



*Biomarkers for Brain Disorders Conference 2013 - Cambridge*

# Definition of an EADC-ADNI Harmonized Protocol for Hippocampal Segmentation

Martina Bocchetta

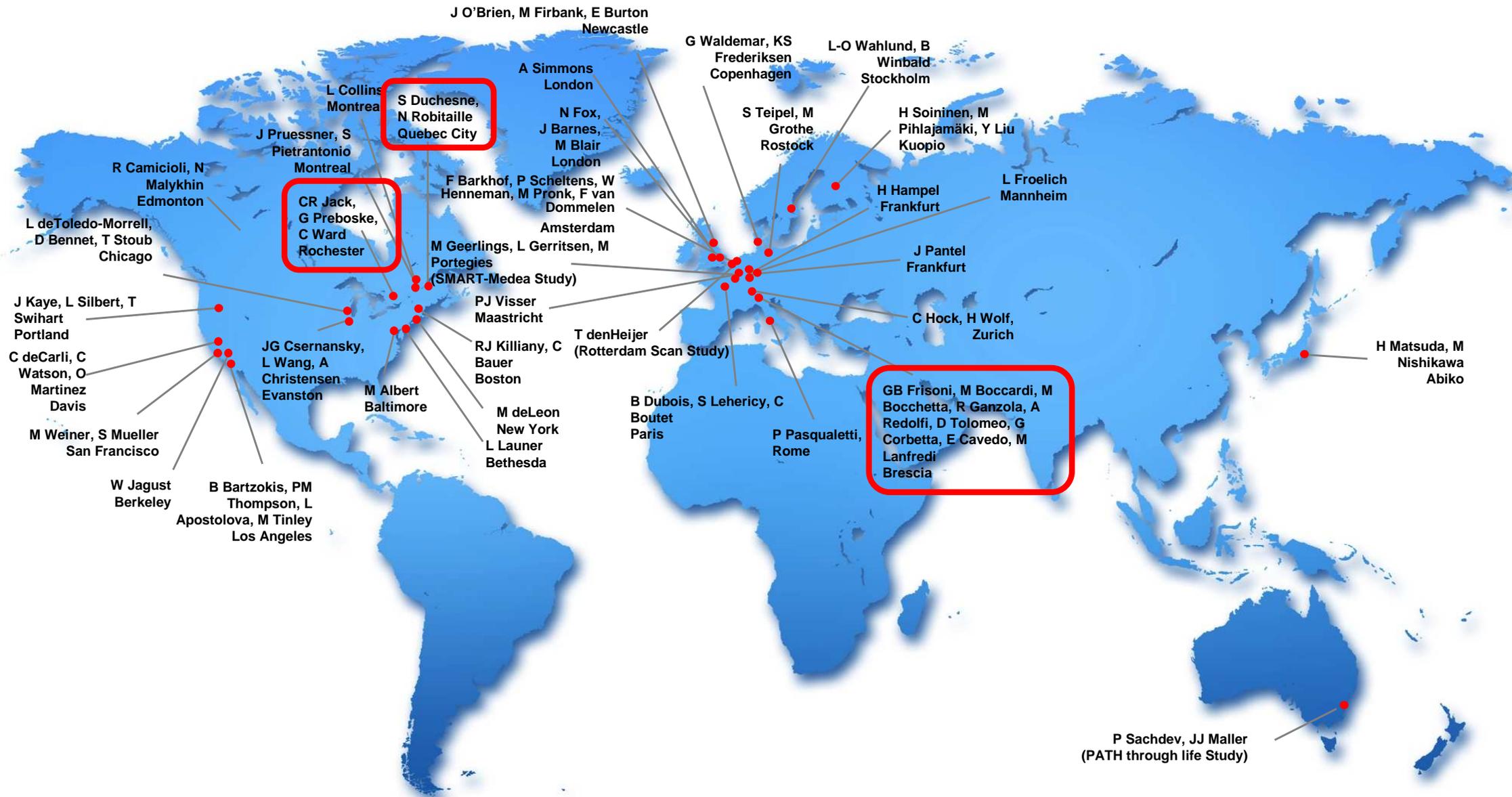
**Principal Investigators: Giovanni B Frisoni & Clifford R Jack**  
**Project Coordinator: Marina Boccardi**

