Not the neocortex: Modeling the hippocampus, basal ganglia, thalamus, and cerebellum in health and illness

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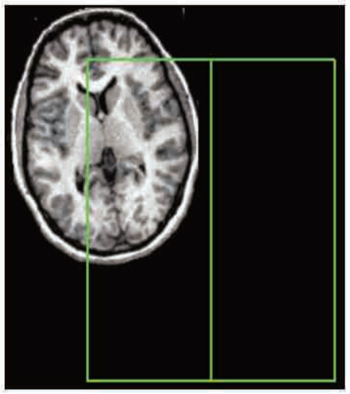
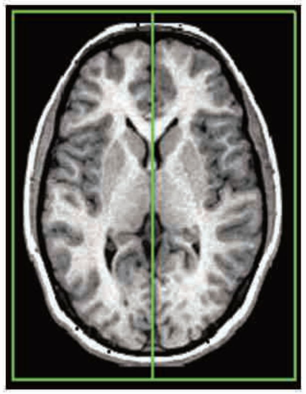
Subtle changes in brain morphology detected *in vivo*

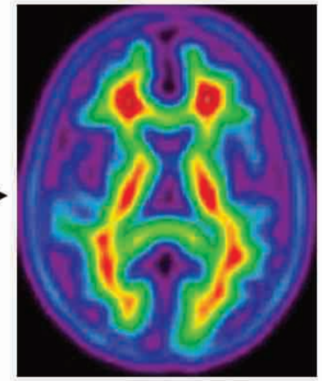


“Native” MRI

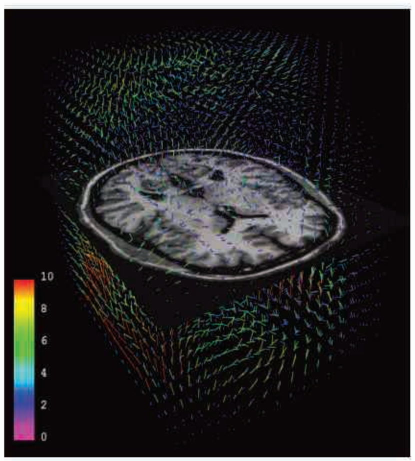


Registered MRI

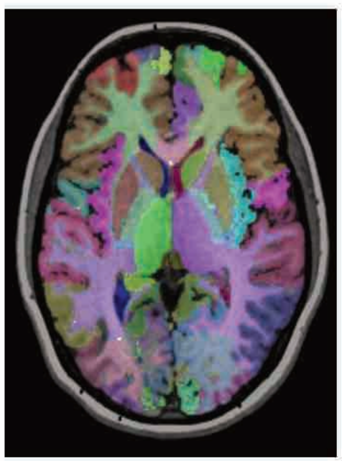
Tissue Classification



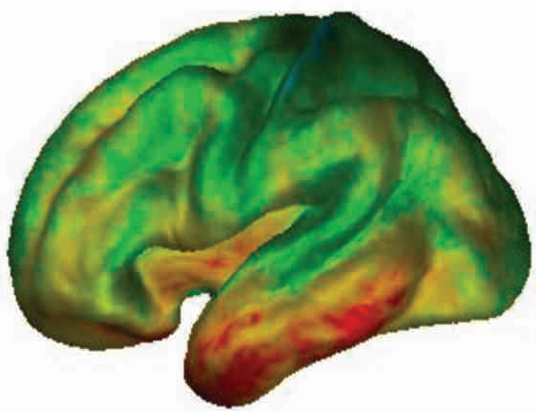
White-matter Density



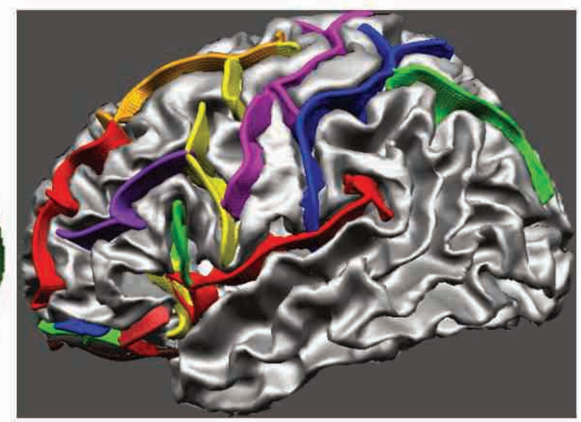
Deformation field



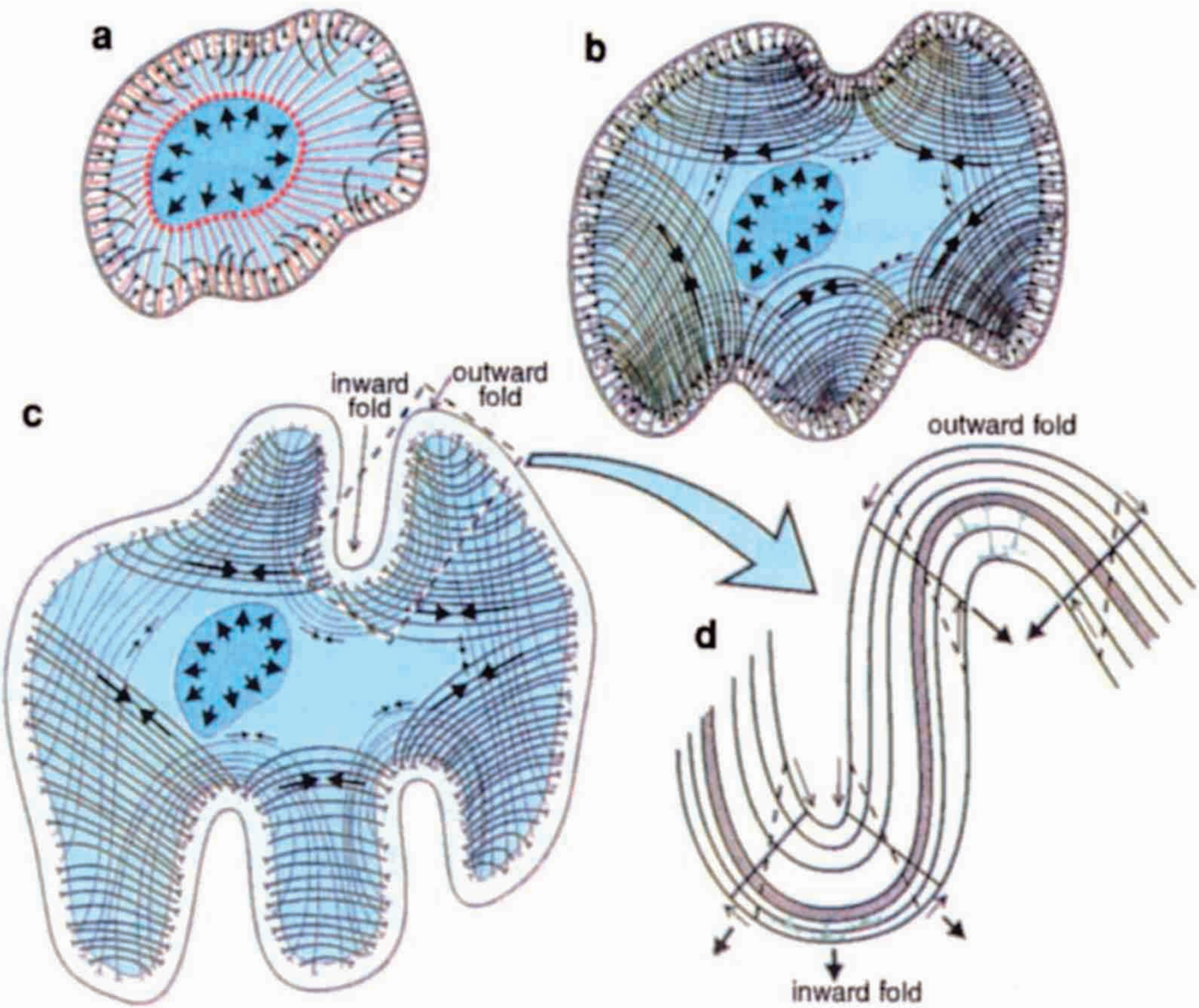
Segmentation



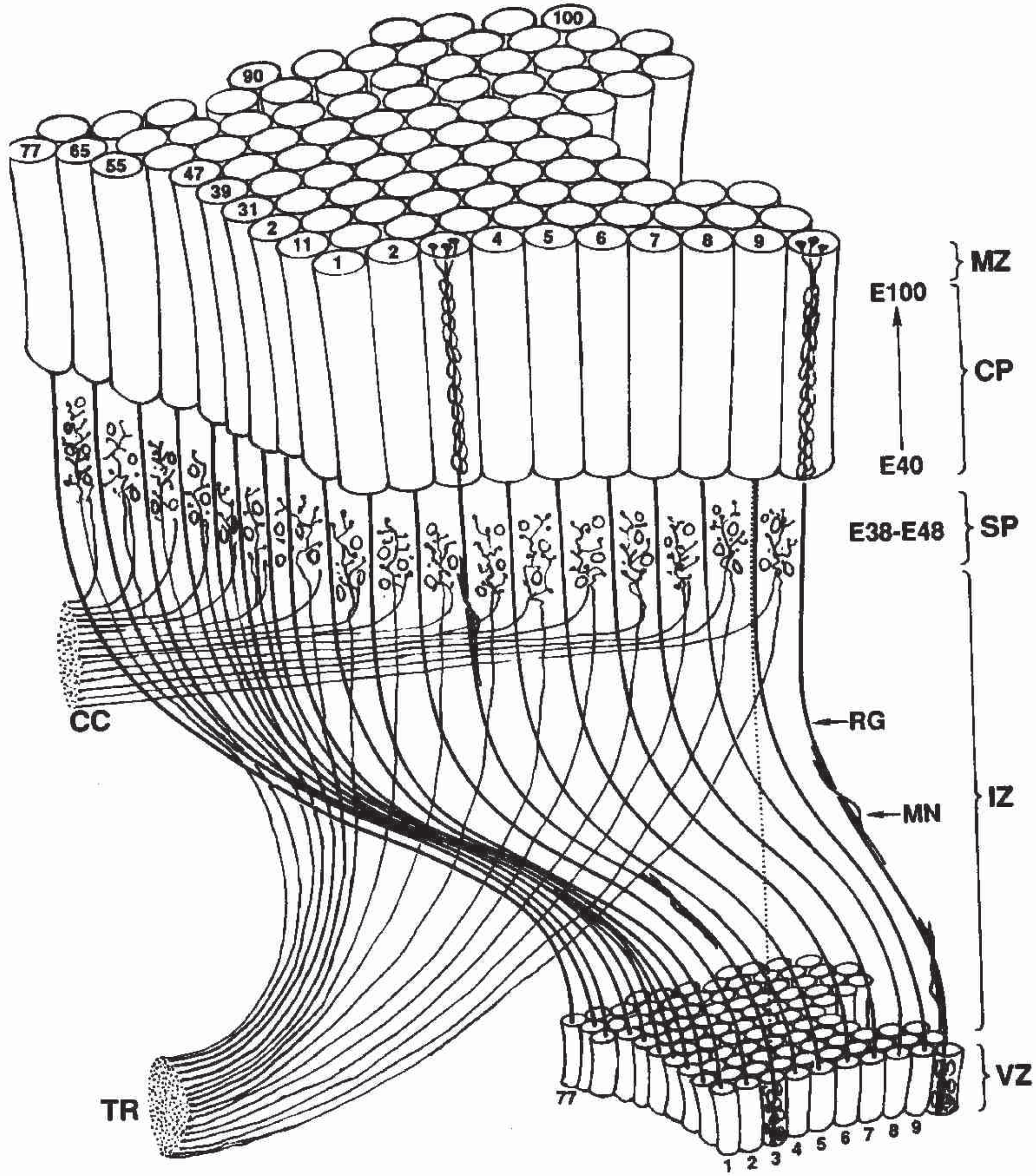
Cortical thickness



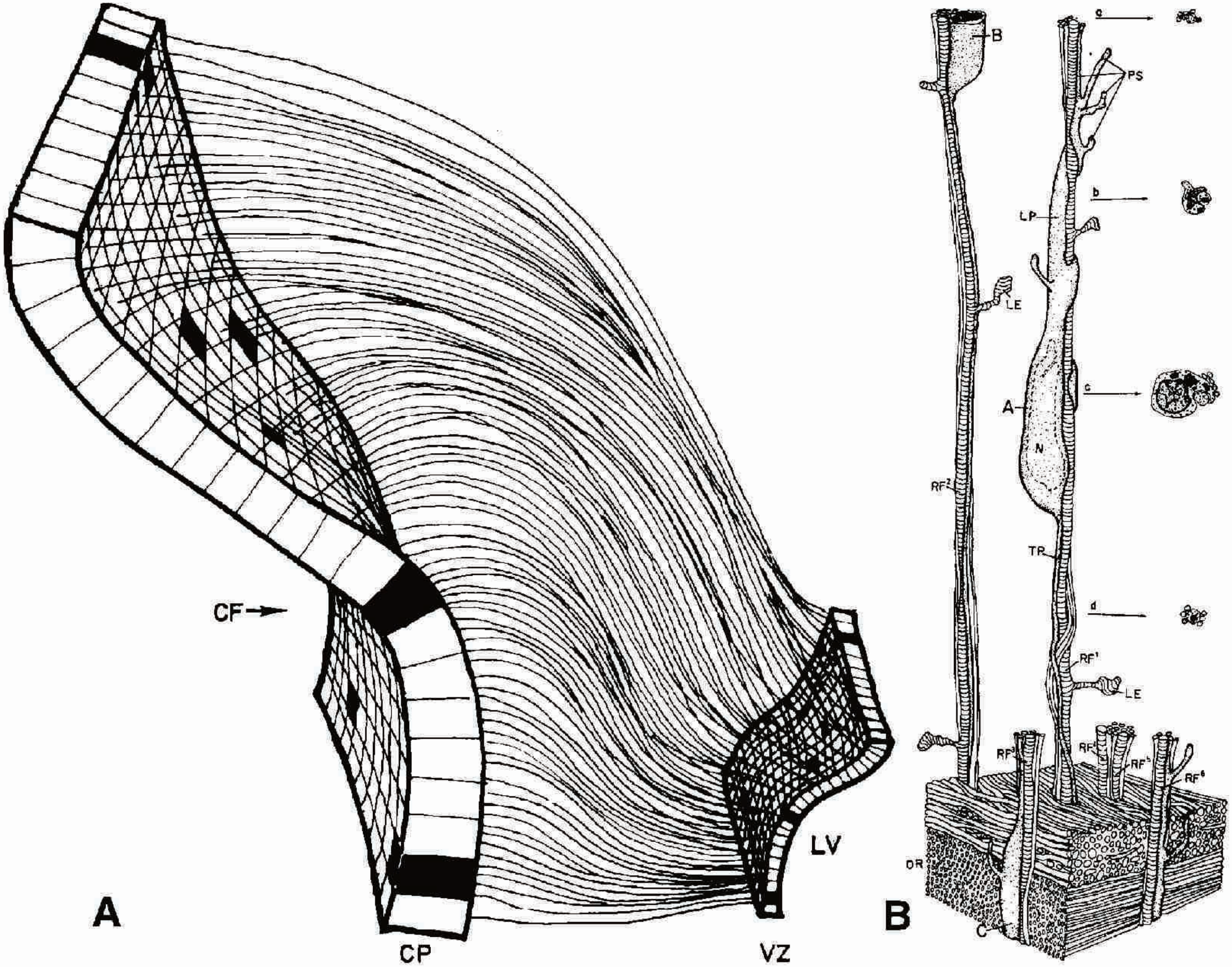
Cerebral sulci



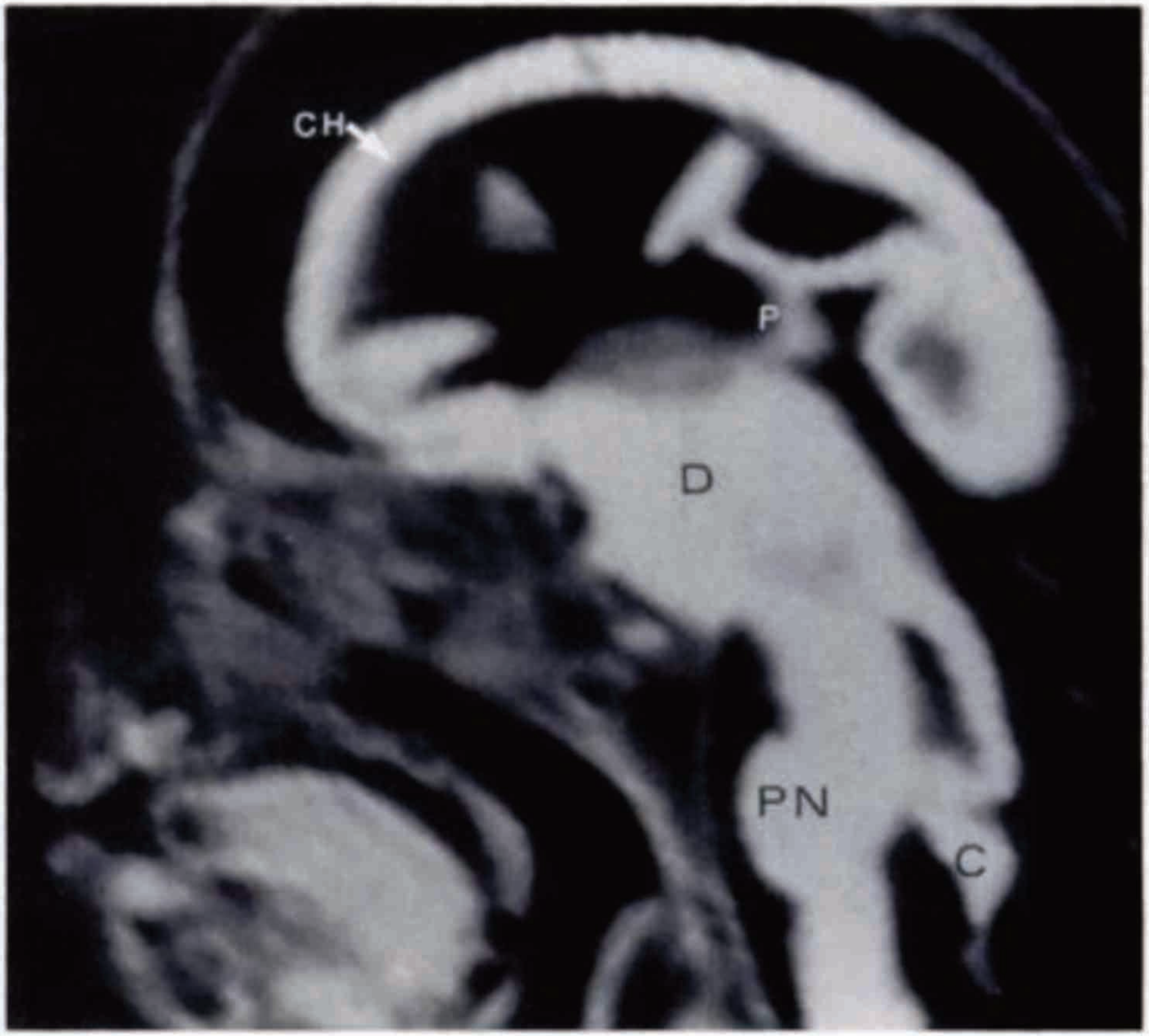
Van Essen, Nature Neuroscience. 1997.



