AIC - Honolulu, July 10

Development of a harmonized protocol for hippocampal tracing
An EADC-ADNI joint effort

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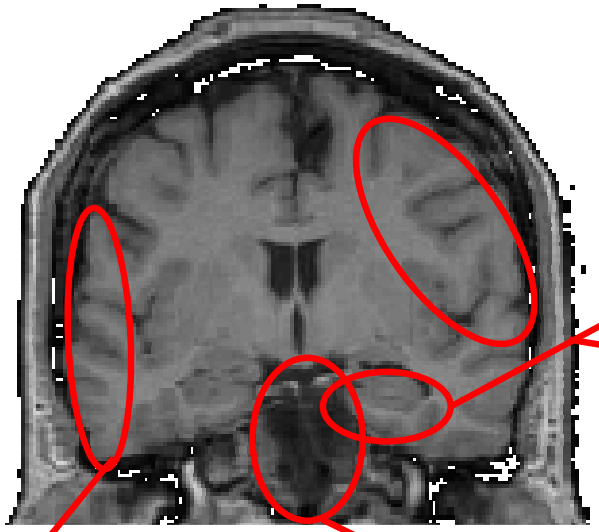
DISCLOSURES

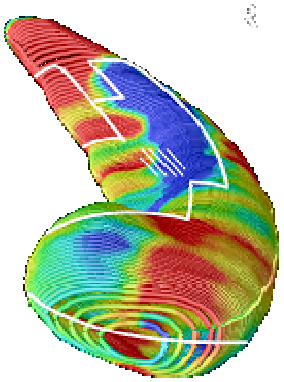
Funded in part thanks to an unrestricted grant by Lilly and Wyeth

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; **Jack** Contract – Pfizer; consulting – Élan; **Lehericy** Consultant - EISAI, Janssen-Cilag

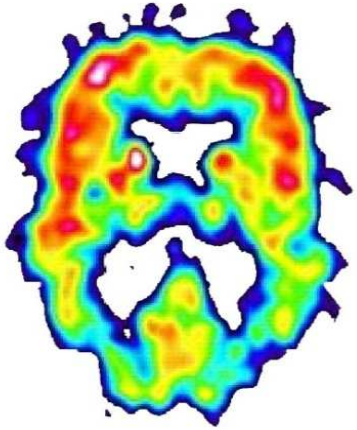
BACKGROUND
Hippocampal volume as a diagnostic marker



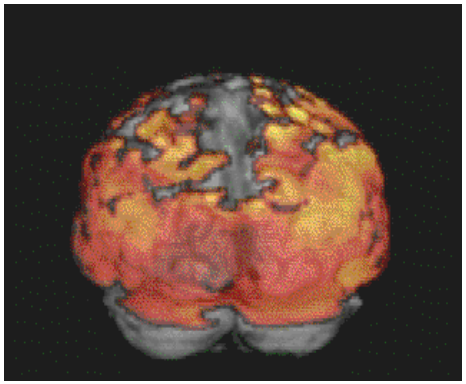
Structure:
MR hippo volumetry

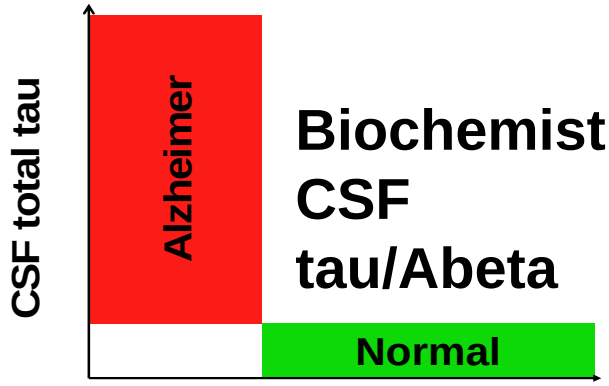


Function:
FDG PET



Amyloid deposits:
PET





Biochemistry:
CSF
tau/Abeta

Dubois, Feldman et al.,
Lancet Neurol 2007

BACKGROUND

Hippocampal volume as an outcome measure in trials of disease modifiers

Drug	Study	Effect	Segment. method	Ref
Tramiprosate	Alphase	68% (100 mg) 120% (150 mg)	Not mentioned	Gauthier et al., JNHA 2009
Atorvastatin	ADCLT	"CHV* mm^3 -134±174 vs -583±354 *p*> .05"	Manual protocol Insausti et al., 1998 AJNR; Machulda et al., 2001, Neuroimage	Sparks et .a,l CCJM,2008
	LEADe	"significant at *p*<.05"	MIDAS (semiautomated)	Jones et al., Alz&Dem 2008 Feldman et al., Neurology 2010
AN1792		"CHV* % 3.78±2.63 vs 2.86±3.19 *p* = 0.124"	Manual protocol Watson et al., 1992, Neurology	Fox N et al., Neurology, 2005
Xaliproden	Sanofi-Aventis Trials	"significant atrophy" §	Not mentioned	From Vellas B et al. (Review), Lancet Neurol.,2008
Donepezil		"CHV* % -6.14±3.49vs -4.50±2.28 *p*= 0.07" ε4 carriers only	Manual protocol Jack et al., 1989;Radiology Jack et al., 2004; Neurology	Jack CR et al., Neurobiol. Aging, 2008

