

Measuring subtle changes in brain shape in mice and humans

Jason Lerch

SickKids[®]

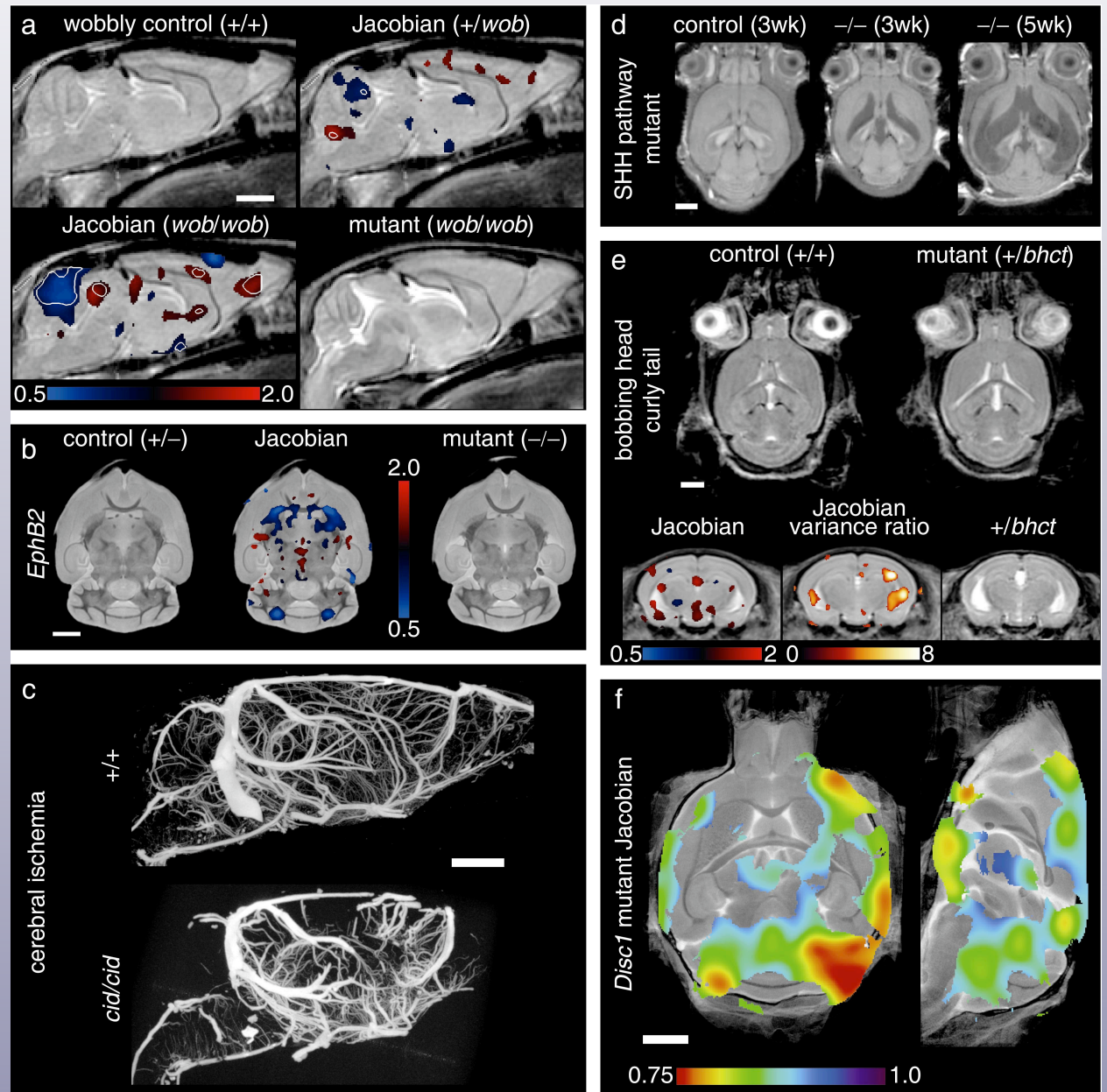
Mice
MOUSE IMAGING CENTRE

Whither this talk?

- Main theme: measuring changes in neuroanatomy.
- Focus on two methods:
 - non-linear registrations and deformation based morphometry.
 - Cortical thickness.

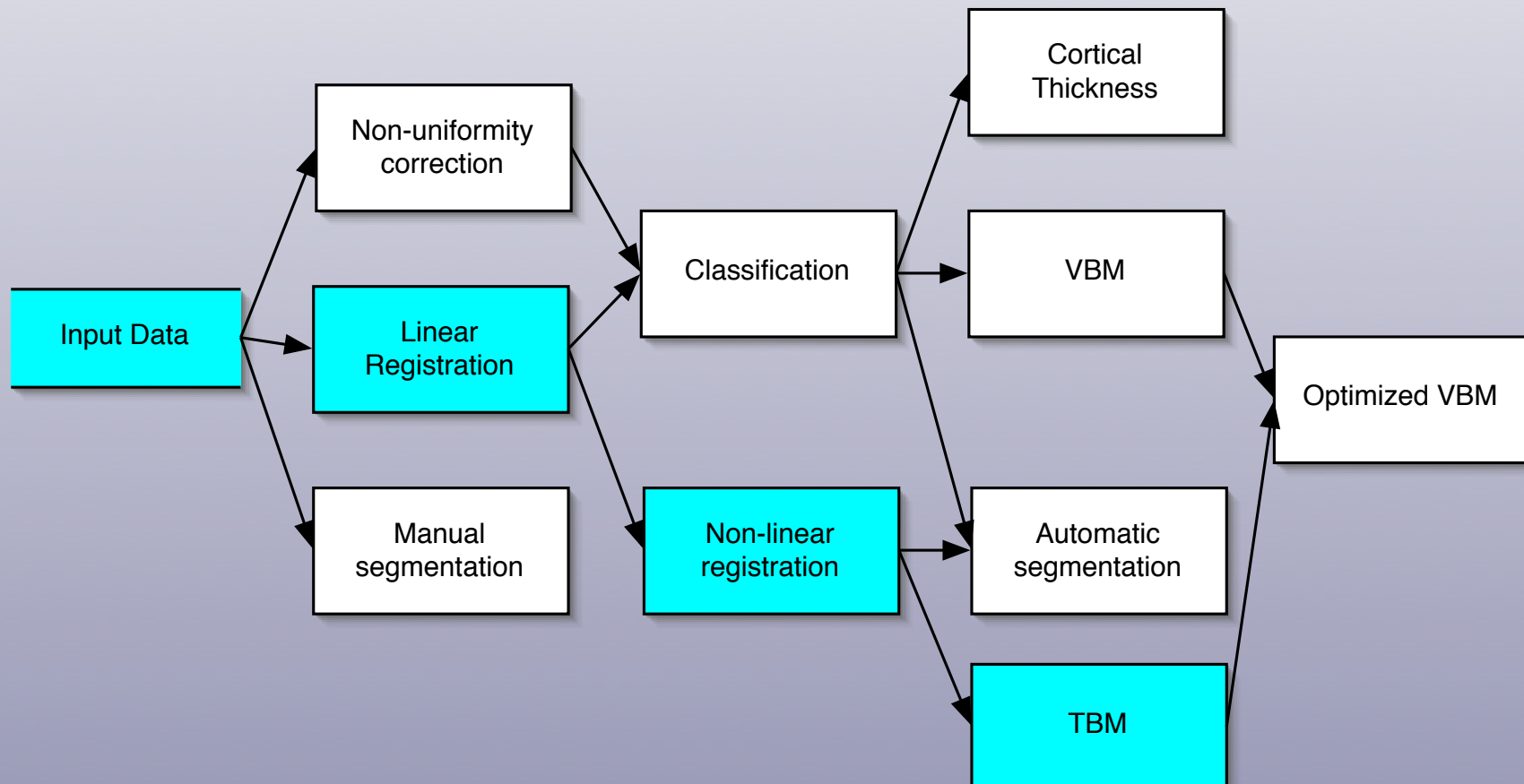
Behaviour \leftrightarrow Anatomy

- 15 mouse models with behavioural mutations.
- 13 showed abnormal neuroimaging findings.



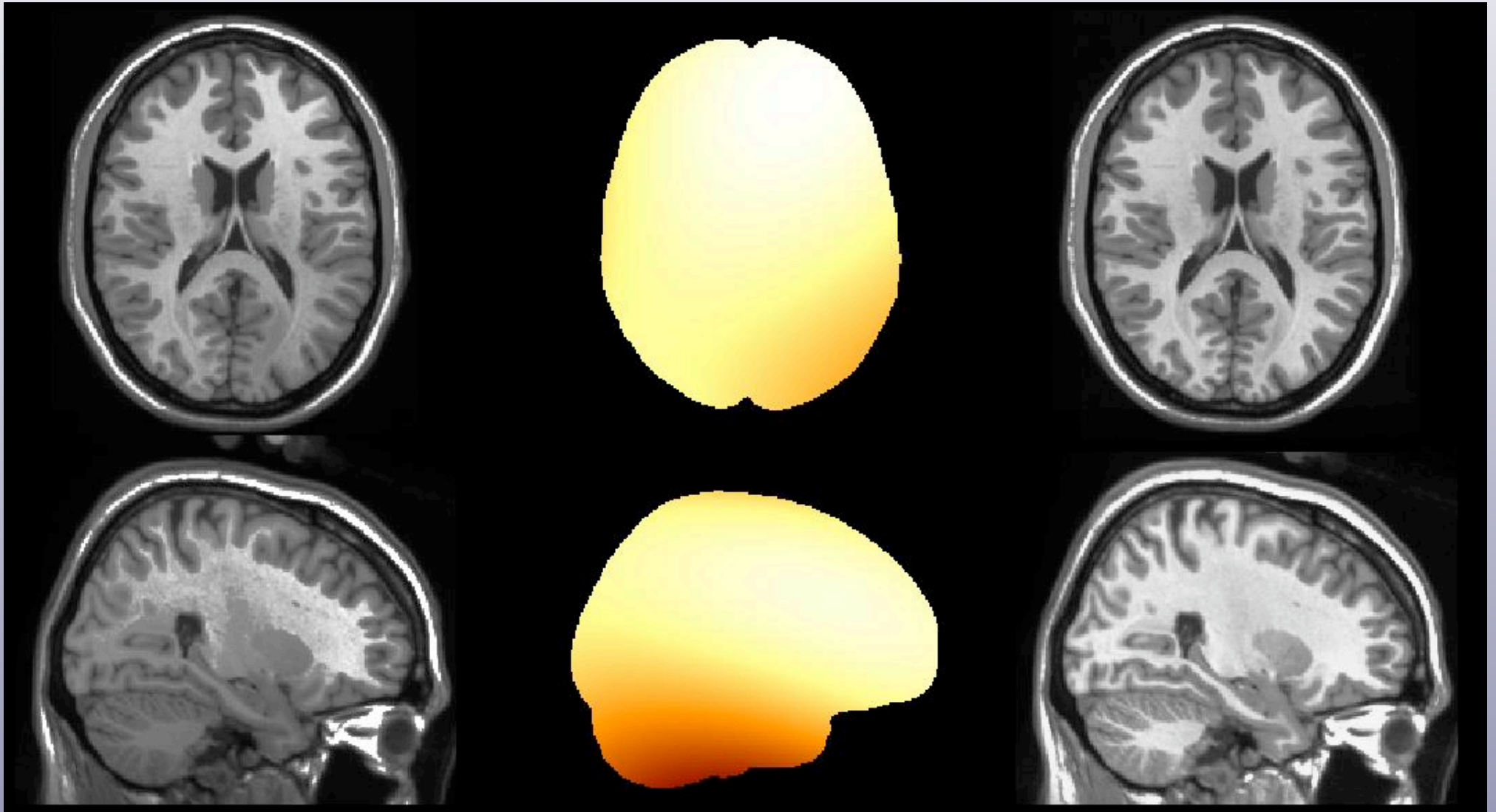
Tensor Based Morphometry

- The goal: localize differences in brain shape.

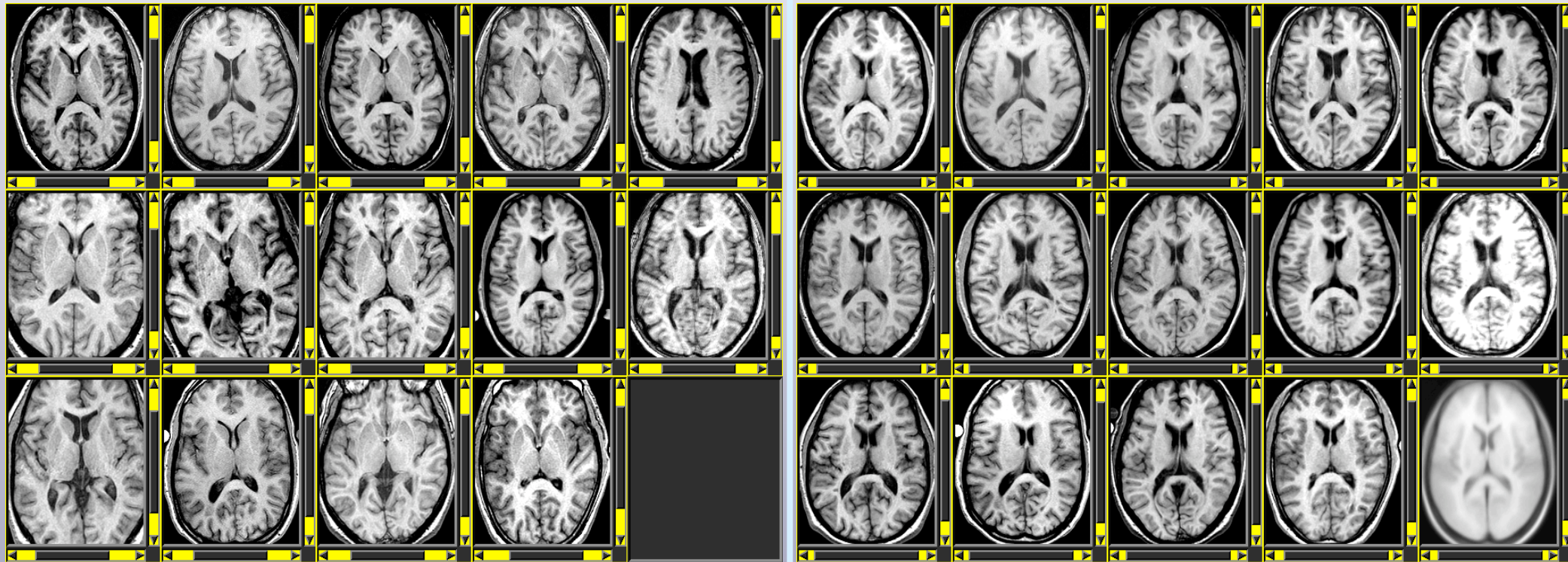


Non-uniformity correction

Sled, Zijdenbos, Evans: IEEE-TMI Feb 1998



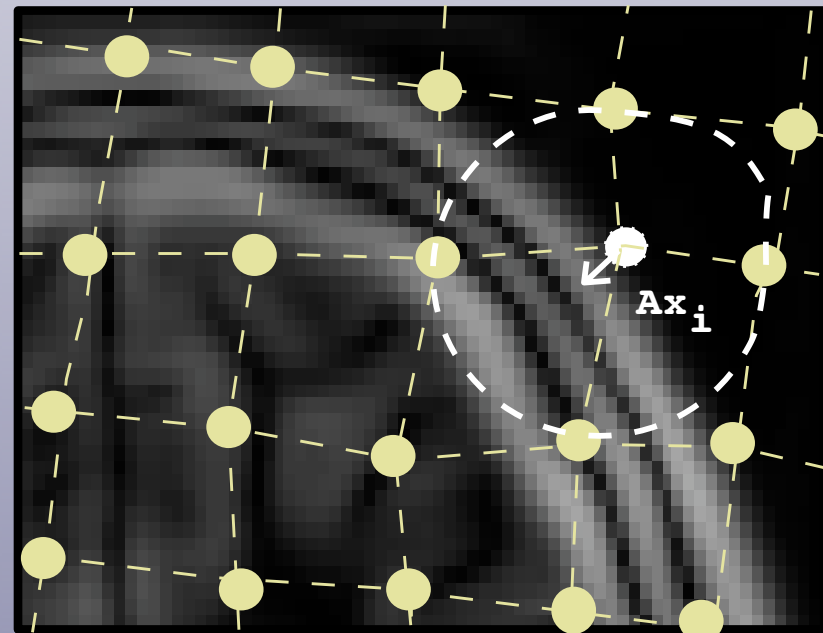
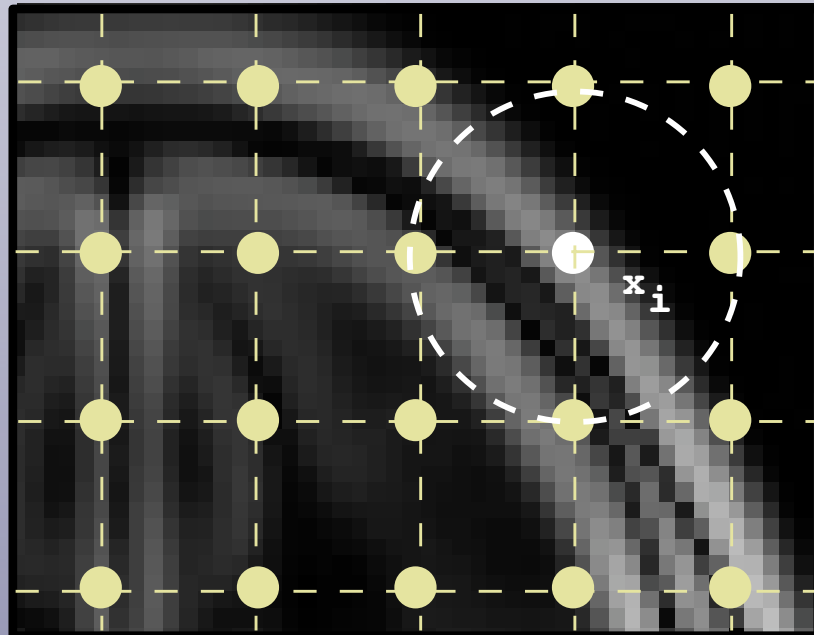
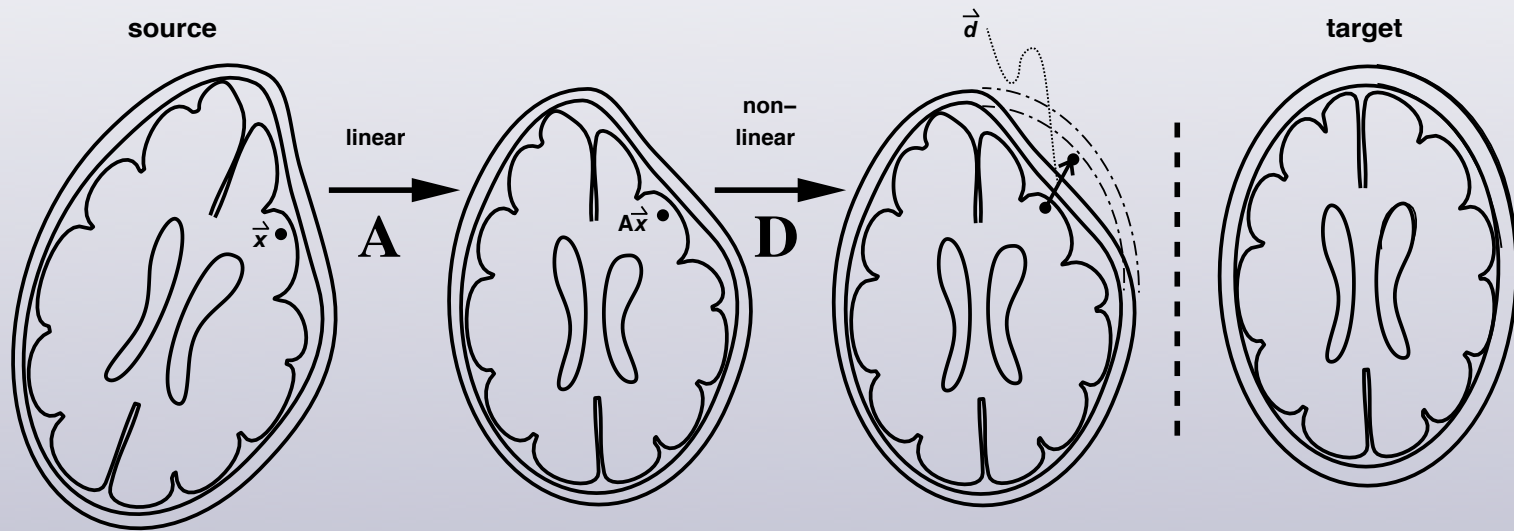
Spatial Normalization



