Measuring Brain Change over Time

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Outline

- Motivation: What's the big deal? Why do I need a whole lecture on this?
- Image Registration Concerns
- Statistical Concerns
- fMRI & Learning

What's the big deal? Why do we need a whole lecture on this?

- "Despite this early recognition of [problems with asymmetric registration in longitudinal analyses], many (probably most) studies employing image registration for longitudinal data over the past decade have used methods with some form of asymmetry" *Ridgeway, Leung, & Ashburner, (2015) Brain Mapping: An Encyclopedic Reference.*

- "Longitudinal neuroimaging studies have yielded novel discoveries, yet a careful scrutiny of the literature reveals that the statistical methods commonly lack maturity and sophistication." *Bernal-Rusiel et al., 2013, Neuroimage*

The typical scenario…

- You decide to do a study
- There is a long list of difficult things to figure out: IRB, patients, scheduling, scan sequences, stimulus/response regime, image analysis…and there is limited time.
- Isn't longitudinal analysis the same as cross sectional analysis with an additional covariate?
- No: Longitudinal designs and analysis have several unique issues that need to be considered before beginning data collection

If it's so hard, why bother?

- Given a $1 Million budget (~ 200 scans) and a mandate to study the effect of aging (60+), is it better to scan 200 subjects of different ages or to scan 66 subjects at three different time points?
- Pros, Cons, & Tradeoffs
  - Time to complete study
  - Potential for dropout
  - Causality
  - Power

Why bother with longitudinal design?

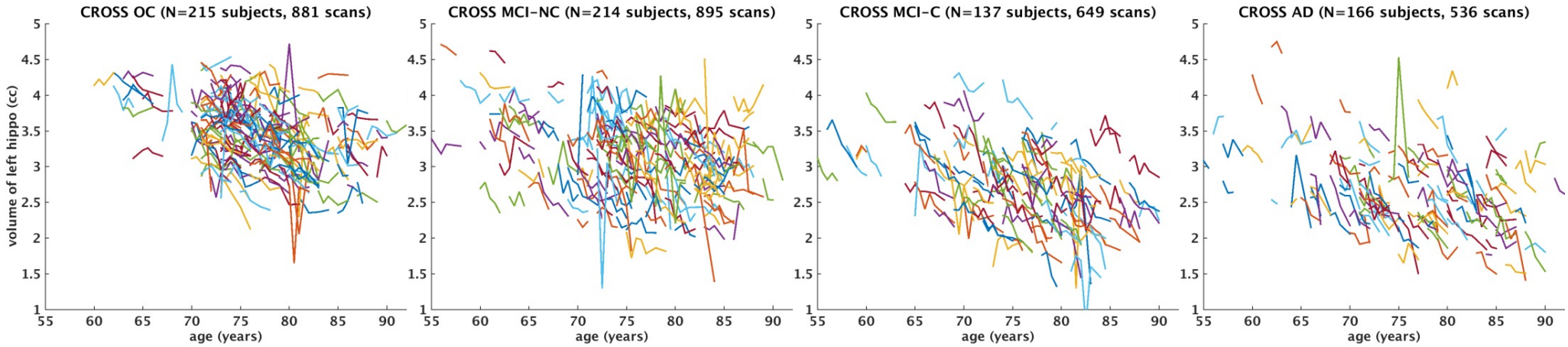
- True causality is impossible to establish without longitudinal studies (e.g. birth year effects)
- The only way to study learning
- Power: Longitudinal imaging is particularly powerful for the evaluation of response to treatment Ridha et al. (2008) report a five-fold reduction in the number of subjects with longitudinal design.

Why bother with longitudinal design?

Cross Sectional Analysis

(Each time point treated independently)

Left Hippocampal Volume in ADNI subjects



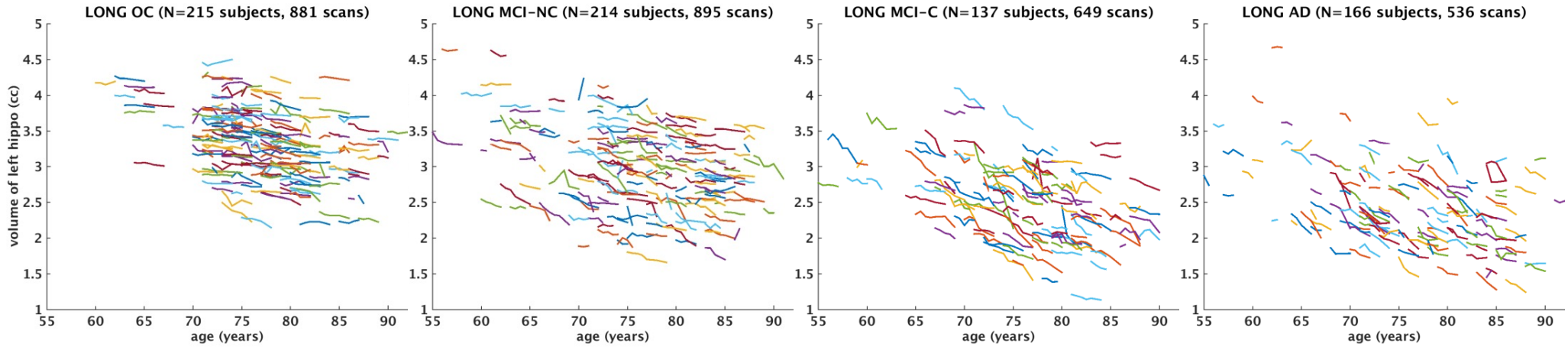
Elderly Controls | Stable MCI | MCI Converters | Alzheimer's

Slide courtesy of Bruce Fischl, work done with Martin Reuter, Mert Sabuncu and Doug Greve

Why bother with longitudinal design?

Longitudinal Analysis

Left Hippocampal Volume in ADNI subjects



Elderly Controls | Stable MCI | MCI Converters | Alzheimer's

Longitudinal analysis leveraging the knowledge that the same subject is being imaged over time greatly increases sensitivity

Slide courtesy of Bruce Fischl, work done with Martin Reuter, Mert Sabuncu and Doug Greve

Why bother with longitudinal design?

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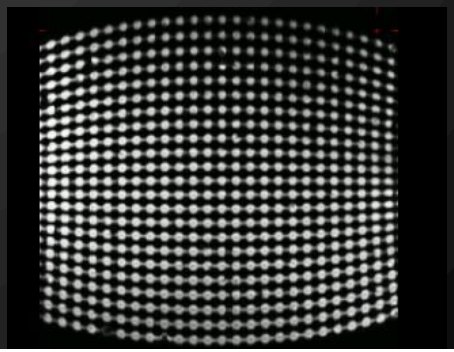
- The only way to study learning
- Power: Longitudinal imaging is particularly powerful for the evaluation of response to treatment Ridha et al. (2008) report a five-fold reduction in the number of subjects with longitudinal design.
- But, the additional sensitivity of longitudinal designs leads to a greater susceptibility to bias

With great power, comes great bias

- Science is about separating the thing you care about (the signal) from the things that you don't (the noise)
- In cross sectional designs the vast majority of the noise is inter-subject variability. People differ -- a lot
- This inter-subject noise dwarfs many other sources of noise and bias
- Longitudinal designs eliminate inter-subject variance, making it much easier to detect the signal, but also much easier to be confounded by various sources of bias
- Example: Geometric distortions



A Cautionary Tale

- Launched in October of 2004
- 4000+ Scans
- $60 Million funding (NIA, NIBIB, Pharma)
- ADNI GO, ADNI 2 additional $70-90 Million (wikipedia)
- 439 peer reviewed publications to date

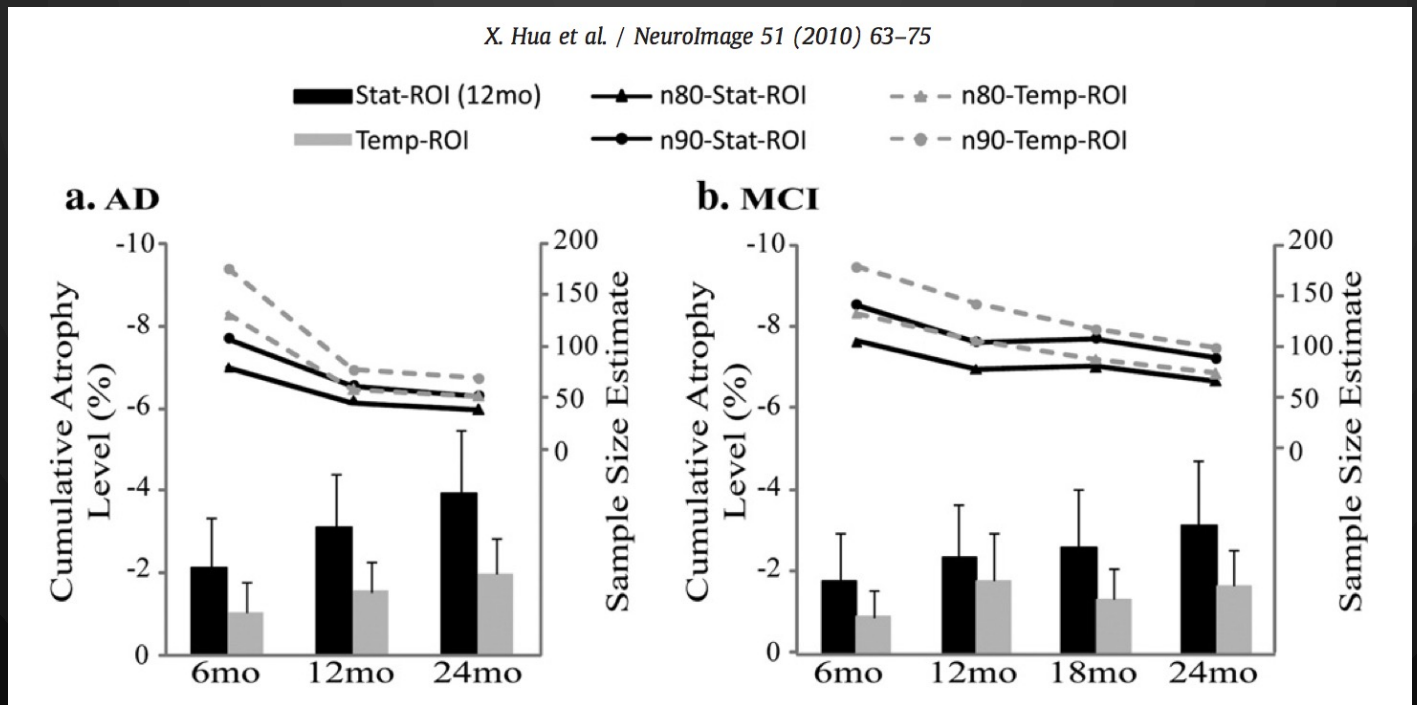
A Cautionary Tale

ADNI
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

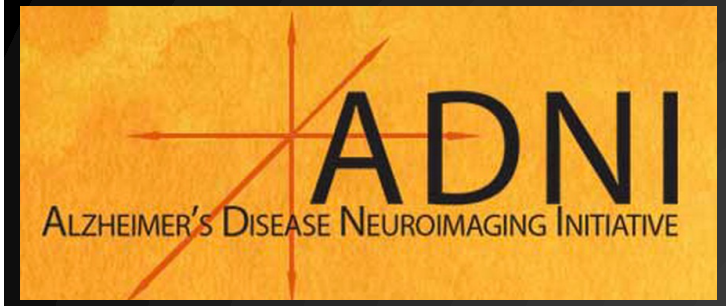
ELSEVIER
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

