Hippocampal atrophy on MRI in frontotemporal lobar degeneration and Alzheimer’s disease.

Key words:
Hippocampus, Alzheimer’s disease, Frontotemporal Lobar Degeneration, MRI

Authors names:
Laura A. van de Pol, MD 1, Anke Hensel, PhD 2, Wiesje M. van der Flier, PhD 1, Pieter-Jelle Visser, MD, PhD 1, Yolande A.L. Pijnenburg, MD 1, Frederik Barkhof, MD, PhD 3, Hermann Josef Gertz, MD, PhD 2, Philip Scheltens, MD, PhD 1

Affiliations:
1 Department of Neurology, Alzheimer Center, VU Medical Center, Amsterdam, the Netherlands
2 Department of Psychiatry, University of Leipzig, Germany
3 Department of Radiology, Alzheimer Center, VU Medical Center, Amsterdam, the Netherlands

Corresponding Author:
Laura van de Pol
VUMC, Department of Neurology
PO Box 7057
1007 MB Amsterdam, the Netherlands
phone: +31-20-4440183
fax: +31-20-4440715
L.vandepol@vumc.nl

Financial disclosures: none

Word count:
Abstract: 220 words
Text: 1460 words
Title: 89 characters
ABSTRACT

Background: Hippocampal atrophy on MRI is an early characteristic of Alzheimer's disease (AD). However, hippocampal atrophy may also occur in other dementias, like frontotemporal lobar degeneration (FTLD).

Aim: To investigate hippocampal atrophy on MRI in FTLD and its three clinical subtypes, in comparison to AD, using volumetry and a visual rating scale.

Methods: Forty-two patients with FTLD (17 frontotemporal dementia, 13 semantic dementia and 12 progressive non-fluent aphasia), 103 patients with AD and 73 controls were included. Hippocampal volumetry and the easily applicable medial temporal lobe atrophy (MTA) rating scale were applied to assess hippocampal atrophy.

Results: Multivariate analysis of variance (MANOVA) for repeated measures showed a significant effect of diagnostic group on hippocampal volume. There was a significant diagnosis by side (left versus right) interaction. Both FTLD and AD showed hippocampal atrophy compared to controls. Results of the visual MTA rating scale confirmed these findings. Within the FTLD subtypes marked differences in hippocampal atrophy existed. Frontotemporal dementia and semantic dementia showed bilateral hippocampal atrophy and in semantic dementia the left hippocampus was smaller than in AD. Finally, in non-fluent progressive aphasia no significant hippocampal atrophy was detected.

Conclusion: We provide evidence that hippocampal atrophy is not only a characteristic of AD, but also occurs in FTLD. The three clinical subtypes of FTLD show different patterns of hippocampal atrophy.
INTRODUCTION

Subjects with frontotemporal lobar degeneration (FTLD) present with alterations in personality and cognitive dysfunction. Three clinical subtypes can be distinguished by their neurobehavioral profile: frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PA). These subtypes have overlapping neuropathological substrates, and all result in progressive degeneration of the frontotemporal lobes.

Subjects with Alzheimer’s disease (AD) presents with episodic memory impairment. On MRI, hippocampal atrophy is an early marker of AD, differentiating AD patients from controls. However, hippocampal atrophy may also occur in FTLD. Although previous studies have investigated hippocampal atrophy in FTD and SD, none of these studies included all three FTLD subtypes.

Our aim was to investigate hippocampal atrophy on MRI in FTLD and its three clinical subtypes, in comparison to AD. We used both hippocampal volumetry and an easily applicable visual rating scale for medial temporal lobe atrophy (MTA).

METHODS

Subjects
A total of 145 subjects were included from two centers. At the University of Leipzig eight FTLD patients (four FTD, one SD, three PA) and 44 AD patients were recruited. From the Alzheimer Center of the VU Medical Center in Amsterdam 34 FTLD patients (13 FTD, 12 SD, 9 PA) and 59 AD patients were included. Forty-two controls were recruited from the LEILA75+-study and among patients’ spouses in Leipzig and 31 controls were recruited through advertisements and among patients’ spouses and friends in Amsterdam.

