The human memory circuit:

Volumetric assessment of hippocampal subfields and white matter over the course of healthy versus pathological aging

Roberto S.C. Amaral

MSc Candidate

>cobraLab_
computational brain anatomy

McGill

Supervisor: Dr. M. Mallar Chakravarty

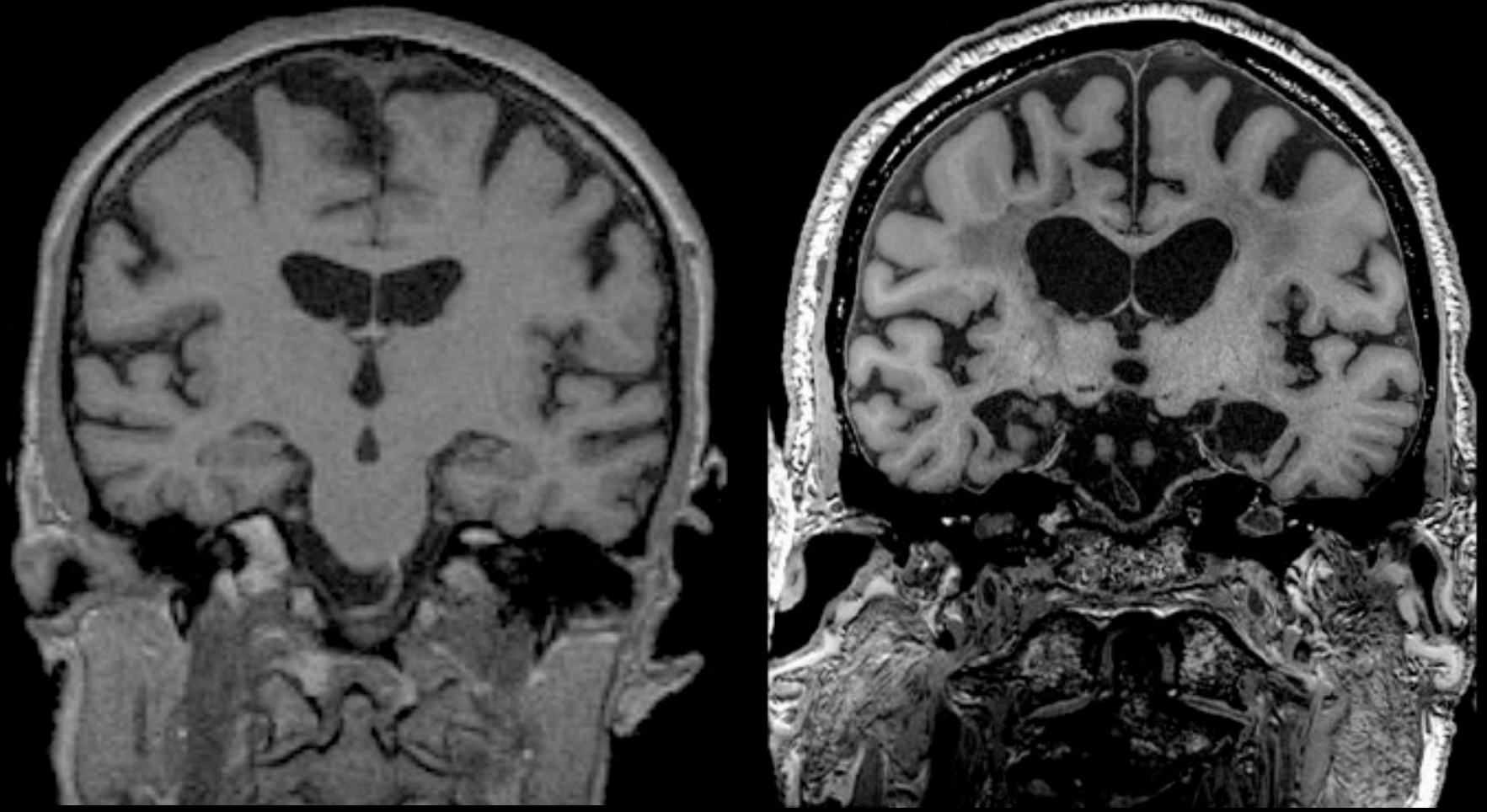
Cerebral Imaging Center,

Douglas Mental Health University Institute,

Montreal, Canada

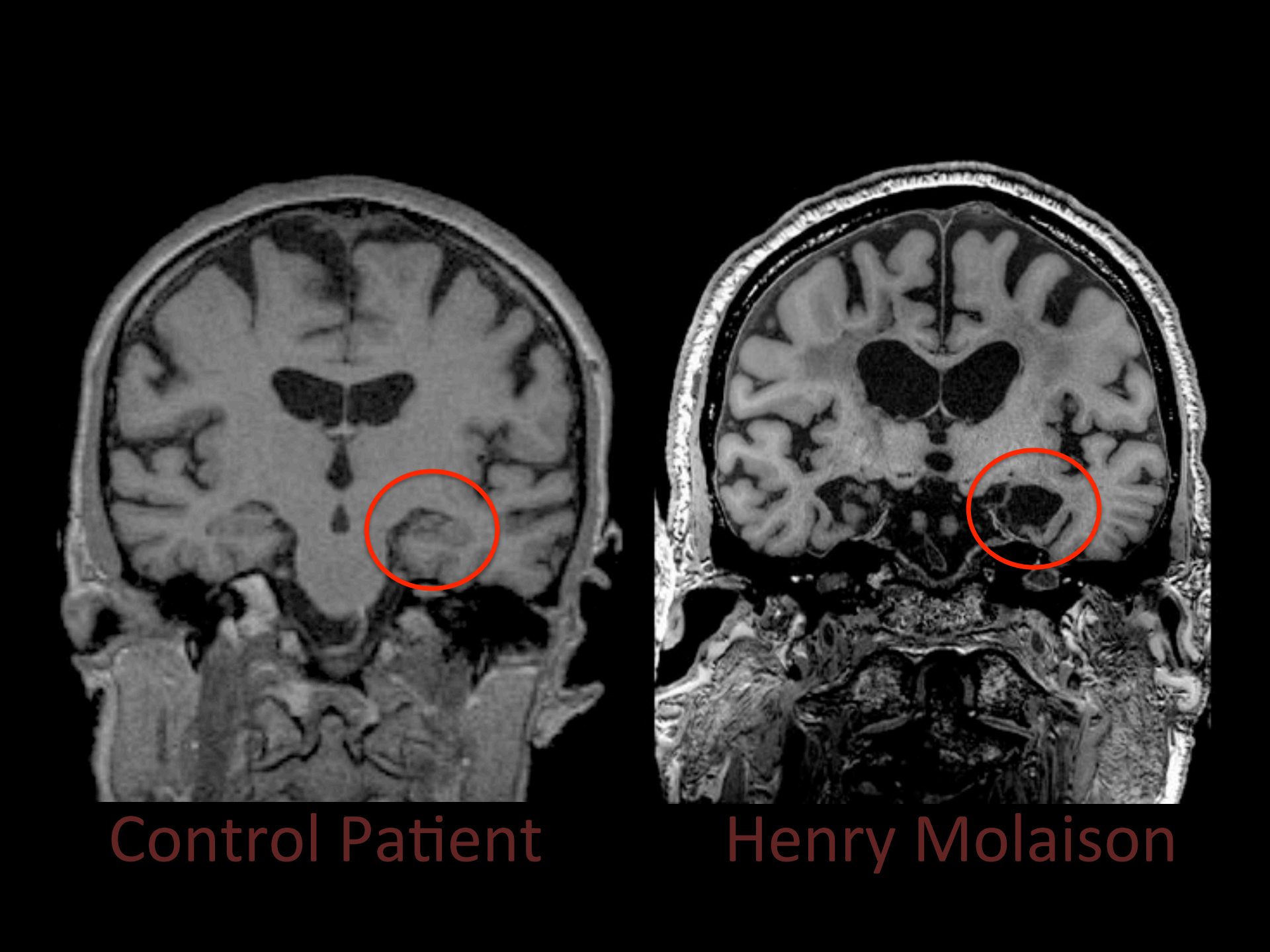
Douglas
INSTITUT UNIVERSITAIRE EN SANTÉ MENTALE
MENTAL HEALTH UNIVERSITY INSTITUTE

Henry Molaison



Control Patient

Henry Molaison


Control Patient
Henry Molaison

Dr. Brenda Milner

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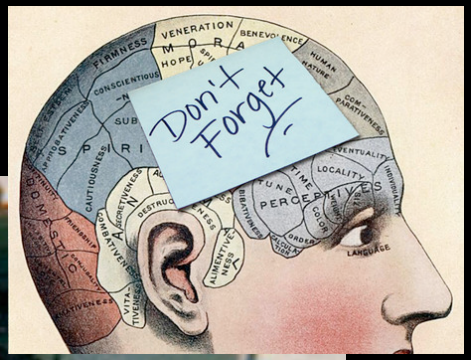
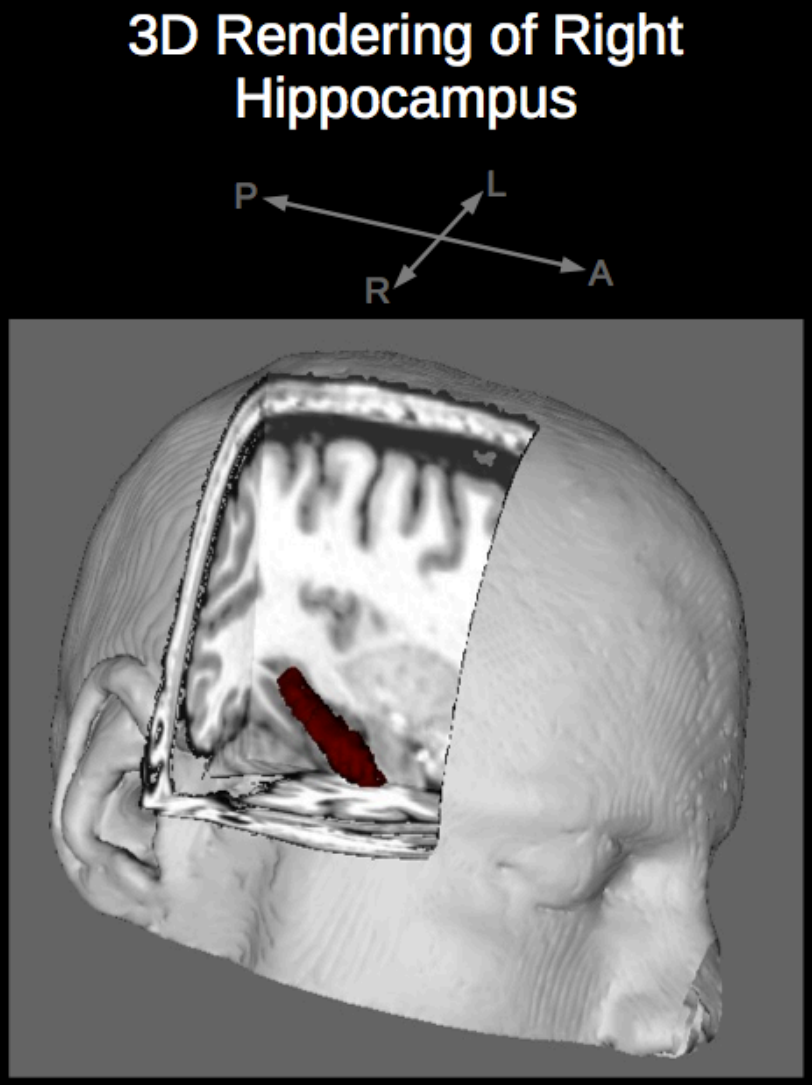
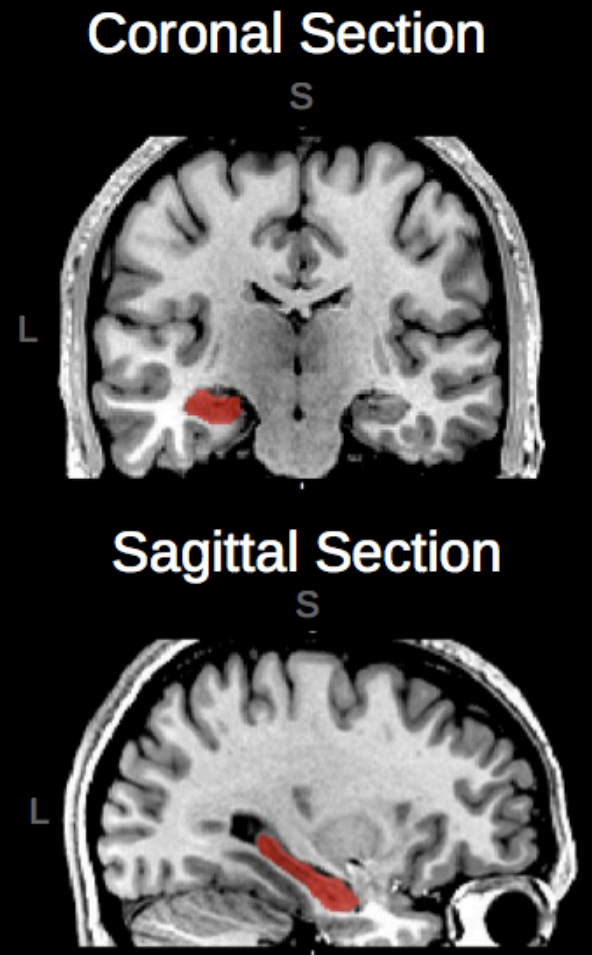