LENITEM - Laboratory of Epidemiology, Neuroimaging & Telemedicine

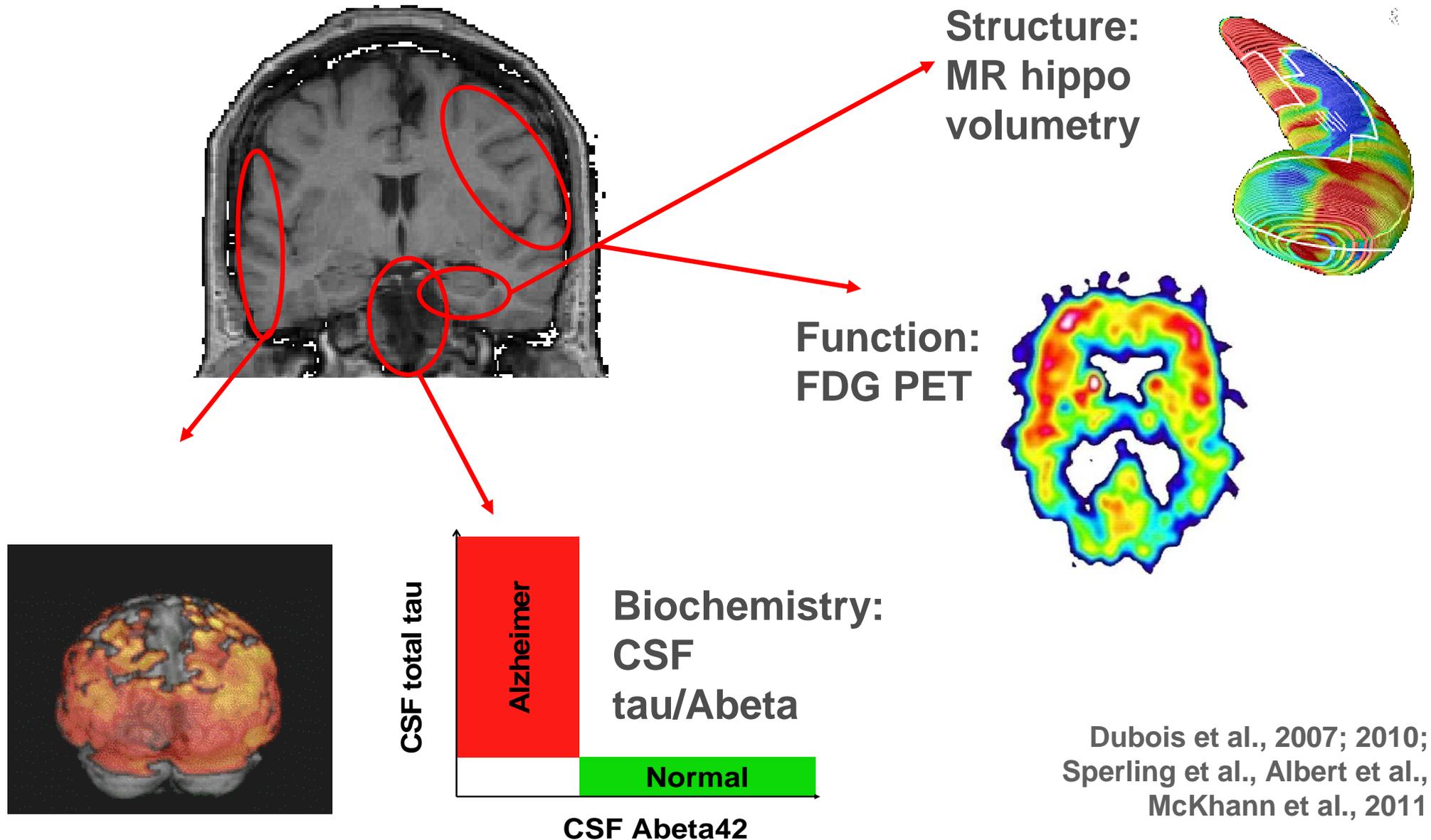


**IRCCS**  
**CENTRO SAN GIOVANNI DI DIO FATEBENEFRATELLI – BRESCIA**  
Centro Nazionale per lo Studio e la Cura  
della Malattia di Alzheimer e Malattie Mentali

# The EADC-ADNI Working Group on the Harmonized Protocol for Hippocampal Volumetry

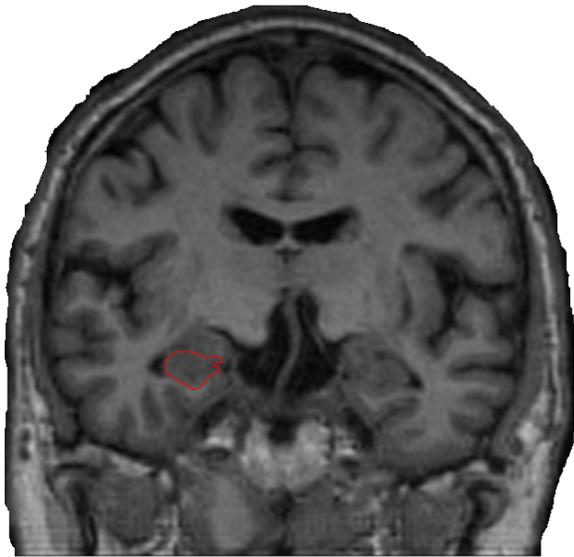


# New diagnostic criteria and biomarkers for AD



# BACKGROUND

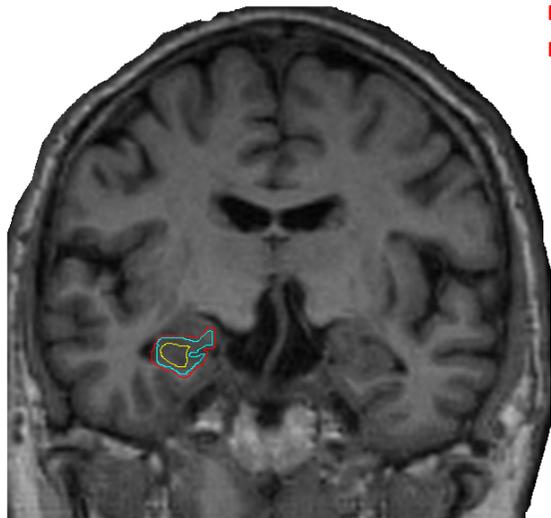
## The effect of different segmentation protocols



Volume

≠

≠



Ref.	Med border	Lat border	Inf border	Norm. hippo vol (cm3)	
				Left	Right
Watson et al.	Mesial edge of temporal lobe	Temp horn of lat ventr	Incl subicular complex & uncal cleft w/ border separating subicular complex from parahip gyrus	4.903	5.264
Zipursky et al.	Regional outline at choroidal fissure	Not mentioned	The interface of hippo tissue and parahippol gyrus WM	1.990	2.070