* CHV= Change in hippocampal volume; § referenced link not working

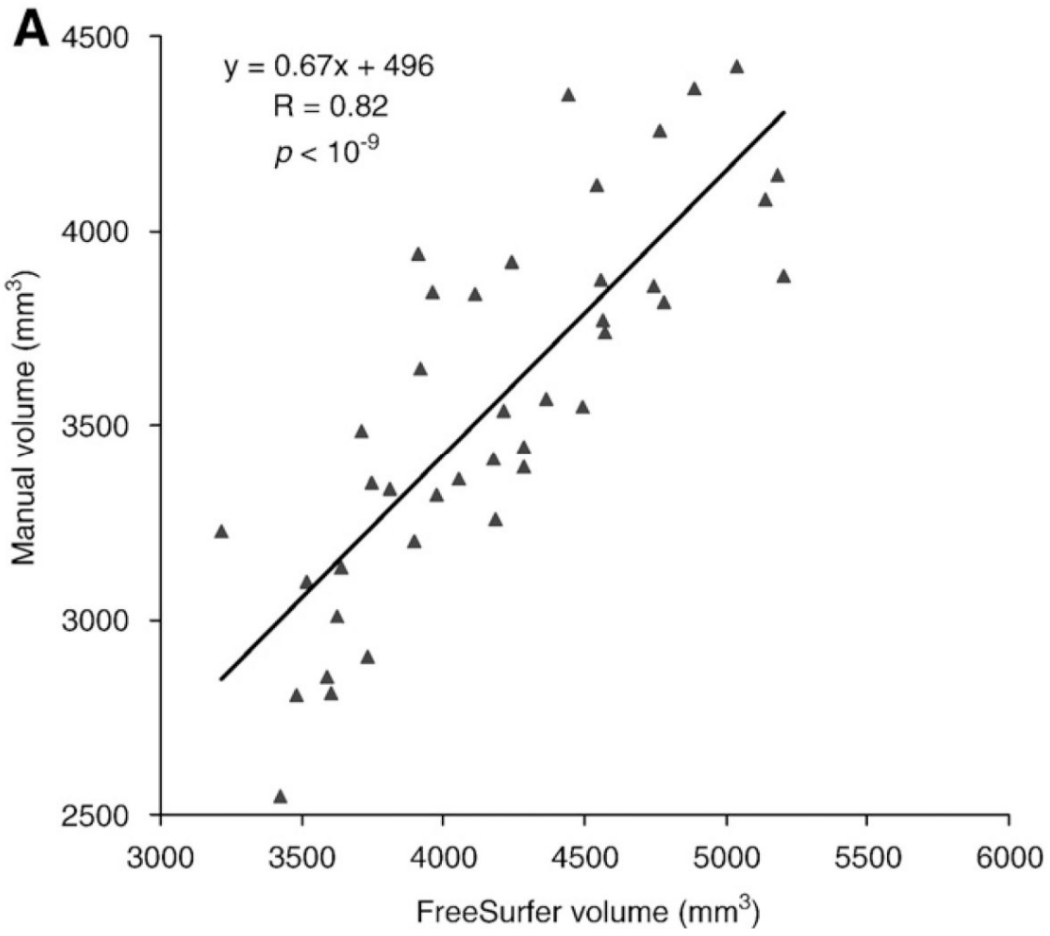
BACKGROUND
The effect of segmentation protocols on hippocampal volume

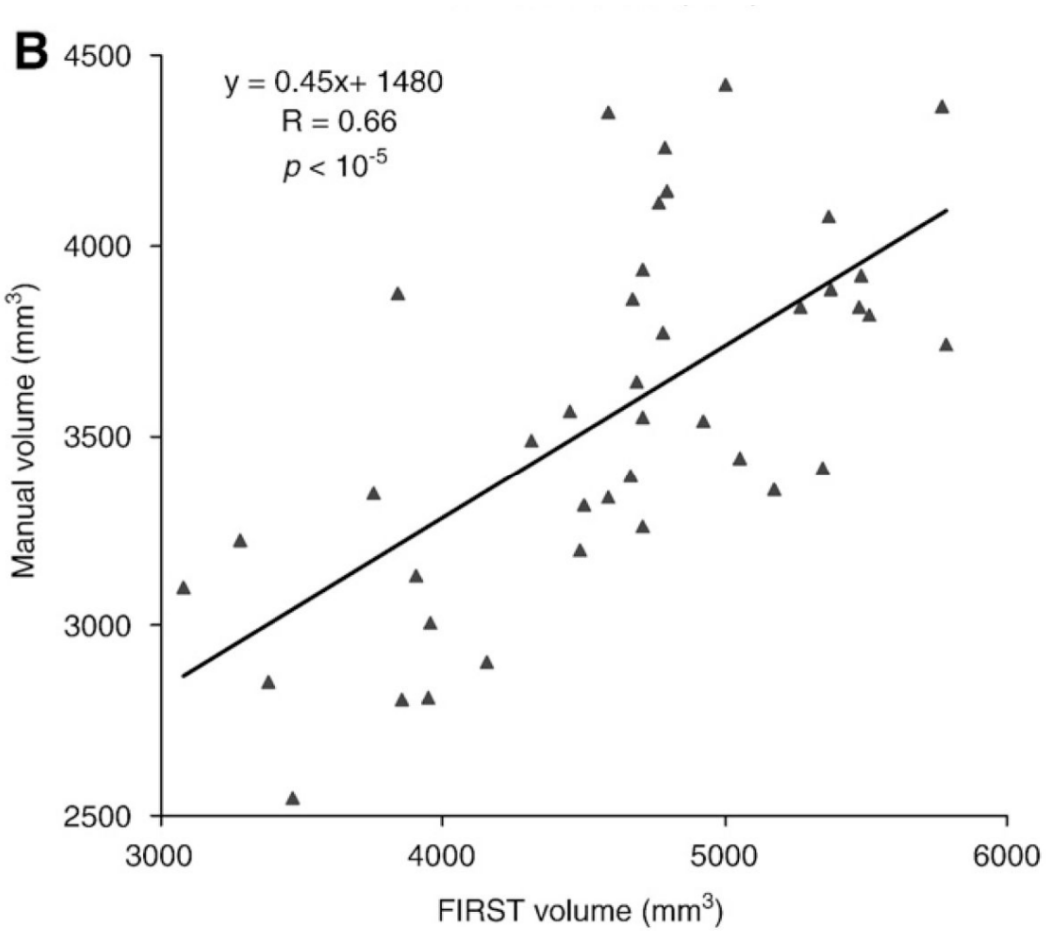
Ref.	Med border	Lat border	Inf border	Norm. hippo vol (cm^3)	
				Left	Right
Watson et al.	Mesial edge of temporal lobe	Temp horn of lat ventr	Incl subicular complex & uncal cleft w/ border separating subicular complex from parahippo gyrus	**4.903**	**5.264**
Zipursky et al.	Regional outline at choroidal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

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

BACKGROUND

Hippocampal volume (manual segmentation) as gold standard for automated segmentation algorithms