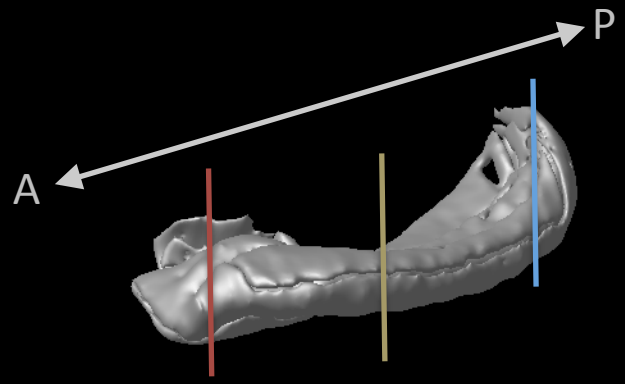
Henry Molaison

Classical Assessment of HC Volumetry



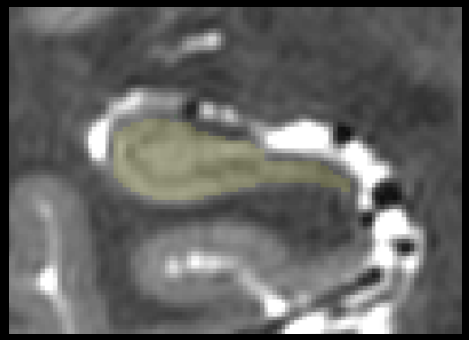


A move towards specificity…

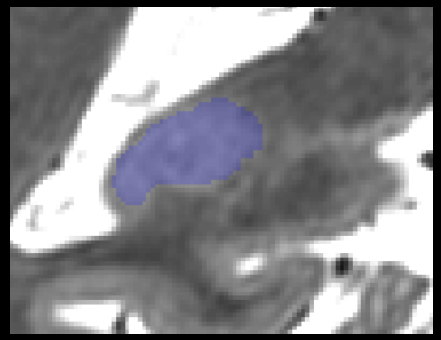


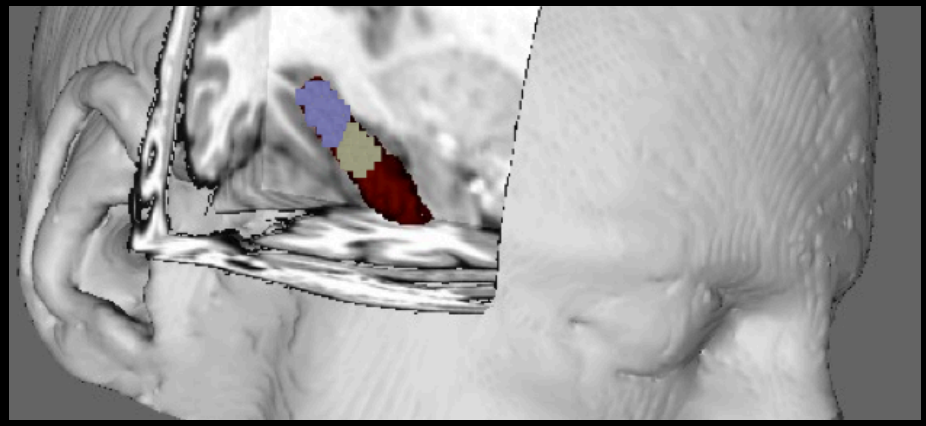
HEAD

BODY



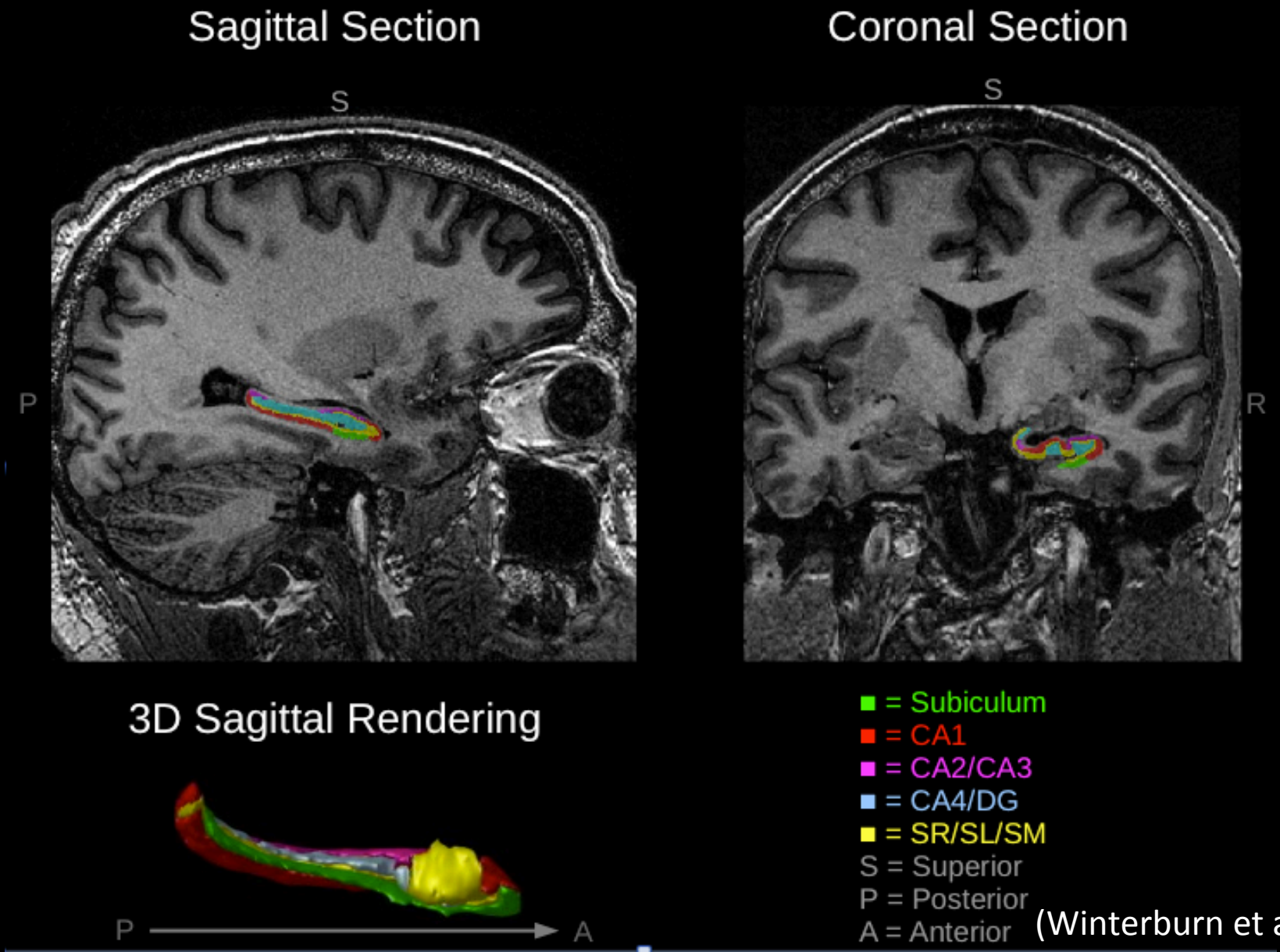
TAIL





A = Anterior
P = Posterior
L = Lateral
S = Superior

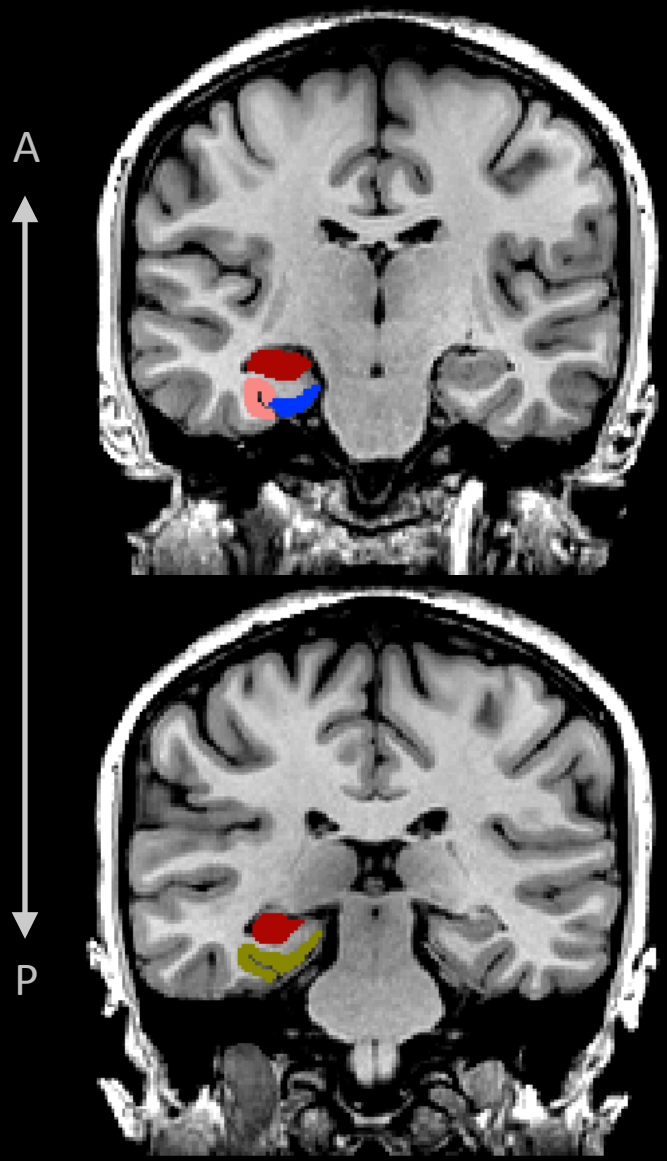
Assessing the HC in its entirety

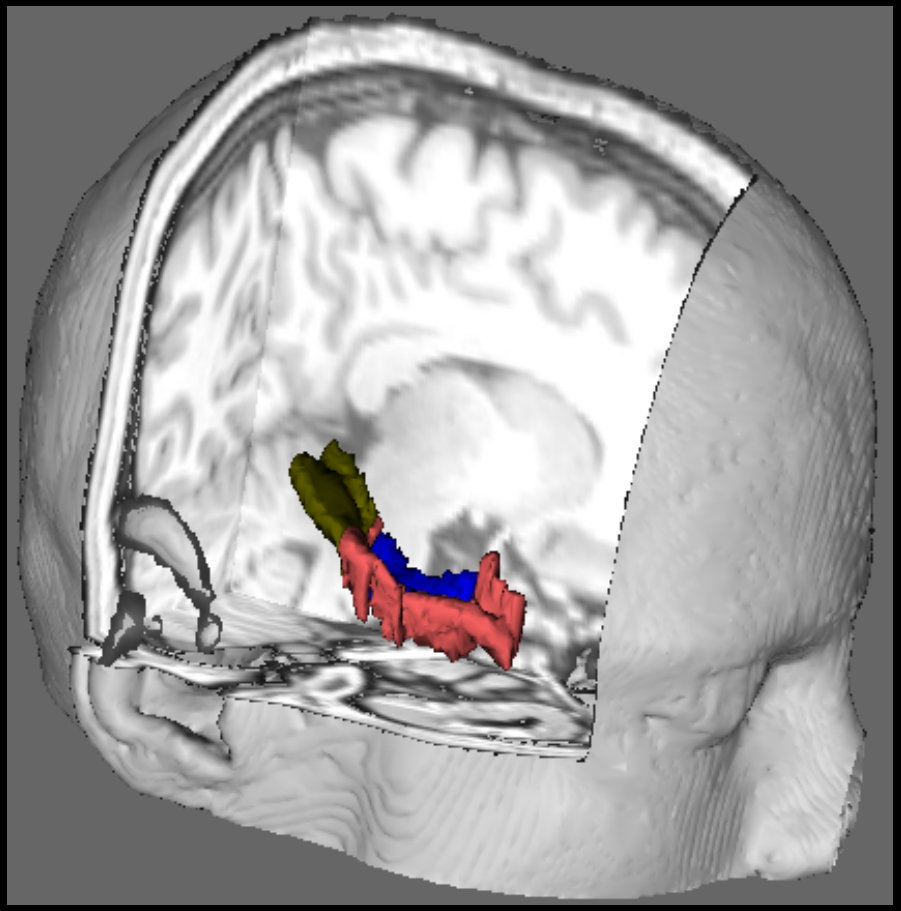


(Winterburn et al., 2013)

However the HC is not alone…

Inputs

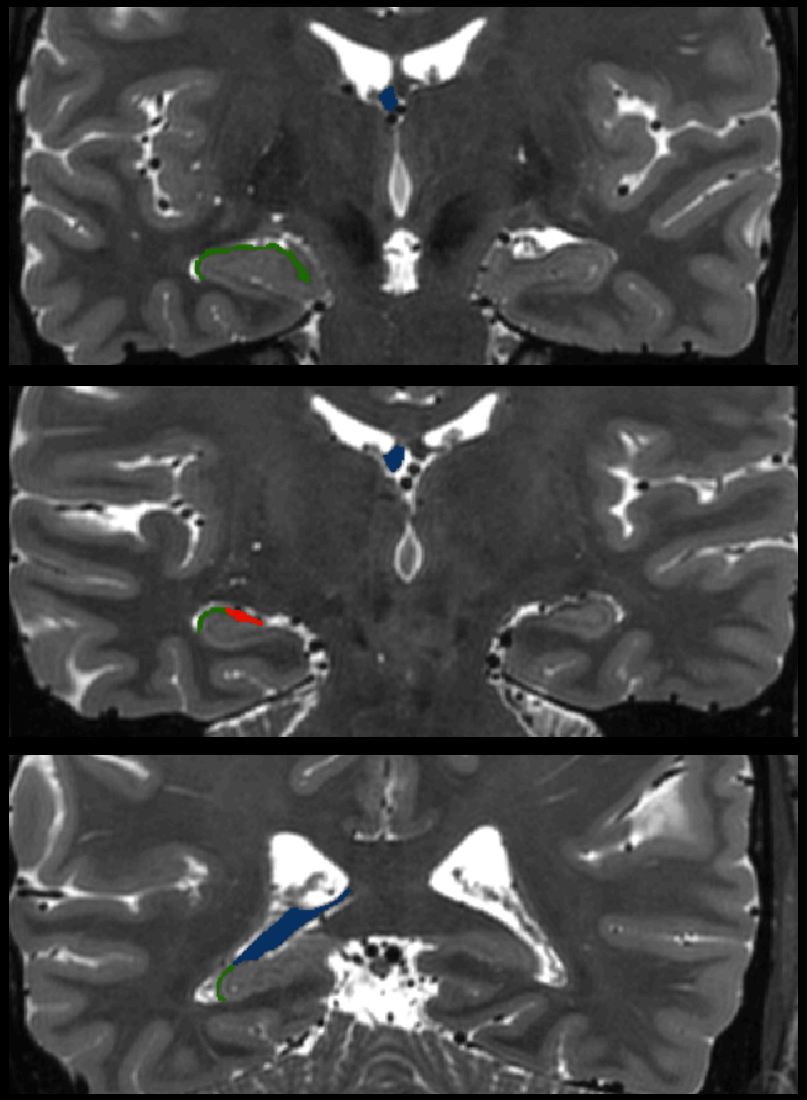




Perirhinal Cortex
Parahippocampal Cortex
Entorhinal Cortex
Hippocampus

However the HC is not alone…

Outputs

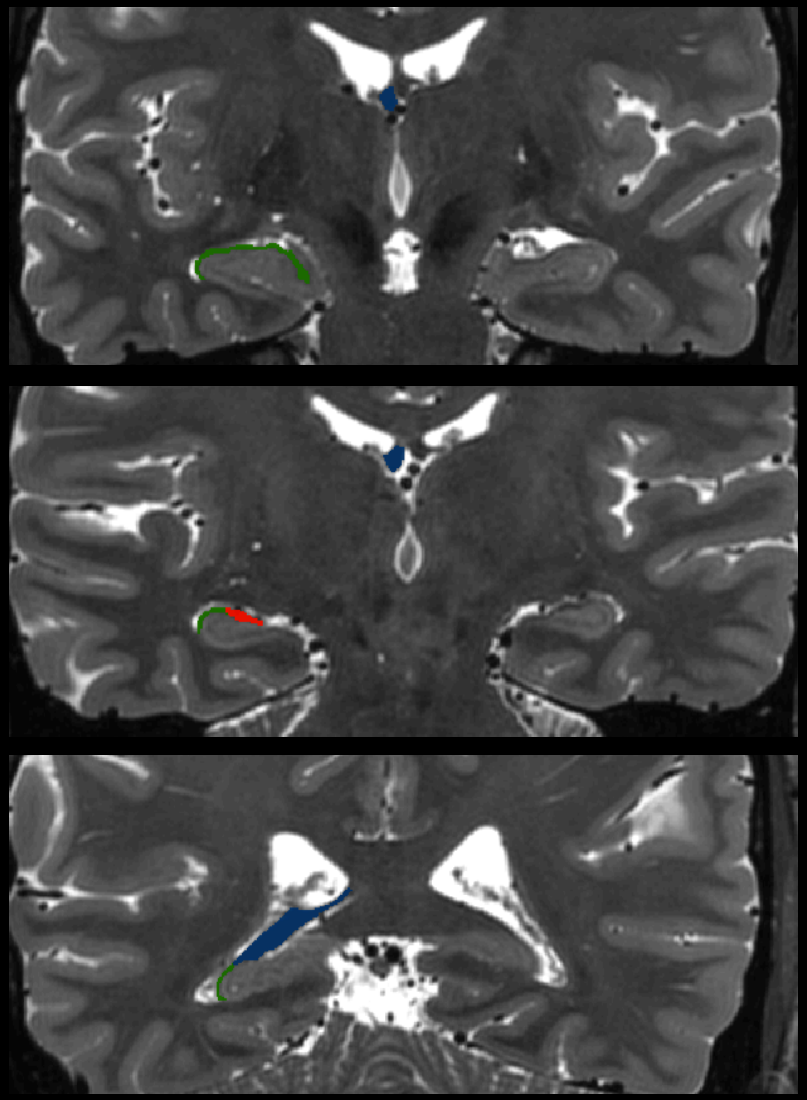


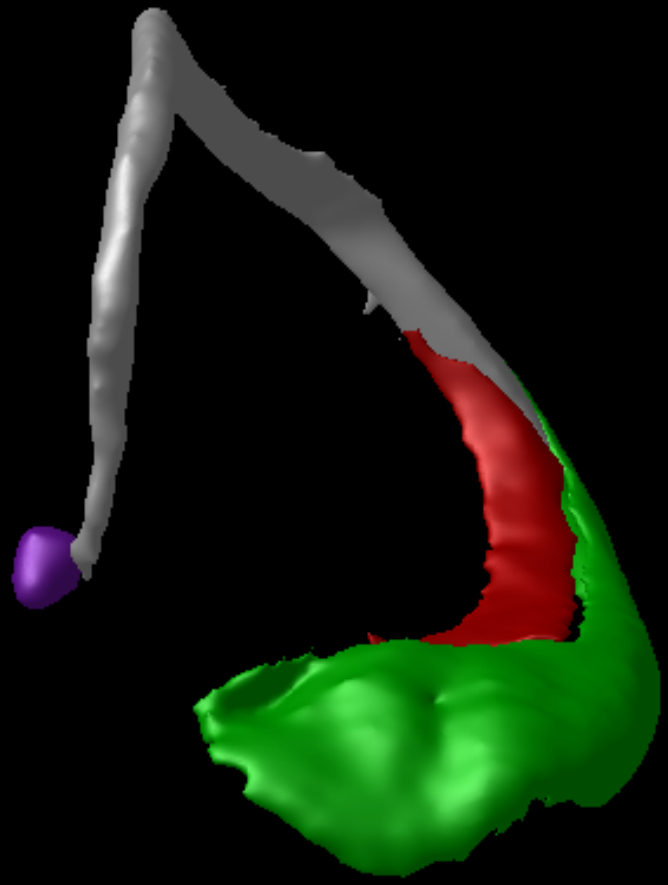
Alveus
Fimbria

Fornix / Fornix
Mammillary Bodies

However the HC is not alone…

Outputs





Alveus
Fimbria

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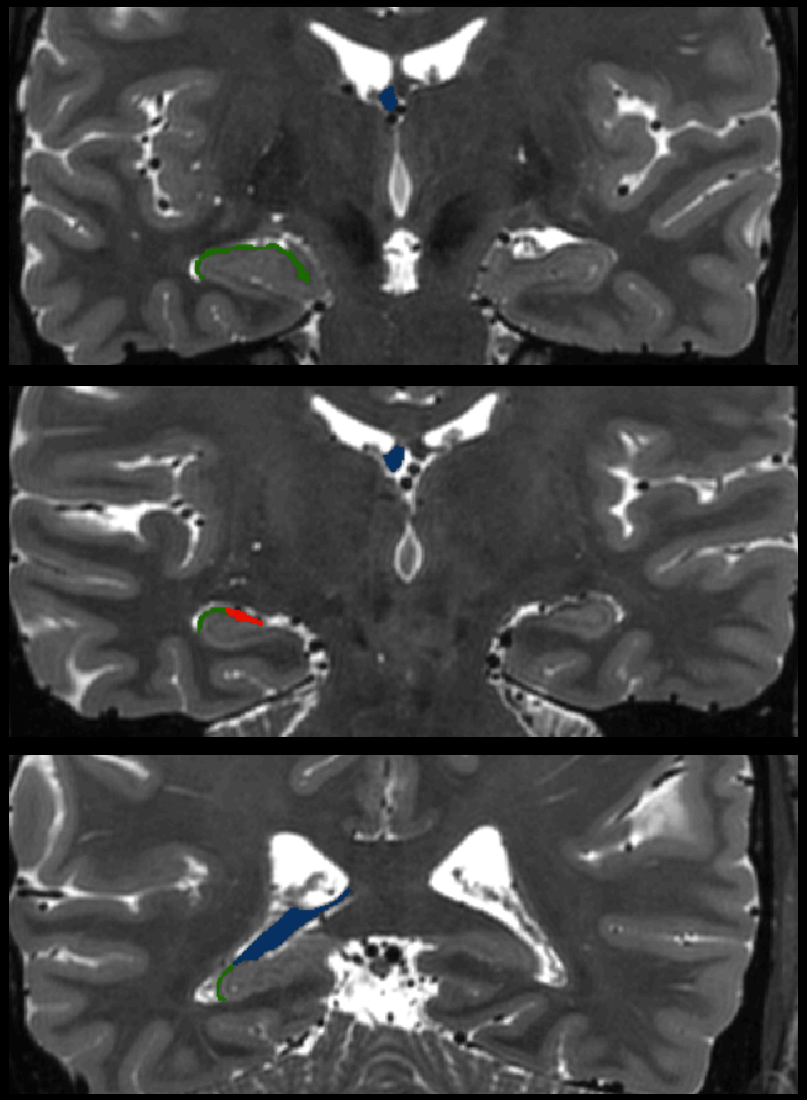
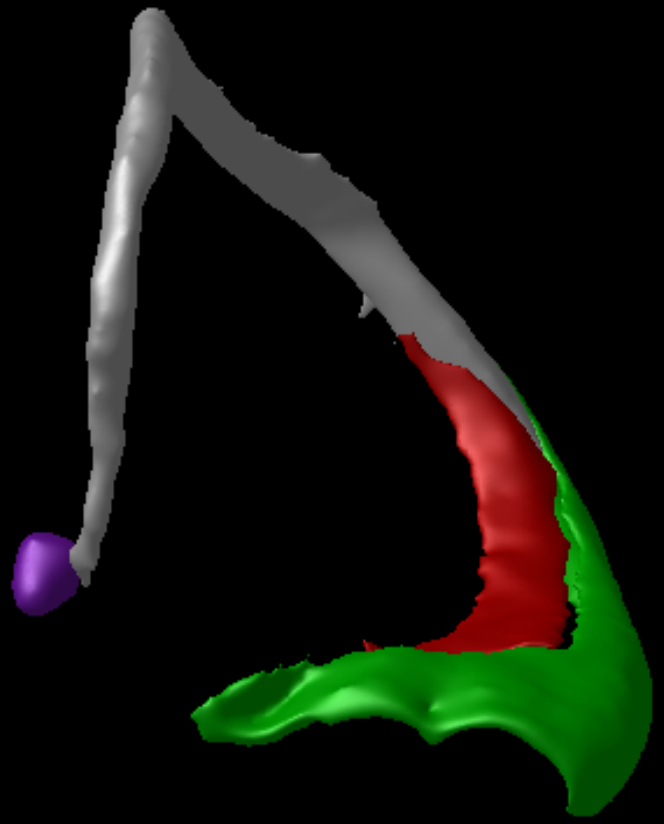




Alveus
Fimbria

Fornix / Fornix
Mammillary Bodies

Literature Gap

- Over 50 different protocols for segmentation of WHOLE hippocampus (Boccardi et al., 2011)
- Over 21 different protocols for segmentation of the hippocampal SUBFIELDS (Yushkevich et al., 2015)
- Increasing number of studies on segmentation of MTL cortices

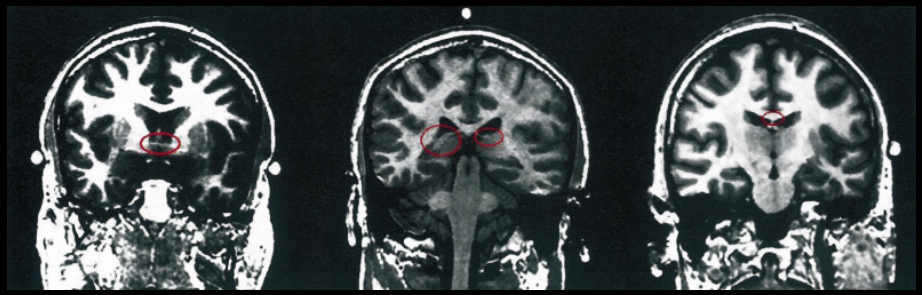
Begs the Questions:

Are these white matter structures important?
Can we segment these structures in MRI images?
Can they tell us anything about certain populations (healthy versus pathological aging)?

