



IPA, The Hague, September 8, 2011

# Development of a harmonized protocol for hippocampal tracing

*An EADC-ADNI joint effort*

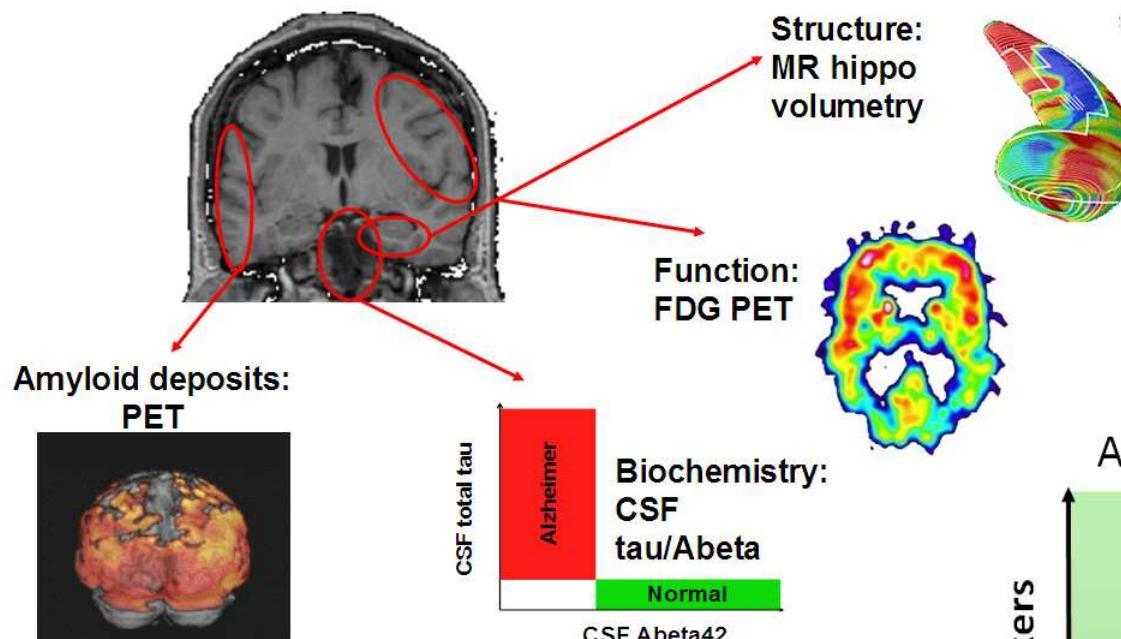
Martina Bocchetta, PsyD

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

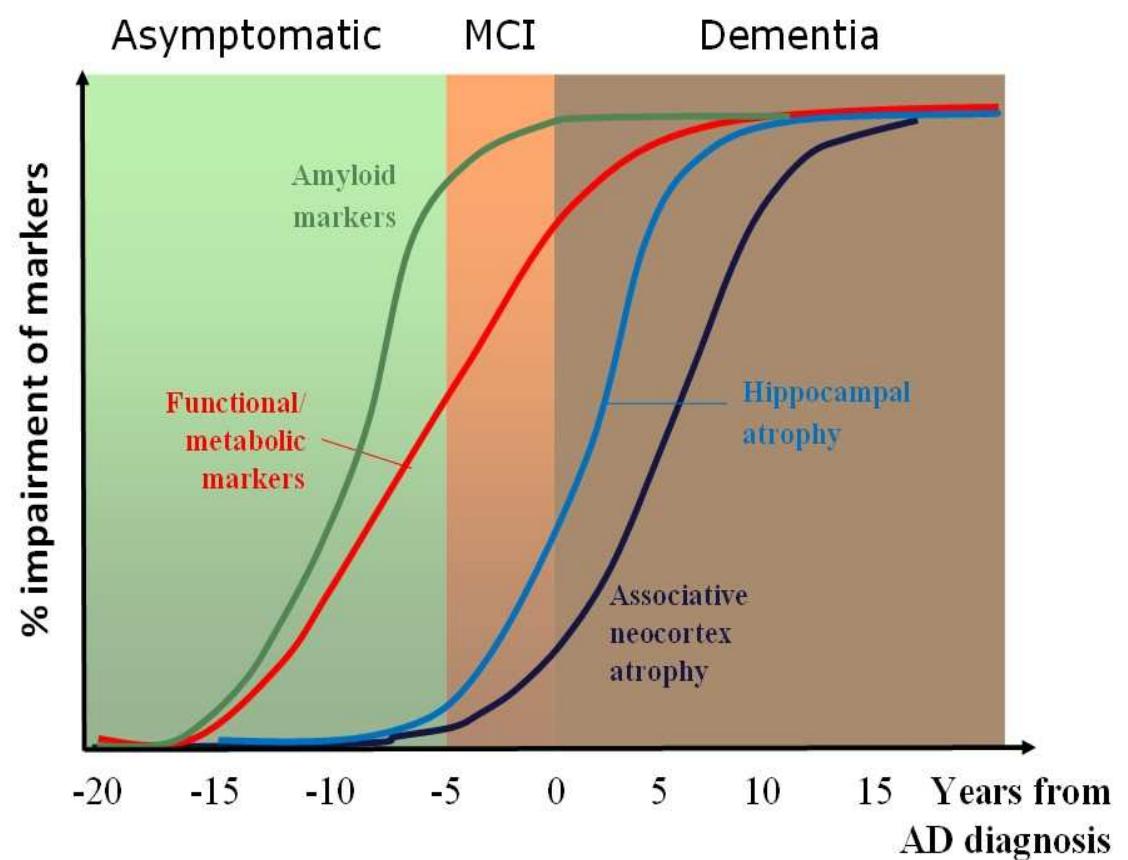
funded by: alzheimer's association\*

# BACKGROUND

## Revised Criteria (early diagnosis)



Dubois et al., Lancet Neurol 2007;6:734-736  
Jack et al., Alzheimer Dement 2011;1-6



