



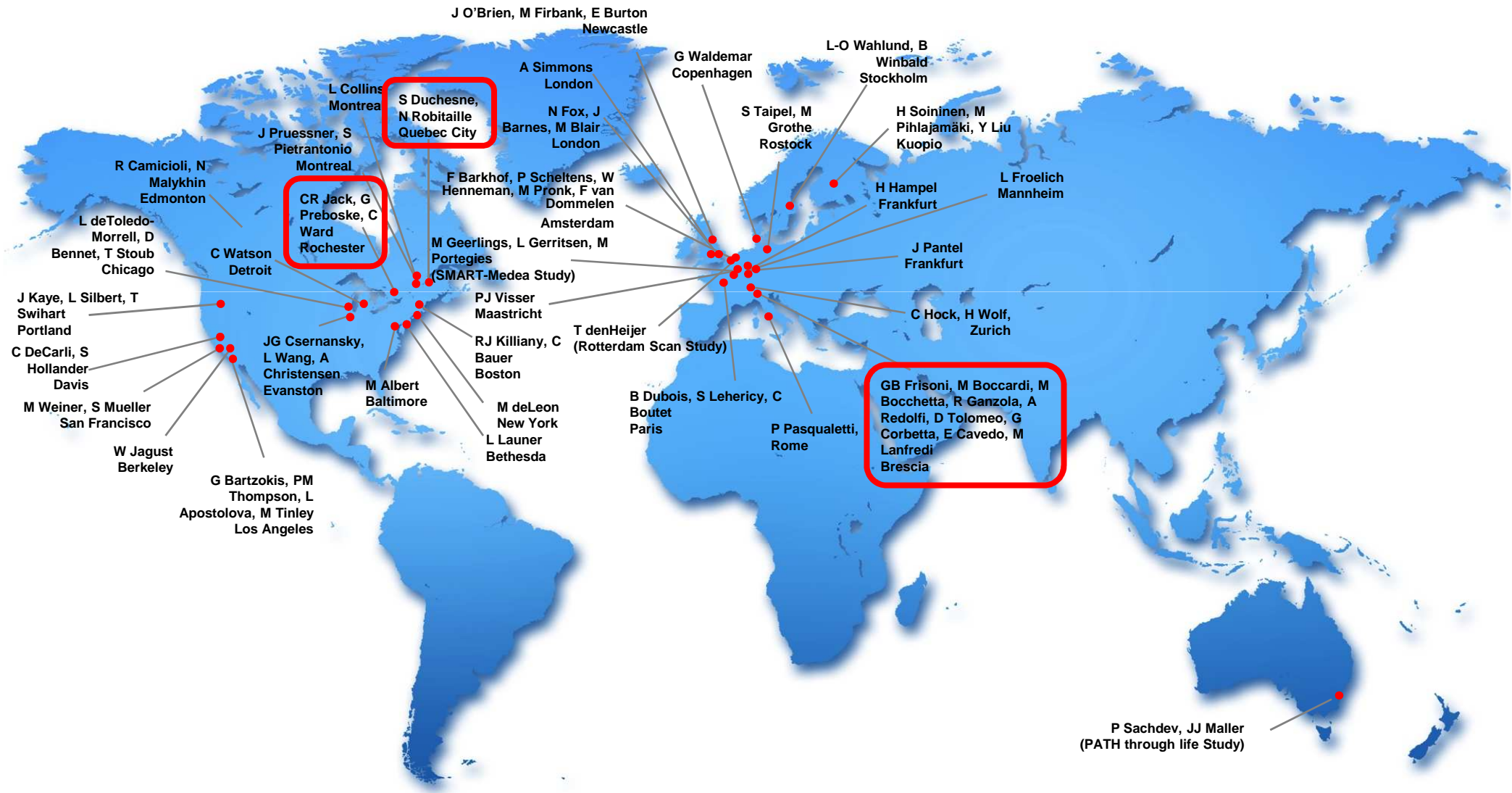
# **Delphi Consensus for a Harmonized Protocol for Manual Hippocampal Segmentation: an EADC-ADNI Project**