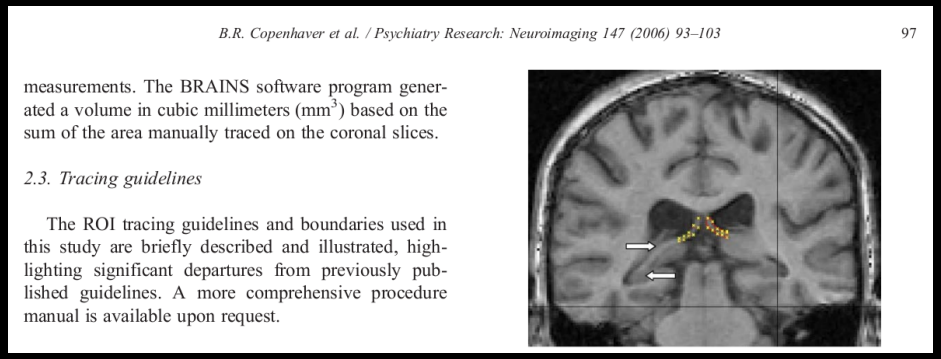
Previous Segmentation of Alveus, Fimbria and Fornix

Past Protocols for Segmentation of WM Regions:

- Zeineh et al., 2012
- Copenhaver et al., 2006
- Wang et al., 2003
- Zahajszky et al., 2001
- Kuzniecky et al., 1999
- Bilir et al., 1998
- Gale et al., 1993



(Zahajszky et al., 2001)



B.R. Copenhaver et al. / Psychiatry Research: Neuroimaging 147 (2006) 93–103 97

measurements. The BRAINS software program generated a volume in cubic millimeters (mm^3) based on the sum of the area manually traced on the coronal slices.

2.3. Tracing guidelines

The ROI tracing guidelines and boundaries used in this study are briefly described and illustrated, highlighting significant departures from previously published guidelines. A more comprehensive procedure manual is available upon request.

(Copenhaver et al., 2006)

Issues:

1. Most fail to include full extent of the fornix
2. Do not include other divisions of white matter (i.e. alveus, fimbria)
3. Do not provide enough protocol information for proper segmentation
4. Lack high quality MRI imaging protocols

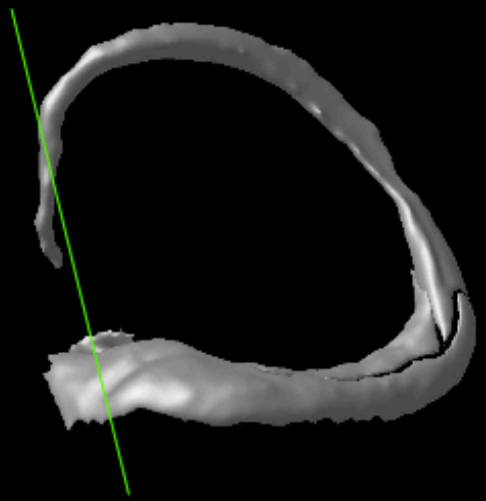
Designing a Segmentation Protocol

- Used MINC Display for segmentation
- Employed a tri-planar approach + 3D reconstruction to guide tracing
- Anatomical resources used included atlases and papers (Duvernoy, 2005; Mai et al., 2008; Talairach and Tournoux, 1988; Amaral & Insausti, 1990)
- Protocol To fit with Winterburn et al., 2013 segmentation protocol for hippocampal subfields and for any resolution

Designing a Segmentation Protocol

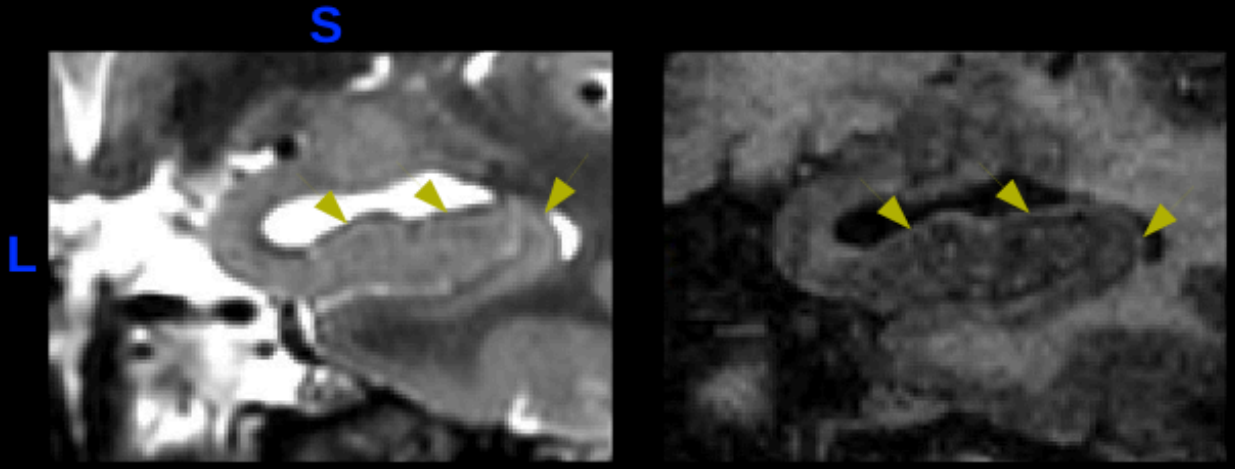
- Tracings completed on 5 healthy participants (2 male, 3 female; aged 29-57; average age of 37 years)
- T1 and T2-Weighted scans completed at high resolution (0.3mm isotropic)