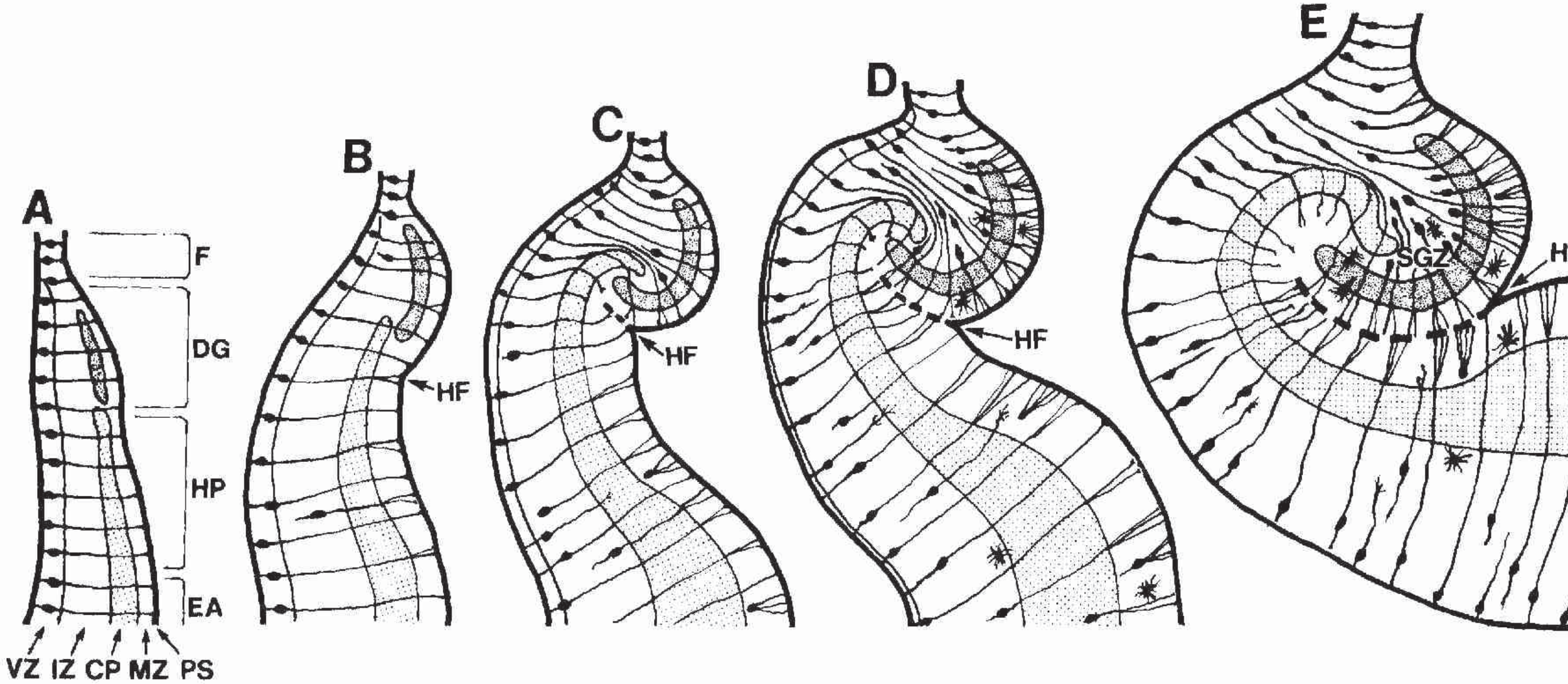
Rakic, Science, 1988



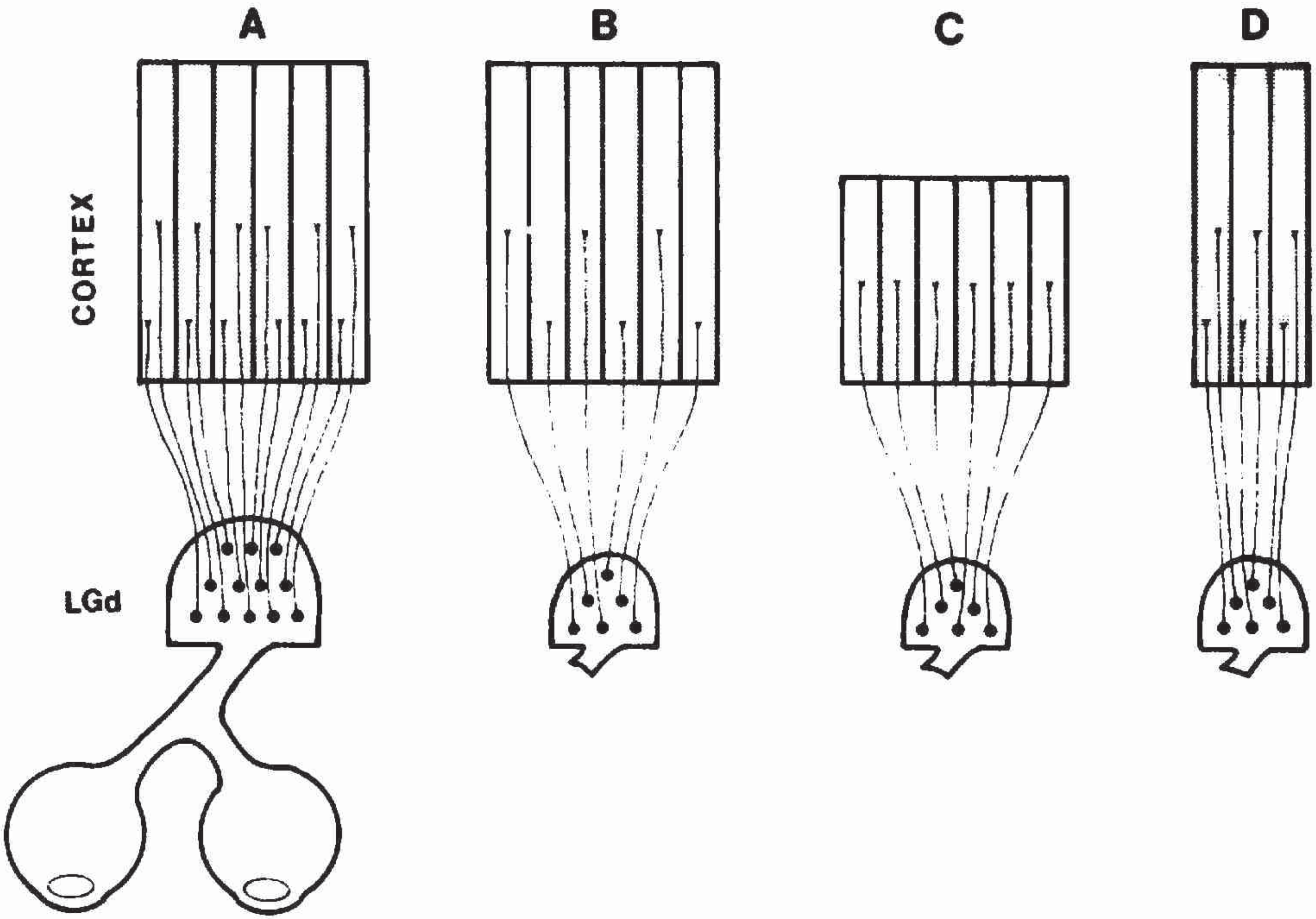
Rakic, Cerebral Cortex, 2003



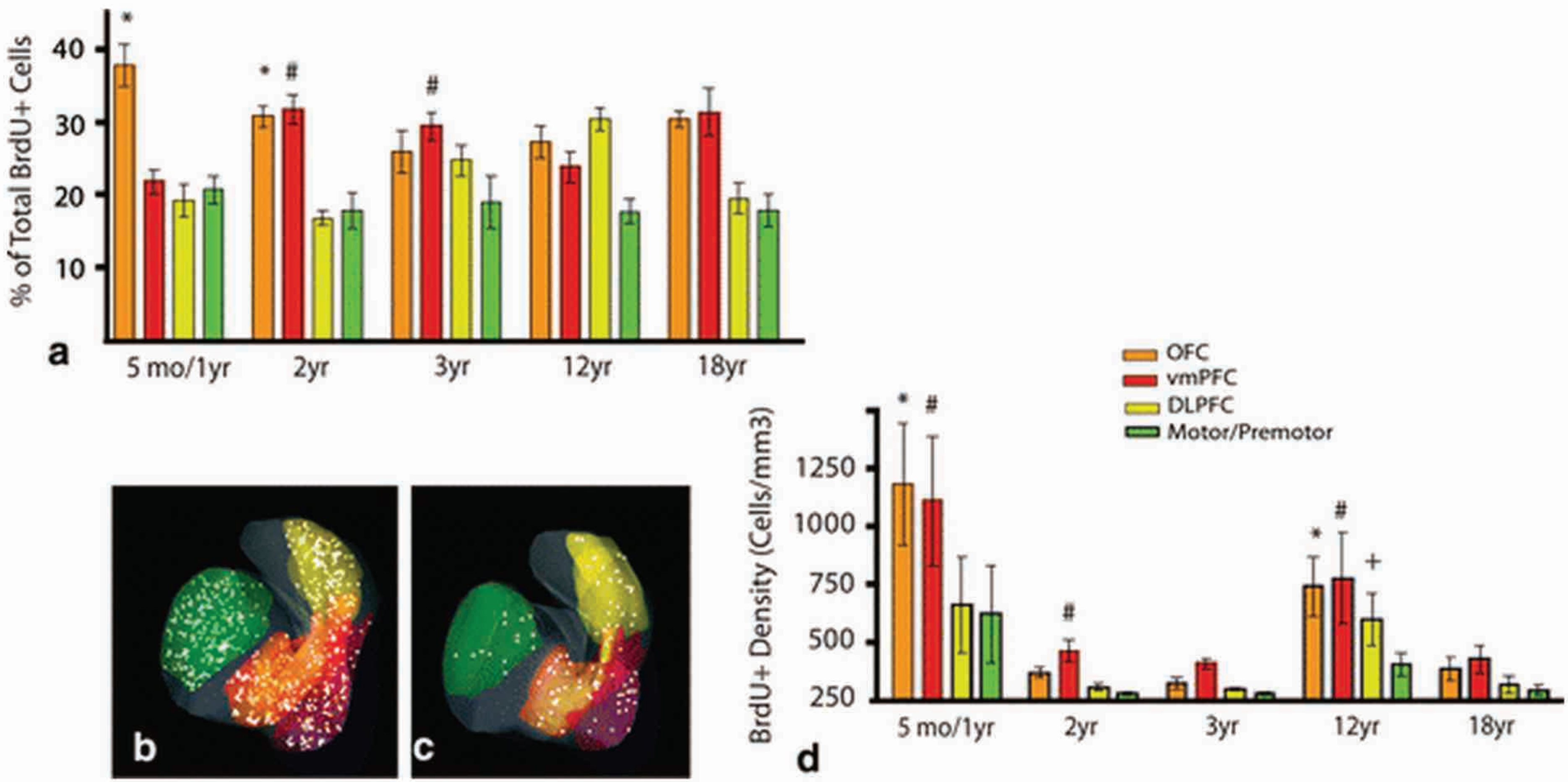
Hansen et al., Radiographics, 1993



Eckenhoff and Rakic, Journal of Comparative Neurology, 1984

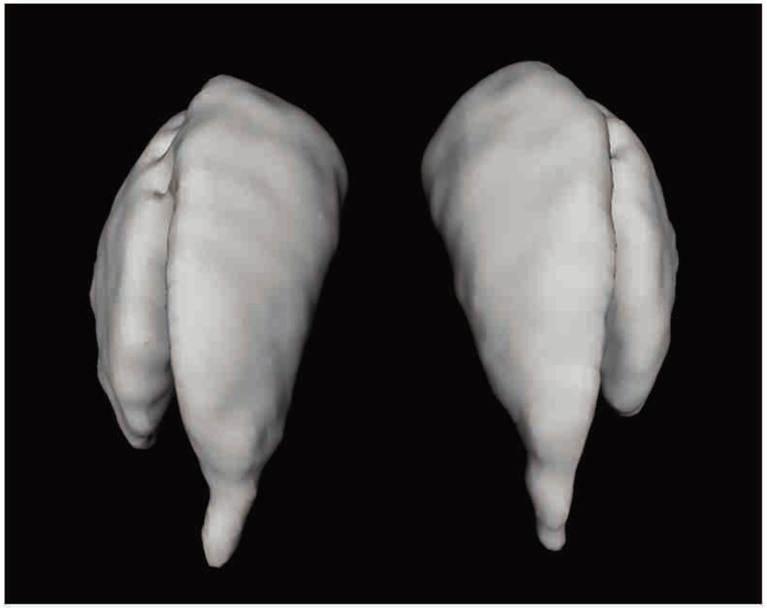


Rakic, Science, 1988



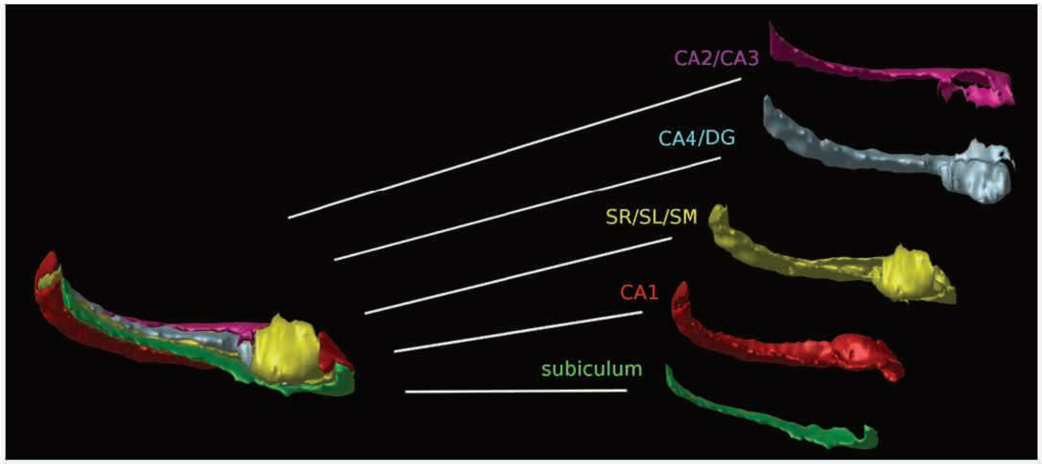
Stopczynski, Polosky, and Haber,
Brain Structure and Function, 2008

1. Shape can be used as a neurodevelopmental endophentoype

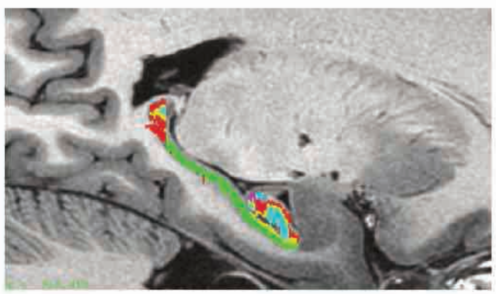


1. Shape can be used as a neurodevelopmental endophentoype

2. Shape is a strong predictor of ageing and cognitive ability

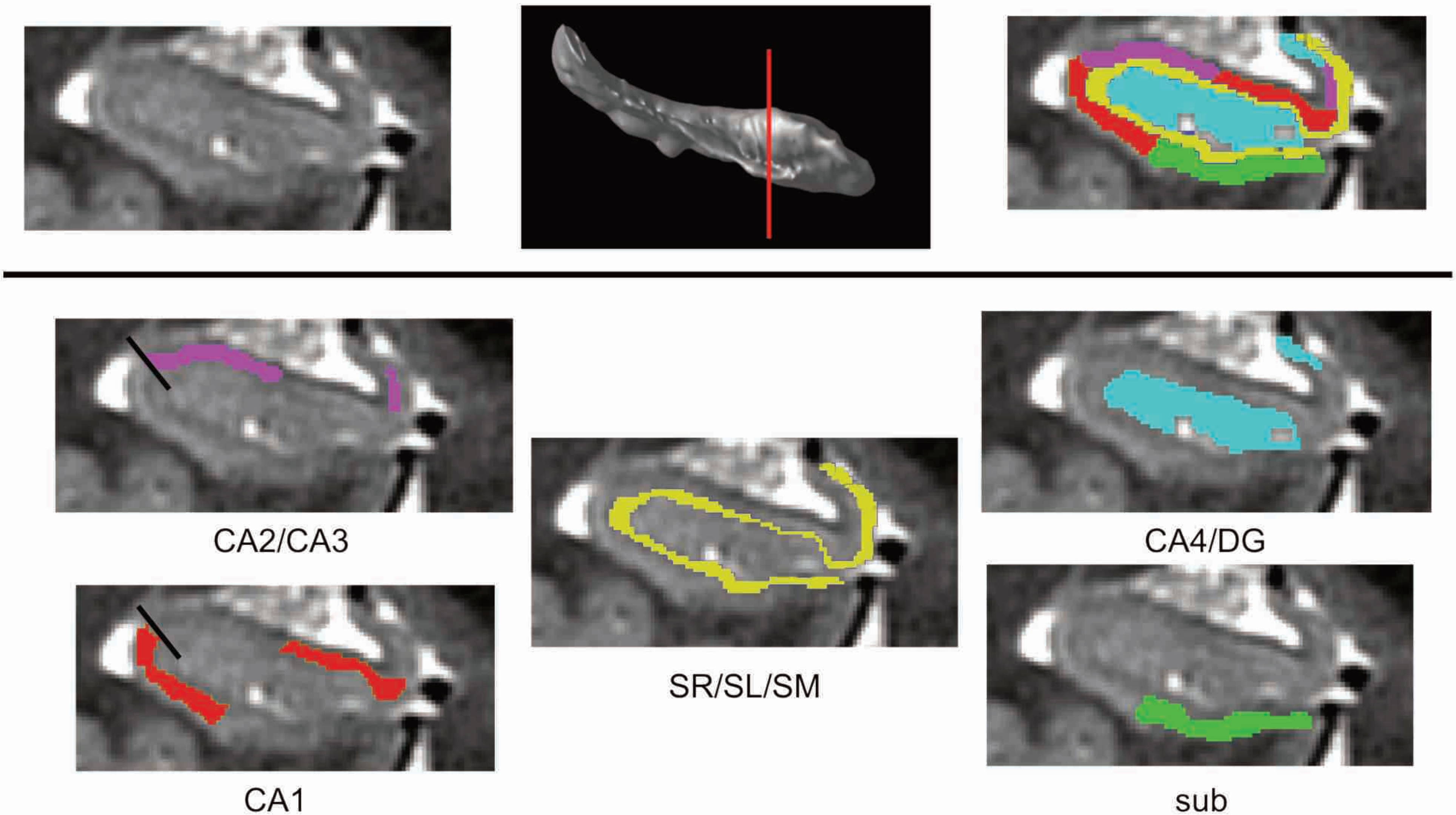


Segmentation is a type of cartography



Idea: use manually segmented images (atlases) as **guides** when segmenting a new image

Segmentation rules for the hippocampal head

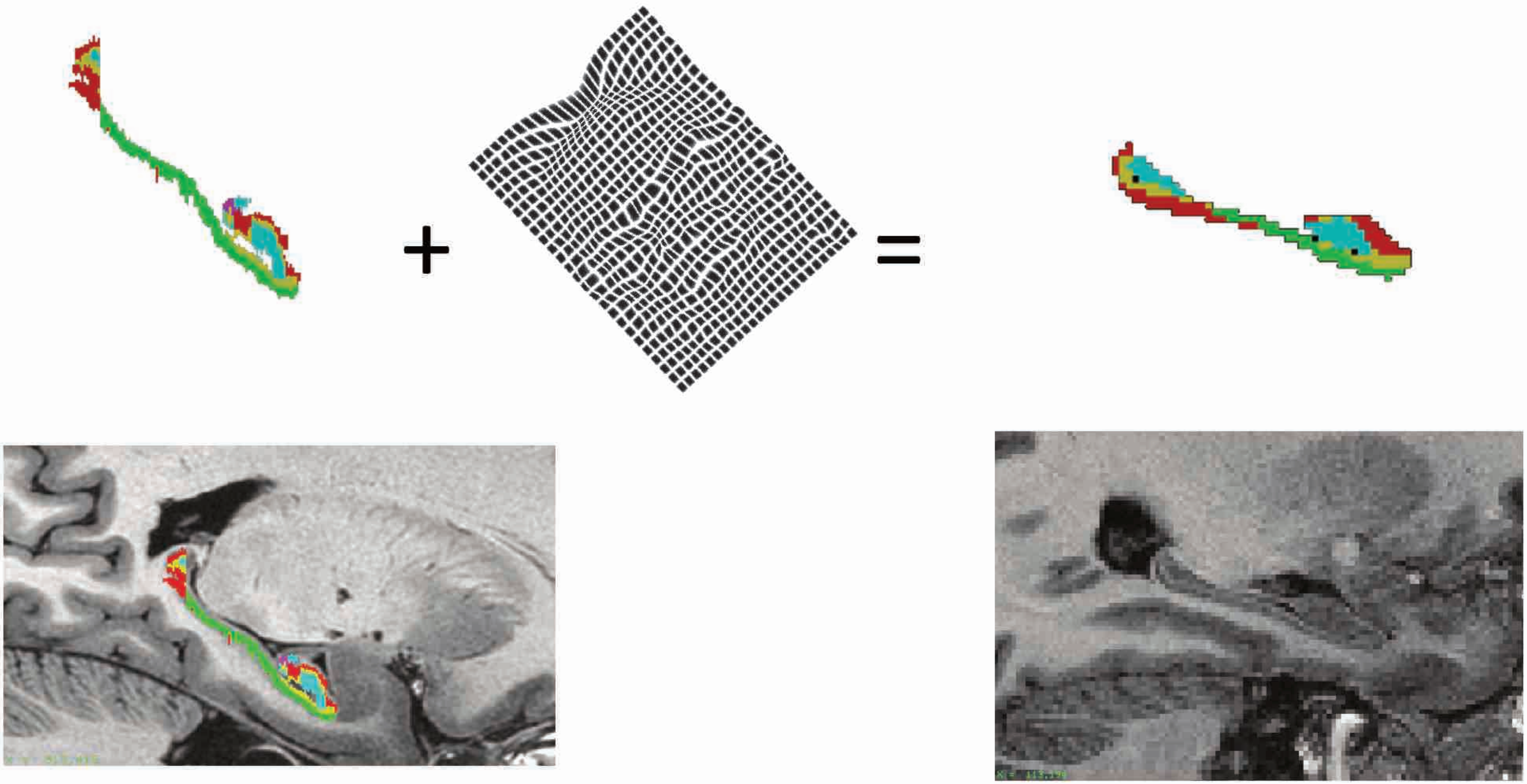


Winterburn et al., *NeuroImage 2013*

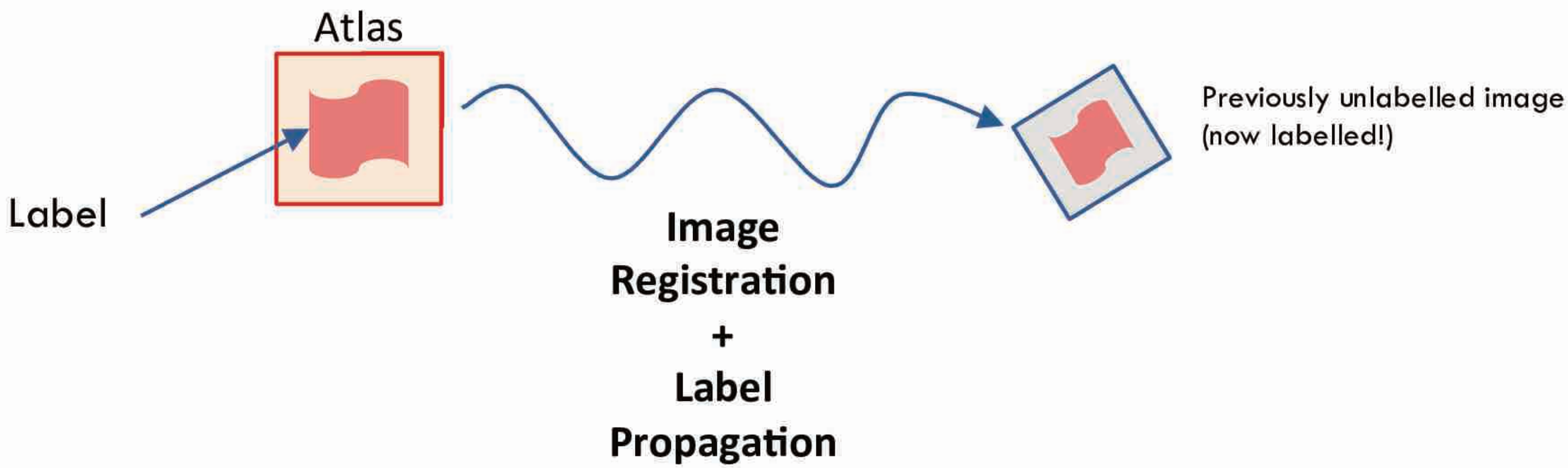
Reliability data

Region	Manual	0.3 mm Translation	0.99 Scaling	1.01 Scaling
CA1	0.78 (0.77 - 0.79)	0.66 (0.65 - 0.68)	0.64 (0.59 - 0.71)	0.67 (0.60 - 0.76)
CA2/CA3	0.64 (0.56 - 0.73)	0.54 (0.47 - 0.64)	0.35 (0.23 - 0.46)	0.43 (0.34 - 0.54)
CA4/Dentate Gyrus	0.83 (0.81 - 0.85)	0.70 (0.65 - 0.75)	0.68 (0.6 - 0.74)	0.67 (0.58 - 0.72)
SR/SL/SM	0.71 (0.68 - 0.73)	0.69 (0.66 - 0.72)	0.74 (0.69 - 0.79)	0.72 (0.67 - 0.8)
Subiculum	0.75 (0.72 - 0.78)	0.60 (0.52 - 0.66)	0.59 (0.42 - 0.67)	0.60 (0.41 - 0.68)
Whole Hippocampus	0.91 (0.90 - 0.92)	0.85 (0.84 - 0.86)	0.87 (0.86 - 0.91)	0.88 (0.86 - 0.91)

