Estimating the Impact of Differences among Protocols for Manual Hippocampal Segmentation on Alzheimer's Disease-Related Atrophy: Preparatory Phase for a Harmonized Protocol

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Introduction

To quantify the impact of the differences among Magnetic Resonance Imaging (MRI)-based hippocampal segmentation protocols on volume estimates of Alzheimer's disease (AD)-related atrophy, in order to support evidence-based decisions for an internationally harmonized protocol. A harmonized procedure is required, since quantitative MRI should help diagnosis and tracking of AD. A survey of segmentation protocols allowed to operationalize the landmarks variability into segmentation units (SUs) (Figures), and their impact on volume estimates has been preliminarily quantified.

Methods

A power analysis was carried out on a preliminary sample of 20 ADNI subjects (4 by each degree of severity of hippocampal atrophy at the visual scale by Scheltens et al., 1992), to define the sample size allowing reliable computation. Then, we manually traced each SU within the right and left hippocampi of a sample of 77 *Alzheimer's Disease Neuroimaging Initiative (*ADNI) participants, which included Mild Cognitive Impairment (MCI) patients who subsequently converted to AD and AD patients, all with abnormal Cerebrospinal Fluid (CSF) Aβ levels, and controls (CTRL), with normal CSF Aβ levels (Tab. 1).

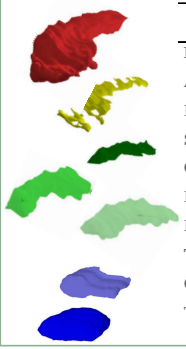
Results

The power analysis indicated a required sample size for the quantification of SUs impact on AD-related volume differences of n=77 (31 CTRL, 23 MCI, 23 AD). All Sus had good ICC values (Tab 2). The average volume difference between patients and controls was 538 mm3, with Minimum Hippocampus (red SU in Figures) contributing to over 66% of this difference, Tail (blue SUs in Figures) over 20%, Alveus/Fimbria (yellow SU in Figures) 6%, Subiculum (green SUs in Figures) over 5%. The SU volume differences between patients and controls were significant for all SUs except the Subiculum (Tabs 3 and 4).

Tab. 1 Sociodemographic features of the ADNI sample of 77 subjects: 31 controls with normal CSF Aβ levels, 23 (subsequently converted) MCI, and 23 AD patients. All MCI and AD had abnormal CSF Aβ levels.

	CTRL (n=31)	MCI (n=23)	AD (n=23)	*p* MCI vs CTR	*p* AD vs CTR	*p* MCI vs AD	*p* AD+MCI vs CTR
Age, years	75.7 (5.2)	76.1 (5.6)	76.3 (5.6)	0.816	0.704	0.895	0.718
Gender, female	15 (48.4%)	11 (47.8%)	11 (47.8%)	0.999	0.999	0.999	0.961
Education, years	16 (3)	15.6 (3.4)	15.2 (3.4)	0.732	0.791	0.697	0.511
CSF $A\beta_{1-42}$ levels, pg/ml	242.7 (25.2)	133.7 (23.4)	136 (26.3)	<0.0005	<0.0005	0.755	<0.0005

Tab 2 Intra- and inter-rater reliability of SUs computed on 20 ADNI subjects (4 by each degree of severity of hippocampal atrophy at the visual scale by Scheltens et al., 1992)



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

Tab. 3 Segmentation Units volumes in controls, MCI and AD patients. Numbers denote mean volume (mm3) and standard deviation (in parentheses) of Segmentation Units. *p* denotes significance on t-test. Data are obtained on the ADNI sample of 77 subjects.

LEFT HIPPOCAMPUS

	Controls (n=31)	MCI (n=23)	AD (n=23)	*p* MCI vs CTR	*p* AD vs CTR	*p* MCI vs AD	*p* AD+MCI vs CTR
MinH	1467 (204)	1122 (263)	1023 (251)	<0,0005	<0,0005	0,199	<0,0005
Alveus/fimbria	248 (45)	232 (61)	200 (48)	0,269	<0,0005	0,055	0,01
Subiculum	243 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Oblique line	196 (67)	178 (66)	176 (53)	0,338	0,262	0,936	0,207
Morphology	243 (72)	220 (84)	213 (64)	0,279	0,118	0,754	0,121
Horizontal line	234 (72)	210 (78)	211 (62)	0,243	0,221	0,957	0,153
Tail	485 (131)	383 (99)	353 (101)	0,003	<0,0005	0,307	<0,0005
Crura	190 (74)	177 (70)	146 (69)	0,538	0,034	0,14	0,101
End Tail	296 (120)	206 (76)	206 (86)	0,003	0,004	0,984	<0,0005
MaxHV	2443 (291)	1957 (348)	1788 (342)	<0,0005	<0,0005	0,105	<0,0005