**M Boccardi, M Bocchetta, L Apostolova, J Barnes, G Bartzokis, G Corbetta, C DeCarli, L deToledo-Morrell, M Firbank, R Ganzola, L Gerritsen, W Henneman, RJ Killiany, N Malykhin, P Pasqualetti, JC Pruessner, A Redolfi, N Robitaille, H Soininen, D Tolomeo, L Wang, C Watson, H Wolf, S Duchesne, CR Jack Jr, GB Frisoni.**

Disclosures: the project is funded by the Alzheimer's Association, and co-funded by unrestricted grants from Lilly and Wyeth (part of the Pfizer group)



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



# BACKGROUND

Over 40 different segmentation protocols

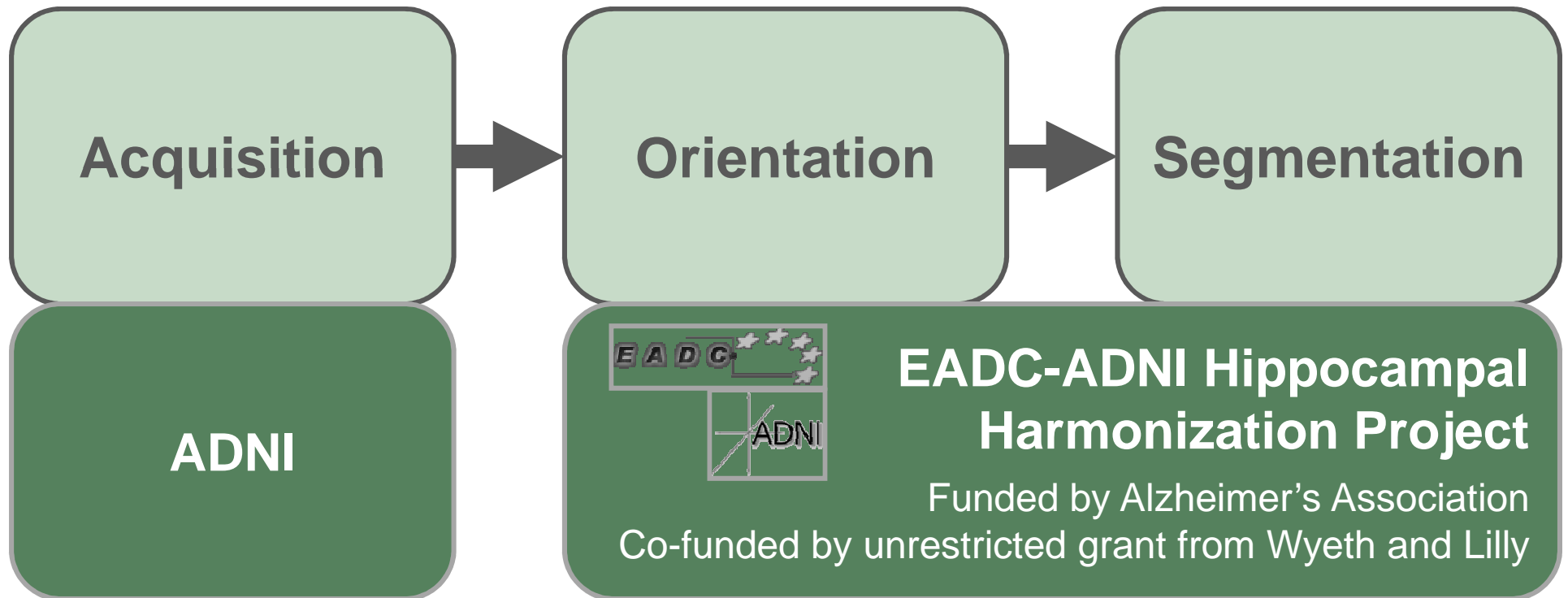
Ref.	Med border	Lat border	Inf border	Norm. hippo vol (cm <sup>3</sup> )	
				Left	Right
Watson et al.	Mesial edge of temporal lobe	Temp horn of lat ventr	Incl subicular complex & uncal cleft w/ border separating subicular complex from parahippo gyrus	<b>4.903</b>	<b>5.264</b>
Zipursky et al.	Regional outline at choroidal fissure	Not mentioned	The interface of hippocampal tissue and parahippocampal gyrus white matter	<b>1.990</b>	<b>2.070</b>

