AIC – Paris 2011

Impact of Differences among Protocols for Manual Hippocampal Segmentation on Alzheimer's Disease-Related Atrophy: Preparatory Phase for a Harmonized Protocol

M Boccardi, M Bocchetta, R Ganzola, N Robitaille, Gabriele Corbetta, Daniele Tolomeo, P Pasqualetti, A Redolfi, G Bartzokis, R Camicioli, JG Csernansky, MJ de Leon, L deToledo-Morrell, RJ Killiany, S Lehéricy, J Pantel, JC Pruessner, H Soininen, C Watson, S Duchesne, C Jack, GB Frisoni

DISCLOSURES

Funded by Alzheimer's Association grant n. 174022
Funded in part thanks to an unrestricted grant by
Lilly and Wyeth/Pfizer

Bartzokis Research support – Janssen; Consultant - Lilly, Pfizer, Novartis; **Csernansky** Consultant Eli Lilly; **Duchesne** Research support - Agfa HealthCare Inc.; funding as a partner in the project; **Frisoni** Consultant Wyeth; **Jack** Contract – Pfizer; consulting – Élan; **Lehericy** Consultant - EISAI, Janssen-Cilag

BACKGROUND

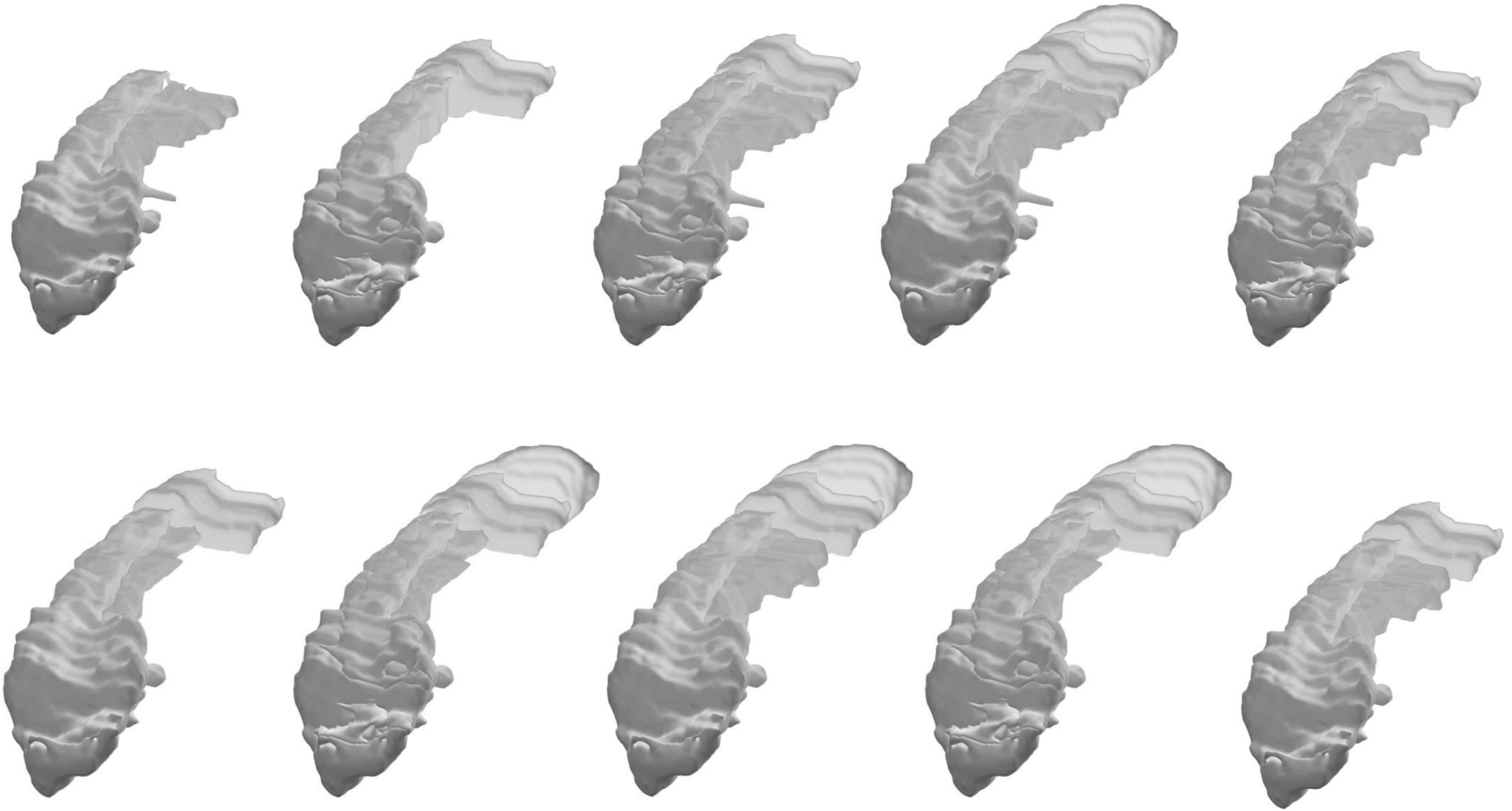
Need of standard hippocampal atrophy quantification:

- Biomarker for early diagnosis

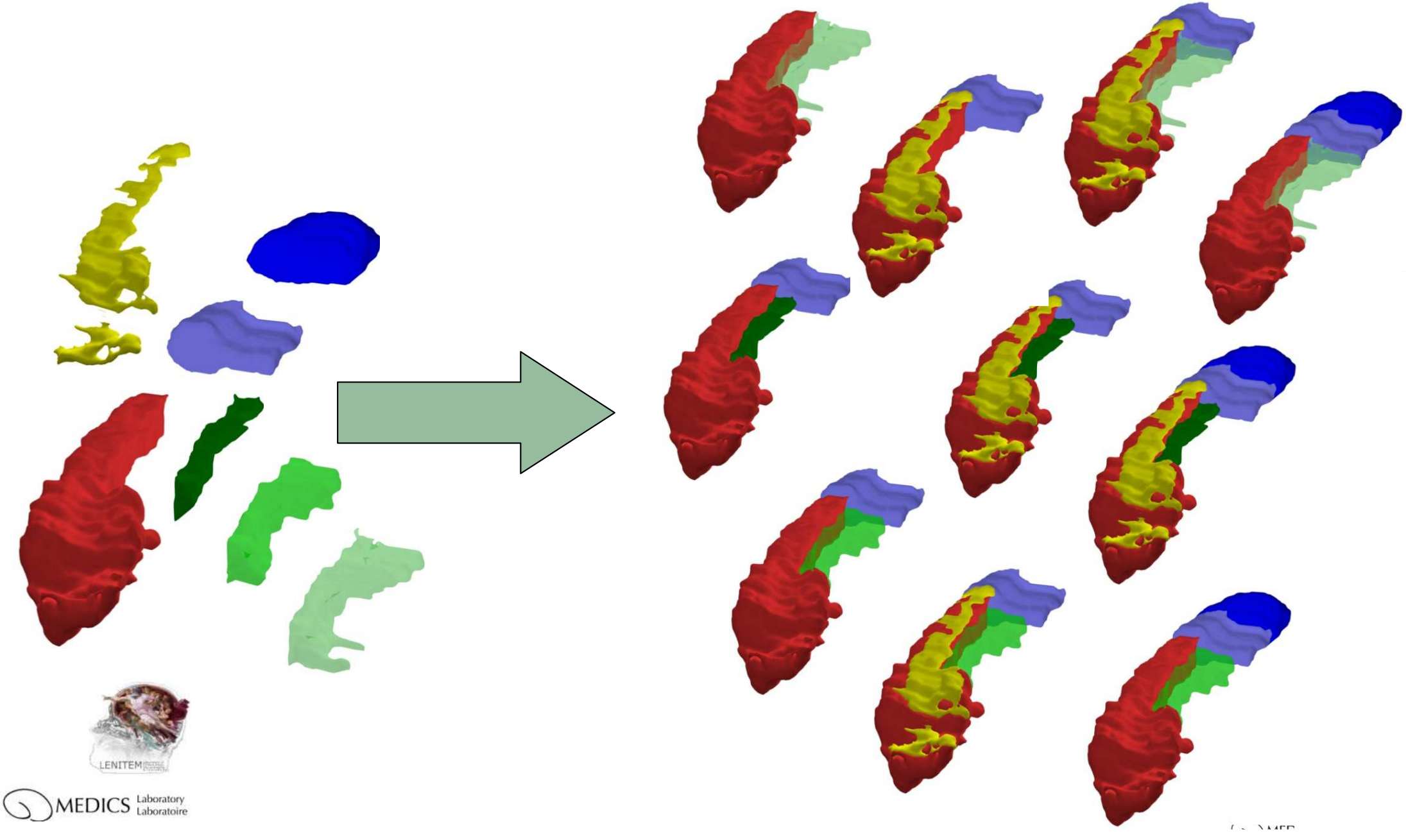
- Surrogate marker tracking disease progression in clinical trials

- Validation of automated segmentation algorithms

HARMONIZED PROTOCOL ?



HARMONIZED PROTOCOL ?

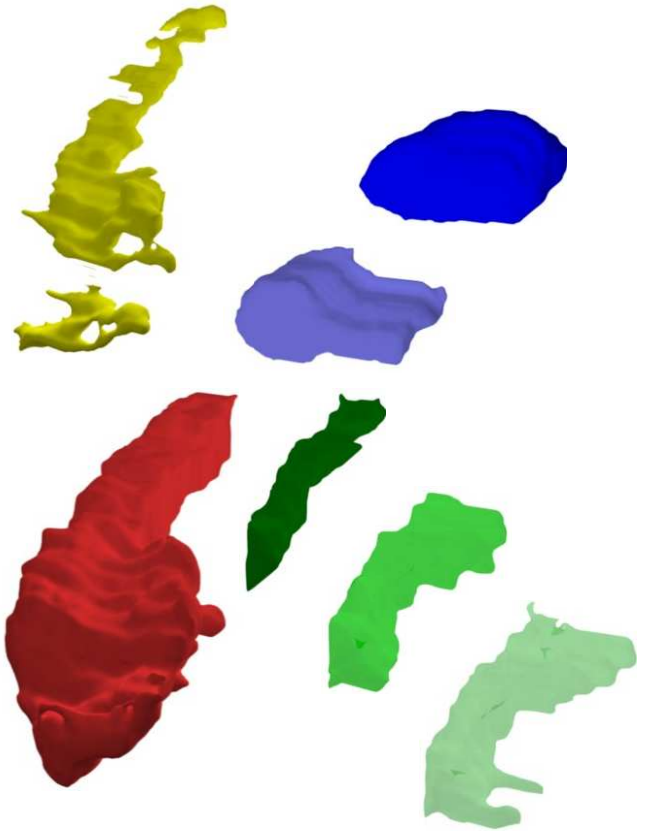


MEDICS Laboratory Laboratoire

AIM

To provide quantitative values about:

test-retest variability
impact on total hippo volume
informativeness for differences
between AD and controls