Morey et al., NeuroImage 2009

AIMS

IMMEDIATE: To operationalize protocols differences in order to quantify their impact on:

- test-retest variability
- total hippo volume
- differences between AD and controls

FINAL: To feed quantitative info to a panel of experts to achieve a consensus for a harmonized protocol with a Delphi procedure

OPERATIONALIZATION
Selection of segmentation protocols

From the pool of (original) protocols identified by Geuze 2005 (n=14) and by Konrad 2009 (n=42), we selected 10 protocols based on:

i) 3D T1 MRI with field strength greater than 1 Tesla
ii) only and the whole (most) hippocampus
iii) reliability measures on at least 10 subjects
iv) slice thickness lower than 3 mm
v) validated on AD/MCI samples, or most used in the AD literature

+ 2 further (particularly detailed) protocols

OPERATIONALIZATION
Authors' check

For each protocol:
features extraction, tracing and author's certification

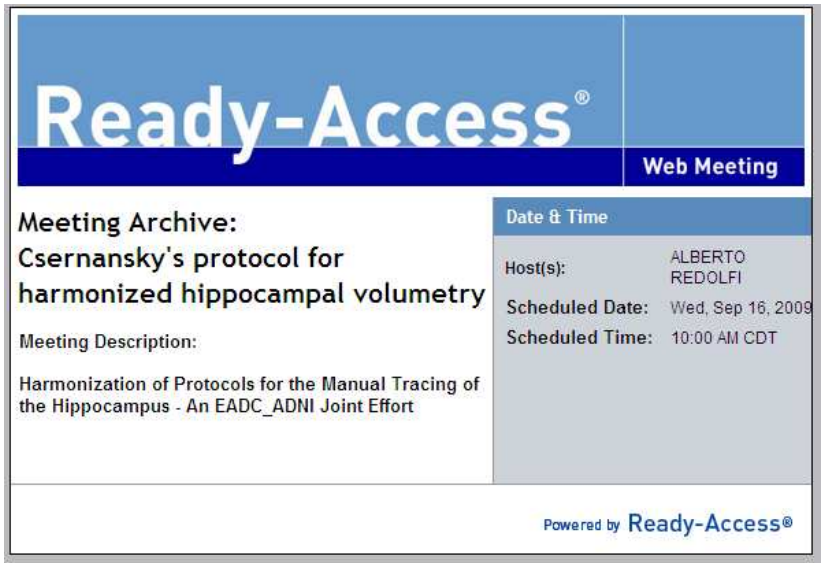
Areas explicitly included	Areas explicitly excluded	Most anterior slice	Most posterior slic
CA regions, dentate gyrus, subiculum, alveus, fimbria, part of the fasciolar gyrus (FG)	Andreas-Retzius gyrus (ARG), the part of the FG that is adjacent to ARG, crus of fornix	slice where one of the following is visible: alveus, temporal horn of lateral ventricle (uncal recess) or amygdala	slice where an ovoid mas gray matter started to app inferomedially to the trigone lateral ventricle

BOUNDARIES			
	Lateral border	Inferior border	Medial border	Superior border
HEAD	temporal horn of lateral ventricle (uncal recess)	uncal cleft (if visible)	CSF of ambient cistern	temporal horn of lateral ver (uncal recess) and alve
BODY	temporal horn of lateral ventricle (uncal recess)	White matter of the parahippocampal gyrus	CSF of ambient cistern	superior ex quadrigem
TAIL	Discrimination of HT from FG and crus of fornix using arbitrary borders	adjacent white matter	atrium of lateral ventricle	Discrimination using arbitra

CTRL

AD

X 12



OPERATIONALIZATION

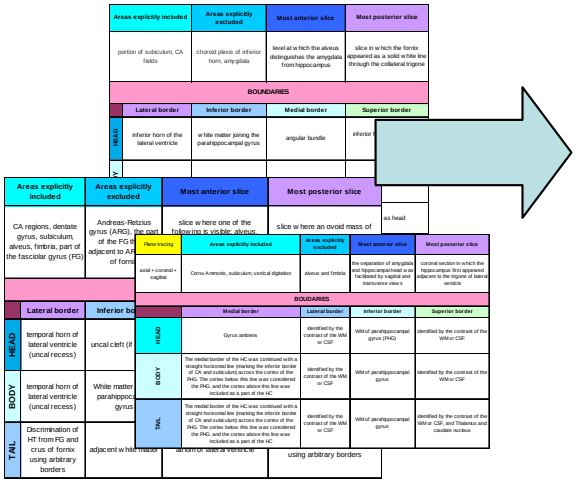
Extraction of similarities and differences

