



Standardization of hippocampal volumetry as a diagnostic marker for Alzheimer's disease: an EADC- ADNI effort



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and the Hippocampal Harmonization
Global Consortium*



**IRCCS
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**Centro Nazionale per lo Studio e la Cura
della Malattia di Alzheimer e Malattie Mentali**

Standard Operating Procedures badly needed

Ref.	Med border	Lat border	Inf border	Norm. hippo vol (cm ³)	
				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 parahippo gyrus	4.903	5.264
Zipursky et al.	Regional outline at choroidal fissure	Not mentioned	The interface of hippocampal tissue and parahippocampal gyrus white matter	1.990	2.070

2.5-fold



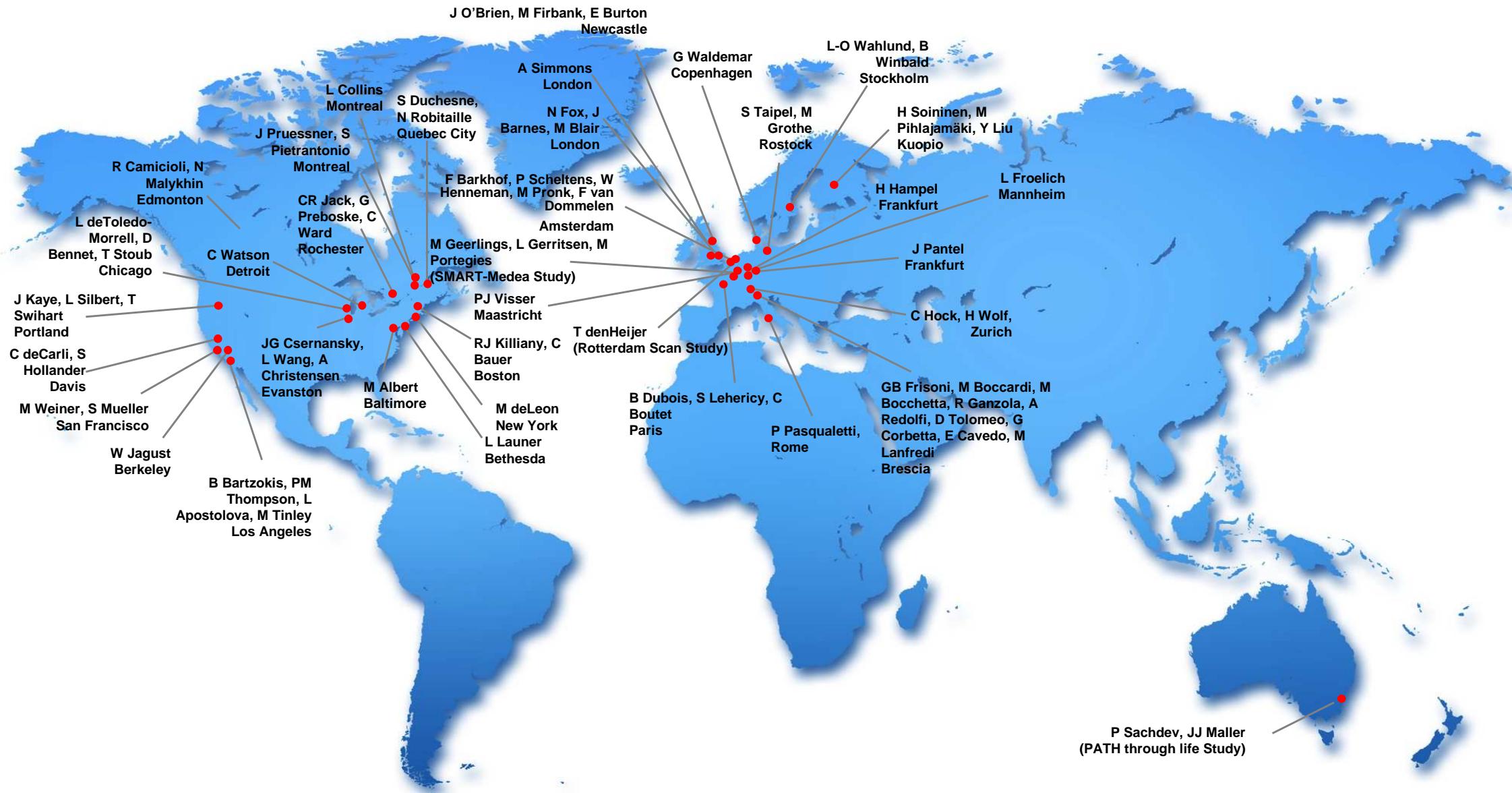
New diagnostic criteria and biomarkers for AD