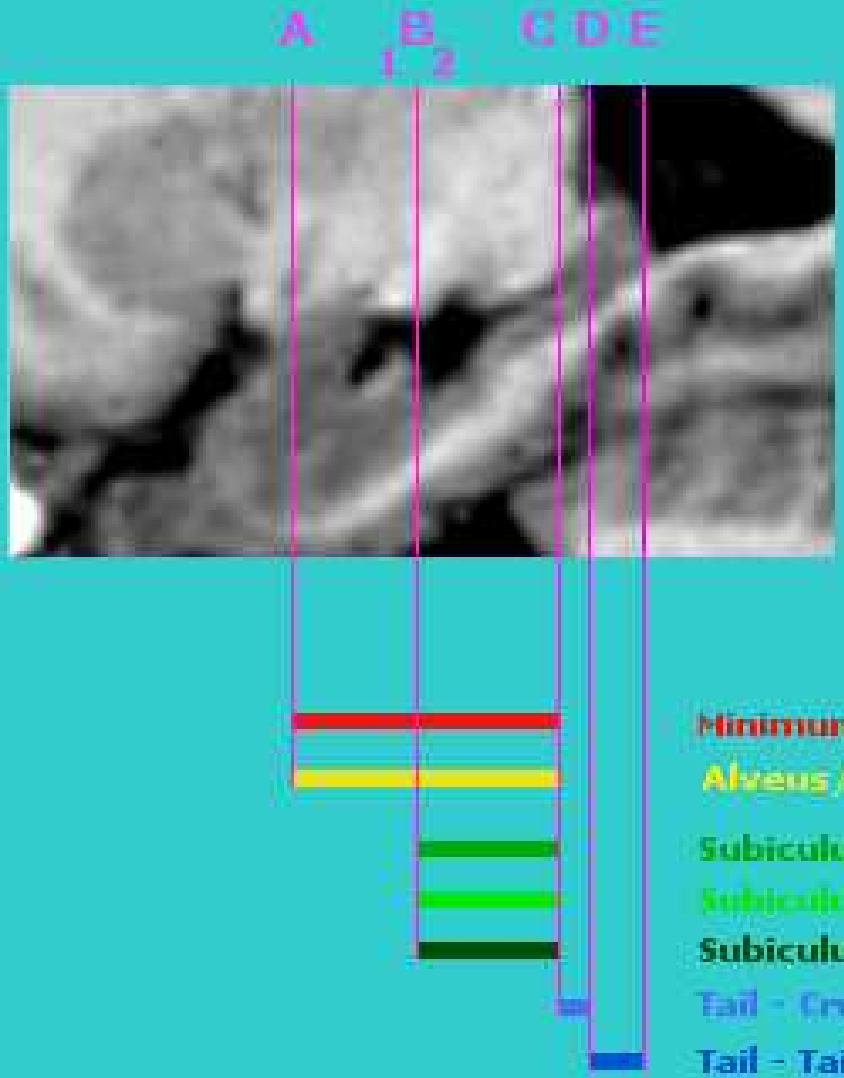


For the Experts participating to the Delphi Panel

Subjects sample

	CTRL (n=31)	MCI (n=23)	AD (n=23)	*p* MCI vs CTRL	*p* AD vs CTRL	*p* MCI vs AD	*p* AD+MCI vs CTRL
Age, years	75.74 (5.18)	76.09 (5.58)	76.30 (5.58)	0.816	0.704	0.895	0.718
Gender, female	15 (48.4%)	11 (47.8%)	11 (47.8%)	0.999	0.999	0.999	0.961
Education, years	15.97 (2.98)	15.57 (3.38)	15.17 (3.38)	0.732	0.791	0.697	0.511
CSF $A\beta_{1-42}$ levels, pg/ml	242.68 (25.21)	133.74 (23.36)	136.04 (26.25)	<0.0005	<0.0005	0.755	<0.0005

3)

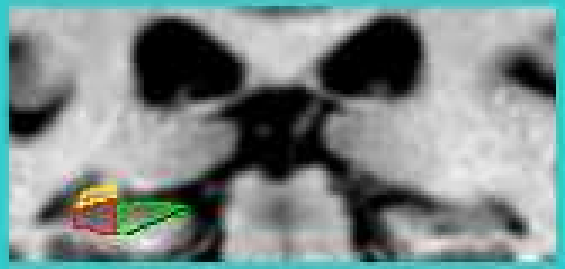

A
B1
B2
C
D
E
Minimum Hippocampus
Alveus/Fimbria
Subiculum - Horizontal Line
Subiculum - Morphology
Subiculum - Oblique Line
Tail - Crura
Tail - Tail End