- Anatomical accuracy
- Some geometric rules will apply



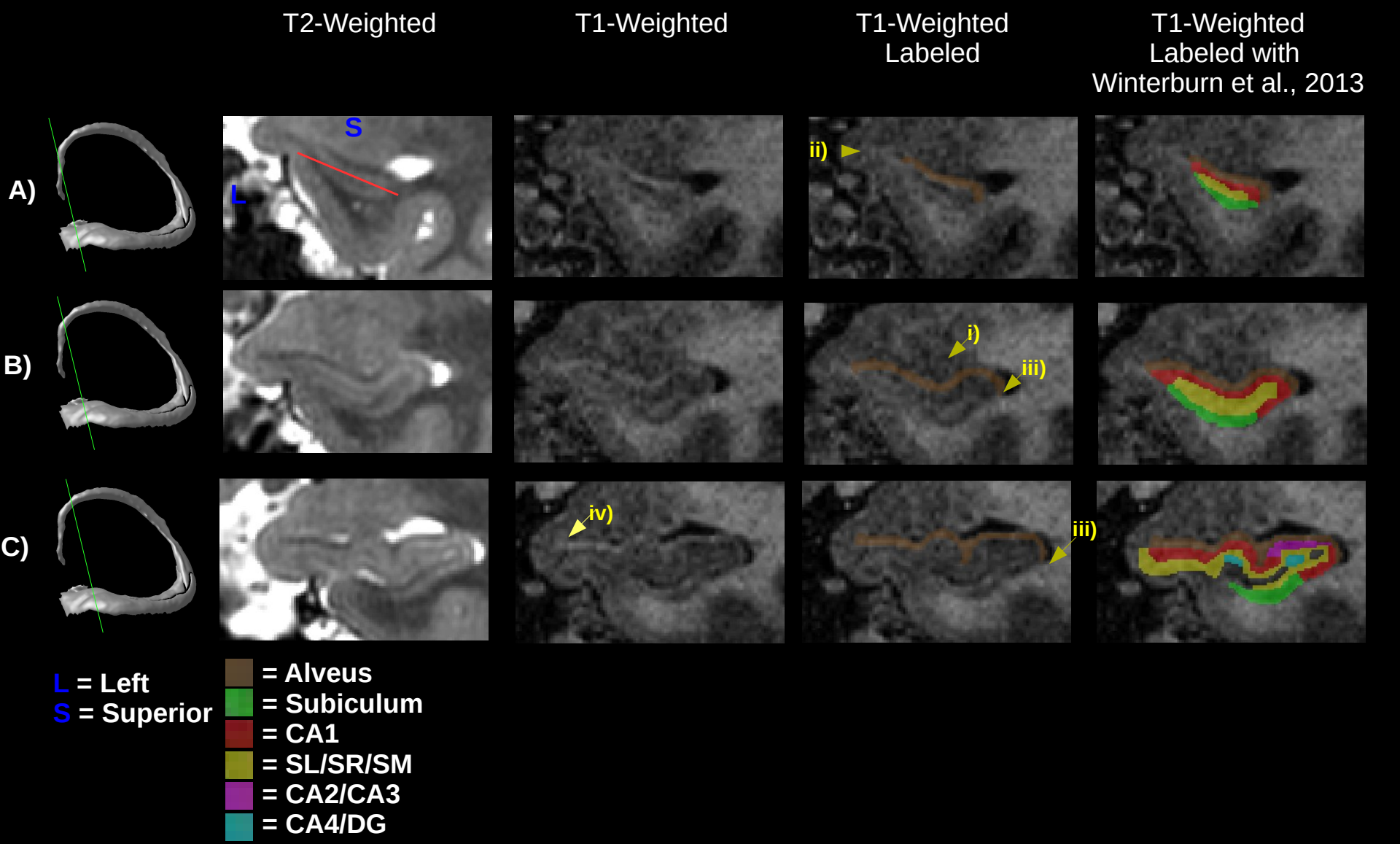
T2-Weighted

T1-Weighted

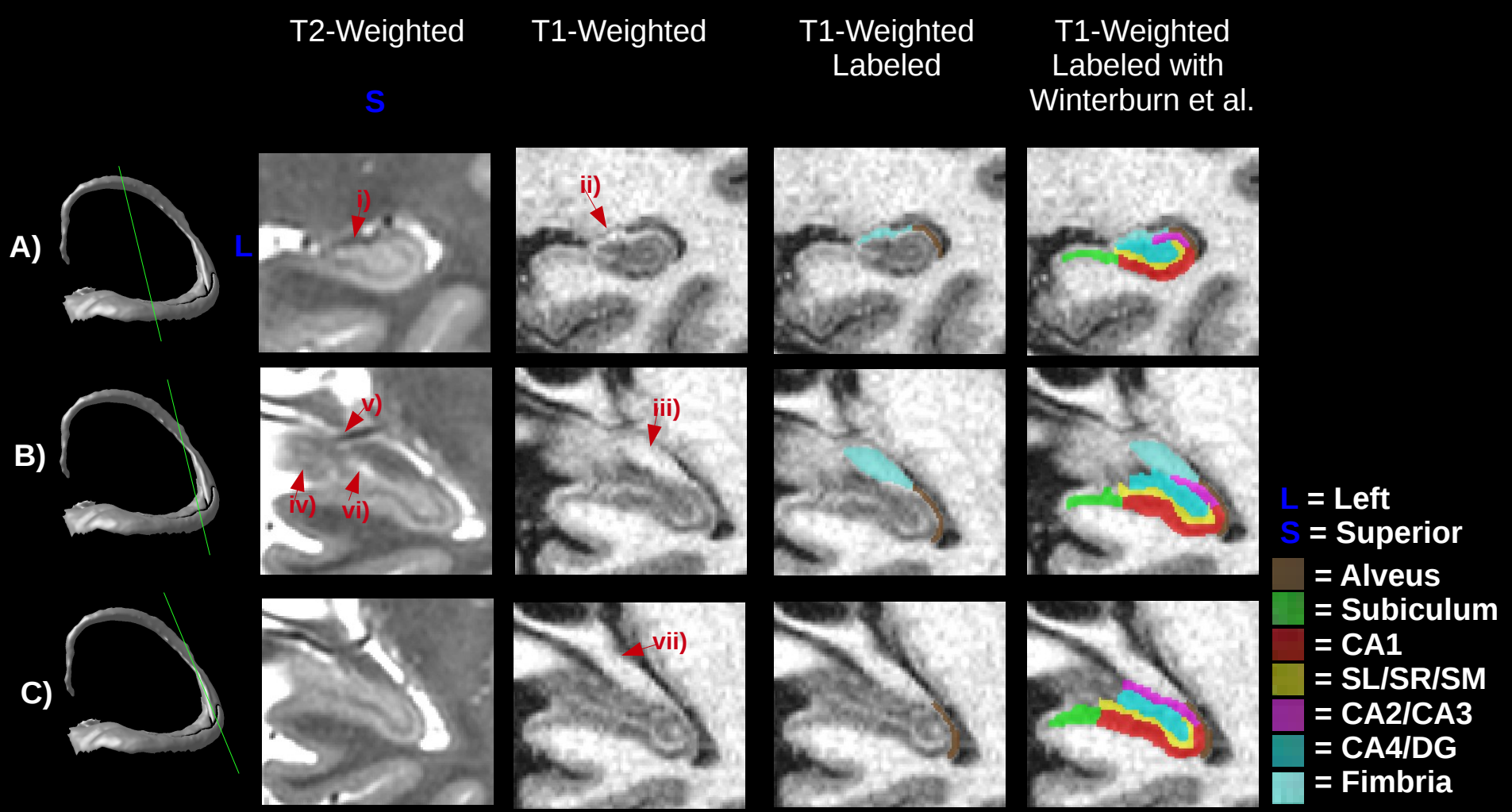


L = Left
S = Superior

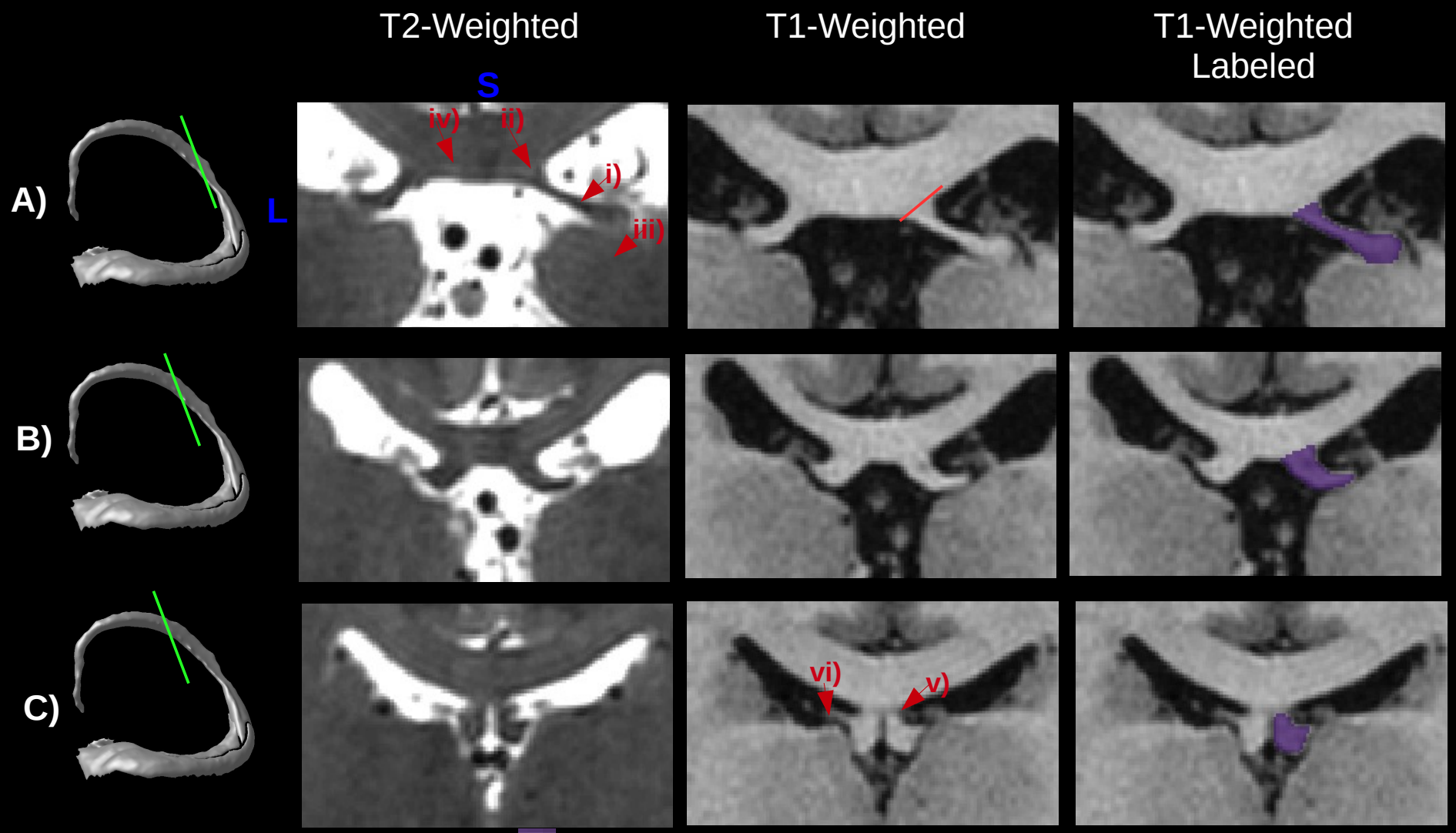
Manual Protocol - Alveus



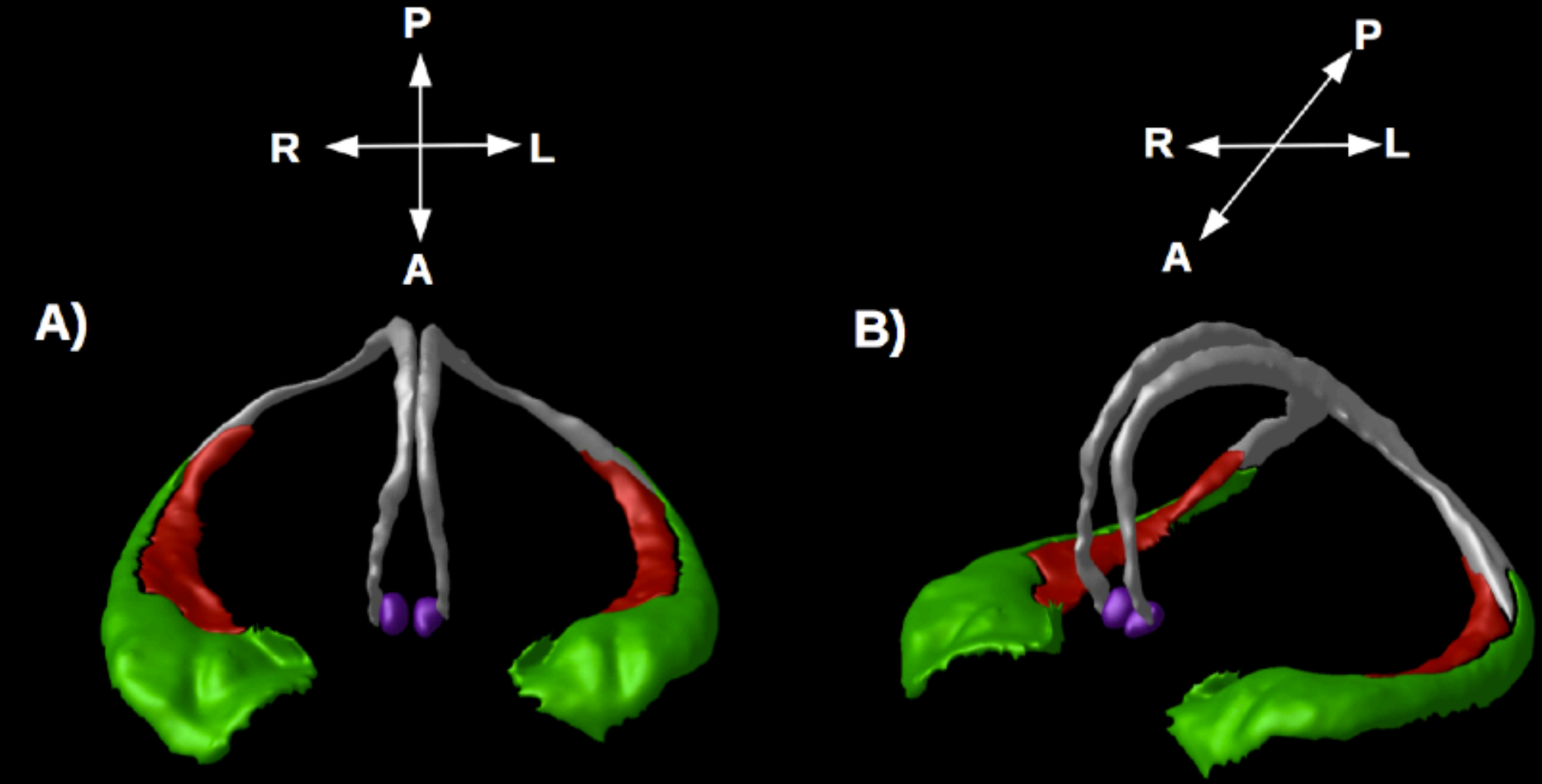
Manual Protocol - Fimbria



Manual Protocol - Fornix



Manual Protocol - Fornix

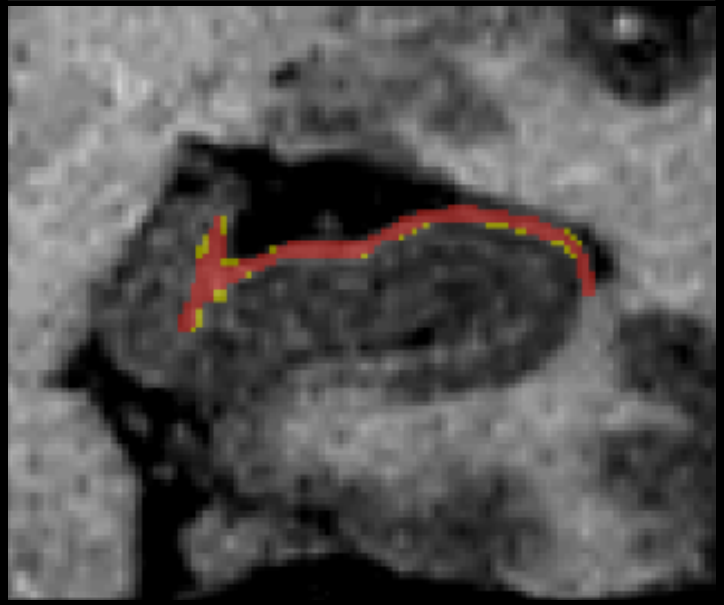


Reliability of Protocol

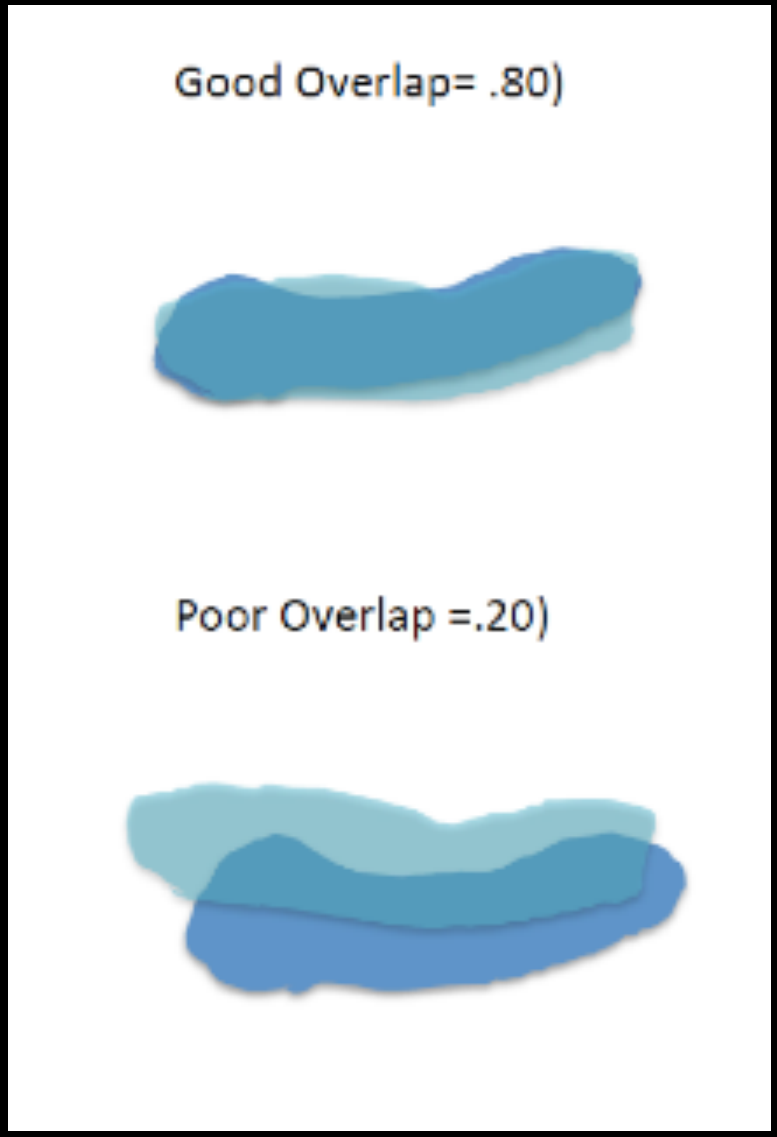
Reliability Measured using
Dice's Kappa (Dice, 1945) where:

1 = perfect overlap
0 = no overlap

Superimpose Label 1 on Label 2



= Areas of Mismatch
= Areas of Overlap



Reliability of Protocol - Results

- Completed on two hemispheres (1 male, 1 female)
- Tracing completed 6 months after first tracing

Intra-Rater Reliability as Measured by Dice's Kappa

Structure	Left	Right
Alveus	0.90	0.90
Fimbria	0.90	0.86
Fornix	0.87	0.87
Total White Matter	0.90	0.89

Average intra-rater reliability was calculated using Dice's volumetric Kappa. A score of 0 represents no overlap between test and retest labels, whereas a value of 1 represents a complete overlap.

Healthy vs. Pathological Aging

1 - Healthy Aging Cohort

- OASIS Dataset
- Aged 18-95 years (n = 315 ; av. age = 44.8)
- 1mm isotropic data
- T1 images

2 - Alzheimer's Disease Cohort

- ADNI 3T Baseline Dataset
- Controls (n= 47), MCI (n= 69), AD (n=47)
- 1mm isotropic data
- T1 images

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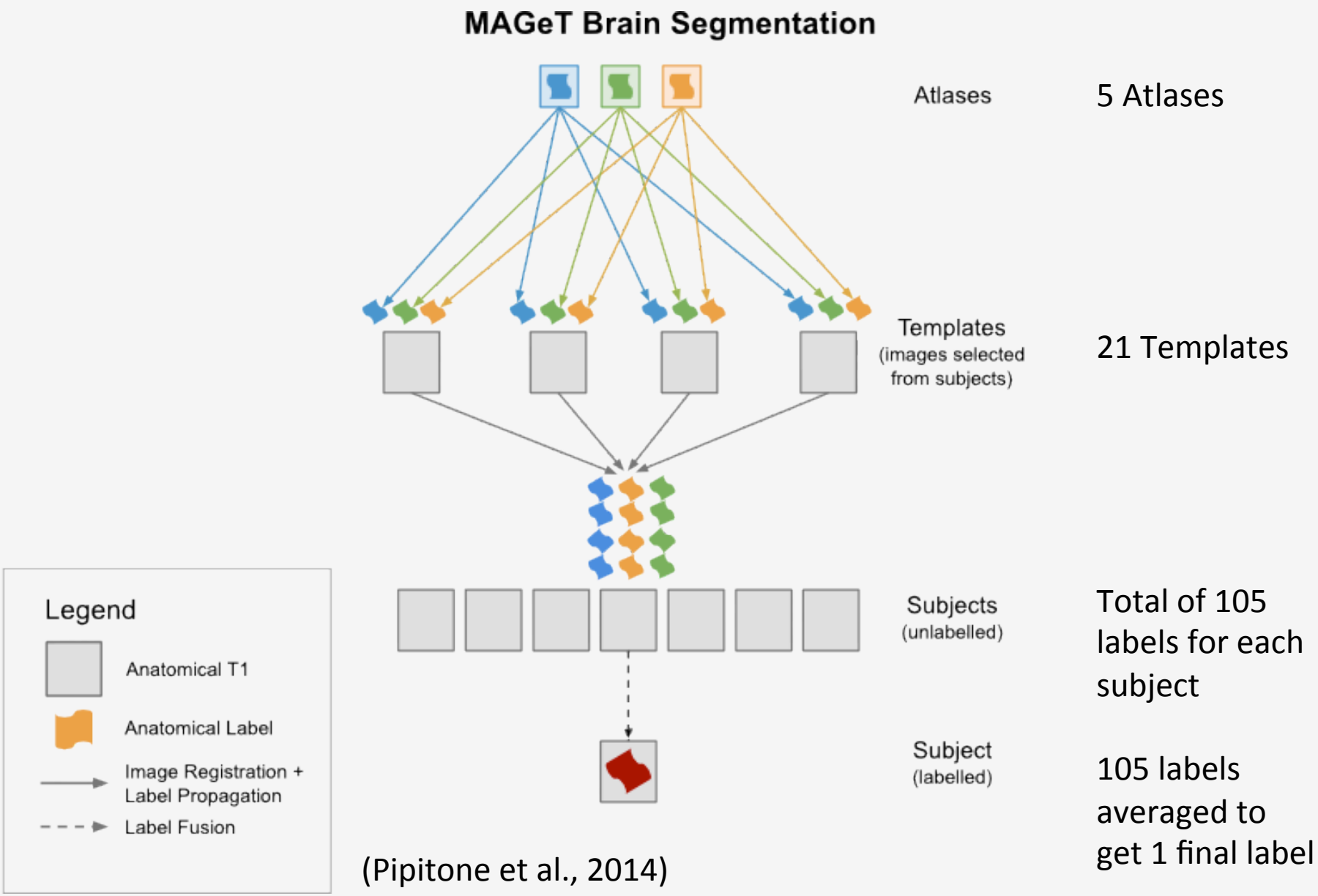
Automatic Segmentation – MAGeT Brain



(Pipitone et al., 2014)

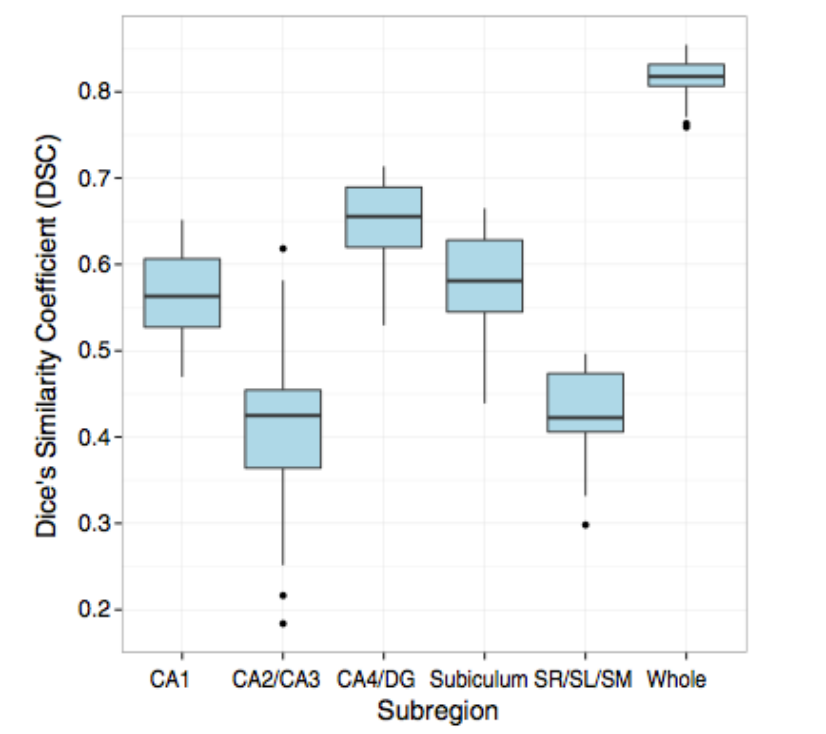
5 Atlases

21 Templates

Total of 105 labels for each subject

105 labels averaged to get 1 final label

MAGeT Brain Previously Validated for use in Hippocampal Subfields (Pipitone et al., 2014)



- High resolution (0.3mm isotropic) images of Winterburn Atlas down-sampled to 0.9mm
- MAGeT Brain used to automatically segment the same images
- Dice's Kappa used to compare overlap between down-sampled "Gold Standard" and MAGeT output

Subfield	MAGeT	0.9 mm translation
CA1	0.56 ± 0.05	0.27 ± 0.03
CA2/CA3	0.41 ± 0.10	0.12 ± 0.05
CA4/DG	0.65 ± 0.05	0.42 ± 0.05
SR/SL/SM	0.43 ± 0.05	0.19 ± 0.04
Subiculum	0.58 ± 0.06	0.14 ± 0.04

(Pipitone et al., 2014)

MAGeT Brain Results – Quality Control

Quality Control was rigorously assessed using a slice-per-slice pass fail system:

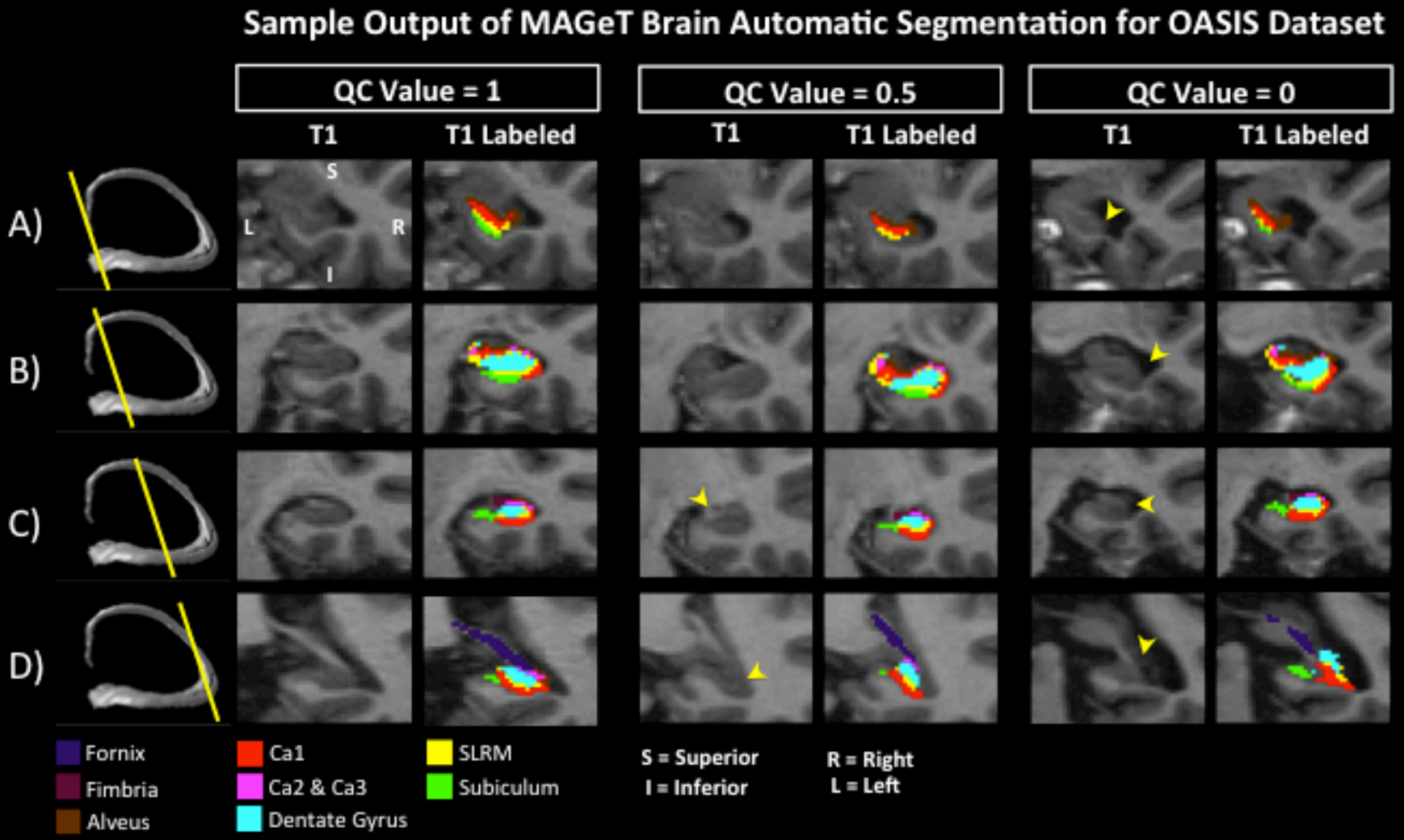
1 = **Perfect** (under 5 slices with segmentation fault)
0.5 = **Good** (between 5-10 slices having segmentation faults)
0 = **Fail** (over 10 slices having significant errors)