**Not comparable**

# **Standard Operating Procedures needed**

**STANDARDIZED BIOMARKER**

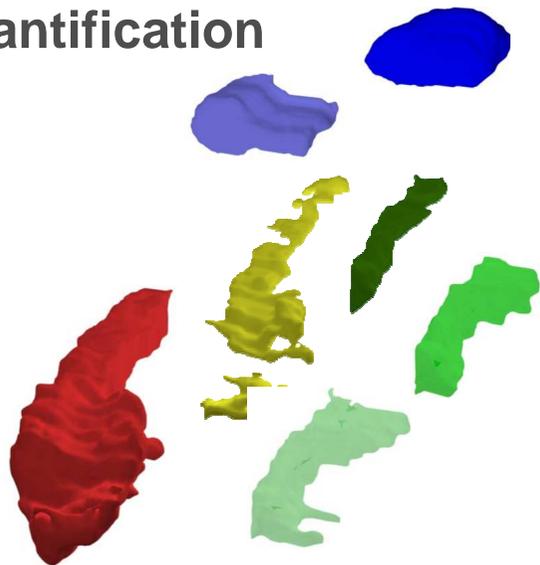
**FOR EARLY DIAGNOSIS**

**CLINICAL TRIALS**

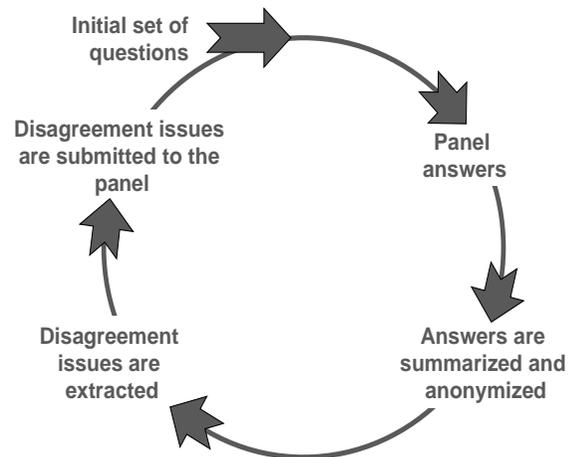
**AUTOMATED SEGMENTATION ALGORITHMS**

# Aims & Project structure

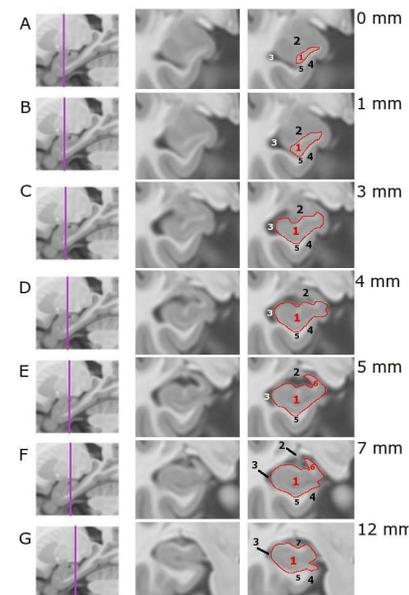
## Operationalization & quantification



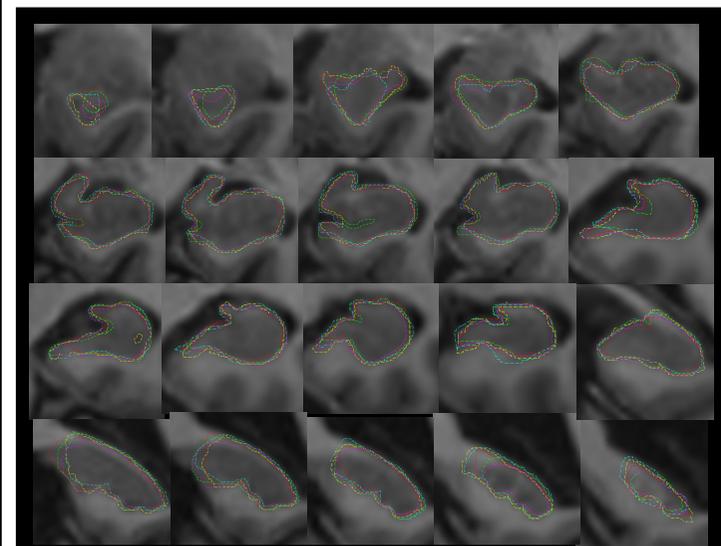
## Delphi panel



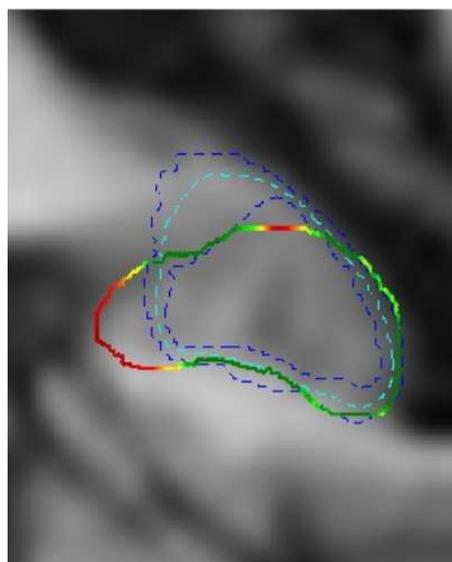
## Harmonized Protocol



## Benchmark images

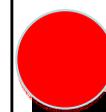


## Qualification platform



## Validation

**We are here**



### Naïve Tracers



# Authors of the Hippocampal Segmentation Protocols



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J. Pantel  
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J. Pruessner  
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H. Soininen  
Kuopio



C. Watson  
Detroit

# Preliminary Phase

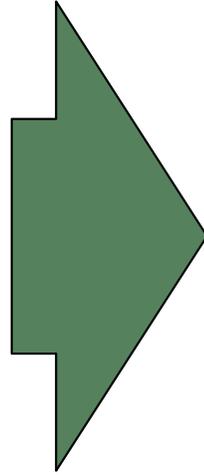
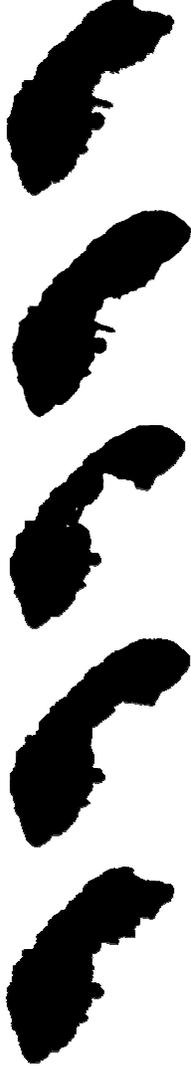
## Survey