Segmentation Label Propagation

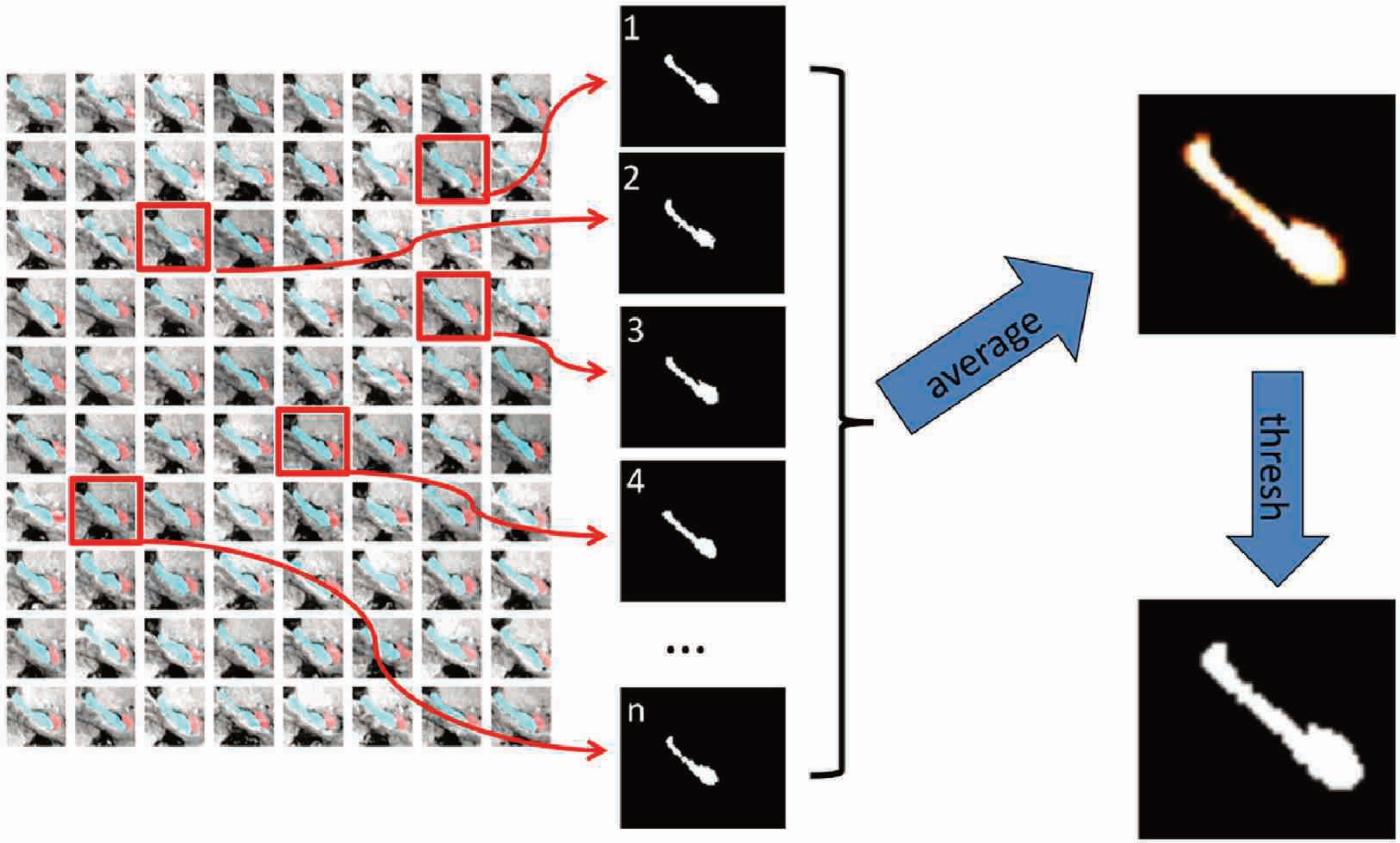


Atlas-based segmentation



- atlas segmentation errors
- registration errors
- resampling errors

Multi-atlas based segmentation



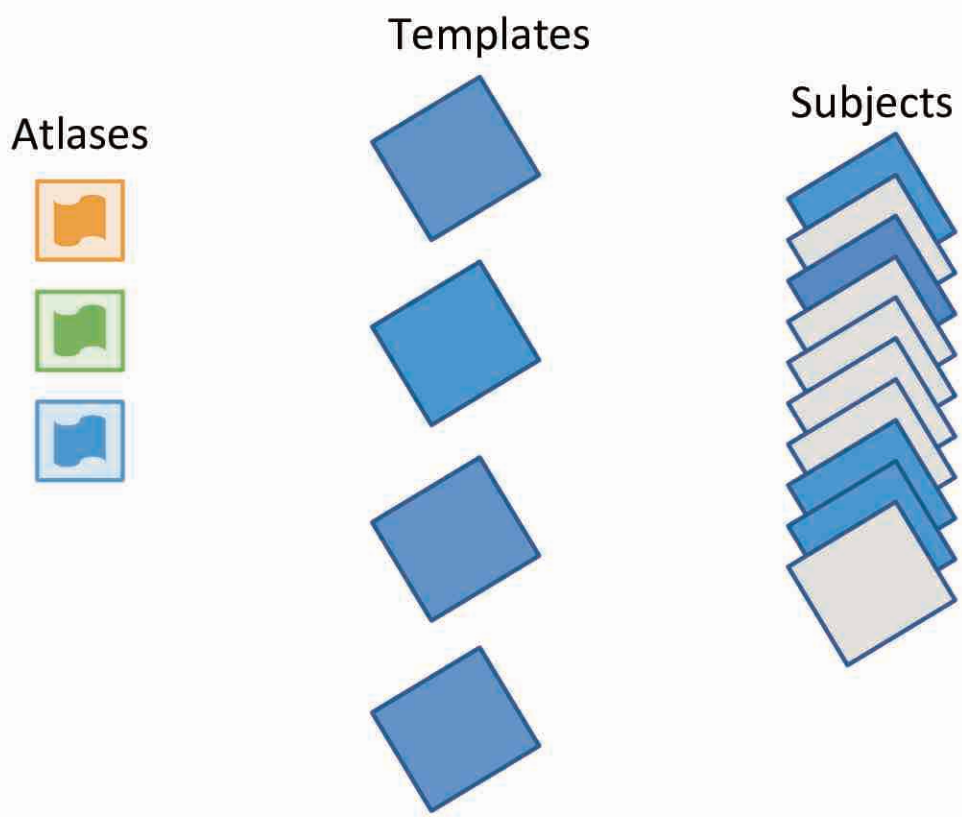
Collins and Pruessner. NeuroImage , 2010

MAGeT Brain

Multiple **A**utomatically **Ge**nerated **T**emplates Brain segmentation

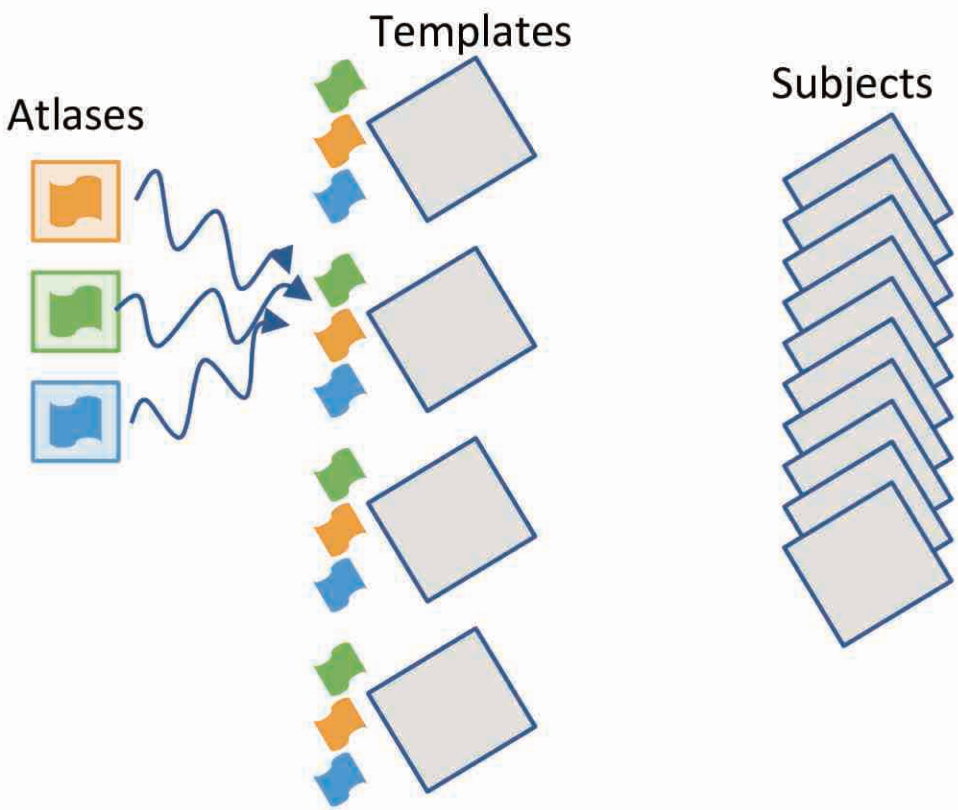
MAGeT Brain

Step 1: Take a sample from the unlabelled subjects.



MAGeT Brain

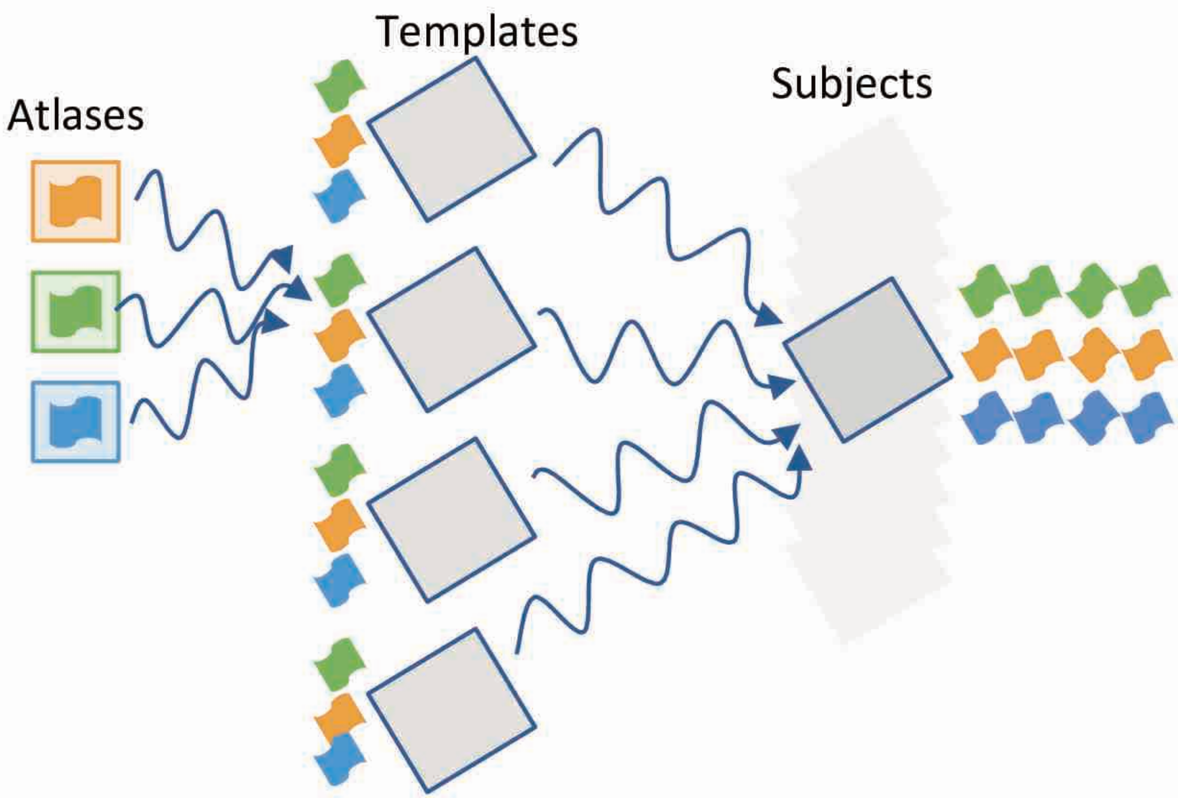
Step 2: **Each** template image gets labelled by **each** atlas



Chakravarty et al., Human Brain Mapping 2013

MAGeT Brain

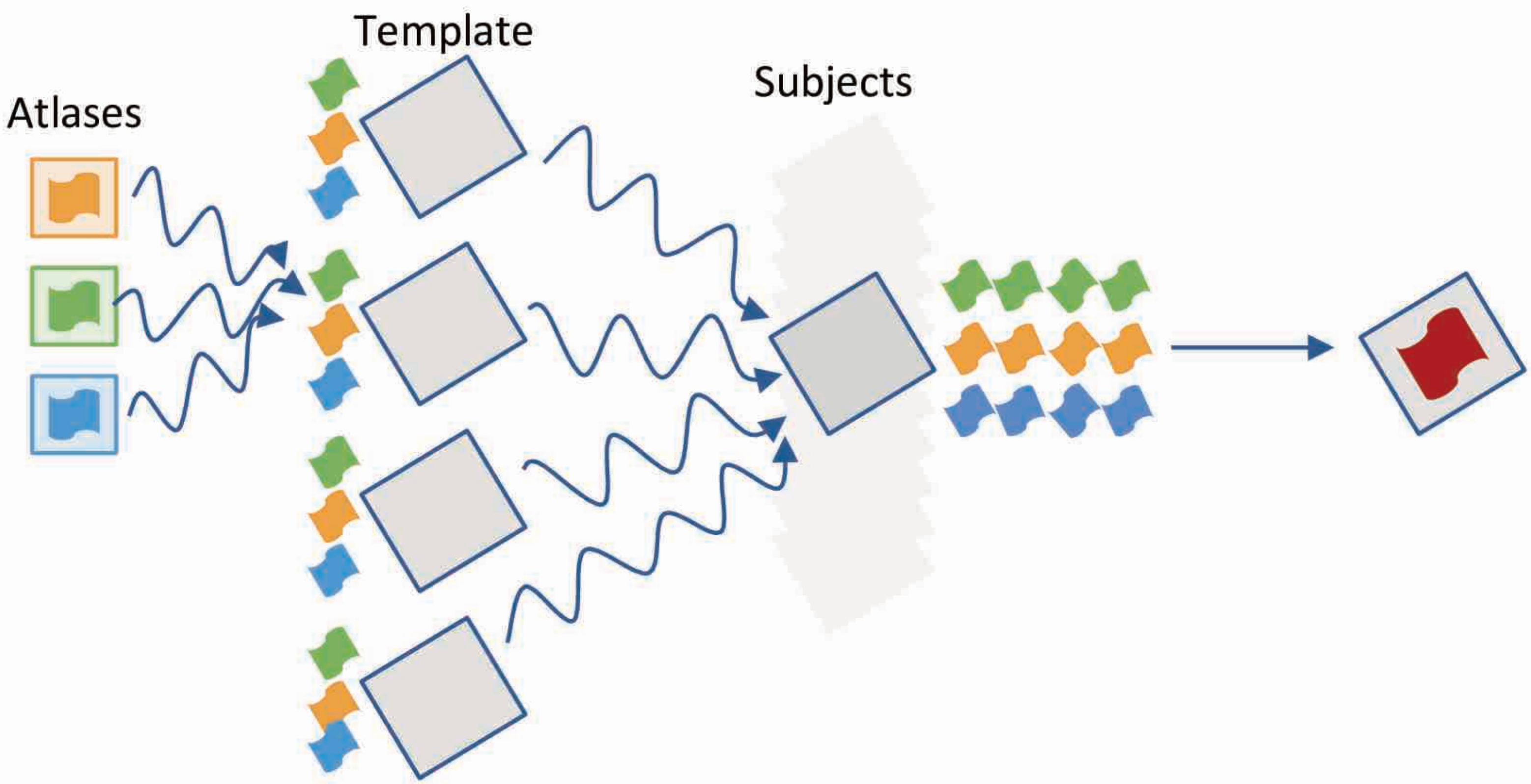
Step 3: **Each** template labels **each** subject image



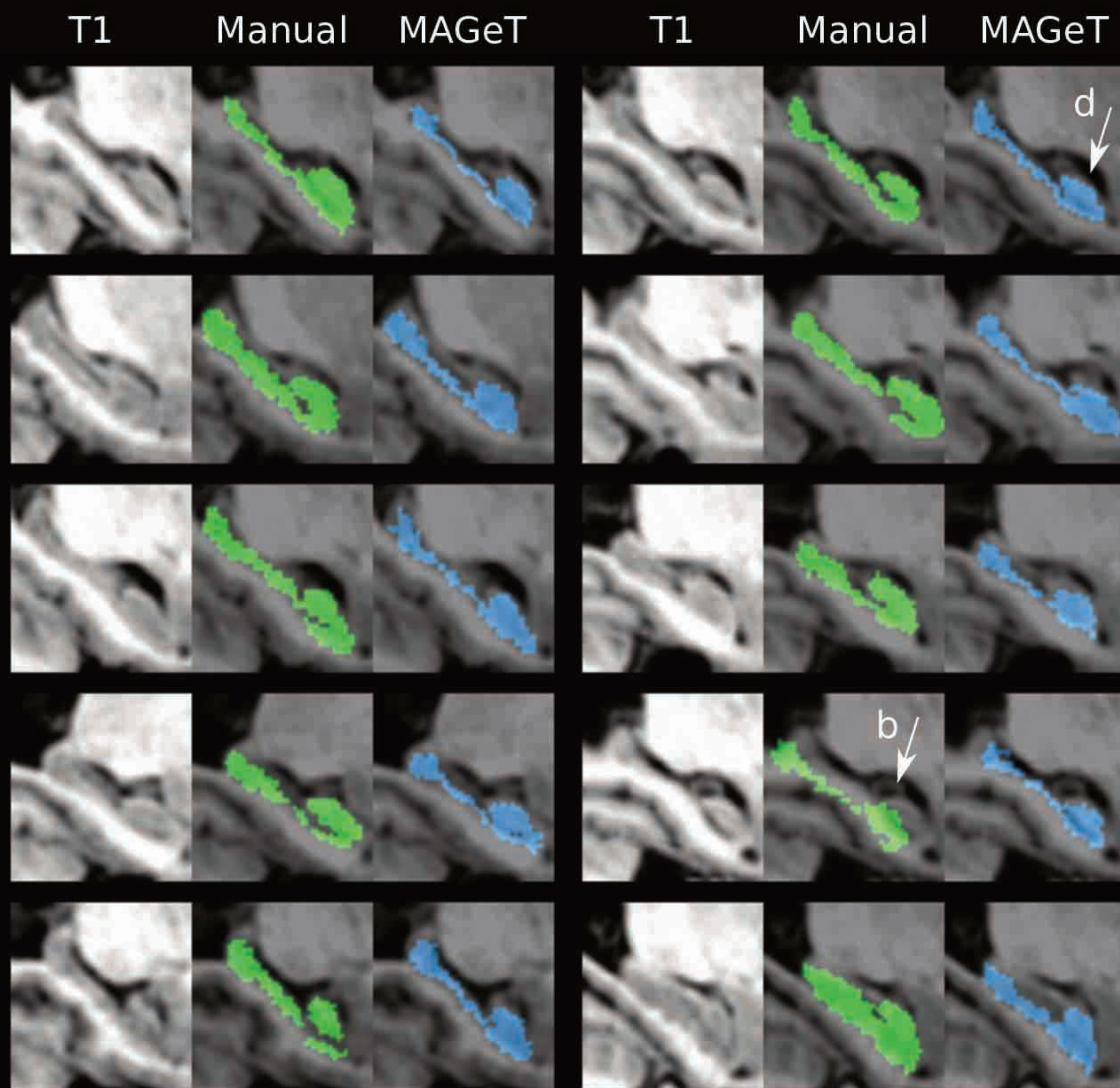
Chakravarty et al., Human Brain Mapping 2013