Dubois et al., 2007; 2010 – Sperling et al., Albert et al., McKhann et al, 2011

	Modality	Measurement
Hippocampal volume	3D T1 MR	 EADC-ADNI harmonized protocol AA-funded study P.I. GB Frisoni, co-P.I. CR Jack
Temporo-parietal hypometabolism	FDG PET	 Head-to-head comparison of metrics Spontaneous study Frisoni, Jagust, Reiman, Herholz
CSF Ab42 and tau	Lumbar puncture	 CSF Harmonization Project AA-funded study P.I. Bengt Winblad  BIOMARKAPD EU Joint Programming for Neurodeg Diseases P.I. Bengt Winblad
Cortical amyloid deposition	Amyloid PET	SOPs developed by ligand manufacturers



The Hippocampal Harmonization Global Consortium



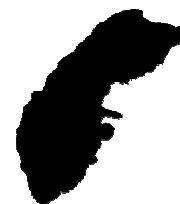
Preliminary Phase

Survey

(Boccardi et al., JAD 2011)



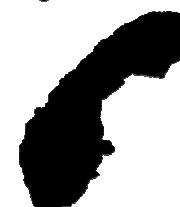
Jack, 1994;
deToledo-Morrell, 2004



Pruessner, 2000
Malykhin, 2007



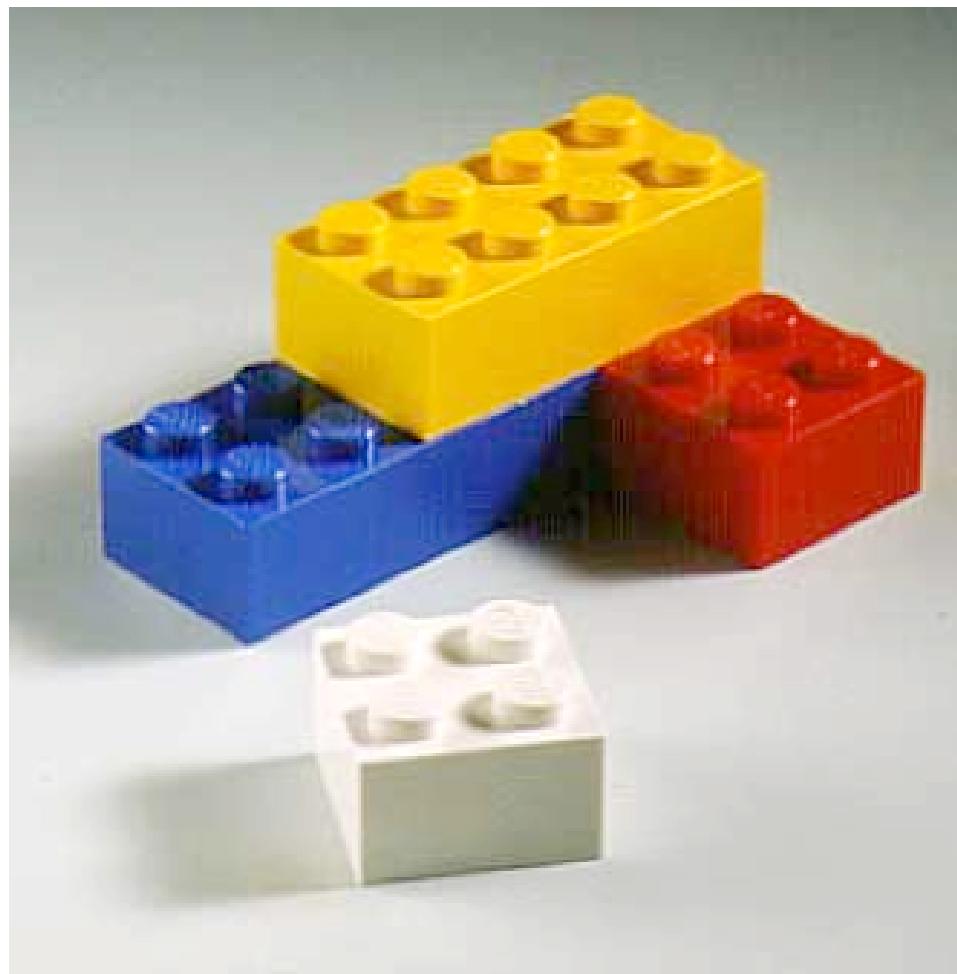
Pantel, 2000



Killiany, 1993
Bartzokis, 1998



**Extraction of maximum common denominator
("LEGO blocks" or Segmentation Units)**



Preliminary Phase

Survey

(Boccardi et al., JAD 20119)



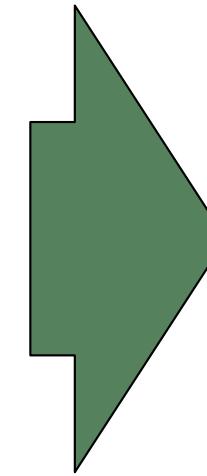
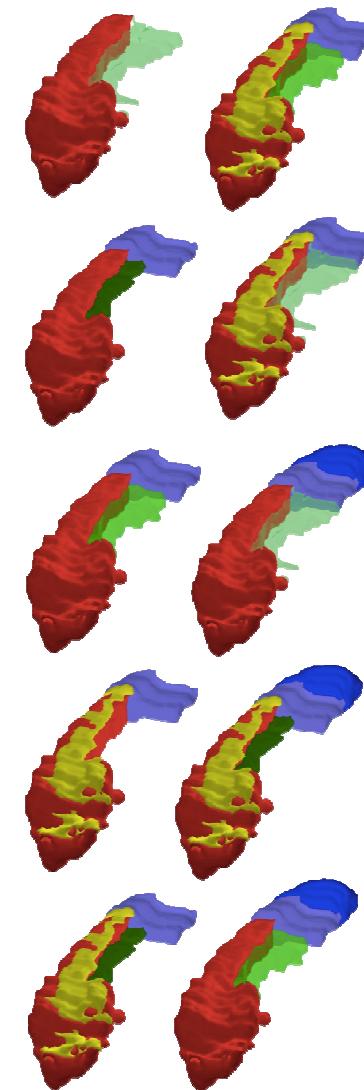
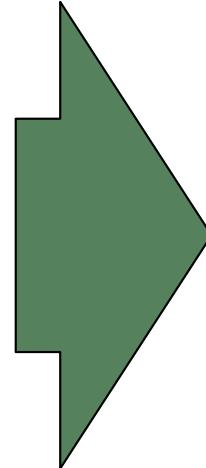
Jack, 1994;
deToledo-Morrell, 2004