Frisoni et al., Nat Rev Neur 2010;6:66-77

# BACKGROUND

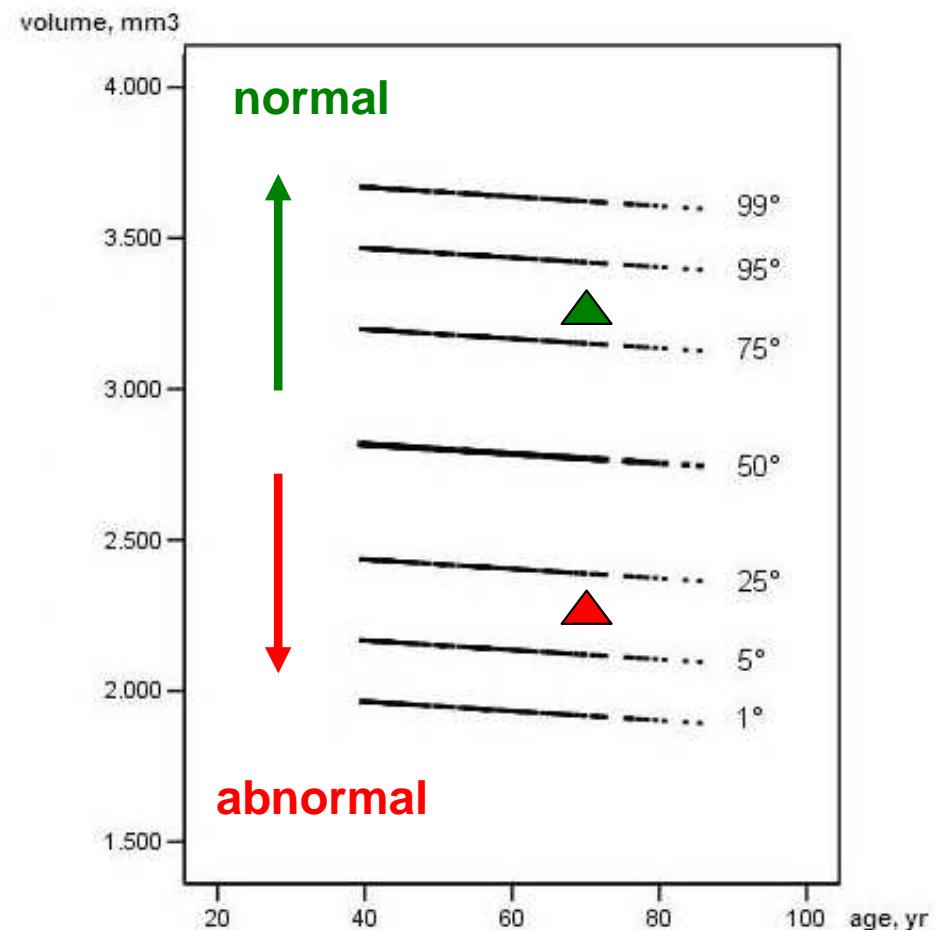
## Hippocampal atrophy as a diagnostic marker