Scan Numbers after Quality Control

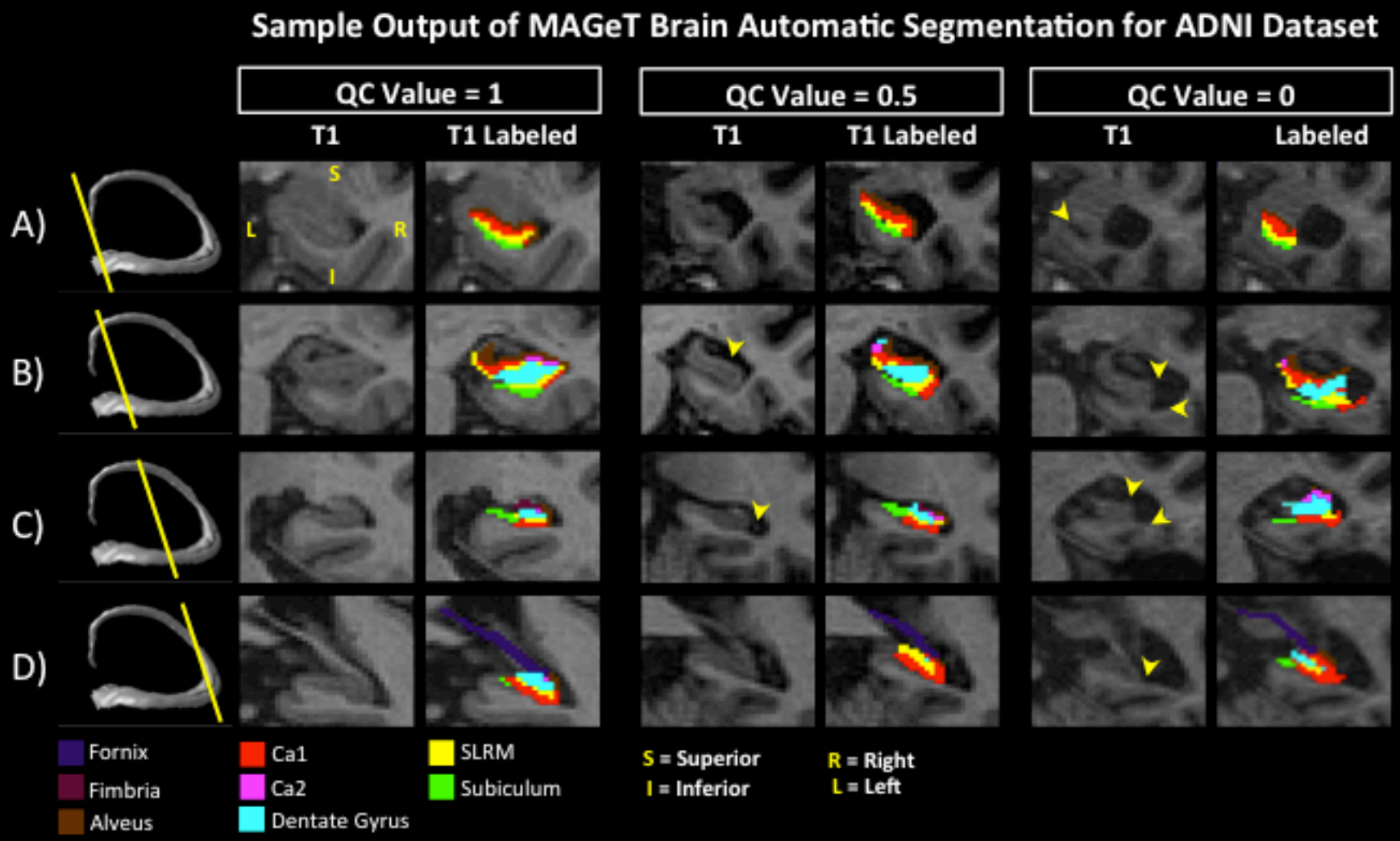
QC VALUE	OASIS	ADNI
1	252	98
0.5	44	47
0	19	6
Total Pass	296	145
Total	315	151

Summary of OASIS and ADNI cohort numbers post - quality control. Numbers correspond to: 1 = Perfect; 0.5 = Good; 0 = Fail.

MAGeT Brain Results – OASIS Dataset

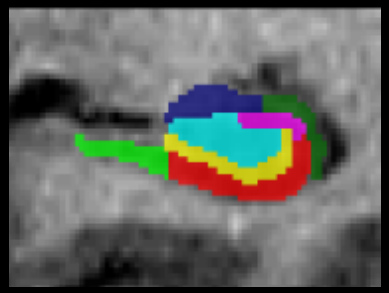


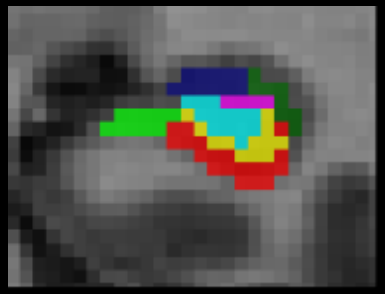
MAGeT Brain Results – ADNI Dataset

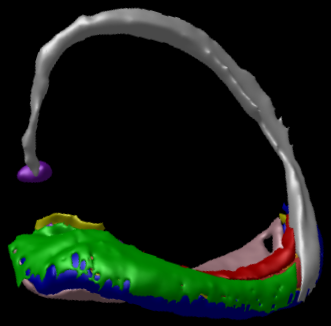


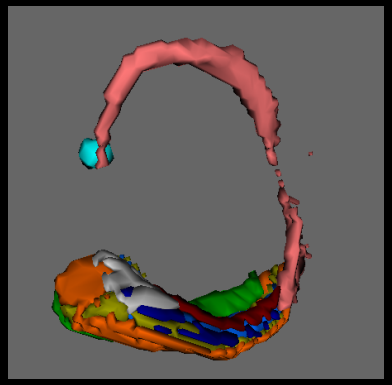
White Matter (0.3mm)

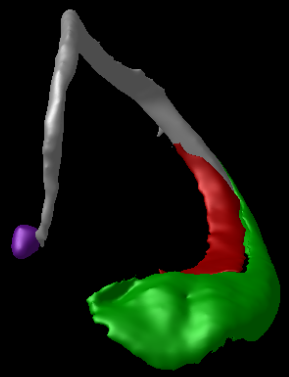
White Matter (1mm)

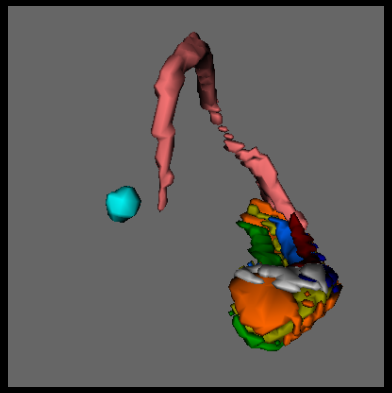












- Fornix
- Fimbria
- Alveus
- Ca1
- Ca2 & Ca3
- Dentate Gyrus
- SLRM
- Subiculum
- Mammillary Body

A = Anterior

P = Posterior

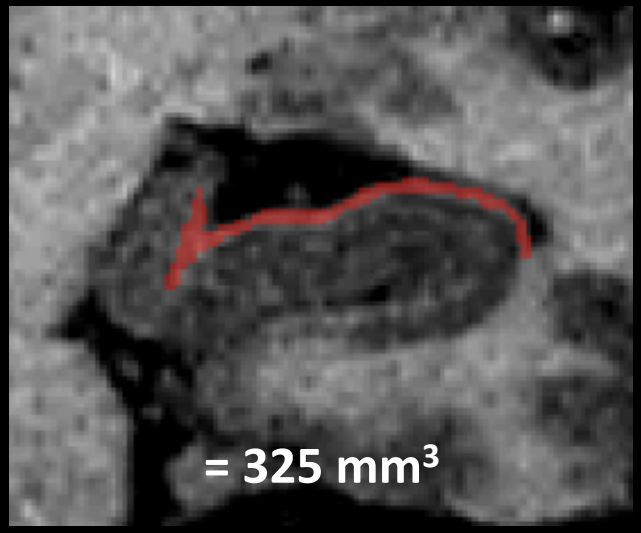
R = Right

MAGeT Brain Reliability

Is MAGeT Brain consistently identifying these structures correctly?

If this is TRUE than any healthy individual scanned at two different time points should yield the same volume account.

Scan #1 Volume



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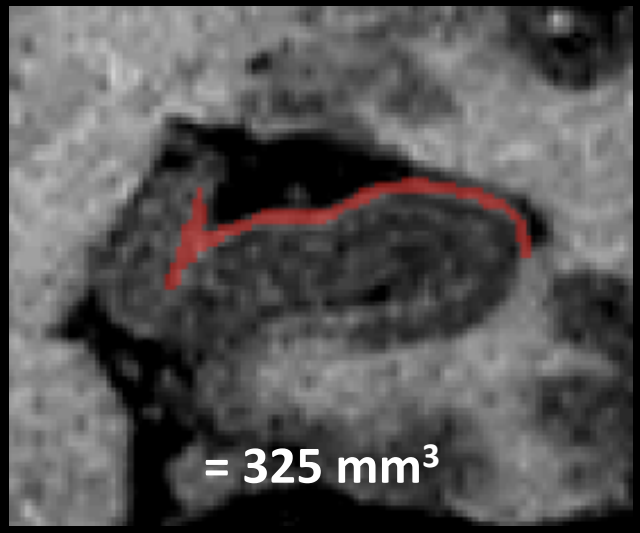
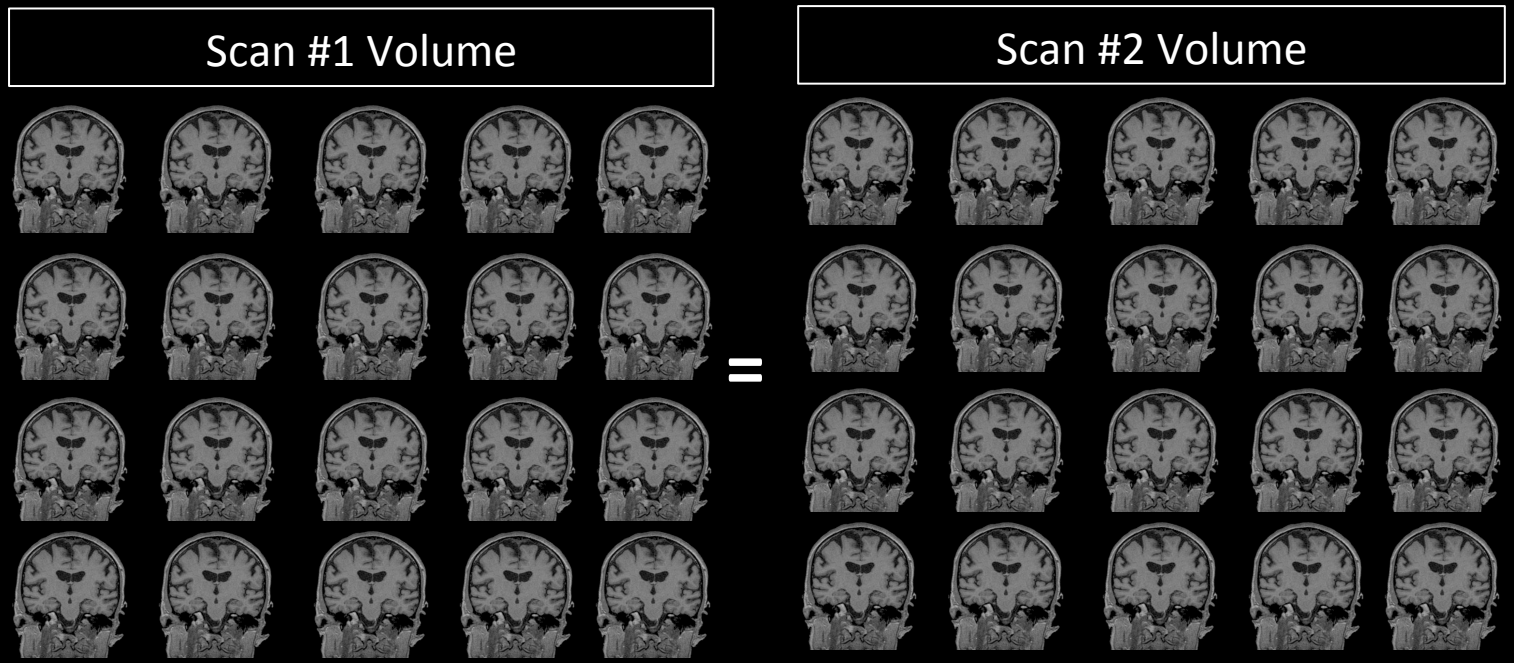
Scan #2 Volume



MAGeT Brain Reliability

Is MAGeT Brain consistently identifying these structures correctly?

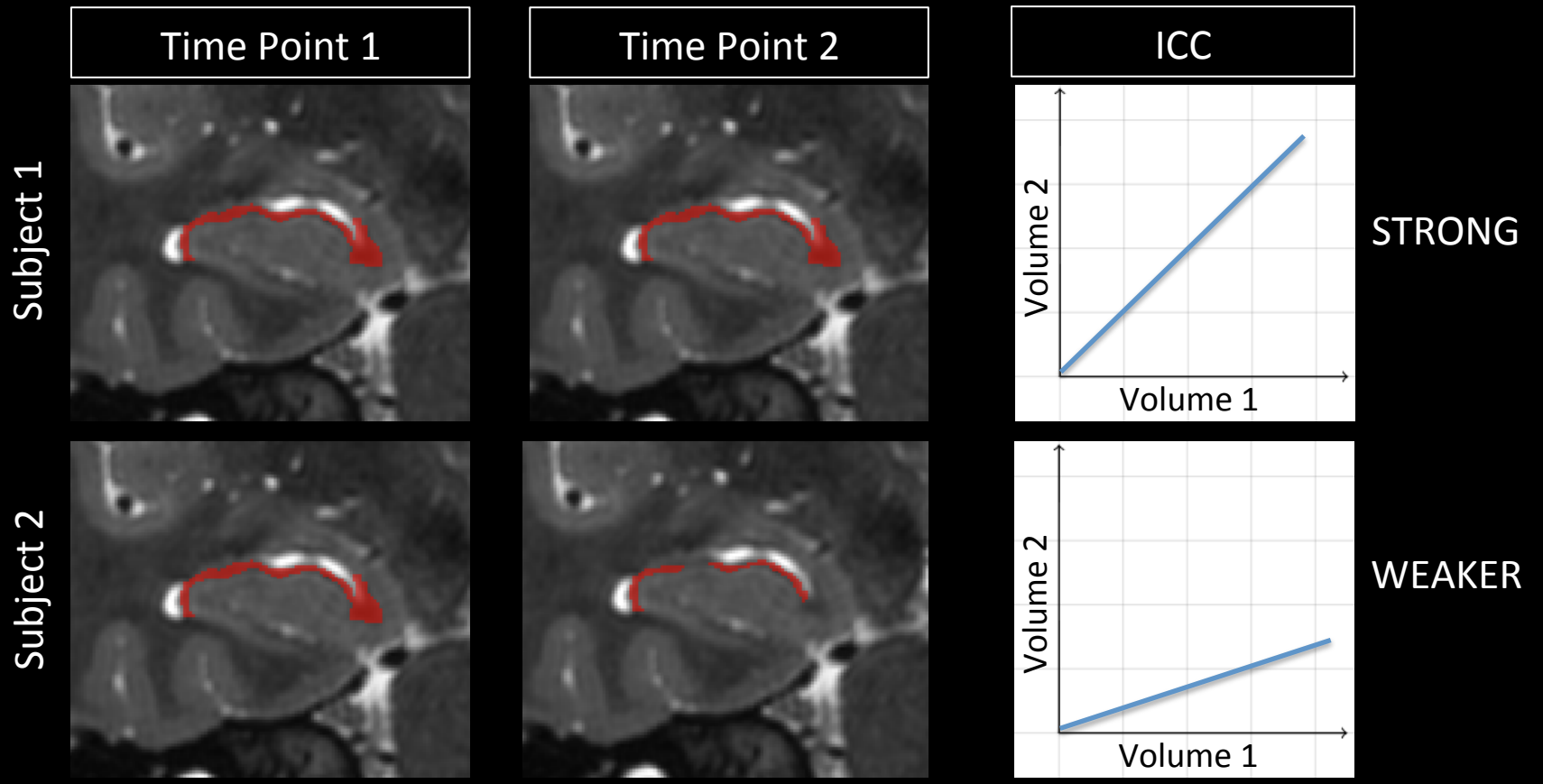
The OASIS Dataset includes 20 individuals who were re-scanned after their initial visit with a delay no longer than 90 days



Assessing Reliability Using Intraclass Correlation (ICC):

A correlation done between the two volumes (i.e. at **timepoint 1** and **timepoint 2**)

0 = no correlation, volumes are not the same
1 = perfect correlation, volumes are the same