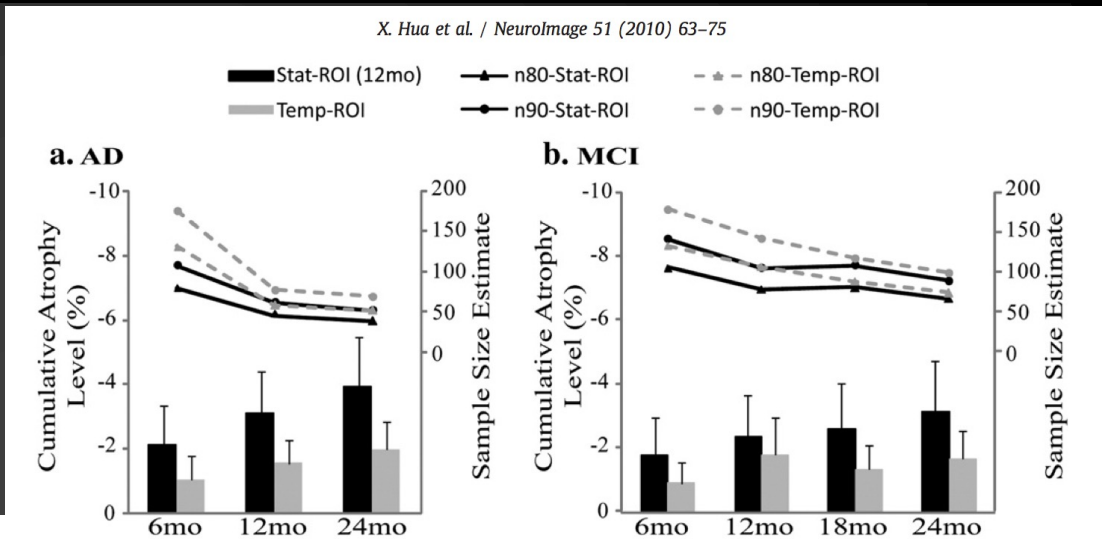
Mapping Alzheimer's disease progression in 1309 MRI scans: Power estimates for different inter-scan intervals☆

Xue Hua [a], Suh Lee [a], Derrek P. Hibar [a], Igor Yanovsky [c], Alex D. Leow [a,b], Arthur W. Toga [a], Clifford R. Jack Jr. [d], Matt A. Bernstein [d], Eric M. Reiman [e], Danielle J. Harvey [f], John Kornak [h,l], Norbert Schuff [g,h], Gene E. Alexander [k], Michael W. Weiner [g,h,i,j], Paul M. Thompson [a,*]
and the Alzheimer's Disease Neuroimaging Initiative



A Cautionary Tale





Comments and Controversies

Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates

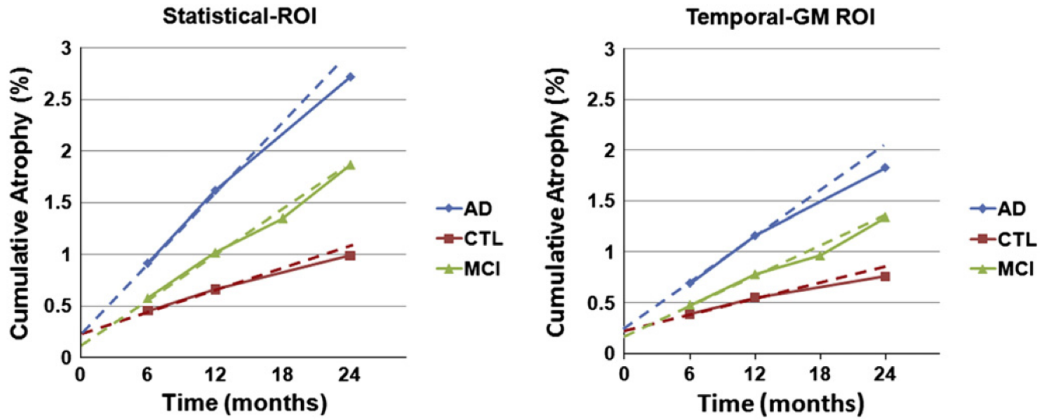
Wesley K. Thompson [a,b,*], Dominic Holland [c,d]
and the Alzheimer's Disease Neuroimaging Initiative [1]

- "more than 50% of the decline in Stat-ROI over a period of 24 months occurs within the first 6 months after baseline in both AD and MCI groups"
- However other studies have shown "rates of brain atrophy tend to accelerate as disease progresses from preclinical to early AD"
- "Using publicly-available ADNI data, this temporal pattern is also found in a group of identically-processed healthy controls, strongly suggesting that methodological bias is corrupting the measures. The resulting bias seriously impacts the validity of conclusions reached using these measures"

A Cautionary Tale

ADNI
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

X. Hua et al. / NeuroImage 57 (2011) 5–14



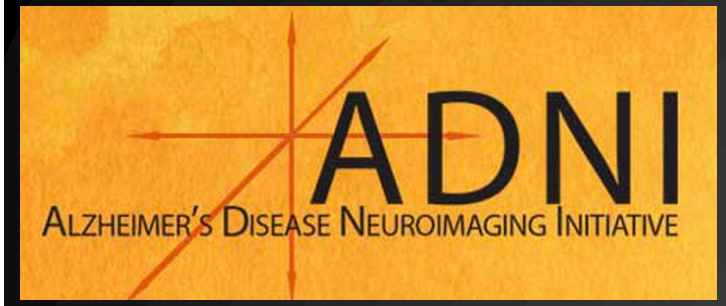
Comments and Controversies

Accurate measurement of brain changes in longitudinal MRI scans using tensor-based morphometry

Xue Hua [a,1], Boris Gutman [a,1], Christina P. Boyle [a], Priya Rajagopalan [a], Alex D. Leow [b,c,d], Igor Yanovsky [a], Anand R. Kumar [c], Arthur W. Toga [a], Clifford R. Jack Jr. [e], Norbert Schuff [f,g], Gene E. Alexander [h], Kewei Chen [i,j], Eric M. Reiman [i,k,l], Michael W. Weiner [f,g,m], Paul M. Thompson [a,*] and the Alzheimer's Disease Neuroimaging Initiative [2]

"We carefully studied and agreed with the main argument in Thompson and Holland's letter and have developed a solution to the problem by using inverse-consistent registration"

A Cautionary Tale



Comments and Controversies

Algorithms, atrophy and Alzheimer's disease: Cautionary tales for clinical trials

Nick C. Fox [a,*], Gerard R. Ridgway [a,b], Jonathan M. Schott [a]

[a] *The Dementia Research Centre, UCL Institute of Neurology, University College London, London WC1N 3BG, UK*
[b] *Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, University College London WC1N 3AR, UK*

Lessons and Observations:

1. All authors should be commended: the scientific process worked.
2. Open data is a very good thing.
3. Longitudinal measures should be symmetric (A->B = B<-A) and transitive (A->B + B->C = A->C)
4. Measure should be validated with more established technique (e.g. ROI volumes)

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- Motivation: What's the big deal? Why do I need a whole lecture on this?
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Approaches to Longitudinal Registration

- Unbiased registration is mostly an issue with structural imaging

- Common Approaches
- Simply do cross-sectional (Giedd et al., 1999, Nature Neuro) analysis, but you will lose sensitivity
- Direct, edge motion
  - Boundary Shift Interval (BSI)
  - SIENA
- Deformation Based Morphometry (DBM)
  - Longitudinal FSL-VBM
  - ANTS
  - SPM12
- Cortical Surface Measures: FreeSurfer Longitudinal Pipeline

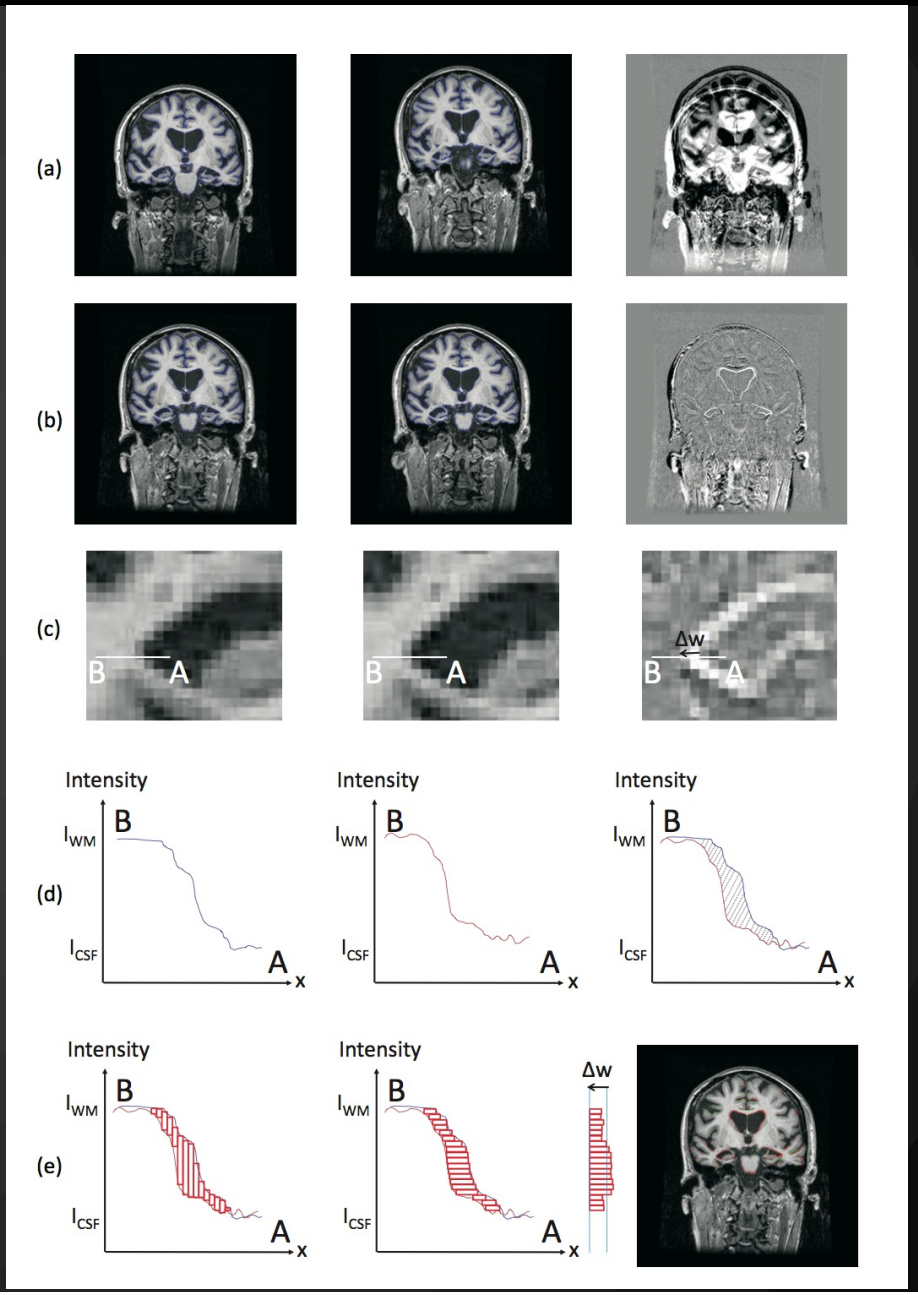
Measuring Change

Comparing Heights

- Direct vs. indirect measures of change
- Each measure has error, so one measurement is more precise than two
- Boundary Shift Interval & SIENA