Before
Registration

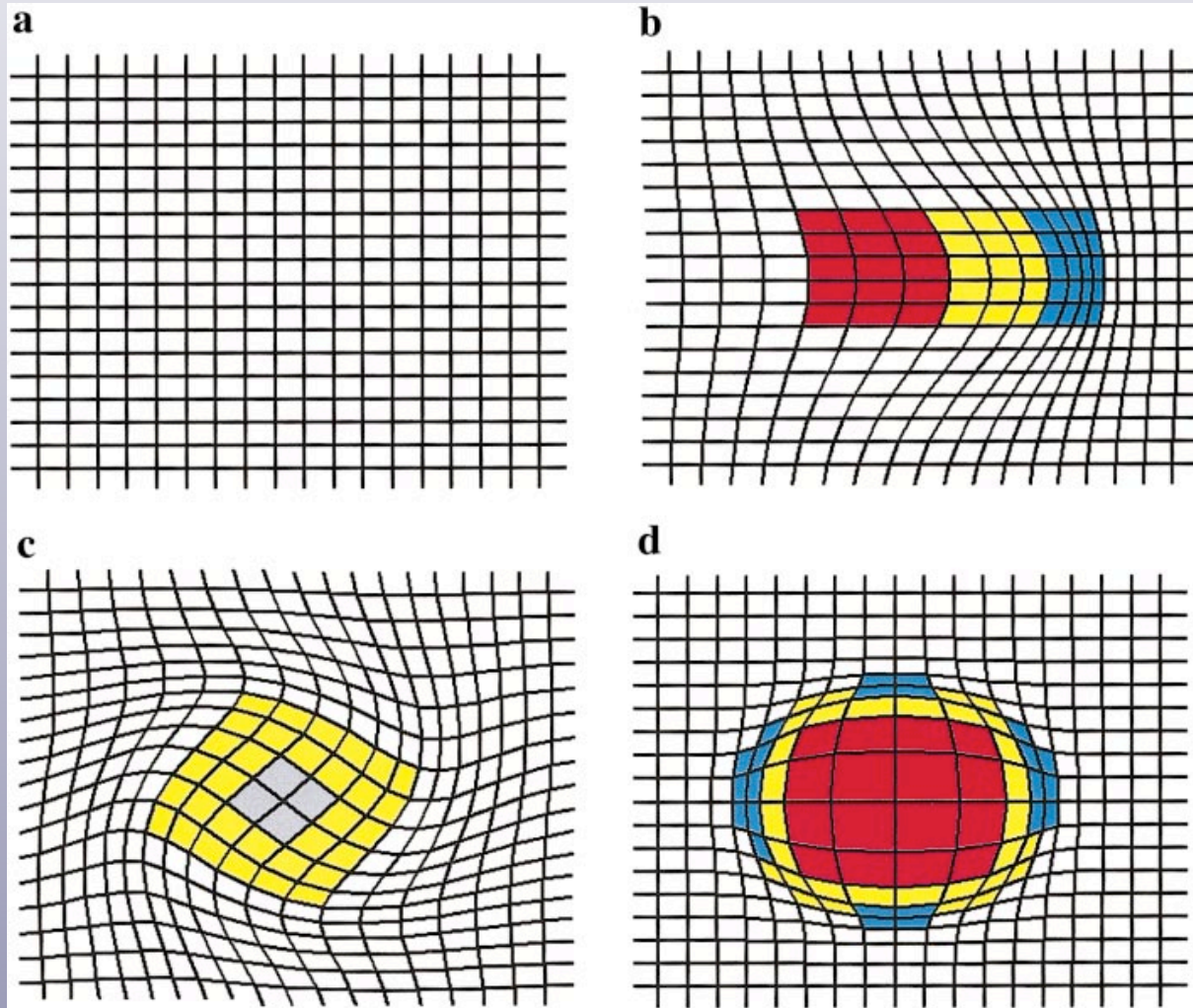
After
Registration

Deformations



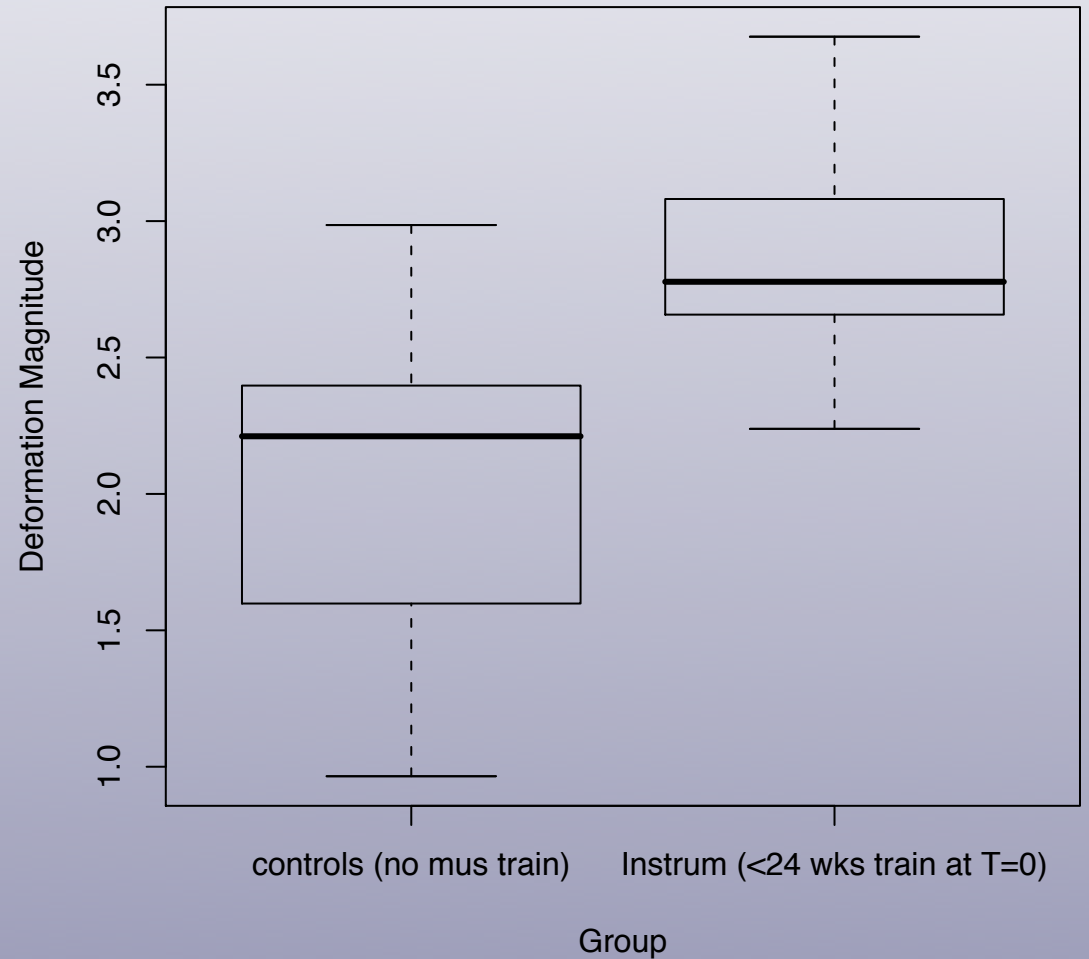
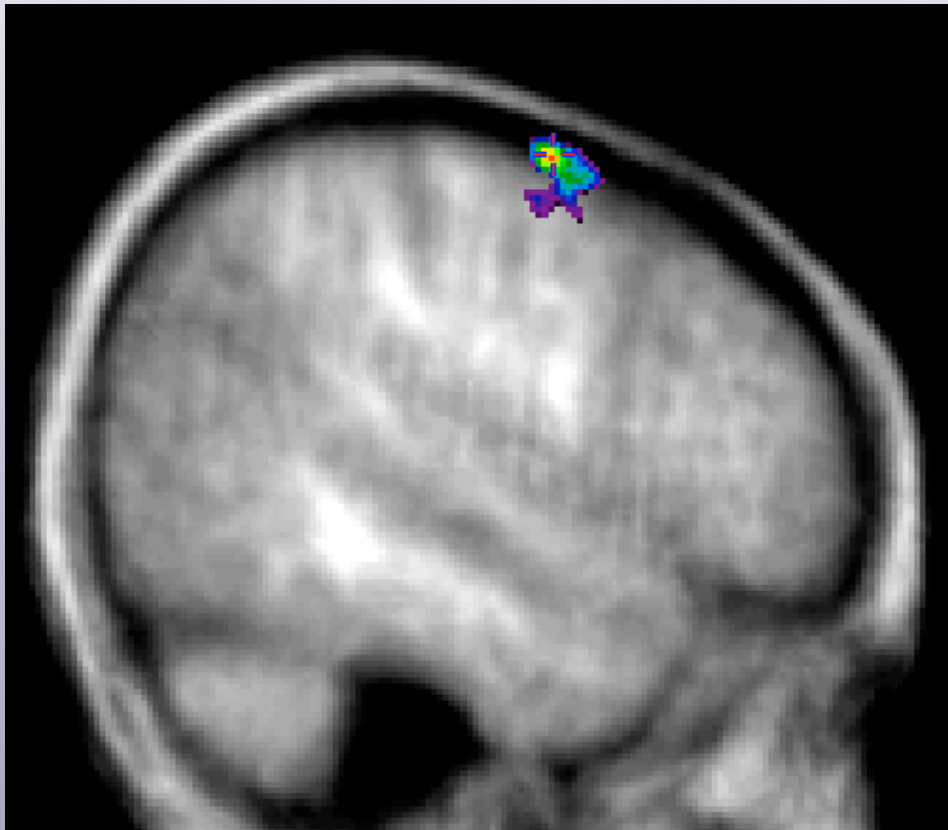
(from Collins, 1994)

Jacobians

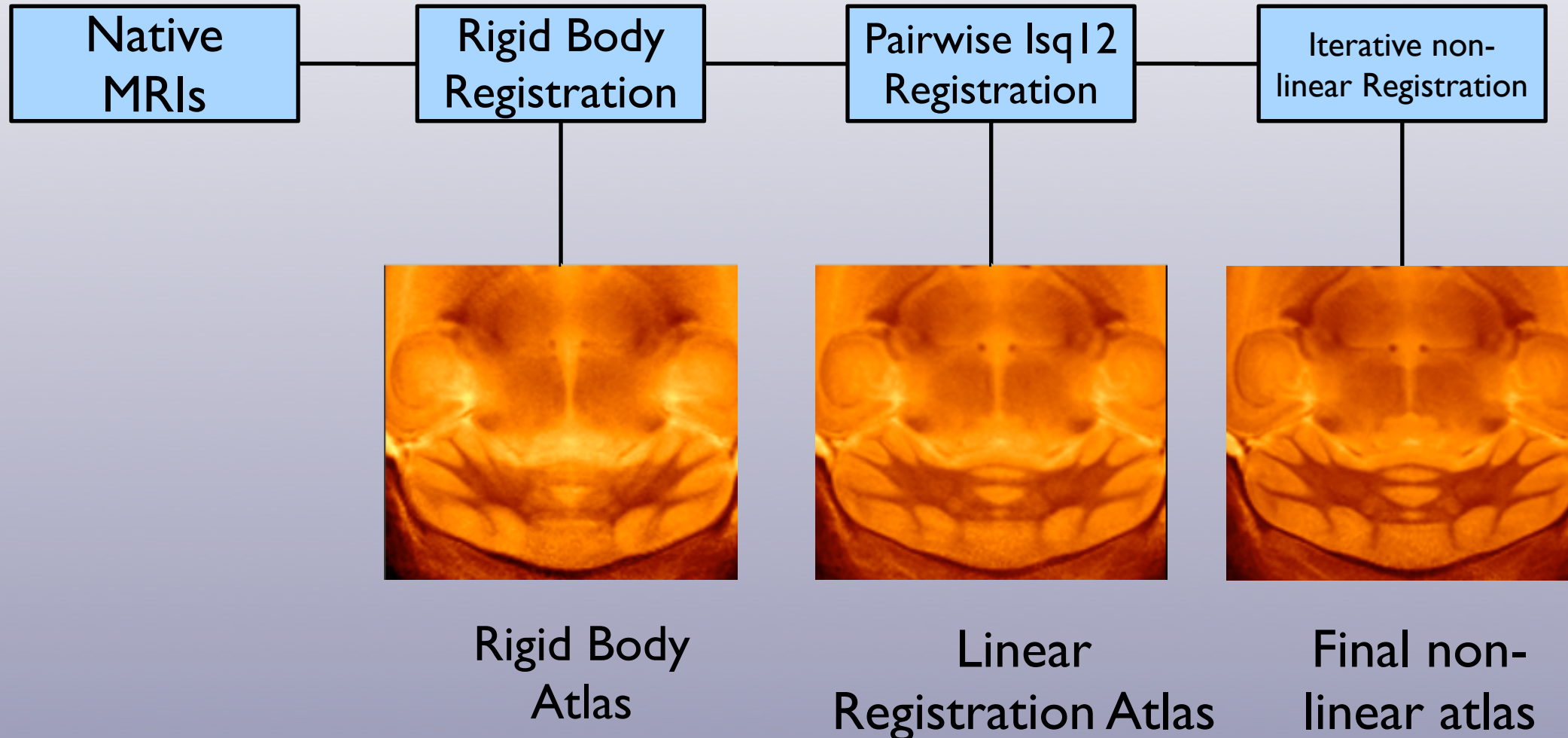


(from Chung, 2003)