Geuze et al., Mol Psychiatry 2005;10:147-59

Konrad et al., Neuroimage, 2009;47:1185-95



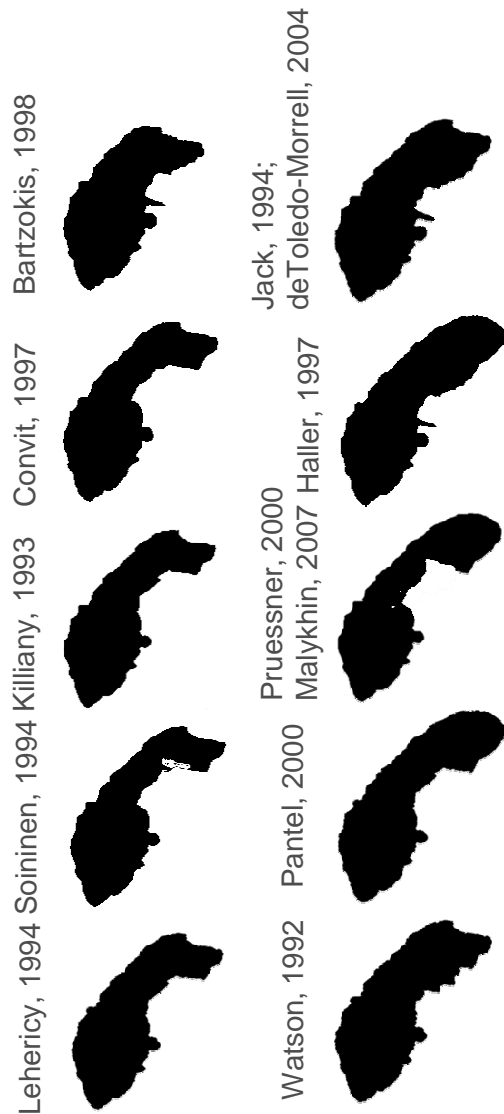
# AIM: achieve a Harmonized Protocol for Hippocampal Volumetry