Pruessner, 2000
Malykhin, 2007

Pantel, 2000

Bartzokis, 1998
Convit, 1997

Operationalization of differences into segmentation units



Assessment of measurement properties of SUs



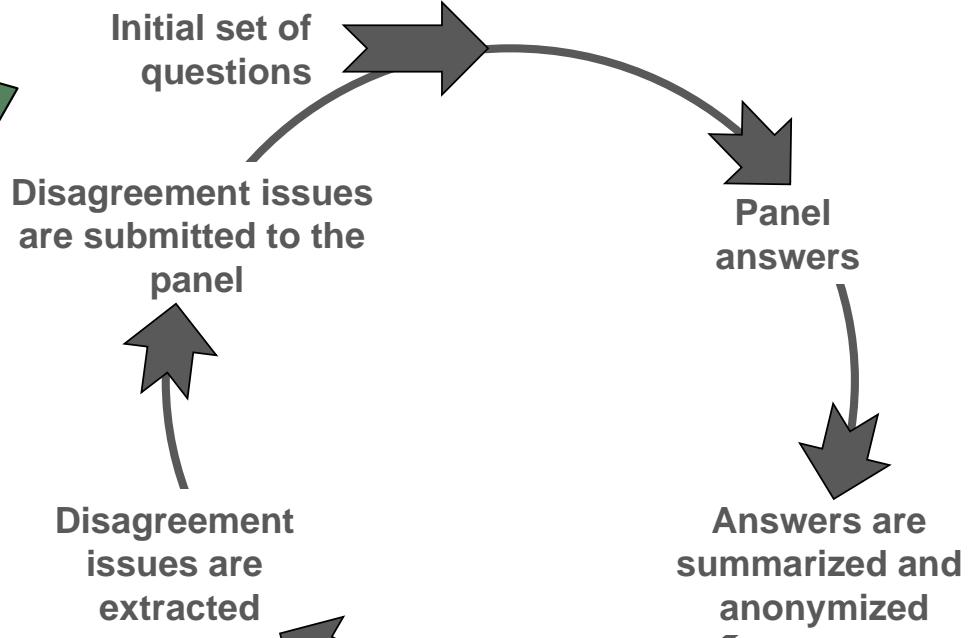
Consensual Definition of Harmonized Protocol

