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Hippocampal morphometry in population-based incident Alzheimer's disease and vascular dementia: the HAAS

Ann I Scher,[1,2] Yuan Xu,[3] Esther S C Korf,[4] Stephen W Hartley,[1,2] Menno P Witter,[5] Philip Scheltens,[4] Lon R White,[6] Paul M Thompson,[7] Arthur W Toga,[7] Daniel J Valentino,[7] Lenore J Launer[2]

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[1]Department of Preventive Medicine and Biometrics, Uniformed Services University, Bethesda, Maryland, USA
[2]Laboratory of Epidemiology, Demography, and Biometry; National Institute on Aging, NIH, Bethesda, Maryland, USA
[3]Cedars-Sinai Medical Center, Los Angeles, California, USA
[4]Vrije University Medical Center, Department of Neurology and Alzheimer Center, Amsterdam, The Netherlands
[5]Department of Anatomy and Neurosciences, Vrije University Medical Center, Amsterdam, the Netherlands
[6]Kuakini Medical Center, Honolulu, Hawaii, USA
[7]Laboratory of Neuro Imaging Department of Neurology, UCLA School of Medicine, Los Angeles, California, USA

Correspondence to
Ann I Scher, Uniformed Services University, Department of Preventive Medicine and Biometrics, 4301 Jones Bridge Road Bethesda, Maryland, 20814, USA; ascher@usuhs.mil

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ABSTRACT

Background Hippocampal changes may be a useful biomarker for Alzheimer's disease if they are specific to dementia sub-type. We compare hippocampal volume and shape in population-based incident cases of Alzheimer's disease and vascular dementia (VaD).

Methods Participants are Japanese-American men from the Honolulu Asia Aging Study. The following analysis is based on a sub-group of men with mild incident Alzheimer's disease (n=24: age=82.5±4.6) or incident VaD (n=14: age=80.5±4.5). To estimate hippocampal volume, one reader, blinded to dementia diagnosis, manually outlined the left and right formation of the hippocampus using published criteria. We used 3-D mapping methods developed at the Laboratory of Neuro Imaging (LONI) to compare regional variation in hippocampal width between dementia groups.

Results Hippocampal volume was about 5% smaller in the Alzheimer's disease group compared to the VaD group, but the difference was not significant. Hippocampal shape differed between the two case groups for the left ($p<0.04$) but not right ($p<0.21$) hippocampus. The specific region of the hippocampus that most consistently differed between the Alzheimer's disease and VaD cases was in the lateral portion of the left hippocampus. Our interpretation of this region is that it intersects the CA1 sub-region to a great extent but also includes the dentate gyrus (and hilar region) and subiculum.

Conclusion As indicated by shape analysis, there are some differences in atrophy localisation between the Alzheimer's disease and VaD cases, despite the finding that volume of the hippocampi did not differ. These findings suggest hippocampal atrophy in Alzheimer's disease may be more focal than in VaD.

INTRODUCTION

Hippocampal atrophy is characteristic for Alzheimer's disease[1] but has also been noted in vascular dementia (VaD)[2] memory impairment and, to some extent, in normal ageing.[3]

While these conditions may result from different processes to some extent, they do share common pathophysiological mechanisms.[4] Examining similarities in brain structure across disease groups may help us to better understand the challenge to clinically identify sensitive and specific biomarkers of dementing diseases.

In a prior study,[5] we demonstrated that structural imaging techniques developed at the Laboratory of Neuro Imaging (LONI) at University of California, Los Angeles (UCLA) were sensitive to morphometric differences in the hippocampi of a community-based sample of very old men with clinically diagnosed Alzheimer's disease compared to an equally elderly group of non-demented men. In this analysis, we consider whether volumetric and regional shape analysis differs between the two major dementia sub-types, Alzheimer's disease and VaD.

METHODS

Study participants are older men (mean age 81.8±4.6) from the Honolulu Asia Aging Study (HAAS).[6] Selection of the study participants for this MRI sub-study and case ascertainment methods have been described in detail elsewhere.[5] The Kuakini Medical Center Institutional Review Board approved this study (IRB number T3274). In the HAAS, all respondents signed informed consent forms, except those who were demented, for whom an informed caretaker signed the consent.