# METHODS

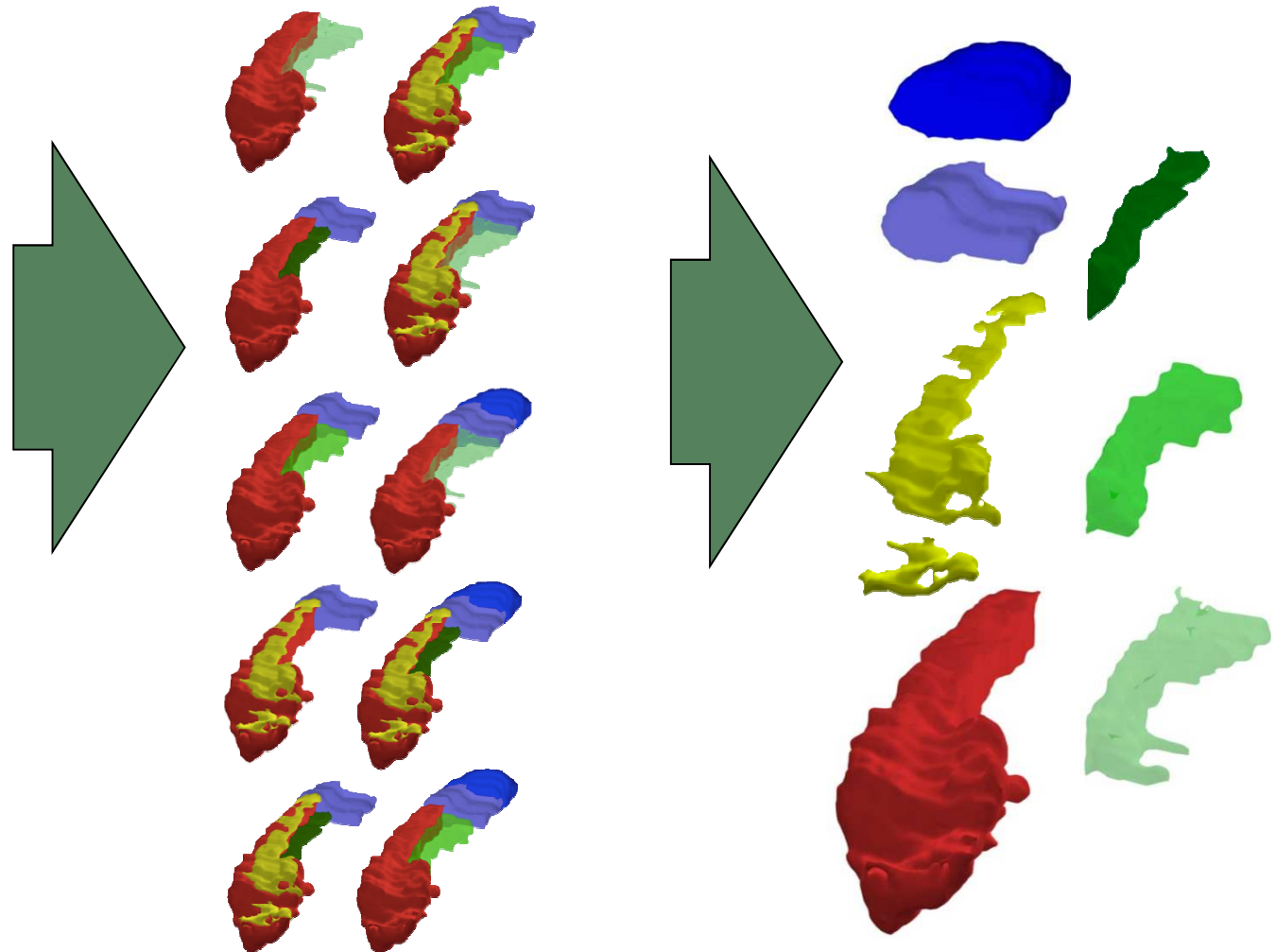
## Survey

(Boccardi et al., JAD 2011)



## Operationalization of differences into Segmentation Units

(Boccardi et al., accepted on Alzheimer's and Dementia)



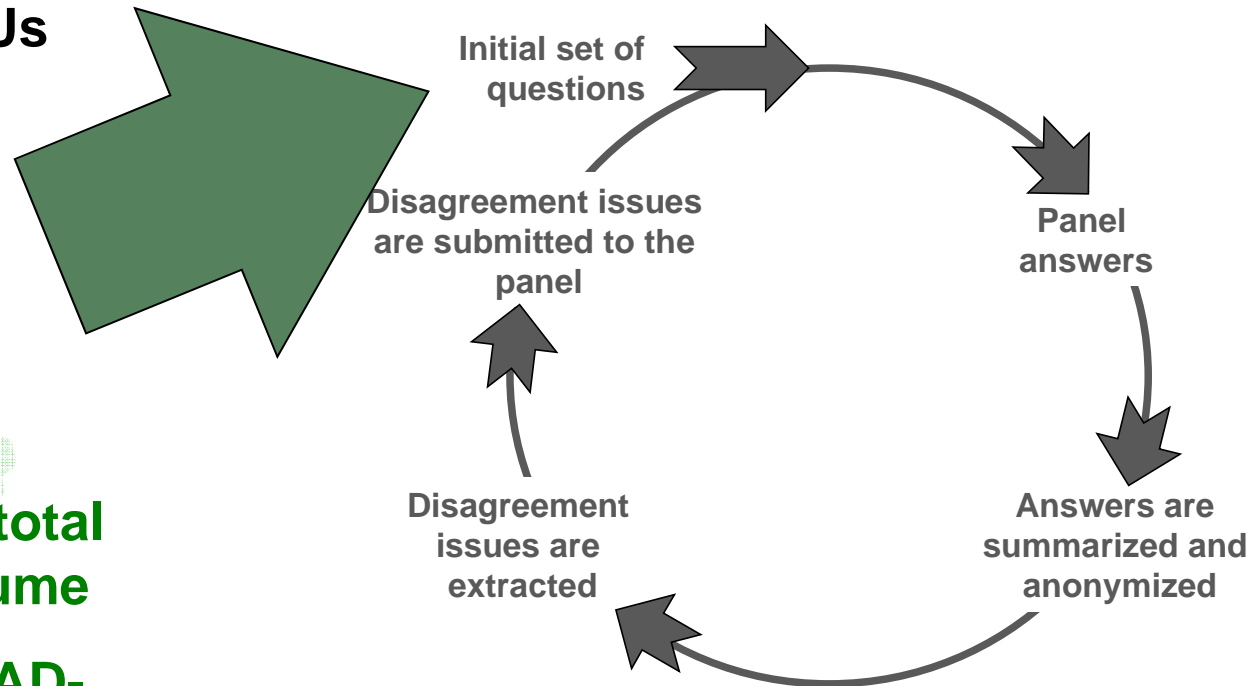
## Assessment of measurement properties of SUs