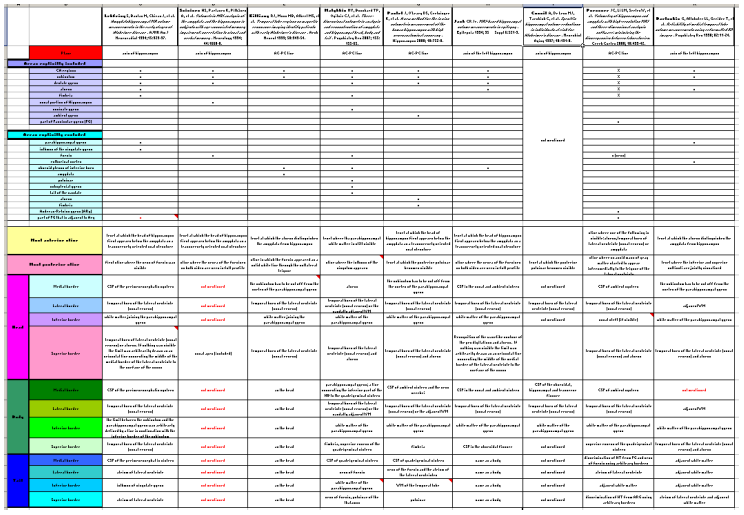
Harmonized language

Reduction of redundancy

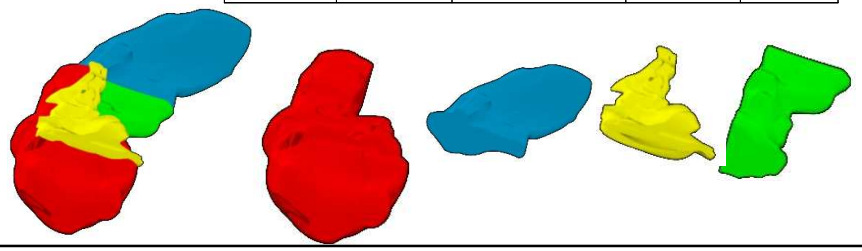
Extraction of (harmonized) differences

Definition of segmentation units and subunits





Plane of tracing				
Axis of hippocampus [B,C,J,L,S]		AC-PC line [H,K,M,Pa,Pr]		
Most posterior slice				
Where inferior and superior colliculi are jointly visualized [B]	Where crus of fornix is visible in full profile [C,K,L]	Where the crura of the fornices are seen in full profile on both sides [J,S]	Where gray matter is visible inferomedially to the trigone of the lateral ventricle [H,M*,Pa*,Pr]	
Superior border				
Lower border of alveus/fimbria [B,H,K,Pa,S]	Upper border of alveus/fimbria [C,J,L,M,Pr]	Horizontal line from the superior border of the quadrigeminal cistern to the lateral ventricle (tail) [Pr]		
Separation subiculum/enthorinal cortex				
vertical line from the CA to the WM of the parahippocampal gyrus [C]	45° line connecting the most inferior part of the subiculum medially to the cistern (head and body) [Pr]	Oblique line with same inclination of parahippocampal WM, connecting the inferior part of the subiculum to the quadrigeminal cistern [K,L,M¥]	Orizontal line from the highest medial point of the parahippocampal WM to the cistern [B,H,M¥]	Line outlining the contour of white matter of parahippocampal gyrus [Pa,S]



Protocols (first author)	Citations	Cit. AD & hippo* literature	Inclusion	Justification of exclusion/inclusion
Killiany, 1993	**241**	**147**	**Yes**	**Satisfying inclusion criteria**
Convit, 1997	**189**	**108**	**Yes**	**Satisfying inclusion criteria**
Soininen, 1994	**194**	**81**	**Yes**	**Satisfying inclusion criteria**
Watson., 1992	*433*	*70*	*Yes*	*The protocol is particularly detailed; among the most cited in the general literature, and the 4th most cited in the AD literature*
Lehericy, 1994	**107**	**65**	**Yes**	**Satisfying inclusion criteria**
deToledo-Morrell, 2004	**77**	**44**	**Yes**	**Satisfying inclusion criteria**
Pruessner, 2000	**229**	**42**	**Yes**	**Satisfying inclusion criteria**
Sheline, 1996	790	34	No	Author not available
Haller, 1997	**125**	**32**	**Yes**	**Satisfying inclusion criteria**
Bogerts, 1990	435	20	No	Amygdala included in the tracing
Bigler, 1997	134	20	No	Slice thickness 3 mm
Cook, 1992	337	14	No	Plexus choroideus included
Bremner, 1995	641	13	No	Only hippocampal body included; slice thickness 3mm.
Pantel, 2000	**74**	**12**	**Yes**	**Satisfying inclusion criteria**
Steffens, 2002	43	12	No	slice thickness 3 mm
Narr, 2004	78	12	No	Intrarater computed on 1 subject, interrater on 6 subjects
Jack, 1994	**65**	**11**	**Yes**	**Satisfying inclusion criteria**
Shenton, 1992	798	9	No	Amygdala included in the tracing
Bartzokis, 1993	**77**	**7**	**Yes**	**Satisfying inclusion criteria**
Mervaala, 2000)	166	6	No	slice thickness 3 mm
Honeycutt, 1998	30	6	No	**Satisfying inclusion criteria**
Barr, 1997	34	5	No	slice thickness 3.1 mm
Zipursky, 1994	162	5	No	excludes the most posterior region of body and tail; slice thickness 3mm
Giedd, 1996	211	4	No	Sample: Ages 4-18 Years
von Gunten, 2000	52	4	No	**Satisfying inclusion criteria**
Kates, 1997	131	4	No	**Satisfying inclusion criteria**
Ashtari, 1999	70	3	No	slice thickness 3.1 mm
Lloyd., 2004	38	3	No	**Satisfying inclusion criteria**
Hastings, 2004	82	3	No	**Satisfying inclusion criteria**
Neumeister, 2005	77	3	No	slice thickness 6 mm
MacMillan, 2003	47	3	No	**Satisfying inclusion criteria**
Malykhin, 2007	*7*	*2*	*Yes*	*Particularly detailed*

Plane of tracing			
Axis of hippocampus [B,C,J,L,S,dTM,W]	AC-PC line [H,K,M,Pa,Pr]		
Most posterior slice			
Where inferior and superior colliculi are jointly visualized [B]	Where crus/crura of fornix/ces is/are visible in full profile [C,dTM,J•,K,L,S,W]	Where gray matter is visible inferomedially to the trigone of the lateral ventricle [H,M•,Pa•,Pr]	
Superior border			
Lower border of alveus/fimbria [B,H,K,Pa,S]	Upper border of alveus/fimbria [C,dTM,J,L,M,Pr,W]		
Separation subiculum/enthorinal cortex			
vertical line from the CA to the WM of the parahippocampal gyrus [C]	Oblique line with same inclination of parahippocampal WM, connecting the inferior part of the subiculum to the quadrigeminal cistern [K,L,M¥,Pr,W]	Orizontal line from the highest medial point of the parahippocampal WM to the cistern [B,dTM,H,J¥]	Line outlining the contour of white matter of parahippocampal gyrus [Pa,S]

