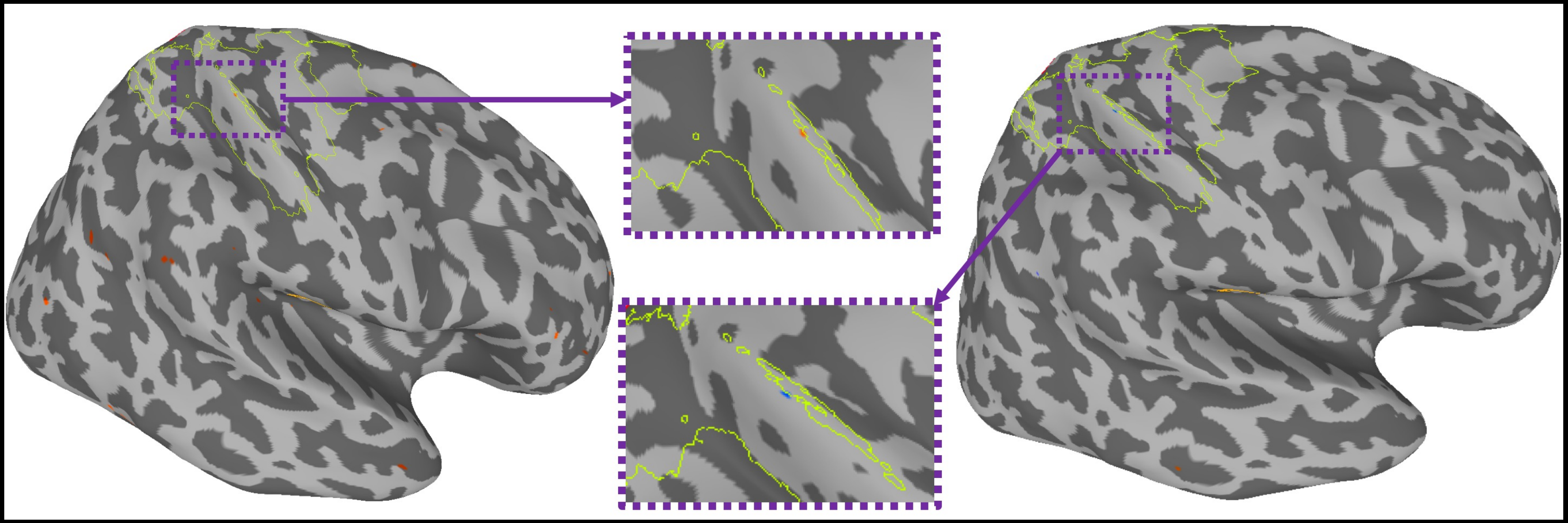
Clusters do not survive correction

Impact of training on brain structure

Correlation between change in thickness and change in performance

Short-term
Motor learning

Long-term
Motor learning

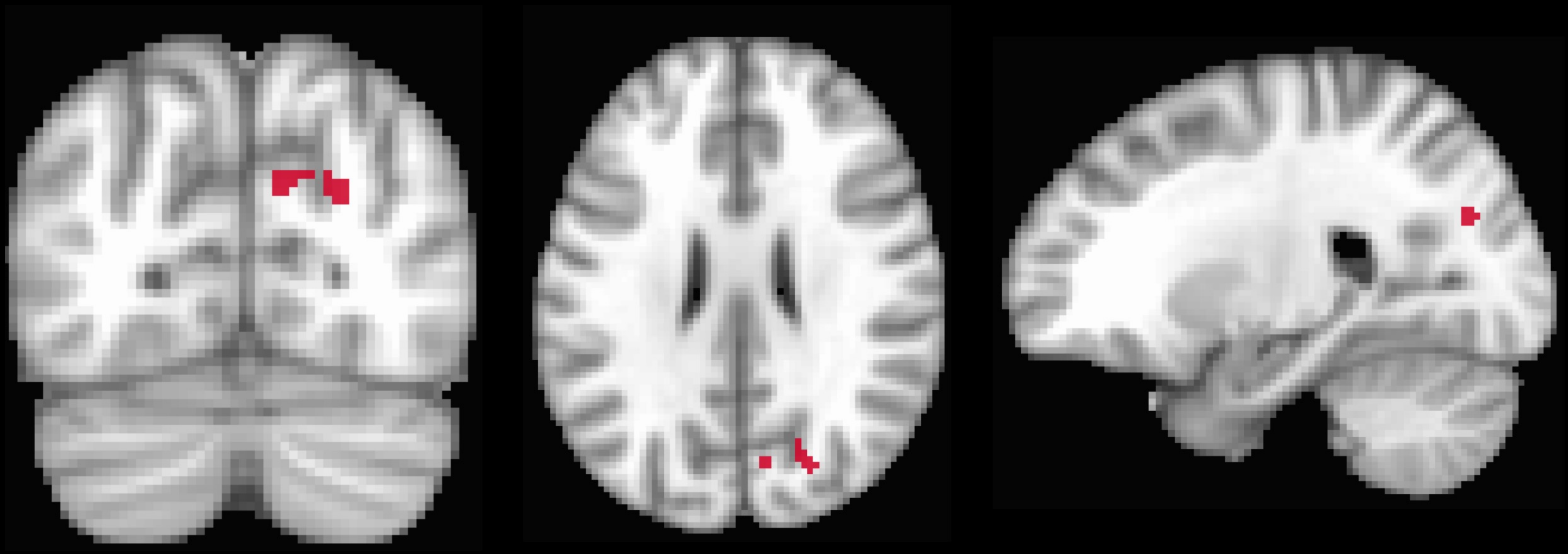


Positive Correlation :
↑ Cortical Thickness
↑ Motor Performance

Negative Correlation :
↓ Cortical Thickness
↑ Motor Performance

Impact of training on brain structure (Gray matter volume)

Correlation between change in GMV and change in performance



Long-term Motor learning

Positive Correlation : ↑ Gray Matter Volume ↑ Motor Performance

Study Summary

- The rest controls helped identify time-of-day as a significant confound
- MRI measures are sensitive enough to detect this effect!
- Important to keep in mind for longitudinal and cross-sectional designs
- Time-of-day impacts T_1W, DTI, and Resting state measures
- It's not just a confound – physiological phenomenon
- Multimodal MRI data can help understand possible mechanism
- 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

Outline

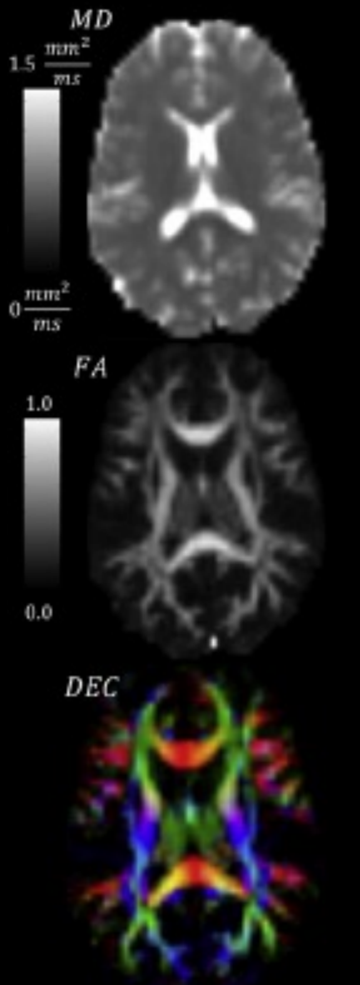
- The future of imaging changes in brain anatomy

The future of imaging changes in brain anatomy

- MRI has limited biological specificity
- More robust and quantitative maps of biophysical properties of tissue microstructure
- Validation studies that help understand the biological correlates of MRI changes
- Methods to pull together converging evidence from Multimodal MRI maps
- Statistical methods for proper inference

Maps from the Diffusion Propagator

DTI parameters



Avram et al., NeuroImage 2016

Image brain changes boldly, but cautiously

Thank you for your attention!

Thanks also to members of the Baker lab and Pierpaoli lab

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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Journal of Neuroscience Methods
journal homepage: www.elsevier.com/locate/jneumeth

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]

Some reading recommendations

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg
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NeuroImage

Full Length Articles

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

CrossMark

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]

Image brain changes boldly, but cautiously

Questions/ Comments?