# METHODS

## 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  
Los Angeles



J. Barnes  
London



G. Bartzokis  
Los Angeles



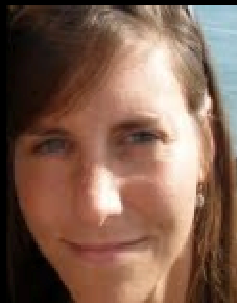
C. DeCarli  
Sacramento



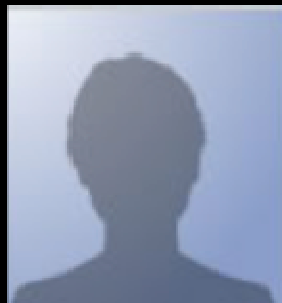
L. de Toledo-Morell  
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Amsterdam



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R. Killiany  
Boston



N. Malykhin  
Edmonton



J. Pruessner  
Montreal



H. Soininen  
Kuopio



L. Wang  
Chicago



C. Watson  
Detroit



H. Wolf  
Zurich



# METHODS

- **On-line questionnaire** accessible with **private credentials**
- **9-levels Lickert's scale** for expressing level of agreement
- **Boxes** for a) justification to answers b) free comments
- **Fisher's exact** (for Lickert) and **Binomial** (for dichotomized agreement/disagreement) to evaluate statistical significance for convergence

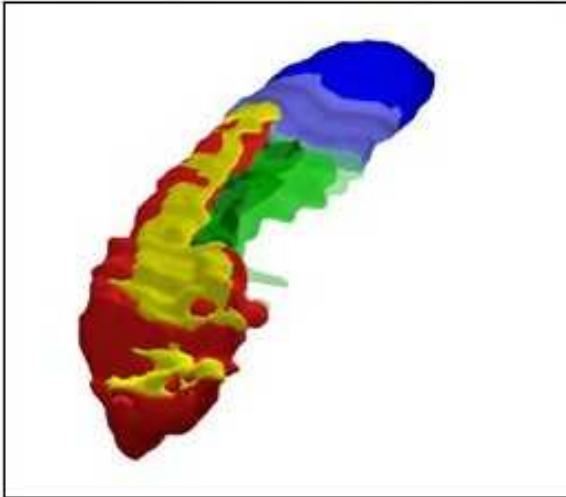
In subsequent rounds:

- Feedback about previous answers:
  - a. summary of **reasons** for different answers
  - b. **original answers** anonymized
  - c. **statistics** about convergence on previous rounds
  - (d. further info when possible/necessary)



# METHODS

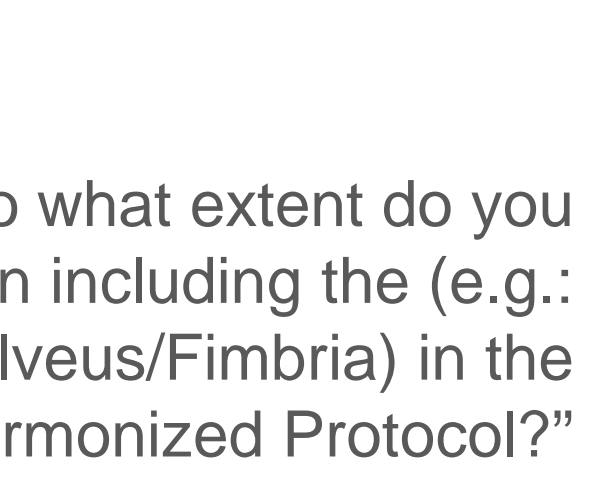
SUs composing the total hippocampus



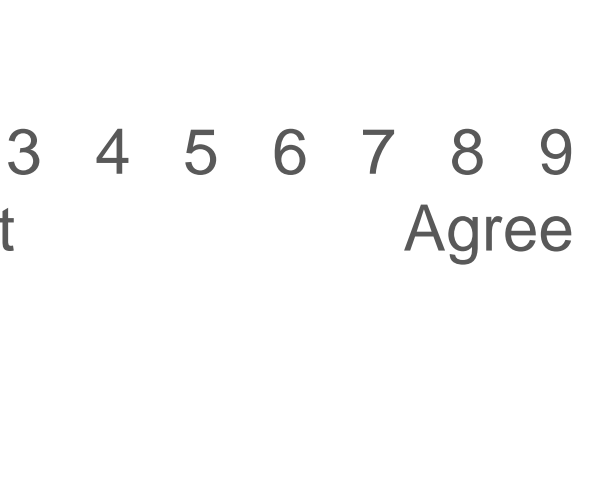
3D models and denomination of individual SUs