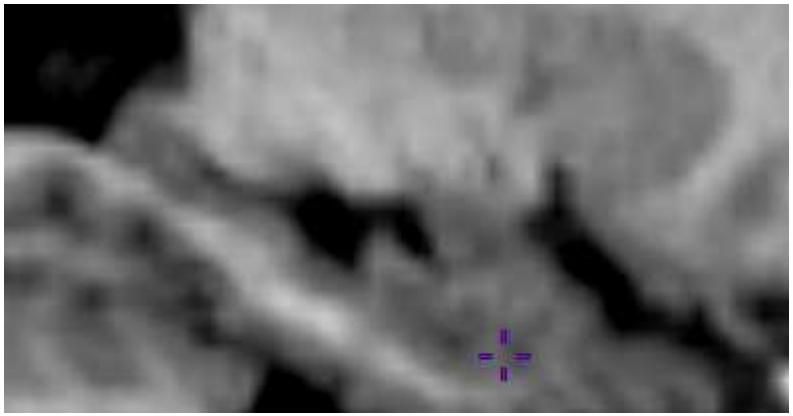
PROTOCOLS FEATURES EXTRACTION
Plane of tracing

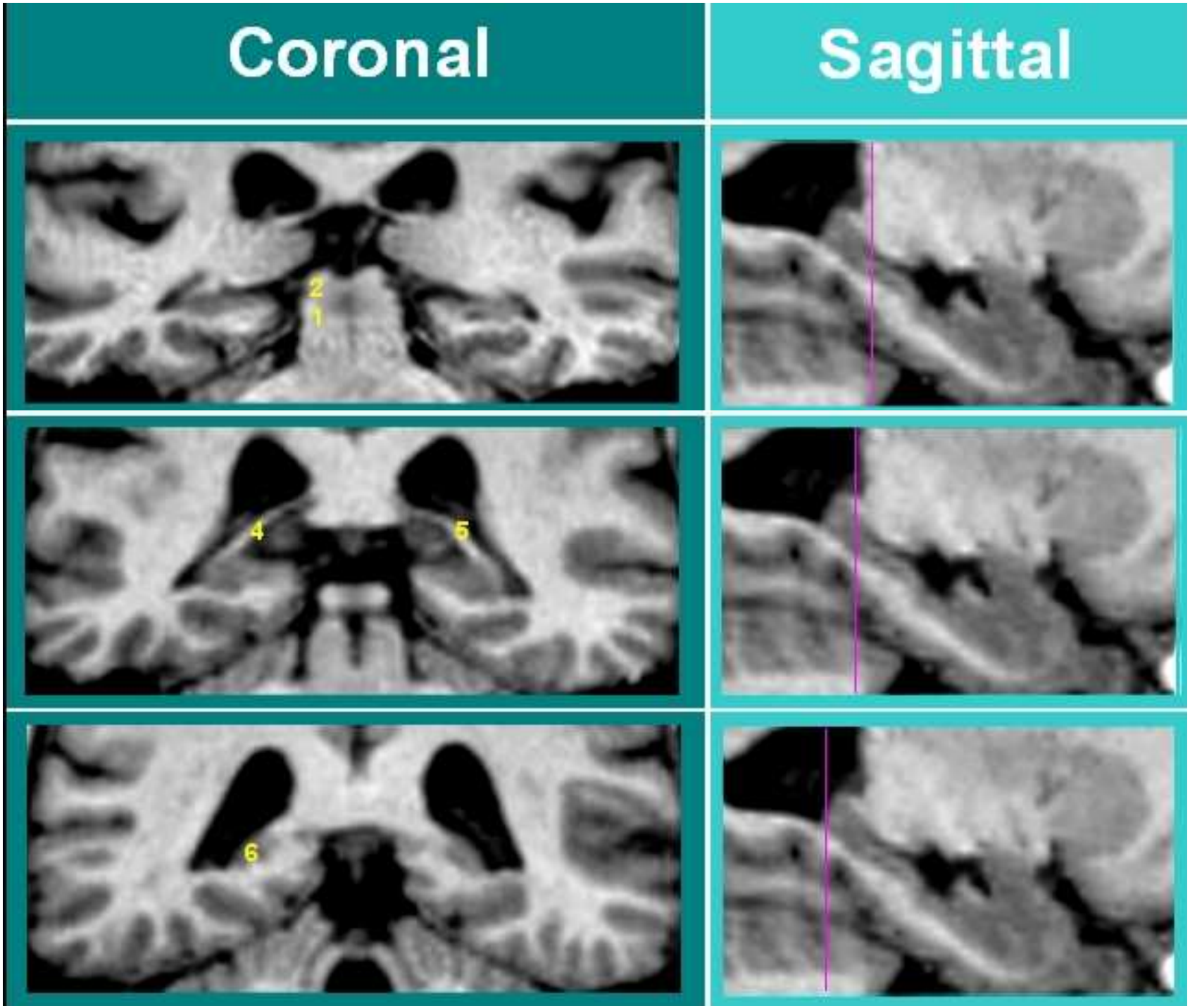
Axis of hippocampus

B. Bartzokis et al 1998
C. Convit et al 1997
dTM. deToledo-Morrell et al 2004
J. Jack 1994
L. Lehéricy et al 1994
S. Soininen et al 1994
W. Watson et al 1992

AC-PC

H. Haller-Csernansky et al 1997
K. Killiany et al 1993
M. Malykhin et al **2007**
Pa. Pantel et al **2000**
Pr. Pruessner et al **2000**