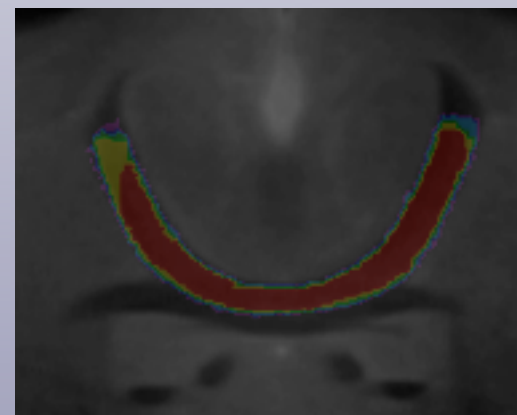
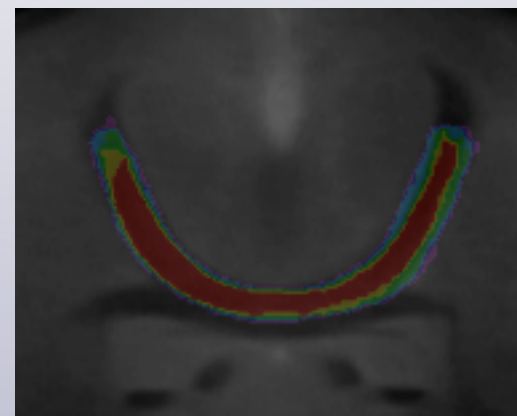
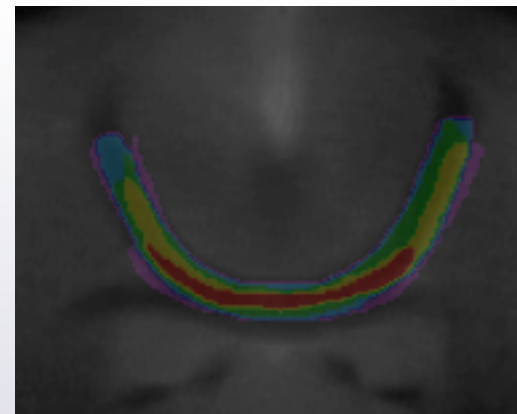
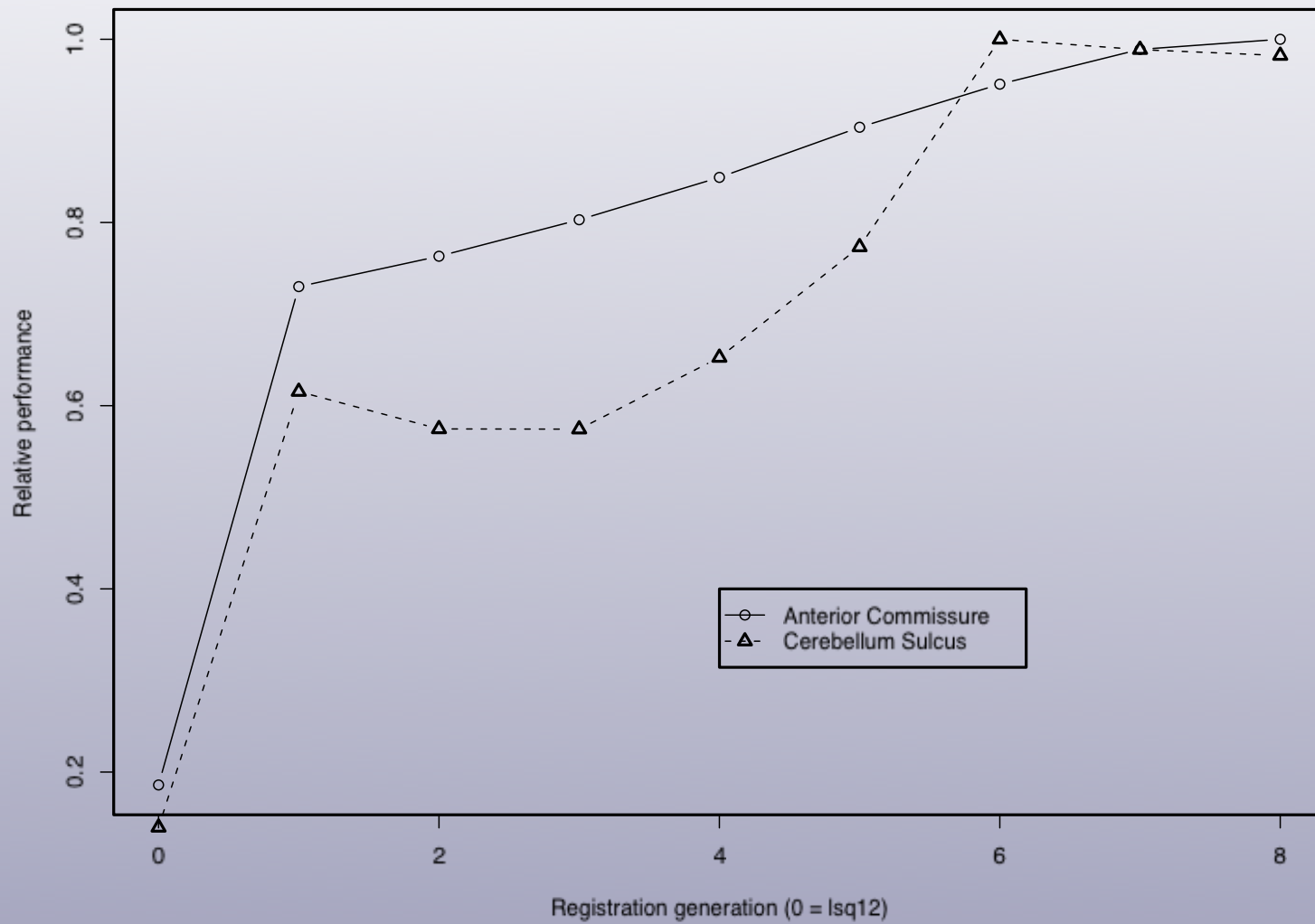
Effect of musical training



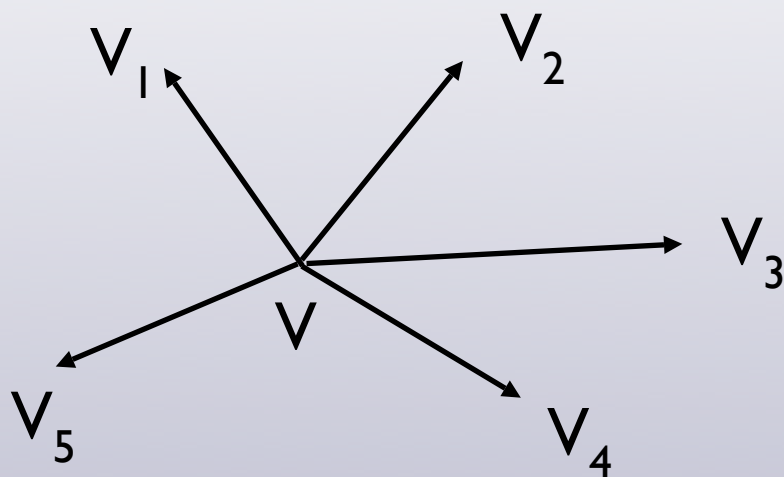
Atlas Creation



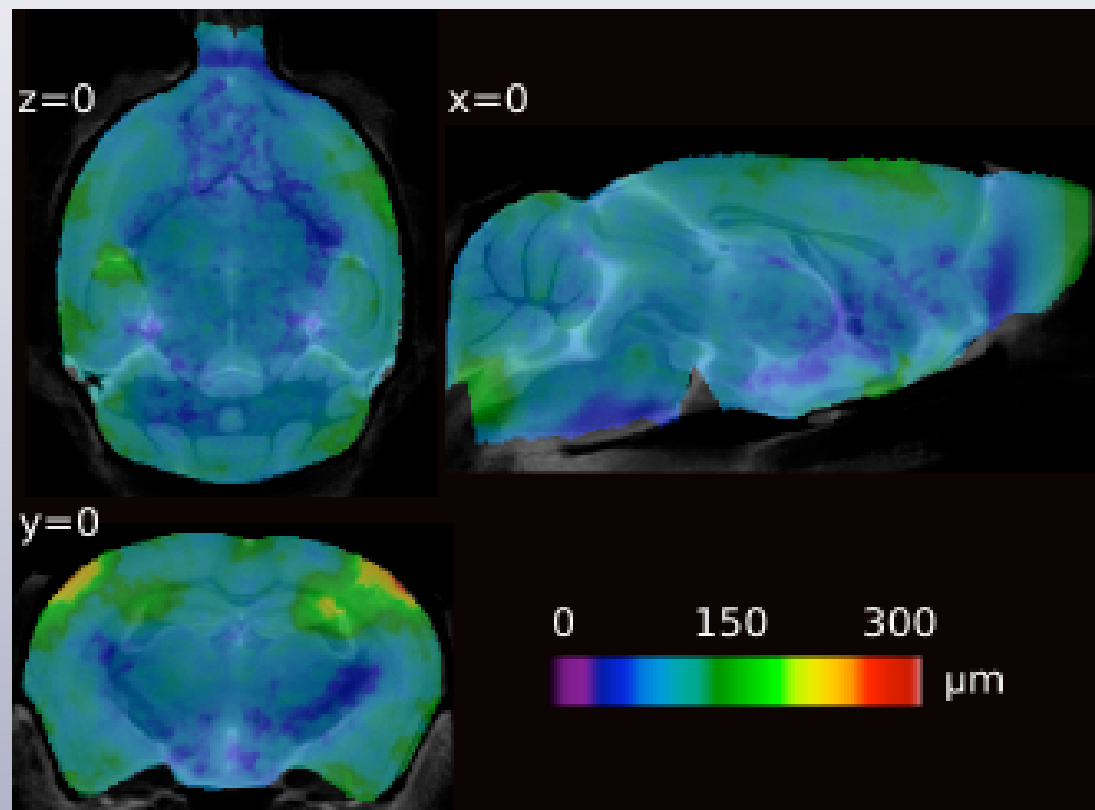
Registration performance



Measuring morphological variability

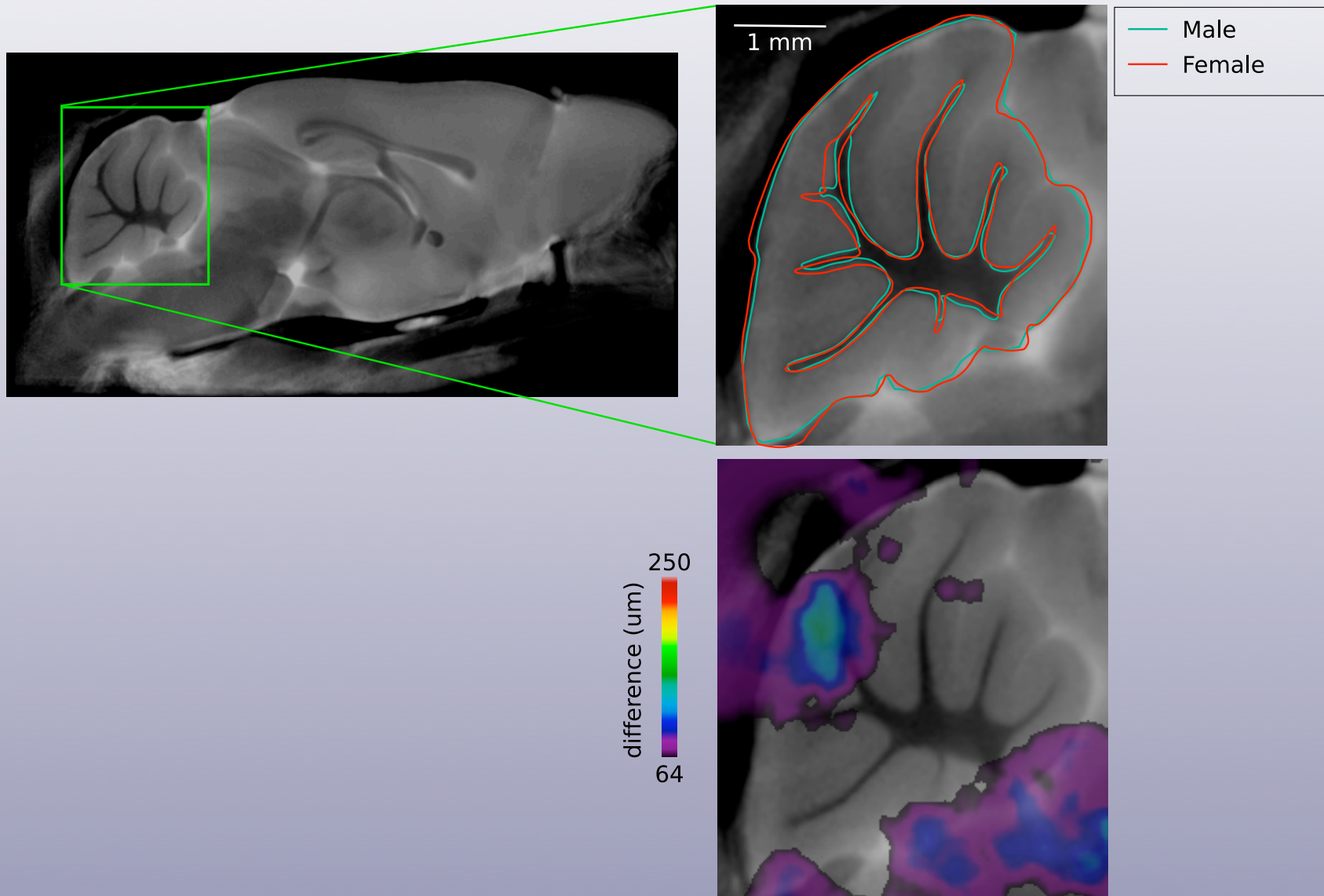


Displacement vectors
(from the atlas to
individual images)
encode
correspondence
between homologous
locations



Average displacement

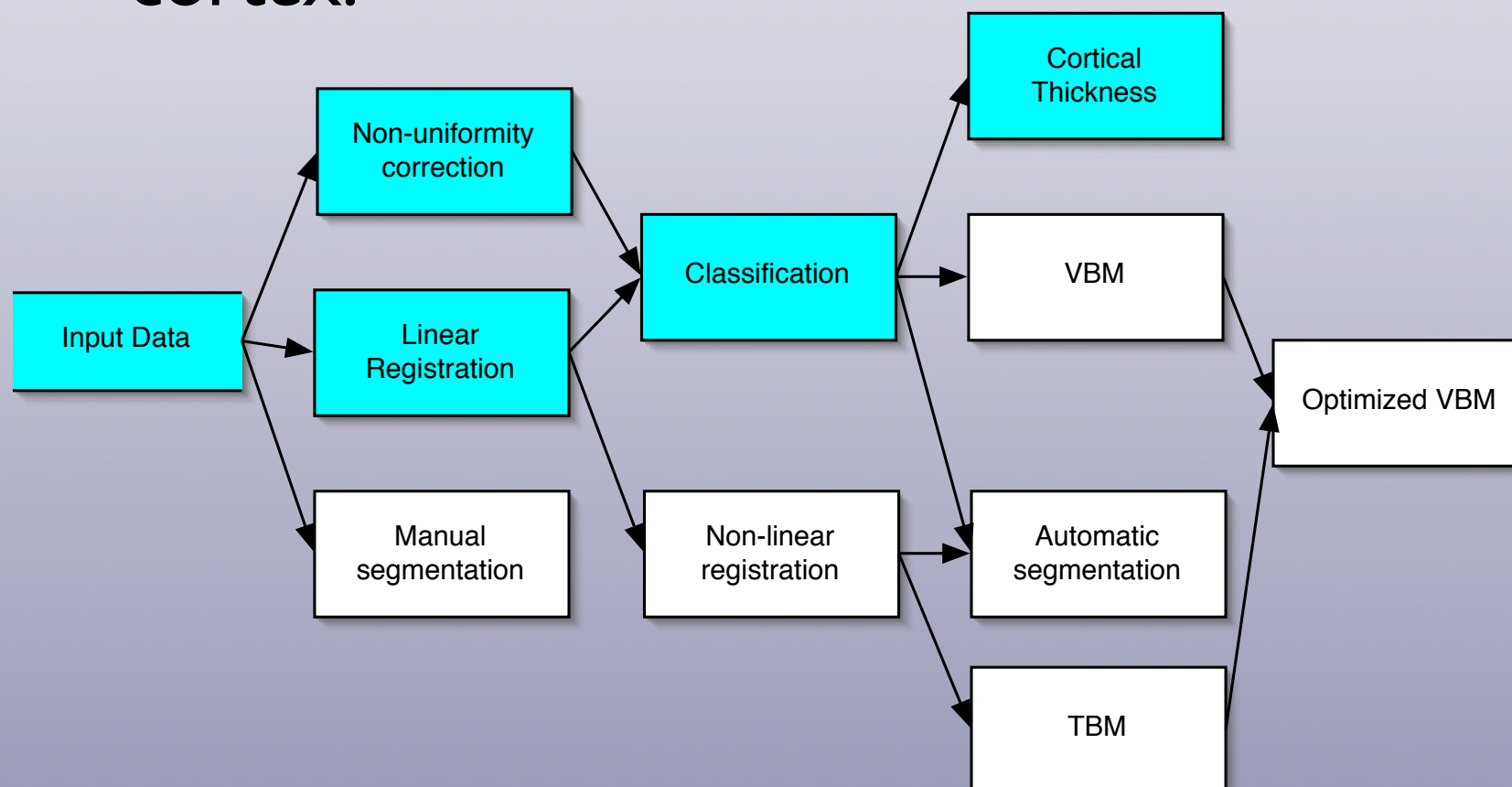
Deformation differences



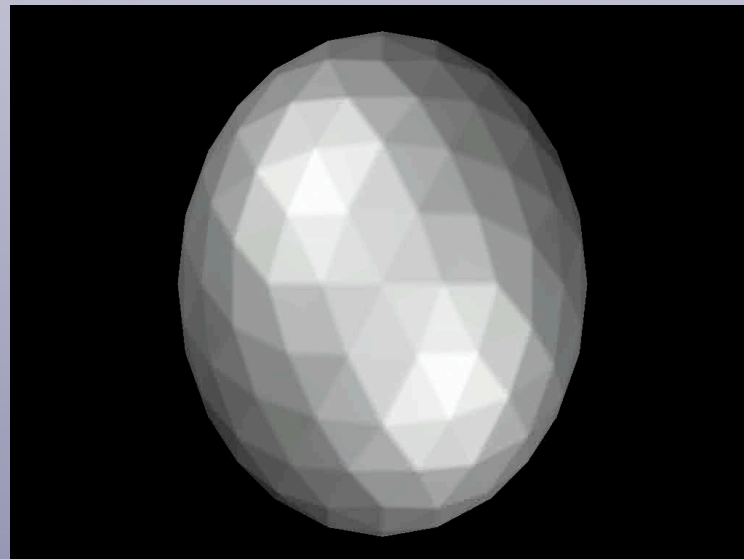
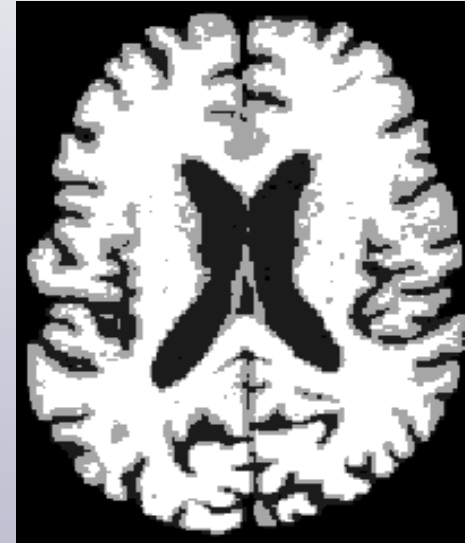
Spring S, Lerch JP, Henkelman RM. Sexual dimorphism revealed in the structure of the mouse brain using three-dimensional magnetic resonance imaging. *NeuroImage*, in Press.