Measuring Change

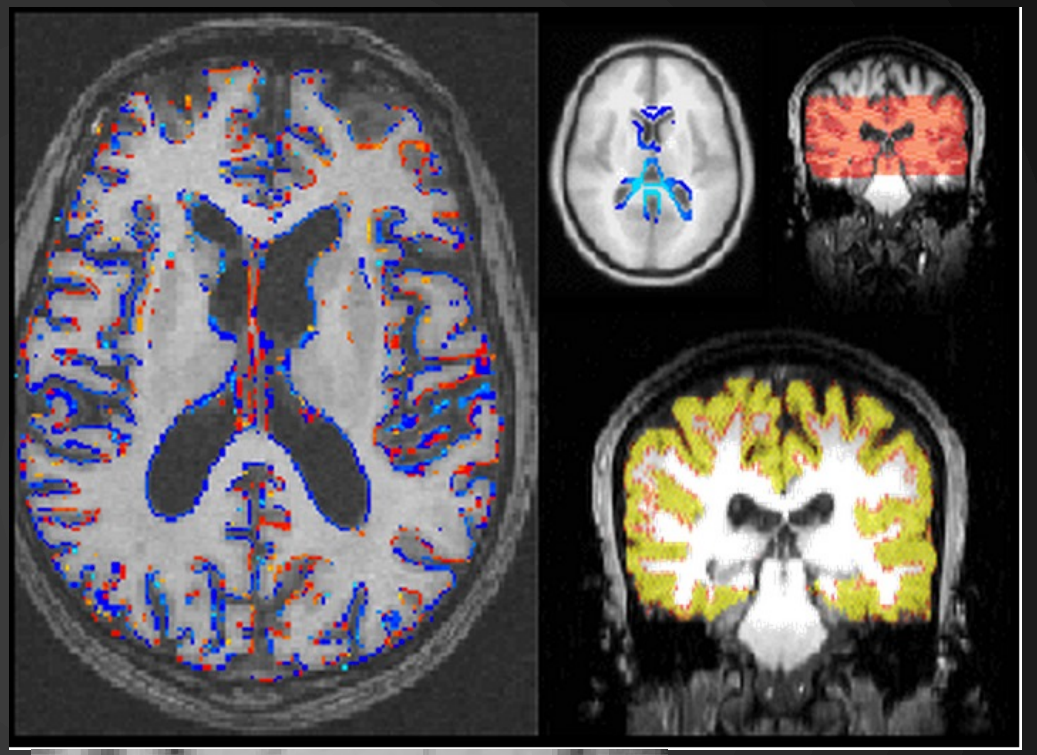
Boundary Shift Integral (BSI)
(Freeborough & Fox, 1997)

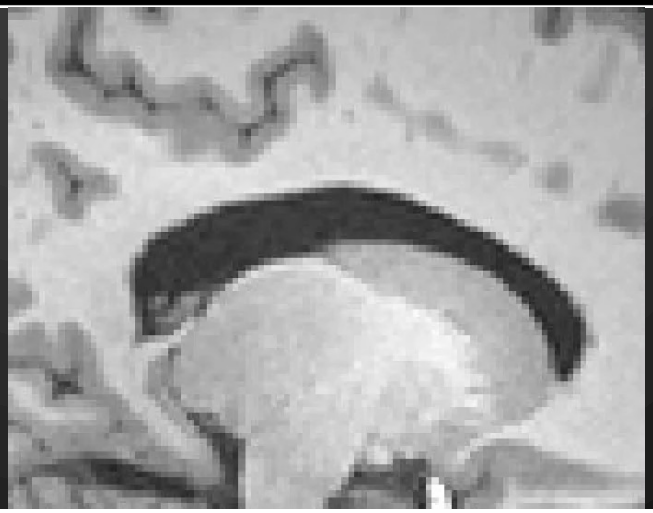


Measuring Change

SIENA

- Measures shift in edges across two time points
- Sensitive to atrophy and hydration changes (Kempton et al., 2011)
- Comparison with BSI shows consistency (Smith et al. 2007, Neuroimage)

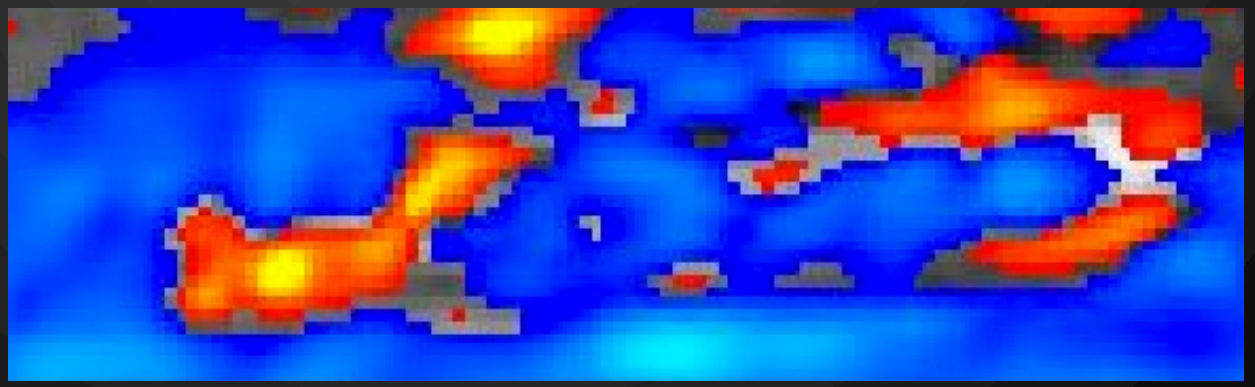




Deformation Based Morphometry

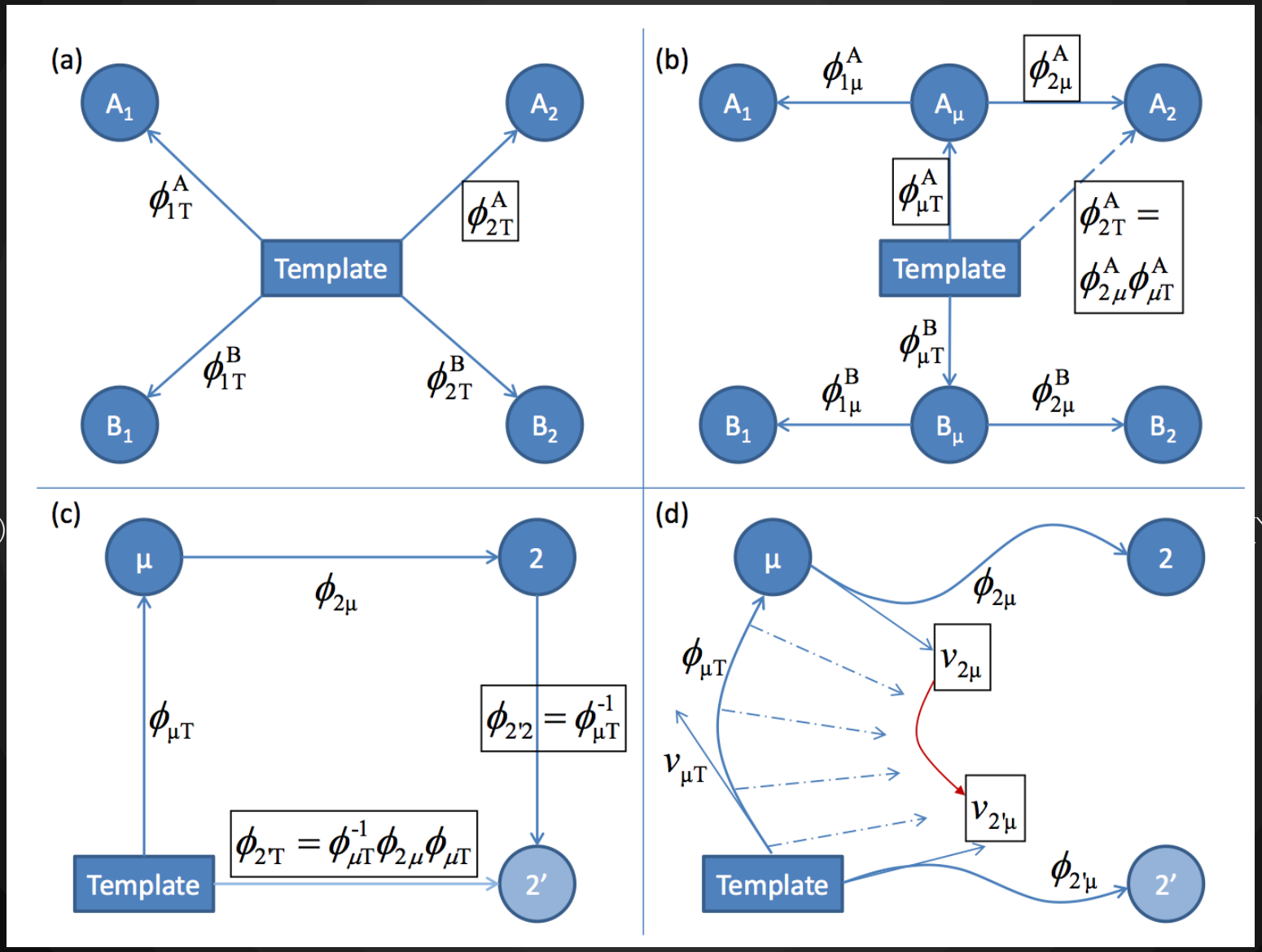
Single Subject

Average Template
(N=14)



Deformation Based Morphometry :Template Creation

Rao et al. (2004)

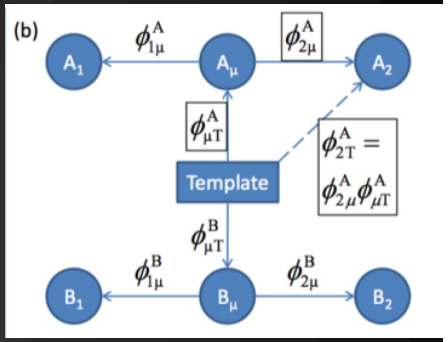


(Younes et al., 2008)

Ridgeway, Leung, & Ashburner (2015) Brain Mapping: An Encyclopedic Reference

Longitudinal VBM (FSL)

- Steps to avoid bias are explained in Douaud et al. 2009, Brain
  - Rigid, midpoint registration within subject
  - Minimal and uniform interpolation, though not mathematically rigorous