MAGeT Brain

Step 4: **Fuse** all labels for a subject

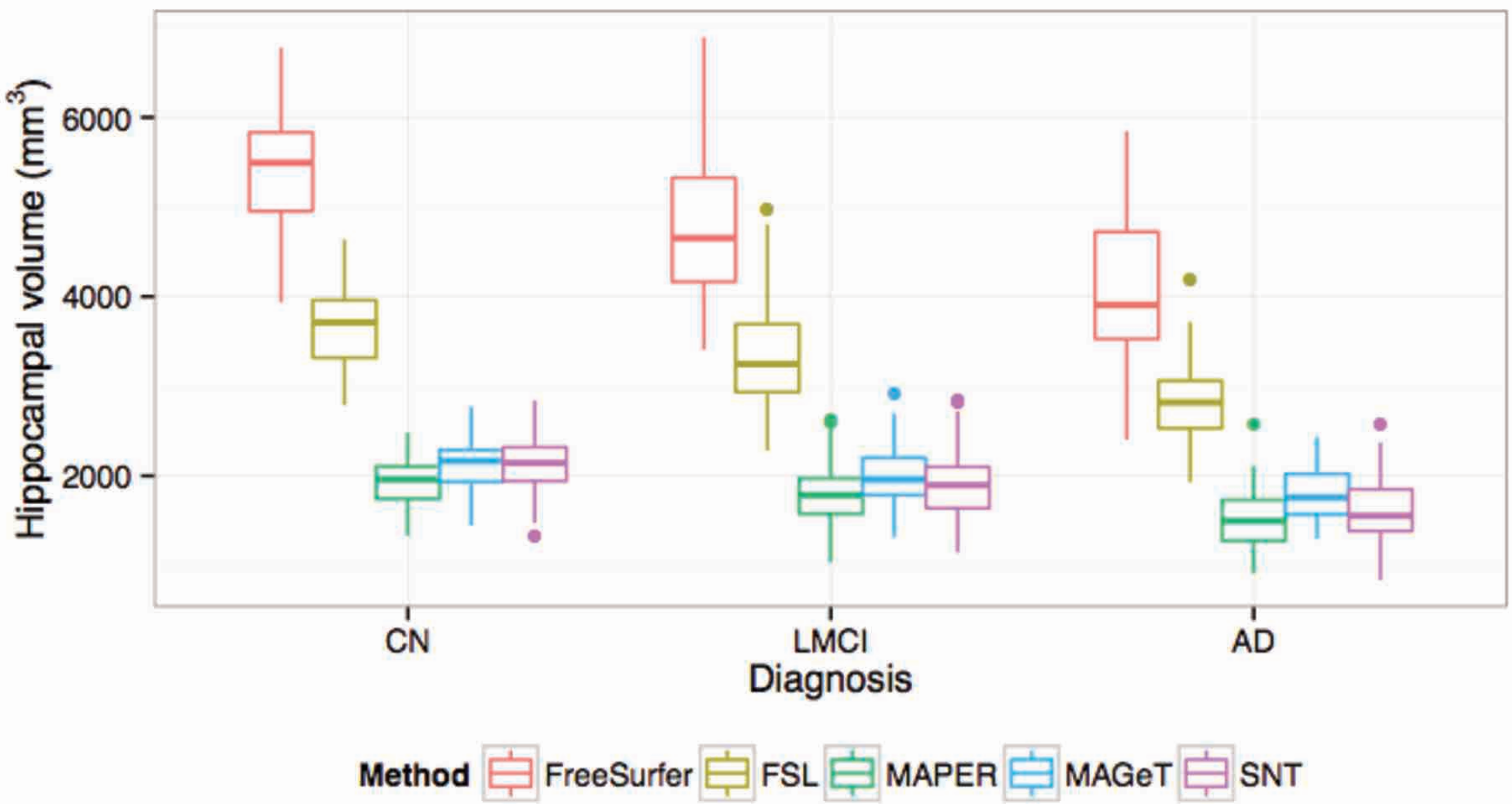


Chakravarty et al., Human Brain Mapping 2013



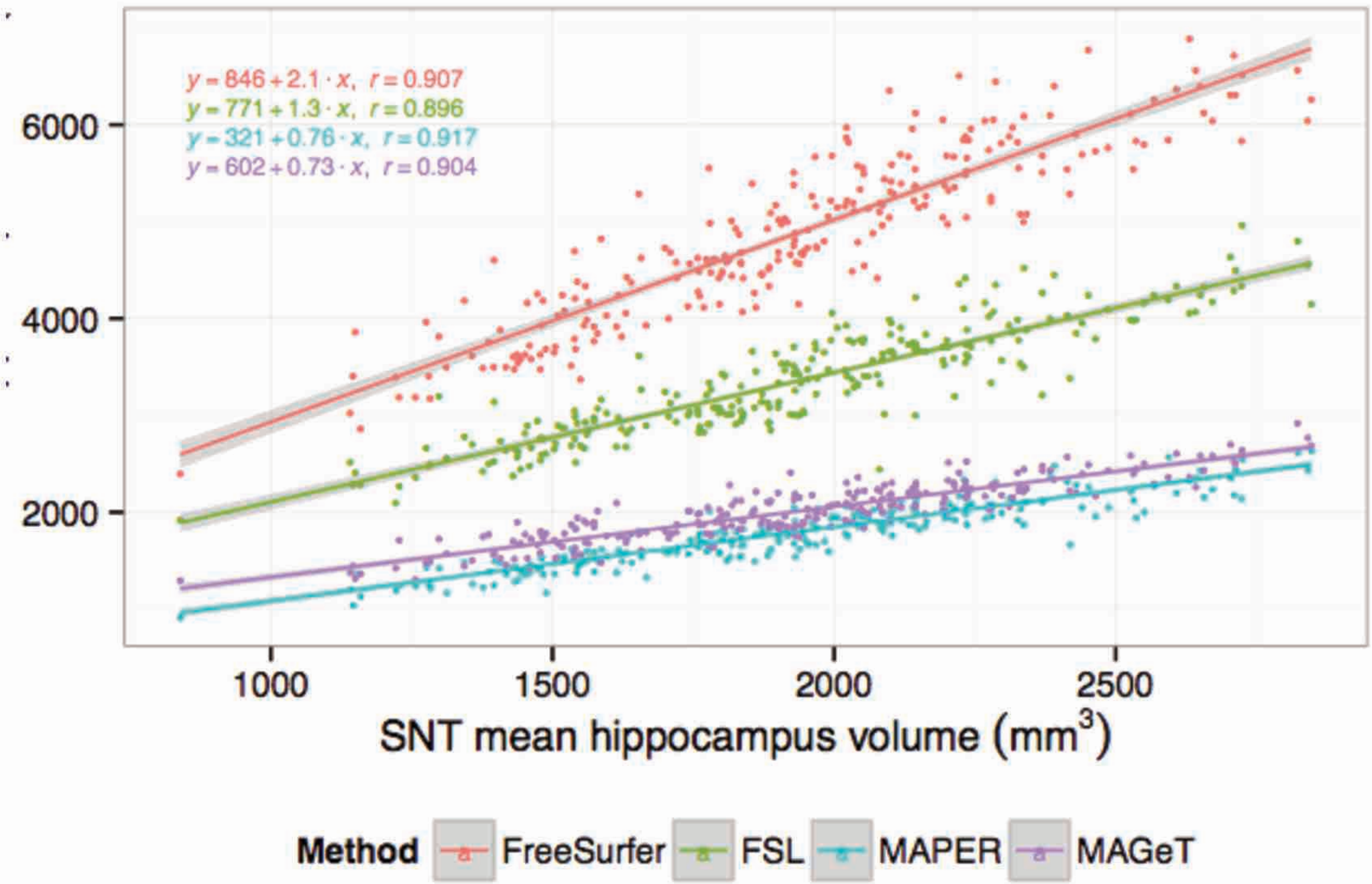
Pipitone et al., *NeuroImage 2014*

Comparison to other methods



Pipitone et al., NeuroImage, 2014

Comparison to other methods

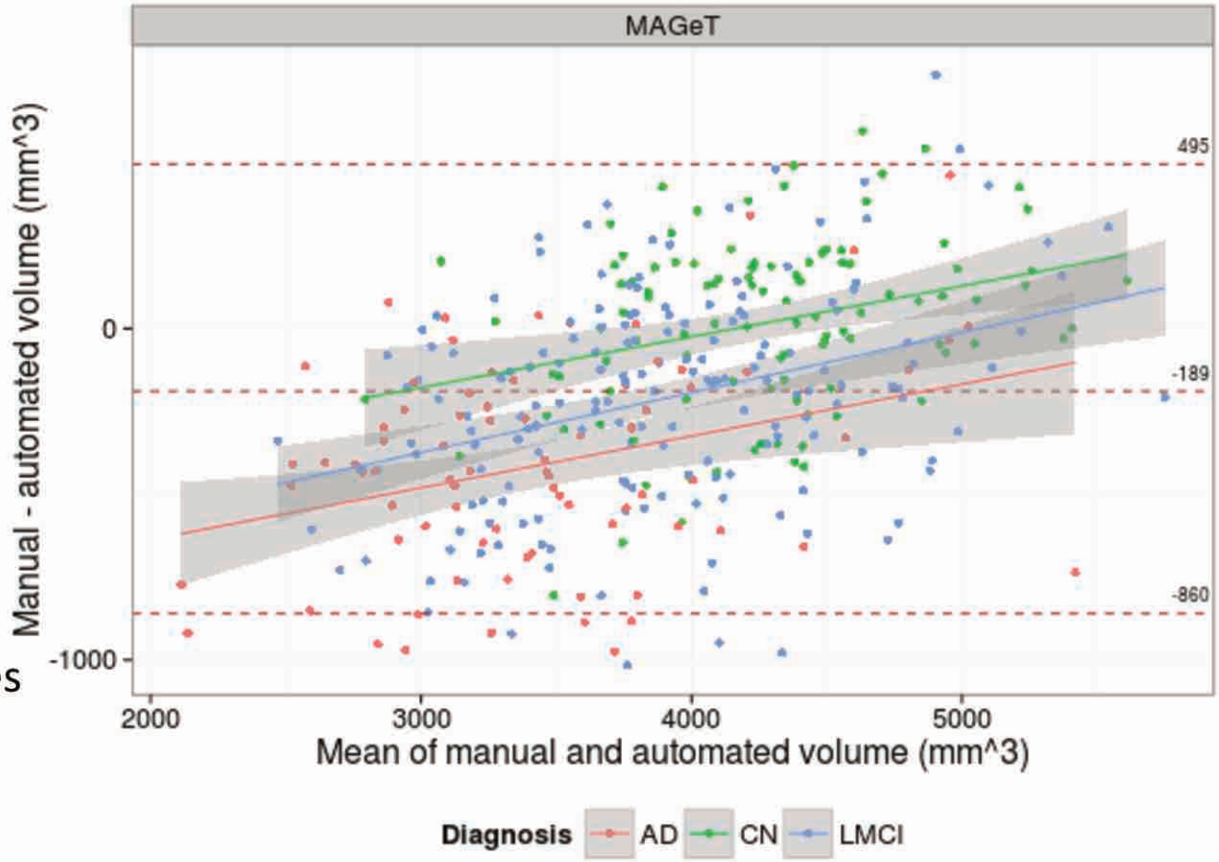


Pipitone et al., NeuroImage, 2014

Bias estimate – Bland Altman Plot

Under-
estimates
volume

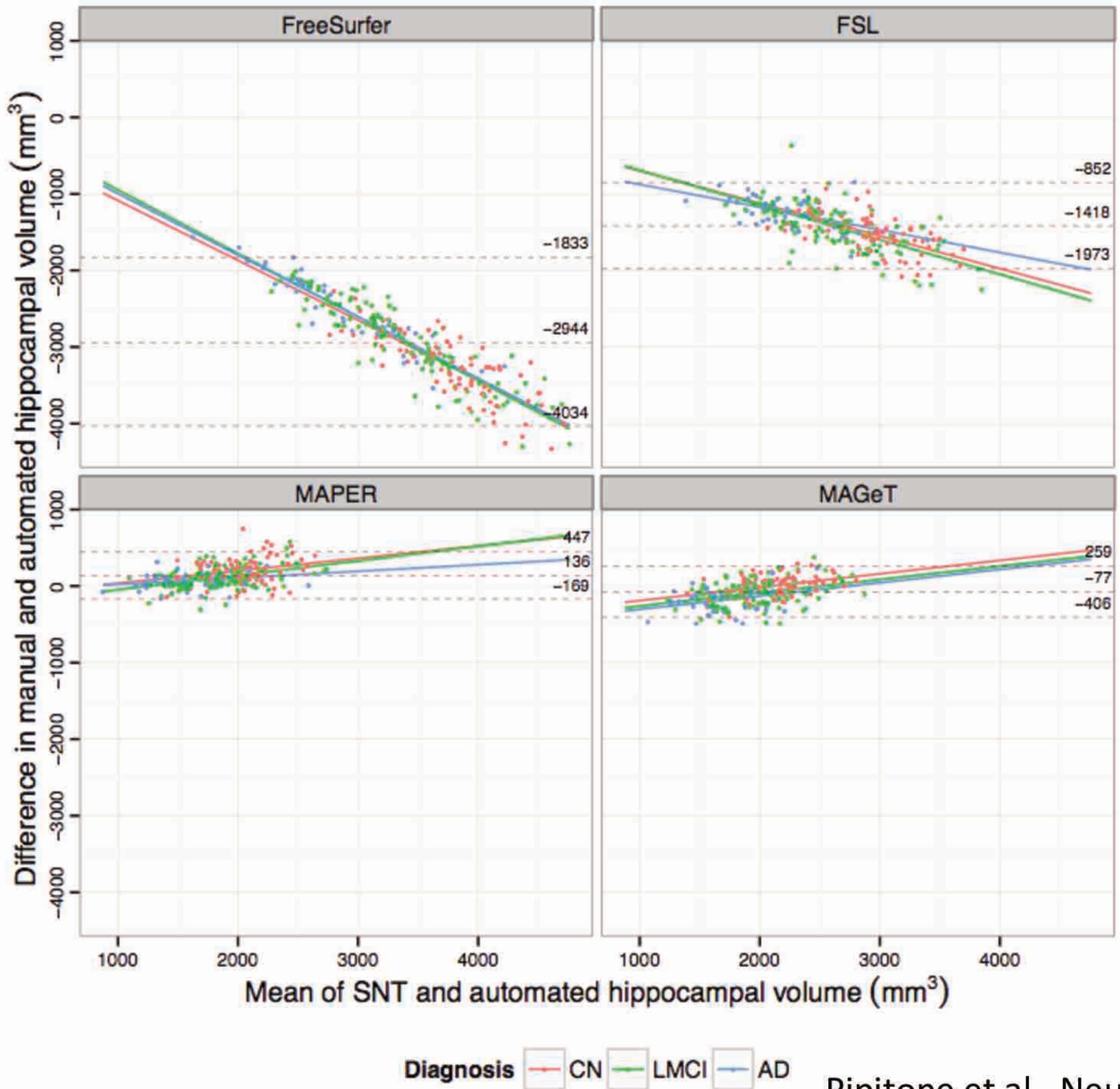
Over-estimates
volume



Smaller HC

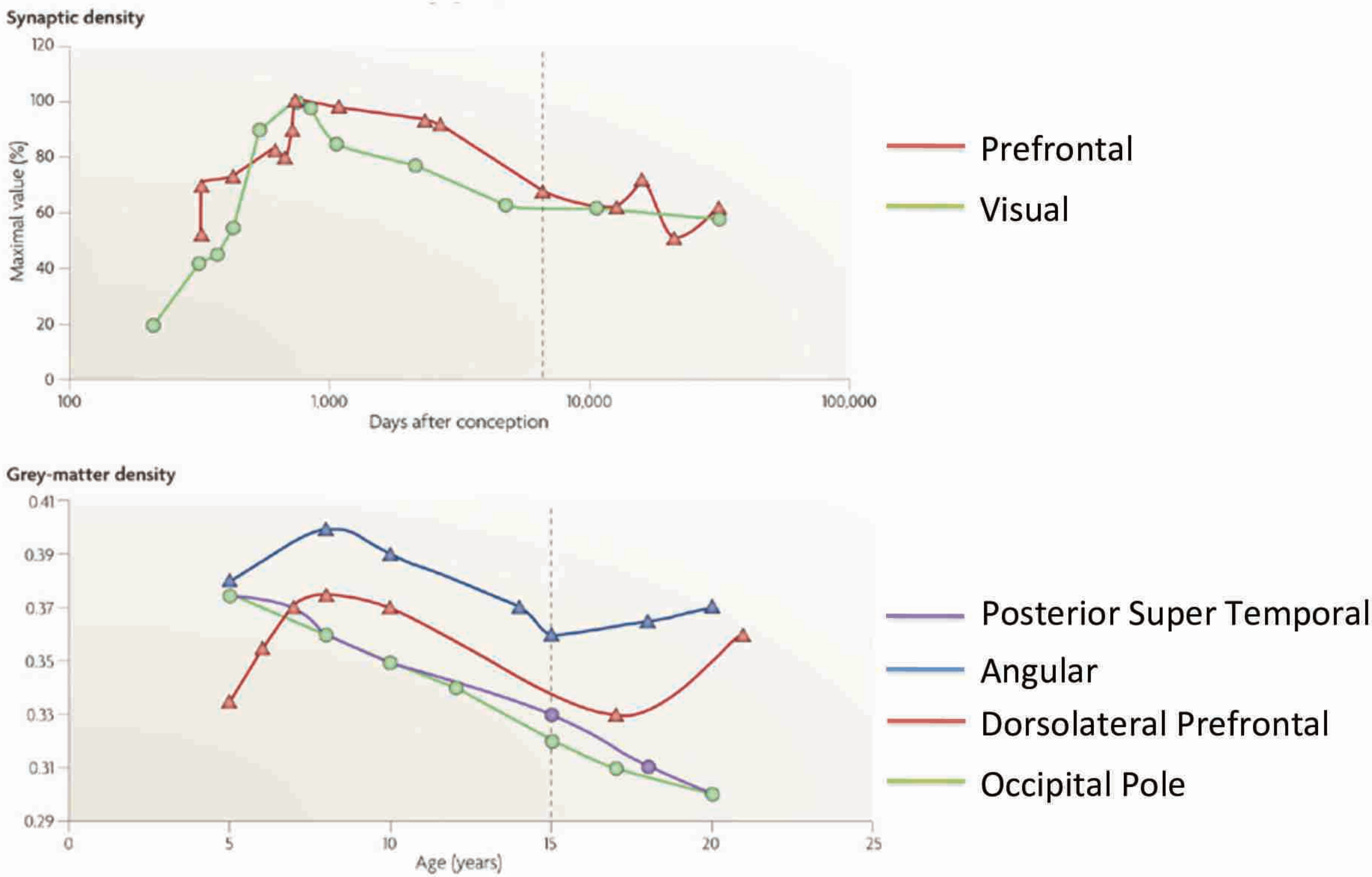
Larger HC

Pipitone et al., NeuroImage, 2014



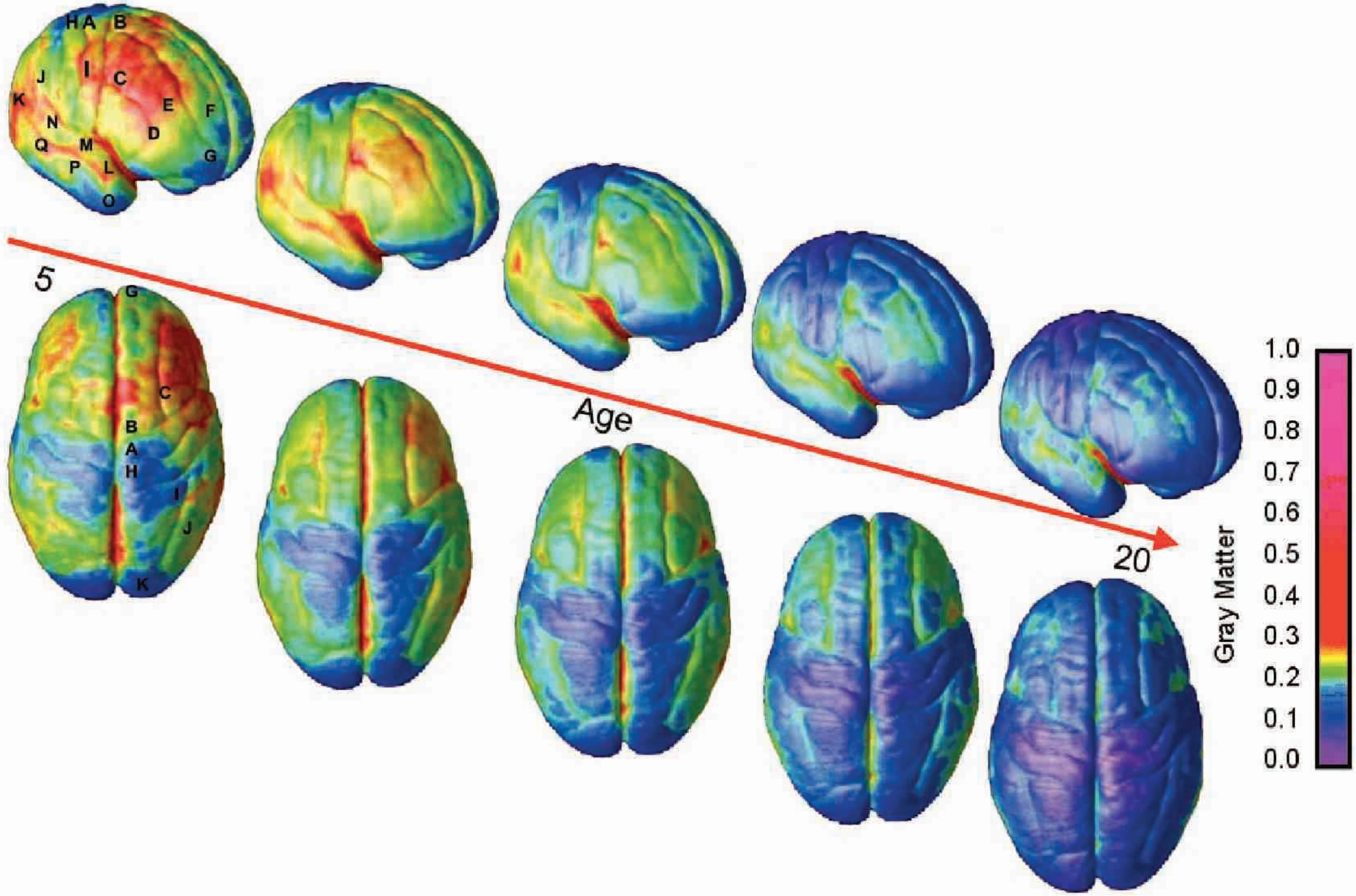
Pipitone et al., NeuroImage, 2014

Normal brain development



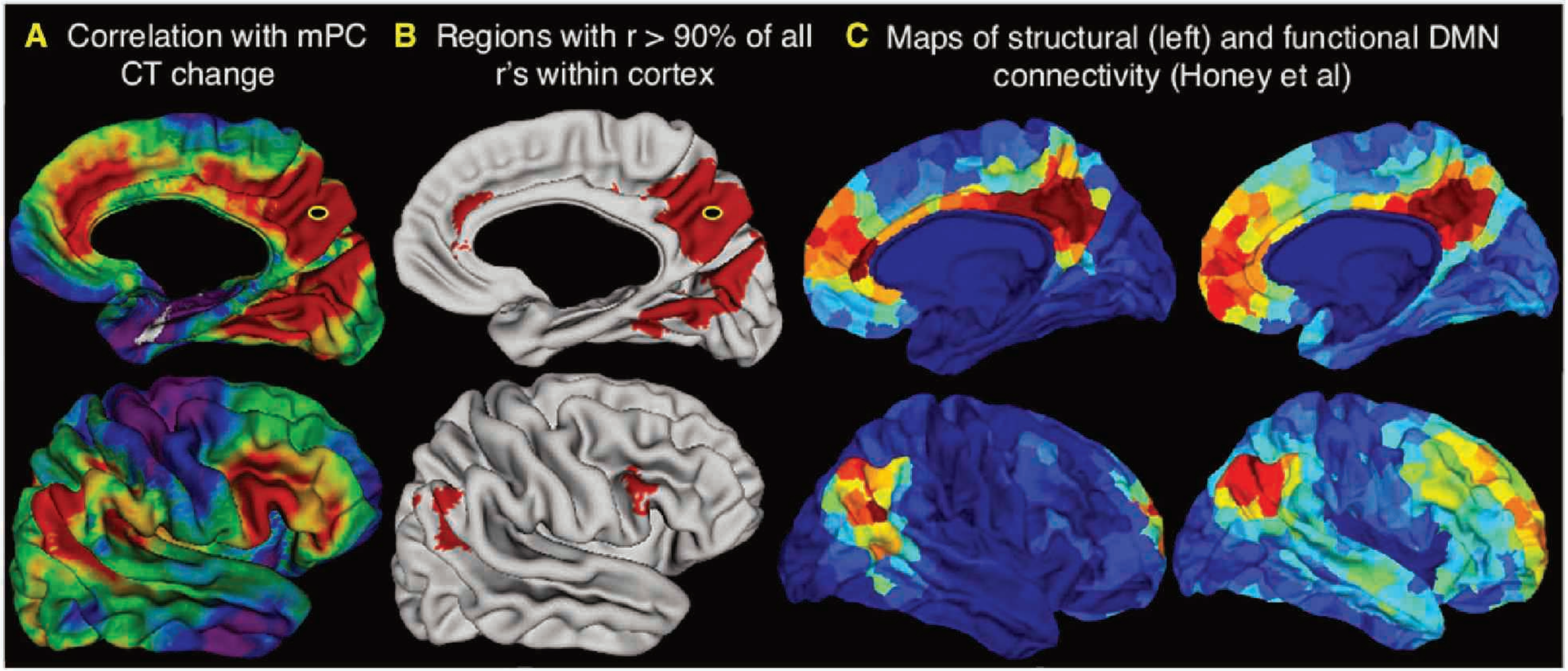
Paus, Keshavan, and Giedd. *Nat Rev Neurosci*. 2008.