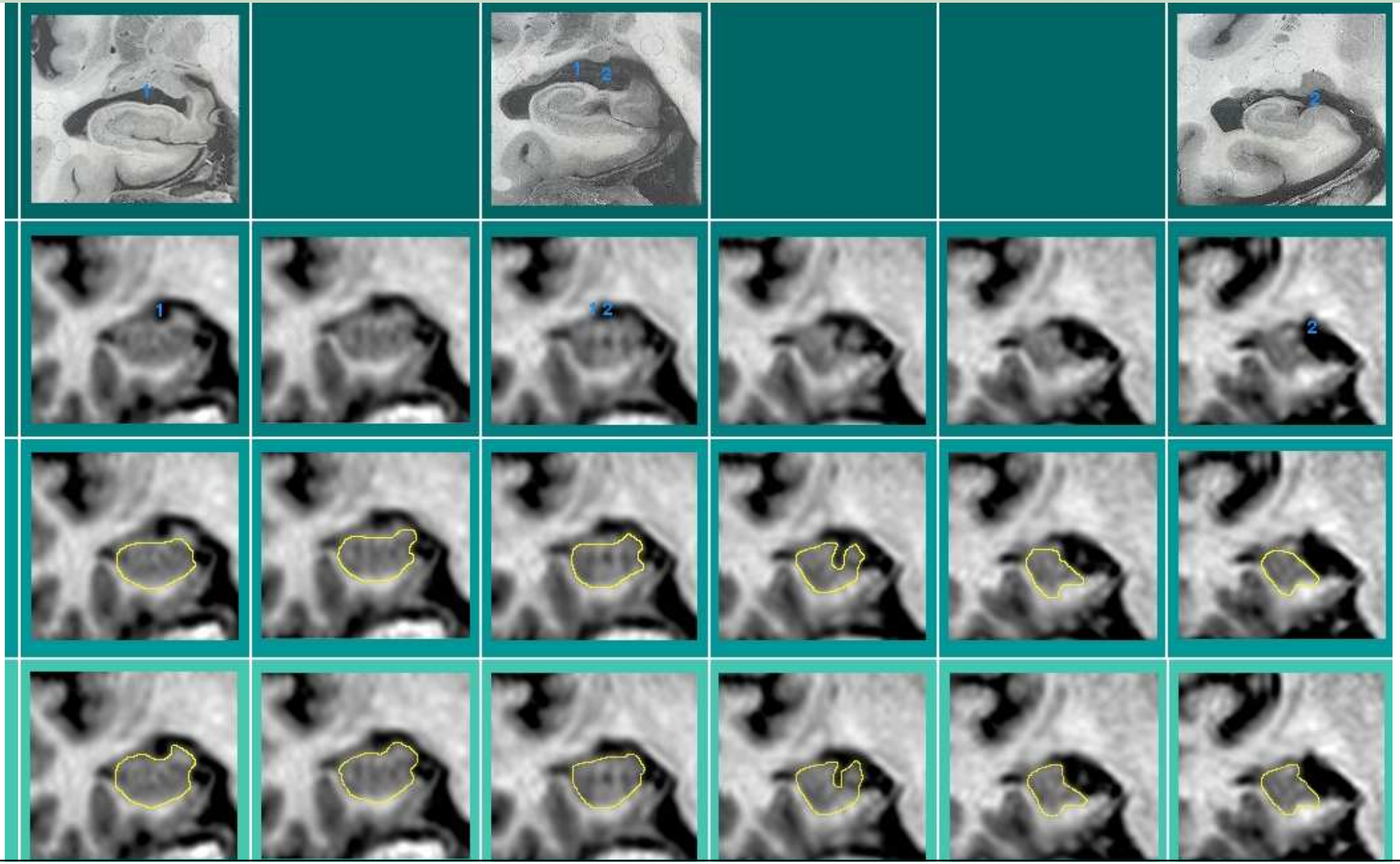


A. Level where the inferior (1) and superior (2) colliculi are jointly visualized [B]

B. Slice where the crus/crura of fornix/ces are visible in full profile (4,5) [C,dTM,J,K,L,S,W]

C. Slice where an ovoid mass of gray matter (6) appears inferomedially to the trigone of the lateral ventricle (posterior to anterior) [H, M, Pa, Pr]

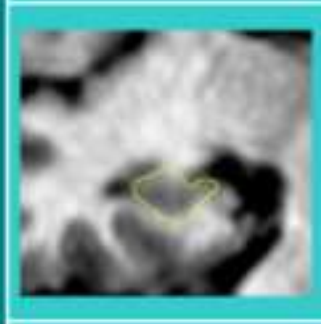
PROTOCOLS FEATURES EXTRACTION
Upper border



PROTOCOLS FEATURES EXTRACTION
Medial border

Arbitrary lines

Vertical line [C]

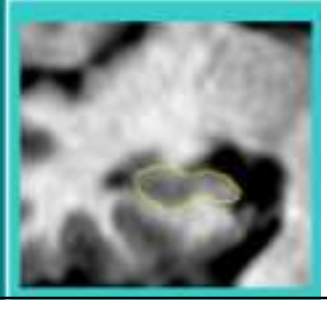


Line with same inclination WM

[K, L, M, Pr, W]

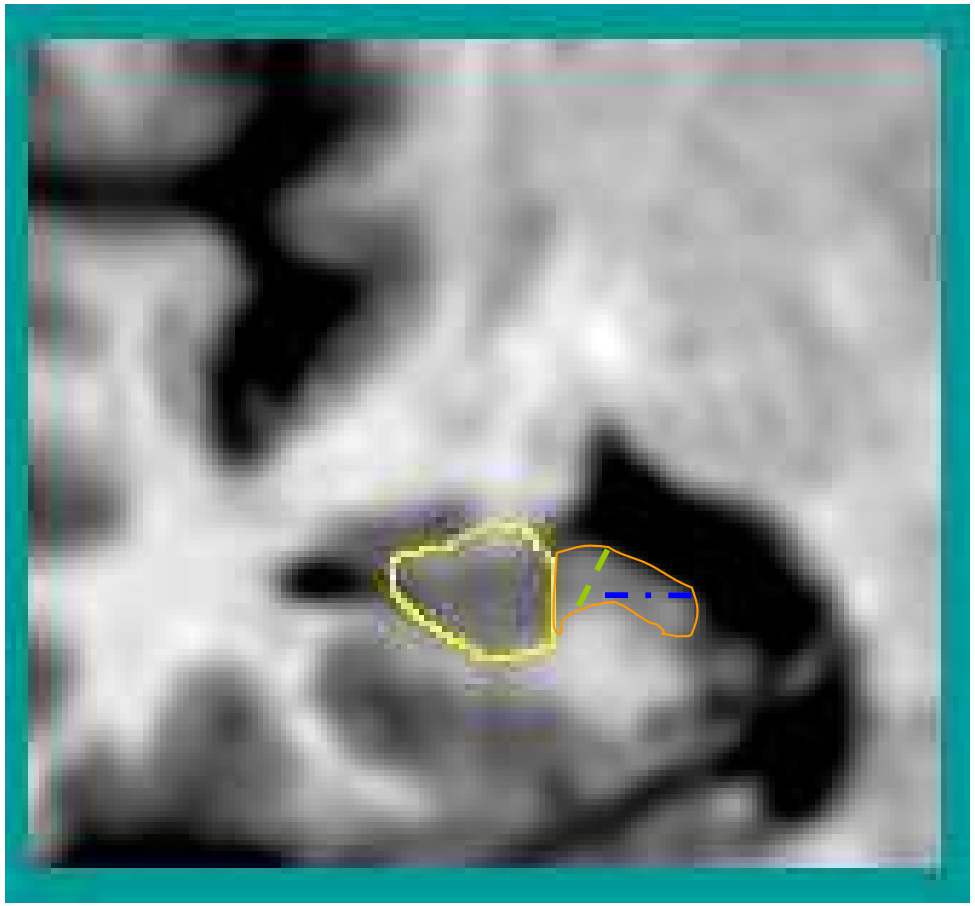
Horizontal line

[B, dTM, H, J]