A

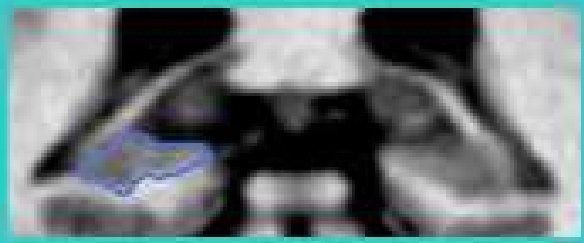
B 1

2

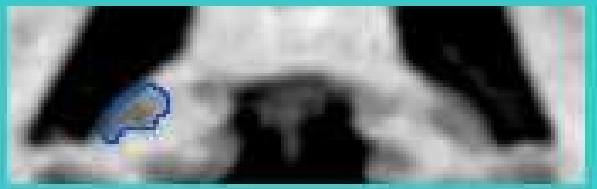
C



D



E



LEFT HIPPOCAMPUS							
	CTRL (n=31)	**MCI (n=23)**	**AD (n=23)**	***p*** **MCI vs CTRL**	***p*** **AD vs CTRL**	***p*** **MCI vs AD**	***p*** **AD+MCI vs CTRL**
MinH	1467 (204)	1122 (263)	1023 (251)	<0,0005	<0,0005	0,199	<0,0005
Alveus/fimbria	248 (45)	232 (61)	200 (48)	0,269	<0,0005	0,055	0,01
Subiculum	243 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Oblique line	196 (67)	178 (66)	176 (53)	0,338	0,262	0,936	0,207
Morphology	243 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Horizontal line	234 (72)	210 (78)	211 (62)	0,243	0,221	0,957	0,153
Tail	485 (131)	383 (99)	353 (101)	0,003	<0,0005	0,307	<0,0005
Crura	190 (74)	177 (70)	146 (69)	0,538	0,034	0,14	0,101
End Tail	296 (120)	206 (76)	206 (86)	0,003	0,004	0,984	<0,0005
MaxHV	2443 (291)	1957 (348)	1788 (342)	<0,0005	<0,0005	0,105	<0,0005
RIGHT HIPPOCAMPUS							
	CTRL (n=31)	**MCI (n=23)**	**AD (n=23)**	***p*** **MCI vs CTRL**	***p*** **AD vs CTRL**	***p*** **MCI vs AD**	***p*** **AD+MCI vs CTRL**
MinH	1462 (232)	1214 (247)	1061 (241)	<0,0005	<0,0005	0,039	<0,0005
Alveus/fimbria	255 (47)	258 (71)	225 (65)	0,84	0,05	0,103	0,35
Subiculum	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Oblique line	181 (67)	167 (71)	150 (46)	0,455	0,059	0,334	0,122
Morphology	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Horizontal line	220 (78)	203 (83)	182 (54)	0,459	0,053	0,309	0,117
Tail	487 (151)	349 (115)	349 (131)	0,001	0,001	0,999	<0,0005
Crura	187 (75)	169 (68)	140 (69)	0,37	0,025	0,17	0,058
End Tail	301 (120)	181 (113)	209 (110)	<0,0005	0,006	0,394	<0,0005
MaxHV	2429 (303)	2029 (372)	1820 (369)	<0,0005	<0,0005	0,062	<0,0005

LEFT HIPPOCAMPUS

	CTRL (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTRL	% MCI vs CTRL (impact)	% diff AD vs CTRL	% AD vs CTRL (impact)
MinH	1467 (204)	60%	1122 (263)	1023 (251)	23,5%	71%	30%	68%
Alveus/fimbria	248 (45)	10%	232 (61)	200 (48)	6,5%	3%	19%	7%
Subiculum	243 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	4,5%
Oblique line	196 (67)	8%	178 (66)	176 (53)	9%	3,5%	10%	3%
Morphology	243 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	4,5%
Horizontal line	234 (72)	9%	210 (78)	211 (62)	10%	5%	10%	3,5%
Tail	485 (131)	20%	383 (99)	353 (101)	21%	21%	27%	20,5%
Crura	190 (74)	8%	177 (70)	146 (69)	6,5%	2,5%	23%	6,5%
End Tail	296 (120)	12%	206 (76)	206 (86)	30%	18,5%	30%	14%
MaxHV	2443 (291)	100%	1957 (348)	1788 (342)	20%	100%	27%	100%

RIGHT HIPPOCAMPUS

	CTRL (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTRL	% MCI vs CTRL (impact)	% diff AD vs CTRL	% AD vs CTRL (impact)
MinH	1462 (232)	60%	1214 (247)	1061 (241)	17%	62%	27%	66%
Alveus/fimbria	255 (47)	11%	258 (71)	225 (65)	-1%	-0,5%	12%	5%
Subiculum	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Oblique line	181 (67)	8%	167 (71)	150 (46)	8%	3,5%	17%	5%
Morphology	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Horizontal line	220 (78)	9%	203 (83)	182 (54)	7,5%	4%	17%	6%
Tail	487 (151)	20%	349 (115)	349 (131)	28,5%	34,5%	28,5%	22,5%
Crura	187 (75)	8%	169 (68)	140 (69)	10%	4,5%	25%	7,5%
End Tail	301 (120)	12%	181 (113)	209 (110)	40%	30%	31%	15%
MaxHV	2429 (303)	100%	2029 (372)	1820 (369)	16,5%	100%	25%	100%