Assessment of measurement properties of SUs



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

Delphi panel



Delphi Panel



L. Apostolova
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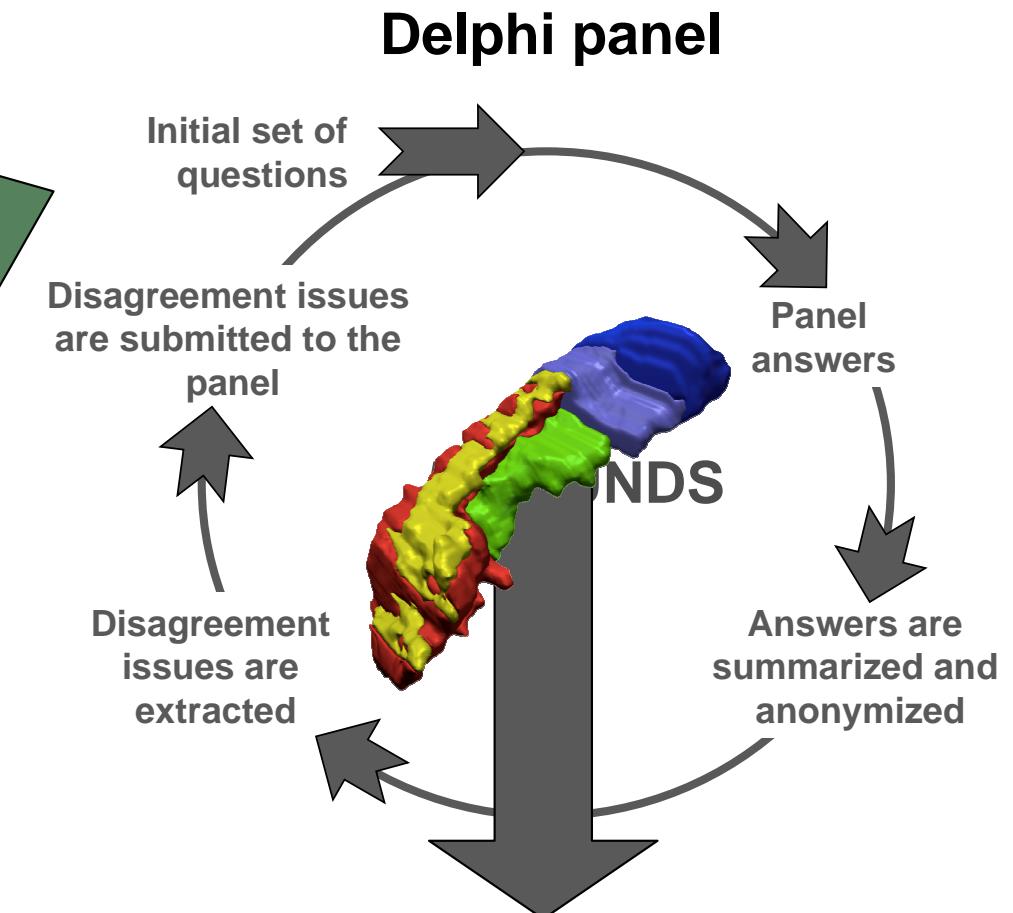
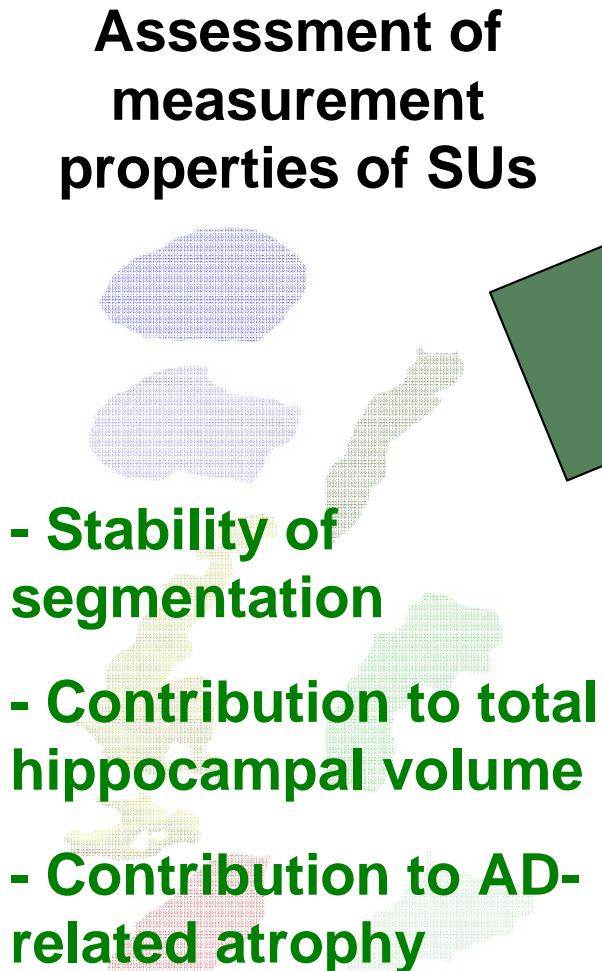