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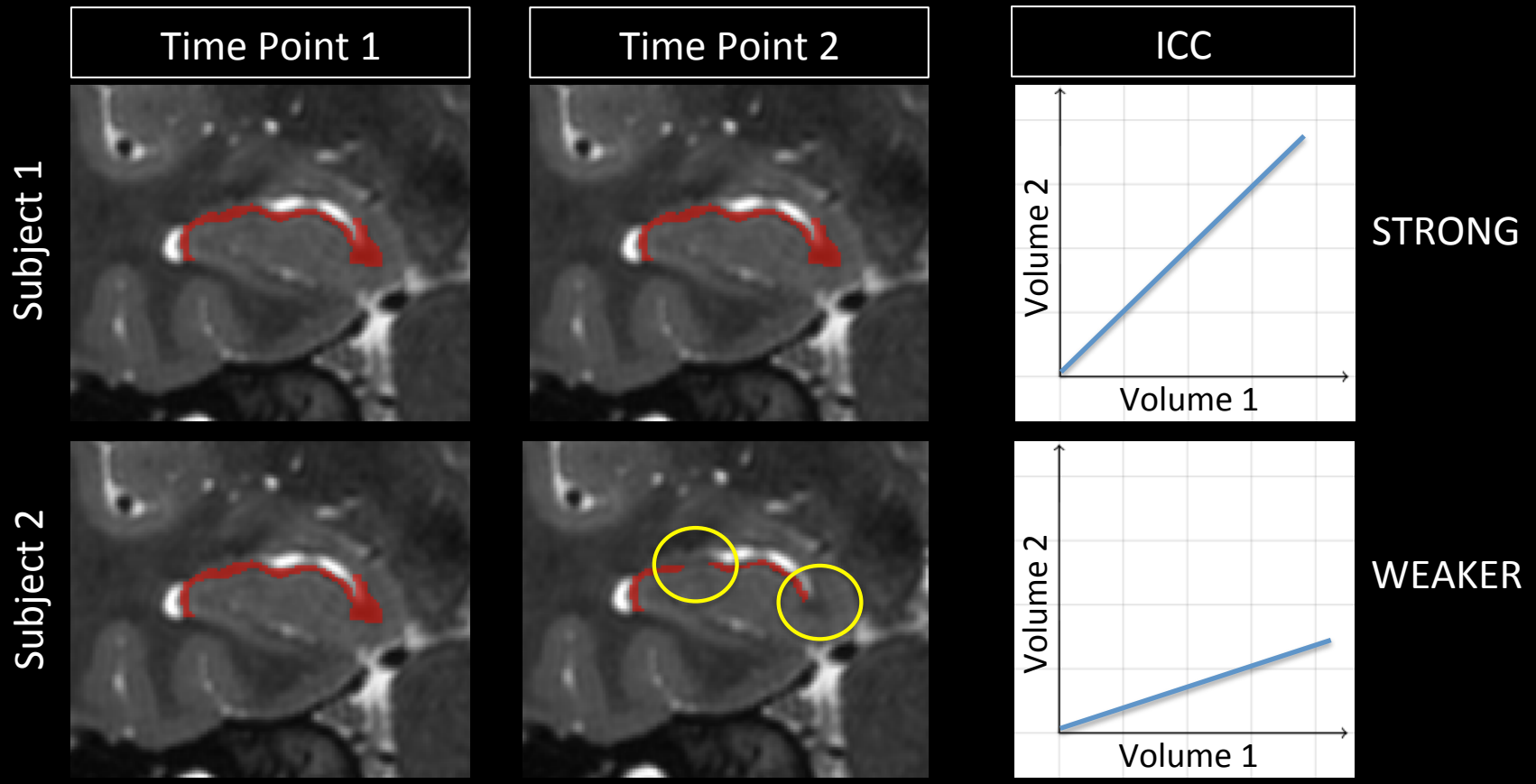


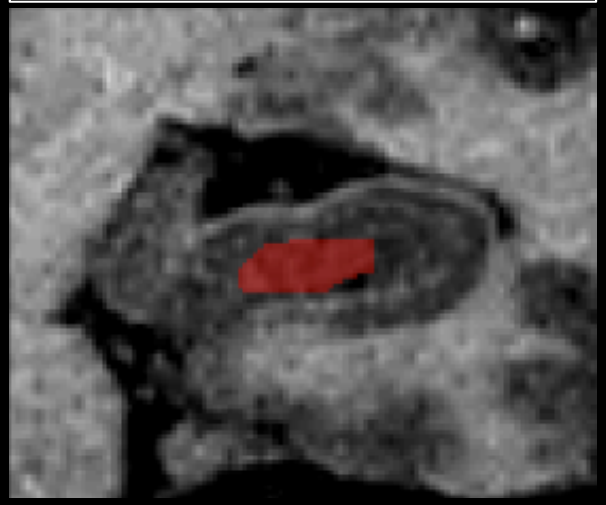
Assessing Reliability Using Intraclass Correlation (ICC) Results:

Structure	Right	Left
Ca1	0.98	0.95
Ca2 & Ca3	0.95	0.94
Dentate Gyrus	0.94	0.96
SLRM	0.96	0.96
Subiculum	0.96	0.96
Mammillary Bodies	0.79	0.85
Alveus	0.96	0.93
Fimbria	0.91	0.96
Fornix	0.99	0.99
White Matter	0.99	0.98
Hippocampus	0.99	0.98
White Matter Bilateral	0.99	
Hippocampus Bilateral	0.99	
TOTAL	0.99	

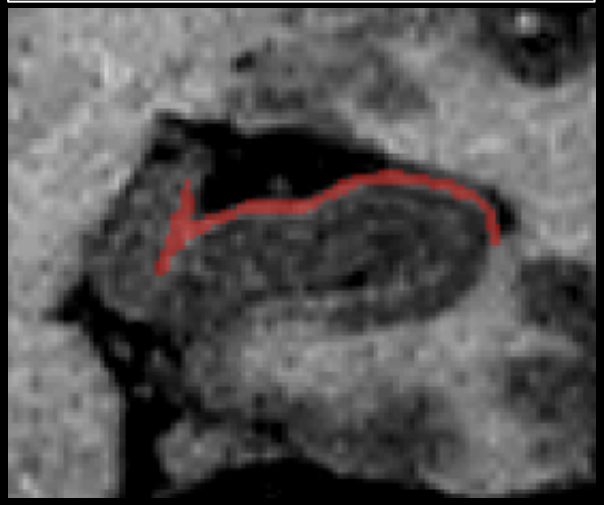
The Caveat of Using ICC

Overlap is **NOT** being measured, rather correlation between volume only

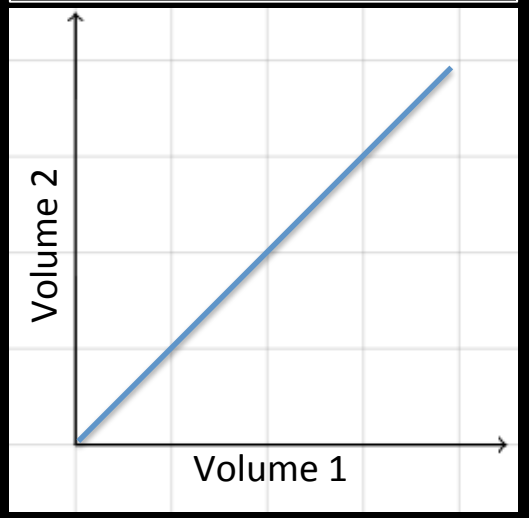
Time Point 1



Time Point 2



ICC



Can we test overlap (Dice's Kappa) for anatomical precision?

Labels produced from Scan 1 were rigidly registered (with 6 degrees of freedom) to their repeat scan (i.e. Scan 2) in order to employ Dice Kappa overlap metric.

Assessing Reliability Using Dice's Kappa:

Structure	Right	Left
Ca1	0.76	0.77
Ca2 & Ca3	0.64	0.63
Dentate Gyrus	0.82	0.84
SLRM	0.65	0.68
Subiculum	0.75	0.73
Mammillary Bodies	0.83	0.81
Alveus	0.61	0.65
Fimbria	0.69	0.73
Fornix	0.79	0.80
White Matter	0.70	0.73
Hippocampus	0.73	0.72
White Matter Bilateral	0.71	
Hippocampus Bilateral	0.73	
TOTAL	0.73	

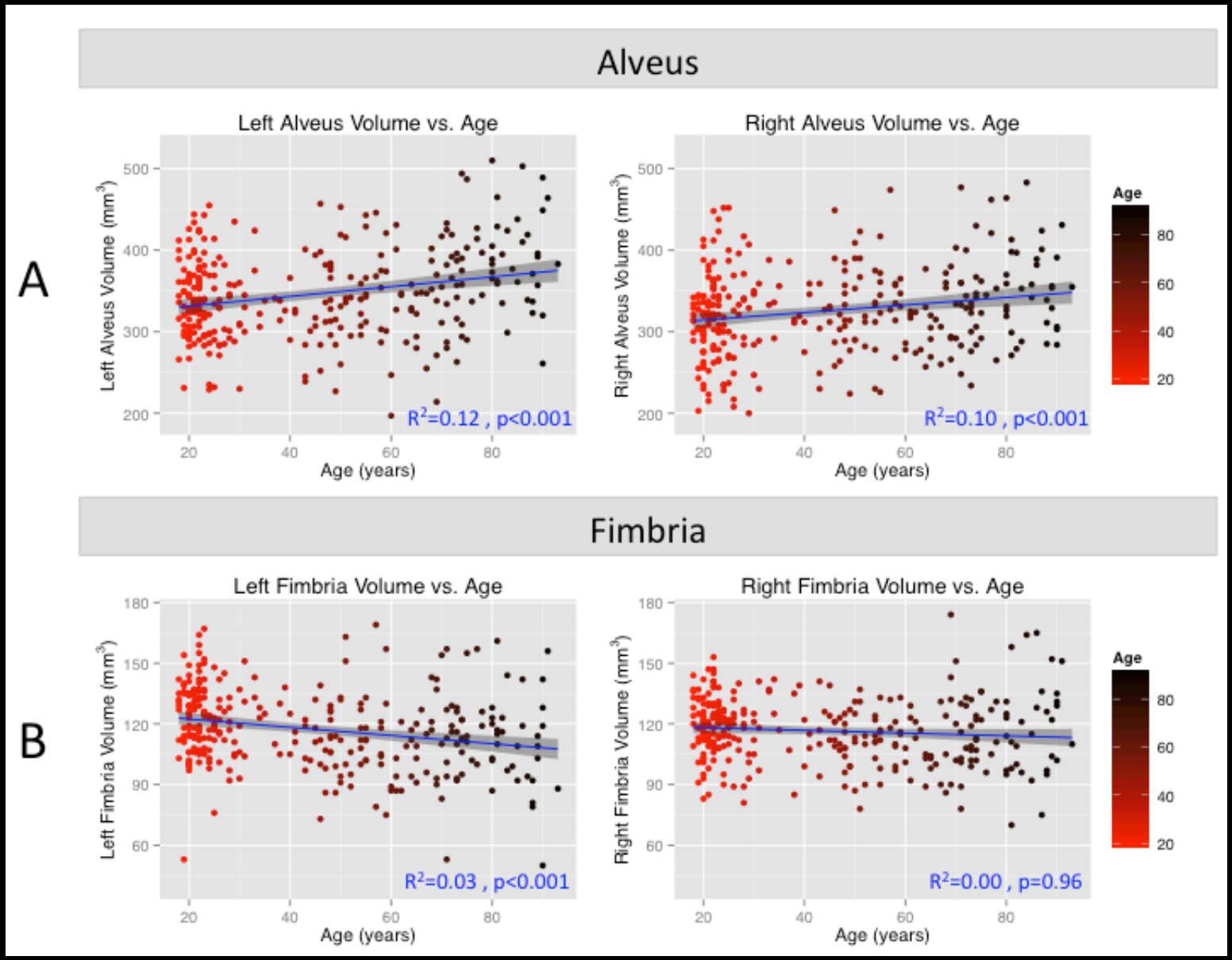
Results

1. OASIS Dataset (Healthy Aging)

2. ADNI Dataset (Pathological aging; AD & MCI)

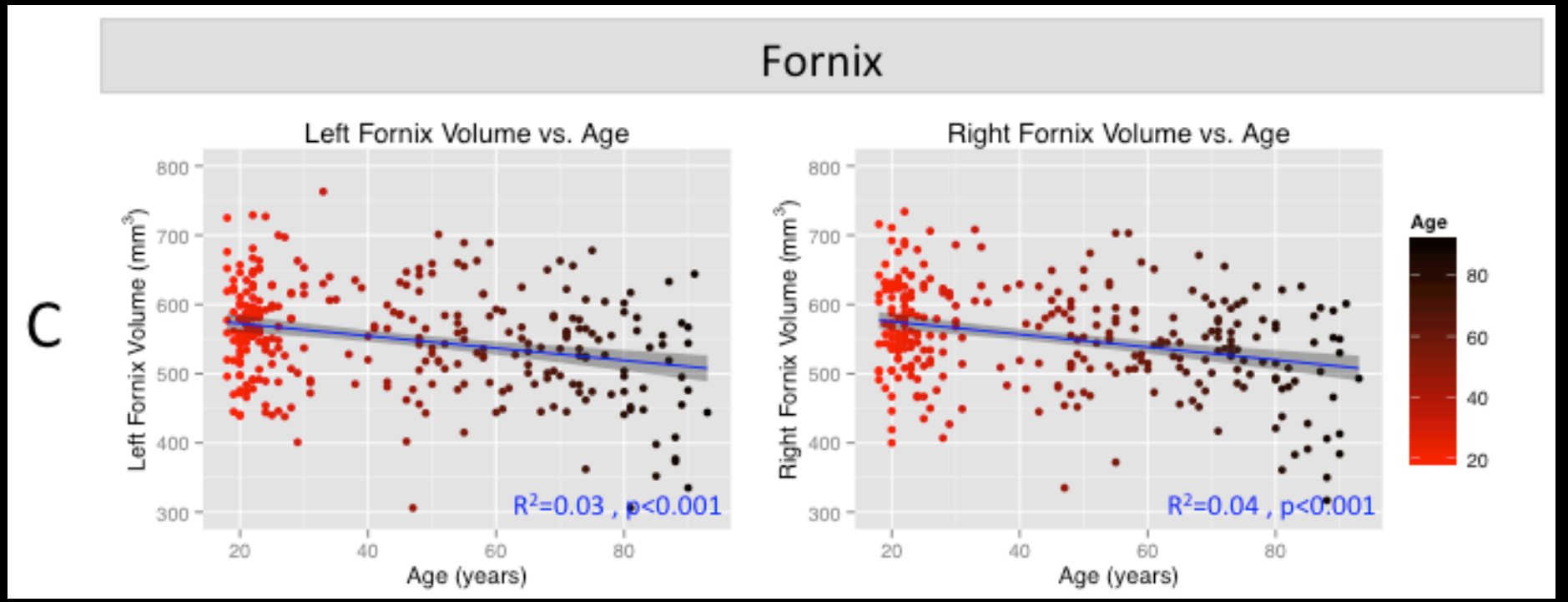
1 – OASIS Dataset

1 - OASIS Dataset (WM)



General Linear model accounting for sex and estimated total intracranial volume (eTIV)

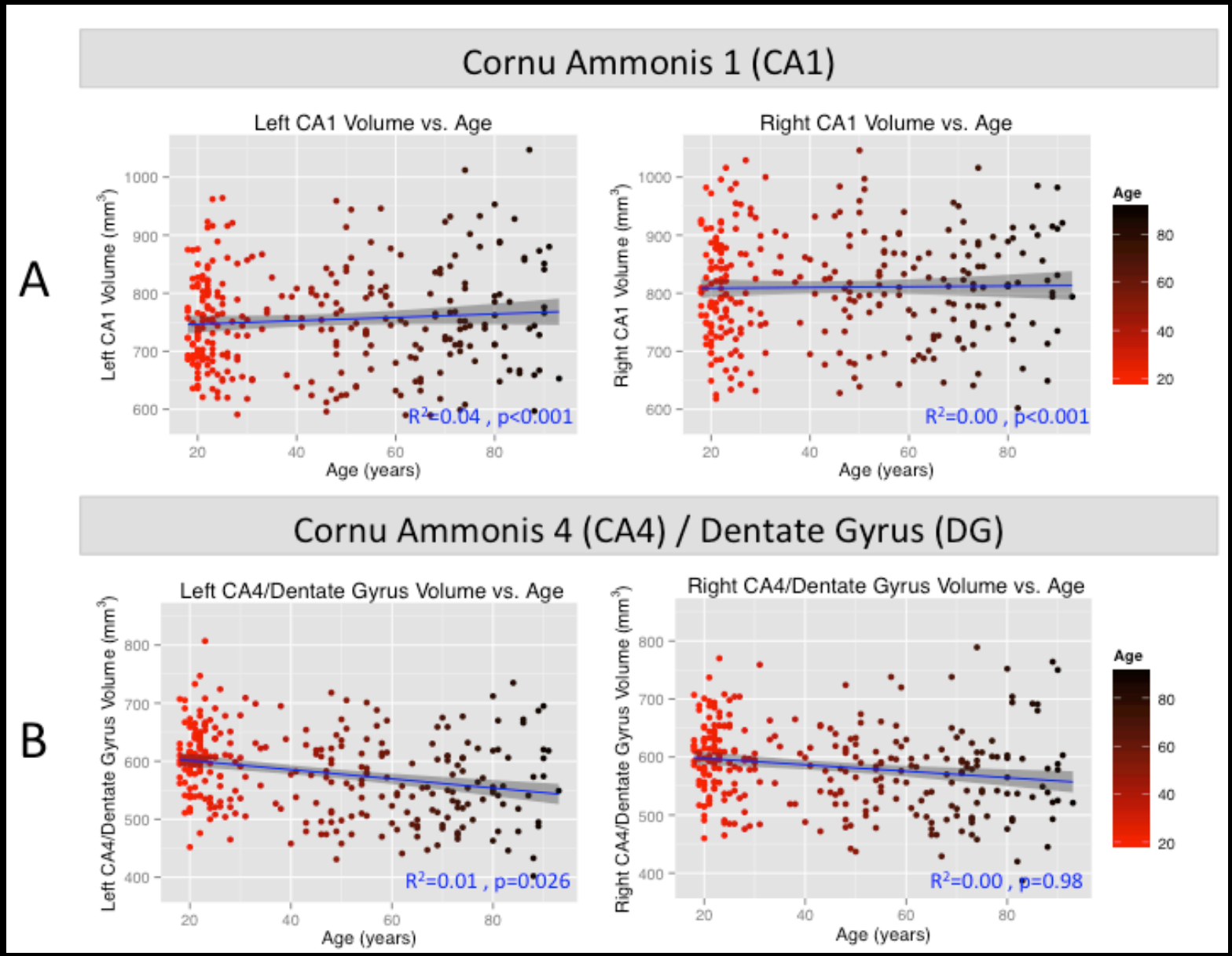
1 - OASIS Dataset (WM)



Finding is consistent with DTI literature supporting decrease in fornix (Chen et al., 2015; Kantarci et al., 2014; Sala et al., 2012)