Cortical Thickness

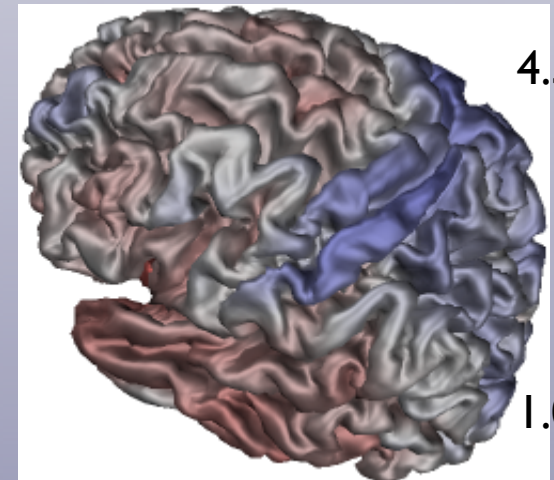
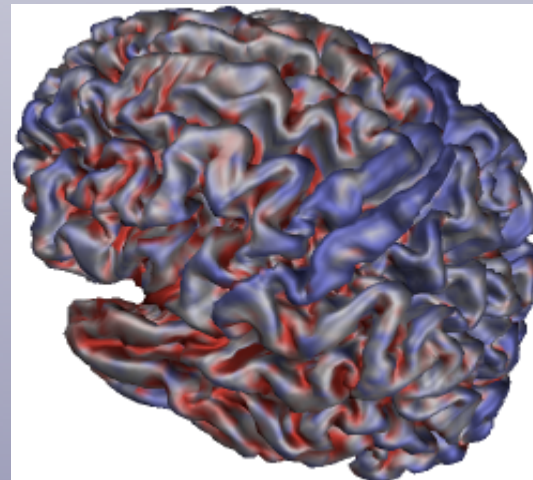
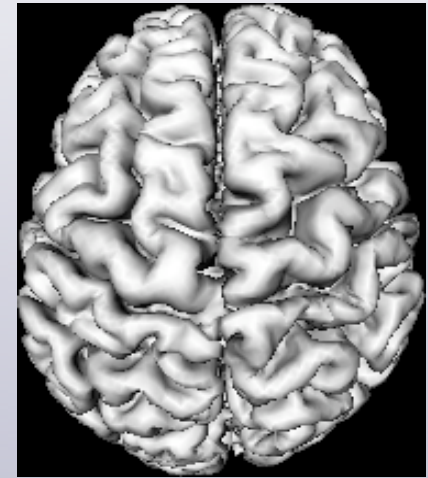
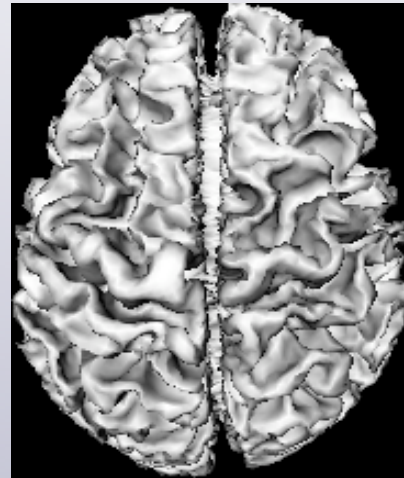
- The goal: measure the thickness of the cortex.



Processing Steps in Pictures



Processing Continued

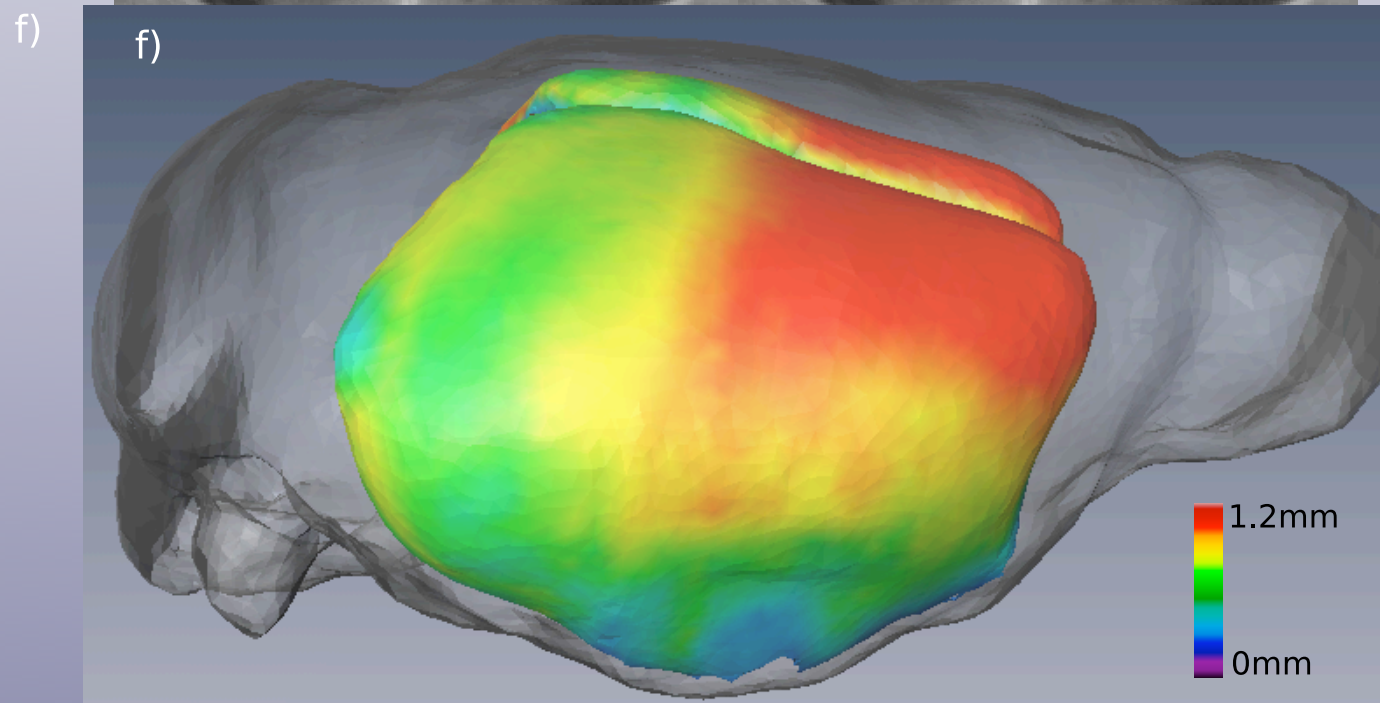
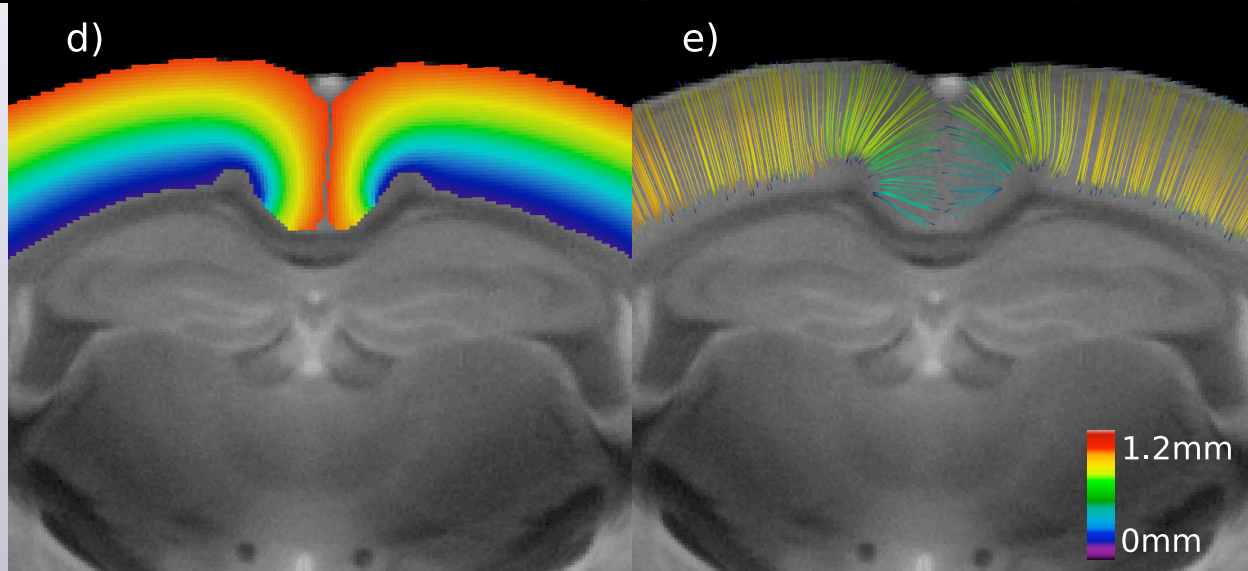
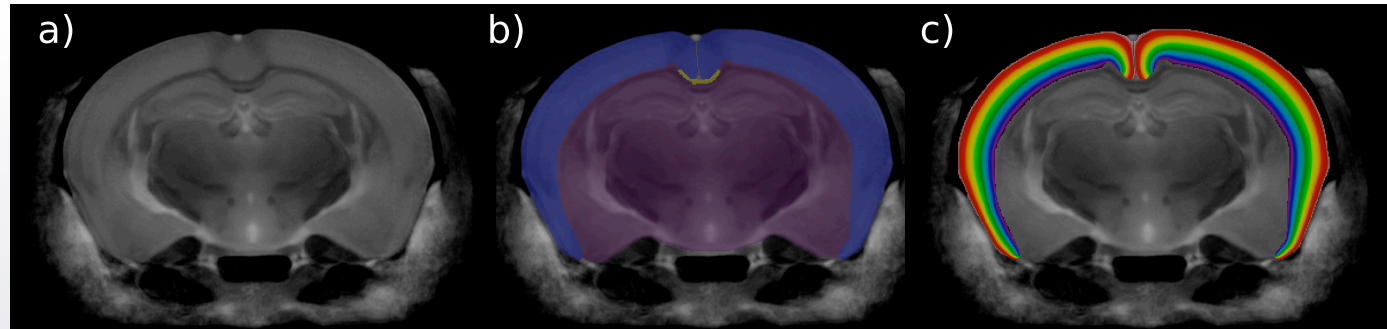


4.5mm



1.0mm

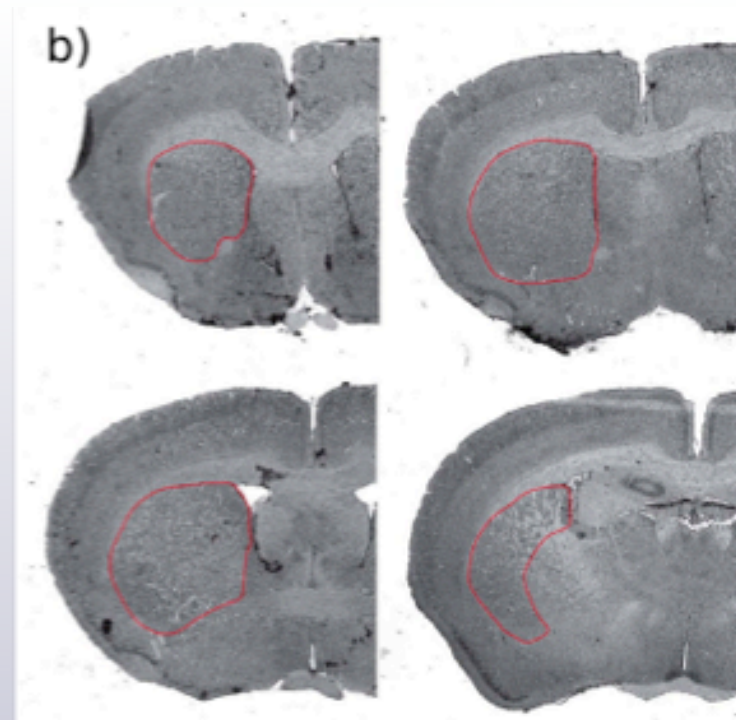
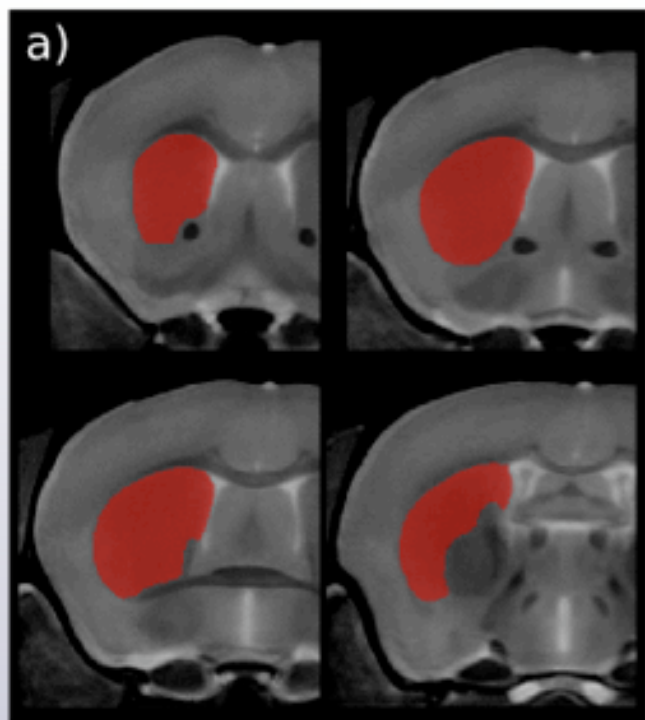
Mouse Cortical Thickness



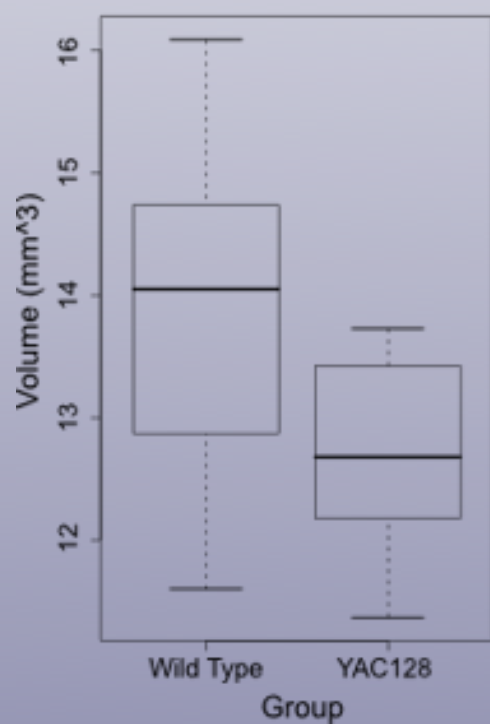
Huntington's Mouse

- YAC128 mouse: 120 CAG repeats on the human huntingtin gene.
- Behavioural (motor) abnormalities at 9 months.
- Histopathology quite similar to human Huntington's disease.

