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▶ **To cite this version:**

Yanica Klein-Koerkamp, Rolf A Heckemann, Kylee Ramdeen, Olivier Moreaud, Sandrine Keignart, et al.. Amygdalar Atrophy in Early Alzheimer's Disease. Current Alzheimer Research, 2014, 11 (3), pp.239-252. 10.2174/1567205011666140131123653 . hal-00959516

**HAL Id: hal-00959516**
**https://hal.science/hal-00959516**

Submitted on 14 Mar 2014

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*Current Alzheimer Research*, 2014, *11*, 000-000 

# Amygdalar Atrophy in Early Alzheimer's Disease

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**Abstract:** Current research suggests that amygdalar volumes in patients with Alzheimer's disease (AD) may be a relevant measure for its early diagnosis. However, findings are still inconclusive and controversial, partly because studies did not focus on the earliest stage of the disease. In this study, we measured amygdalar atrophy in 48 AD patients and 82 healthy controls (HC) by using a multi-atlas procedure, MAPER. Both hippocampal and amygdalar volumes, normalized by intracranial volume, were significantly reduced in AD compared with HC. The volume loss in the two structures was of similar magnitude (~24%). Amygdalar volume loss in AD predicted memory impairment after we controlled for age, gender, education, and, more important, hippocampal volume, indicating that memory decline correlates with amygdalar atrophy over and above hippocampal atrophy. Amygdalar volume may thus be as useful as hippocampal volume for the diagnosis of early AD. In addition, it could be an independent marker of cognitive decline. The role of the amygdala in AD should be reconsidered to guide further research and clinical practice.

**Keywords:** Automatic segmentation, brain, hippocampus, MRI, neuropsychology.

## INTRODUCTION

The neuropathology of Alzheimer's disease (AD) is characterized by neuronal loss, first affecting the medial temporal lobe (MTL) [1, 2]. In particular, subregions of the hippocampus [3-6] and entorhinal cortex [7] undergo massive pathological changes, leading to progressive memory impairments [8-11]. Several studies suggest that hippocampal atrophy is the best neuroimaging-derived marker of disease and disease progression. However, hippocampal atrophy is associated with a range of other neurological pathologies [12-15], thus limiting its specificity to AD. With advances in automated volumetric segmentation, structures that were previously difficult to assess are now more reliably segmented and evaluated. This has led to the discovery of other structures that undergo change in the course of dementia, notably, other limbic structures close to the hippocampus. In particular, the amygdala has recently received increased attention. Tables **1** and **2** list studies that focus on amygdalar atrophy in mild to moderate AD (Table **1**) and moderate to severe AD (Table **2**), along with factors that influence (1) the magnitude of atrophy measured (i.e., participants' characteristics and segmentation procedures); and (2) the association with clinical features (i.e., information related to correlation analysis between cognitive scores and neuroanatomical volumes). Given our interest in amygdalar volume, we have included only those studies that consider data for this structure. Reduction of amygdalar volume compared to elderly HC was a robust finding in *post mortem* studies [16-20] and in groups that included mildly and severely affected AD patients compared with elderly HC, as shown in Tables **1** and **2** (Clinical Dementia Rating or CDR scores ranging from 0.5 to 3 [4]; Mini-Mental Score Examination or MMSE ranging from 5 to 21 [21]; MMSE ranging from 2 to 27 [22]; MMSE ranging from 11 to 25 [23]). This observation suggests that the diagnosis of AD may be improved if amygdalar volume is considered in addition to hippocampal volume [24]. However, findings are more contradictory for earlier stages of the disease, such as AD patients

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***Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.*