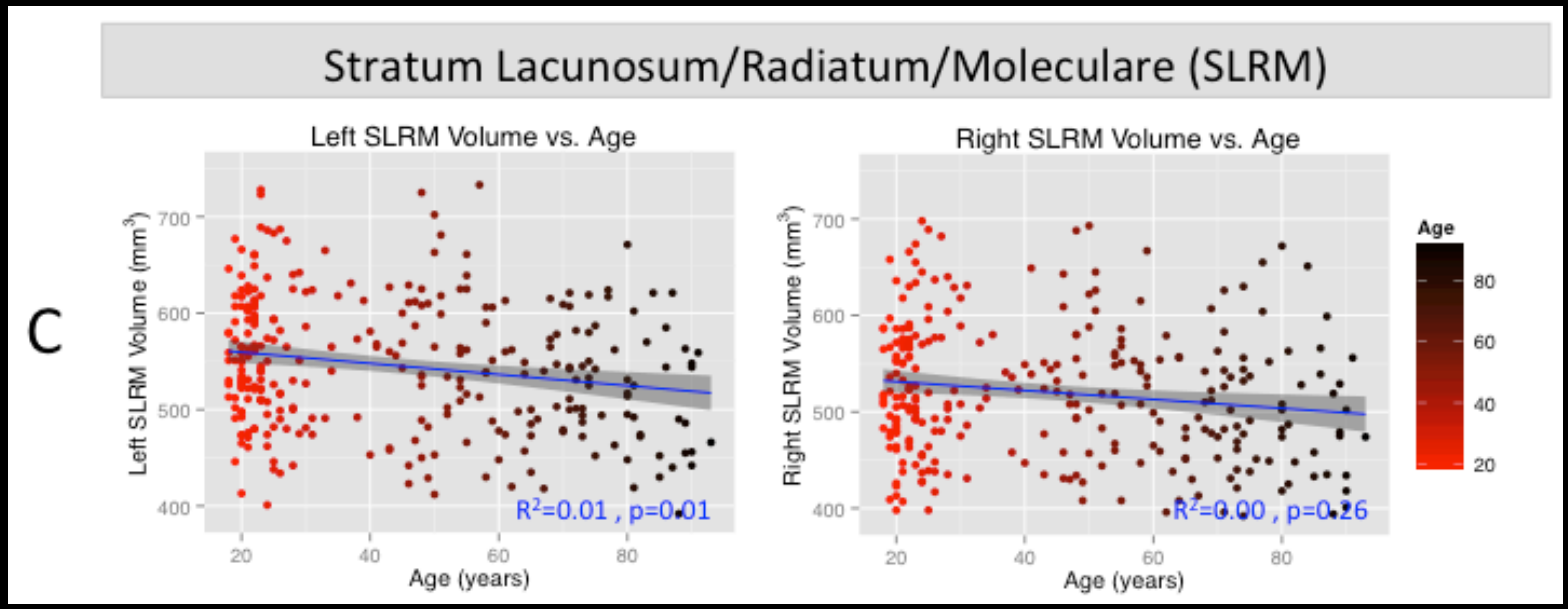
General Linear model accounting for sex and estimated total intracranial volume (eTIV)

1 - OASIS Dataset (HC subfields)



General Linear model accounting for sex and estimated total intracranial volume (eTIV)

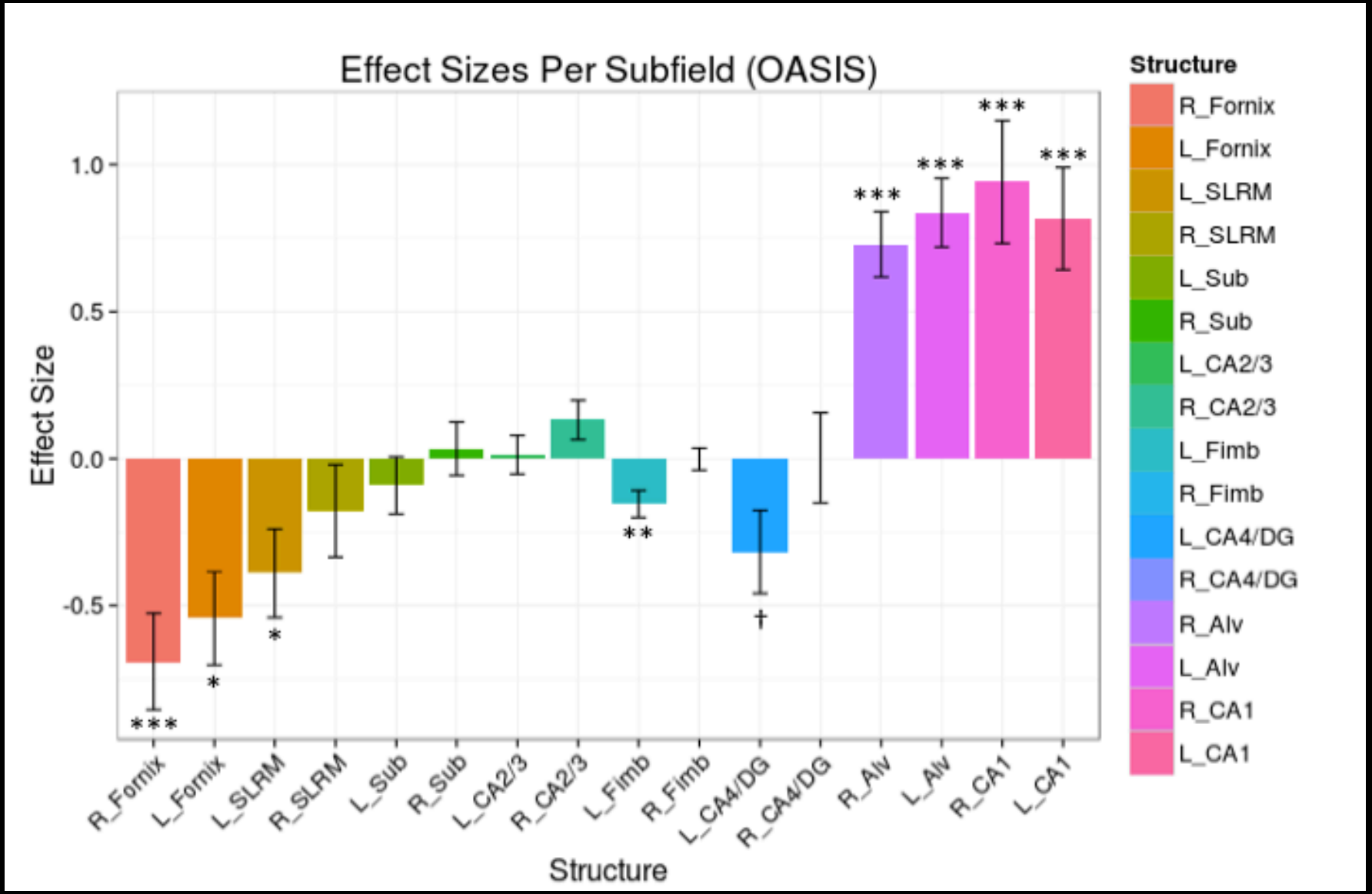
1 - OASIS Dataset (HC subfields)



Past studies indicate Ca1 preservation (i.e. no change; also Ca1 decreases), volume loss in subiculum and Dentate Gyrus/Ca3 regions across healthy aging (Mueller et al., 2007; Mueller & Weiner, 2009; La Jolie et al., 2010)

General Linear model accounting for sex and estimated total intracranial volume (eTIV)

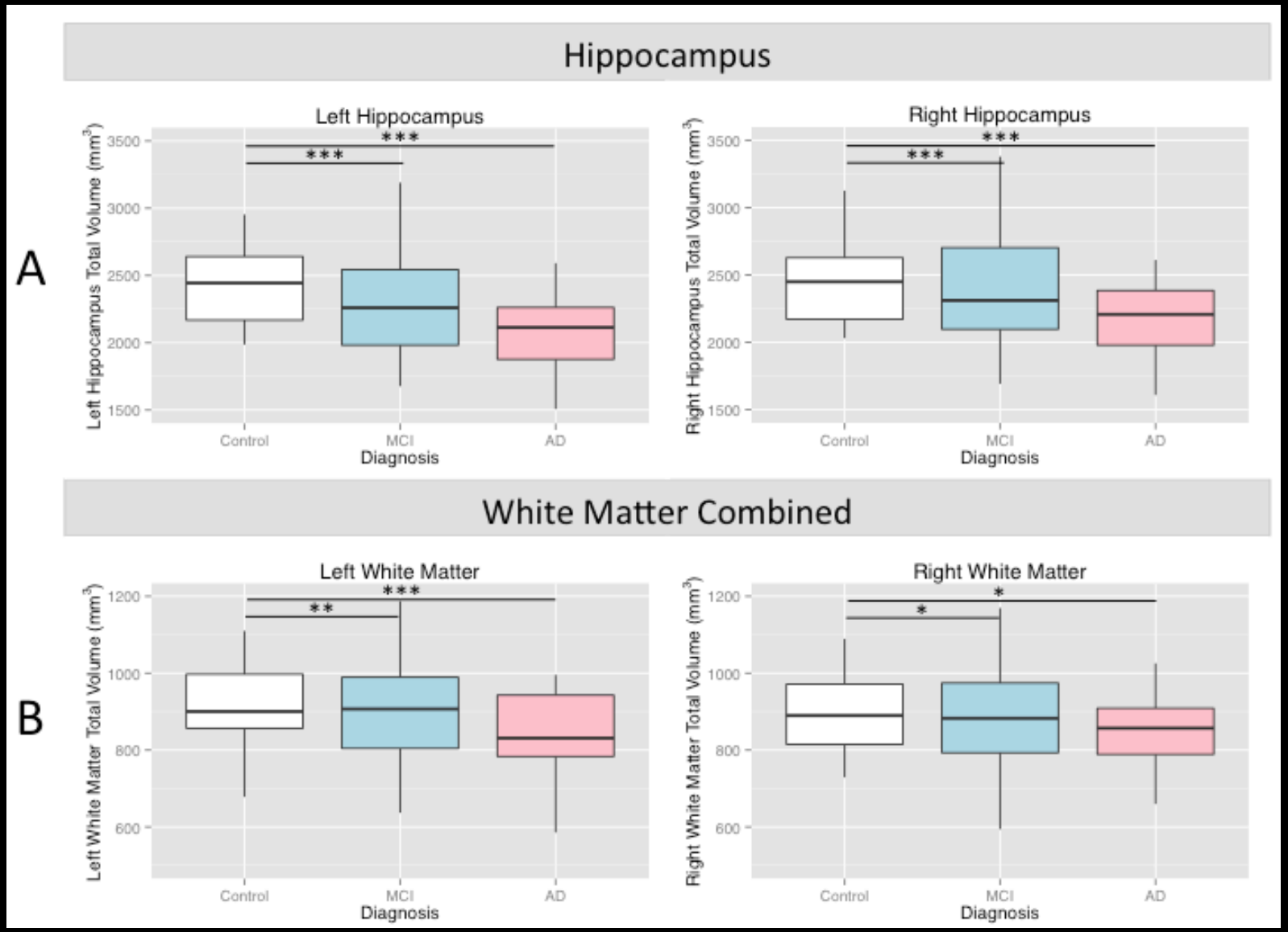
1 - OASIS Dataset: Effect Size



*p<.05, **p<0.01, ***p<0.001, † indicates significance prior to bonferroni correction

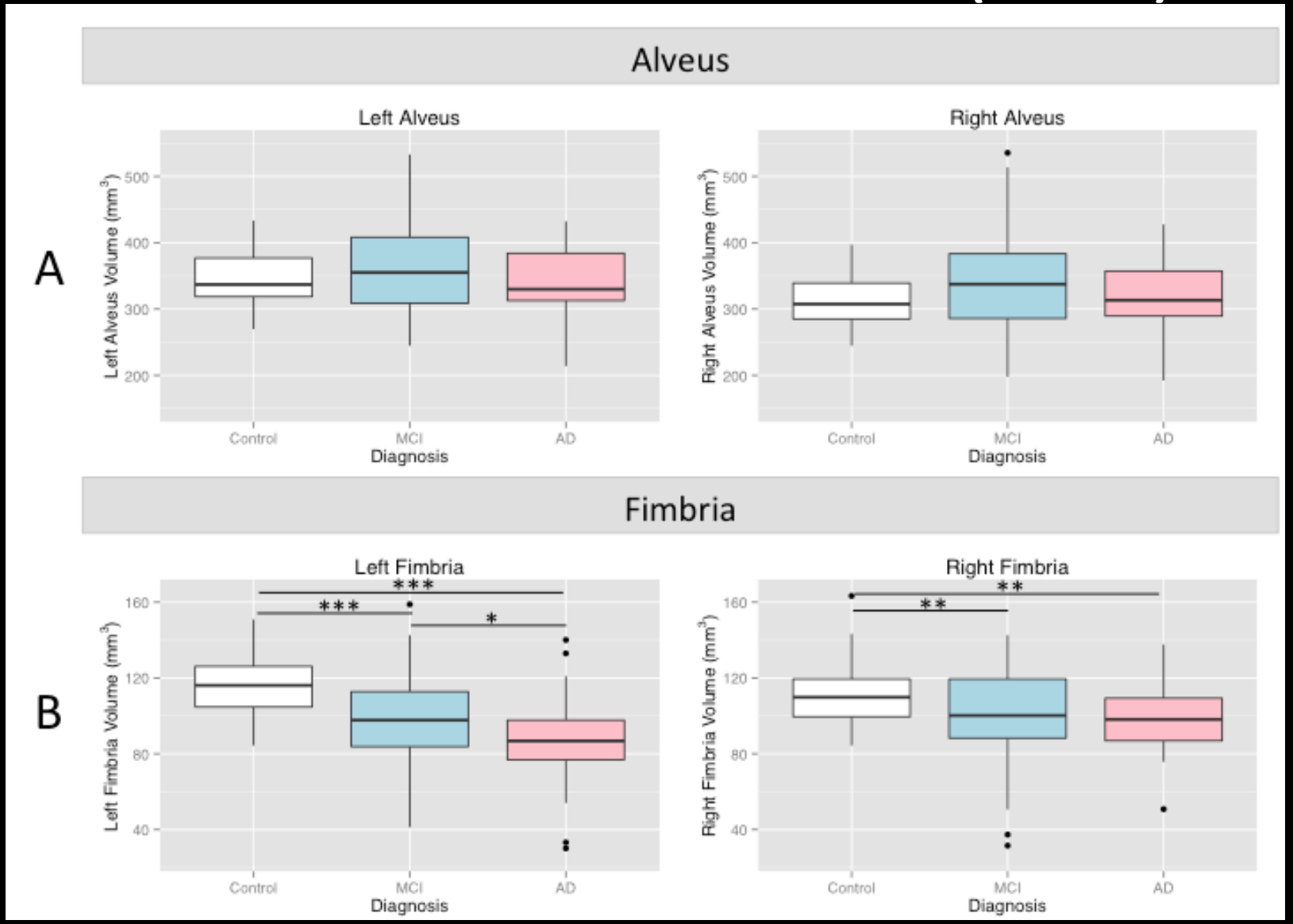
2 – ADNI Dataset

2 – ADNI Dataset



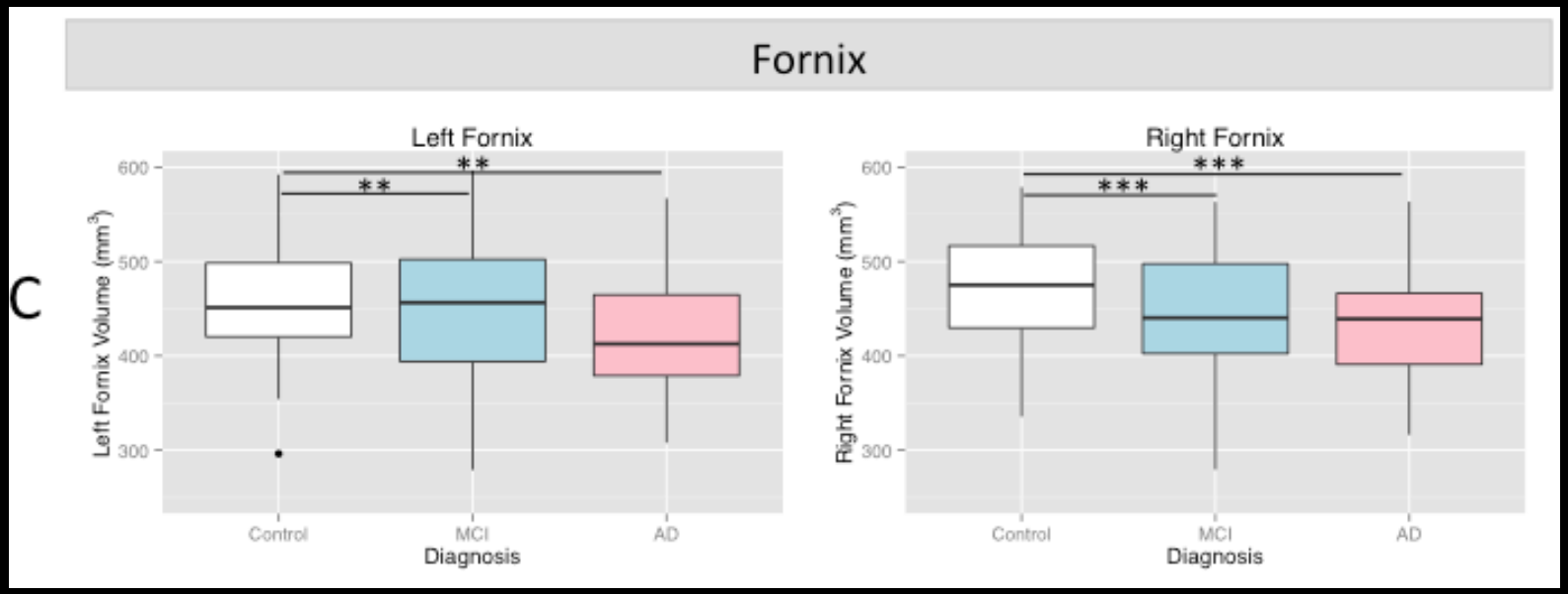
General Linear model accounting for age, sex and estimated total intracranial volume (eTIV)
*p<.05, **p<0.01, ***p<0.001,

2 – ADNI Dataset (WM)



General Linear model accounting for age, sex and estimated total intracranial volume (eTIV)
*p<.05, **p<0.01, ***p<0.001,

2 – ADNI Dataset (WM)