marker for disease state and neurodegeneration progression



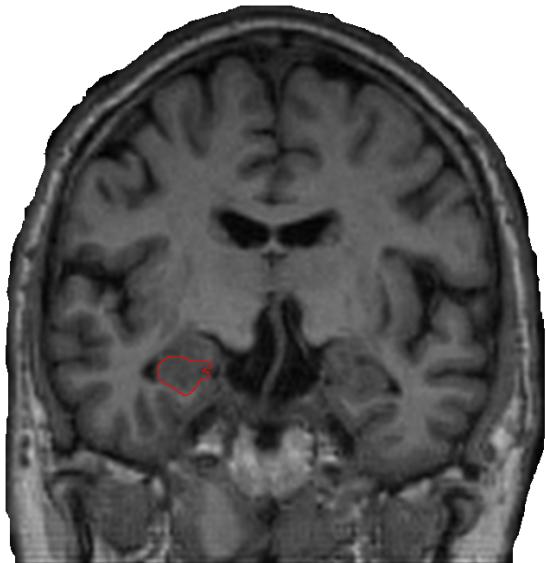
Supportive marker for early diagnosis

Outcome in clinical trials disease-modifying drugs

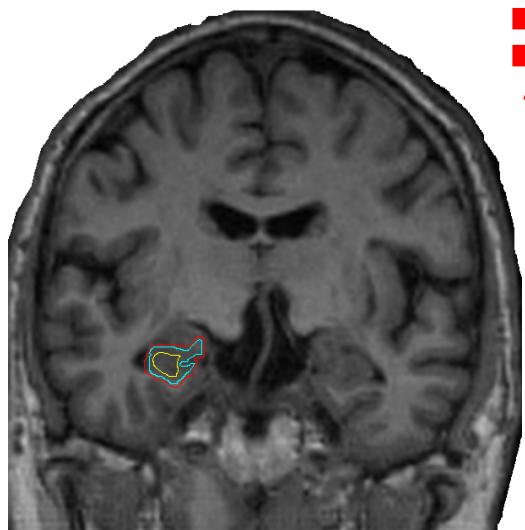


# BACKGROUND

## The effect of different segmentation protocols



# Volume



A red symbol consisting of two parallel diagonal lines forming an '≠' shape, indicating non-equivalence.



A red symbol consisting of two parallel diagonal lines forming an '≠' shape, indicating non-equivalence.

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 subiculum complex & uncal cleft w/ border separating subiculum complex from parahippocampal gyrus	4.903	5.264
Zipursky et al.	Regional outline at choroidal fissure	Not mentioned	The interface of hippocampus and parahippocampal gyrus WM	1.990	2.070

# Not comparable

# **BACKGROUND**

## **Need for Homogeneity**

**STANDARDIZED BIOMARKER**

**FOR EARLY DIAGNOSIS  
CLINICAL TRIALS**

**AUTOMATED SEGMENTATION ALGORITHMS**

# **AIM**

**To develop a harmonized protocol  
for hippocampal volumetry**

**INTERNATIONAL CONSENSUS**

# The Workgroup

<b>EADC CENTERS</b>	N Fox, London, UK A Simmons, London, UK GB Frisoni, Brescia, IT S Teipel, Rostock, DE	C Hock, Zurich, CH L-O Wahlund, Stockholm, SE H Soininen, Kuopio, FI	F Barkhof / P Scheltens, Amsterdam, NE B Dubois / S Lehérici, Paris, FR H Hampel / J Pantel, Univ. Frankfurt, DE
<b>ADNI CENTERS</b>	J Kaye, Portland, OR CR Jack, Rochester, MN C DeCarli, UC Davis, CA G Bartzokis, UCLA, CA	M De Leon, New York, NY R Killiany, Boston USM, MA PM Thompson, LoNI, UCLA, CA J Csernansky, Northwestern U, ILL	L deToledo-Morrell, Rush UMC, Chicago, ILL D Bennet, Rush UMC, Chicago, ILL M Weiner / S Mueller, UCSF, CA M Albert, John Hopkins U, Baltimore, MD
<b>OTHER CENTERS</b>	C Watson, WSU, Detroit, MI J O'Brien, Newcastle, UK	J Pruessner, McGill U, QC, Canada	R Camicioli / N Malykhin, U Alberta, AB, Canada
<b>POPULATION BASED STUDIES</b>	SMART-Medea Study, MI Geerlings, NE	PATH through life, P Sachdev /JJ Maller	T denHeijer, Rotterdam Scan Study, NE
<b>STATISTICAL WORKING GROUP</b>	P Pasqualetti, AFaR, Roma, IT	S Duschesne, Laval Univ, QC, Canada	L Collins, MNI, McGill, Montreal, Canada
<b>ADVISORS</b>	<i>Clinical issues:</i> P J Visser, Maastricht, NE <i>EADC PIs:</i> B Winbald / L Froelich	<i>Dissemination &amp; Education:</i> G Waldemar, Copenhagen, DK <i>ADNI PI:</i> M Weiner, UCSF, CA	<i>Population Studies:</i> L Launer, NIA, Bethesda / W Jagust, Berkeley, CA
<b>Personnel in Brescia</b>	<i>Coordination and execution:</i> M Boccardi, M Bocchetta, R Ganzola	<i>Technical issues:</i> A Redolfi, G Corbetta, D Tolomeo	<i>Advisor:</i> M Pievani