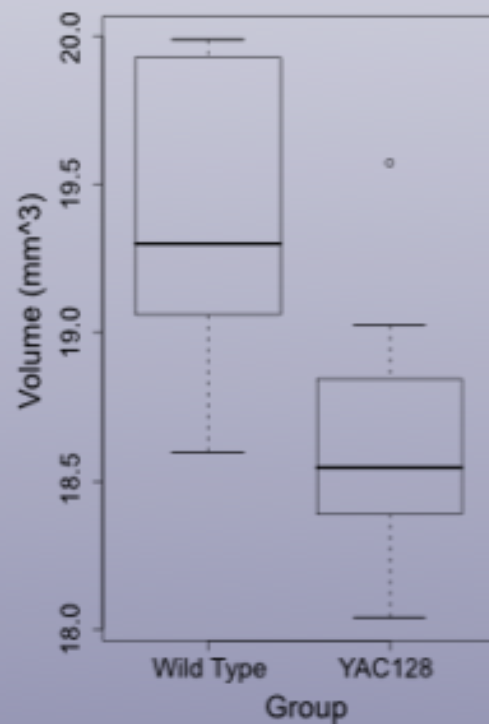
Collaboration with Jeffrey Carroll and Michael Hayden, UBC



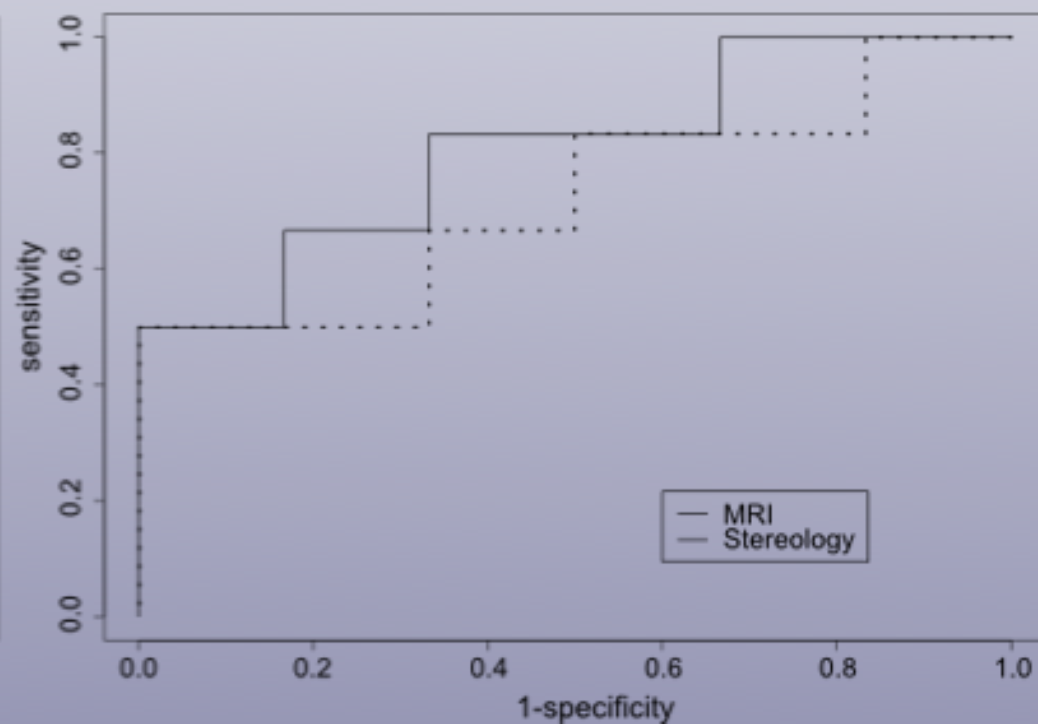
c) Stereology



MRI

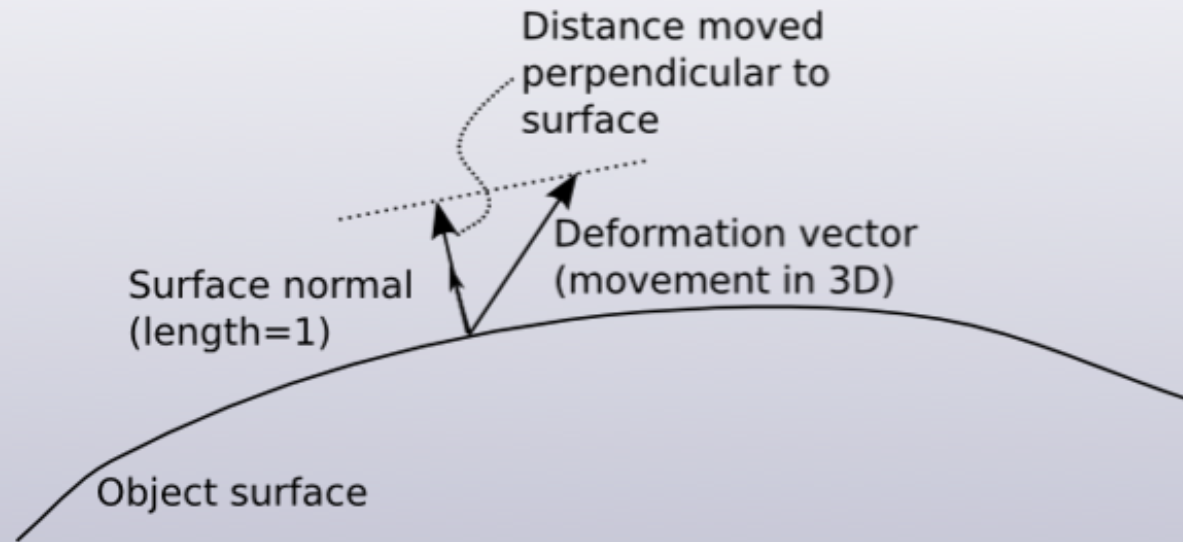


d)

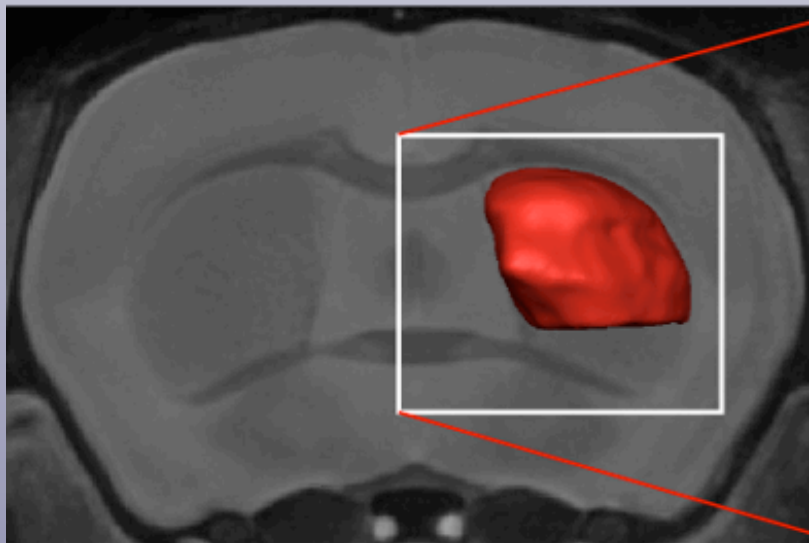


Assessing shape of striatum

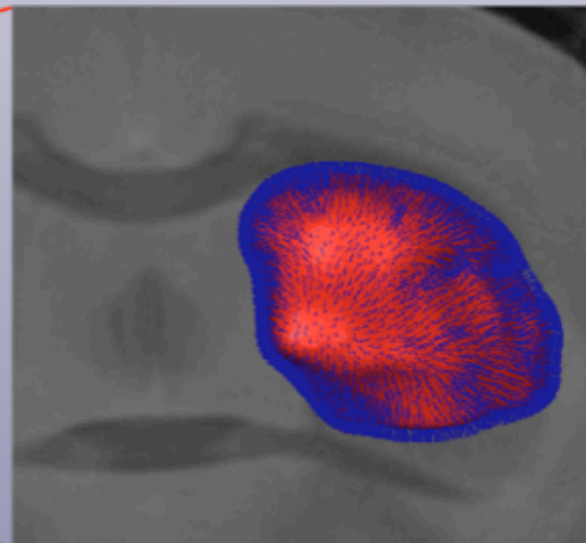
a)



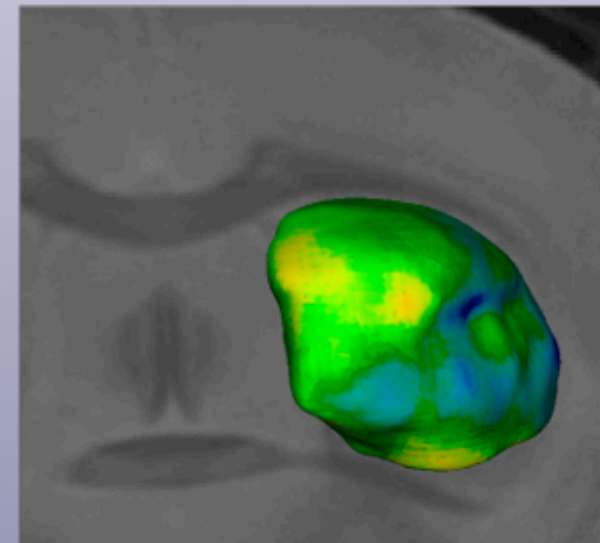
b)



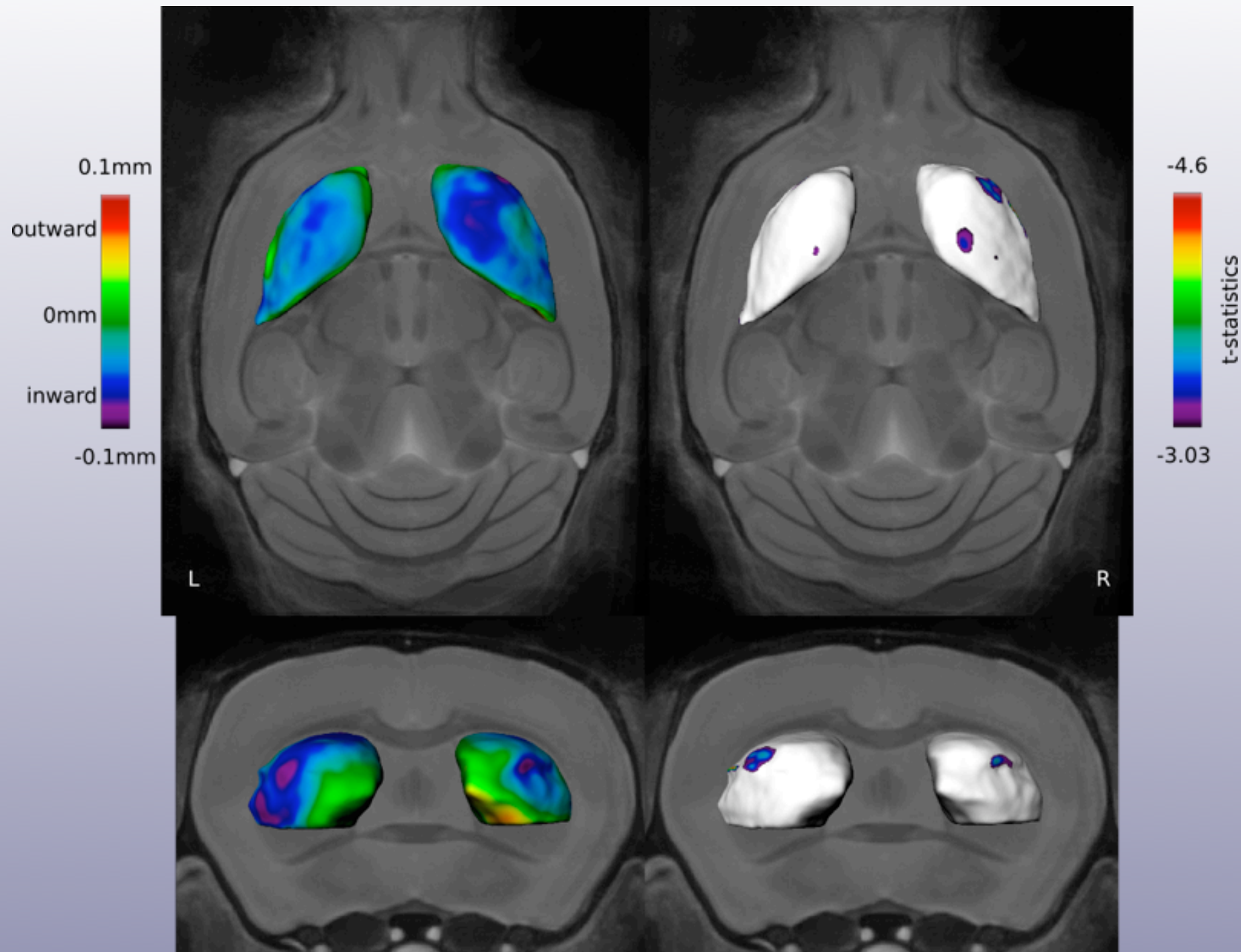
c)



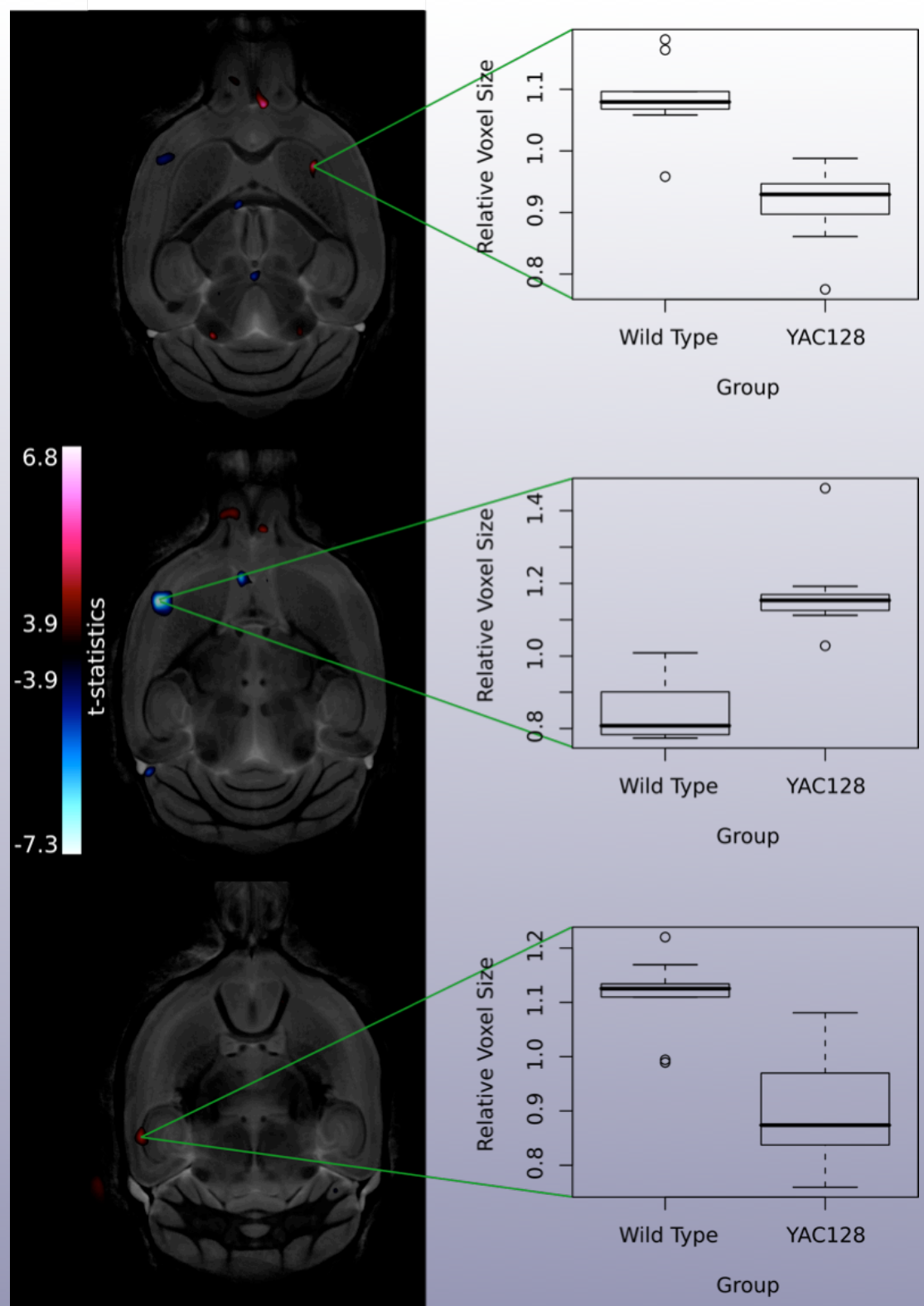
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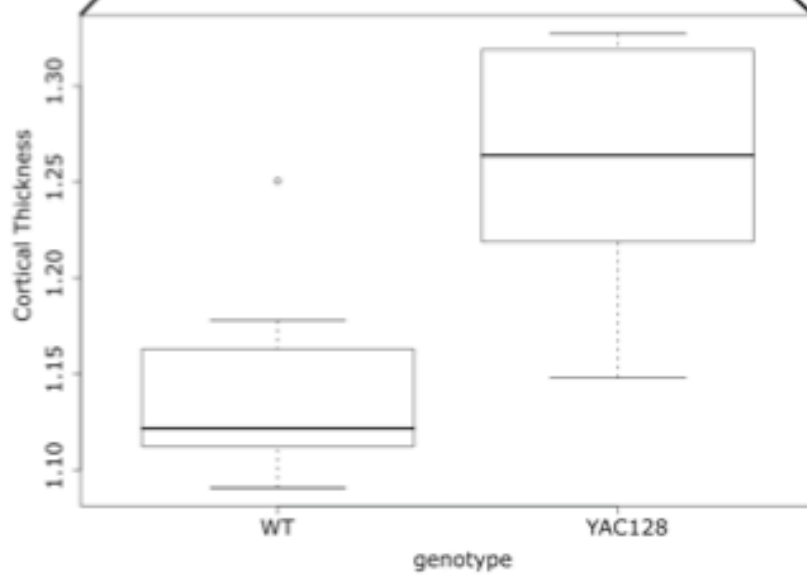
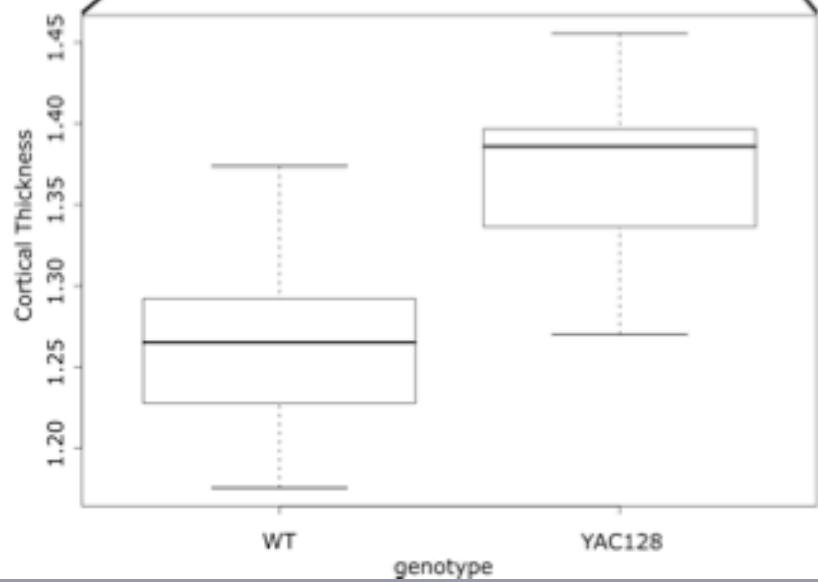
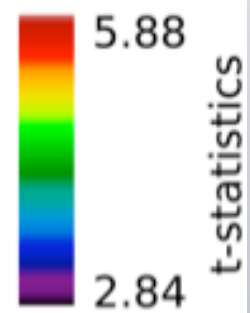
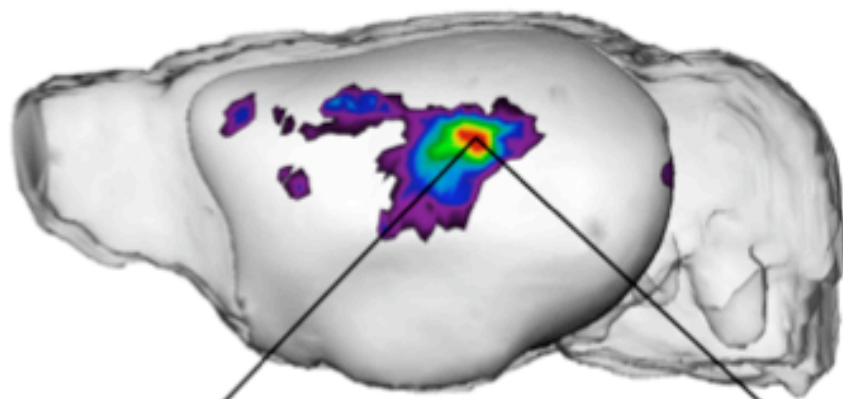
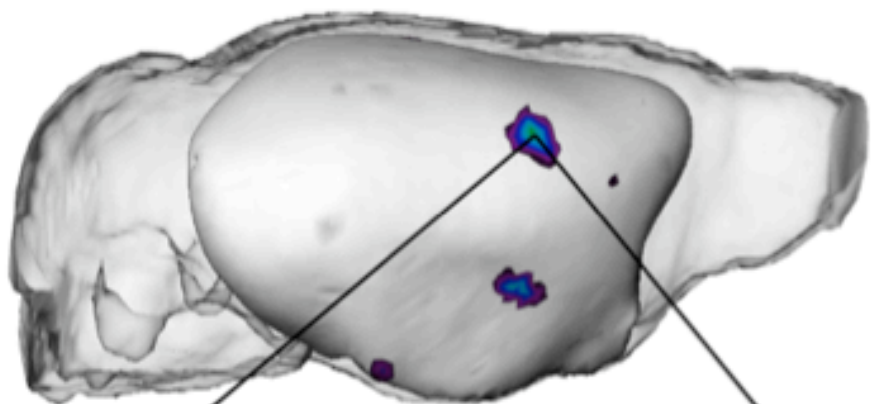
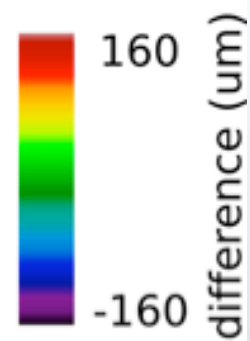
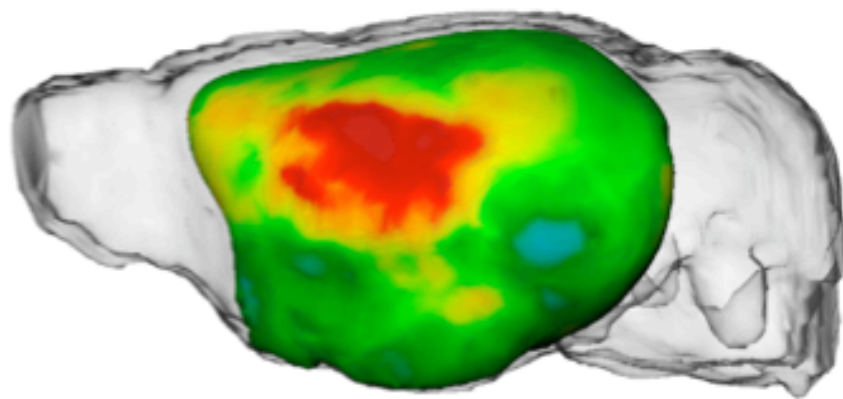
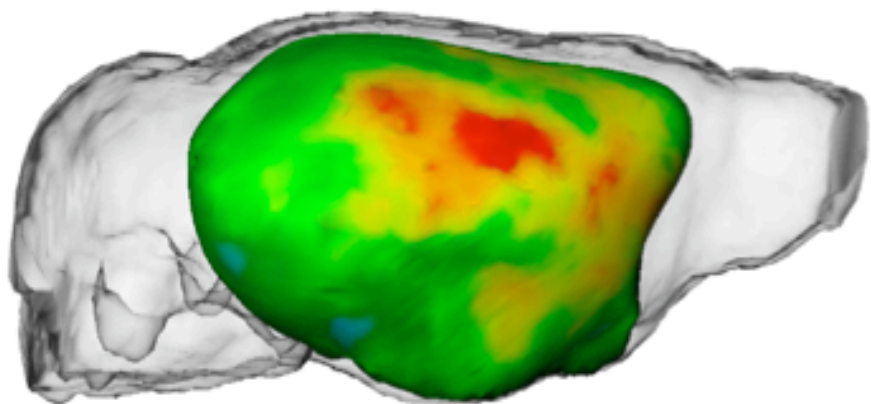