Normal brain development: GM Volume



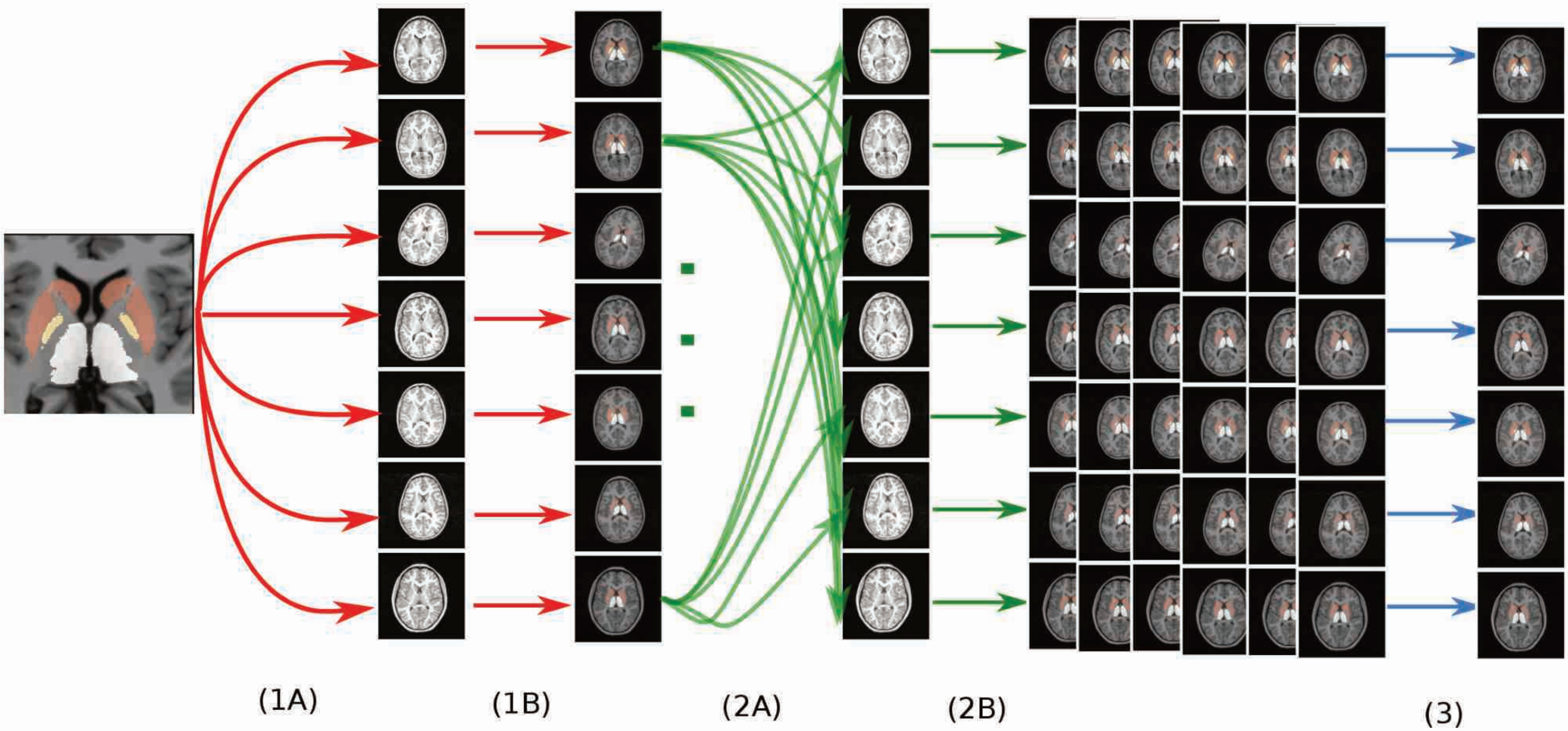
Gogtay *et al*. PNAS. 2004.

Neuroanatomical coupling through development

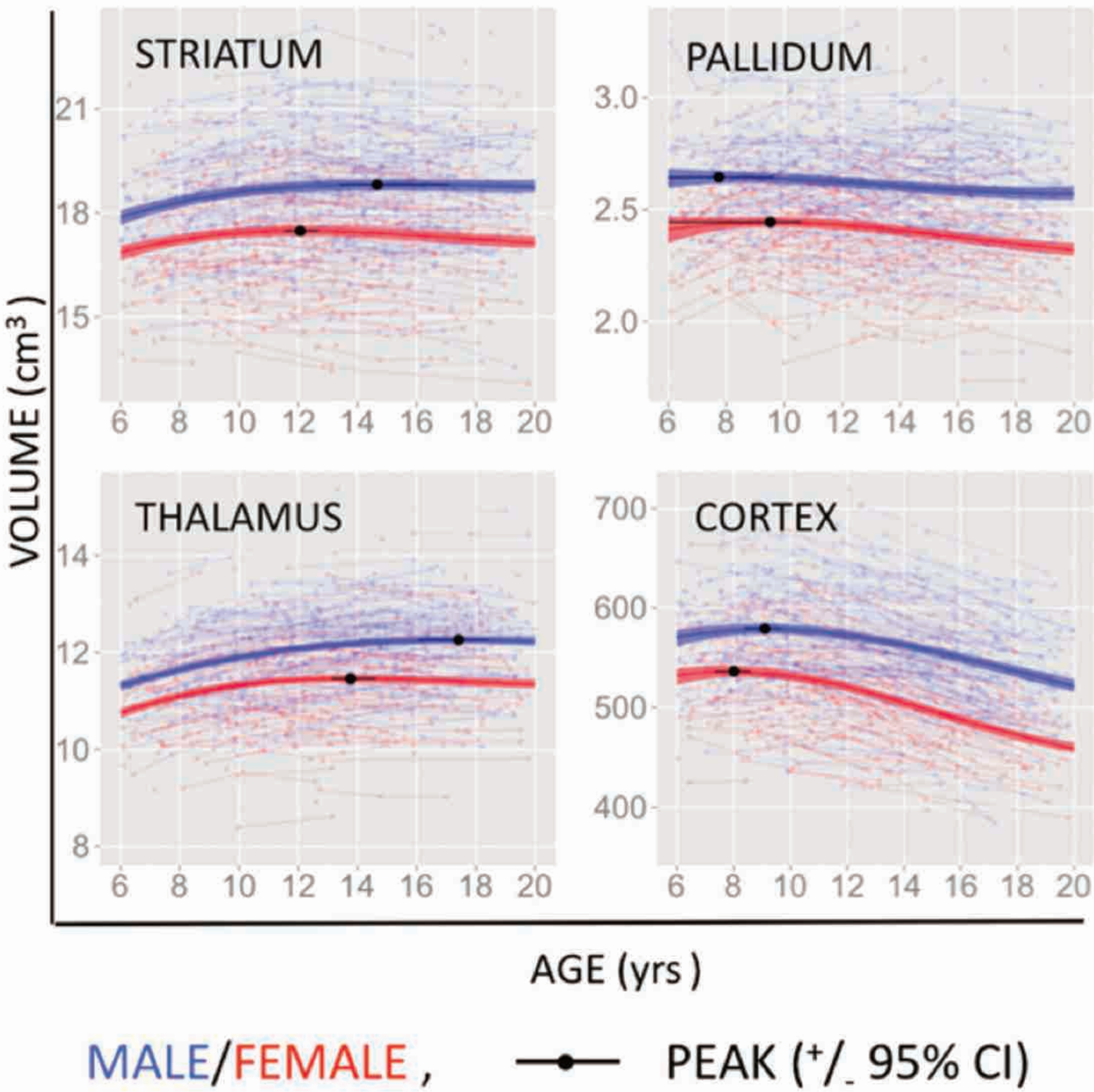


Raznahan *et al*. Neuron. 2011.

MAGeT Brain

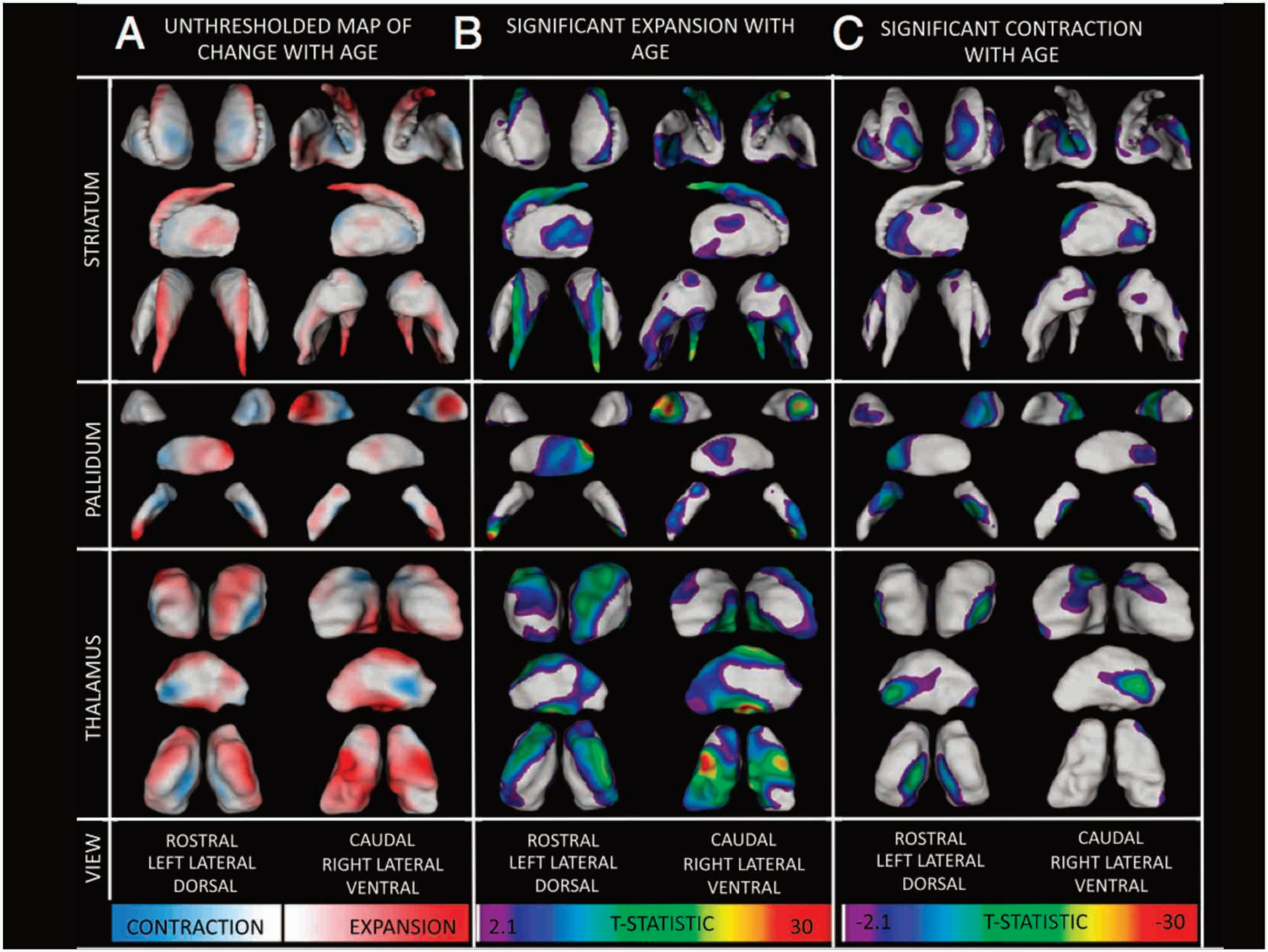


Chakravarty et al., Human Brain Mapping, 2013.

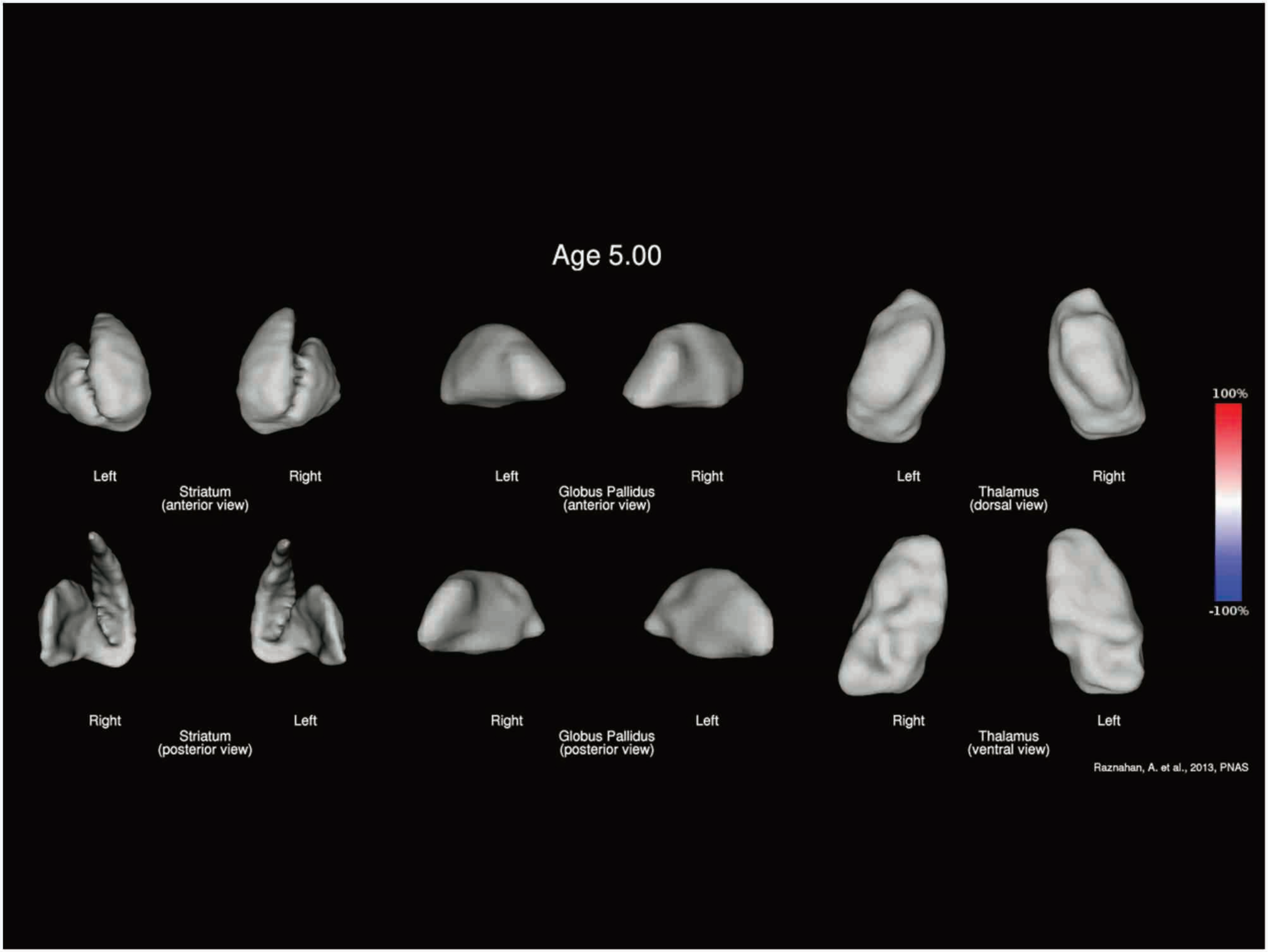


Longitudinal mapping of >600 individuals
Over 1,300 MRI volumes

Raznahan et al., PNAS, *2014.*



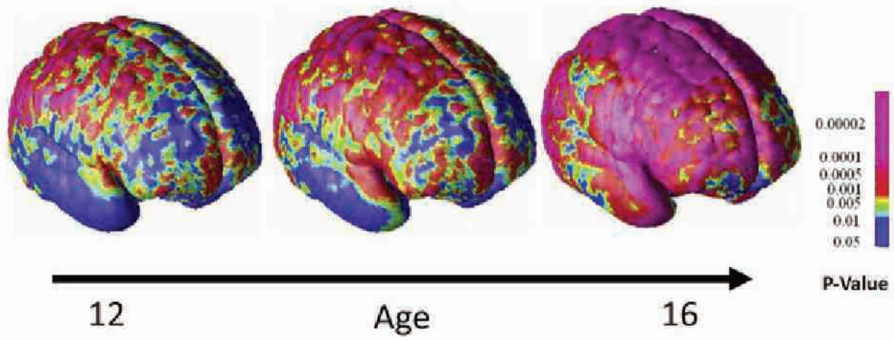
A UNTHRESHOLDED MAP OF CHANGE WITH AGE
B SIGNIFICANT EXPANSION WITH AGE
C SIGNIFICANT CONTRACTION WITH AGE
STRIATUM
PALLIDUM
THALAMUS
VIEW
ROSTRAL
LEFT LATERAL
DORSAL
CAUDAL
RIGHT LATERAL
VENTRAL
CONTRACTION
EXPANSION
2.1
T-STATISTIC
30
-2.1
T-STATISTIC
-30


Age 5.00
Left
Striatum
(anterior view)
Right
Left
Globus Pallidus
(anterior view)
Right
Left
Thalamus
(dorsal view)
Right
100%
-100%
Right
Striatum
(posterior view)
Left
Right
Globus Pallidus
(posterior view)
Left
Right
Thalamus
(ventral view)
Left
Raznahan, A. et al., 2013, PNAS

Grey matter deficits in childhood onset schizophrenia (COS)

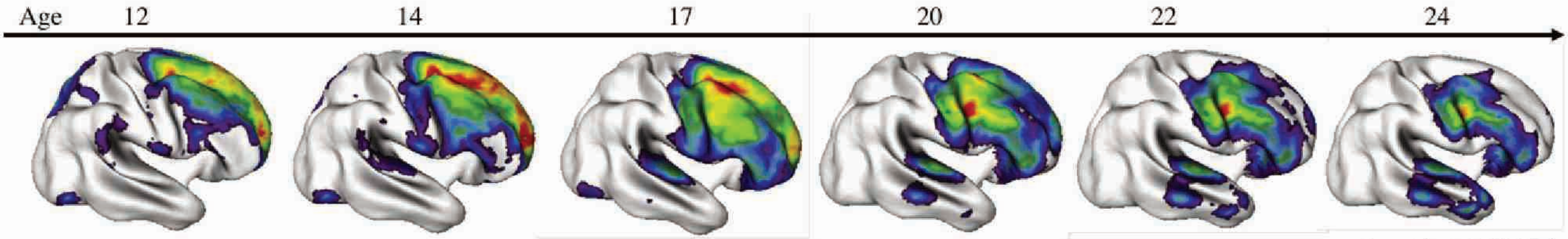
A. Parietal-Frontal Progression of GM Loss During Adolescence

COS vs Healthy P maps



Thompson et al PNAS 2001

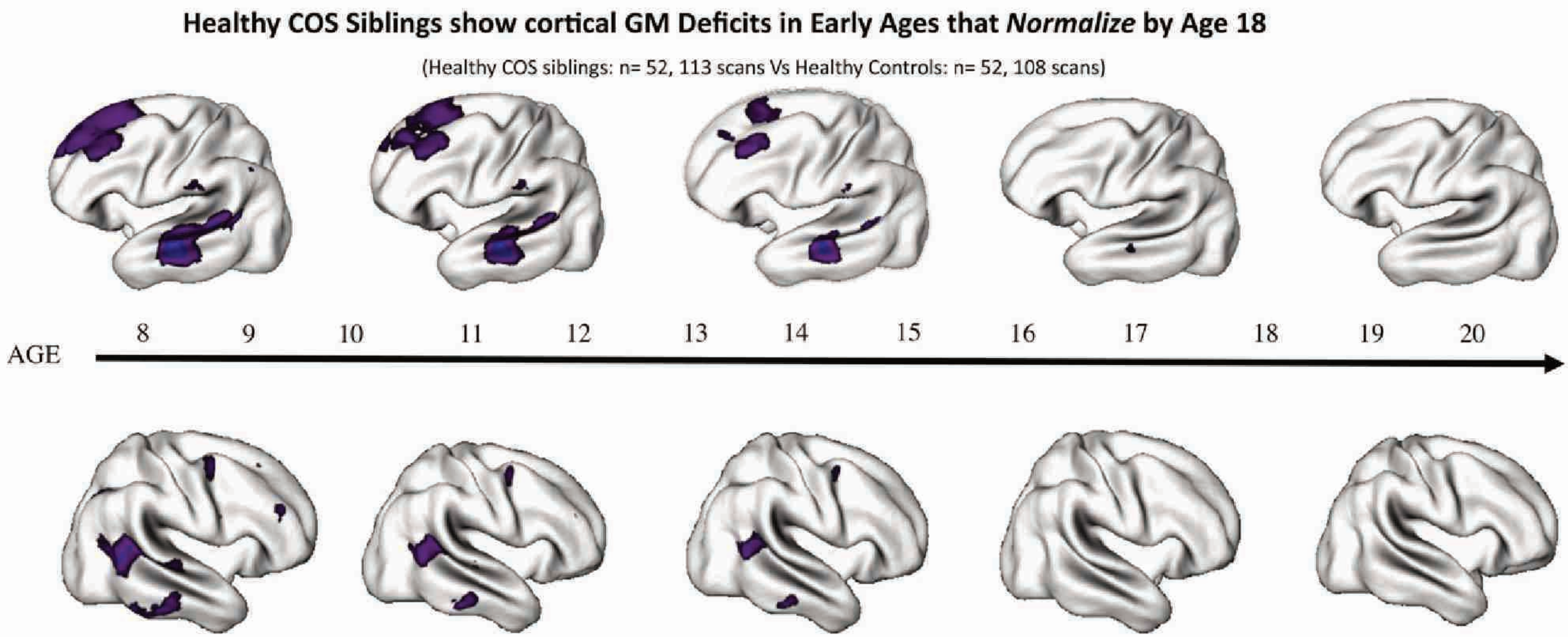
B. The GM loss Declines and is Circumscribed to Prefrontal and Temporal Cortices By Age 24



Greenstein et al. JCPP 2006

Rapoport and Gogtay. *Int. J. Devl. Neurosci.* 2011

Siblings of childhood onset schizophrenia patients (COSSIBs)

