

M Boccardi, M Bocchetta, R Ganzola, N Robitaille, A Redolfi, G Bartzokis, R Camicioli, JG Csernansky, MJ de Leon, L de Toledo-Morrell, RJ Killiany, S Lehéryc, J Pantel, JC Pruessner, H Soininen, C Watson, S Duchesne, CR Jack, GB Frisoni.

LENITEM - IRCCS - S. Giovanni di Dio - Fatebenefratelli Brescia, Italy (MB, RG, AR, MBocch, GBF); Dept Radiology, Université Laval and Centre de Recherche Université Laval - Robert Giffard, Quebec City, Canada (NR, SD); Dept Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA (GB); Dept Psychiatry & Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (JGC); New York University School of Medicine, Center for Brain Health, New York, NY (MJD); Dept Neurological Sciences, Rush University, Chicago, Illinois; Department Anat Neurobiol, Boston University School of Medicine (RJK); Center for Neuroimaging Research - CENIR and Dept Neuroradiology, Université Pierre et Marie Curie-Paris 6, Groupe Hospitalier Pitié-Salpêtrière, Paris, France (SL); Dept Biomed Engineering, Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada. (NVM); Dept Psychiatry Psychotherapy, University of Frankfurt/Main, Germany (JP); Centre for Studies in Aging, McGill Centre for Studies in Aging, Department of Psychiatry, McGill University, Montreal, Quebec, Canada (JCP); Dept Neuroscience Neurology, University of Kuopio and Kuopio University Hospital, Kuopio, Finland (HS); Wayne State University School of Medicine, 8D-University Health Center, St. Antoine, Detroit, MI (CW); Dept Diagnostic Radiology, Mayo Clinic and Foundation, Rochester, MN (CJ).

Background

Hippocampal atrophy is a key diagnostic marker for early-preclinical Alzheimer's disease (AD), but manual tracing on magnetic resonance (MR) images (present gold standard procedure) results in heterogeneous volumetric estimates (2 to 5.3 cm³) depending on the adopted segmentation protocol.

Objective

To define a harmonized protocol for the manual segmentation of the hippocampus.

Methods

We selected 12 most used tracing protocols in the AD literature (Figure 2). One rater carried out complete tracings on two prototypical 1.5T MR scans (0.99x0.99 mm²) (one control and one matched AD, ADNI subjects) on 1.2 mm slices, using each protocol. Individual interactive web conferences with the primary author of each protocol allowed to check or correct the execution of the tracing. We extracted the differences among the author-certified protocols, operationalized them into segmentation units (Figure 1) in order to compute their influence on total hippocampal volume, difference due to AD, and reliability measures in the manual tracing. Then, we traced and re-traced the segmentation units on 20 ADNI subjects (4 for each severity degree at the MTA scale - Scheltens et al., 1992) and, for each, we quantified their intra-rater reliability and impact on volume and differences.

Figure 1. 3D rendering of the differences among the 12 protocols, operationalized based on the certified tracings. Red=Minimum hippocampal body, common to all protocols; Yellow=alveus/fimbria; Green= different criteria to trace the medial border at the level of the subiculum; Blue= different criteria to trace the most caudal slice (tail).