Results



Changes throughout the brain





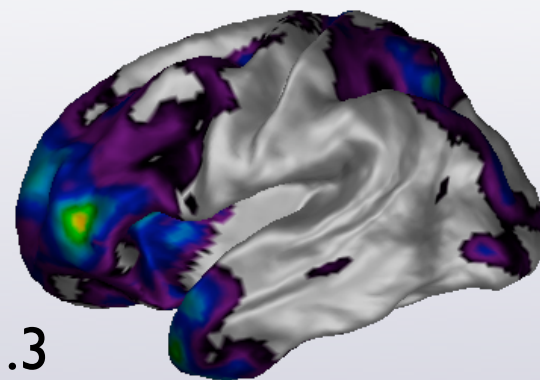
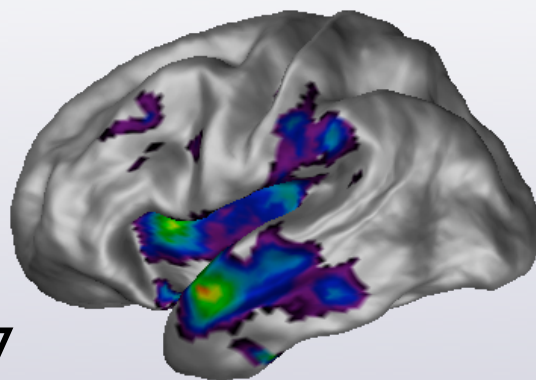
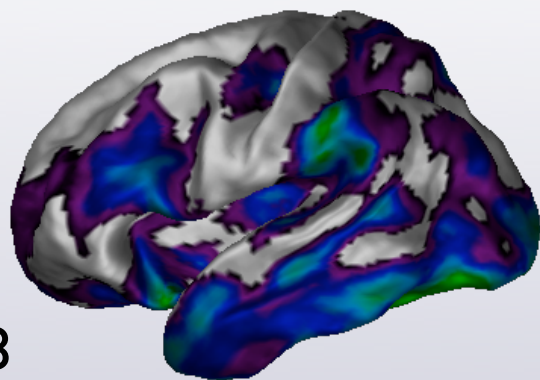
Alzheimer's Disorder (AD)

- AD: age-related disease marked by neuropathological features and brain atrophy.
- Subjects scanned at the Ludwig-Maximilians Universität, Munich, Germany.
- Patient group: probable AD (NINCDS-ARDRA).

Group

MMSE

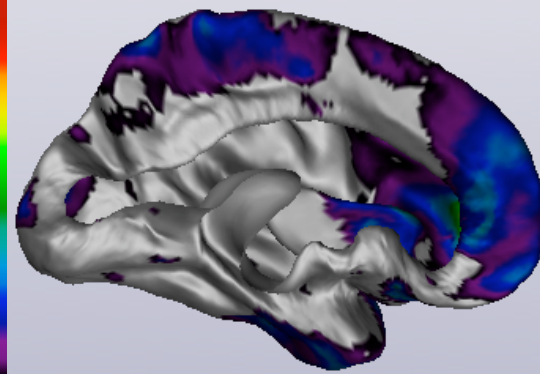
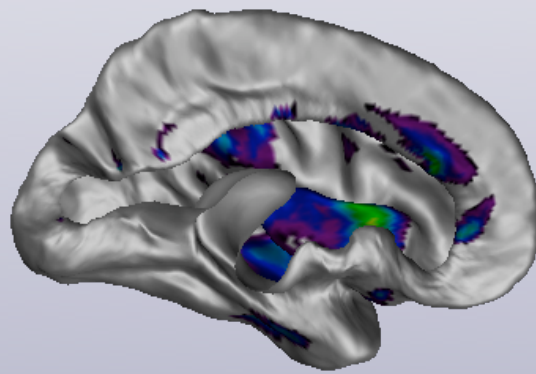
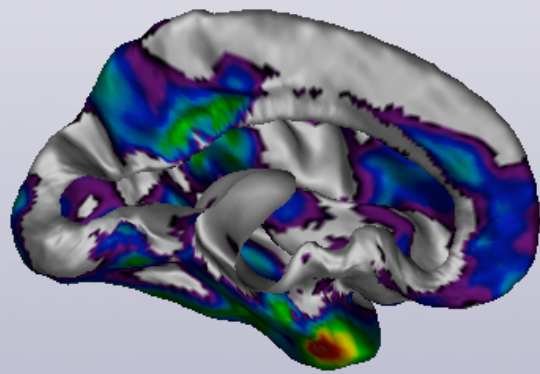
Progression



-6.8

5.7

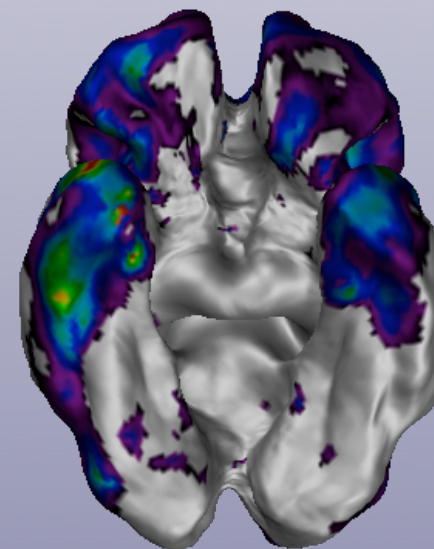
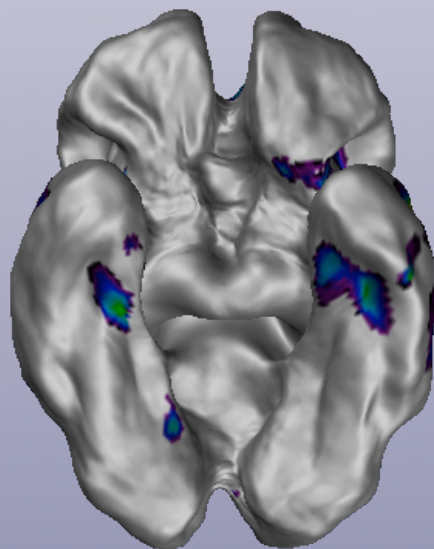
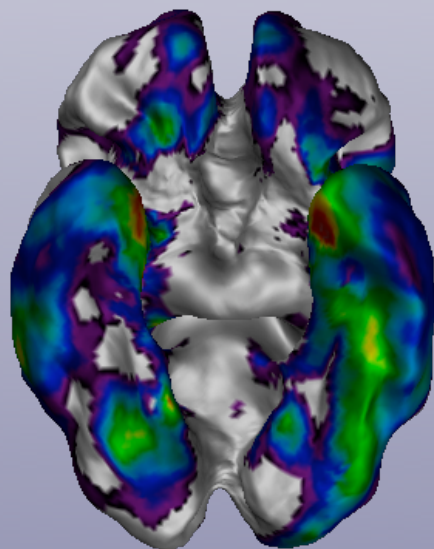
-11.3



-2.4

2.4

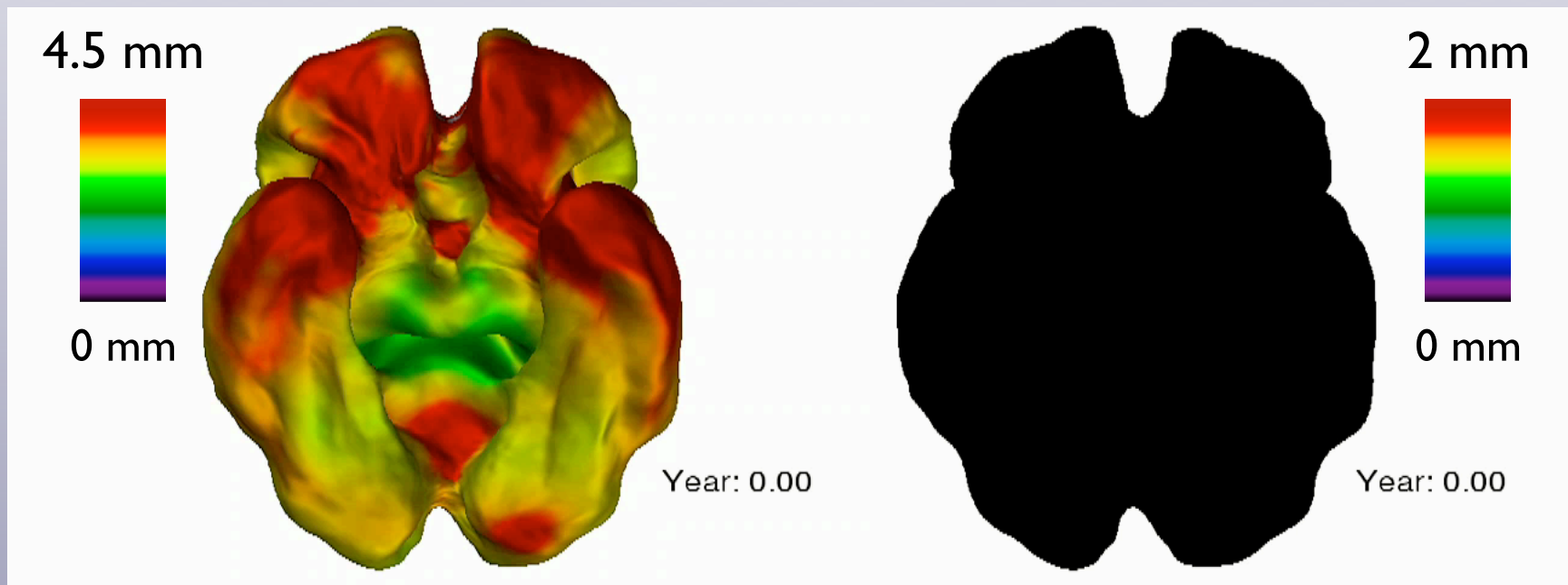
-2.4



AD progression

Cortical Thickness

Thickness Loss



Predicting AD

The Goal: use nothing but cortical thickness information to reproduce the clinical diagnosis.

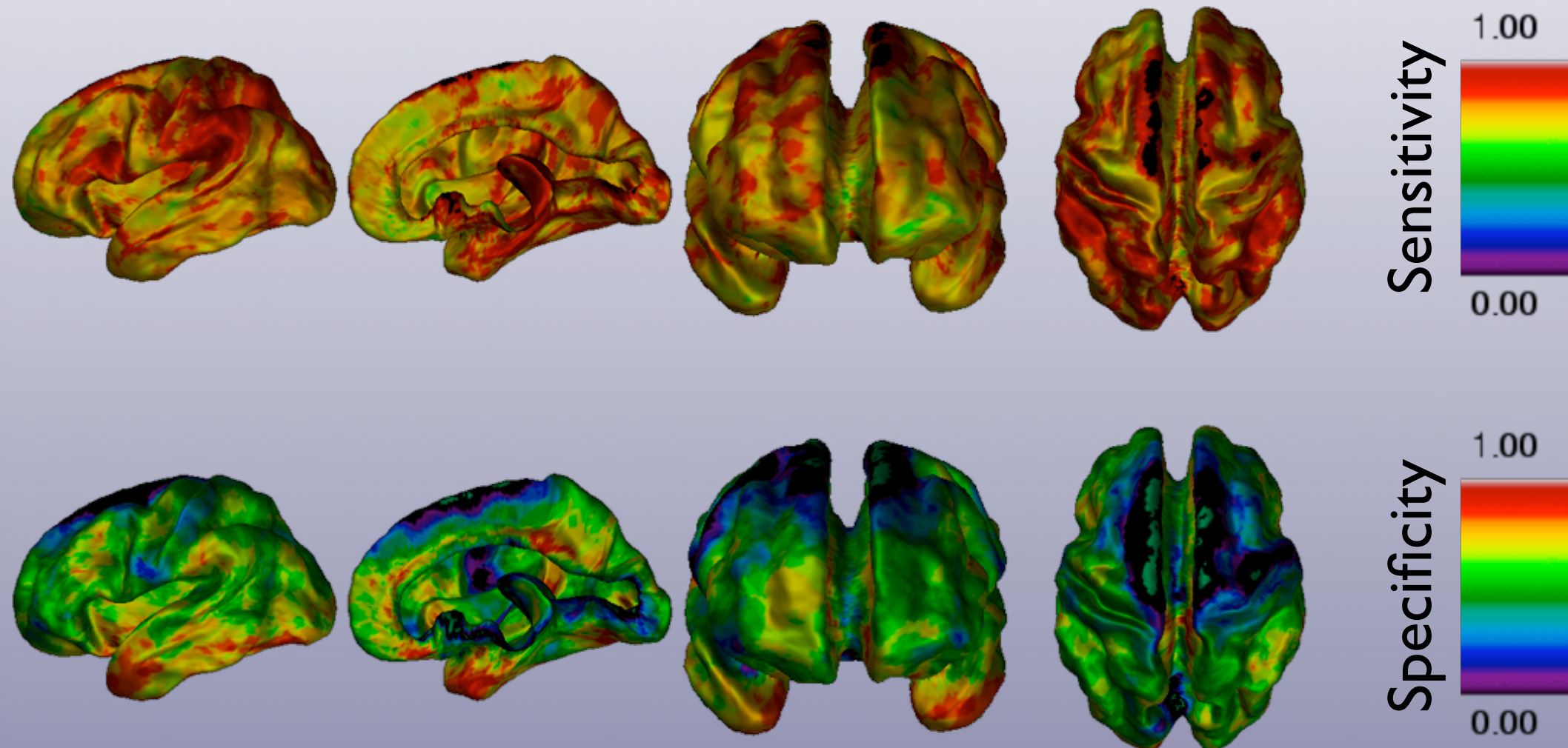
Use discriminant functions at each point (either linear or quadratic discriminants or logistic regression).