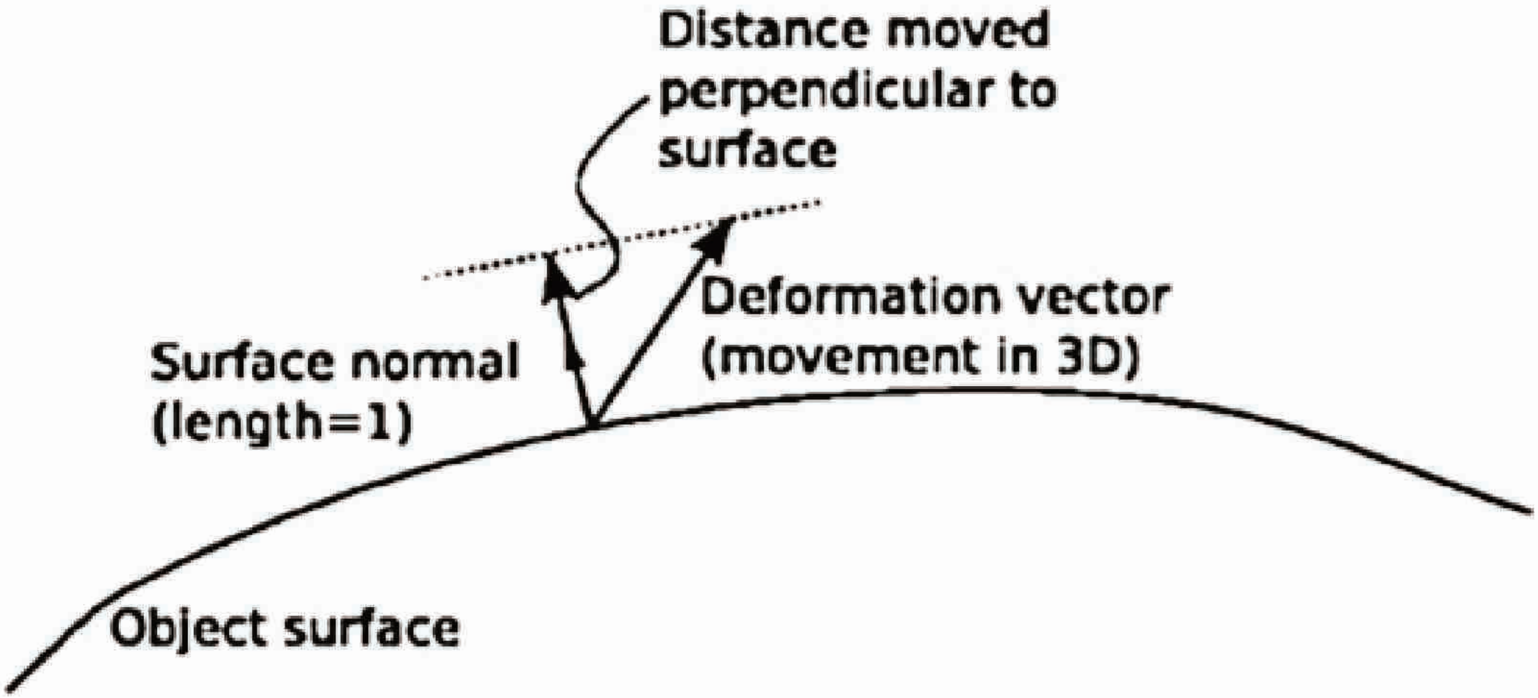


Rapoport and Gogtay. *Int. J. Devl. Neurosci. 2011*

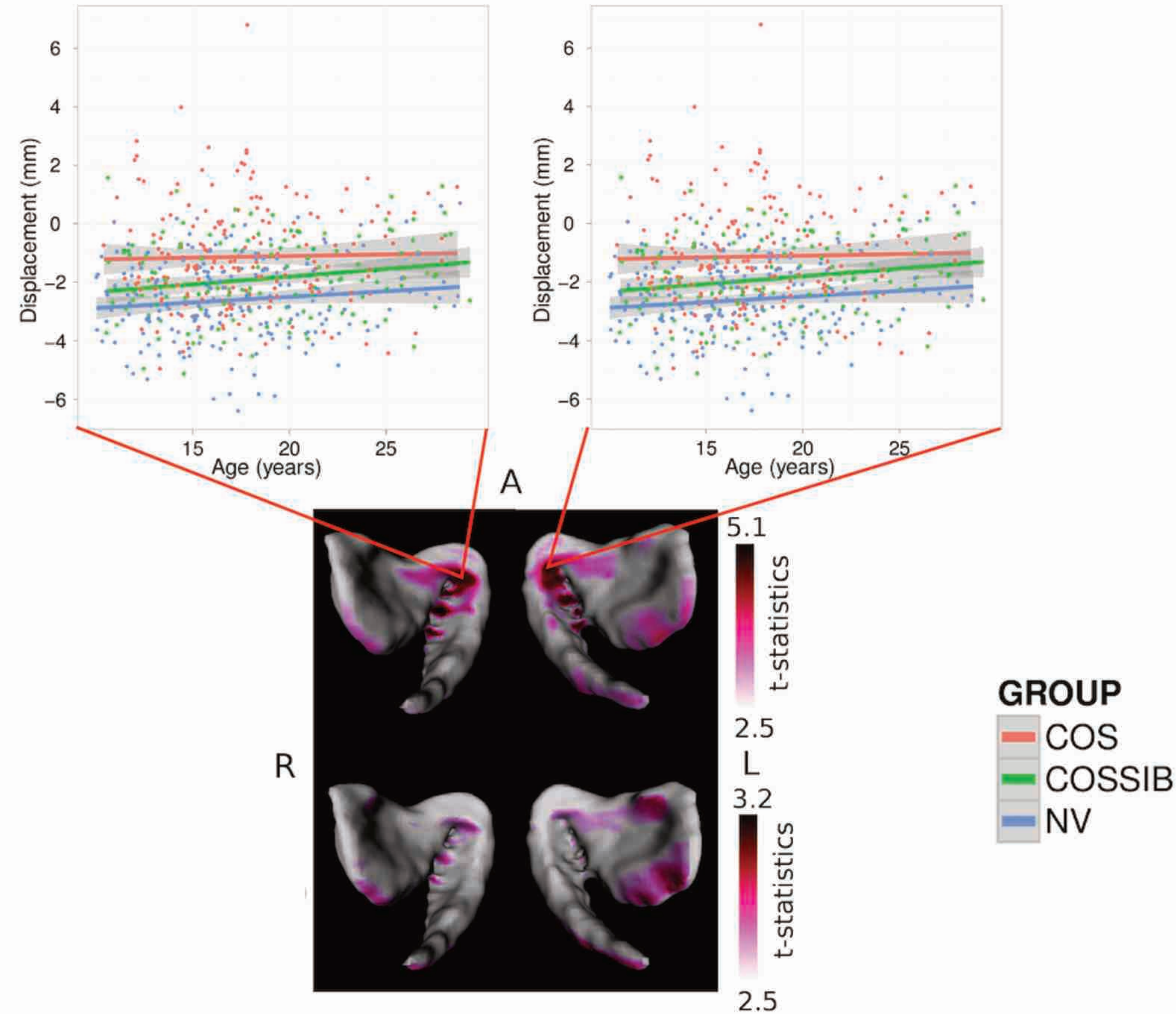
Striatal volume and morphology in COS and COSSIBs

- National Institute of Mental Heath COS Cohort
- Magnetic Resonance Imaging (MRI) since 1990
  - Longitudinal data acquisition
  - 94 COS (208 scans)
  - 86 Healthy COS sibilings (171 scans)
  - 110 match healthy controls (270 scans)
- GE Signa 1.5T MR system
  - coronal (3D) SPGR
  - TR = 14ms, TE = 3 ms
  - 256 x 192 acquisition matrix
  - 124mm slices; voxel size: 0.94 x 0.94 x 1.5 mm^3

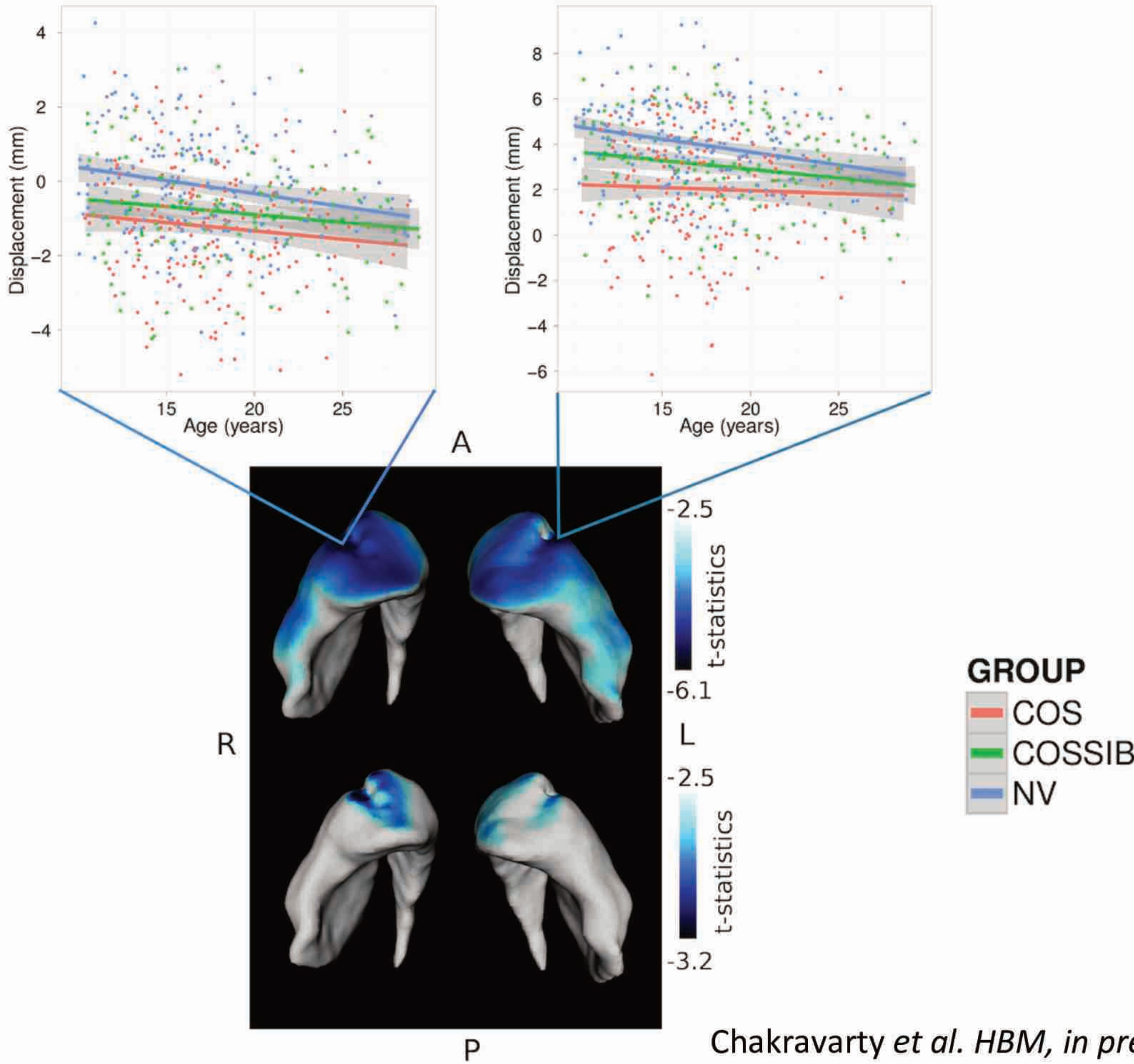
Surface-based shape analysis



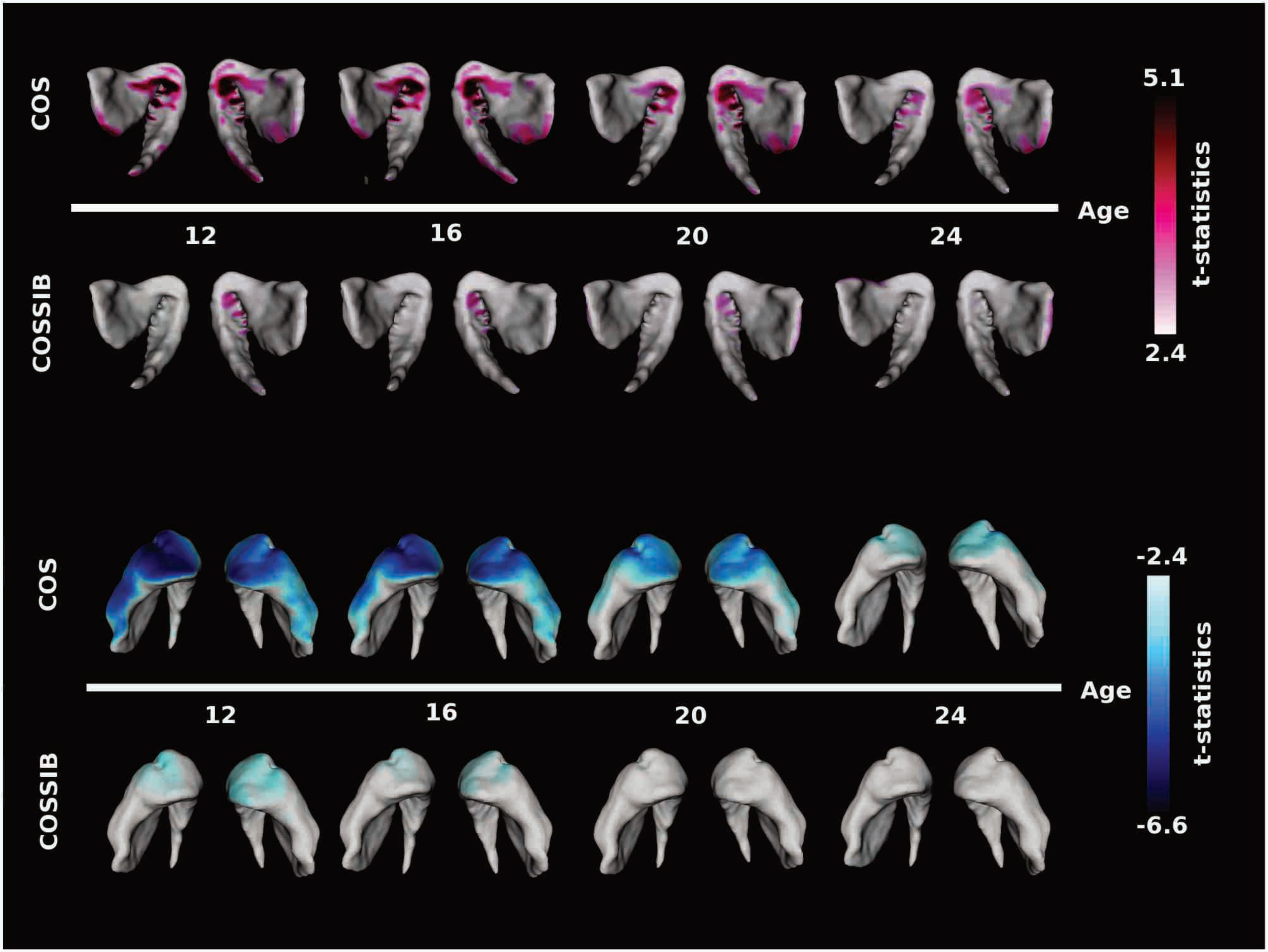
Lerch *et al. NeuroImage.* 2008.



Chakravarty *et al. HBM, in press*



Chakravarty *et al. HBM, in press*



COS
COSSIB
Age
12
16
20
24
5.1
2.4
t-statistics
COS
COSSIB
Age
12
16
20
24
-2.4
-6.6
t-statistics

Hippocampal subfields through the lifespan

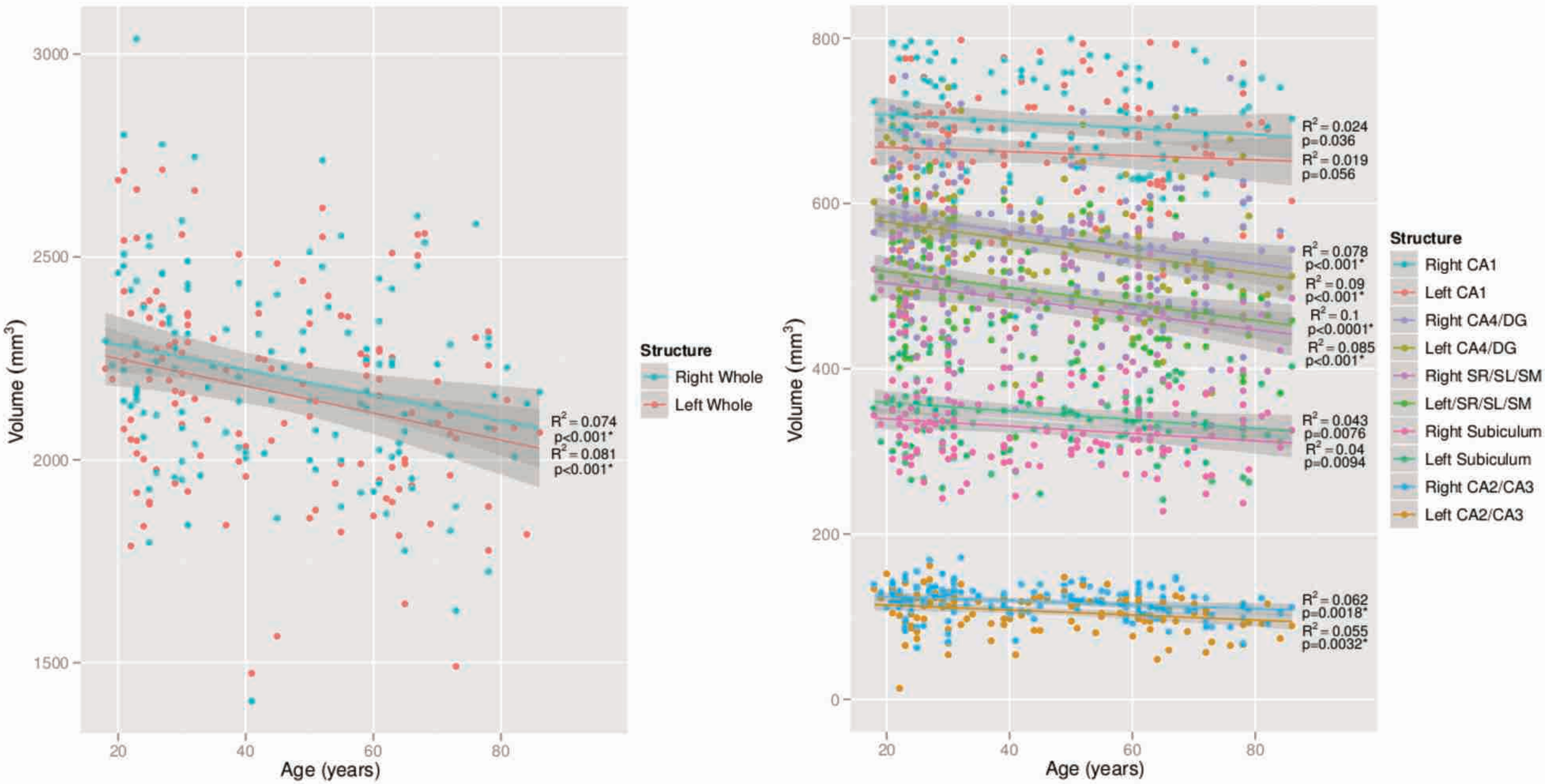
Demographic	Healthy Controls (n=137)	
	Mean	SD
Age	45.39	19.02
Education (years)	15.42	1.95
WTAR (IQ)	117.87 (3 NA)	7.83
MMSE	29.33 (2 NA)	0.92
	N	
Gender	72M	65F
Handedness	129 R	9 L

NA = Test not administered

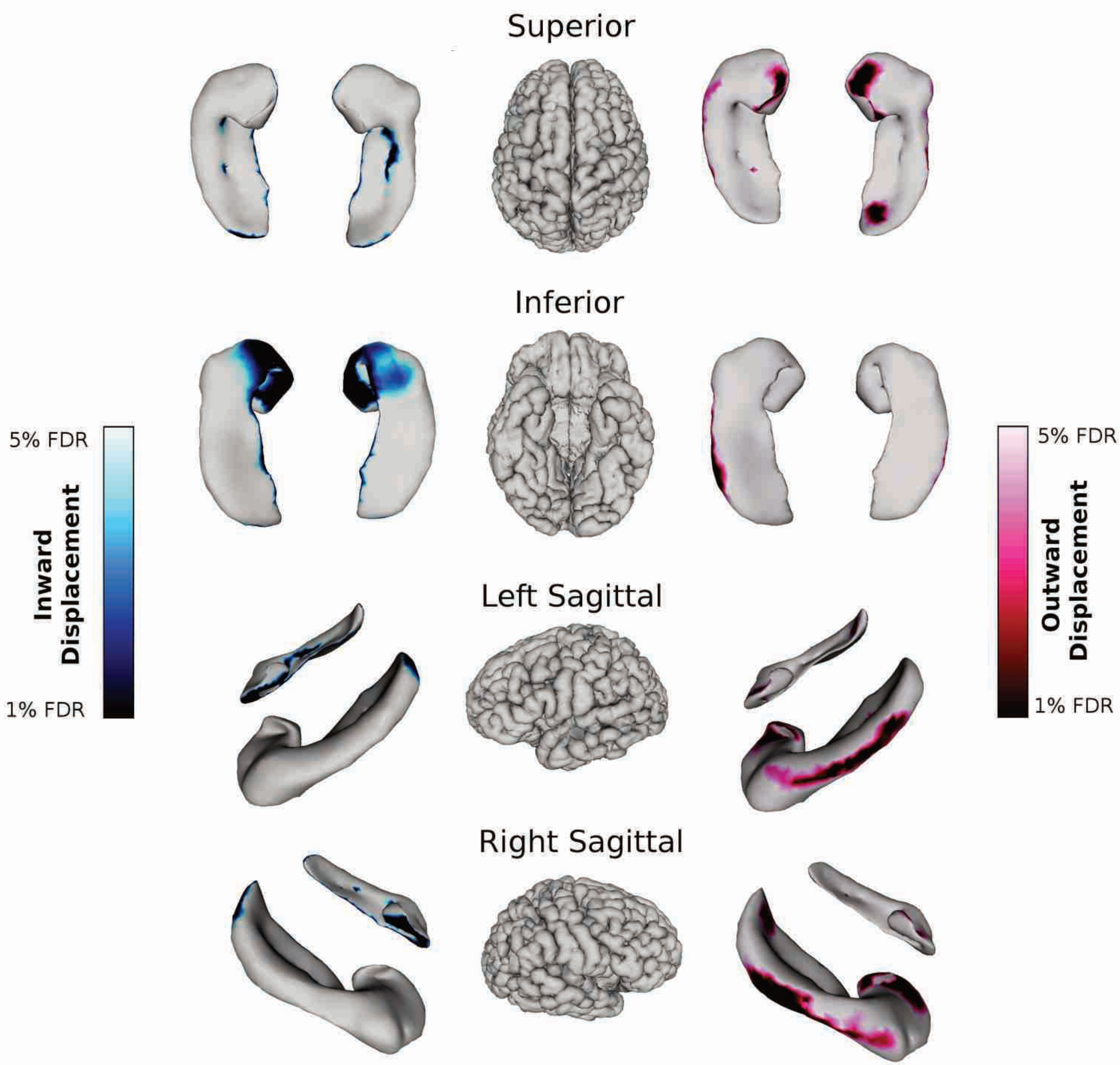
WTAR = Wechsler Test of Adult Reading

MMSE= Mini Mental State Examination

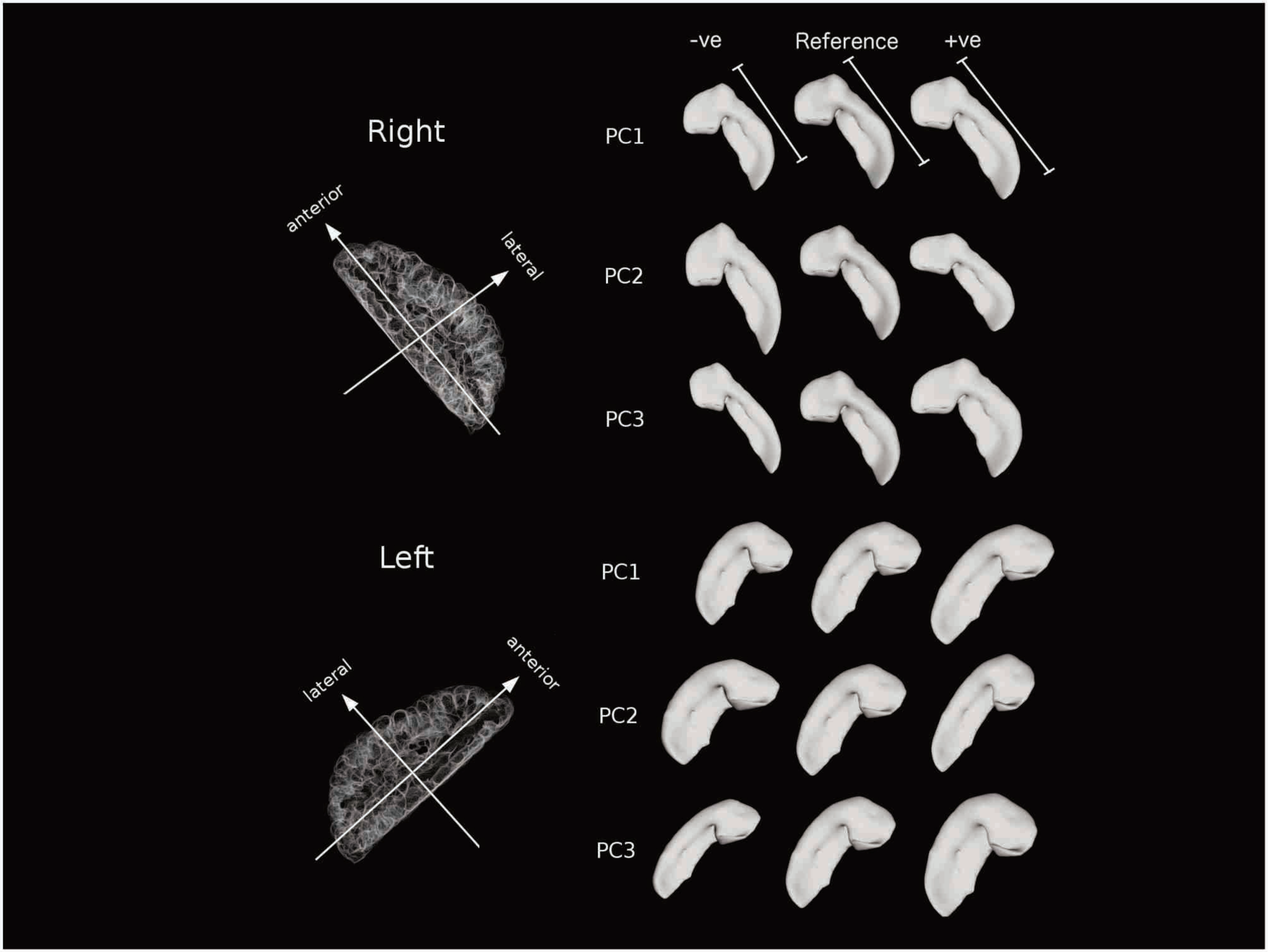
Age Range 18-86



Volume (mm³)
Age (years)
Structure
Right Whole
Left Whole
R² = 0.074
p<0.001*
R² = 0.081
p<0.001*
Volume (mm³)
Age (years)
Structure
Right CA1
Left CA1
Right CA4/DG
Left CA4/DG
Right SR/SL/SM
Left/SR/SL/SM
Right Subiculum
Left Subiculum
Right CA2/CA3
Left CA2/CA3
R² = 0.024
p=0.036
R² = 0.019
p=0.056
R² = 0.078
p<0.001*
R² = 0.09
p<0.001*
R² = 0.1
p<0.0001*
R² = 0.085
p<0.001*
R² = 0.043
p=0.0076
R² = 0.04
p=0.0094
R² = 0.062
p=0.0018*
R² = 0.055
p=0.0032*



Voineskos, Winterburn et al., *submitted*



-ve
Reference
+ve
Right
PC1
PC2
PC3
anterior
lateral
Left
PC1
PC2
PC3
lateral
anterior

Cognitive ability and shape

Changes in cognitive scores with age based on a general linear model (with sex included in the model). Rates of decrease are normalized to population means. R^2 values are adjusted and apply to the effect of age only.