# Preliminary Phase

## Operationalization of differences

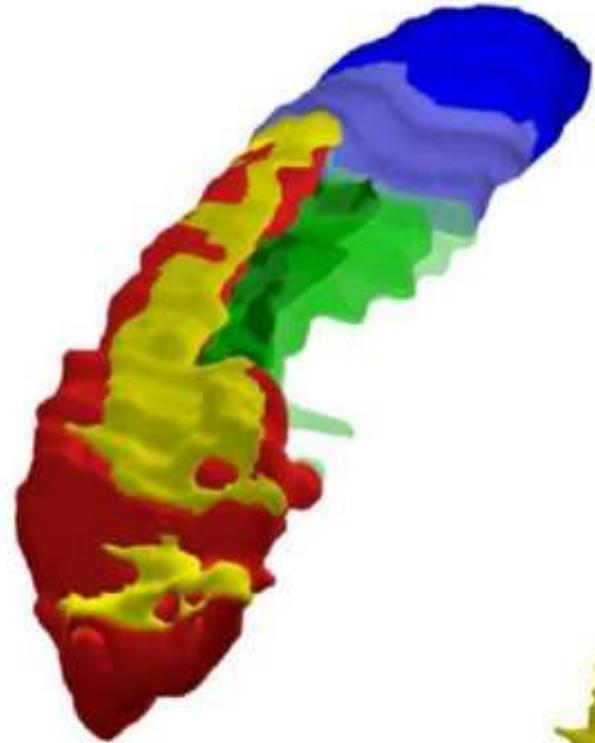
Selection of 12 Protocols

Certified extraction of landmarks

Extraction of (harmonized) differences

Operationalization of differences into SUs





Alveus/Fimbria



Minimum Hippocampus



Crura



Oblique Line



Tail End



Morphology



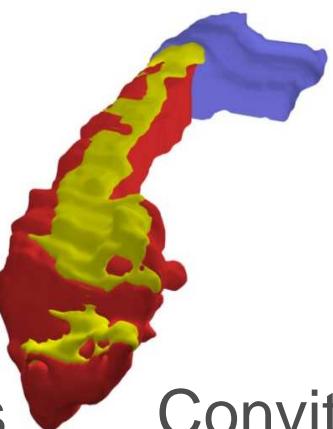
Horizontal Line



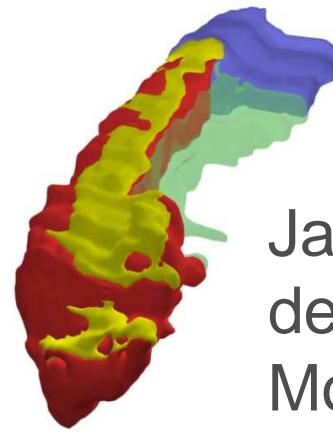
LENITEM



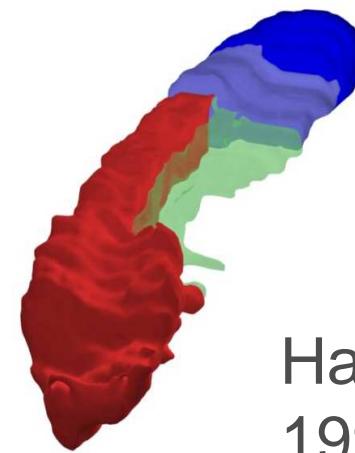
Bartzokis,  
1998



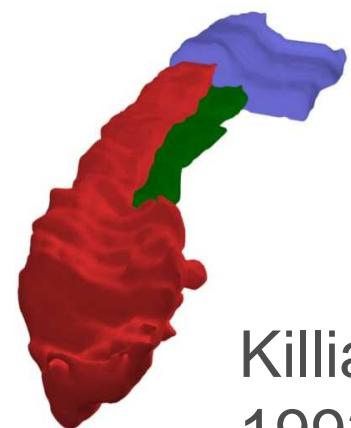
Convit,  
1997



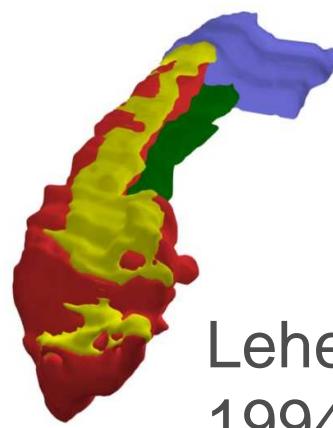
Jack, 1994;  
deToledo-  
Morrell,  
2004