C. Watson
Detroit



H. Wolf
Zurich

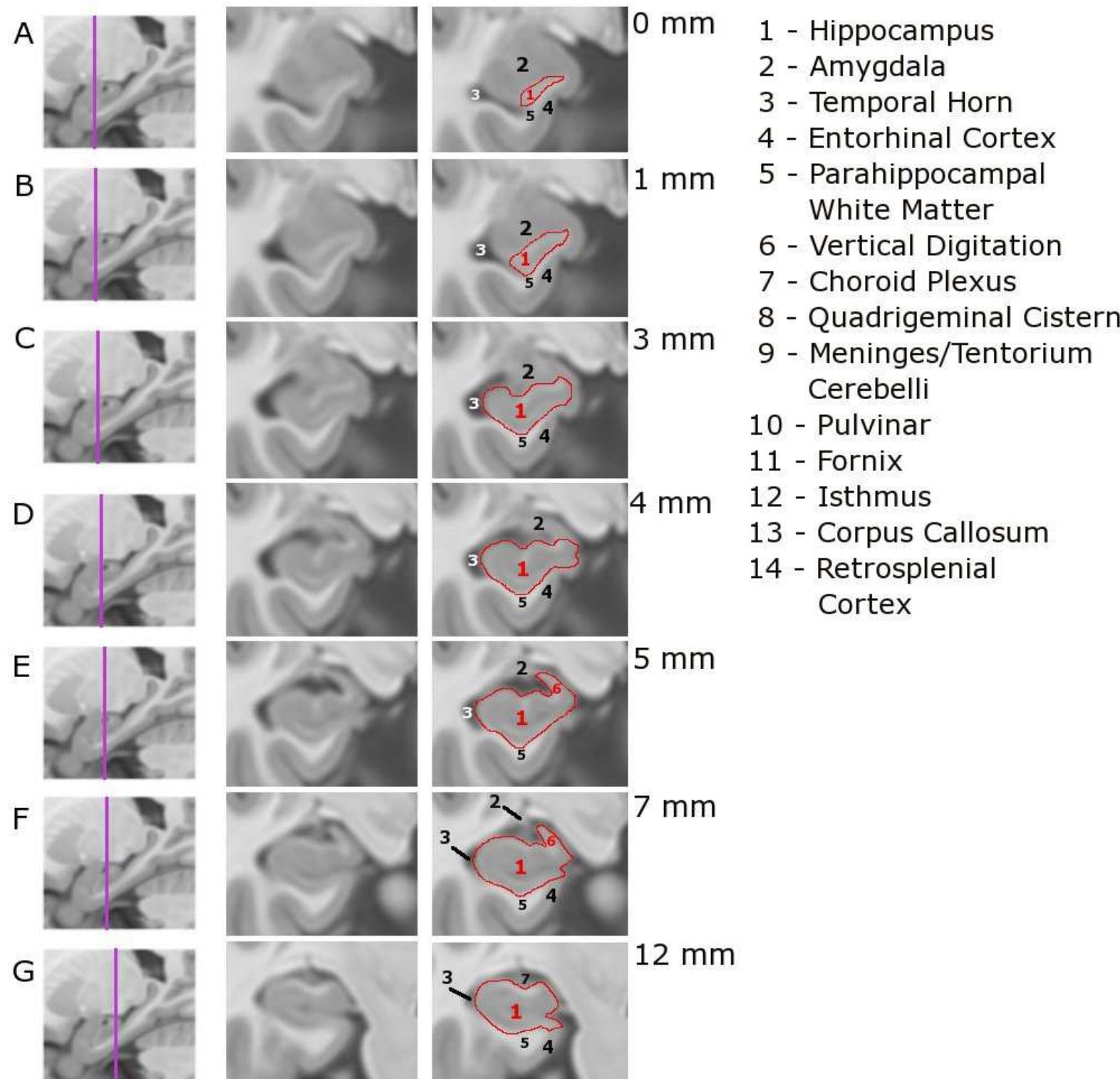
Consensual Definition of Harmonized Protocol