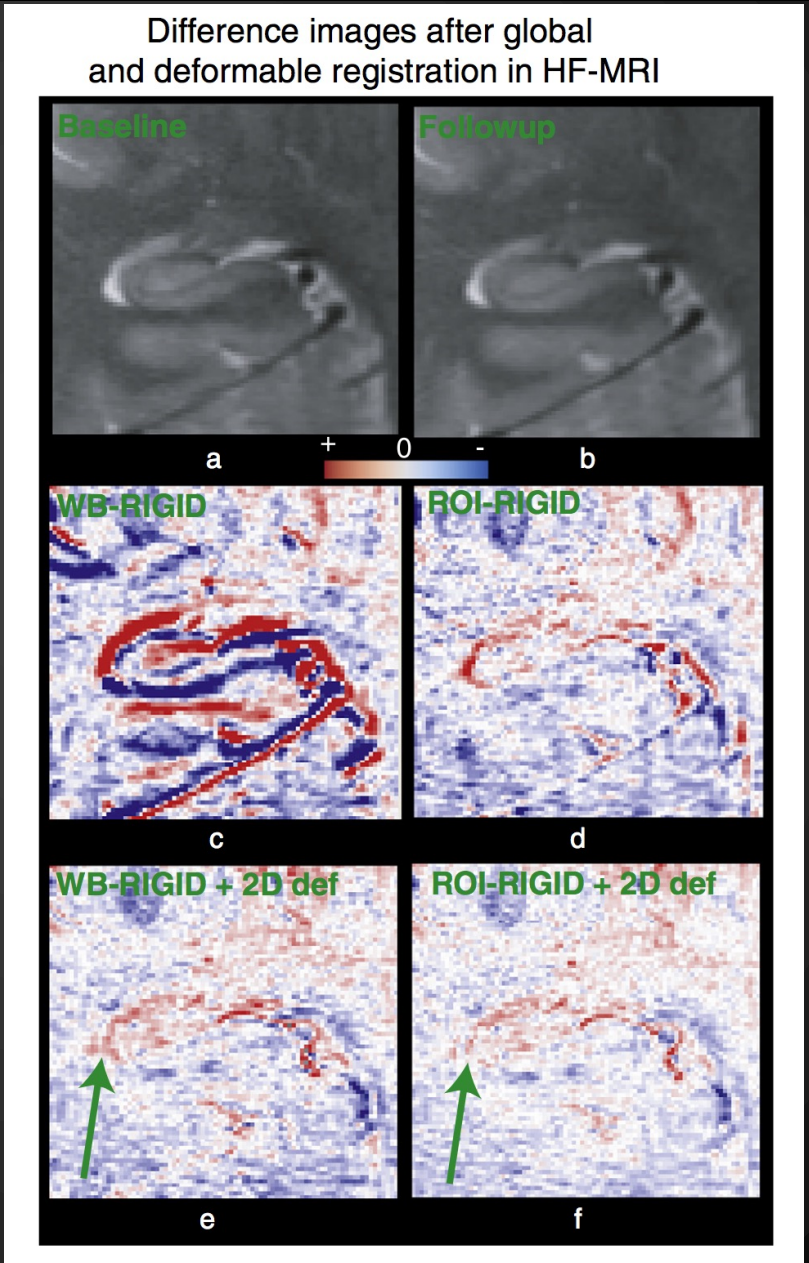


- Modified versions of the FSL-VBM pipeline available here: https://fmrif-intranet.nimh.nih.gov/projects/longitudinal-vbm-pipeline/files

DBM : ANTS

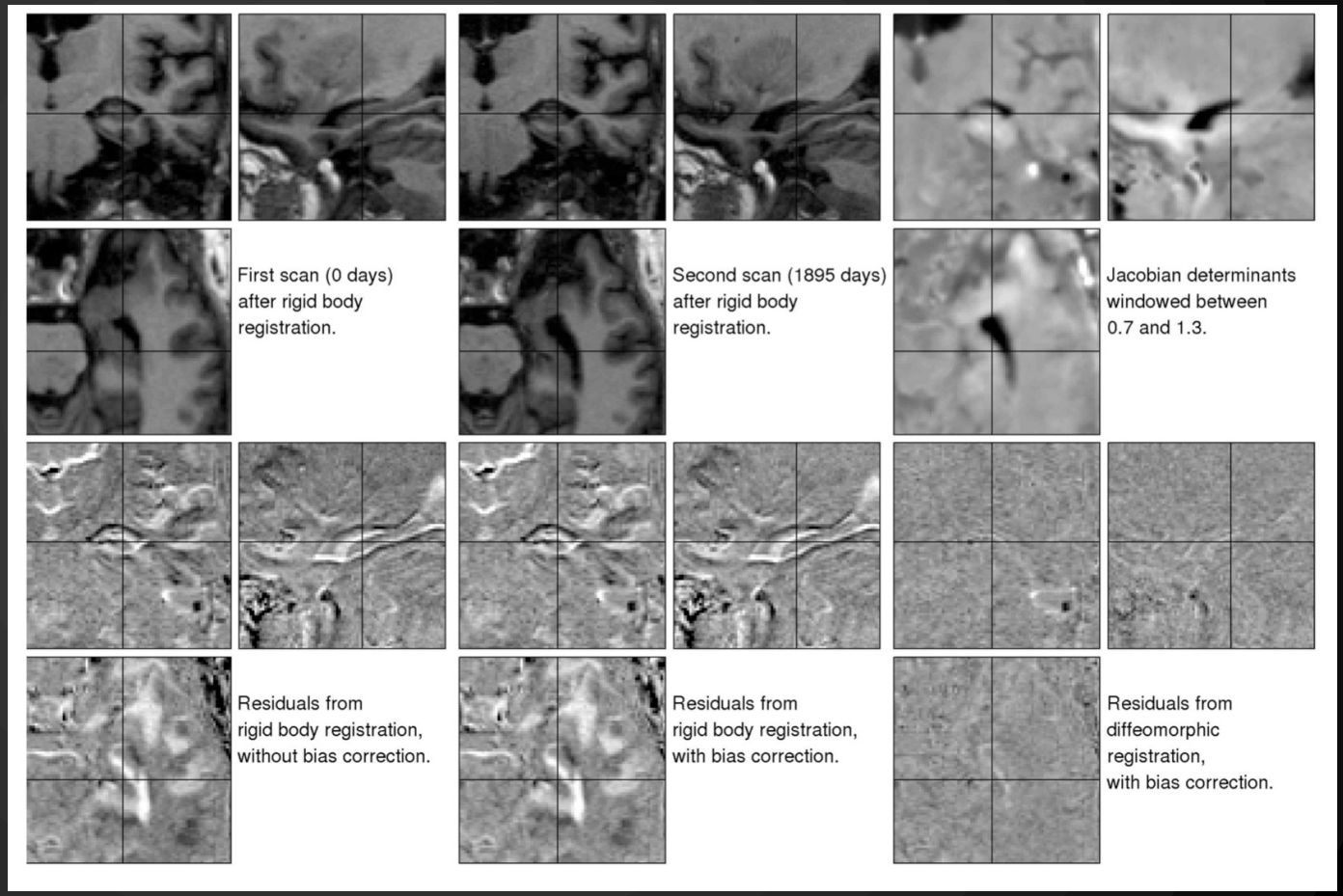
ANTS: Longitudinal change in Hippocampus

- Determined to be the most accurate and consistent non-linear deformation software in an independent evaluation of 14 different algorithm (Klein et al., 2009, Neuroimage).
- Contains scripts to handle longitudinal DBM without introducing bias



SPM12 : Symmetric diffeomorphic modeling

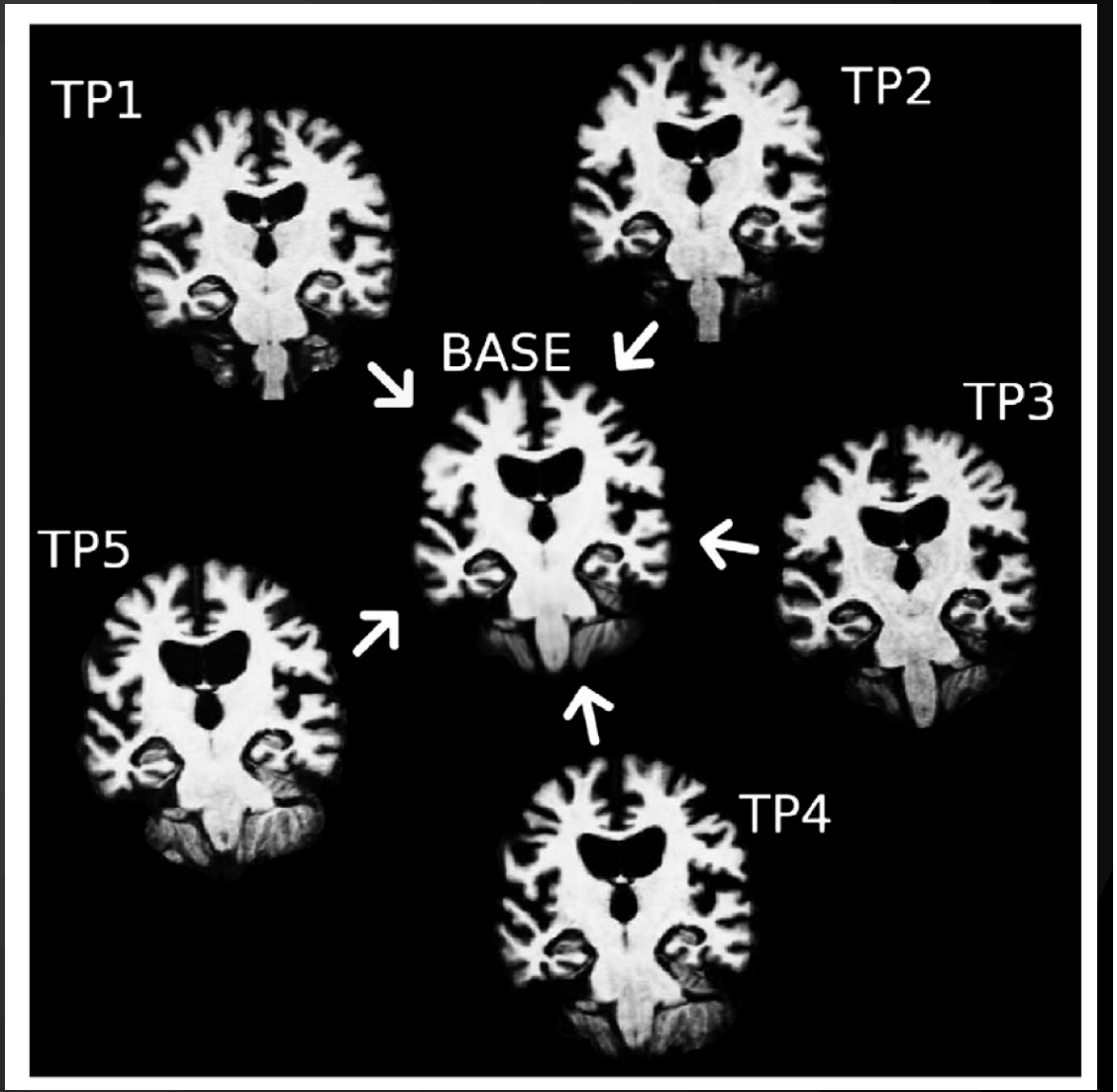
- Necessarily symmetric
- Incorporates intensity inhomogeneity correction
- Currently only works for pairs



MCI, 7 year follow up. Ashburner, J., Ridgway, G.R., 2012. Symmetric diffeomorphic modeling of longitudinal structural MRI. Front Neurosci 6, 197.