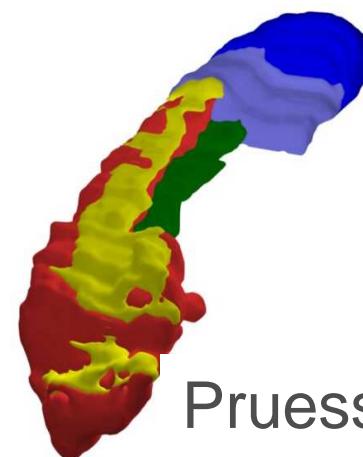
Haller,  
1997



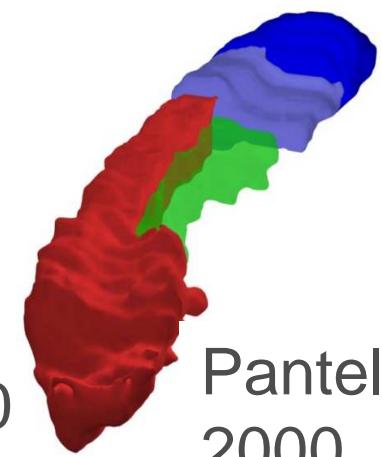
Killiany,  
1993



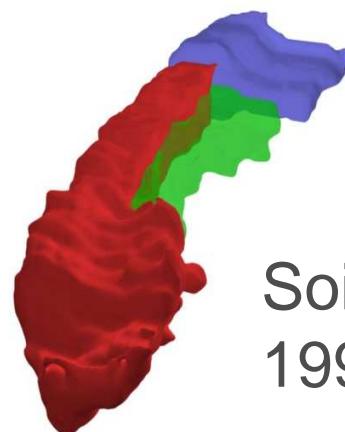
Lehericy,  
1994



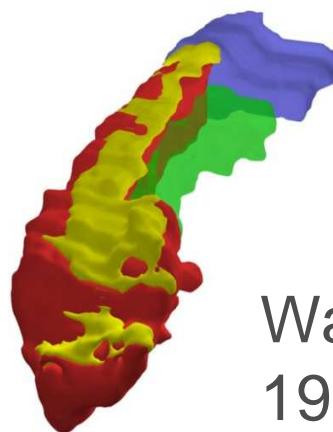
Pruessner, 2000  
Malykhin, 2007



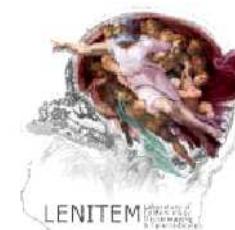
Pantel,  
2000



Soininen,  
1994



Watson,  
1992



# Preliminary Phase

## Quantification of segmentation units features

Effect on re-test variability

Contribution

- to total volume
- to AD-related differences



**Delphi  
Questionnaires**

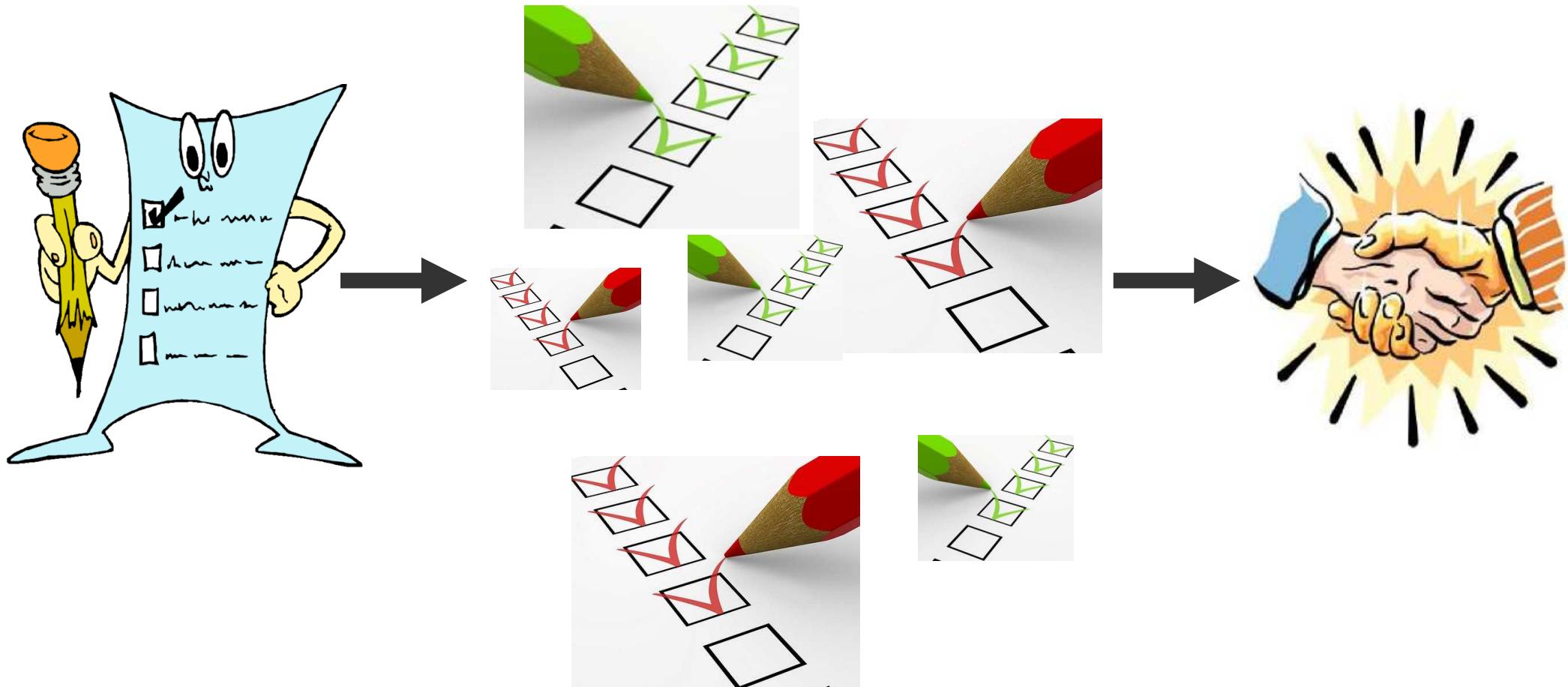


	Intra-rater	Inter-rater	LEFT HIPPOCAMPUS										RIGHT HIPPOCAMPUS									
			Controls (n=31)	% of total hippoc.	MCI (n=31)	% of total hippoc.	AD (n=33)	% of total hippoc.	% diff MCI vs CTR (impaired)	% MCI vs CTR	% diff AD vs CTR (impaired)	% AD vs CTR	% diff MCI vs CTR (impaired)	% MCI vs CTR	% diff AD vs CTR (impaired)	% AD vs CTR						
<b>MinH</b>	0.1	0.1	1467 (294)	10%	3122 (683)	10.23 (235)	1023 (255)	10.23 (235)	6.5%	3%	19%	7%	6.5%	6.5%	6.5%	6.5%	0.1	0.1	0.1	0.1		
<b>Alveus/fimbria</b>	0.1	0.1	1467 (294)	11%	232 (81)	220 (44)	213 (64)	9.5%	5%	12%	4.5%	5%	5%	12%	4.5%	5%	5%	5%	5%	5%	5%	
<b>Subiculum</b>	0.1	0.1	248 (45)	10%	243 (72)	10%	216 (53)	9.5%	3.5%	10%	3.5%	3.5%	3.5%	10%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	
<b>Oblique line</b>	0.1	0.1	243 (72)	10%	243 (72)	10%	220 (44)	10.23 (235)	21.5%	10%	10%	10%	21.5%	10%	10%	10%	10%	10%	10%	10%	10%	
<b>Tail</b>	0.1	0.1	1467 (294)	12%	485 (110)	20%	311 (78)	31.1 (101)	21%	21%	27%	20.5%	21%	27%	20.5%	21%	27%	20.5%	21%	27%	20.5%	
<b>Crura</b>	0.1	0.1	1467 (294)	12%	190 (70)	8%	177 (70)	14.6 (69)	6.5%	2.5%	2.5%	6.5%	14.6 (69)	6.5%	2.5%	6.5%	14.6 (69)	6.5%	2.5%	6.5%	14.6 (69)	
<b>Morphology</b>	0.1	0.1	243 (72)	12%	296 (110)	12%	206 (68)	30%	18.5%	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	