This analysis is based on MRI sub-study participants who were clinically diagnosed with incident Alzheimer's disease (n=24: age=82.5±4.6) and incident VaD (n=14: age=80.5±4.5); subjects with mixed (Alzheimer's disease and vascular) dementia were excluded. Diagnosis of dementia (by DSM-IIR criteria) and Alzheimer's disease (by NINDS–ADRDA criteria) and VaD (by California criteria) have been described previously.[6]

Imaging protocol

Scans were acquired with a GE Signa Advantage, 1.5-Tesla machine at Kuakini Medical Center, Honolulu, using a scan protocol described previously.[7] The well-described protocol developed for the Cardiovascular Health Study[8] was used to assess large and small vessel infarcts, white matter lesions, and global atrophy. Hippocampal volume was obtained by manual drawing of ROI by one rater blind to clinical data. The intraclass correlation coefficient for the intrareader agreement of the hippocampal volume was 0.97. The left and right hippocampus was identified per Jack criteria[9] and described previously for this cohort.[7]

Hippocampal shape analysis

Using the manually delineated hippocampi, we created an average left and right hippocampus for the Alzheimer's disease and the VaD groups, with already described software developed at the Laboratory of Neuro Imaging at UCLA.[10] The

distance to the medial axis at each surface point was calculated for each individual subject. This distance was compared between the two case groups, and statistical significance was calculated with permutation testing.[10] In most cases, differences in distance to the medial axis were regions in which the VaD hippocampus was larger than the Alzheimer's disease hippocampus, so we only present these results. Results are presented as distance maps (showing the extent of the difference) and probability maps (showing the statistical significance of the difference). Significance levels are colour-coded as red for $p<0.01$ level and yellow for $p<0.05$ level.

Statistical analysis

In addition to neuropsychological and MRI characteristics, the case groups were compared on age, blood pressure measured at exam four,[5] and depression symptoms.[11] Statistical analyses were performed using Stata (Version 8, Stata Corporation).

RESULTS

Characteristics of the study sample

The Alzheimer's disease and VaD cases were both early dementia cases, as evident from the similarities in neurocognitive status as assessed by the Cognitive Abilities Screening Instrument (CASI) and Clinical Dementia Rating Scale (CDR) (tables 1 and 3 online for other neurocognitive tests). Most cases were CDR stage 1 (78% of Alzheimer's disease cases, 85% of VaD cases, excluding those with unknown CDR stage). As expected, for most measures, the VaD group had more lacunae, cortical and subcortical infarcts and white matter abnormalities than the Alzheimer's disease cases (table 1). Age-adjusted total intracranial volume (TICV) was similar among groups: Alzheimer's disease cases, 1476 (1431–1520) cm^3; VaD cases, 1512 (1451–1573) cm^3.

Table 1 Summary characteristics of the incident AD and VaD subjects

	AD ($n=24$)	VaD ($n=14$)
Age (mean, SD)	82.5 (4.6)	80.5 (4.5)
Systolic BP (mm Hg mean, SD)	134 (15)	137 (19)
Depressive symptomatology (CESD>=9), (%)	18.2	14.3
CASI @ exam 4 (median, (95% CI))†	80 (75 to 86)	81 (78 to 86)
CASI @ exam 5 (median, (95% CI))††	67 (58 to 70)	67 (58 to 72)
CDR @ exam 5 (%)		
Stage 1	14 (58%)	11 (79%)
Stage 2	3 (13%)	2 (14%)
Stage 3	1 (4%)	0 (0%)
Missing/UNK	6 (25%)	1 (7%)
Measures of global atrophy (median, (95% CI))		
Ventricle size	4.5 (4 to 6)	5 (5 to 6)
Central sulcus width	4 (3 to 4.3)	4.5 (4 to 5.2)
Normalised central sulcus width	0.026 (0.019 to 0.029)	0.026 (0.019 to 0.035)
Semi-quantitative large and small vessel disease		
Lacunae (one or more) (%)	12.5	85.7**
Cortical infarcts (one or more) (%)	0.0	21.4*
Subcortical infarcts (one or more) (%)	0.0	14.3
White matter grade (median, (95% CI))	1.5 (1 to 3)	3.5 (2 to 5)*

Ventricle size Scale ranges from 0 to 9.
Central sulcus width Scale ranges from 0 to 9.
Normalised central sulcus width Central sulcus width divided by inner table width.
White matter grade Scale ranges from 0 to 9.
*$p<0.05$, **$p<0.01$, AD versus VaD, ranksum test (medians), t test (means), or χ^2 (proportions).
†Exam 4 was conducted in 1991–1993, and the cases did not yet meet criteria for AD.
††Exam 5 was conducted in 1995–1996, and was the first HAAS exam in which the cases met criteria for AD.
AD, Alzheimer's disease; CASI, cognitive abilities screening instrument; CDR, clinical dementia rating scale; CESD, center for epidemiologic studies depression scale; VaD, vascular dementia.