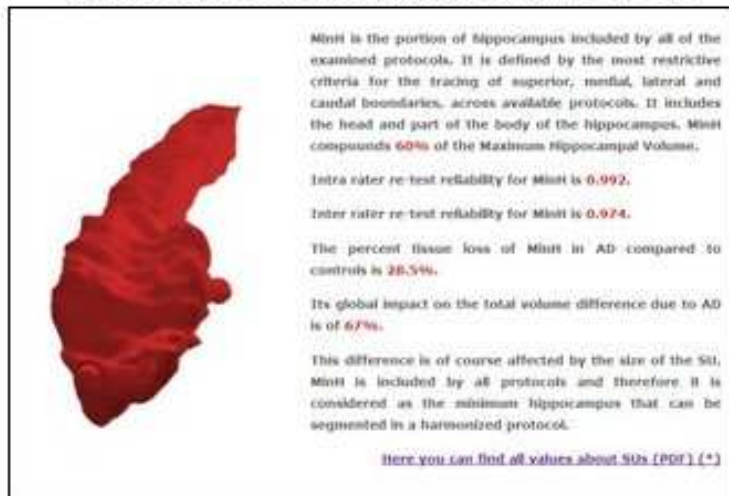
Interactive 3D models



representing panelists' choices



Quantitative information for individual SUs



“To what extent do you agree in including the (e.g.: Alveus/Fimbria) in the Harmonized Protocol?”