<b>Horizontal line</b>	0.1	0.1	234 (72)	12%	296 (110)	12%	206 (68)	30%	18.5%	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	
<b>Tail</b>	0.1	0.1	485 (110)	12%	2443 (291)	10%	197 (54)	1788 (424)	20%	100%	27%	100%	197 (54)	20%	100%	27%	197 (54)	20%	100%	27%	197 (54)	
<b>Crura</b>	0.1	0.1	190 (70)	12%	296 (120)	12%	206 (68)	30%	18.5%	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	30%	18.5%	14%	206 (68)	
<b>End Tail</b>	0.1	0.1	296 (120)	12%	2443 (291)	12%	197 (54)	1788 (424)	20%	100%	27%	100%	197 (54)	20%	100%	27%	197 (54)	20%	100%	27%	197 (54)	
<b>MaxHV</b>	0.1	0.1	2443 (291)	12%	2443 (291)	12%	1788 (424)	12.14 (307)	100 (248)	6.5%	6.5%	6.5%	100 (248)	6.5%	6.5%	6.5%	100 (248)	6.5%	6.5%	6.5%	100 (248)	
<b>Subiculum</b>	0.1	0.1	243 (72)	12%	255 (47)	11%	258 (71)	225 (65)	4%	0.5%	12%	5%	258 (71)	225 (65)	4%	0.5%	12%	5%	0.5%	12%	5%	
<b>Oblique line</b>	0.1	0.1	255 (47)	12%	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6.5%	208 (89)	184 (56)	8%	4%	18%	6.5%	4%	18%	6.5%	
<b>Tail</b>	0.1	0.1	225 (79)	12%	487 (151)	20%	340 (115)	349 (131)	7.5%	4%	17%	6.5%	340 (115)	349 (131)	7.5%	4%	17%	6.5%	4%	17%	6.5%	
<b>Morphology</b>	0.1	0.1	181 (51)	12%	181 (51)	12%	160 (49)	140 (49)	4.5%	2.5%	2.5%	6.5%	160 (49)	140 (49)	4.5%	2.5%	2.5%	6.5%	4.5%	2.5%	6.5%	
<b>Horizontal line</b>	0.1	0.1	225 (79)	12%	301 (120)	12%	181 (133)	209 (110)	40%	30%	31%	15%	209 (110)	40%	30%	31%	15%	15%	31%	15%		
<b>Tail</b>	0.1	0.1	487 (151)	12%	349 (115)	12%	349 (131)	0.001	0.001	0.999	<-0.0005	0.001	349 (115)	0.001	0.001	0.999	<-0.0005	0.001	0.001	0.999	<-0.0005	
<b>Crura</b>	0.1	0.1	187 (75)	12%	169 (68)	0.37	0.023	0.17	0.058	0.17	0.058	0.17	0.058	0.17	0.058	0.17	0.058	0.17	0.058	0.17	0.058	
<b>End Tail</b>	0.1	0.1	301 (120)	12%	181 (133)	10%	-0.0005	0.008	0.394	-0.0005	0.008	-0.0005	0.394	-0.0005	0.008	0.394	-0.0005	0.008	0.394	-0.0005		
<b>MaxHV</b>	0.1	0.1	2429 (303)	20%	2029 (372)	10%	1820 (369)	1820 (369)	16.5%	100%	25%	100%	1820 (369)	16.5%	100%	25%	100%	16.5%	100%	25%	100%	