(Boccardi et al., JAD 2011)

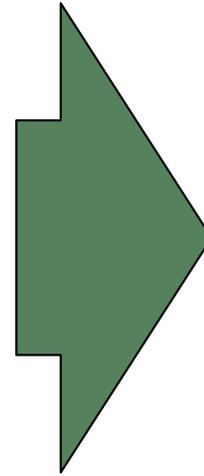
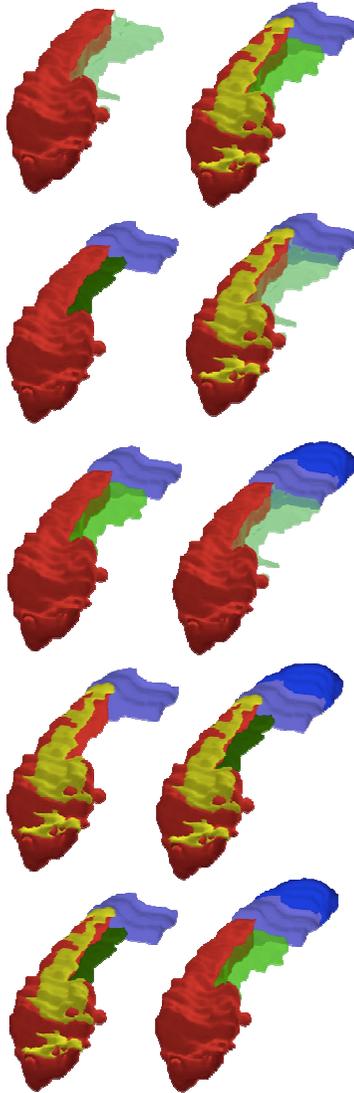
Lehericy, 1994 Soininen, 1994 Killiany, 1993 Convit, 1997 Bartzokis, 1998



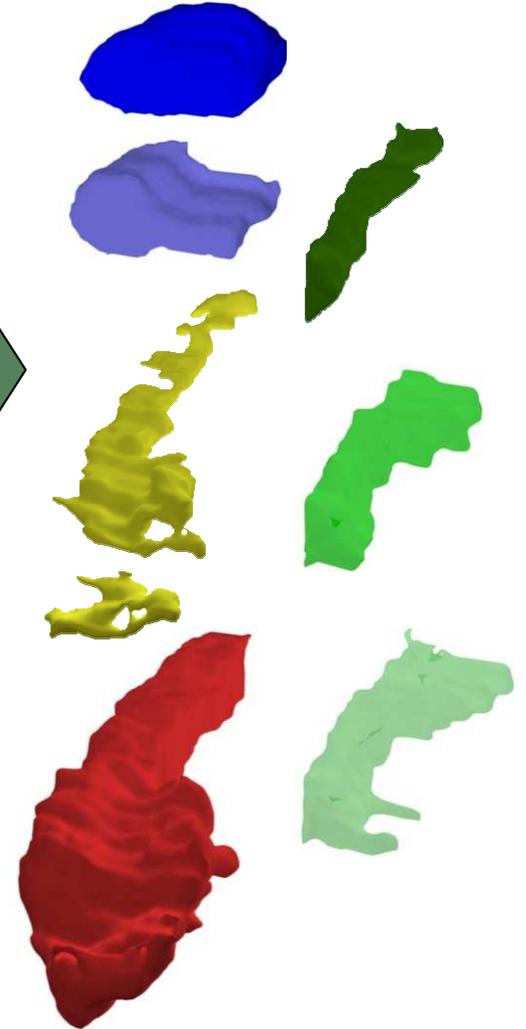
Watson, 1992 Pantel, 2000 Pruessner, 2000 Malykhin, 2007 Haller, 1997 Jack, 1994; deToledo-Morrell, 2004



## Operationalization of differences into segmentation units



## Assessment of measurement properties of SUs



# SUs Quantification: Reliability

	<b>Intra-rater</b>	<b>Inter-rater</b>
<b>MinH</b>	0.992 (0.980-0.997)	0.974 (0.936-0.990)
<b>Alveus/Fimbria</b>	0.863 (0.687-0.944)	0.885 (0.734-0.953)
Minimum Hippocampus + Alveus/Fimbria	0.993 (0.983-0.997)	0.973 (0.934-0.989)
<b>Subiculum</b>		
Oblique line	0.964 (0.911-0.985)	0.907 (0.781-0.962)
Morphology	0.981 (0.952-0.992)	0.937 (0.848-0.975)
Horizontal line	0.980 (0.951-0.992)	0.932 (0.836-0.972)
<b>Tail</b>		
Crura	0.998 (0.994-0.999)	0.937 (0.847-0.974)
Tail End	0.988 (0.971-0.995)	0.905 (0.775-0.961)

(Boccardi et al., in press 2013)

# SUs Quantification: Informative Value

LEFT HIPPOCAMPUS						
	CTR (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% diff AD vs CTR
<b>MinH</b>	1,467 (204)	60%	1,122 (263)	1,023 (251)	23.5% **	30% **
<b>Alveus/Fimbria</b>	248 (45)	10%	232 (61)	200 (48)	6.5%	19% **
<b>Subiculum</b>	243 (72)	10%	220 (84)	213 (64)	9.5%	12%
Oblique line	196 (67)	8%	178 (66)	176 (53)	9 %	10%
Morphology	243 (72)	10%	220 (84)	213 (64)	9.5%	12%
Horizontal line	234 (72)	9%	210 (78)	211 (62)	10%	10%
<b>Tail</b>	485 (131)	20%	383 (99)	353 (101)	21% *	27% **
Crura	190 (74)	8%	177 (70)	146 (69)	6.5%	23% *
Tail End	296 (120)	12%	206 (76)	206 (86)	30% *	30% *
<b>MaxH</b>	2,443 (291)	100%	1,957 (348)	1,788 (342)	20% **	27% **