Compute the sensitivity and specificity that each point on the cortex has in reproducing the clinical diagnosis.

Sensitivity: Prediction of AD given diagnosis is AD

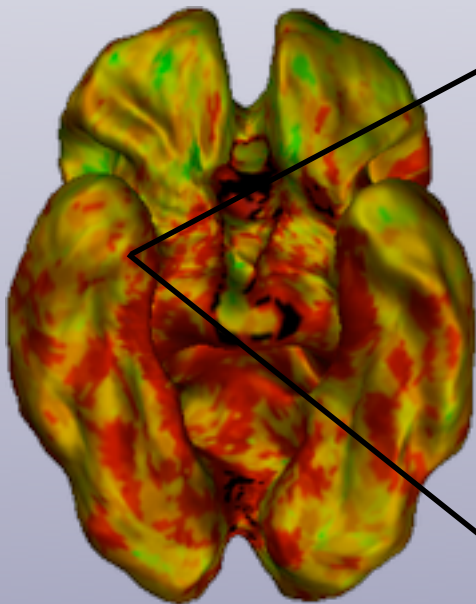
Specificity: Prediction of Control given diagnosis of control

Per Vertex Diagnostics

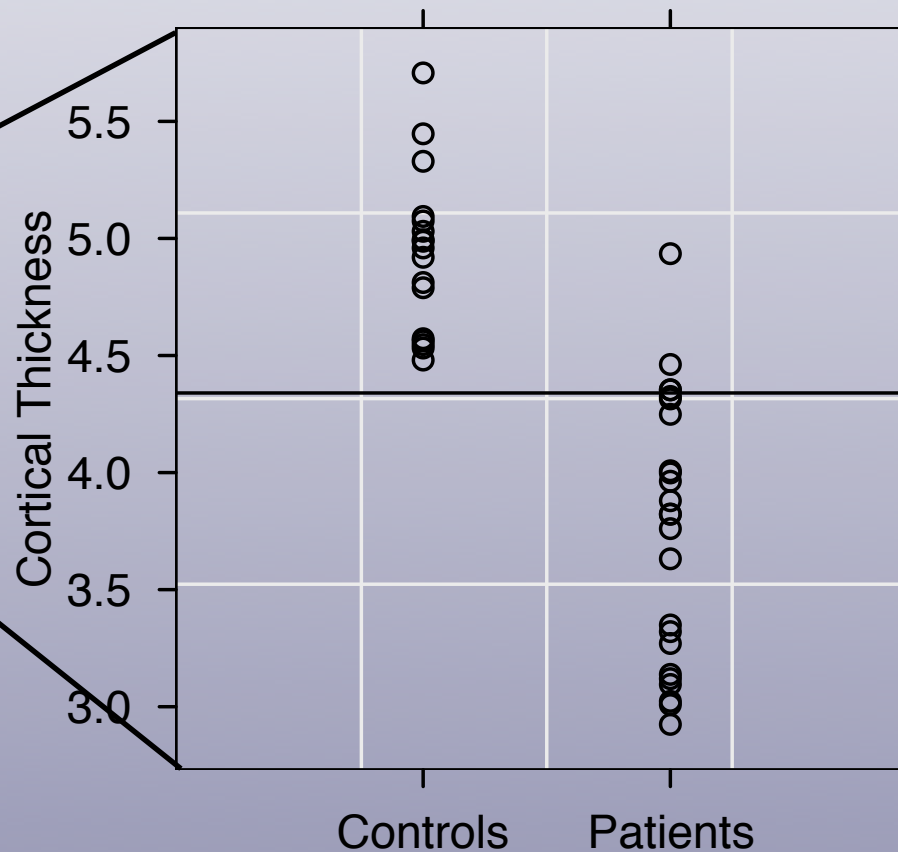


Diagnosis Illustrated

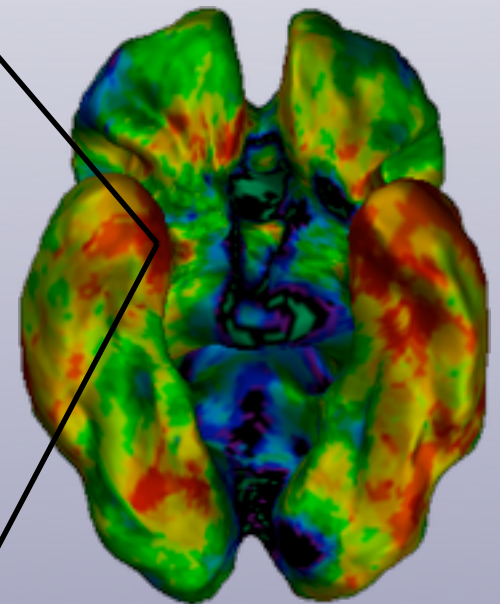
Sensitivity



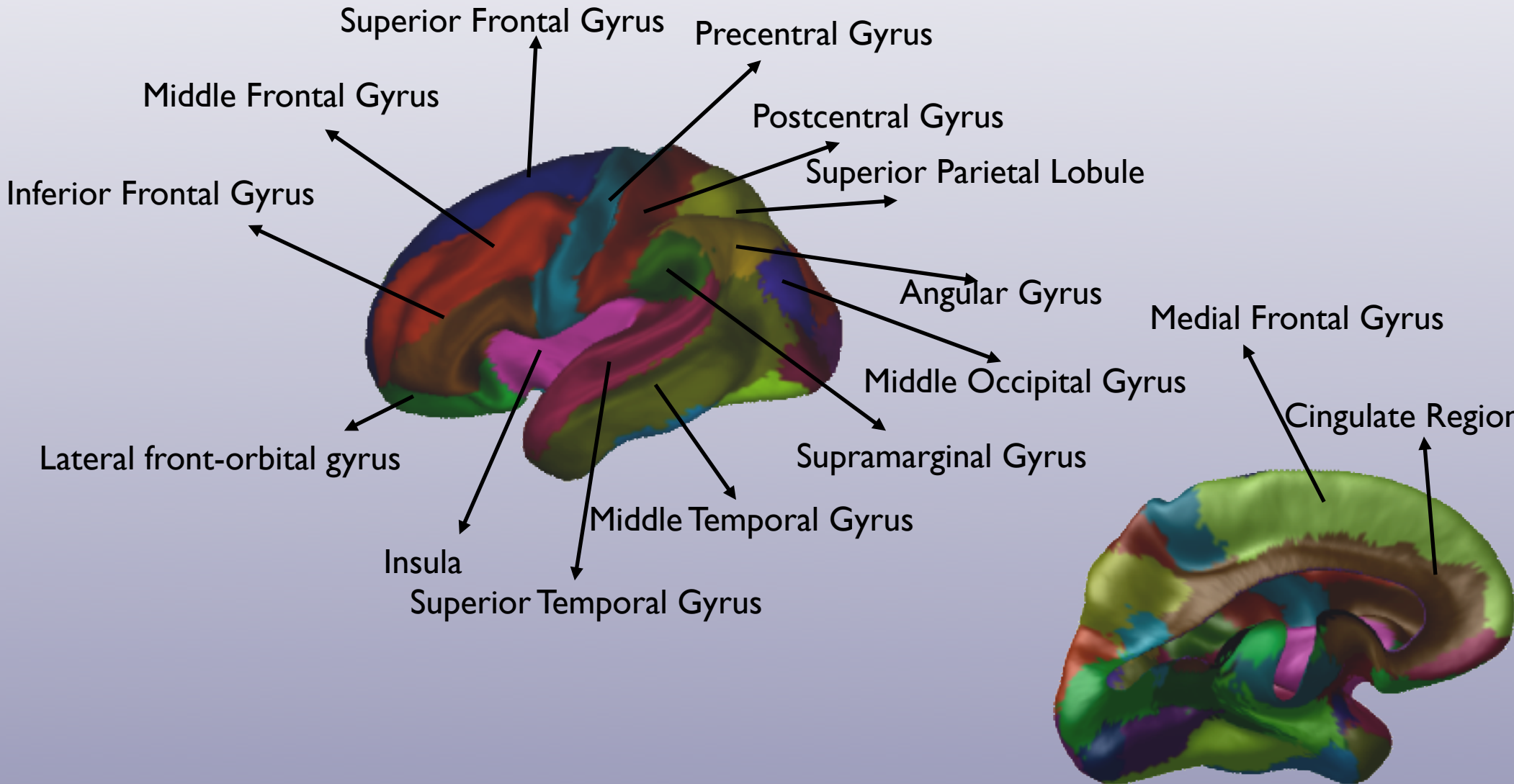
Right Entorhinal Cortex



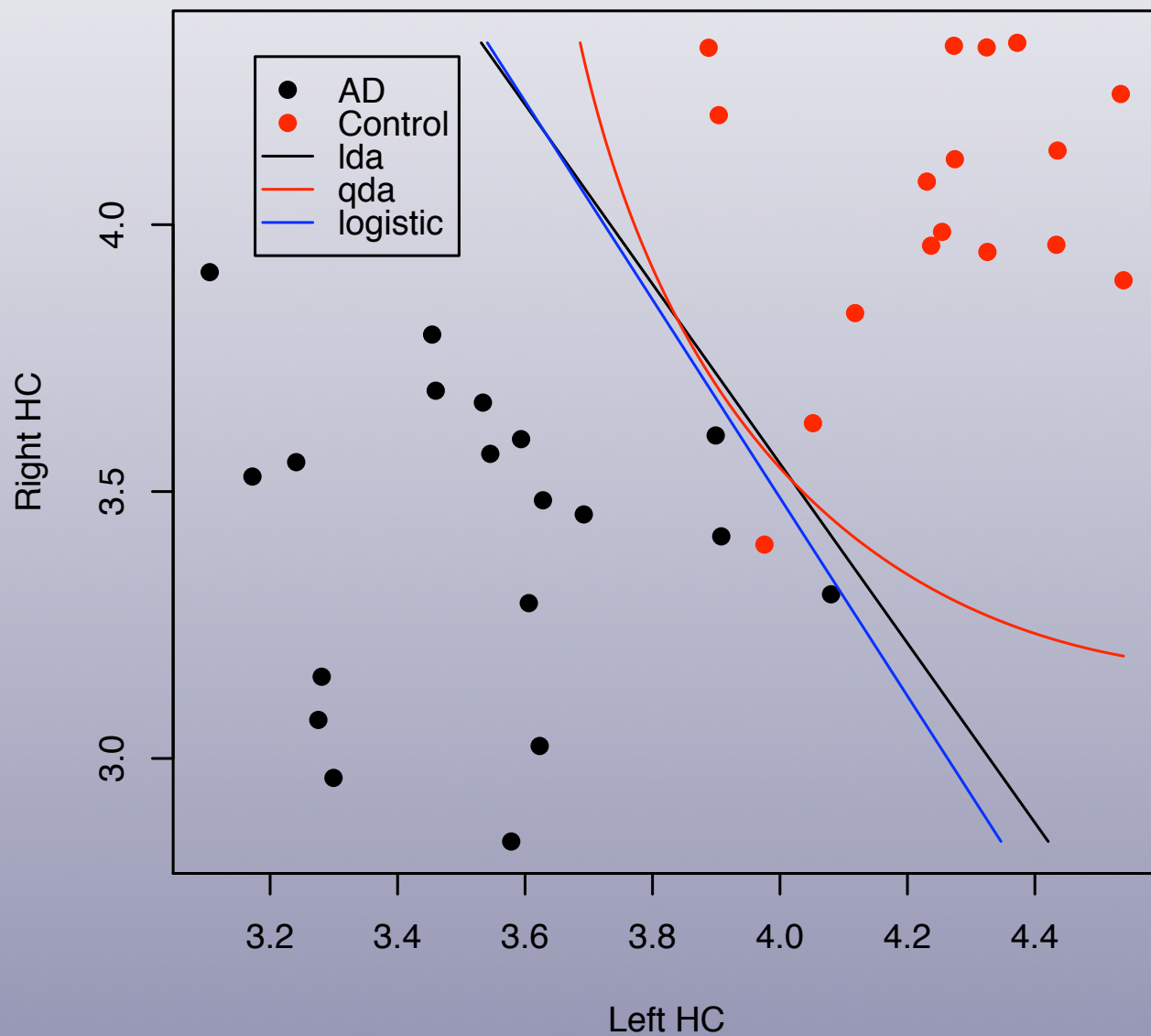
Specificity



Surface Coordinate System



Diagnoses on Areas



Predictive Ability

- One vertex had perfect sensitivity and specificity
- A few vertices in the PHG had perfect specificity and only one false negative.
- Perfect prediction can also be accomplished by one point from each PHG plus the MMSE score.

Mapping Anatomical Correlations Across Cerebral Cortex (MACACC)

- Hypothesis: the thickness of the cortex across associated areas will change in a correlated fashion.
- Corollary Hypothesis: these correlations can be influenced by developmental patterns and cognitive factors.

Cross-cortical Correlations

- Correlated change: as one part of the cortex changes in thickness another part features a statistically correlated change.
- Measured using Pearson's r - which takes on a value between 1 and -1 defining the strength of the correlation.

MACACC-strength

- Correlation strength: every vertex is correlated with every other vertex; correlation strength is the mean Pearson's r value of all (40,961) correlations.

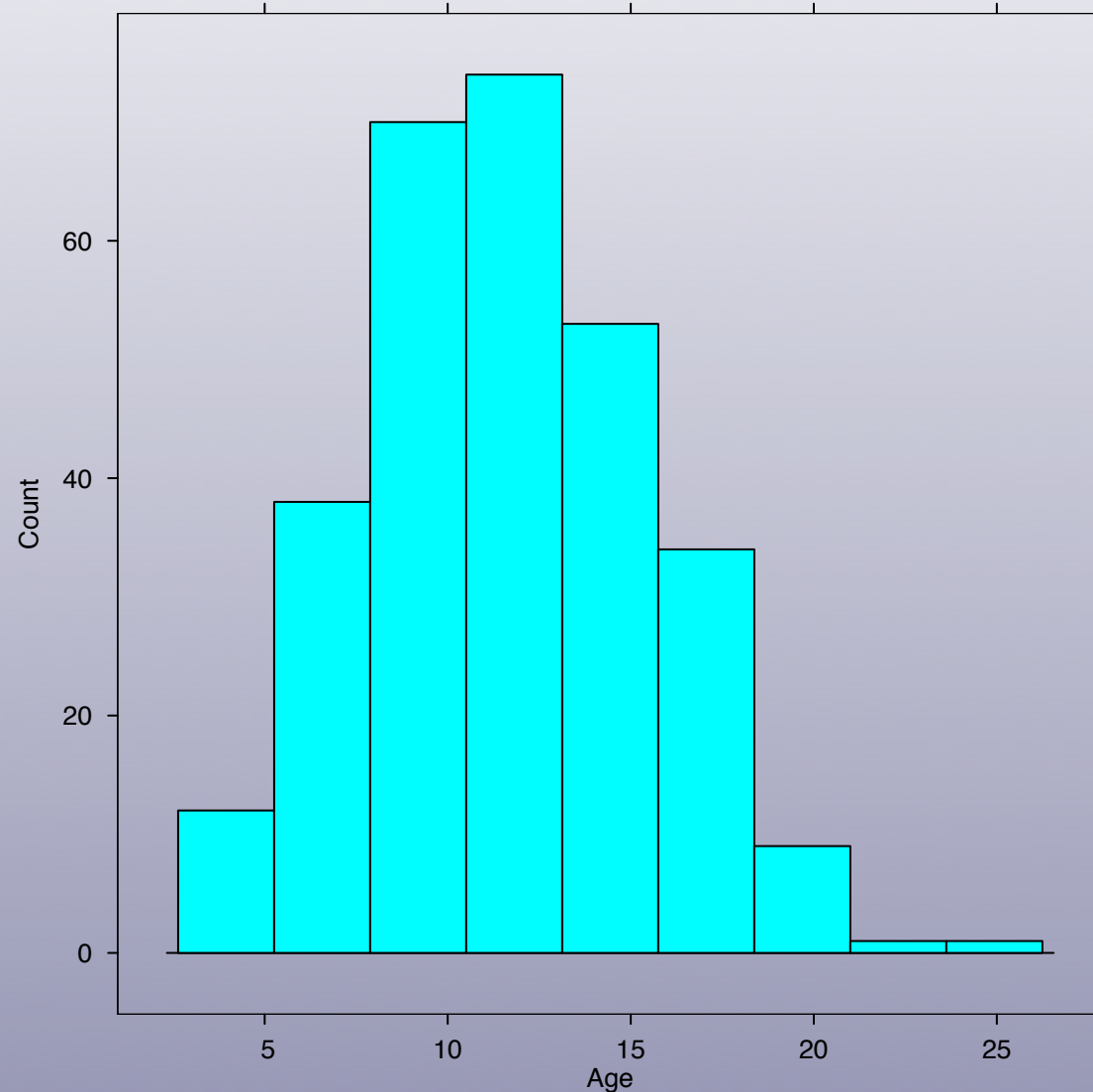
<i>Vertex</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>n</i>	<i>Strength</i>
<i>1</i>	1	0.7	0.55	0.89	0.79
<i>2</i>	0.7	1	0.66	0.43	0.70
<i>3</i>	0.55	0.66	1	0.29	0.63
<i>n</i>	0.89	0.43	0.29	1	0.65