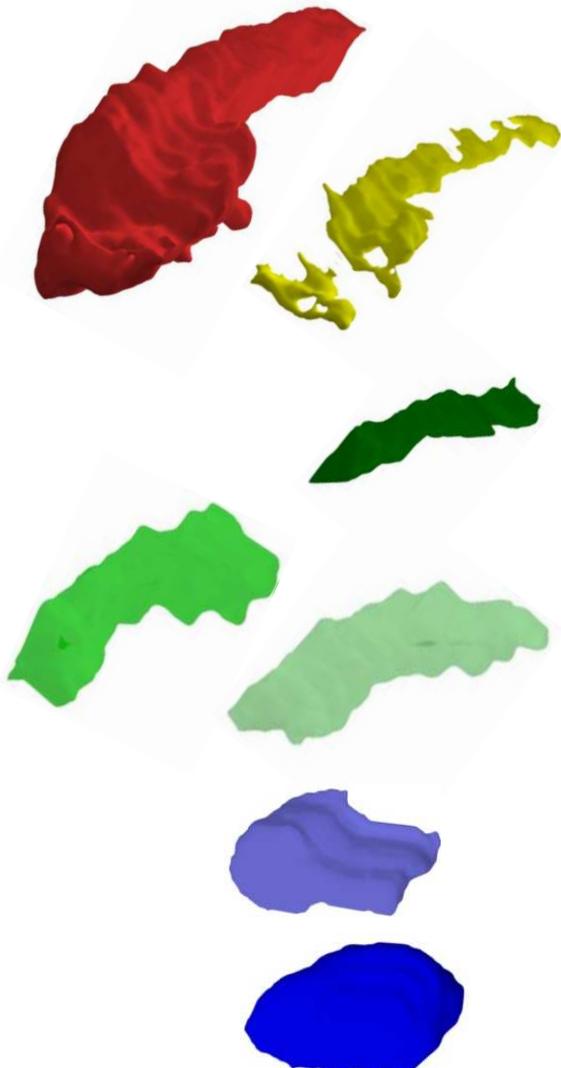
FUNDED BY THE ALZHEIMER'S ASSOCIATION AND UNRESTRICTED GRANTS FROM LILLY INTERNATIONAL AND WYETH INTERNATIONAL (A PART OF THE PIZER GROUP)

# Delphi Method



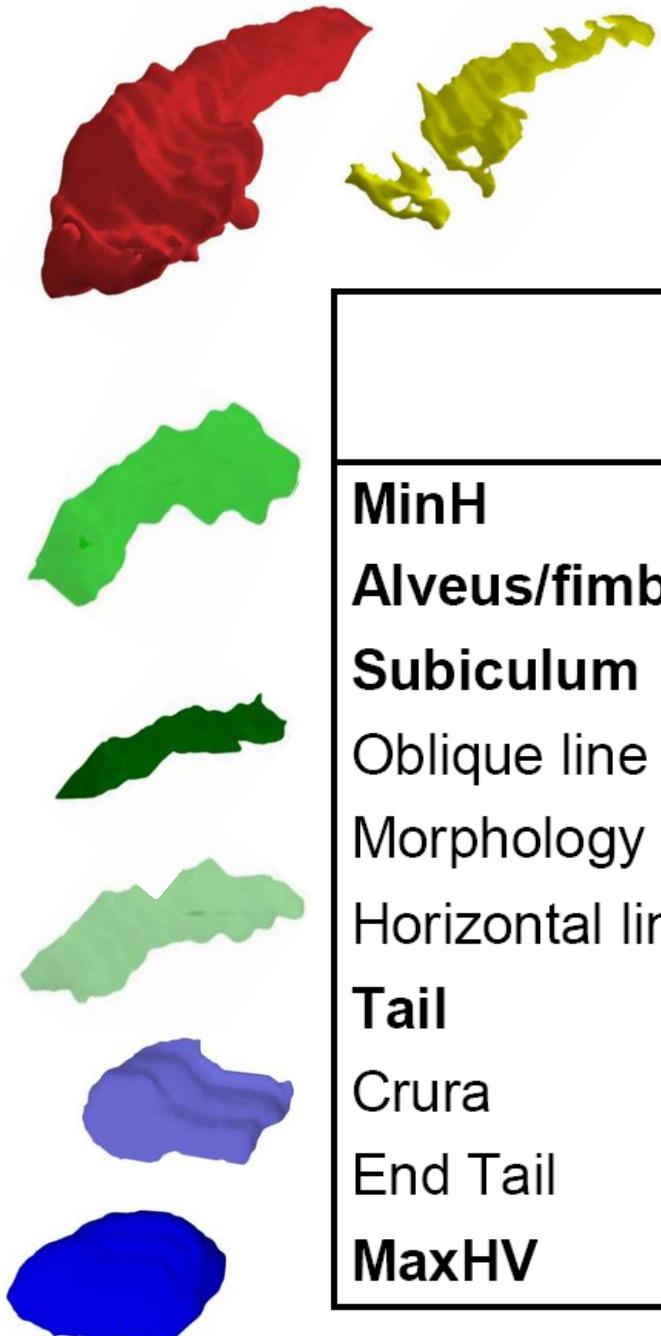
# Reliability Value

ADNI subjects: 8 controls, 12 patients.