(Boccardi et al., in press 2013)

# Delphi Panel



L. Apostolova  
Los Angeles



J. Barnes  
London



G. Bartzokis  
Los Angeles



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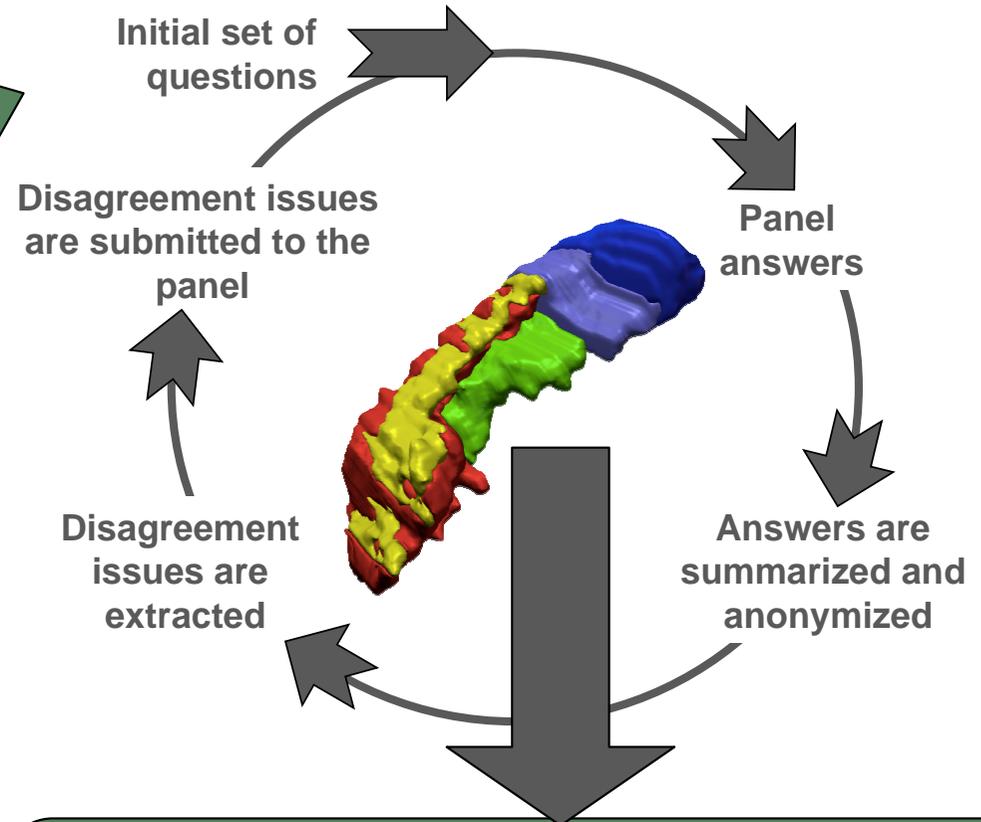
H. Wolf  
Zurich

# Consensual Definition of Harmonized Protocol

## Assessment of measurement properties of SUs

- Stability of segmentation
- Contribution to total hippocampal volume
- Contribution to AD-related atrophy