Subjects underwent a standard battery of examinations, including history taking, medical and neurological examination, laboratory tests and psychometric evaluation. Brain MRI was acquired between 0-3 months after initial evaluation. Dementia severity was assessed with the Clinical Dementia Rating scale (CDR). Diagnoses of FTLD and AD were made by multidisciplinary teams, based on clinical criteria. Although brain MRI contributed to the diagnostic process, it should be noted that hippocampal volumes and MTA scores were not used. All subjects provided written informed consent for their clinical data being used for research.

MRI
In Leipzig participants were scanned on a 1.5-Tesla scanner (Siemens Vision, Erlangen, Germany), whilst in Amsterdam scanning was performed on a 1.0-T scanner (Siemens Magnetom Impact Expert, Erlangen, Germany). A three-dimensional T1-weighted MPRAGE sequence was acquired (parameters: Leipzig: TR11.4ms, TE4.4 ms, transverse orientation, matrix: 256x256, voxel size: 0.90x0.90x1.5mm, Amsterdam: TR15 ms, TE7 ms, coronal orientation, matrix: 256x256, voxel size: 0.98x0.98x1.49mm.)
Hippocampal volumes were analyzed using in-house software of the Max-Planck-Institute of Human Cognitive and Brain Sciences. Volumetric datasets were aligned with the stereotactical coordinate system, using the anterior and posterior commissure as reference points, scaled to an isotropical voxel resolution of 1 mm. Six hippocampal cross-sections were segmented manually in the coronal plane. Hippocampal measures started behind the amygdala at the slice in which the area of the hippocampal head appeared maximal and were continued posteriorly at 3 mm-intervals. Manual outlining of the hippocampus was shown to have a high inter-rater reliability (intraclass correlation: 0.996).

Visual rating of hippocampal atrophy was performed on coronal T1-weighted images. The MTA-scale ranges from zero (no atrophy) to four (severe atrophy). The intra-rater agreement was good as determined on 20 MRI scans (κ = 0.68). Raters were blinded to the clinical information and each others results. To correct for headsize, the midsagittal intracranial area (ICA) was manually outlined following Pantel's technique.

**Statistical analysis**

Group differences in hippocampal volumes were examined using multi-variate analysis of variance (MANOVA) for repeated measures with diagnostic group as between-subjects variable, side (left versus right) as within-subjects variable and age, sex, ICA and type of scanner as covariates. To evaluate group differences of left and right hippocampal volumes separately, additional ANOVAs with post hoc Bonferroni tests were performed, including the same covariates. Group differences in MTA scores were tested using Kruskal-Wallis tests with post hoc Mann-Whitney-U tests. To correct for multiple comparisons the significance level for this analysis was p<0.01.

**RESULTS**

Group characteristics are presented in table 1. Age differed between the groups (F[2, 215]=18.8, p<0.001). AD patients were older than FTLD patients and younger than controls. FTLD patients had a longer disease duration than AD patients. FTLD patients had a larger ICA than AD patients and controls (F[2, 215]=5.1, p<0.01). There were no differences between groups in distribution of sex or CDR score.
<table>
<thead>
<tr>
<th></th>
<th>Controls, n=73</th>
<th>FTLD, n=42</th>
<th>AD, n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>75 (8)</td>
<td>65 (7)**#</td>
<td>71 (9)*</td>
</tr>
<tr>
<td>Sex M:F</td>
<td>34:39</td>
<td>26:16</td>
<td>43:60</td>
</tr>
<tr>
<td>CDR\textsuperscript{a,b}</td>
<td>-</td>
<td>1 (0.5-3)</td>
<td>1 (0.5-3)</td>
</tr>
<tr>
<td>Disease duration (y)\textsuperscript{a,c}</td>
<td>-</td>
<td>6 (1-13)#</td>
<td>3 (1-13)</td>
</tr>
<tr>
<td>ICA (cm$^2$)</td>
<td>146 (12)</td>
<td>151 (11)**#</td>
<td>145 (11)</td>
</tr>
<tr>
<td>Left hippocampus (cm$^3$)</td>
<td>1.69 (0.21)</td>
<td>1.43 (0.24)**</td>
<td>1.37 (0.24)**</td>
</tr>
<tr>
<td>Right hippocampus (cm$^3$)</td>
<td>1.75 (0.19)</td>
<td>1.61 (0.28)**</td>
<td>1.46 (0.24)**</td>
</tr>
<tr>
<td>Left MTA\textsuperscript{d}</td>
<td>1.34 (0.78)</td>
<td>2.41 (0.94)**</td>
<td>2.38 (0.84)**</td>
</tr>
<tr>
<td>Right MTA\textsuperscript{d}</td>
<td>1.37 (0.77)</td>
<td>2.07 (0.92)**</td>
<td>2.39 (0.87)**</td>
</tr>
</tbody>
</table>