	Intra-rater	Inter-rater
<b>MinH</b>	0.992	0.974
<b>Alveus/fimbria</b>	0.863	0.885
MinH+Alveus/fimbria	0.993	0.973
<b>Subiculum</b>		
Oblique line	0.964	0.907
Morphology	0.981	0.937
Horizontal line	0.980	0.932
<b>Tail</b>		
Crura	0.998	0.937
End Tail	0.988	0.905
<b>MaxHV</b>	0.993	0.967

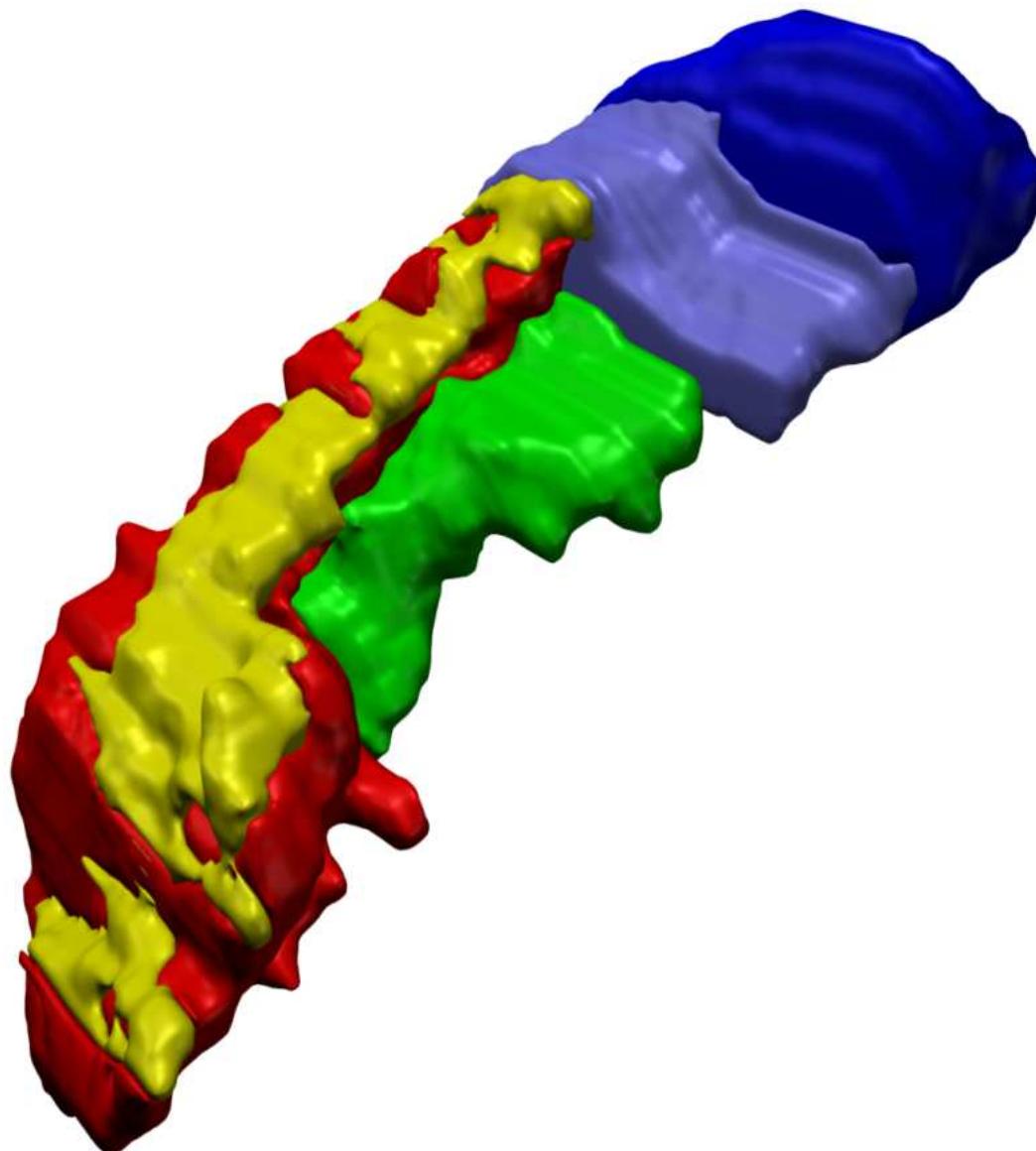
# Informative value for AD-related atrophy



ADNI subjects: 31 controls, 46 patients.

	% of total hippo	% diff AD vs CTR	% AD vs CTR (impact)	p-value AD vs CTRL
<b>MinH</b>	60%	29%	67%	<0.0005
<b>Alveus/fimbria</b>	11%	16%	6%	0.05
<b>Subiculum</b>	9%	15%	5.5%	0.04
Oblique line	8%	14%	4%	0.06
Morphology	9%	15%	5.5%	0.04
Horizontal line	9%	14%	5%	0.05
<b>Tail</b>	20%	28%	21.5%	0.001
Crura	8%	24%	7%	0.03
End Tail	12%	31%	14.5%	0.006
<b>MaxHV</b>	100%	26%	100%	<0.0005

# Delphi Panel – Preliminary Results



# Next Steps

## Final Delphi Rounds

Harmonized Protocol Definition

## Harmonized Protocol Validation

neuropathological data and currently used protocols

## Web-based system for Tracer Qualification

future use in research and clinical trials

by 2012

# Acknowledgements

**Alzheimer's Association  
Lilly and Wyeth/Pfizer**

and

**All partners!**

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

Contact: [hippocampal.protocol@gmail.com](mailto:hippocampal.protocol@gmail.com)