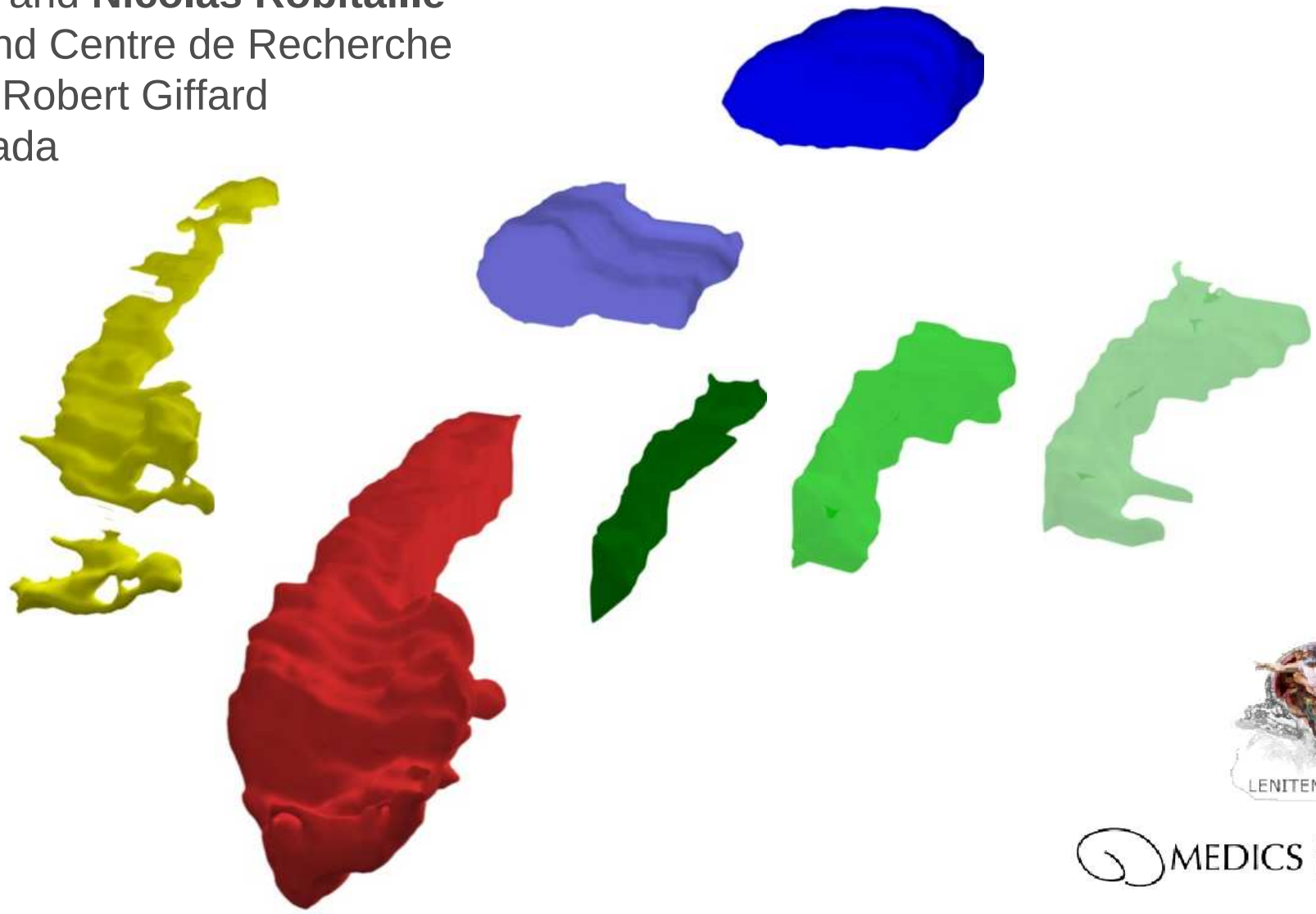
Morphological details

[Pa, S]



3D RENDERING & COMPUTATIONS

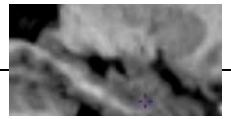
Rendering by
Simon Duchesne and **Nicolas Robitaille**
Université Laval and Centre de Recherche
Université Laval – Robert Giffard
Québec City, Canada



LENITEM

MEDICS Laboratory
Laboratoire

MODELING & COMPUTATIONS



Plane of tracing

Axis of hippocampus [B,C,J,L,S,dTM,W]

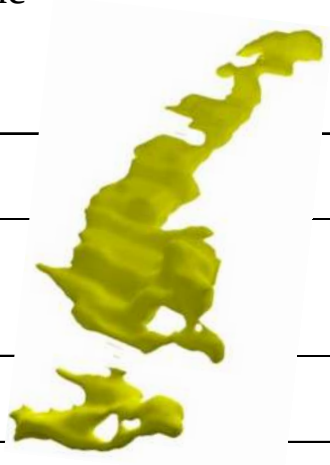
AC-PC line [H,K,M,Pa,Pr]

Most posterior slice

Where inferior and superior colliculi are jointly visualized [B]

Where crus/crura of fornix/ces is/are visible in full profile [C,dTM,J•,K,L,S,W]

Where gray matter is visible inferomedially to the trigone of the lateral ventricle [H,M•,Pa•,Pr]