FreeSurfer Longitudinal Pipeline

- Very advanced & user-friendly longitudinal processing stream
- Works with multiple time points
- Complete symmetry
- Longitudinal statistical suite (LME) also available



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Coding Your Data

- Cross sectional data: "wide"

ID	Metric1	Metric2	Metric3
1	10	5	6
2	20	4	6
3	30	3	6

Wide Format

Coding Your Data

- Cross sectional data: "wide"
- Alternative: "tall"
- Also "Person" vs. "Person-Period"
- Stacking, splitting, reshaping

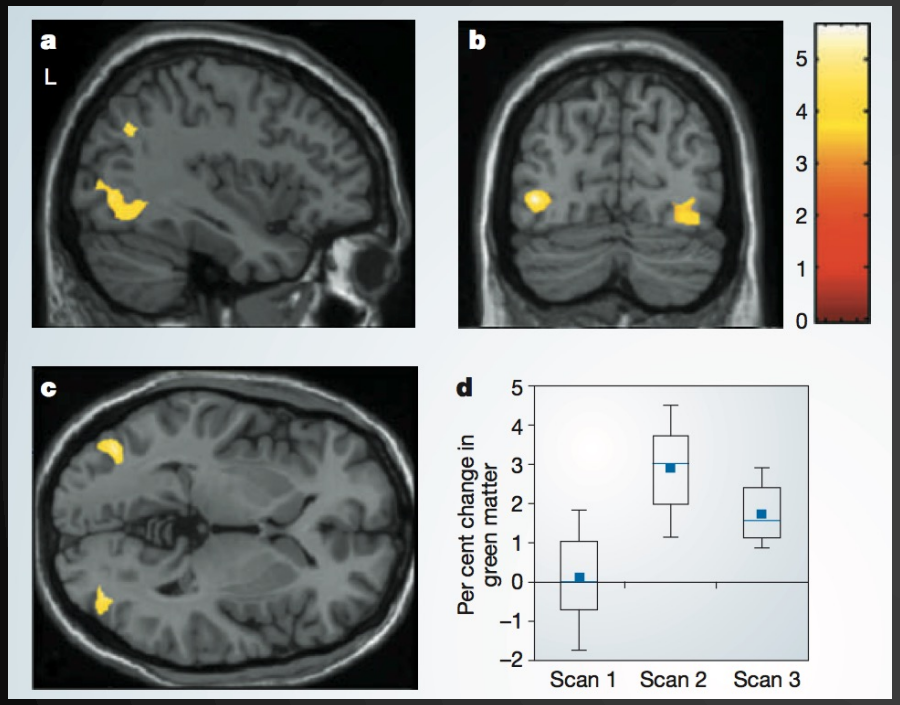
ID	Metric1	Metric2	Metric3
1	10	5	6
2	20	4	6
3	30	3	6

Wide Format

Tall Format

ID	variable	value
1	Metric1	10
2	Metric1	20
3	Metric1	30
1	Metric2	5
2	Metric2	4
3	Metric2	3
1	Metric3	6
2	Metric3	6
3	Metric3	6

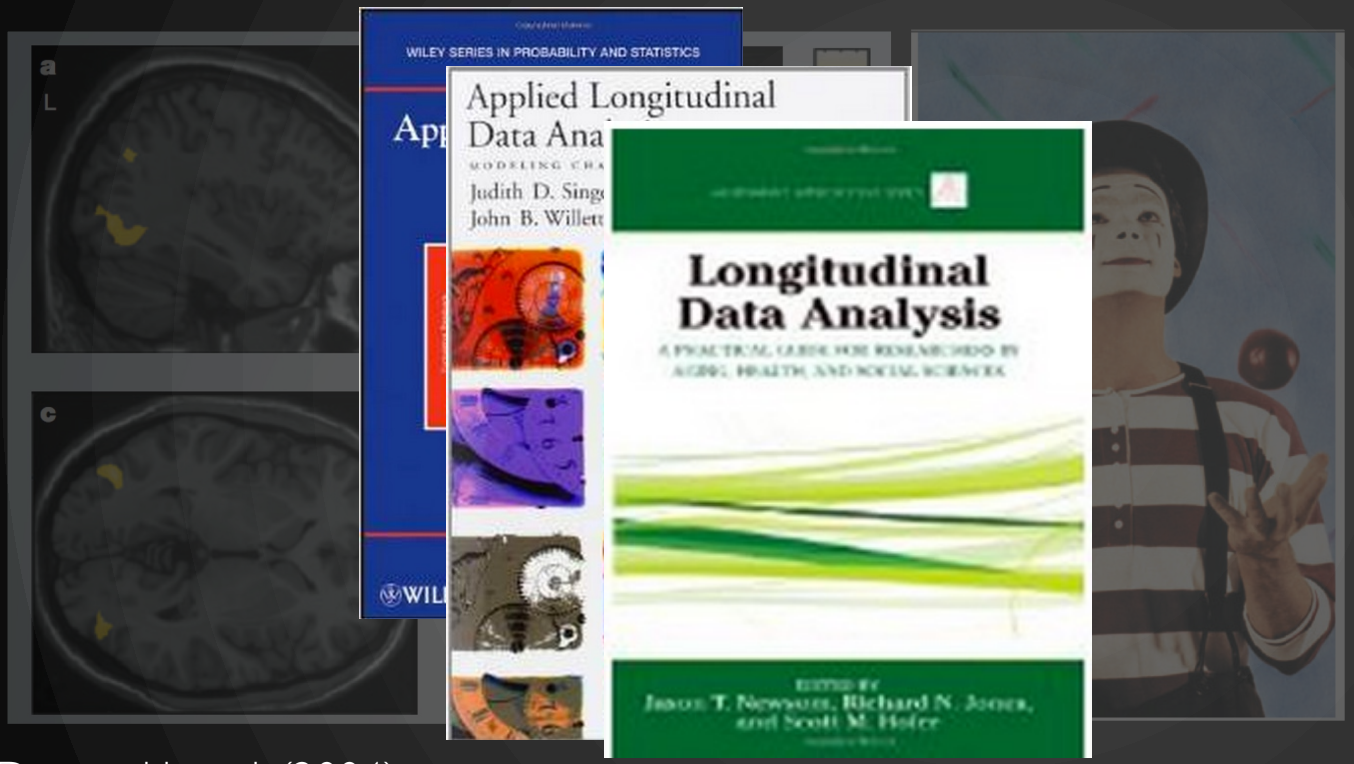
Assumption of Stability



Draganski et al., 2004, Nature

- Implicit null hypothesis: Grey matter does not change over time

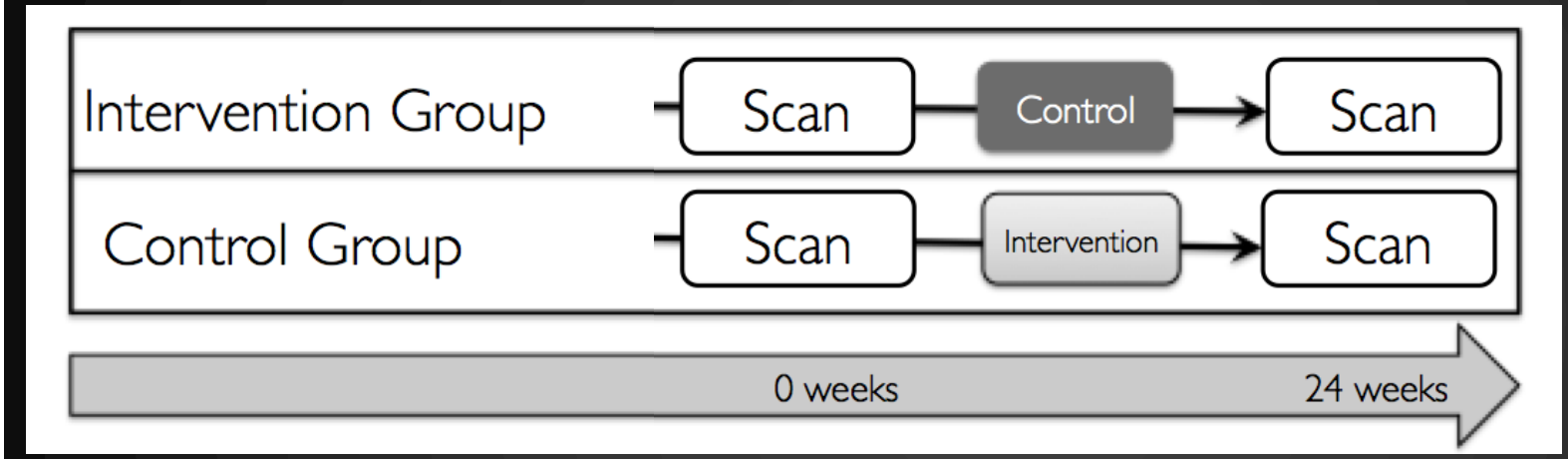
Assumption of Stability

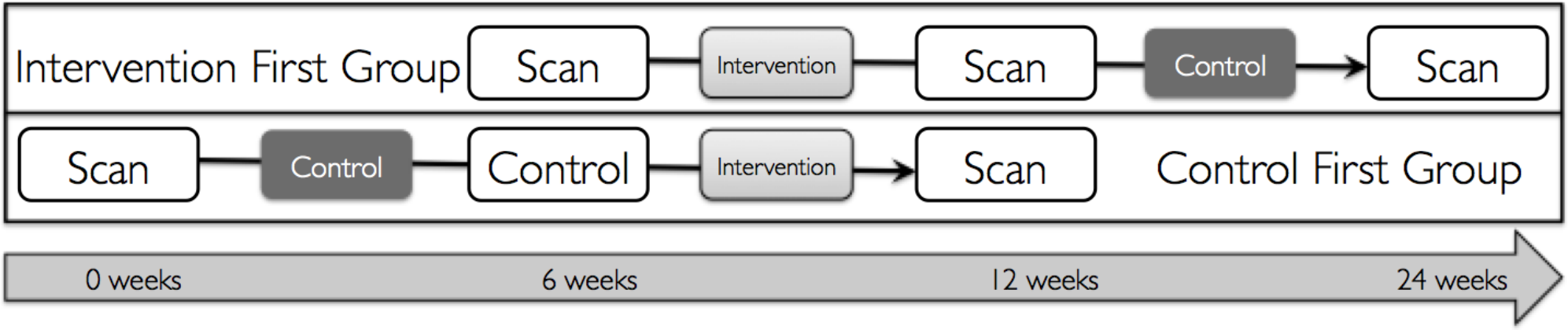


Draganski et al. (2004)

- Implicit null hypothesis: Grey matter does not change over time
- Accepted practice throughout biostatistics: Change is the null hypothesis
  - Many, if not most, natural and biological systems change over time (seasonal & circadian cycles, scanner drift, habituation, practice, etc.)