Values are expressed as mean (standard deviation) or median (range).
Raw hippocampal volumes are presented, but these were subsequently corrected for age, sex, ICA and type of scanner.
ANOVA with post hoc Bonferroni tests was used unless stated otherwise.
\textsuperscript{a}Mann-Whitney U test, \textsuperscript{b}CDR-score was missing for 1 FTLD and 1AD patient, \textsuperscript{c}data on disease duration was missing for 5 AD patients, \textsuperscript{d}Kruskal-Wallis test with post hoc Mann-Whitney-U tests.
* differs from controls (p<0.05), ** differs from controls (p<0.01), # differs from AD (p<0.01)
FTLD: Frontotemporal Lobar Degeneration, AD: Alzheimer’s Disease, CDR: Clinical Dementia Rating scale, ICA: Intracranial Area, MTA: Medial Temporal lobe Atrophy
Group differences in hippocampal volume were examined using MANOVA for repeated measures. The main effect of diagnosis was significant ($F[2, 211]=49.6, p<0.001$), whereas the main effect of side (left versus right) was not ($F[1, 211]=3.3, p=0.07$). In addition, there was a significant diagnosis by side interaction ($F[2, 211]=8.2, p<0.001$, table 1).

ANOVA with post hoc Bonferroni tests were used to evaluate group differences of left and right hippocampal volumes separately (left:$F[2, 211]=48.0, p<0.001$; right:$F[2, 211]=39.7, p<0.001$, table 1). AD and FTLD patients had smaller hippocampal volumes bilaterally, compared to controls ($p<0.001$). The differences in hippocampal volumes between AD and FTLD were not significant.

Group differences in MTA-scores were analyzed using Kruskal-Wallis tests with post hoc Mann-Whitney-U tests. This analysis yielded comparable results, FTLD and AD groups having more MTA bilaterally, compared to controls ($p<0.001$). FTLD and AD patients had comparable MTA-scores bilaterally (left: $p=0.91$, right: $p=0.04$).

In an additional analysis hippocampal volumes in the three FTLD subtypes were evaluated separately. ANOVAs using the five diagnostic groups with age, sex, ICA and type of scanner as covariates were carried out, applying post hoc Bonferroni tests (figure 1). As observed before, bilateral hippocampal volumes differed according to group (left: $F[4, 209]=29.5, p<0.001$ right: $F[4, 209]=23.0, p<0.001$). Different distributions of hippocampal atrophy compared to AD and controls were found in the three clinical FTLD subtypes. Firstly, FTD patients showed bilateral hippocampal atrophy similar to patients with AD (both sides: FTD<controls, $p<0.001$; FTD=AD, $p=1.00$). Secondly, SD patients showed bilateral hippocampal atrophy as well (both sides: SD<controls, $p<0.001$). Moreover, the left hippocampus was affected to a greater extent than in AD patients (left: SD<AD, $p=0.03$; right: SD=AD, $p=1.00$), reflecting asymmetry in SD. Finally, PA patients had a left hippocampal volume intermediate to that seen in controls and AD patients (PA=controls, $p=0.12$; PA=AD, $p=0.26$), while the right hippocampus was spared (PA=controls, $p=1.00$; PA>AD, $p=0.011$). In a direct comparison between FTLD subgroups, left hippocampal volume in SD was reduced compared to PA, whereas left hippocampal volume in FTD was intermediate to SD and PA (FTD=SD, $p=0.16$; FTD=PA, $p=0.79$; SD<PA, $p=0.001$). Right hippocampal volumes were not significantly different between the three subgroups (FTD=SD, $p=1.00$; FTD=PA, $p=0.06$; SD=PA, $p=0.08$).