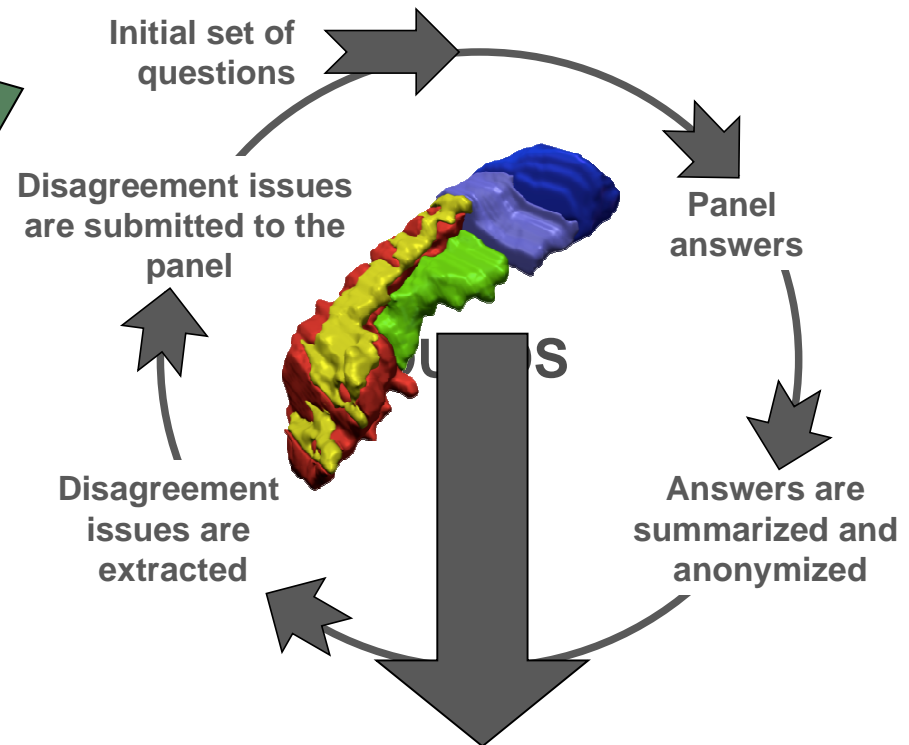
1 2 3 4 5 6 7 8 9  
Do not agree Agree

# RESULTS

## Assessment of measurement properties of SUs

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

## Delphi panel

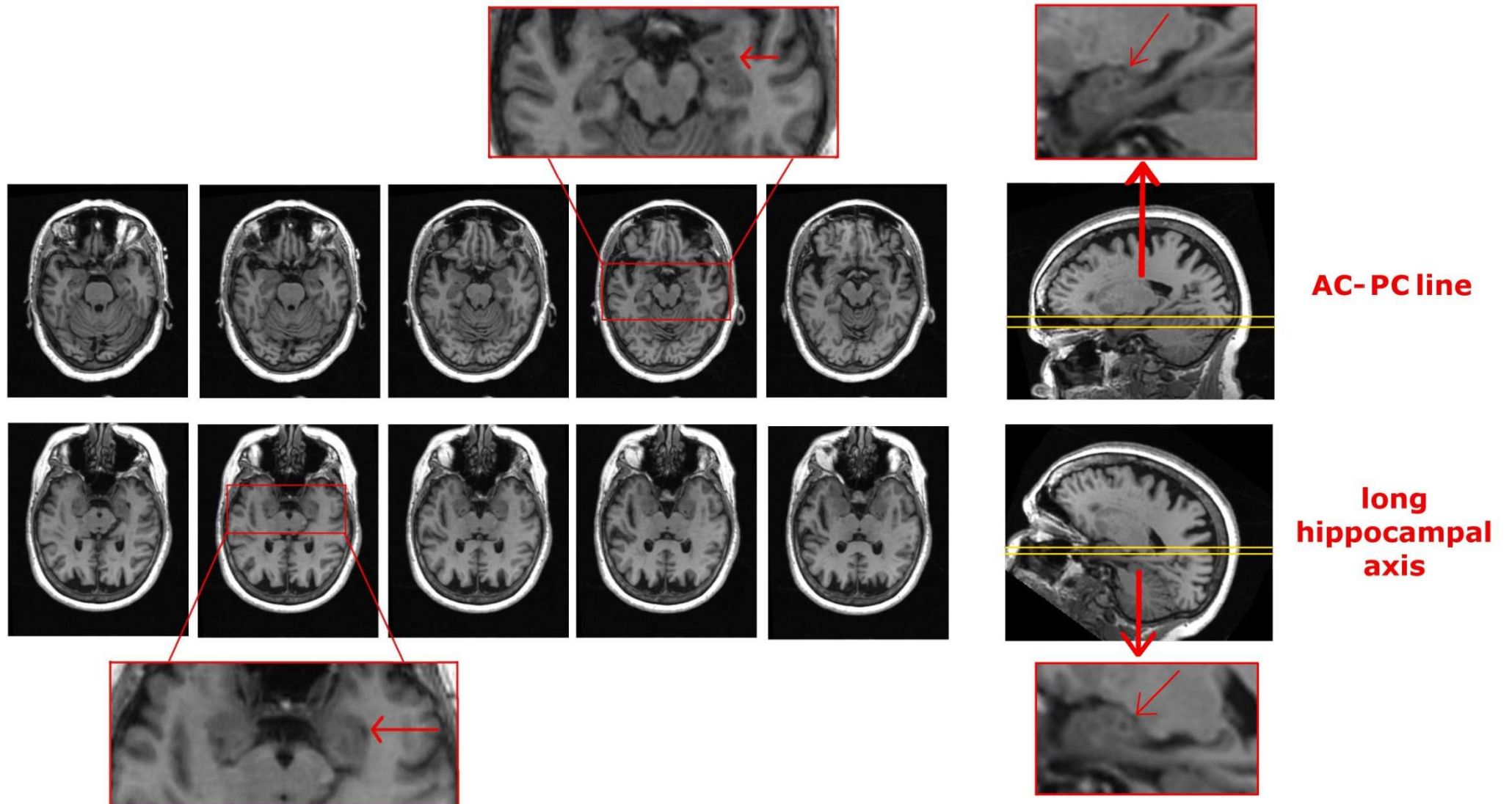


Covers 100% of hippo proper  
Captures 100% of AD atrophy  
Very high IRR & TRTR:  $<.96$