RIGHT HIPPOCAMPUS

	Controls (n=31)	MCI (n=23)	AD (n=23)	*p* MCI vs CTR	*p* AD vs CTR	*p* MCI vs AD	*p* AD+MCI vs CTR
MinH	1462 (232)	1214 (247)	1061 (241)	<0,0005	<0,0005	0,039	<0,0005
Alveus/fimbria	255 (47)	258 (71)	225 (65)	0,84	0,05	0,103	0,35
Subiculum	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Oblique line	181 (67)	167 (71)	150 (46)	0,455	0,059	0,334	0,122
Morphology	225 (79)	208 (89)	184 (56)	0,459	0,042	0,294	0,109
Horizontal line	220 (78)	203 (83)	182 (54)	0,459	0,053	0,309	0,117
Tail	487 (151)	349 (115)	349 (131)	0,001	0,001	0,999	<0,0005
Crura	187 (75)	169 (68)	140 (69)	0,37	0,025	0,17	0,058
End Tail	301 (120)	181 (113)	209 (110)	<0,0005	0,006	0,394	<0,0005
MaxHV	2429 (303)	2029 (372)	1820 (369)	<0,0005	<0,0005	0,062	<0,0005

LEFT HIPPOCAMPUS

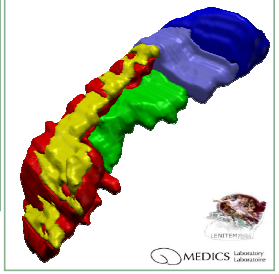
	Controls (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% MCI vs CTR (impact)	% diff AD vs CTR	% AD vs CTR (impact)
MinH	1467 (204)	60%	1122 (263)	1023 (251)	23,5%	71%	30%	68%
Alveus/fimbria	248 (45)	10%	232 (61)	200 (48)	6,5%	3%	19%	7%
Subiculum	243 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	4,5%
Oblique line	196 (67)	8%	178 (66)	176 (53)	9%	3,5%	10%	3%
Morphology	243 (72)	10%	220 (84)	213 (64)	9,5%	5%	12%	4,5%
Horizontal line	234 (72)	9%	210 (78)	211 (62)	10%	5%	10%	3,5%
Tail	485 (131)	20%	383 (99)	353 (101)	21%	21%	27%	20,5%
Crura	190 (74)	8%	177 (70)	146 (69)	6,5%	2,5%	23%	6,5%
End Tail	296 (120)	12%	206 (76)	206 (86)	30%	18,5%	30%	14%
MaxHV	2443 (291)	100%	1957 (348)	1788 (342)	20%	100%	27%	100%

RIGHT HIPPOCAMPUS

	Controls (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% MCI vs CTR (impact)	% diff AD vs CTR	% AD vs CTR (impact)
MinH	1462 (232)	60%	1214 (247)	1061 (241)	17%	62%	27%	66%
Alveus/fimbria	255 (47)	11%	258 (71)	225 (65)	-1%	-0,5%	12%	5%
Subiculum	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Oblique line	181 (67)	8%	167 (71)	150 (46)	8%	3,5%	17%	5%
Morphology	225 (79)	9%	208 (89)	184 (56)	8%	4%	18%	6,5%
Horizontal line	220 (78)	9%	203 (83)	182 (54)	7,5%	4%	17%	6%
Tail	487 (151)	20%	349 (115)	349 (131)	28,5%	34,5%	28,5%	22,5%
Crura	187 (75)	8%	169 (68)	140 (69)	10%	4,5%	25%	7,5%
End Tail	301 (120)	12%	181 (113)	209 (110)	40%	30%	31%	15%
MaxHV	2429 (303)	100%	2029 (372)	1820 (369)	16,5%	100%	25%	100%

Tab. 4 Informative value of Segmentation Units for AD-related atrophy. Volumes (SD) are the same as in Table 3. Percent values denote the proportion of the SU compared to the total hippocampal volume (% of total hippo), the percent difference of the SU between groups (% diff), and the impact of the SU on the total volume difference between patients and controls.

Figure Rendering of the Preliminary Harmonized Hippocampus, composed by the sum of all SUs chosen by the majority of panelists. This is a preliminary result from the first round of the Delphi Panel. Details and other issues regarding the tracing protocol are still under evaluation by the panel of experts.



Conclusions

Reliability of individual SUs and how informative they are in identifying AD-related atrophy are being used by a panel of experts to define which SUs should be included in a harmonized protocol. (Figure shows the preliminary results from the first round of the Delphi Panel.)