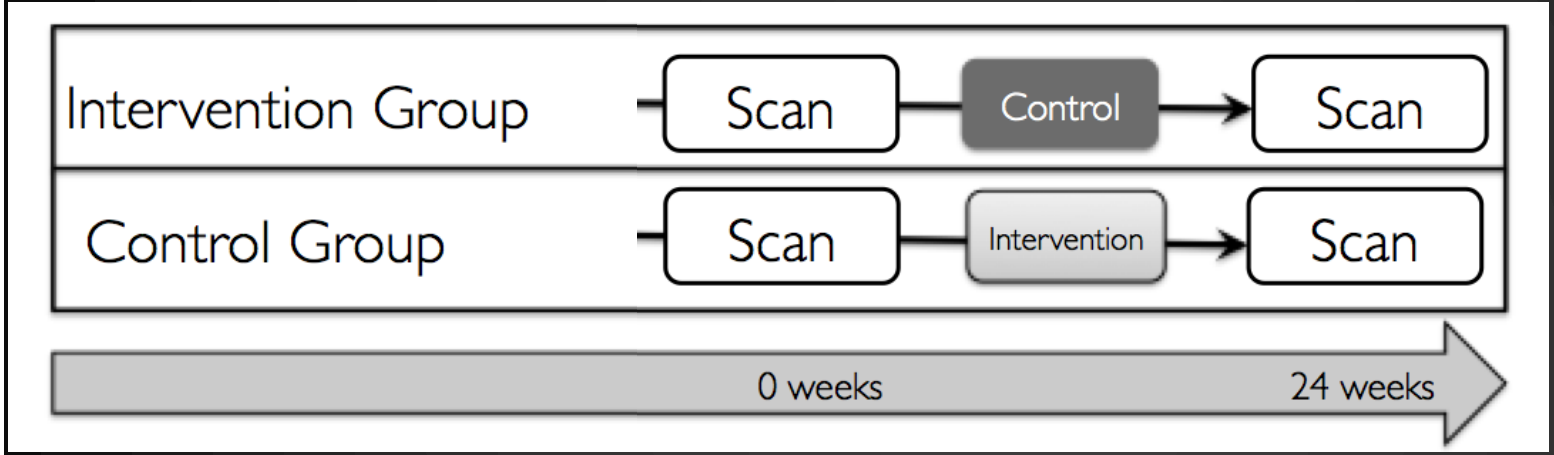
Possible Designs





The Imager's Fallacy

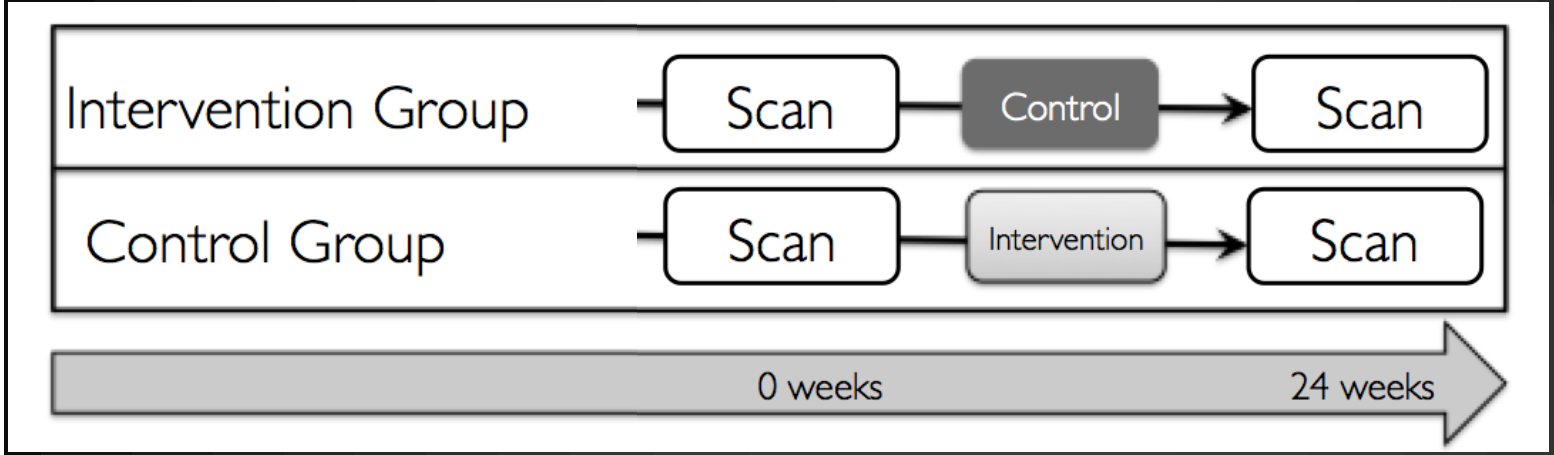
- Two-group Design

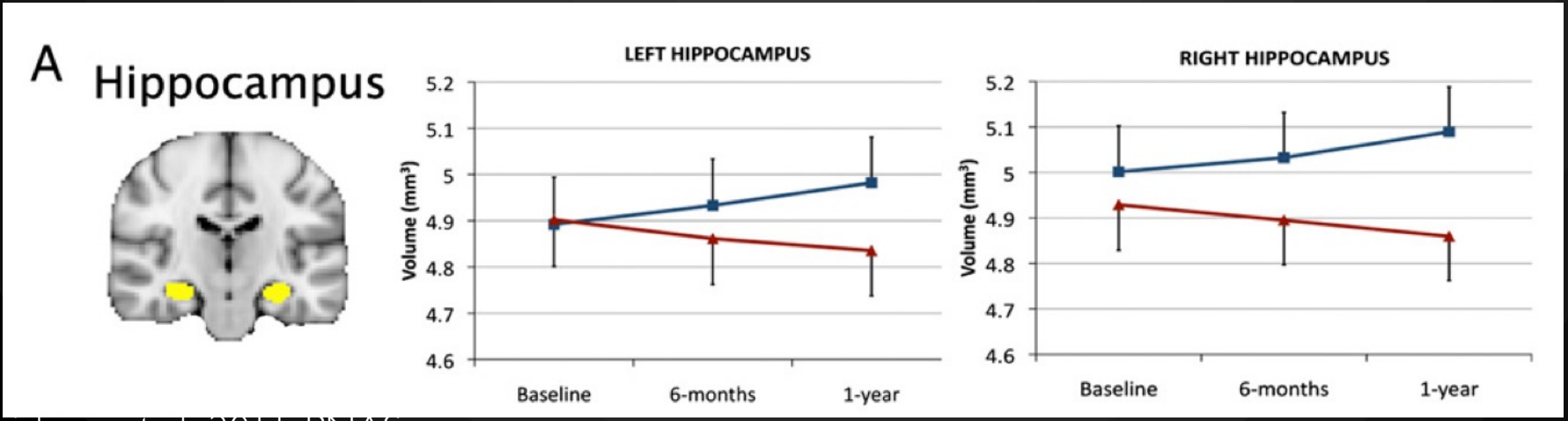


"The Imager's Fallacy" (Polldrack et al. 2009; Henson 2005)

- Showing a significant change in the intervention condition and failing to show a change in the control condition
- P=0.04 & P=0.06?
- One must show the two conditions are different to prove an affect of the intervention (e.g. Repeated measured ANOVA)

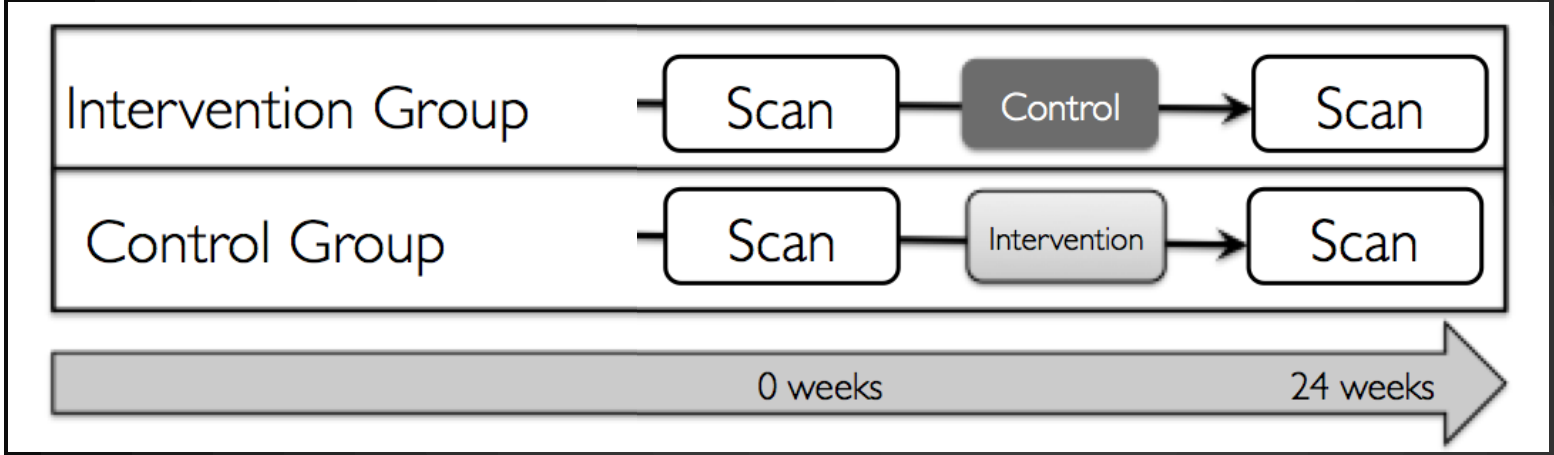
Two-group Design



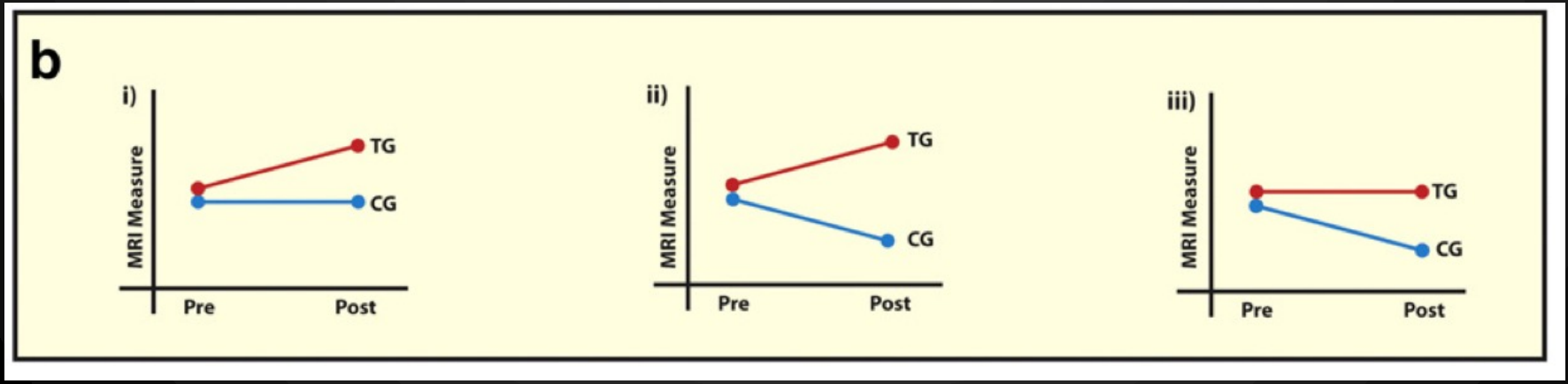


Erickson et al., 2011, PNAS

Two-group Design



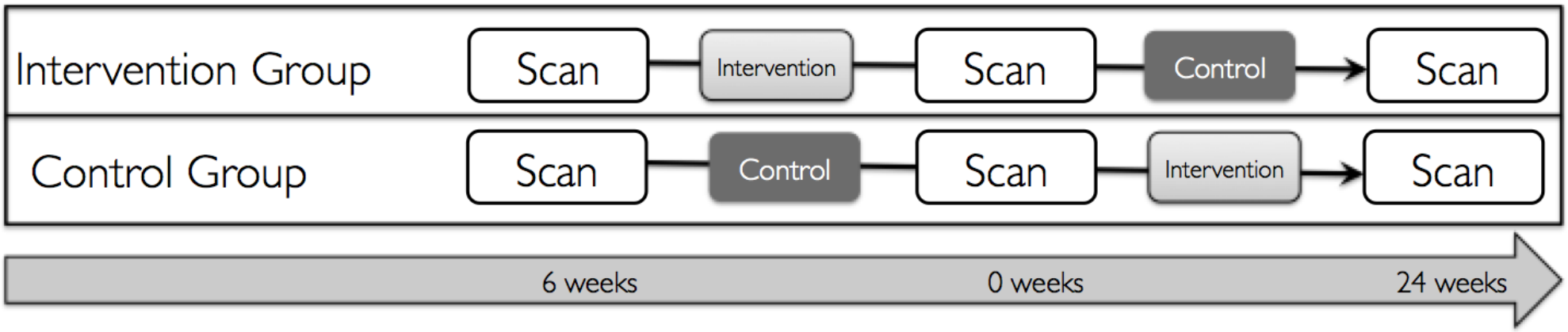
Repeated Measures ANOVA Interaction Issues