Hippocampal volume

Crude total hippocampal volume was 4903 (±857) mm^3 in the Alzheimer's disease group and 5344 (±740) mm^3 in the VaD group (table 2). For purposes of comparison, we note that crude hippocampal volume was 5540 (±805) mm^3 in the sub-sample of non-demented men from this cohort.[5] The difference in age and TICV-adjusted hippocampal volume between the Alzheimer's disease and VaD groups did not reach significance for the left (6.4% smaller in Alzheimer's disease group, $p<0.23$), right (4.1% smaller in Alzheimer's disease group, $p<0.44$) or total (5.1% smaller in Alzheimer's disease group, $p<0.31$) hippocampus (table 2).

Shape analysis

The shape of the left hippocampus ($p<0.04$, permutation test), but not the right hippocampus ($p<0.21$, permutation test), differed between the Alzheimer's disease and VaD cases. Figure 1 shows the regions where the Alzheimer's disease hippocampus is smaller than the VaD hippocampus. The figures show the absolute percent difference between the two groups (left column) and the statistical significance of the difference (right column). All figures show the hippocampus from four orientations: right hippocampus in front, left hippocampus in front, from below and from above. Together, these shape analyses are consistent with the volume results (table 2).

DISCUSSION

In this community-based sample of very old clinically diagnosed mild incident Alzheimer's disease and VaD cases, we found no significant differences in hippocampal volume between the sub-types of dementia. However, based on the results of the permutation testing, there were hippocampal shape differences in the left hippocampus, but not the right.

The specific region of the hippocampus that most consistently differed between the Alzheimer's disease and VaD cases is the lateral portion of the left hippocampus. Our interpretation of this region is that it intersects the CA1 sub-region, to a great extent, but also includes the dentate gyrus (and hilar region) and subiculum. However, we cannot rule out involvement of regions adjacent to the CA1 such as CA2 or the adjacent most distal portion of CA3. Results are largely consistent with our earlier analysis comparing clinically diagnosed Alzheimer's disease cases to a non-demented elderly control group,[5] suggesting that this region is specific to Alzheimer's disease-related hippocampal changes and is independent of changes associated with normal ageing. We note that our Alzheimer's disease and VaD subjects were clinically diagnosed and that persons who die with a diagnosis of Alzheimer's disease or VaD can have a range of pathology in their brains.[12]

Table 2 Average hippocampal volume for the incident AD and VaD cases

	AD ($n=24$)	VaD ($n=14$)	AD versus VaD* (%)
Left hippocampus	2390 (453)	2606 (348)	6.4
Right hippocampus	2513 (467)	2738 (431)	4.1
Total hippocampus	4903 (857)	5344 (740)	5.1
Left–right	123 (334)	131 (257)	40.8

*The age and TICV-adjusted difference, expressed as a percentage of AD volume.
AD, Alzheimer's disease.; VaD, vascular dementia.