MACACC Group Differences

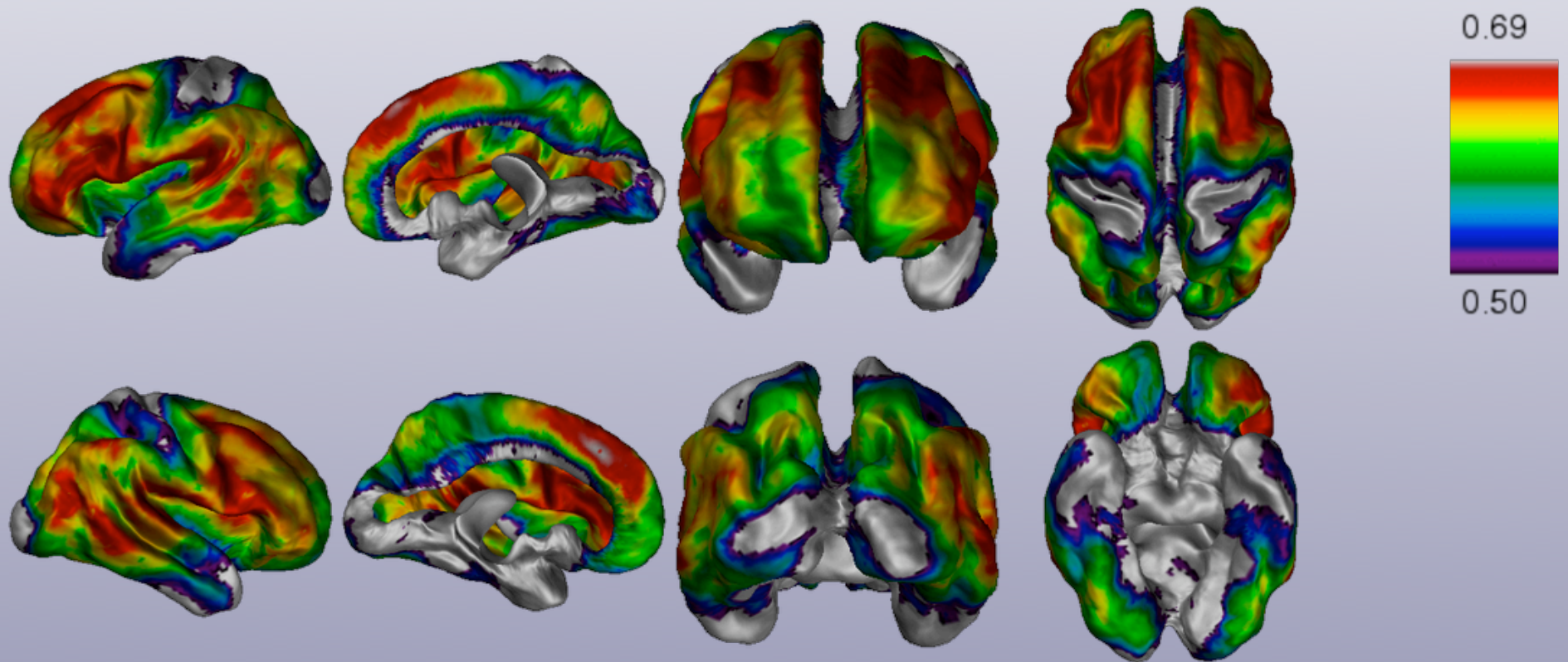
- Two fundamental questions that can be asked:
 - is the direction of the correlation with the seed region different?
 - is the variance of the correlation with the seed region different?

Study Sample

- NIMH Child Psychiatry Branch Data.
- 292 subjects.
- Cross-sectional.
- All normal controls

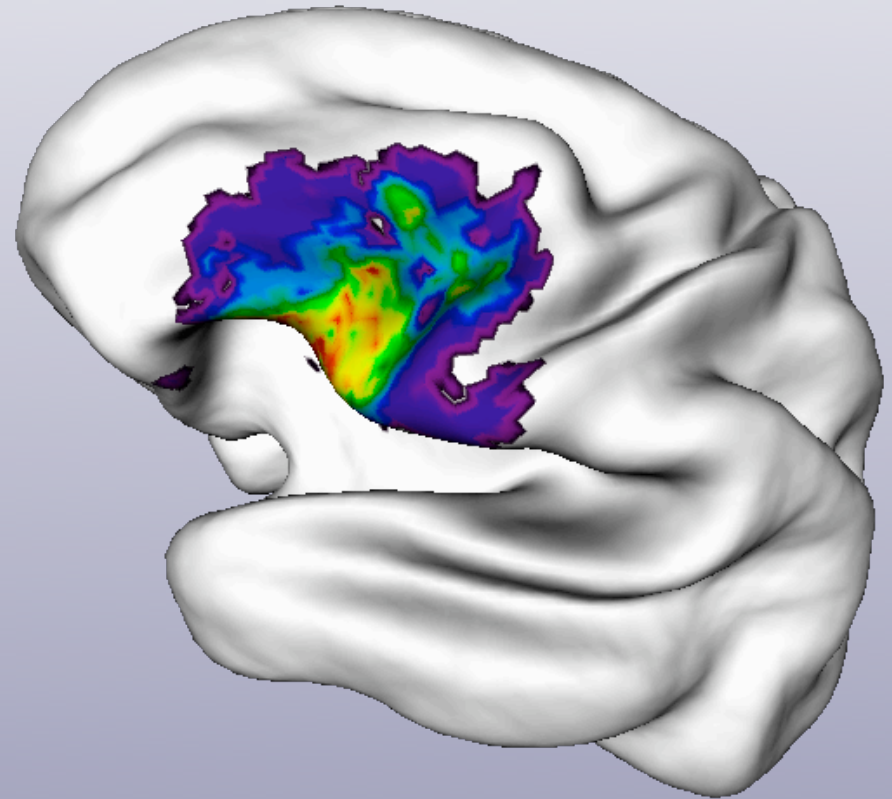


MACACC-strength



Seed region: BA 44

- BA 44, as defined by probabilistic map of 10 subjects (Amunts et al)
- Part of Broca's Area



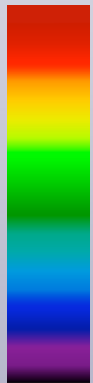
Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B. and Zilles, K. (1999) Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* **412**, 319-341.

BA 44 correlation

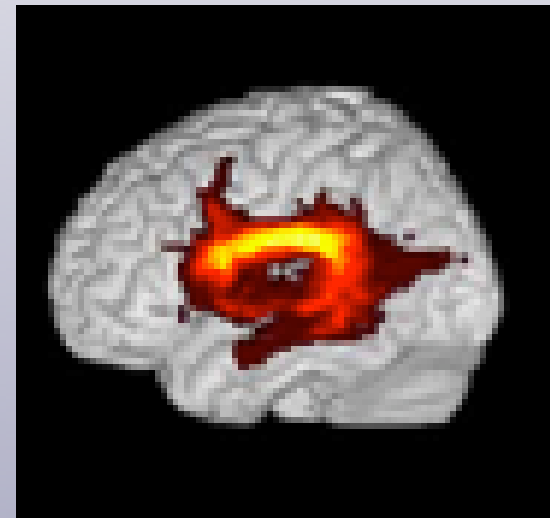
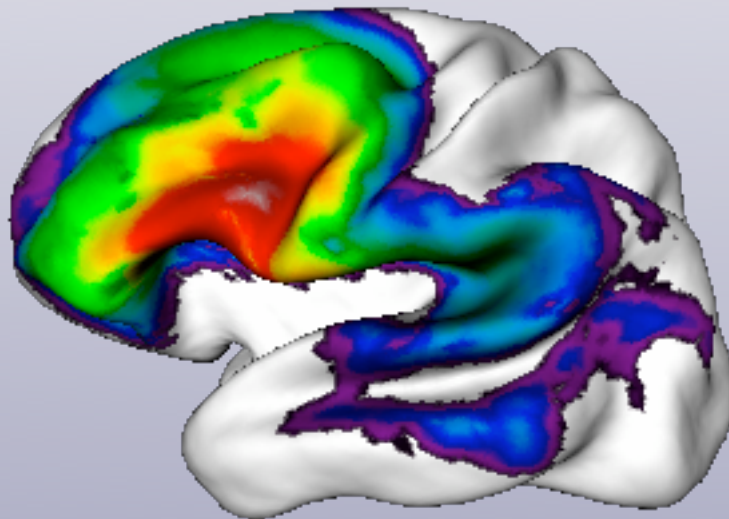
Cross-cortical correlation

DTI probability map*

1.0



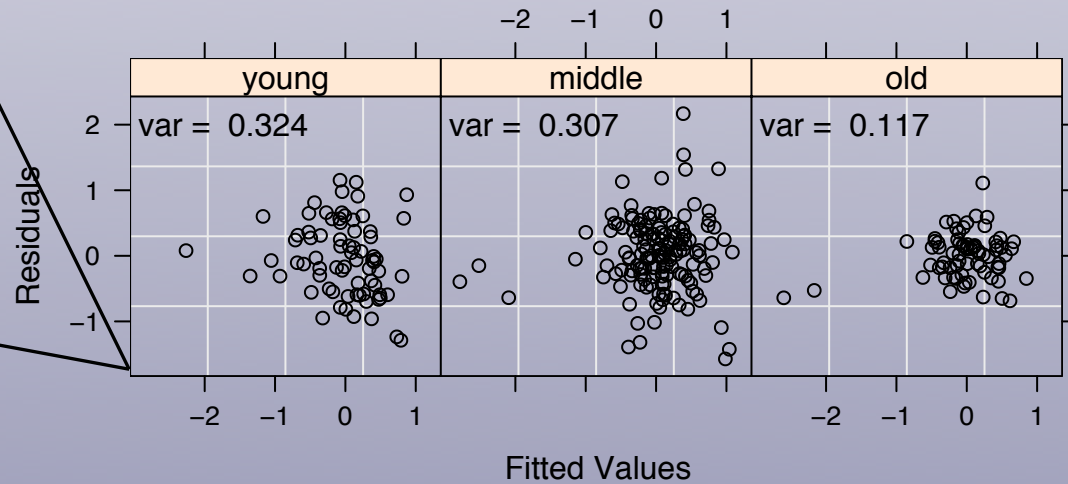
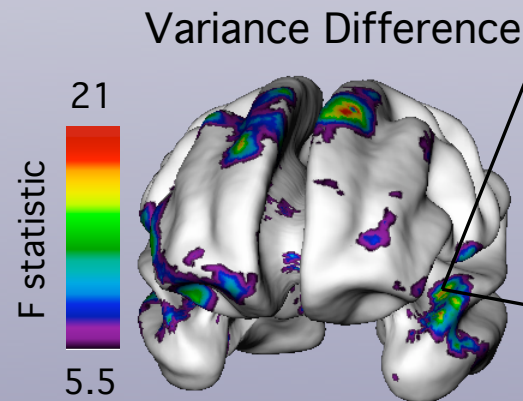
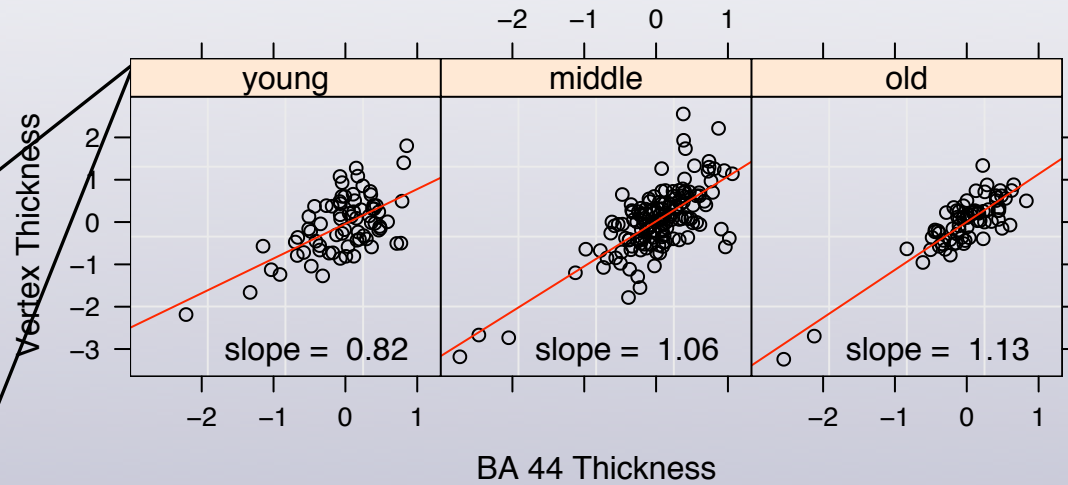
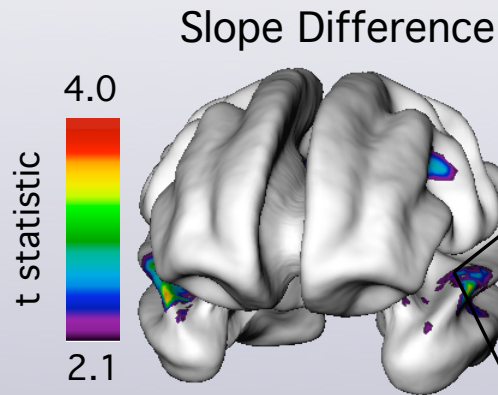
0.8



* Parker, G. J., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A., Ciccarelli, O. and Lambon Ralph, M. A. (2005) Lateralization of ventral and dorsal auditory-language pathways in the human brain. *Neuroimage* **24**, 656-666.

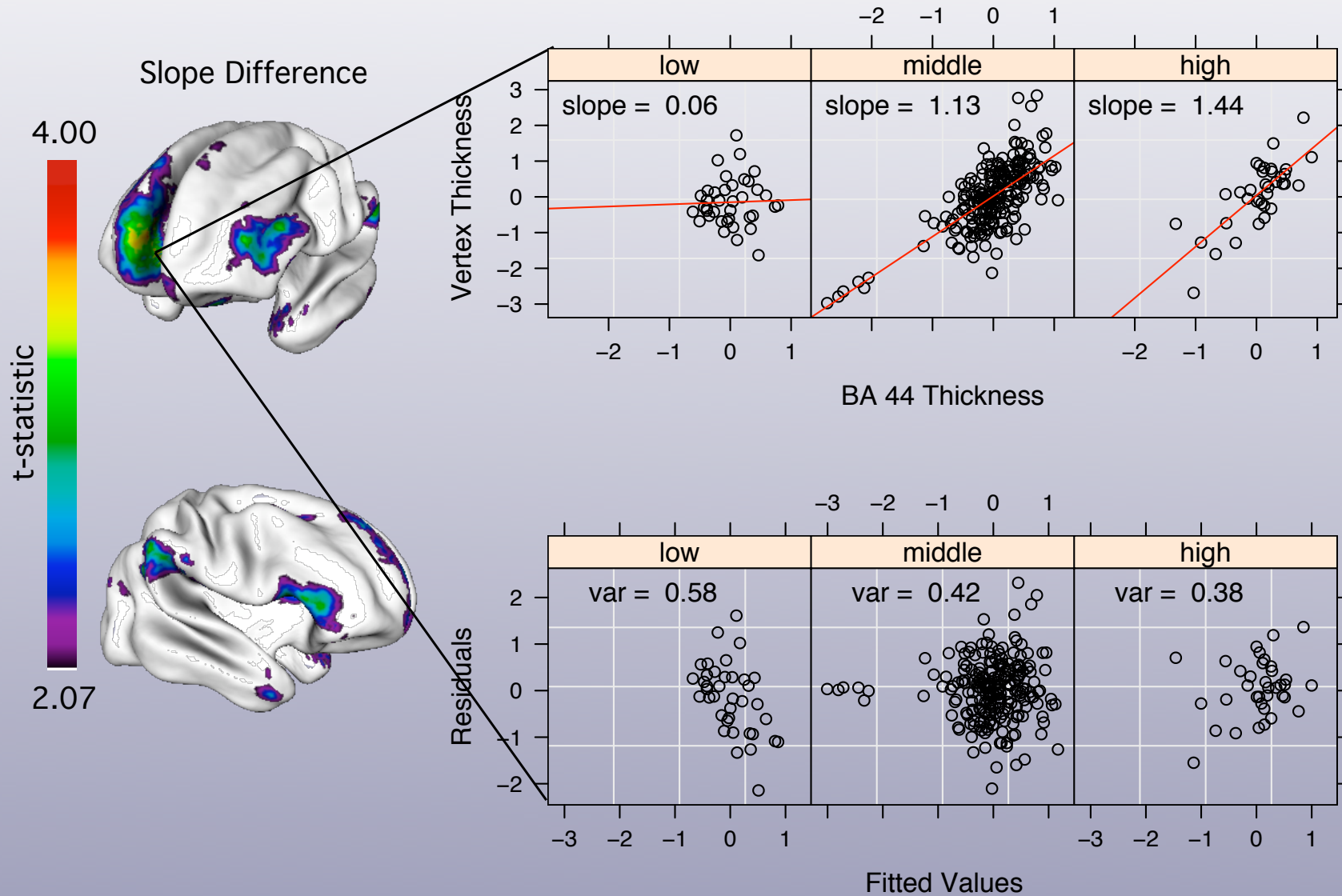
Age Differences

Young: < 8.8 years.
Old: > 14.2 years.



IQ Differences

Low: < 100.
High: > 120.



Acknowledgements



SickKids®

Alan Evans
Alex Zijdenbos
Krista Hyde
Claude Lepage
Yasser Ad-Dab'bagh
Jens Pruessner
Keith Worsley

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Mark Henkelman
Sheena Josselyn
Shoshana Spring
Adelaide Yu

Judith Rapoport
Jay Giedd
Dede Greenstein
Rhoshel Lenroot
Philip Shaw
Jeffrey Carroll
Michael Hayden
Harald Hampel
Stefan Teipel
Gottfried Schlaug