HIPPOCAMPAL VOLUMES IN SUBJECTS AT RISK OF ALZHEIMER'S DISEASE WITH A NEW REGISTRATION TEMPLATE

Bernd Merkel[1,2], Nicola T. Lautenschlager[3], Christopher Steward[1,2], Lucy Vivash[4], Bob Tran[1], David Ames[5], Kay Cox[6], Elizabeth Cyarto[5], Kathryn Ellis[3], Pramit Phal[1], Matthew Sharman[7], Cassandra Szoeke[8], and Patricia Desmond[1,2]

[1]University of Melbourne, Parkville, Victoria, Australia, [2]Radiology, Royal Melbourne Hospital, Parkville, Victoria, Australia, [3]University of Melbourne, Kew, Victoria, Australia, [4]Medicine, University of Melbourne, Parkville, Victoria, Australia, [5]National Ageing Research Institute, Parkville, Victoria, Australia, [6]University of Western Australia, Perth, Western Australia, Australia, [7]Edith Cowan University, Joondalup, Western Australia, Australia, [8]CSIRO, Parkville, Victoria, Australia

Purpose: With increasing longevity worldwide, the prevalence of age-related diseases such as dementia, in particular Alzheimer's Disease (AD), is also increasing. AD is the most common type of dementia, but to date there is no effective treatment. An impediment to therapeutic approaches is the lack of firmly established biomarkers of AD. Potential biomarkers include total tau protein (t-tau) and Aβ42 in cerebrospinal fluid as well as neuroimaging (MRI, PET). The hippocampus (HC) is a brain structure that is selectively vulnerable to pathology in AD with volume loss. Quantitative measures of HC volume loss on MRI have been shown as a strong predictor of AD diagnosis and progression. However, accurate determination of HC volume changes still remains a challenge. In this work, we analyse hippocampal volumes from 10 older adults with subjective memory complaints (SMC) or mild cognitive impairment MCI), who are at increased risk of developing AD in the future. It is our aim to compare HC volumes calculated by automated software methods (FreeSurfer, FSL) with manually drawn ROI volumes, being the gold standard for evaluating HC atrophy, and with an in-house developed template based on healthy older subjects for registration.

Methods: We randomly selected MR images of 25 healthy, older adults (16 Female, 9 Male, mean age: 71.2 ± 7.4, min.age: 60), from the participants of the Australian Imaging Biomarkers and Lifestyle (AIBL) study (Protocol: T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence, voxel size = 1mm isotropic, TR=2300ms, TE=2.98ms, flip angle=9° on a Siemens 3.0T Tim Trio) [1]. Although smaller numbers of subjects generated adequate templates, we chose 25 in order to maximize SNR. We then created a population-based healthy elderly template, using the Advanced Normalization Tools (ANTS) package [2] and compared MRI-based hippocampal volumes (both left and right) of 10 subjects (7 Female, 3 Male, Age: 71.9 ± 4.9), each of them with subjective memory complaints (SMC, n=6) or mild cognitive impairment (MCI, n=4). These patients are part of the AIBL-Active study [3] and their MR images were acquired with the same protocol as mentioned above. Three different approaches were used for volumetric analysis:

1) Manual segmentation: ROIs for the hippocampal volume were drawn on the MR Images by an expert tracer. The traces were performed in the coronal view, using the comprehensive image analysis software Analyze [4].

2) Automated segmentation: volumes were obtained by two freely available software tools, the FreeSurfer Image Analysis Suite v5.1.0 [5] and FSL v5.0 [6]. Both tools are widely used in the field of neuroimaging. In FreeSurfer, no manual intervention was done. Integrated whole brain segmentation and cortical parcellation were used and the estimated HC volumes (left and right) were extracted from the statistical result files. In FSL, we used the FIRST package for subcortical structure segmentation.

3) ANTS template: The SMC or MCI subjects' images were registered to the elderly template with an affine and diffeomorphic registration using a Cross-Correlation (CC) similarity measure with the ANTS package. We used SYN[0.25] for the transformation model, and Gauss[3,0] for the regularization. An elderly atlas ROI for the hippocampus was manually drawn by the same manual tracer using also Analyze [3] on the generated template. Finally, the inverse of the subject-specific registrations to this template were applied to the ROI to determine the HC ROIs in the subject's native space.