Thomas & Baker, 2012, Neuroimage

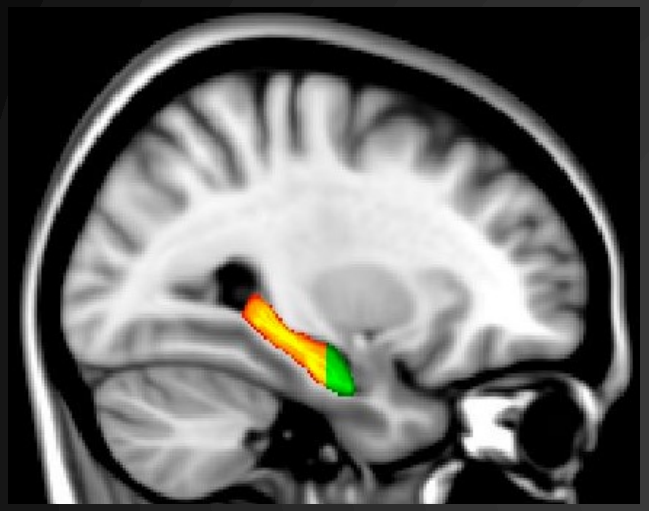
Crossover Design

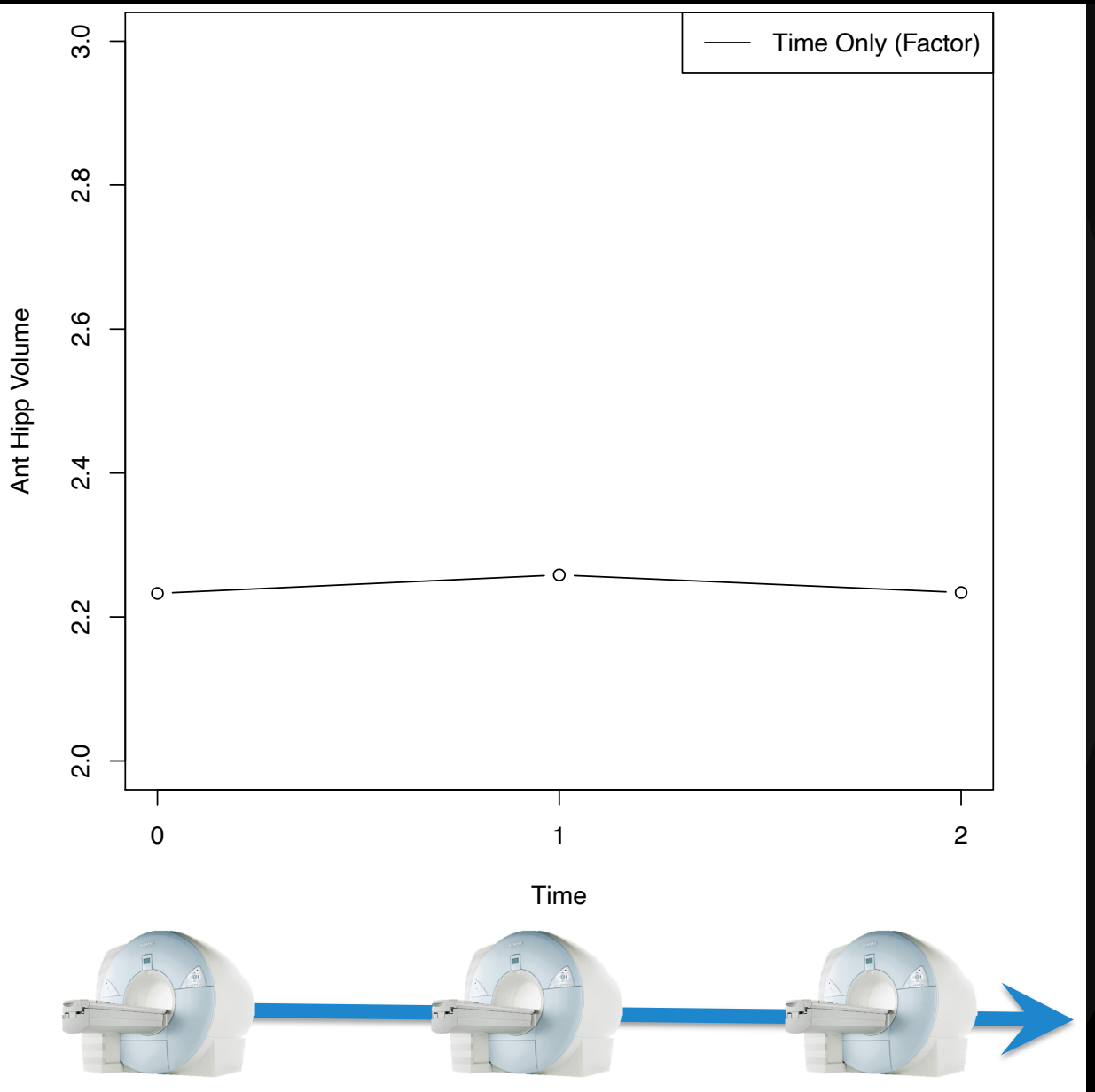
- Crossover Design



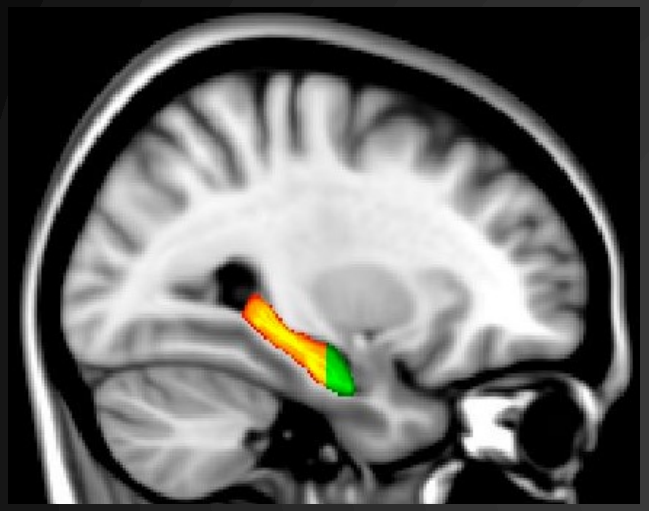
- Very common design in drug studies
- Frequently analyzed using Linear Mixed Effects (LME) approach (See Bernal-Rusiel et al., 2013 & Chen et al., 2013)
- Instead of comparing conditions (is this significantly bigger than that) it involves comparing models with increasing numbers explanatory variables e.g.:
  - Subject
  - Time point
  - Presence of intervention

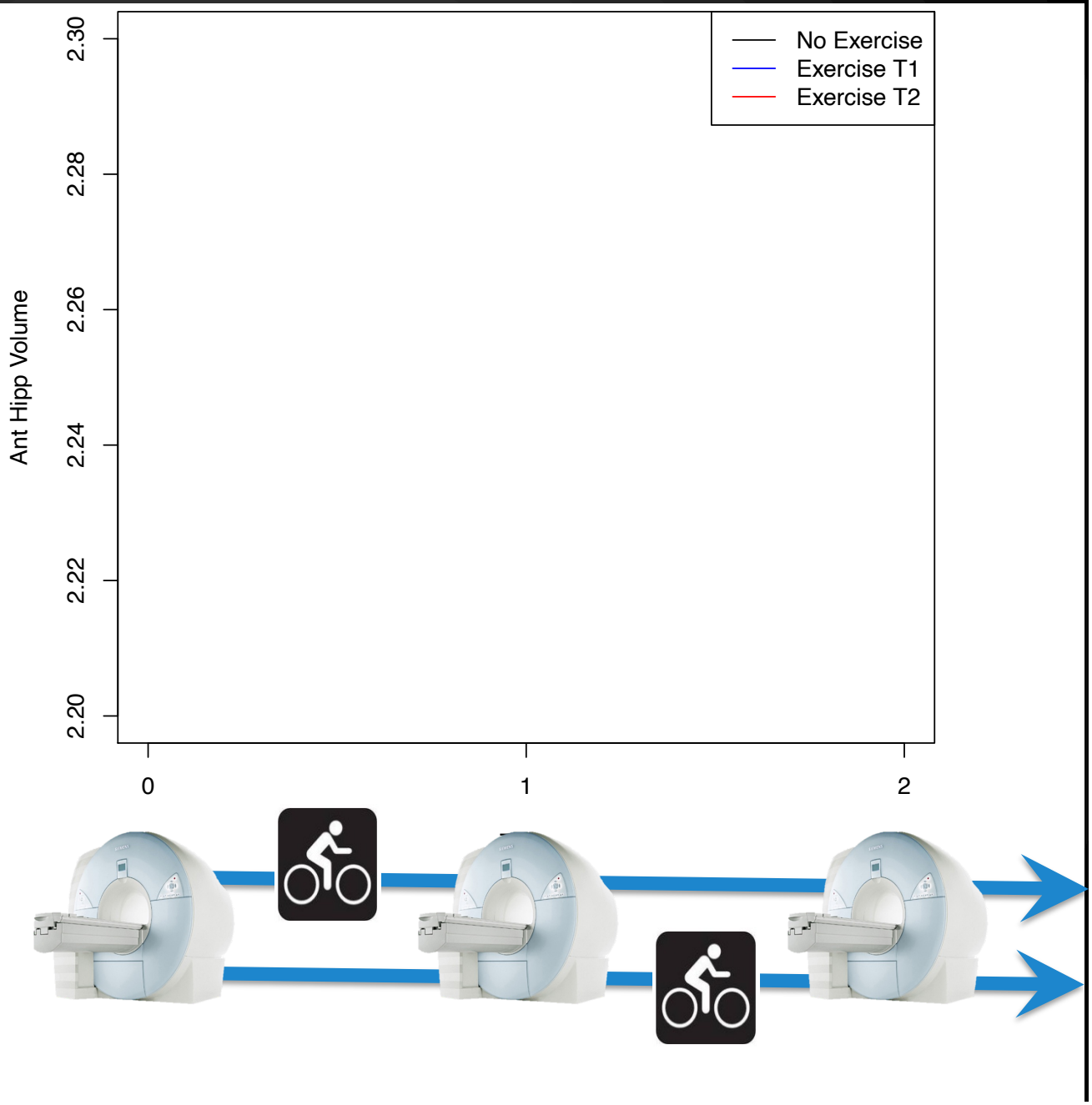
Linear Mixed Effects Model for Change: Null Hypothesis = Time