C

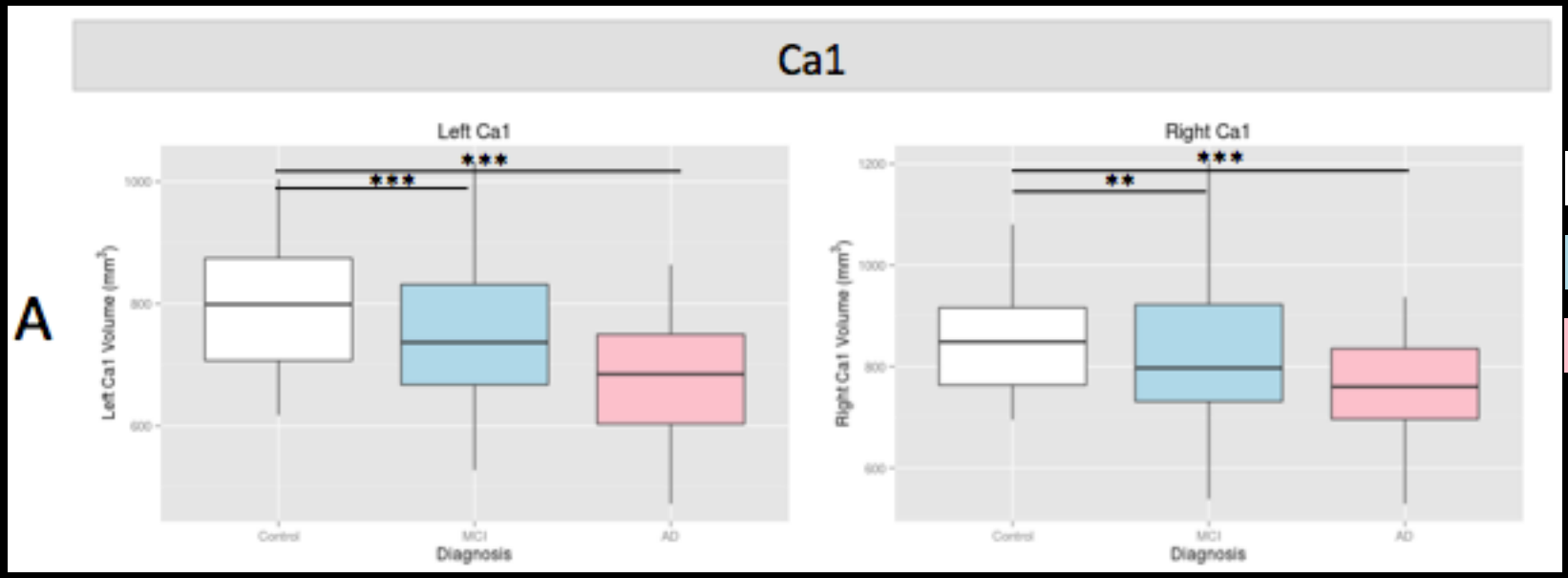
Control
MCI
AD

Hippocampal finding mimicked abundantly in literature (Braak &Braak, 1991; Mouiha &Duchesne, 2011)

Fornix finding also seen prior in DTI literature (Kantarci et al., 2014; Patil et al., 2013)

General Linear model accounting for age, sex and estimated total intracranial volume (eTIV)
*p<.05, **p<0.01, ***p<0.001,

2 – ADNI Dataset (HC)

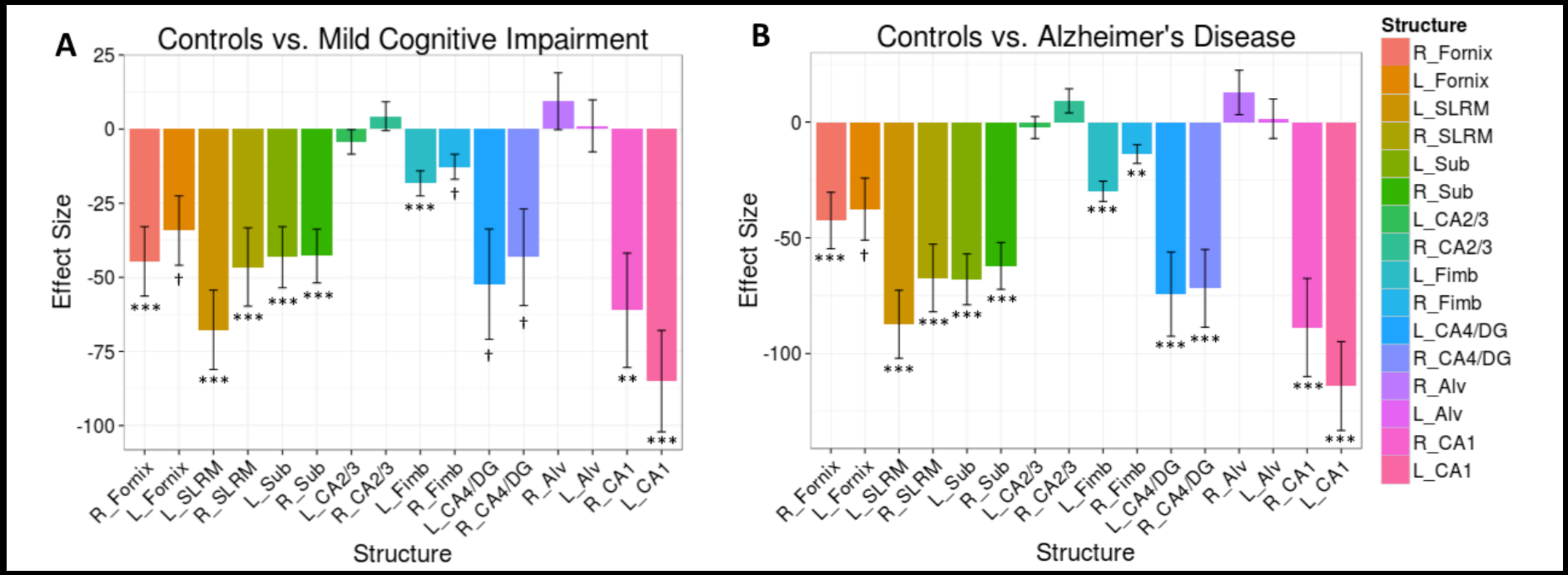


Similar Ca1 results in literature (Christensen et al., 2015)

Ca4/DG, Subiculum, SLRM also found to be significantly different in controls vs AD

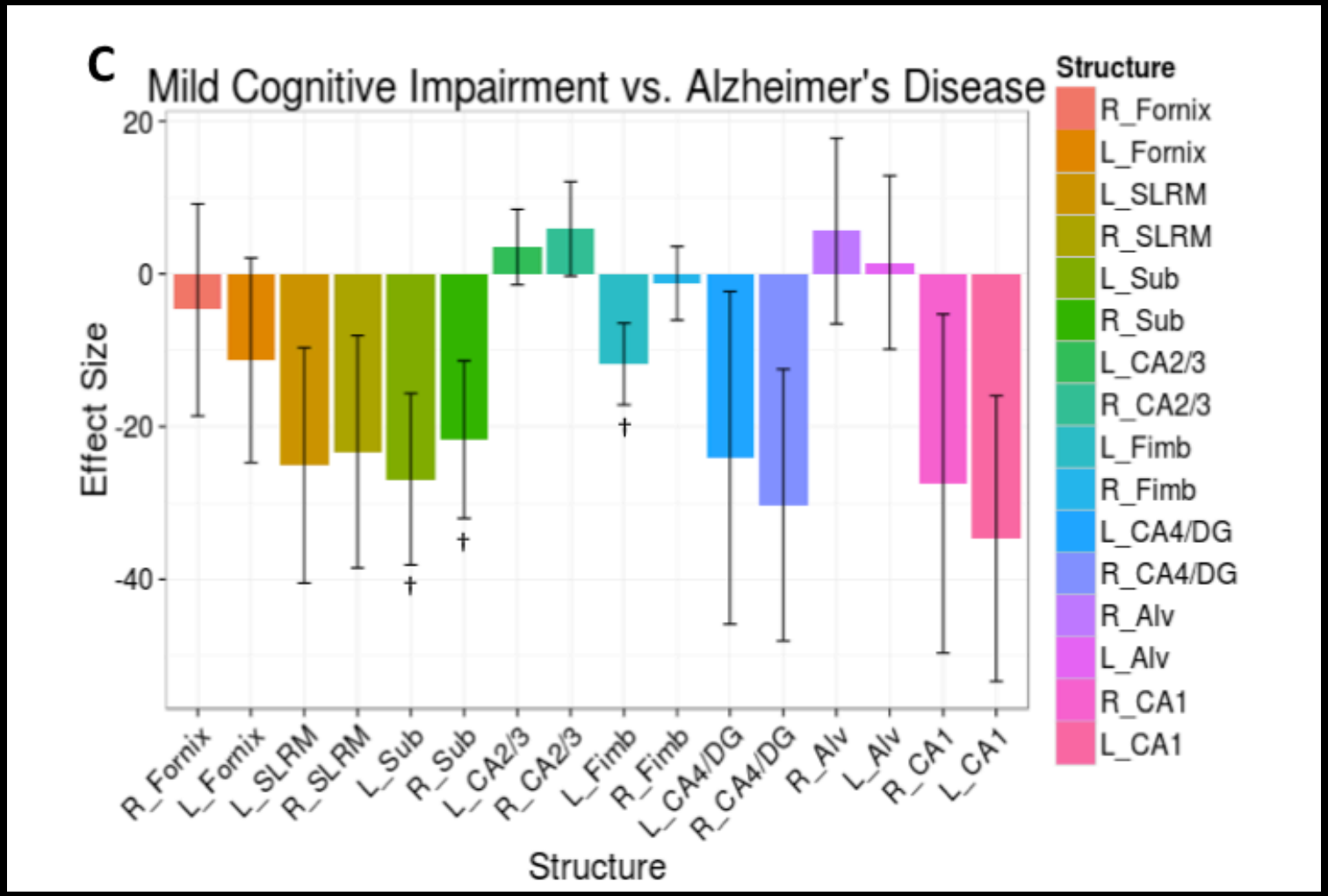
General Linear model accounting for age, sex and estimated total intracranial volume (eTIV)
*p<.05, **p<0.01, ***p<0.001,

2 – ADNI Dataset (Effect Size)



*p<.05, **p<0.01, ***p<0.001, † indicates significance prior to bonferroni correction

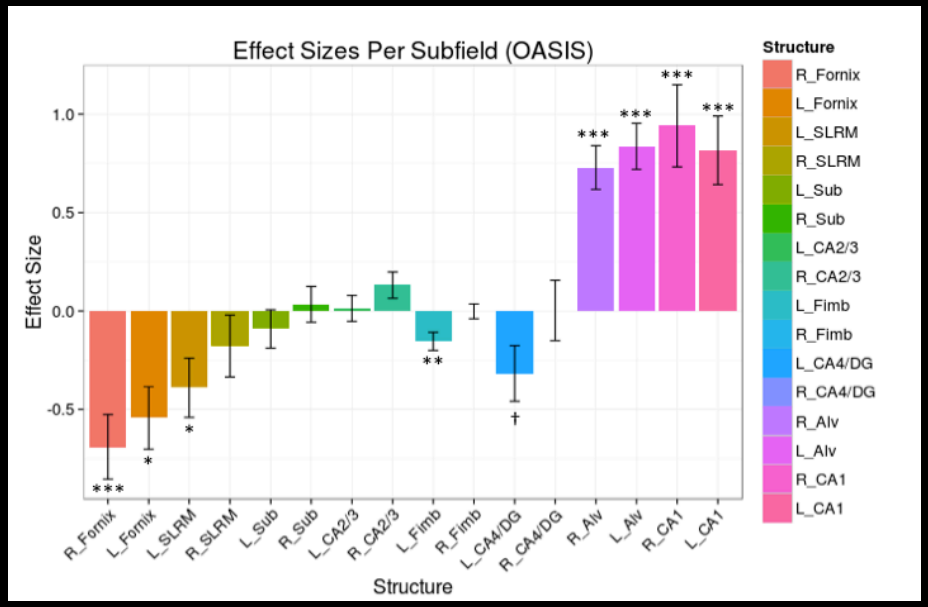
2 – ADNI Dataset (Effect Size)



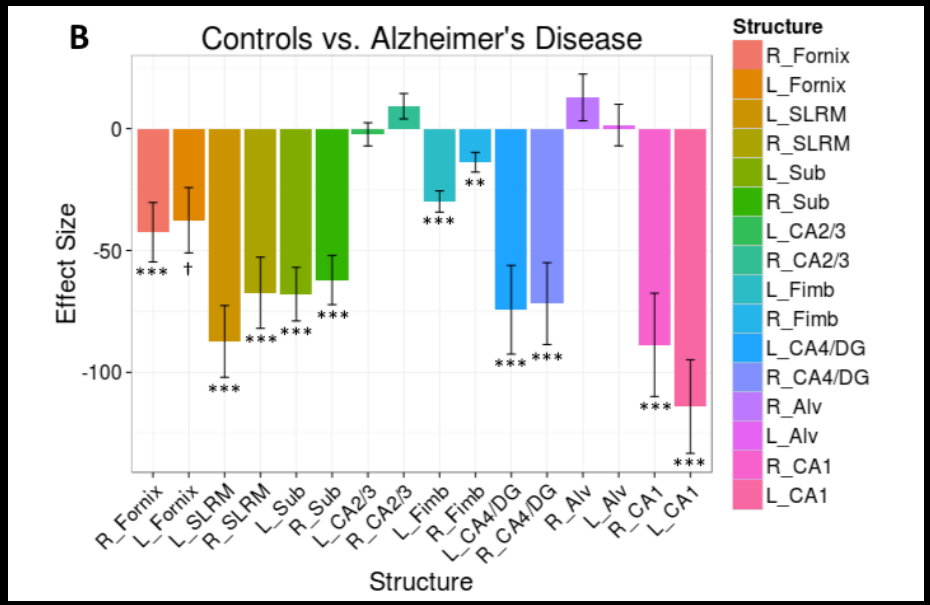
*p<.05, **p<0.01, ***p<0.001, † indicates significance prior to bonferroni correction

Healthy vs Pathological Aging

Healthy Aging



Pathological Aging



*p<.05, **p<0.01, ***p<0.001, † indicates significance prior to bonferroni correction

Summary

- Volumetric changes were evident throughout healthy aging
  - Striking increases in Ca1 subfield and alveus over the course of aging
  - Decreases in fornix, as seen in DTI literature
- Volumetric differences were also present in Controls vs MCI vs AD
  - Compared to controls, AD patients suffered volume loss in fornix and fimbria only
  - Effect size for Ca1 subfield was opposite to healthy aging results
  - No change in alveus were observed
- Such white matter structures may serve as additional biomarkers for disease state, and reveal a marked difference between MCI and AD pathology
- Moreover, specific subfields resistant to age-related change (e.g. Ca1 and alveus), may serve a neuro-protective effect in healthy aging

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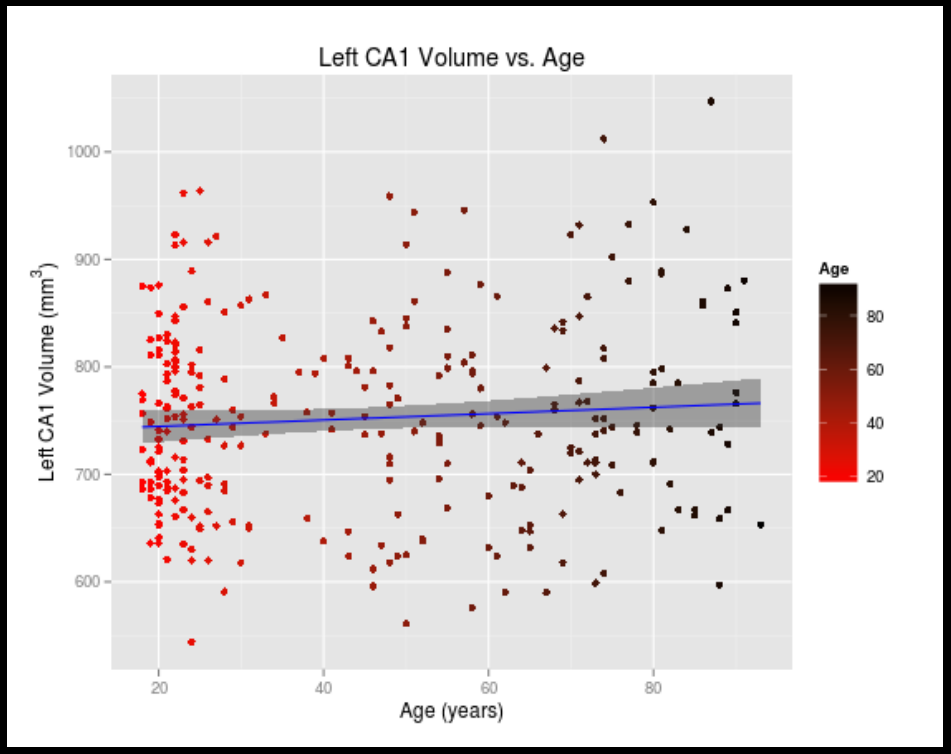
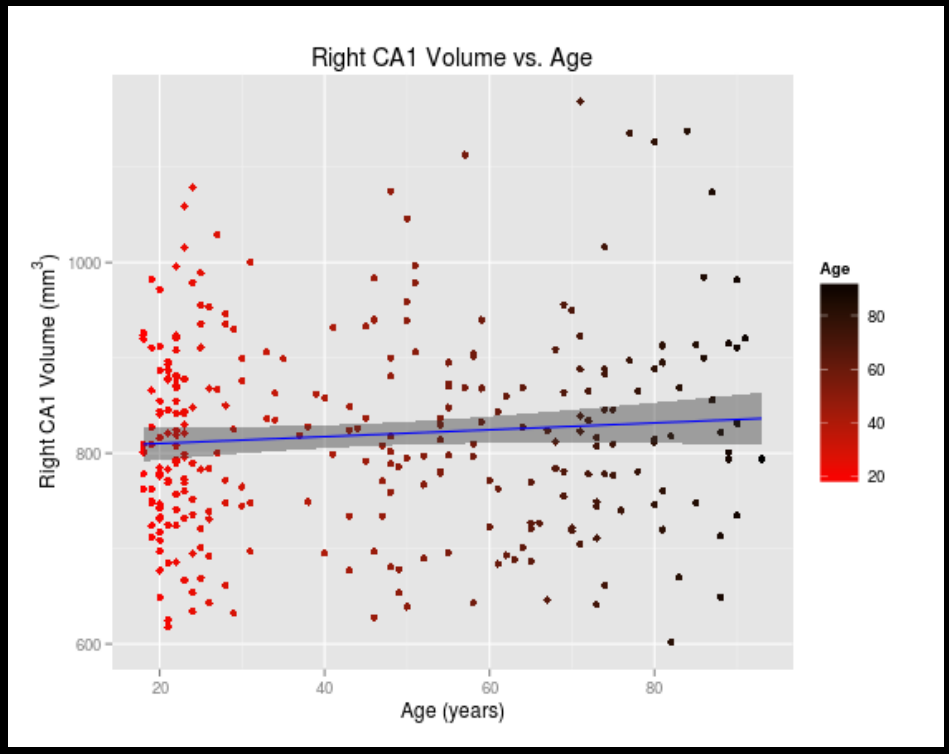

Left CA1 Volume vs. Age
Left CA1 Volume (mm3)
1000
900
800
700
600
20
40
60
80
Age (years)
Age
80
60
40
20


Right CA1 Volume vs. Age
Right CA1 Volume (mm3)
1000
800
600
20
40
60
80
Age (years)
Age
80
60
40
20