Superior border

Lower border of alveus/fimbria [B,H,K,Pa,S]

Upper border of alveus/fimbria [C,dTM,J,L,M,Pr,W]

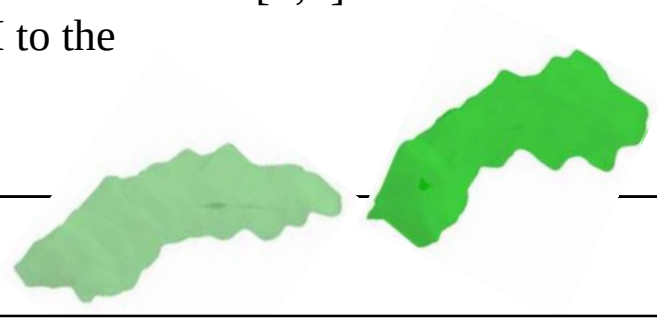
Separation subiculum/enthorinal cortex

vertical line from the CA to the WM of the parahippocampal gyrus [C]

Oblique line with same inclination of parahippocampal WM, connecting the inferior part of the subiculum to the quadrigeminal cistern [K,L,M¥,Pr,W]

Orizontal line from the highest medial point of the parahippocampal WM to the cistern [B,dTM,H,J¥]

Anatomical details [P,S]



Measurements in samples

	Ctrl (n=8)	MCI (n=9)	AD (n=3)	P (K-W; Fisher's)	AD/MCI (n=12)	P (M-W; Fisher's)
Age	75 (4)	77 (6)	77 (5)	0.4	78 (6)	0.2
Sex (F)	2 (25%)	2 (22%)	2 (67%)	0.45	4 (33%)	1.0
Education	16 (1)	17 (2)	15 (2)	0.3	16 (2)	0.5
Scheltens	0.5 (0.5)	2.8 (0.8)	3.7 (0.6)	0.001	3 (1)	<0.0005
Wahlund	1.4	1.7	2.3	0.2	1.8 (1)	0.2

Quantification of segmentation units features

	Controls (n=8)	% of total hippo	MCI/AD (n=12)	% of total hippo	% diff MCI/AD-CT	P (MCI/AD vs Controls)	Intra-rater
MinHB	1763 (283)	64 (5)	1188 (357)	64 (6)	-33%	0.004	0.993
Alveus/fimbria	227 (56)	8 (1)	147 (51)	8 (2)	-35%	0.009	0.872
Subiculum	240 (79)	9 (3)	224 (103)	12 (4)	-7%	0.6	
Oblique line	164 (43)	6 (2)	184 (87)	10 (4)	+12%	0.7	0.965
Morphology	256 (78)	10 (3)	233 (104)	13 (4)	-9%	0.3	0.980
Horizontal line	240 (79)	9 (3)	224 (103)	12 (4)	-7%	0.6	0.981
Tail	508 (151)	19 (6)	276 (125)	16 (7)	-46%	0.005	
Crus/crura	187 (106)	7 (4)	104 (37)	6 (2)	-44%	0.025	0.998
Most caudal	321 (77)	12 (2)	172 (104)	10 (6)	-46%	0.009	0.935
MaxHV	2739 (334)	100	1836 (613)	100	-33%	0.001	

DISCUSSION

The operationalization of the protocols differences gave 4 segmentation units + subunits

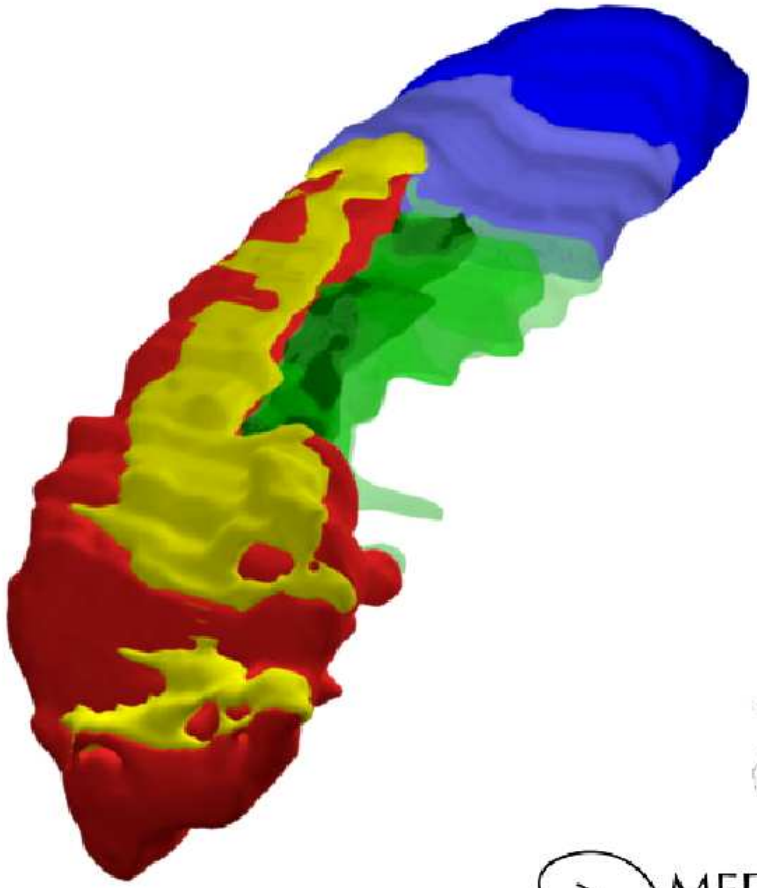
Heterogeneous contribution of units to total hippo volume and to differences between patients and controls

Lowest reliability for alveus/fimbria and most caudal slices

Available online material
www.hippocampal-protocol.net/site/sops-project-outlines.html

TOWARDS A HARMONIZED PROTOCOL

Maximum hippo = sum of all segmentation units in their most inclusive definition



HARMONIZED PROTOCOL = ?+?+?...

?

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HARMONIZED PROTOCOL
Validation & implementation

Validation with neuropathological data

Comparison with currently used protocols

Public tracings and probability maps

Standard environment for tracing, learning, and certification