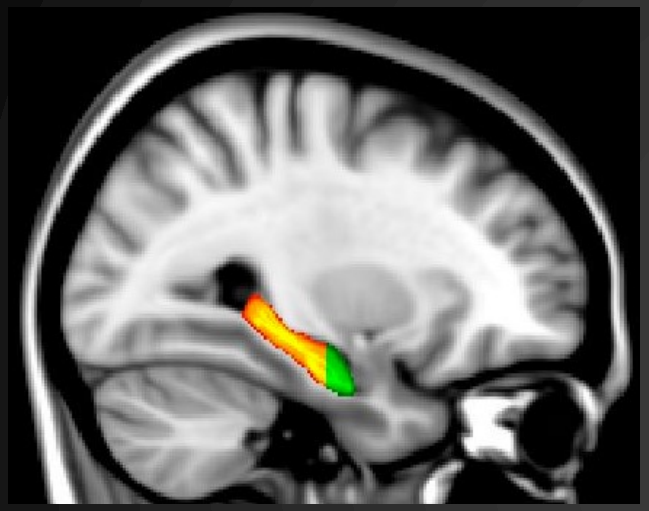


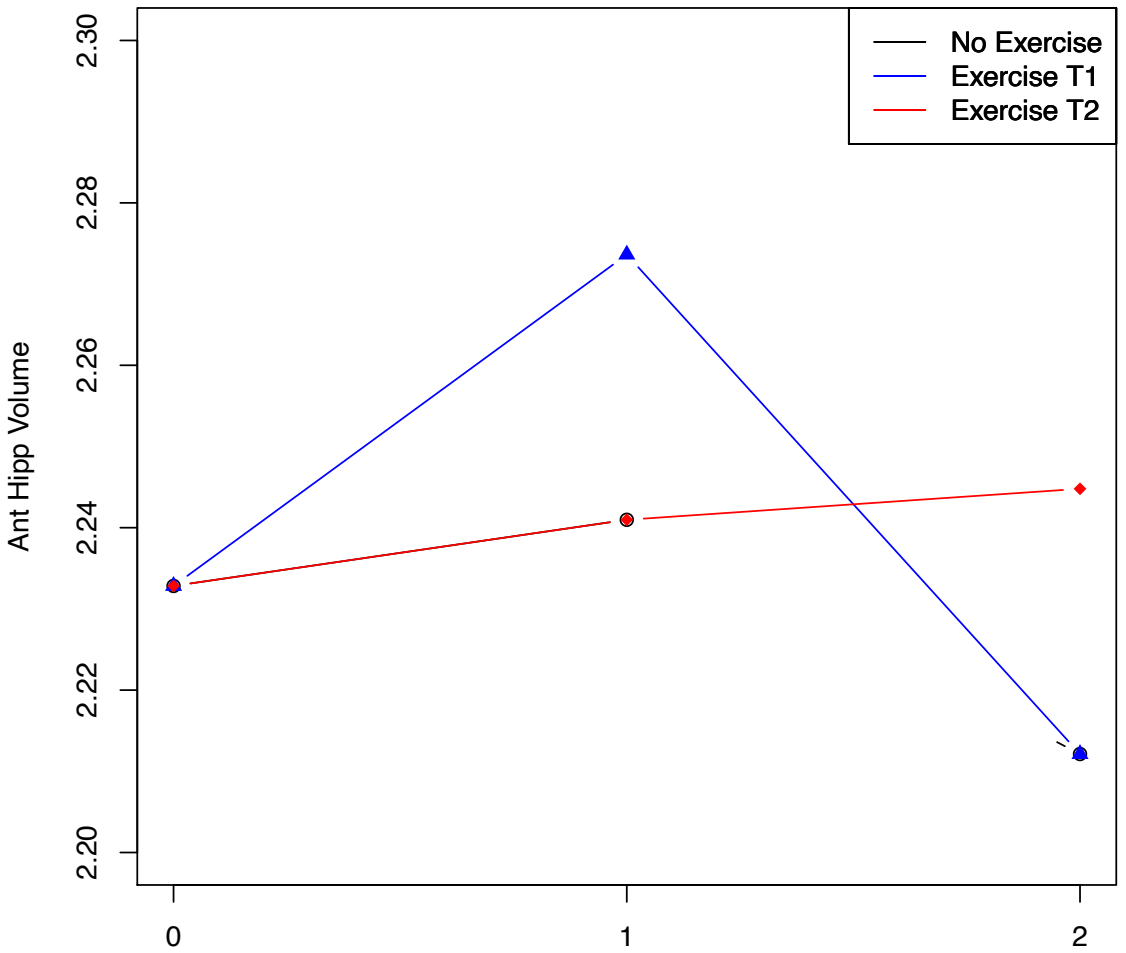
LME Model for Change: Time + Intervention

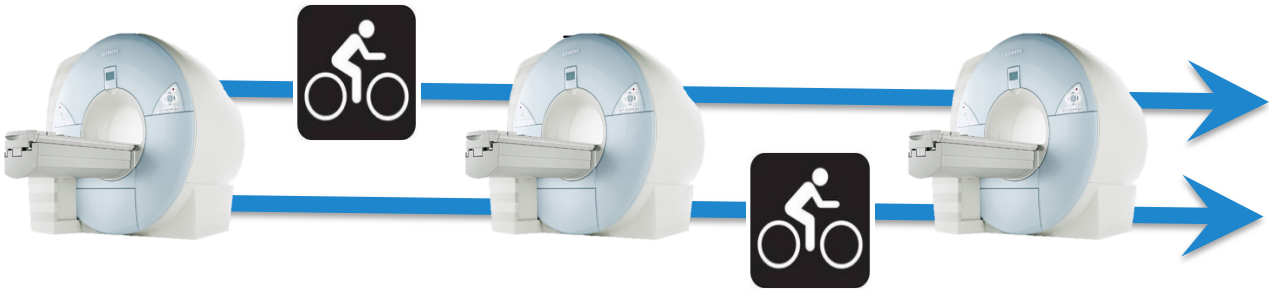




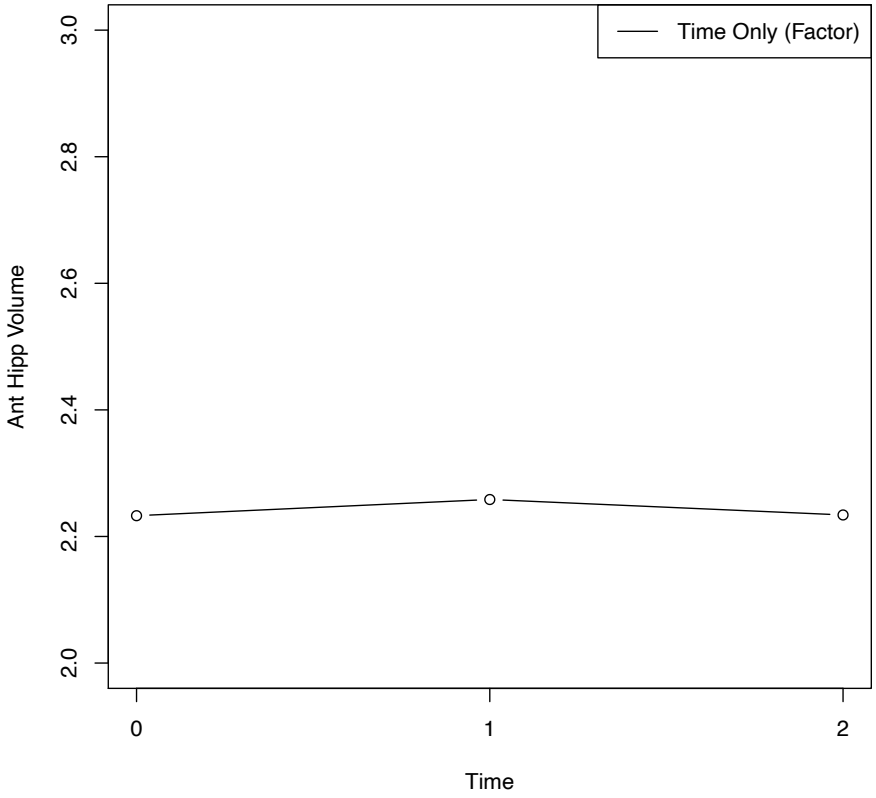
LME Model for Change: Time + Intervention







Linear Mixed Effects Model for Change: Comparing Models



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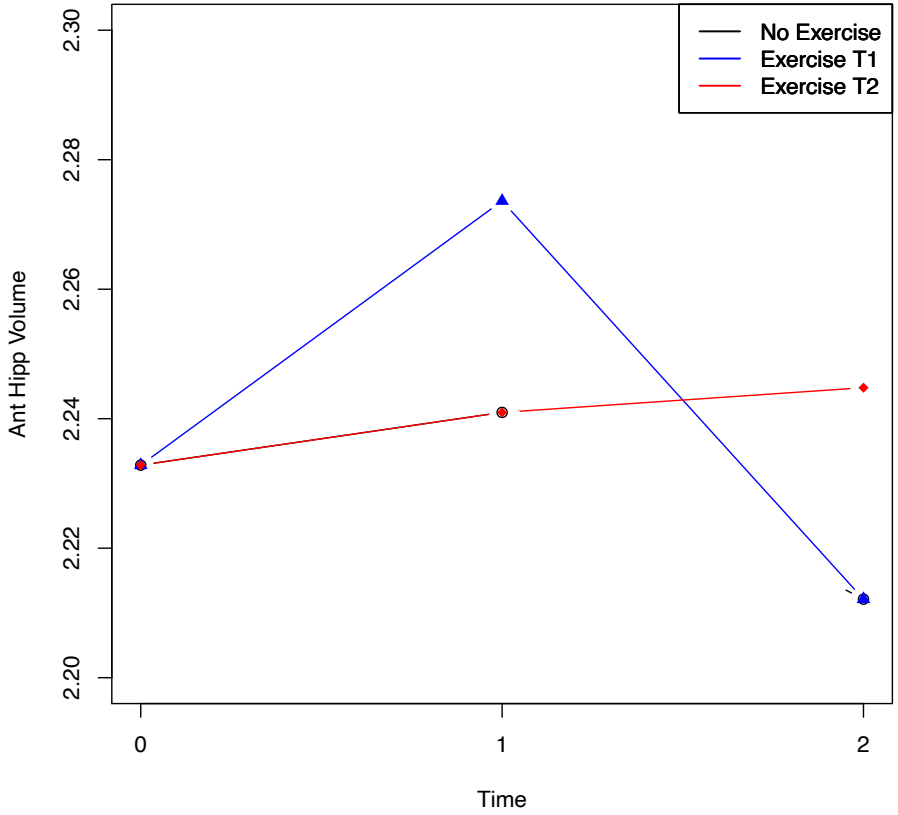


```
> anova(model.timeF, model.Ex)
             Model df       AIC       BIC   logLik   Test  L.Ratio p-value
model.timeF      1  5 -164.2085 -149.2563 87.10426
model.ex         2  6 -166.3731 -148.4305 89.18655 1 vs 2 4.164582  0.0413
```

Longitudinal analysis approaches

- Active debate
  - Repeated Measures ANOVA / GLM
    - Needs balanced design, variance assumptions questionable
    - Underpowered, interactions can be misleading
  - Linear Mixed Effects (LME)
    - Excellent power and versatility
    - Handles missing data
    - Good for complicated designs
    - Somewhat impractical for whole brain (mass univariate analyses) but see Bernal-Rusiel et al., 2013
  - 3d Multivariate Modeling (3dMVM, Chen et al., 2014, Neuroimage)
  - Sandwich Estimator (SwW, Guillaume et al. 2014, Neuroimage)

Consult with a statistician before you begin your study!

Outline

- Motivation: What's the big deal? Why do I need a whole lecture on this?
- Image Processing Concerns
- Statistical Concerns
- fMRI & Learning

fMRI and Learning

NeuroImage 12, 1–13 (2000)
doi:10.1006/nimg.2000.0596, available online at http://www.idealibrary.com on IDEAL®

COMMENTS AND CONTROVERSIES

Imaging Brain Plasticity: Conceptual and Methodological Issues—A Theoretical Review

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Received January 25, 2000

- Studying learning with fMRI is riddled with pitfalls & confounds
- Changes in attention, strategy, performance, and neural structure are difficult to disentangle
- Careful controls are necessary

Key Points

- Longitudinal neuroimaging is very different than cross sectional neuroimaging. It demands special considerations regarding design and analysis. Most neuroimaging papers ignore these considerations – please don't.
- Consult with methodology experts (Gang, Ziad, Bob, etc.) regarding image registration and statistical issues before starting your study
- Removing inter-subject variability adds power, but also increases susceptibility to bias – be careful
- Change is the Null – always have a control group with multiple time points

Key References

- Ridgway, G.R., Leung, K.K., Ashburner, J., (2015) Computing Brain Change over Time. *Brain Mapping: An Encyclopedic Reference*.
- Chen, G., Adleman, N., Leibenluft, E., Saad, Z.S., Cox, R.W., (2014) Applications of Multivariate Modeling to Neuroimaging Group Analysis: A Comprehensive Alternative to Univariate General Linear Model. *Neuroimage* 1–26.

Questions?