Cognitive Task	**Mean Score (SD)**	**Rate of Decrease (%/yr)**	**p**	**R^2**	**t-stat**
Letter Number Sequence (LNS)	16.17 (3.35)	-0.22%	0.021	0.033	-2.33
Cumulative Episodic Memory	97.42 (10.42)	0.11%	0.023	0.026	2.30
List Recall	7.20 (2.15)	-0.59%	<0.0001*	0.14	-4.66
Figure Recall	11.87 (11.87)	-0.71%	<0.0001*	0.14	-4.80
Story Recall	10.28 (1.52)	-0.22%	<0.01*	0.070	-3.31

*Indicates significance after Bonferroni correction for 5 comparisons (p<0.01)

Principal Component	**Eigenvalue**	**Variance Explained**	**Linear Variables**	**R^2**	**p**
Right PC1	5.40	74.19%	Age	0.039	0.010
Right PC2	3.24	9.59%	----	----	----
Right PC3	3.05	7.51%	Figure Recall	0.049	0.011
			Letter Number Sequence	0.030	0.044
			APOE ε4 Status	0.021	0.048
Left PC1	4.92	65.23%	Letter Number Sequence	0.087	0.0005*
Left PC2	3.23	12.10%	----	----	----
Left PC3	3.02	9.33%	----	----	----

Principal Component	**Eigenvalue**	**Variance Explained**	**Linear Variables**	**R^2**	**p**
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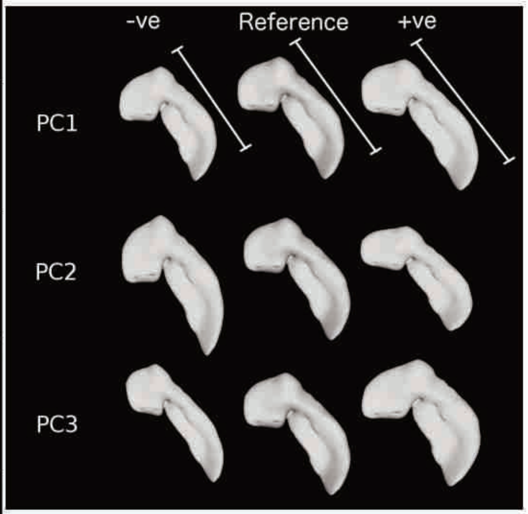
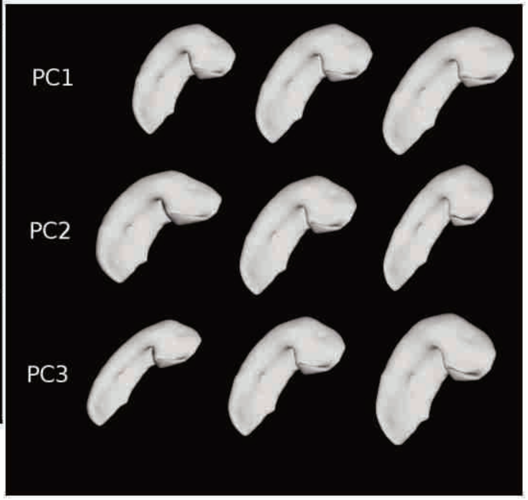
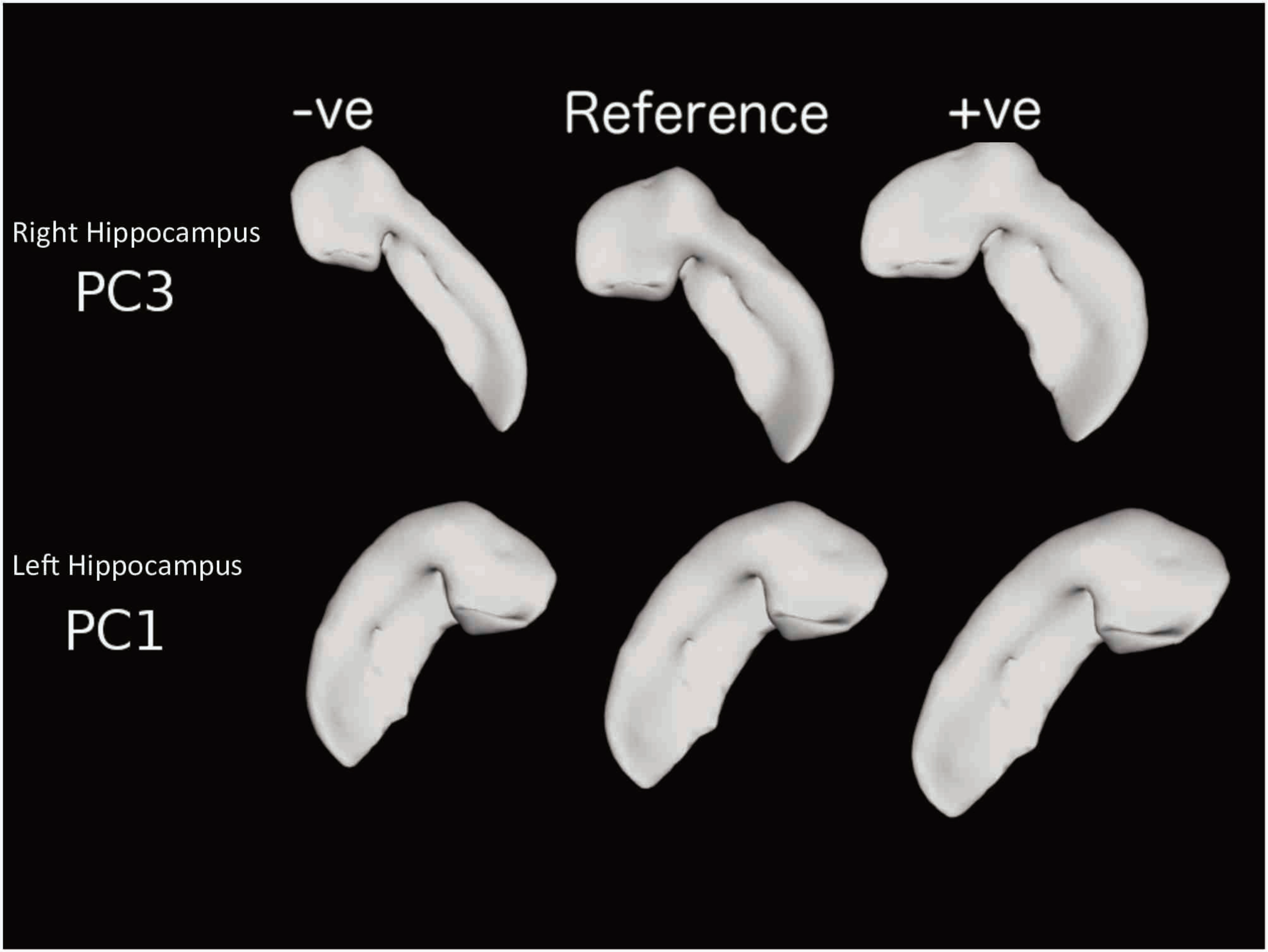
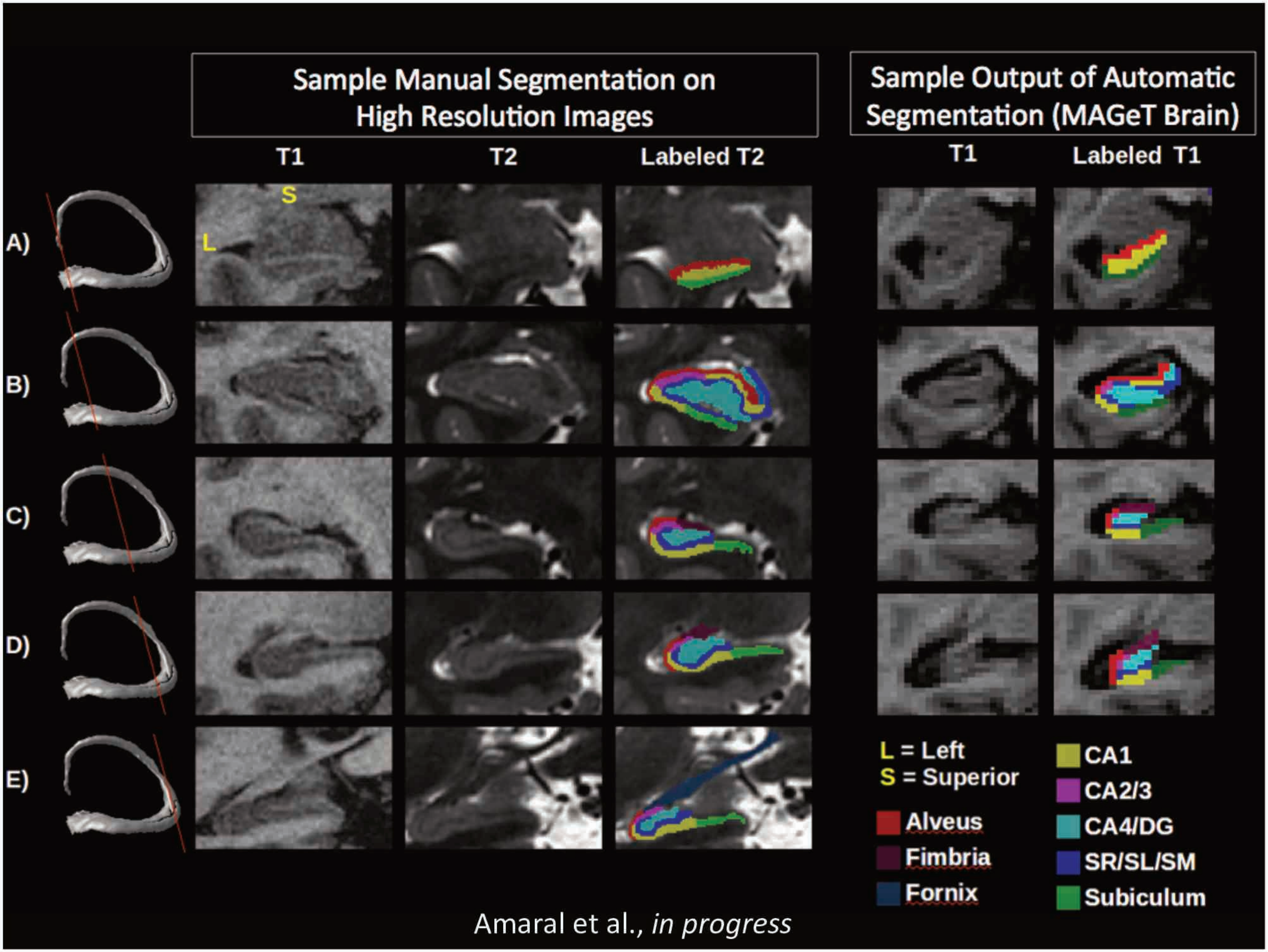
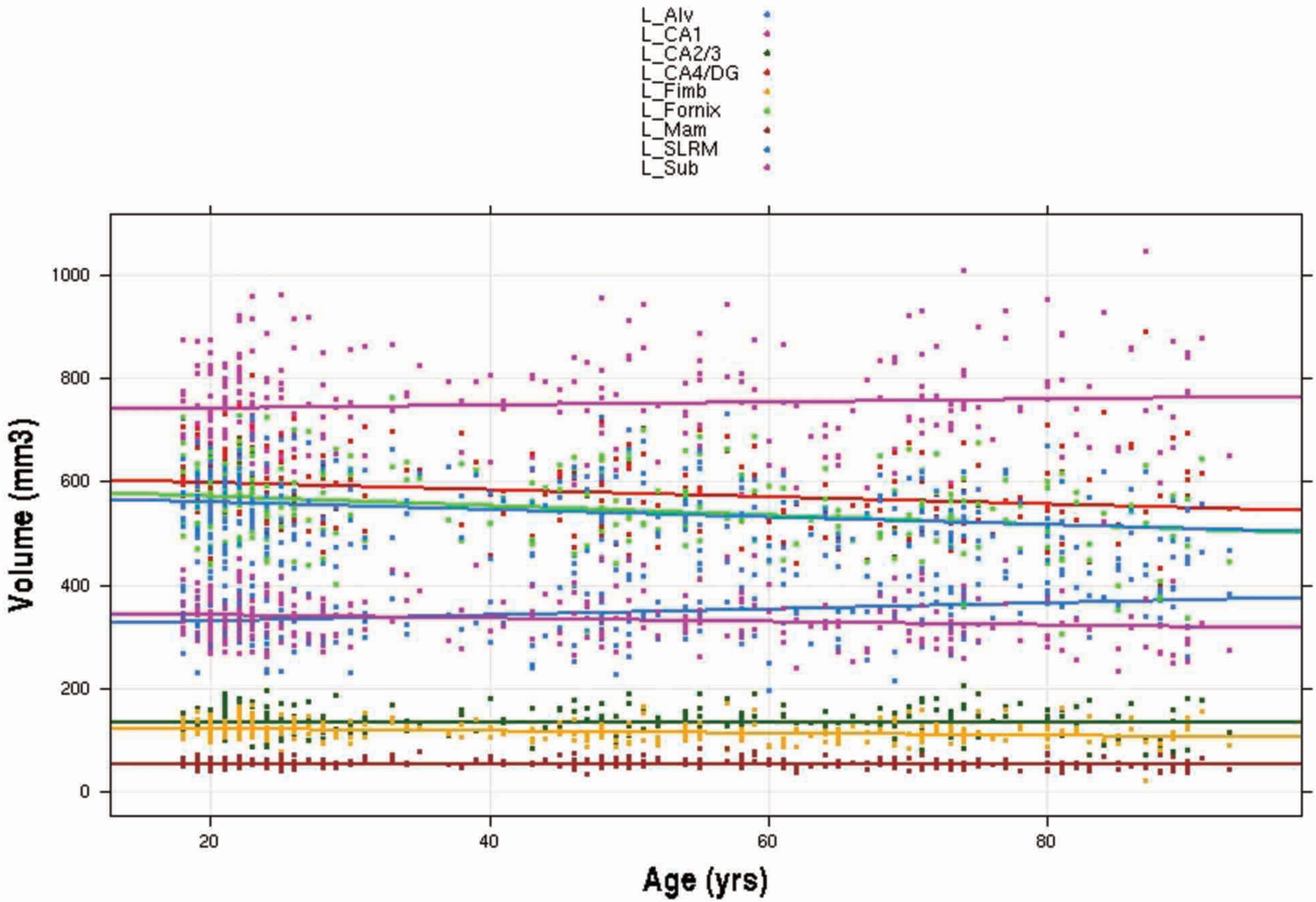
Left PC3	3.02	9.33%	----	----	----



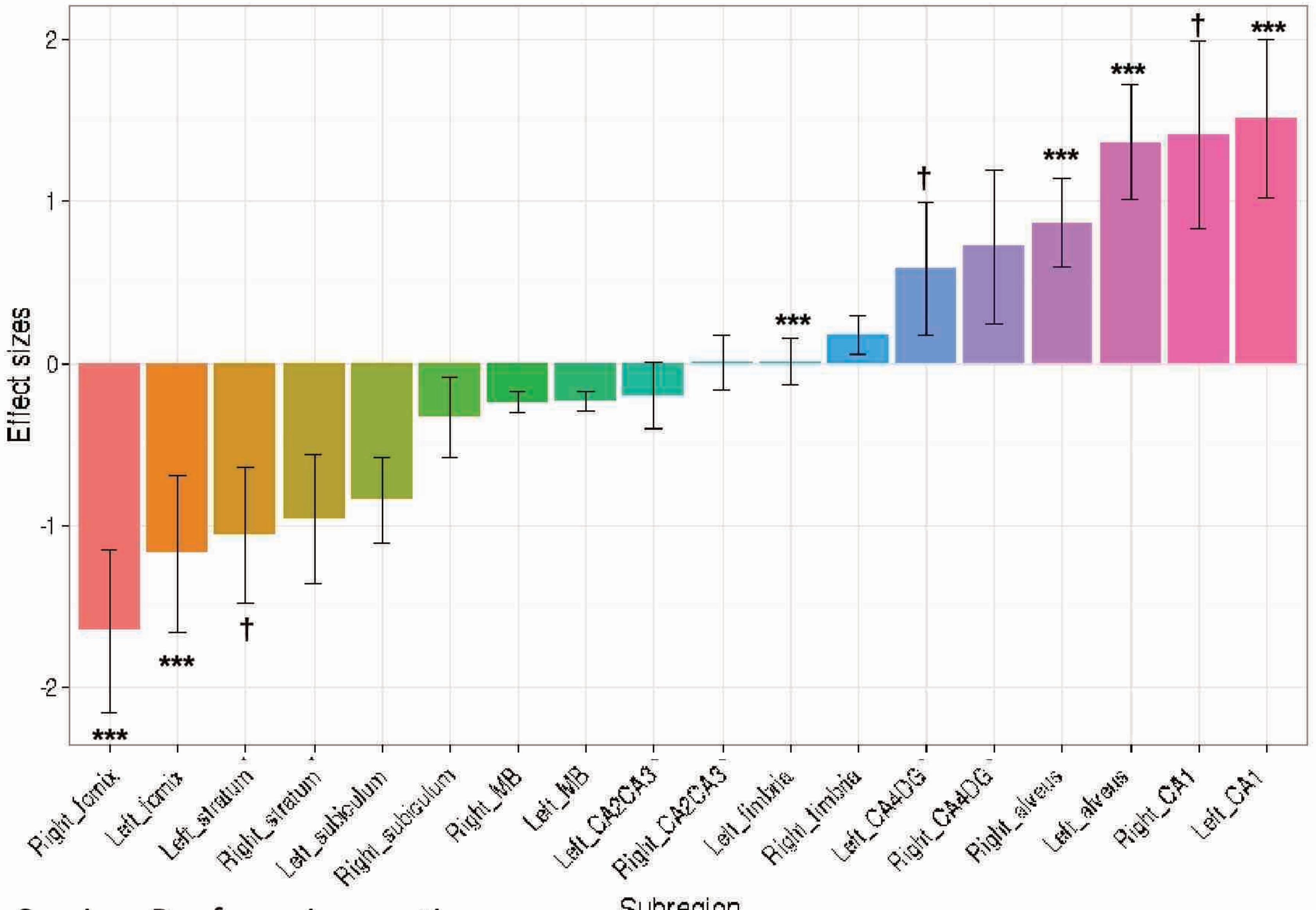



-ve
Reference
+ve
Right Hippocampus
PC3
Left Hippocampus
PC1


Sample Manual Segmentation on High Resolution Images
Sample Output of Automatic Segmentation (MAGeT Brain)
T1
T2
Labeled T2
T1
Labeled T1
S
L
A)
B)
C)
D)
E)
L = Left
S = Superior
Alveus
Fimbria
Fornix
CA1
CA2/3
CA4/DG
SR/SL/SM
Subiculum
Amaral et al., in progress


L_Alv
L_CA1
L_CA2/3
L_CA4/DG
L_Fimb
L_Fornix
L_Mam
L_SLRM
L_Sub
Volume (mm3)
1000
800
600
400
200
0
20
40
60
80
Age (yrs)