Results: All the statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, IL). To compare the different methods, we calculated Pearson correlations and analysed both single left and right HC volumes as well as the total HC volume. As shown in Table 1, FreeSurfer results are generally larger than FSL results, which themselves are larger than our own template and manually drawn ROIs. Without correcting the volumes for IntraCranialVolume (ICV), only the correlations between the manually drawn ROIs in the left and right HC and the ANTS template based measurements were significant at the level of $r \geq 0.686$ ($p<0.05$). Table 2 shows the Pearson correlations across the 4 groups after correcting for ICV. There was a significant correlation in volumes between the ANTS template vs manually drawn ROIs (0.765, p=0.010, left HC and 0.665, p=0.036, right HC) as well as between Freesurfer vs manual volumetry (0.691, p=0.027, left HC and 0.775, p=0.008, right HC). FSL performed worse in both left and right HC with no correlation at all.

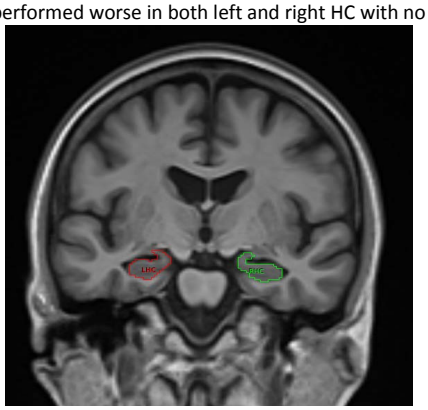

Fig 1: One coronal slice of the healthy elderly template with the manually segmented hippocampi (left red and right green).

	Manual ROI	FSL	Freesurfer	ANTS template
Left Vol.	3051.80 (±404.20)	3480.80 (±1282.07)	3787.60 (±240.71)	2901.00 (±417.42)
Right Vol.	2858.70 (±270.47)	3180.00 (±961.66)	3931.30 (±444.31)	3099.00 (±471.78)
Total	5910.50 (±592.23)	6660.80 (±1974.90)	7718.90 (±628.37)	6000.00 (±850.42)

Table 1: Mean value and standard deviation of left, right and total hippocampal volume for the described different approaches, without ICV correction

	Manual ROI	FSL	FreeSurfer	ANTS template
Manual ROI		r=-0.070 (p=0.848)	r=0.691 (p=0.027)	r=0.765 (p=0.010)
FSL	r=-0.080 (p=0.826)		r=-0.467 (p=0.173)	r=-0.178 (p=0.623)
FreeSurfer	r=0.775 (p=0.008)	r=0.224 (p=0.533)		r=0.461 (p=0.180)
ANTS template	r=0.665 (p=0.036)	r=0.337 (p=0.341)	r=0.520 (p=0.123)	

Table 2: Pearson correlation coefficients for the left (upper right half of the table) and the right (lower left half of the table, blue background)) hippocampal volumes with ICV correction.

Discussion: Accurate, automated HC volumes are desirable if HC volume is to be used as a biomarker in AD. We used the ANTS software [2] and MRI from 25 known healthy controls to produce an older adults' control template. We have shown that the best correlation with the manually drawn ROIs in left HC is achieved by registration to an elderly template, whereas in right HC FreeSurfer showed the best agreement. It is acknowledged, however, the number of patients and calculated HC volumes in this study was small.

Conclusion: Templates for MRI registration, which are based on older adults, may be more accurate in determining HC volume calculation. They are particularly useful if manual segmentations as the gold standard are not feasible or available and may be a quicker alternative to packages like FreeSurfer. However, performing the non-linear registrations may still require significant computing resources in order to achieve results in a reasonable time-frame.

References: [1] Ellis et al., Alzheimers Dement 2010;6:291-6 [2] Avants et al., Med Image Anal. 2008;12(1):26-41, http://www.picsl.upenn.edu/ANTS/ [3] Cyarto et al., BMC Psychiatry 2012; 12:167 [4] Analyze 11.0, http://www.analyzedirect.com/Analyze/ [5] Fischl et al., Neuron 2002; 33:341-355, [6] Jenkinson et al., NeuroImage 2012; 62:782-90