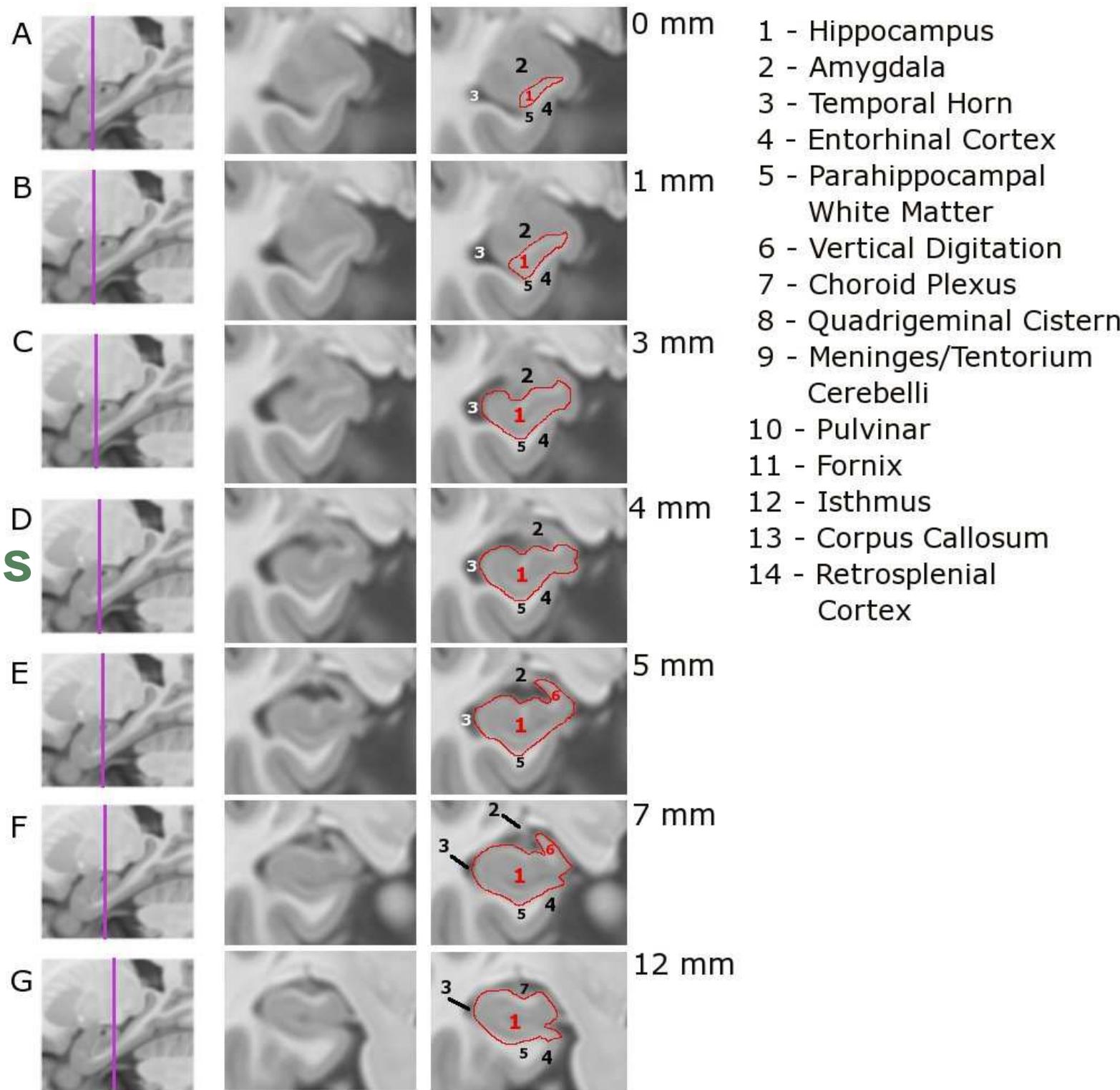
## Delphi panel



Covers 100% of hippo proper  
Captures 100% of AD atrophy  
Very high IRR & TRTR: >.94