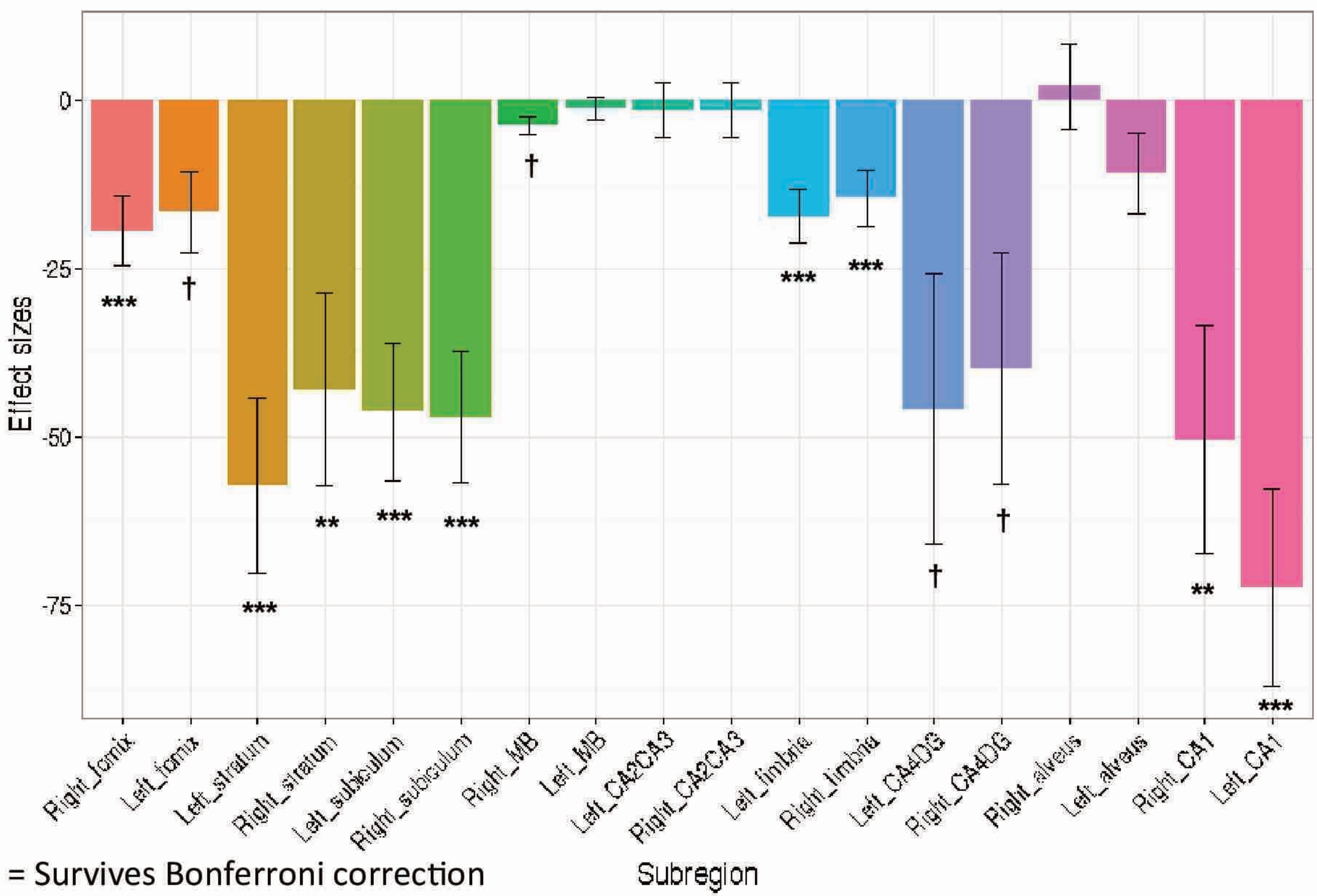
Healthy Aging



*** = Survives Bonferroni correction
† = p<0.05 uncorrected

Amaral et al., *in progress*

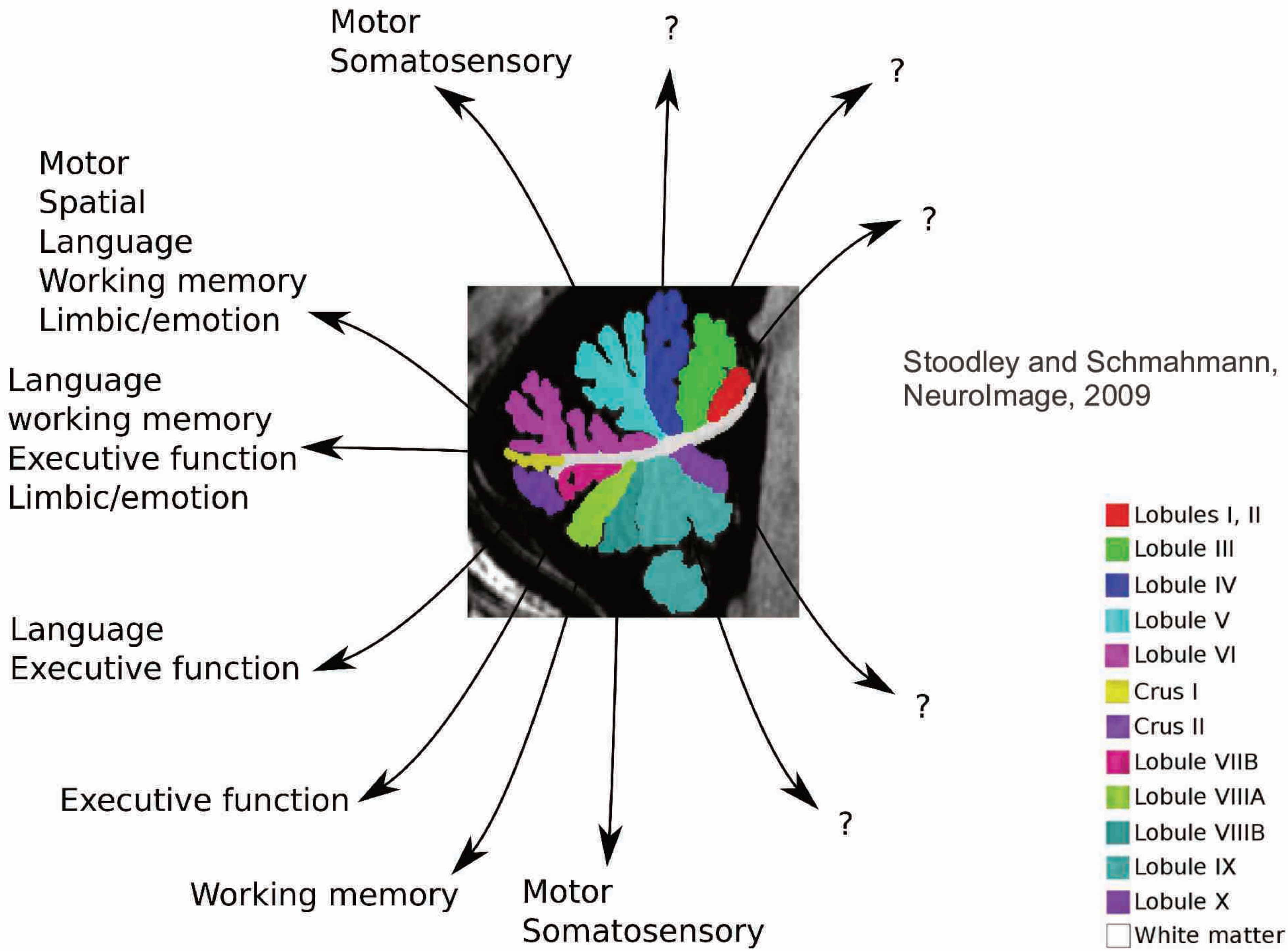
Healthy Controls Vs. Mild Cognitive Impairment



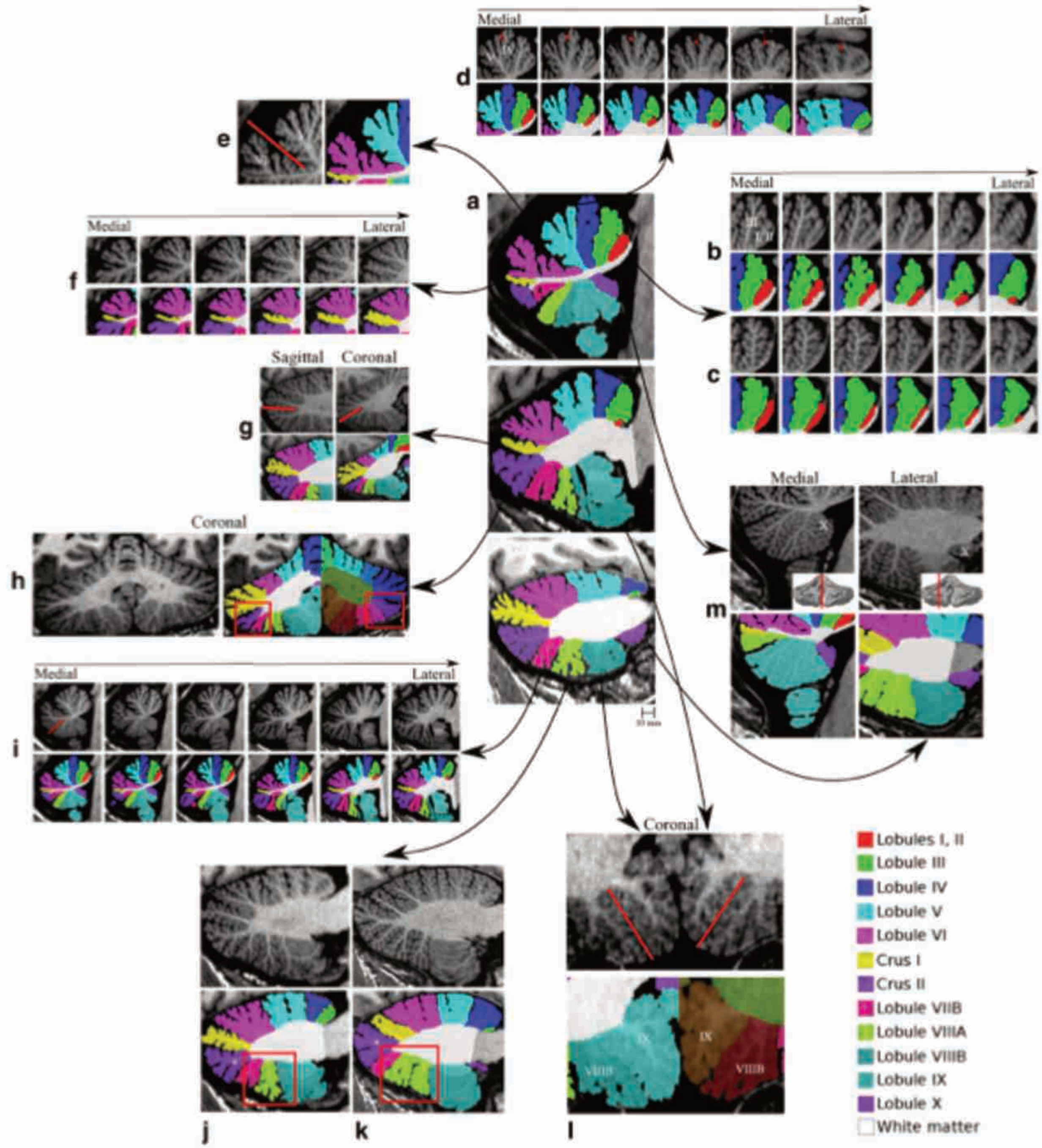
*** = Survives Bonferroni correction

† = p<0.05 uncorrected

Amaral et al., *in progress*



Motor
Somatosensory
?
?
?
Motor
Spatial
Language
Working memory
Limbic/emotion
Language
working memory
Executive function
Limbic/emotion
Stoodley and Schmahmann, NeuroImage, 2009
Lobules I, II
Lobule III
Lobule IV
Lobule V
Lobule VI
Crus I
Crus II
Lobule VIIB
Lobule VIIIA
Lobule VIIIB
Lobule IX
Lobule X
White matter
Language
Executive function
?
Executive function
?
Working memory
Motor
Somatosensory



Park *et al.* NeuroImage, 2014

Author	Finding	Direction of effect	IQ included	ASD:controls
Murakami et al., 1989	Smaller hemisphere, vermal lobules VI through VII	↓	No	10:8
Ekman et al., 1991	No anomalies detected- however absence of a control group.	-	No	15:0
Garber et al., 1992	No difference.	-	No	12:12
Piven et al., 1992	No difference from IQ-matched group, smaller than non-IQ matched group. No difference after accounting for IQ.	-	Yes	15: 15/15 (two control groups)
Holttum et al., 1992	No difference—high-functioning autistic subjects, with matched controls based on age, gender, IQ, race, and SES.	-	Yes	18:18
Courchesne et al., 1994	Two subgroups- one with hypoplasia (86% of ASD), and other with hyperplasia- first to report.	↑↓	No	53:50
Piven et al., 1997	Enlarged cerebellum in ASD.	↑	Yes	35:36
Manes et al., 1999	No difference- ASD vs subjects with mental retardation and comparable IQ.	-	No	27:17
Kardan et al., 2001	Enlarged cerebellum in ASD.	↑	No	22:22
Courchesne et al., 2001	Less gray matter, smaller vermal VI-VII.	↓	No	60:52
Sparks et al., 2002	Enlarged cerebellum in ASD.	↑	Yes	45:26
Scott et al., 2009	Reduced total vermis in ASD (including Asperger's)- only high-functioning group show reduced vermis.	↓	No	48:15
Ecker et al., 2012	No volumetric difference in cerebellum.	-	No	89:89
Riva et al., 2013	Reduced Crus II and vermis gray matter.	↓	Yes	26:21

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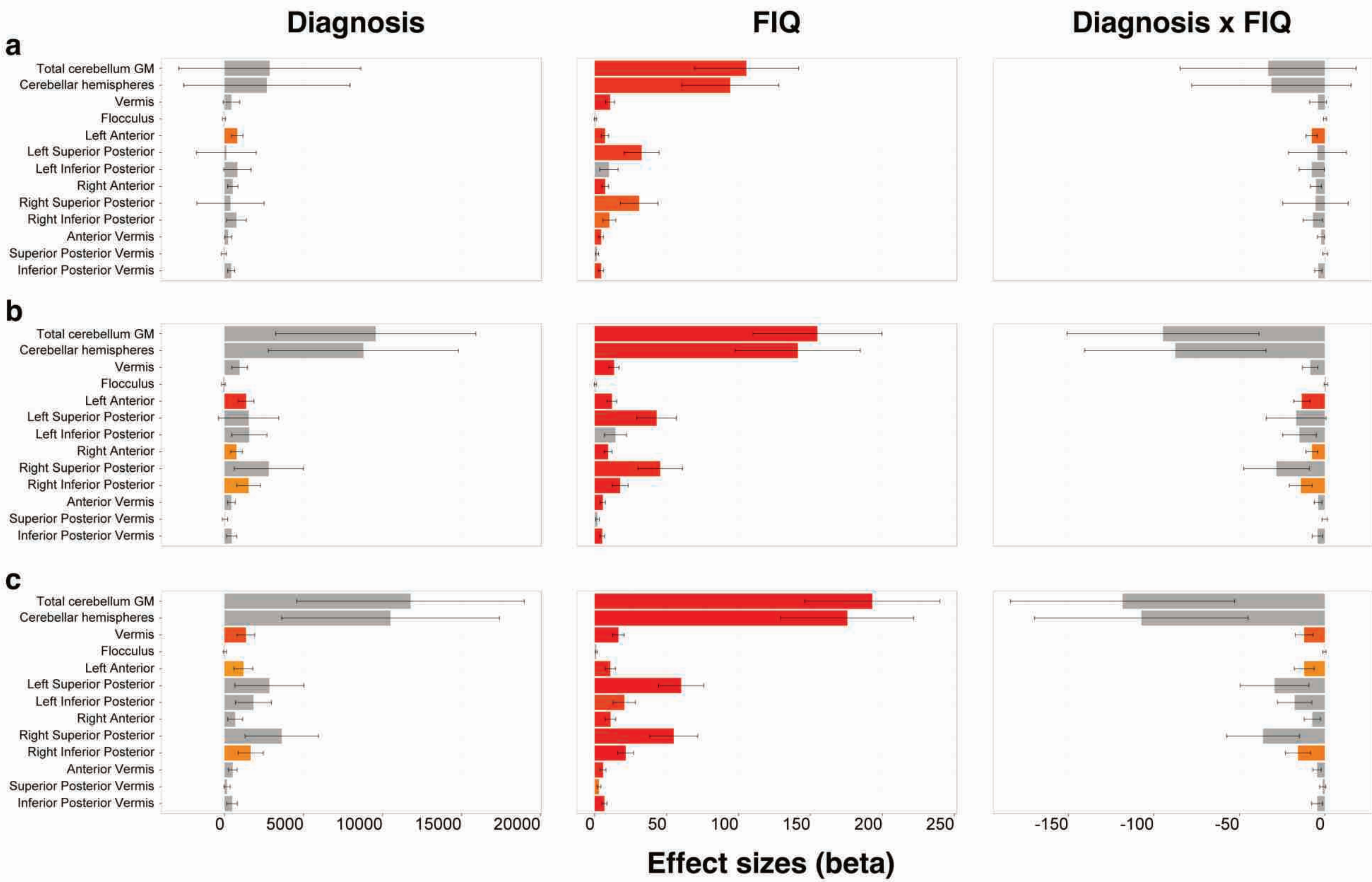
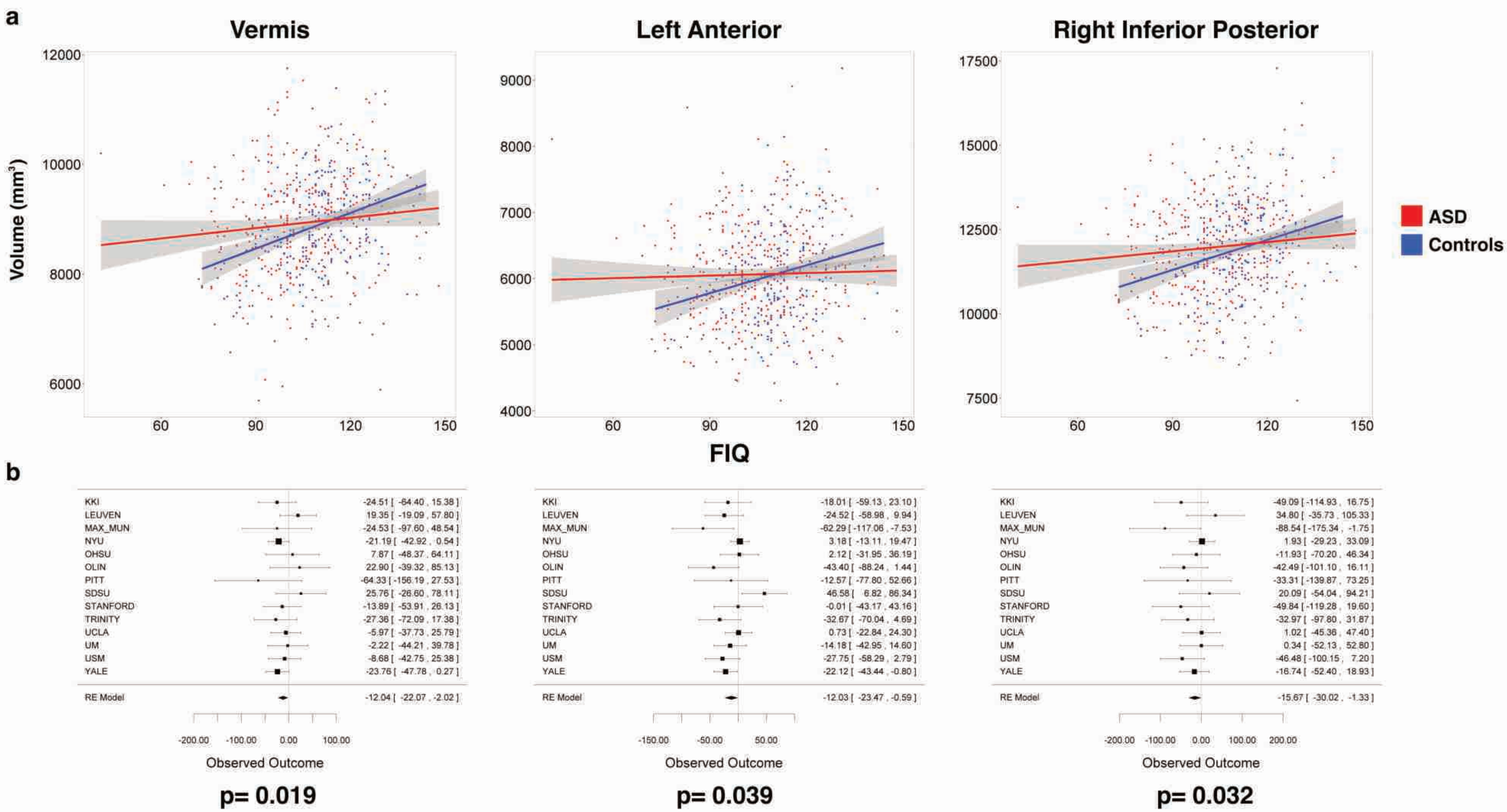


Diagnosis
FIQ
Diagnosis x FIQ
a
b
c
Total cerebellum GM
Cerebellar hemispheres
Vermis
Flocculus
Left Anterior
Left Superior Posterior
Left Inferior Posterior
Right Anterior
Right Superior Posterior
Right Inferior Posterior
Anterior Vermis
Superior Posterior Vermis
Inferior Posterior Vermis
0
5000
10000
15000
20000
0
50
100
150
200
250
-150
-100
-50
0
Effect sizes (beta)


a
Vermis
Left Anterior
Right Inferior Posterior
Volume (mm³)
12000
10000
8000
6000
9000
8000
7000
6000
5000
4000
17500
15000
12500
10000
7500
60
90
120
150
FIQ
ASD
Controls
b
KKI -24.51 [-64.40 , 15.38]
LEUVEN 19.35 [-19.09 , 57.80]
MAX_MUN -24.53 [-97.60 , 48.54]
NYU -21.19 [-42.92 , 0.54]
OHSU 7.87 [-48.37 , 64.11]
OLIN 22.90 [-39.32 , 85.13]
PITT -64.33 [-156.19 , 27.53]
SDSU 25.76 [-26.60 , 78.11]
STANFORD -13.89 [-53.91 , 26.13]
TRINITY -27.36 [-72.09 , 17.38]
UCLA -5.97 [-37.73 , 25.79]
UM -2.22 [-44.21 , 39.78]
USM -8.68 [-42.75 , 25.38]
YALE -23.76 [-47.78 , 0.27]
RE Model -12.04 [-22.07 , -2.02]
-200.00 -100.00 0.00 100.00
Observed Outcome
p= 0.019
KKI -18.01 [-59.13 , 23.10]
LEUVEN -24.52 [-58.98 , 9.94]
MAX_MUN -62.29 [-117.06 , -7.53]
NYU 3.18 [-13.11 , 19.47]
OHSU 2.12 [-31.95 , 36.19]
OLIN -43.40 [-88.24 , 1.44]
PITT -12.57 [-77.80 , 52.66]
SDSU 46.58 [6.82 , 86.34]
STANFORD -0.01 [-43.17 , 43.16]
TRINITY -32.67 [-70.04 , 4.69]
UCLA 0.73 [-22.84 , 24.30]
UM -14.18 [-42.95 , 14.60]
USM -27.75 [-58.29 , 2.79]
YALE -22.12 [-43.44 , -0.80]
RE Model -12.03 [-23.47 , -0.59]
-150.00 -50.00 50.00
Observed Outcome
p= 0.039
KKI -49.09 [-114.93 , 16.75]
LEUVEN 34.80 [-35.73 , 105.33]
MAX_MUN -88.54 [-175.34 , -1.75]
NYU 1.93 [-29.23 , 33.09]
OHSU -11.93 [-70.20 , 46.34]
OLIN -42.49 [-101.10 , 16.11]
PITT -33.31 [-139.87 , 73.25]
SDSU 20.09 [-54.04 , 94.21]
STANFORD -49.84 [-119.28 , 19.60]
TRINITY -32.97 [-97.80 , 31.87]
UCLA 1.02 [-45.36 , 47.40]
UM 0.34 [-52.13 , 52.80]
USM -46.48 [-100.15 , 7.20]
YALE -16.74 [-52.40 , 18.93]
RE Model -15.67 [-30.02 , -1.33]
-200.00 -100.00 0.00 100.00 200.00
Observed Outcome
p= 0.032

www.cobralab.ca

Software:
http://cobralab.ca/software/

Atlases:
http://cobralab.ca/atlases/

Wiki:
https://github.com/CobraLab/documentation/wiki

Questions?