Poster presentations:
Sunday, July 17: Markers for disease tracking, P1-299
Wednesday, July 20: Hot topics, P4-350

Estimating the Impact of Differences among Protocols for Manual Hippocampal Segmentation on Alzheimer's Disease-Related Atrophy: Preparatory Phase for a Harmonized Protocol

Marina Boccardi, Martina Bocchetta, Rossana Ganzola, Nicolas Robitaille, Alberto Redolfi, George Bartzokis, Richard Camicioli, John G. Csernansky, Mony J. de Leon, Leyla deToledo-Morrell, Ronald J. Killiany, Stéphane Lehéricy, Johannes Pantel, Jens C. Pruessner, Hilkka Soininen, Craig Watson, Simon Duchesne, Clifford R. Jack Jr, Giovanni B Frisoni.

LENITEM (Laboratory of Epidemiology, Neuroimaging and Telemedicine) IRCCS – S. Giovanni di Dio – Fatebenefratelli Brescia, Italy (MB, MBocch, RG, AR, GBF); Department of Radiology, Université Laval and Centre de Recherche Université Laval – Robert Giffard, Quebec City, Canada (NR, SD); Department of Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA (GB); Department of Biomedical Engineering, Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada. (RC); Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (JGC); New York University School of Medicine, Center for Brain Health, New York, NY (MJdL); Dept. of Neurological Sciences, Rush University, Chicago, Illinois (LdTM); Department of Anatomy and Neurobiology, Boston University School of Medicine (RJK); Center for Neuroimaging Research - CENIR and Dept of Neuroradiology, Université Pierre et Marie Curie-Paris 6, Groupe Hospitalier Pitié-Salpêtrière, Paris, France (SL); Department of psychiatry and Psychoterapy, University of Frankfurt/Main, Germany (JP); McGill Centre for Studies in Aging, Department of Psychiatry, McGill University, Montreal, Quebec, Canada (JCP); Dept of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland (HS). Wayne State University School of Medicine, 8D-University Health Center, St. Antoine, Detroit, MI (CW); Department of Diagnostic Radiology, Mayo Clinic and Foundation, Rochester, MN (CJ)

Introduction

To quantify the impact of the differences among Magnetic Resonance Imaging (MRI)-based hippocampal segmentation protocols on volume estimates of Alzheimer's disease (AD)-related atrophy, in order to support evidence-based decisions for an internationally harmonized protocol. A harmonized procedure is required, since quantitative MRI should help diagnosis and tracking of AD. A survey of segmentation protocols allowed to operationalize the landmarks variability into segmentation units (SUs) (Figure), and their impact on volume estimates has been preliminarily quantified.

Methods

A power analysis was carried out on a preliminary sample of 20 ADNI subjects (4 by each degree of severity of hippocampal atrophy at the visual scale by Scheltens et al., 1992), to define the sample size allowing reliable computation. Then, we manually traced each SU within the right and left hippocampi of a sample of 77 *Alzheimer's Disease Neuroimaging Initiative* (ADNI) participants, which included Mild Cognitive Impairment (MCI) patients who subsequently converted to AD and AD patients, all with abnormal Cerebrospinal Fluid (CSF) Aβ levels, and controls (CTRL), with normal CSF Aβ levels.

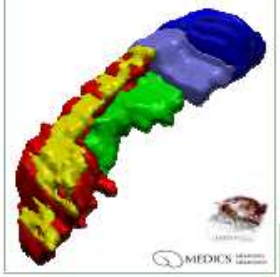
Results

The power analysis indicated a required sample size for the quantification of SUs impact on AD-related volume differences of n=77 (31 CTRL, 23 MCI, 23 AD). The average volume difference between patients and controls was 538 mm3, with Minimum Hippocampus (red SU in Figure) contributing to over 66% of this difference, Tail (blue SUs in Figure) over 20%, Alveus/Fimbria (yellow SU in Figure) 6%, Subiculum (green SUs in Figure) over 5%. The SU volume differences between patients and controls were significant for all SUs except the Subiculum.

Intra- and inter-rater reliability of SUs computed on 20 ADNI subjects (4 by each degree of severity of hippocampal atrophy at the visual scale by Scheltens et al., 1992)

	Intra-rater	Inter-rater
MinH	0.992	0.974
Alveus/fimbria	0.863	0.885
MinH+Alveus/fimbria	0.993	0.973
Subiculum		
Oblique line	0.964	0.907
Morphology	0.981	0.937
Horizontal line	0.980	0.932
Tail		
Crura	0.998	0.937
Tail End	0.988	0.905

Rendering of the Preliminary Harmonized Hippocampus, composed by the sum of all SUs chosen by the majority of panelists. This is a preliminary result from the first round of the Delphi Panel. Details and other issues regarding the tracing protocol are still under evaluation by the panel of experts.



Segmentation Units volumes in controls, MCI and AD patients. Numbers denote mean volume (mm3) and standard deviation (in parentheses) of Segmentation Units. *p* denotes significance on t-test. Data are obtained on an ADNI sample of 77 subjects: 31 controls with normal CSF Aβ levels, 23 (subsequently converted) MCI, and 23 AD patients. All MCI and AD had abnormal CSF Aβ levels.