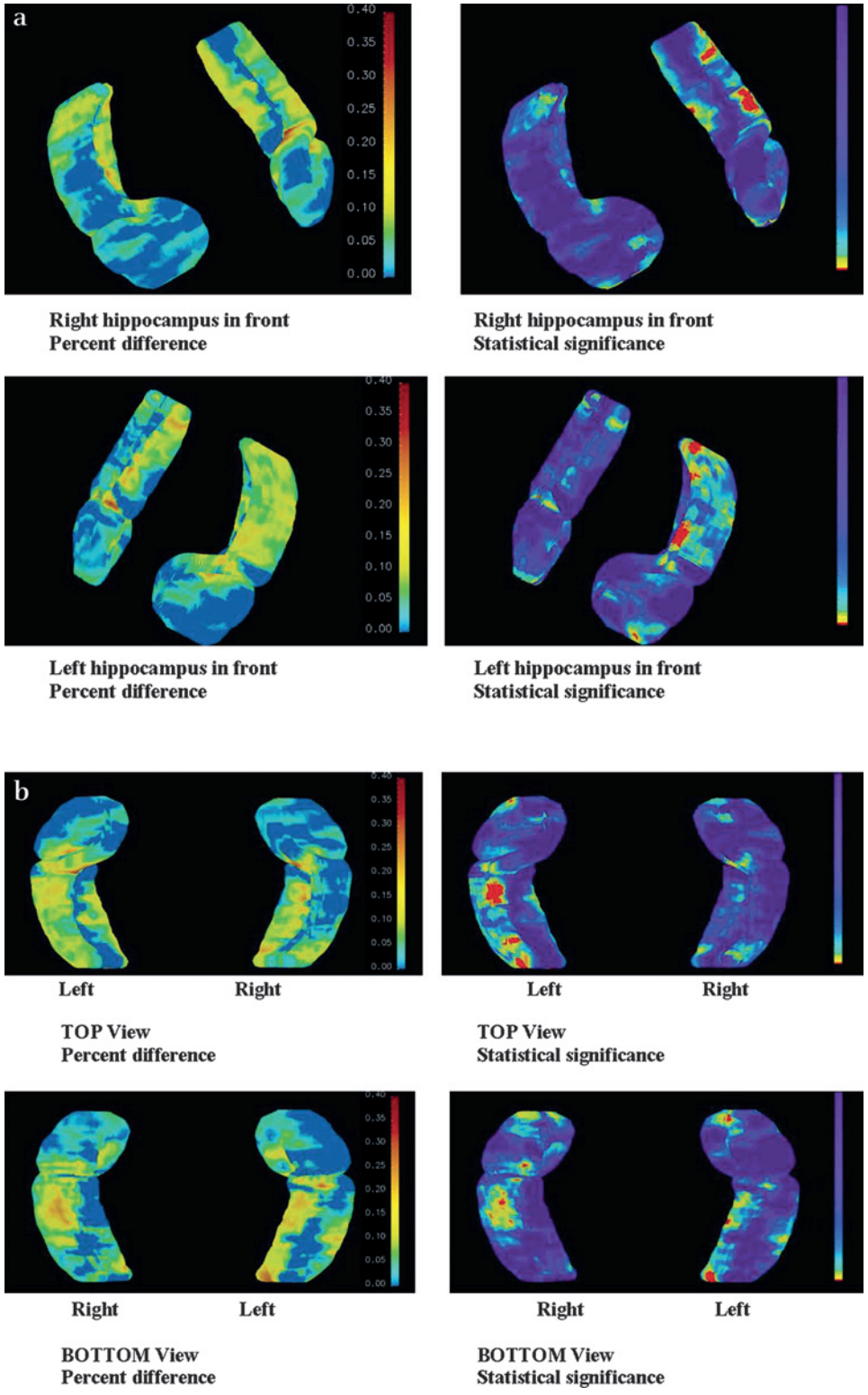

Figure 1 Regional hippocampal shape differences between clinically diagnosed cases with incident Alzheimer's disease (n=24) and vascular dementia (VaD) (n=14) (a, b). Displays those areas in which the distance to the medial axis is smaller in the Alzheimer's disease cases compared to the VaD cases. The figures on the left show the percent difference and the figures on the right show the statistical significance of the difference. Yellow points are significant at the 0.05 level and red points are significant at the 0.01 level.

Although atrophy of the hippocampus is a well-described feature of Alzheimer's disease,[11] there are few studies directly comparing the extent of global or regional volume and shape differences in very old mild cases of Alzheimer's disease and comparably demented VaD cases. In prior studies, hippocampal volume was smaller in cases of Alzheimer's disease cases compared to those with dementia and subcortical ischaemic vascular disease,[13 14] although differences were not always statistically significant. A stereological study of a clinical sample of severe cases further suggests involvement of the CA1 and CA2 sub-regions.[2]

Our results presented herein suggest that the hippocampal atrophy in Alzheimer's disease is more focal than might occur in VaD. Further, the differences between the two sub-types appear to be larger in the left compared to the right hippocampus. The reasons for this asymmetry are uncertain and require further investigation.

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Competing interests None.

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