# Harmonized protocol for manual segmentation based on the Delphi recommendations

32 pages  
 23 figures  
 1 summary-table  
 1 summary-figure



# Master Tracers



L. Apostolova  
Los Angeles



M. Bocchetta  
Brescia



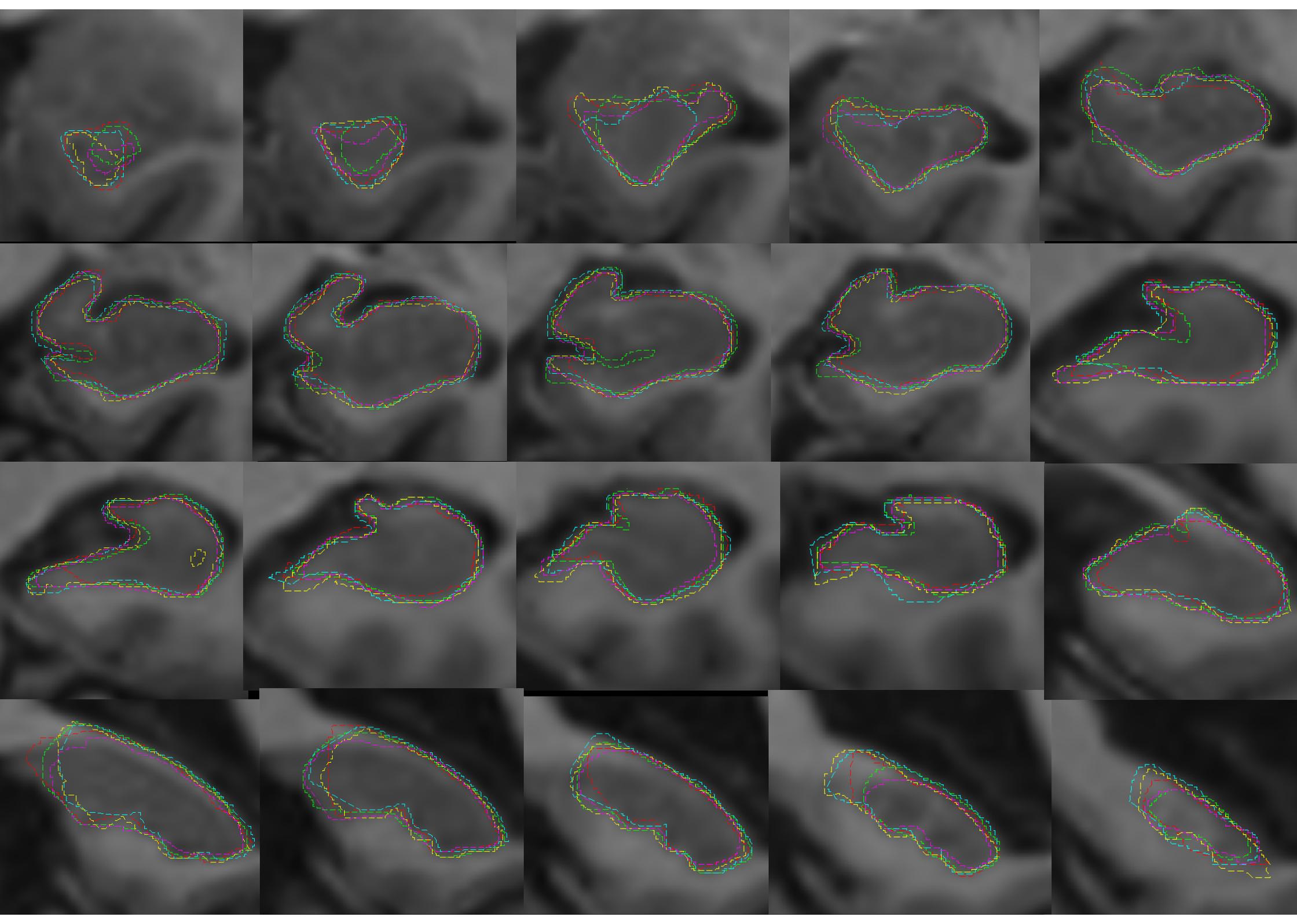
R. Ganzola  
Quebec City



G. Preboske  
Rochester



D. Wolf  
Mainz



# Benchmark Images Reliability

	<b>Left Hippocampus</b>	<b>Right Hippocampus</b>
<b>Intra-rater 1.5T vs 3T (n=10)</b>		
<b>2 levels</b>		
<b>MB</b>	0.982 (0.930-0.996)	0.994 (0.975-0.998)
<b>RG</b>	0.965 (0.867-0.991)	0.977 (0.909-0.994)
<b>GP</b>	0.976 (0.908-0.994)	0.987 (0.947-0.997)
<b>LA</b>	0.949 (0.757-0.988)	0.954 (0.791-0.989)
<b>DW</b>	0.982 (0.931-0.996)	0.988 (0.953-0.997)
<b>Inter-rater (n=10)</b>		
<b>5 levels</b>		
<b>1.5T</b>	0.974 (0.938-0.993)	0.983 (0.958-0.995)
<b>Inter-rater (n=10)</b>		
<b>5 levels</b>		
<b>3T</b>	0.949 (0.860-0.986)	0.965 (0.897-0.991)
<b>Overlapping Value (among 5)</b>		
	0.73	0.75

# Naive Tracers



C. Bauer



M. Blair



C. Boutet



E. Burton



E. Cavedo



A. Christensen



KS. Frederiksen



M. Grothe



M. Lanfredi



O. Martinez



M. Nishikawa



S. Pietrantonio



M. Portegies



G. Preboske



M. Pronk



T. Stoub



T. Swihart



C. Ward



L. Yawu

# Web-Platform



## Manual Tracing of the Hippocampus

[Homepage](#)[Sections](#)[Investigators](#)[Support](#)[Site Map](#)

### User Account

E-Mail:

Password:

[Create an account](#)

[Forgot your password?](#)

### Partners

### Certification Website for Manual Hippocampal Segmentation.

#### Site Access

##### Login Account

You have to login in order to access our Qualification System. If you don't have an account, follow the link below to register. Once you have your own account, you can login, save your progress at any time and access our website.

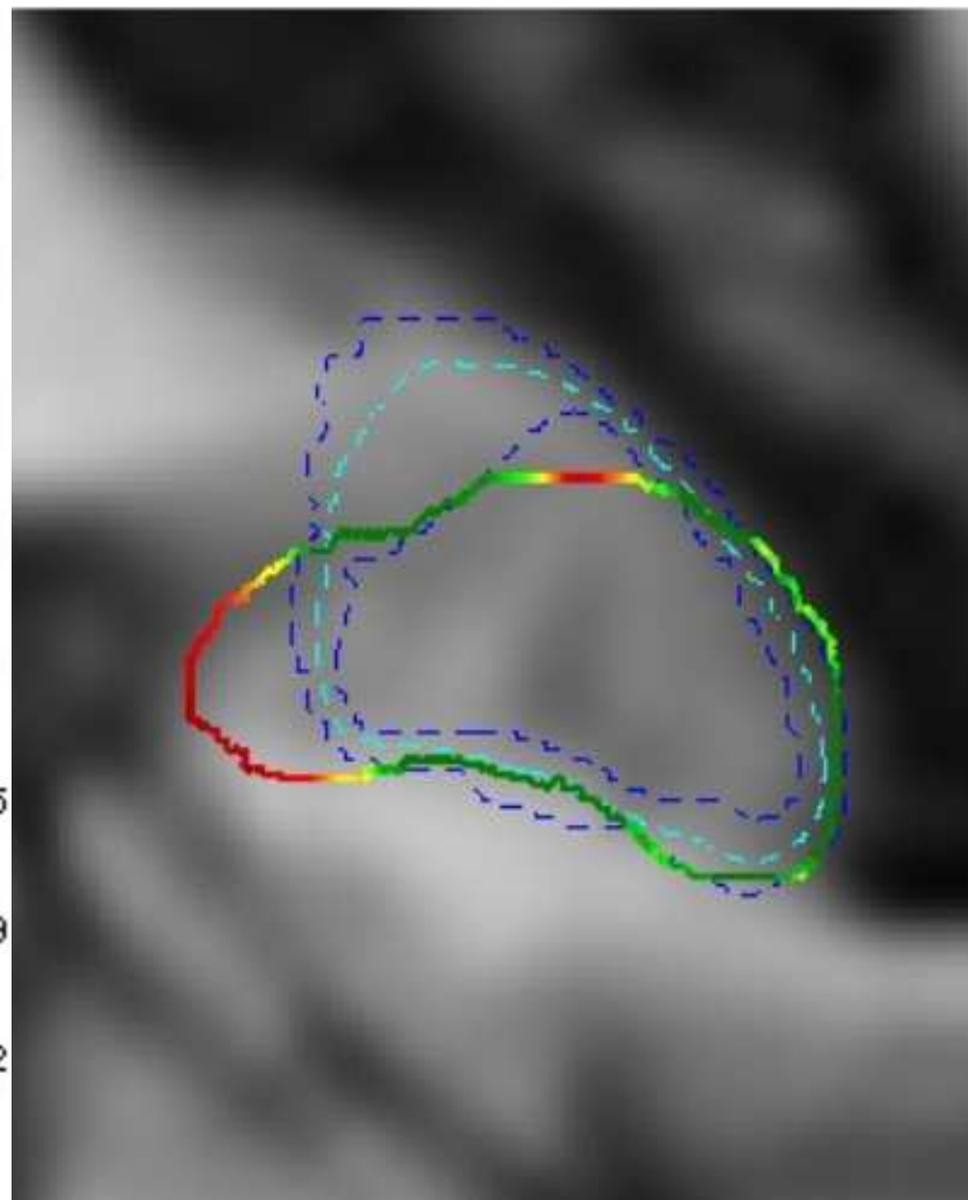
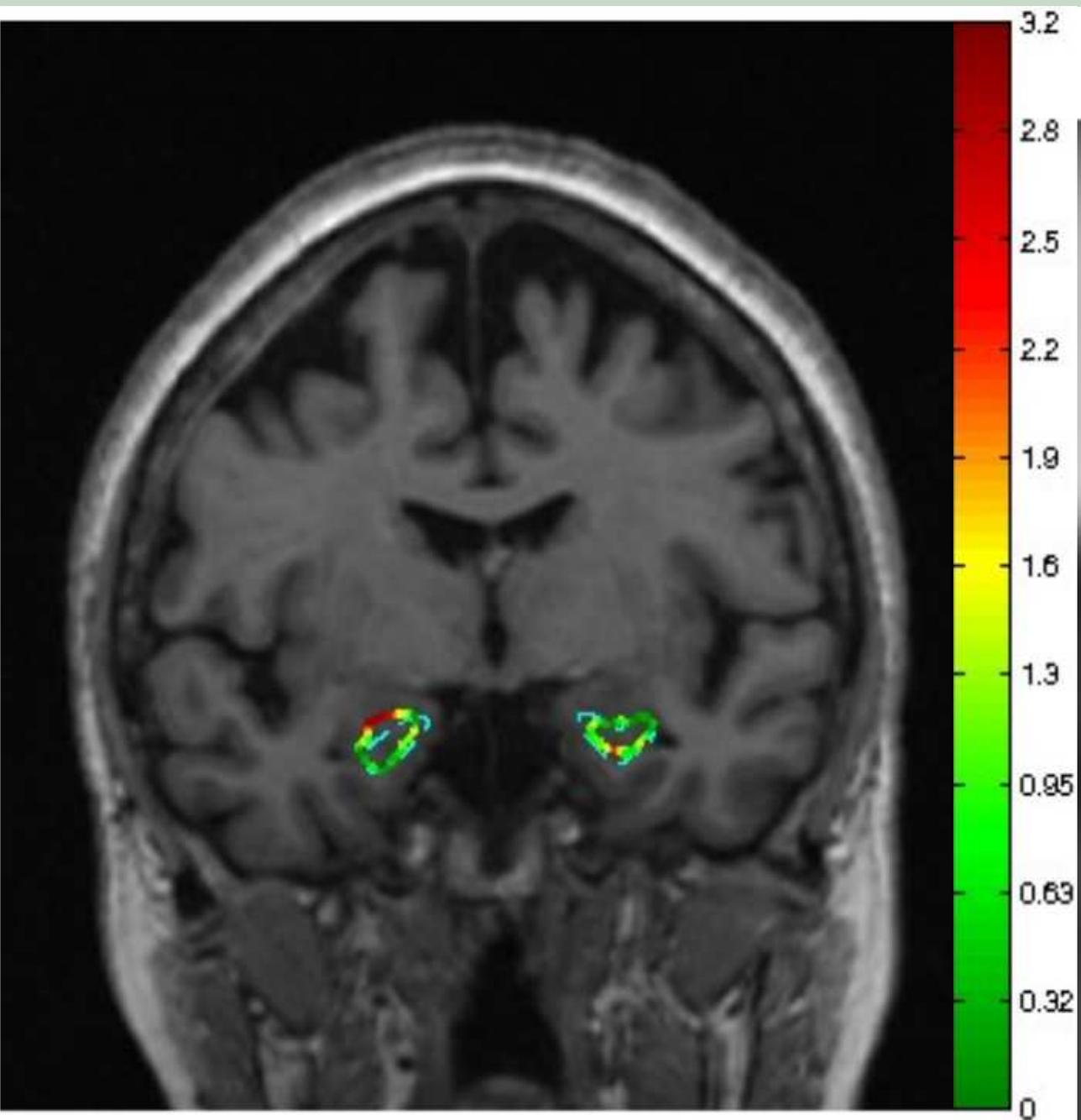
#### About the Harmonization of Hippocampal Protocol Project

