Differences among Protocols for Manual Hippocampal Segmentation: Preparatory Steps to an EADC-ADNI Delphi Panel for the Development of a Harmonized Protocol

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Objective

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.

Background

A harmonized procedure is required, since quantitative MRI should help diagnosis and tracking of AD. A survey of segmentation protocols allowed the identification of anatomical sources of heterogeneity in volume estimates.

Methods

We operationalized landmark differences among protocols into segmentation units (SUs), through extraction of landmarks, semantic harmonization, and convergence of similar variants, in order to achieve a limited number of well defined portions of the hippocampus, that are differentially segmented in different existing protocols (Fig. 1).

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).

Table 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.

	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
Age, years	75.74 (5.18)	76.09 (5.58)	76.30 (5.58)	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	15.97 (2.98)	15.57 (3.38)	15.17 (3.38)	0.732	0.791	0.697	0.511
CSF $A\beta_{1-42}$ levels, pg/ml	242.68 (25.21)	133.74 (23.36)	136.04 (26.25)	<0.0005	<0.0005	0.755	<0.0005

Figure 1: Segmentation Units, representing the landmark differences in tracing criteria among the 12 selected protocols.

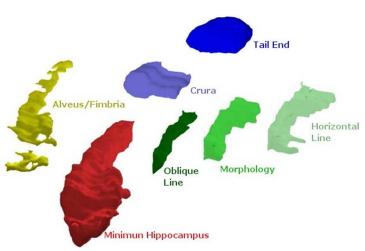


Table 2: Intra- and inter-rater reliability of SUs computed on 20 ADNI subjects (4 by each degree of severity of hippocampal atrophy at the visual scale by Scheltens et al., 1992)

	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
End Tail	0.988	0.905

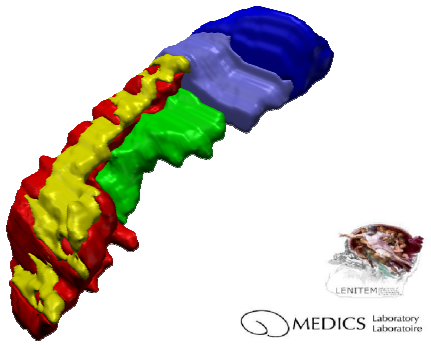
Results

We defined four SUs: Minimum Hippocampus (MinH), Alveus/Fimbria, Tail, and Subiculum. 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 (Table 3).

Table 3: SUs volumes and informative value for AD-related atrophy in controls, MCI and AD patients.
Numbers denote mean volume (mm3) and standard deviation (in parentheses) of SUs, corrected by total intracranial volume. *p* denotes significance on t-test. Percent values denote the proportion of the SU compared to the total hippocampal volume.

LEFT HIPPOCAMPUS	Controls (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% diff AD vs CTR	*p* MCI vs CTR	*p* AD vs CTR
MinH	1467 (204)	60%	1122 (263)	1023 (251)	23,5%	30%	<0,0005	<0,0005
Alveus/fimbria	248 (45)	10%	232 (61)	200 (48)	6,5%	19%	0,269	<0,0005
Subiculum	243 (72)	10%	220 (84)	213 (64)	9,5%	12%	0,279	0,118
Oblique line	196 (67)	8%	178 (66)	176 (53)	9%	10%	0,338	0,262
Morphology	243 (72)	10%	220 (84)	213 (64)	9,5%	12%	0,279	0,118
Horizontal line	234 (72)	9%	210 (78)	211 (62)	10%	10%	0,243	0,221
Tail	485 (131)	20%	383 (99)	353 (101)	21%	27%	0,003	<0,0005
Crura	190 (74)	8%	177 (70)	146 (69)	6,5%	23%	0,538	0,034
End Tail	296 (120)	12%	206 (76)	206 (86)	30%	30%	0,003	0,004
MaxHV	2443 (291)	100%	1957 (348)	1788 (342)	20%	27%	<0,0005	<0,0005
RIGHT HIPPOCAMPUS	Controls (n=31)	% of total hippo	MCI (n=23)	AD (n=23)	% diff MCI vs CTR	% diff AD vs CTR	*p* MCI vs CTR	*p* AD vs CTR
MinH	1462 (232)	60%	1214 (247)	1061 (241)	17%	27%	<0,0005	<0,0005
Alveus/fimbria	255 (47)	11%	258 (71)	225 (65)	-1%	12%	0,84	0,05
Subiculum	225 (79)	9%	208 (89)	184 (56)	8%	18%	0,459	0,042
Oblique line	181 (67)	8%	167 (71)	150 (46)	8%	17%	0,455	0,059
Morphology	225 (79)	9%	208 (89)	184 (56)	8%	18%	0,459	0,042
Horizontal line	220 (78)	9%	203 (83)	182 (54)	7,5%	17%	0,459	0,053
Tail	487 (151)	20%	349 (115)	349 (131)	28,5%	28,5%	0,001	0,001
Crura	187 (75)	8%	169 (68)	140 (69)	10%	25%	0,37	0,025
End Tail	301 (120)	12%	181 (113)	209 (110)	40%	31%	<0,0005	0,006
MaxHV	2429 (303)	100%	2029 (372)	1820 (369)	16,5%	25%	<0,0005	<0,0005

Figure 2: 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. (Fig. 2 shows the preliminary results from the first round of the Delphi Panel.) Updated information on this ongoing project is available at www.hippocampal-protocol.net