# RESULTS

	Round	Median	Likert scores			<i>p</i>
			9 8 7 6	5	4 3 2 1	
			Agree N (%)	Neutral N (%)	Disagree N	
<b>Segmentation Unit selection</b>						
Inclusion of alveus/fimbria	II	9	13 (81%)	0 (0%)	3 (19%)	0.021
Segmentation of subiculum (morphology - I choice)	III	7.5	11 (69%)	4 (25%)	1 (6%)	0.006
Segmentation of subiculum (horizontal - II choice)	III	-	13 (81%)	0 (0%)	3 (19%)	0.021
Inclusion of tail end	III	9	12 (75%)	2 (12.5%)	2 (12.5%)	0.013
Harmonized Hippocampus	II	8	14 (88%)	1 (6%)	1 (6%)	0.001
<b>Segmentation procedures</b>						
Disambiguating amygdala with 3D navigation	II	8	16 (100%)	0 (0%)	0 (0%)	<0.0001
Inclusion of vestigial tissue	III	-	10 (63%)	-	6 (37%)	n.s.
CSF pools	III	8	14 (88%)	0 (0%)	2 (12%)	0.004
Not visible structures (final definition)	III	8	16 (100%)	0 (0%)	0 (0%)	<0.0001
Separating Alveus/Fimbria from fornix	IV	8	12 (82%)	0 (0%)	1 (8%)	0.003
AC-PC Image orientation	V	9	11 (79%)	2 (14%)	1 (7%)	0.006

# RESULTS



# Discussion

## 1. Harmonized Protocol

- Consensual criteria for harmonized hippo segmentation are defined
- They are translated into an operational protocol
- The Harmonized Protocol now requires validation

## 2. Evidence-based Delphi panel

- The justification for answers showed that the quantitative information provided was actually used to weigh pros and cons of each choice, and complement personal experience
- Restrictive criteria for accepting decision (not just majority/median value, but significance at stat test)

## 3. Benchmark images

- 5 Master Tracers are completing segmentations based on the Harmonized Protocol, serving learning and certification of the “naïve” tracers in the validation phase

# FUTURE STEPS

## **1. Develop a qualification environment and thresholds for**

- naïve tracers
- automated algorithms

## **2. Validate on:**

- 1800 ADNI hippocampi segmented by 20 human tracers
- 20x2 (R&L) hippocampi with volume on pathology, neuronal density, and *ex vivo* MR

## **3. Availability of protocol and benchmark masks:**

- Until the end of validation process (summer 2013), restricted to beta-testers based on ad hoc agreements
- Free afterwards



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



## A HARMONIZED PROTOCOL FOR HIPPOCAMPAL VOLUMETRY: AN EADC-ADNI EFFORT

[About the Project](#)[Outcomes](#)[News & Events](#)[References](#)

### PUBLICATIONS

#### Full Papers

Frisoni GB, Jack CR.

Harmonization of magnetic resonance-based manual hippocampal segmentation: A mandatory step for wide clinical use.

Alzheimer's & Dementia, Volume 7, Issue 2, Pages 171-174, March 2011.

Jack CR, Barkhof F, Bernstein MA, Cantillon M, Cole PE, DeCarli C, Dubois B, Duchesne S, Fox NC, Frisoni GB, Hampel H, Hill DLG, Johnson K, Mangin J, Scheltens P, Schwarz AJ, Sperling R, Suhy J, Thompson PM, Weiner M, Foster NL.

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Journal of Alzheimer's Disease, Volume 26, Issue 0, Pages 61-75, January 2011.



# Acknowledgements

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

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

**All partners**

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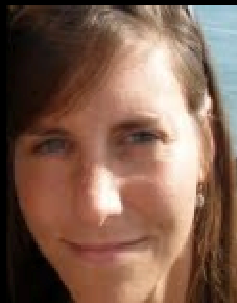
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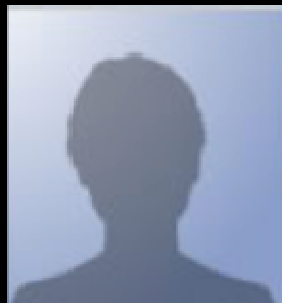
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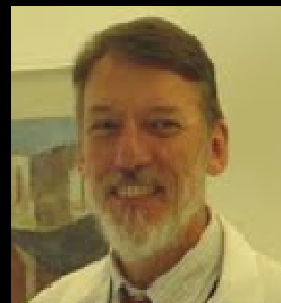
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