**DISCUSSION**

The main findings of this study are twofold. Firstly, we have confirmed that hippocampal atrophy occurs in FTLD, and is not restricted to AD. Furthermore, differences in hippocampal atrophy exist in the three clinical FTLD subtypes. FTD showed bilateral hippocampal atrophy comparable to AD. In SD bilateral hippocampal atrophy was observed, with left-sided hippocampal atrophy exceeding that in AD, whilst in PA hippocampal atrophy was not consistently observed.
Our finding that FTLD and AD both show hippocampal atrophy is consistent with previous studies.\textsuperscript{10-13} Beyond corroborating earlier findings we provide for the first time data on hippocampal atrophy in all three clinical subgroups of FTLD, including PA. Noteworthy is the fact that a proportion of PA patients shows no hippocampal atrophy. A possible explanation may be that neuropathology in PA, especially in the early stages, is mainly concentrated around the Sylvian fissure.\textsuperscript{19}

Differentiation between FTLD and AD is essential in terms of clinical management and pharmacotherapy. Both diseases are diagnosed using clinical criteria,\textsuperscript{1,2} but considerable clinical overlap exists.\textsuperscript{20} We have shown that the presence of hippocampal atrophy on MRI does not exclude a diagnosis of FTLD. Hippocampal atrophy in FTLD may be attributable to co-existing Alzheimer pathology or reflect a different disease. A recent neuropathological study reported consistent involvement of the hippocampus in the early stages of FTLD, without AD neuropathology.\textsuperscript{21}

A limitation of this study is the use of a clinical diagnosis as the gold standard, without neuropathological verification. However, careful follow up of patients without a change in their clinical diagnosis may serve as near to gold standard in clinical studies.\textsuperscript{22} The selection of patients from two centers may have introduced bias, although we corrected for this using type of scanner as a covariate. Also, our method of hippocampal volumetry, segmenting only six cross sections, underestimates absolute volumes, however, this method was shown to be reproducible and sensitive in a previous paper.\textsuperscript{17} One of the strengths of this study is the relatively large group of FTLD patients that enabled us to investigate the three clinical subtypes. Furthermore, since hippocampal volumetry is labour-intensive and not suitable for routine clinical practice, we also used the easily applicable MTA score. In accordance with earlier studies results of both methods were comparable,\textsuperscript{23-25} indicating that the use of this simple scale in daily clinical practice is possible.

In conclusion, hippocampal atrophy is not restricted to AD but occurs in FTLD also. The three clinical subtypes of FTLD subtypes show different patterns of hippocampal atrophy compared to AD and controls.
ACKNOWLEDGEMENTS

This study was supported by a grant from Internationale Stichting Alzheimer Onderzoek (nr: 02502/028809) and the Interdisciplinary Centre for Clinical Research (IZKF) at the University of Leipzig (01KS9504/1, project C8)

Financial disclosures: none

Philip Scheltens is associate editor of the Journal of Neurology, Neurosurgery and Psychiatry. He had no involvement in the review process.

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FIGURE LEGENDS

Figure 1: Boxplot of hippocampal volumes (z-scores) by diagnostic group.
FTLD=Frontotemporal Lobar Degeneration, AD=Alzheimer’s disease, FTD= Frontotemporal Dementia, SD=Semantic Dementia, PA=Progressive non-fluent Aphasia

Based on our control population we corrected for the influence of possible confounders on hippocampal volumes. In the control population multiple linear regression was performed with age, sex, ICA, and type of scanner as independent and hippocampal volume (left and right separately) as dependent variables. On the basis of the resulting model, an expected hippocampal volume for each subject was calculated. This volume was subtracted from the measured volume. The residue of the hippocampal volume was divided by the standard deviation of the residue in the reference population to give a z-score. A z-score below zero indicates a below average volume.