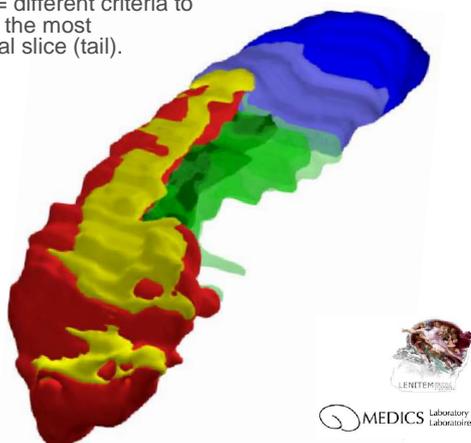
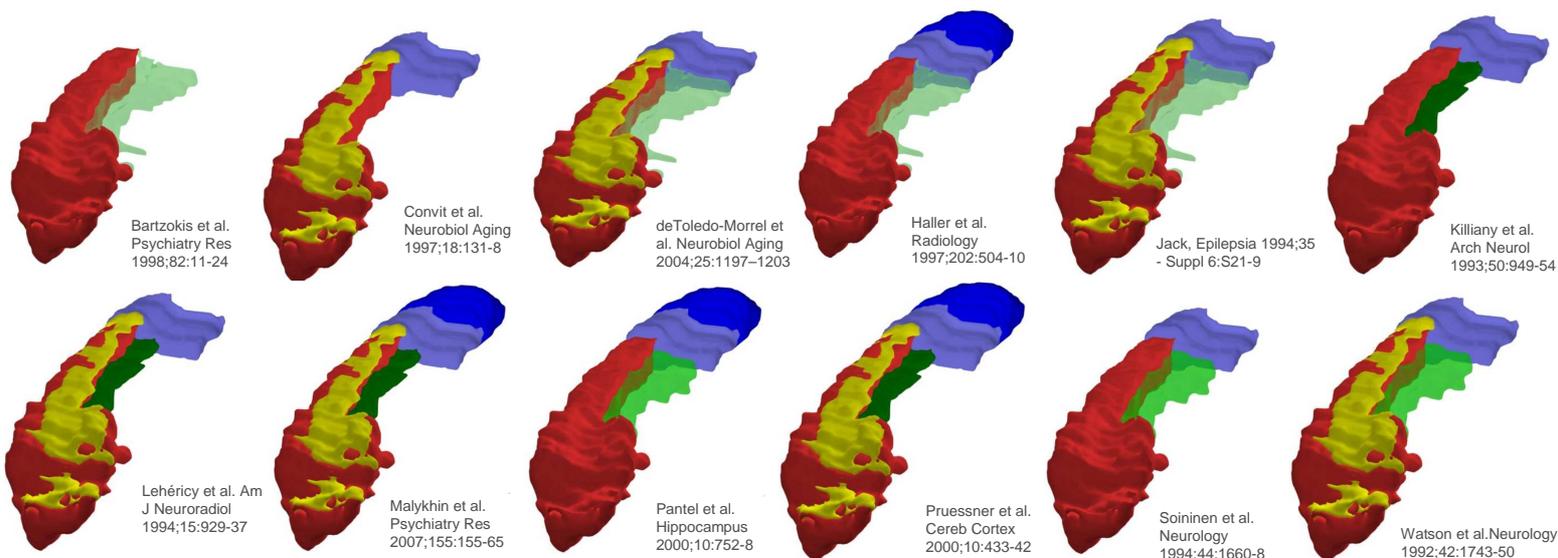


Table. Quantification of impact on total volume, on difference between AD and controls, and on intra-rater reliability of segmentation units. Volumes are in mm³. HB=hippocampal body, HV=Hippocampal volume.

	Controls (n=8)	% of total hippo	MCI/AD (n=12)	% of total hippo	% diff MCI/AD-Controls	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	

Figure 2. 3D rendering of the originally examined protocols, by segmentation units assembly.



Results

The certified protocols (available at www.hippocampal-protocol.net) differed in the definition of the medial border (subiculum, green), of the last slice (tail, blue), and the inclusion of hippocampal white matter (alveus/fimbria, yellow). The impact of these differences, operationalized into segmentation units (SUs) (Figure 1), on total volume, AD difference, and tracing reliability, as computed from the 20 ADNI subjects, is reported in the Table. SUs can also be used to reconstruct the 3D renders of original protocols (Figure 2).

Conclusions

This operationalization, and the quantification of SUs features provide quantitative evidence that will assist an international panel of experts in achieving a consensus for a harmonized protocol for the manual tracing of the hippocampus.