	Controls (n=31)	MCI (n=23)	AD (n=23)	*p* MCI vs CTR	*p* AD vs CTR	*p* MCI vs AD	*p* AD+MCI vs CTR
LEFT HIPPOCAMPUS							
MinH	1467 (204)	1122 (263)	1029 (231)	<0,0003	<0,0003	0,199	<0,0003
Alveus/fimbria	268 (45)	232 (61)	200 (48)	0,269	<0,0003	0,035	0,01
Subiculum	249 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Oblique line	196 (67)	178 (66)	176 (53)	0,938	0,262	0,956	0,207
Morphology	249 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Horizontal line	234 (72)	210 (78)	211 (62)	0,248	0,221	0,937	0,133
Tail	483 (131)	383 (99)	359 (101)	0,003	<0,0003	0,307	<0,0003
Crura	190 (74)	177 (70)	166 (68)	0,398	0,039	0,34	0,101
End Tail	296 (120)	206 (76)	206 (86)	0,003	0,004	0,984	<0,0003
MaxHV	2469 (291)	1957 (368)	1788 (342)	<0,0003	<0,0003	0,105	<0,0003
RIGHT HIPPOCAMPUS							
MinH	1462 (232)	1214 (267)	1061 (281)	<0,0003	<0,0003	0,059	<0,0003
Alveus/fimbria	255 (67)	258 (71)	223 (65)	0,84	0,03	0,103	0,35
Subiculum	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Oblique line	181 (67)	167 (71)	150 (46)	0,455	0,039	0,334	0,122
Morphology	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Horizontal line	220 (78)	203 (83)	182 (54)	0,459	0,033	0,309	0,117
Tail	497 (151)	349 (115)	349 (131)	0,001	0,001	0,999	<0,0003
Crura	187 (73)	169 (68)	140 (69)	0,37	0,023	0,17	0,038
End Tail	301 (120)	181 (113)	209 (110)	<0,0003	0,006	0,394	<0,0003
MaxHV	2429 (303)	2029 (372)	1820 (368)	<0,0003	<0,0003	0,062	<0,0003

Informative value of Segmentation Units for AD-related atrophy. Volumes (SD) are the same as in Table 2. Percent values denote the proportion of the SU compared to the total hippocampal volume (% of total hippo), the percent difference of the SU between groups (% diff), and the impact of the SU on the total volume difference between patients and controls.

	Controls (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% MCI vs CTR (impact)	% diff AD vs CTR	% AD vs CTR (impact)
LEFT HIPPOCAMPUS								
MinH	1467 (204)	30%	1122 (263)	1029 (231)	23,5%	71%	30%	66%
Alveus/fimbria	268 (45)	10%	232 (61)	200 (48)	6,5%	3%	19%	7%
Subiculum	249 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	6,5%
Oblique line	196 (67)	8%	178 (66)	176 (53)	9%	3,5%	10%	3%
Morphology	249 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	6,5%
Horizontal line	234 (72)	9%	210 (78)	211 (62)	10%	5%	10%	6,5%
Tail	483 (131)	20%	383 (99)	359 (101)	21%	11%	27%	20,5%
Crura	190 (74)	8%	177 (70)	166 (68)	6,5%	3,5%	13%	6,5%
End Tail	296 (120)	12%	206 (76)	206 (86)	30%	10,5%	30%	14%
MaxHV	2469 (291)	100%	1957 (368)	1788 (342)	20%	100%	27%	100%
RIGHT HIPPOCAMPUS								
MinH	1462 (232)	30%	1214 (267)	1061 (281)	17%	62%	27%	66%
Alveus/fimbria	255 (67)	11%	258 (71)	223 (65)	-1%	-0,5%	12%	5%
Subiculum	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Oblique line	181 (67)	8%	167 (71)	150 (46)	8%	3,5%	17%	5%
Morphology	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Horizontal line	220 (78)	9%	203 (83)	182 (54)	7,5%	4%	17%	6%
Tail	497 (151)	20%	349 (115)	349 (131)	29,5%	34,5%	29,5%	22,5%
Crura	187 (73)	8%	169 (68)	140 (69)	10%	4,5%	25%	7,5%
End Tail	301 (120)	12%	181 (113)	209 (110)	40%	30%	31%	15%
MaxHV	2429 (303)	100%	2029 (372)	1820 (368)	16,5%	100%	25%	100%

Conclusions

Reliability of individual SUs and how informative they are in identifying AD-related atrophy are being used by a panel of experts to define which SU should be included in a harmonized protocol. Figure shows the preliminary results which came out from the first round of the Delphi Panel.