Covers 100% of hippo proper
Captures 100% of AD atrophy
Very high IRR & TRTR: <.97

Delphi-driven harmonized protocol for manual tracing

31 pages
22 3D figures
1 summary-table
1 summary-figure



Benchmark Images: Volume ICCs

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

Benchmark Images will be used for on-line learning by naive tracers, and validation of automated algorithms

Master Tracers



L. Apostolova
Los Angeles



M. Bocchetta
Brescia



R. Ganzola
Quebec City



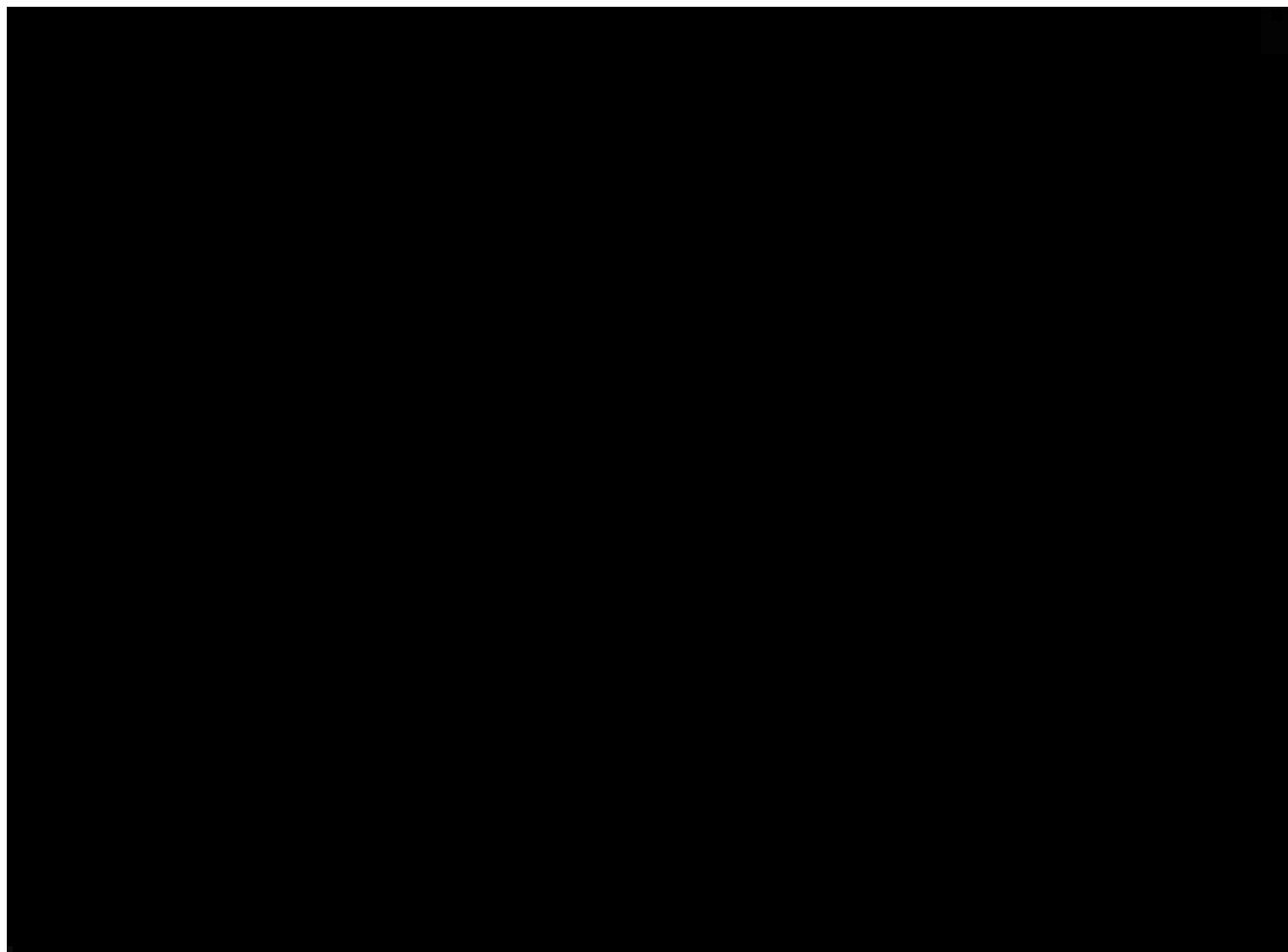
G. Preboske
Rochester



D. Wolf
Mainz

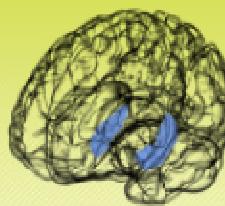
Benchmark Images: 3D overlap

Subject 9, Axis, Right HC, Slice 001



Certification environment

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Manual Tracing of the Hippocampus

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Certification Website for Manual Hippocampal Segmentation.

Site Access
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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

CURRENT ACTIVITIES

Definition of certification thresholds

Validation versus current local protocols on ADNI scans

- 20 naïve tracers will segment hippos of 16 ADNI subjects using local protocols
- The same tracers will use the Harmonized Protocol on the same subjects, 240 hippos each (**2 wanted!**)
- assessment of variance due to side, trace-retrace, atrophy, atrophy rates, scanner, rater

Validation versus current local protocols on ADNI Accepting beta testers

NEXT STEPS

Validation versus neuropathological data

Expansion of segmented ADNI subjects (and labels for automated algorithm validation) to n=150 (funds!**)**

Make public:

- segmentation protocol
- probabilistic maps
- individual masks of segmented ADNI subjects



Acknowledgements



Alzheimer's Association (major funder)

Lilly and Wyeth (part of the Pfizer group)

Co-P.I.: Clifford R Jack

Statistical working group: Simon Duchesne & coll.

Brescia team: Martina Bocchetta, Alberto Redolfi

**ALL PARTNERS OF THE GLOBAL HIPPO HARMO
CONSORTIUM**

Biomarkers in Brain Disease: Challenges and Opportunities

3-5 February 2013

The Møller Centre, Cambridge, UK

Scientific organisers

Giovanni Frisoni IRCCS Fatebenefratelli, Italy

Andreas Jeromin Banyan Biomarkers, USA

Andy Lockhart GlaxoSmithKline, UK

William Potter formerly Merck, USA

Full details at:

www.wellcome.ac.uk/conferences