If you are interested in learning more about the Harmonization of the Hippocampal Protocol Project, please visit the main site at [www.hippocampal-protocol.net](http://www.hippocampal-protocol.net)

alt : [hippo\\_512x384.mpg](#)

This is an initiative supported by ADNI & EADC and MDEIE.

# Qualification Platform



# Qualification Platform (Third training step)

	Overlapping indices versus Benchmark segmentations				Inter-rater ICCs among the 10 “Naïve” tracers (95% CI)	
	3 Tesla		1.5 Tesla		3 Tesla + 1.5 Tesla	
	Dice	Jaccard	Dice	Jaccard	Right	Left
Median	0.91	0.83	0.90	0.81	0.98	0.98
Minimum	0.89	0.80	0.82	0.74	(0.95-0.99)	(0.95-0.99)
Maximum	0.92	0.85	0.91	0.84		

[www.hippocampal-protocol.net](http://www.hippocampal-protocol.net)  
[hippocampal.protocol@gmail.com](mailto:hippocampal.protocol@gmail.com)

# Next Steps

## Harmonized Protocol Validation

neuropathological data  
&  
currently used protocols

## Label Expansion Project For Algorithm Qualification

Funded by:

AA, Ixico, Roche, Bioclinica, Synarc, Brain Image Analysis,  
True Positive Medical Devices Inc.

# Acknowledgements

## **FUNDS:**

**Alzheimer's Association**

**Lilly and Wyeth (part of the Pfizer group)**

**ALL PARTICIPANTS,  
and particularly, in the present phase:**

# Statistical Working Group

## *Quebec City*



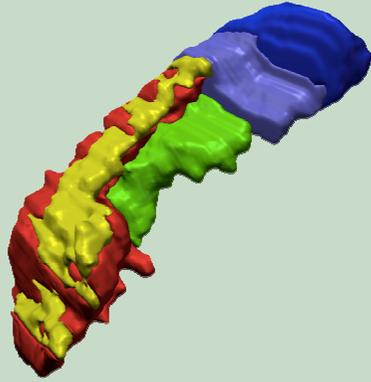
Nicolas Robitaille



Fernando Valdivia



Simon Duchesne



[www.hippocampal-protocol.net](http://www.hippocampal-protocol.net)

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alzheimer's  association®