Delphi Panelists

PI	Delphi Panelist
Barkhoff/Scheltens	Wouter Henneman
George Bartzokis	George Bartzokis
Richard Camicioli	Richard Camicioli / Nikolai Malikhin
John Cserrnansky	Lei Wang
Charles DeCarli	Charles DeCarli
Leyla DeToledo-Morrell	Leyla DeToledo-Morrell
Nick Fox	Josephine Barnes
Mirjam Geerlings	Lotte Gerritsen
Clifford Jack	Clifford Jack / Greg Preboske
Ronald Killiany	Ronald Killiany
John O’Brien	Michael Firbank
Jens Pruessner	Jens Pruessner
Hilkka Soininen	Hilkka Soininen / Maija Pihlajamäki
Paul Thompson	Liana Apostolova
Craig Watson	Craig Watson
Christoph Hock	Henrike Wolf

Delphi Panel

Alveus/Fimbria - QUESTION 1

Alveus/Fimbria (A/F) is the hippocampal white matter covering the dorso-lateral tissue of the hippocampus. The SU relates to how it can be detected and segmented on magnetic resonance images. It is either included or excluded by the available tracing criteria.

A/F compounds the **10.5%** of the Maximum Hippocampal Volume. Intra rater re-test reliability for A/F is **0.863**.

Inter rater re-test reliability for A/F is **0.885**.

Please note that this lower reliability relates to the isolated tracing of the fimbria. Thus this lower reliability would be reflected more in the exclusion of the fimbria, rather than in a segmentation of the hippocampal body that includes the fimbria. Indeed, the tracing of the MinH and A/F as a unique structure has an intra-rater reliability of **0.993**, and an inter-rater of **0.973**.

The percent tissue loss of A/F in AD is **15.5%**.

Its global impact on the total volume difference due to AD is **6%**.

1) Would you include A/F in a harmonized protocol?

- ○ Yes
- ○ No

Please justify your choice:

Vote

Delphi Panel

Subiculum – QUESTION 2

Subiculum - Oblique

Subiculum - Horizontal

Subiculum - Morphology

2) Which criterion do you choose for the segmentation of the medial boundary at the level of the hippocampal body?

- ○ No Subiculum
- ○ Oblique
- ○ Horizontal
- ○ Morphology

Please justify your choice:

Vote

Delphi Panel

Tail End – QUESTION 3

Tail-End includes the most caudal slices where hippocampal tissue can be seen, beyond the crura level.

Issues related to the separation of caudal hippocampal tissue from vestigial hippocampal gray matter will be considered at a later stage. Therefore, we invite you to answer on the inclusion of this SU irrespective to the need to separate it from vestigial gray matter.

Tail-End compounds 12% of the Maximun Hippocampal Volume.

Intra rater re-test reliability for Tail-End is 0.988.

Inter rater re-test reliability for Tail-End is 0.905.

The percent tissue loss of Tail-End in AD is 30.5%.

3) Which criterion do you choose for the segmentation of the tail for a harmonized protocol?

- ○ No Tail
- ○ Crura
- ○ Crura+End Tail

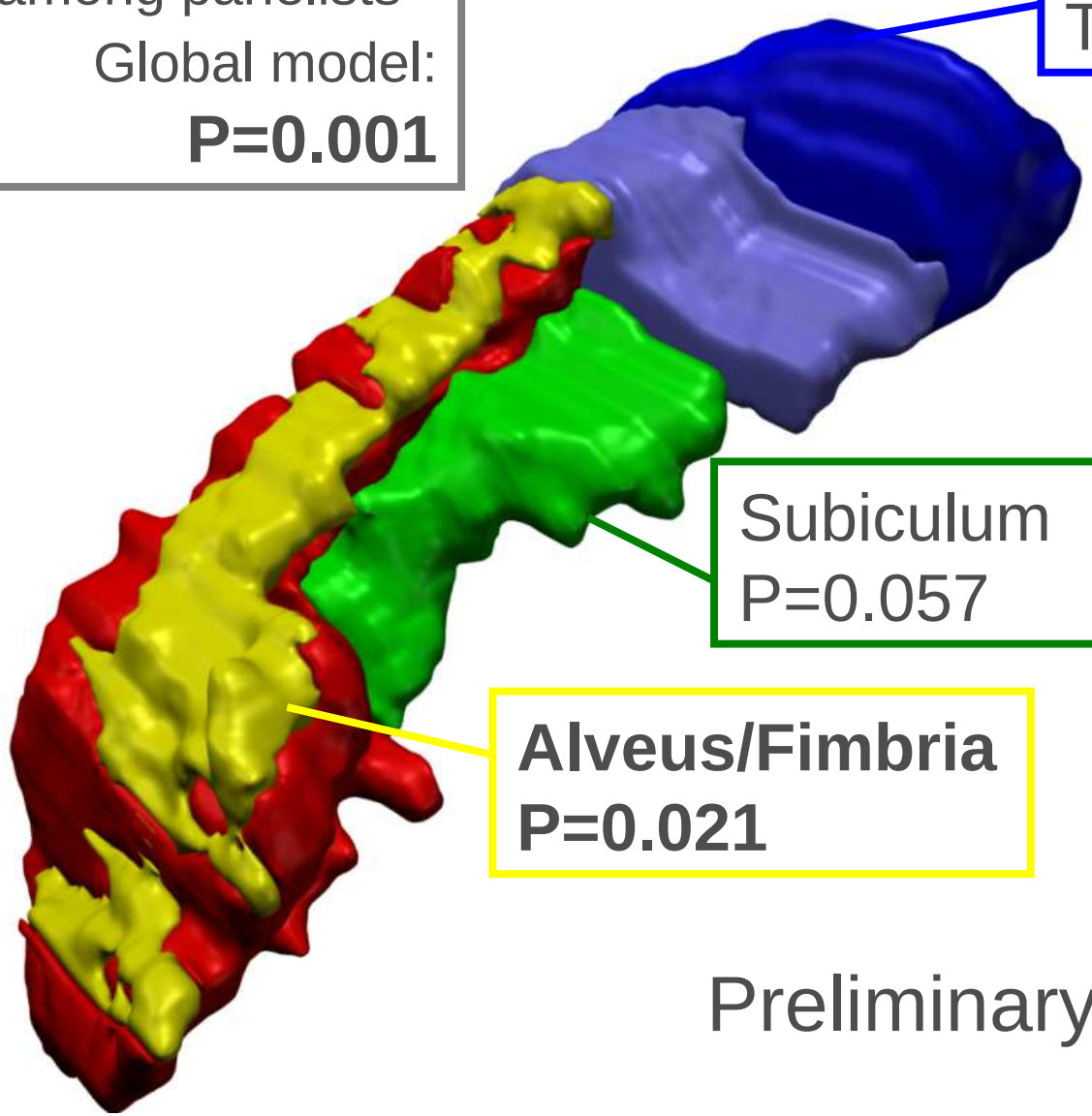
Please justify your choice:

Vote

Its global impact on the total volume difference due to AD is of 14.5%.

Delphi Panel – Preliminary Results

P for agreement among panelists
Global model:
P=0.001



Tail End **P=0.035**

Subiculum
P=0.057

Alveus/Fimbria
P=0.021

Covers **100%** of hippocampus proper

Captures **100%** of AD-related atrophy

Intra-rater (BS-BS): **0.993**

Inter-rater (BS-BS): **0.985**

Preliminary ICC (BS-Mayo-LONI): **0.95**

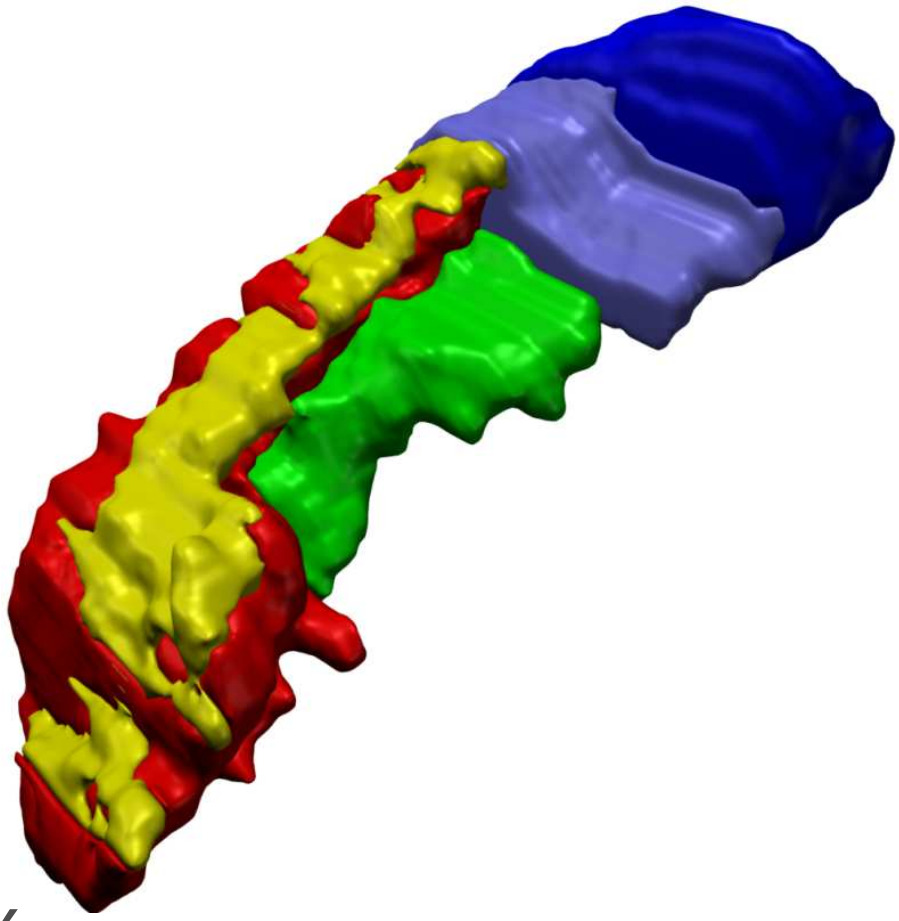
Delphi – Preliminary Results

This model includes some tissue which is **not hippocampus proper**:

- **A/F** is white matter

- Tail end may include some **vestigial tissue**

- The medial boundary of the body may include some **entorhinal** cortex



Discussion

• The **quantitative** information is being used by panelists to complement their experience in weighing pros and cons for the inclusion of each SU

• **Controversial** aspects: more Delphi rounds will be run

• The Harmonized Protocol will represent (hopefully) the optimal **compromise** for:

- Early diagnosis
- Tracking disease progression in clinical trials
- Validation of automatic segmentation algorithms

Info

www.hippocampal-protocol.net

Acknowledgements

Mike & Barbara Urbut, Stuart & Amy Savitz, Harriet K. Burnstein, Chicago, IL

Maria Carrillo, Meredith McNeil
Alzheimer's Association, Chicago IL

All partners!