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**Table 1. Summary of research on amygdalar atrophy in mild to moderate AD.**

| Disease Severity | Population Characteristics | Segmentation Characteristics | Volume data | Hippocampal Volume | Amygdalar Volume | Hippocampal vs. Amygdalar Atrophy | Correlation Analysis of Volumes with Cognitive Score | Regression Analysis of Volumes with Cognitive Score | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Mild | AD = 11; MMSE: HC = 29 (1); AD = 21.5 (5) | Manual. MRI: 1.5T - slice thickness: 5 mm | ICV-normalized volumes | HC = AD (20% loss) | HC > AD (33% loss) | A > H | AD; H and A: no significant correlation with MMSE. AD + HC; A: correlation MMSE | | [31] |
| Mild | HC = 8; AD = 18. Age: HC = 69.2 (2.7); AD = 72.4 (1.5); MMSE: HC = 28.7 (0.4); AD = 22.3 (0.9; 13-27) | Semi-automatic. MRI: 5 mm | ICV-normalized volumes | HC > AD (30% loss) | HC > AD (37% loss) | A = H | AD + HC; H: correlation MMSE, memory (Mattis, Wechsler, Grober Buschke Test, Verbal, Intrusion); A: no significant correlations | | [25] |
| Mild | HC = 40; AD = 24. Age: HC = 79 (3.5); AD = 78.4 (3.2); MMSE: HC = 28.9 (1); AD = 22.1 (1.9) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes; *age as covariate* | | HC > AD (18% loss) | | AD + HC; A: correlation MMSE | | [44] |
| Mild | HC = 7; AD = 8. Age: HC = 70; AD = 72; MMSE: AD = 23.9 (17-29) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | Raw volumes | HC > AD | HC = AD (p=0.06) | A < H | | | [84] |
| Mild | HC = 21; AD = 13. Age: HC = 69.3 (6.8); AD = 71.2 (8.3); MMSE: HC = 29.7 (0.2; 28-30); AD = 23.7 (2.7; 20-28) | Manual. MRI: 1.5T et 0.5T - slice thickness: 5 mm | ICV-normalized volumes; age as *covariate* | HC > AD (19% loss) | HC > AD (33% loss) | | | | [32] |
| Mild | HC = 34; AD = 54. Age: HC = 72 (4); AD = 70 (8); MMSE: HC = 28.4 (1.3); AD = 21.7 (3.7) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | | HC > AD (21% loss) | | AD; A: no significant correlation with MMSE | | [45] |
| Mild | HC = 16; AD = 32. Age: HC = 70 (5); MA = 69 (8); MMSE: HC =28.6 (1.4); AD = 22.8 (3.7) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | HC > AD (38% loss) | HC = AD (16% loss) | | AD; A: no significant correlations (MMSE, verbal memory). H: correlation (MMSE, verbal memory) | | [30] |
| Mild | HC = 94; AD = 118. Age: HC = 74 (5); AD = 75 (6); MMSE: HC = 29 (1); AD = 21 (5) | Automatic. MRI: 1.5T - slice thickness: 1.3 mm | ICV-normalized volumes | HC > AD | HC > AD | | | | [85] |
| Mild | HC 1 = 87; AD 1 = 90. HC 2 = 193; AD 2 = 174. Age: HC 1= 77.7 (7.9); AD 1 = 77.2 (6.7); HC 2= 75.6 (5.1); AD 2 = 75.5 (7.3); MMSE: HC 1 = 28.9 (1.2); AD 1 = 24.6 (3.9); HC 2 = 29.1 (1); AD 2 = 23.3 (2) | Automatic. MRI: 1.5T - slice thickness: 1 mm | Normalized volumes | HC > AD (18.3% loss AD 1; 19.1% loss AD 2) | HC > AD (19.3% loss AD 1; 18.5% loss AD 2) | A = H | AD; H and A: correlation with MMSE and CDR | AD 2; *volumes, age, sex, education as covariates*: H correlations MMSE and CDR. A: no significant correlations | [26] |

**(Table 1) contd….**

| Disease Severity | Population Characteristics | Segmentation Characteristics | Volume data | Hippocampal Volume | Amygdalar Volume | Hippocampal vs. Amygdalar Atrophy | Correlation Analysis of Volumes with Cognitive Score | Regression Analysis of Volumes with Cognitive Score | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Mild | HC = 19; AD = 20. Age: HC = 72.5 (7.8); AD = 72.7 (9.1); MMSE: HC = 29.1 (1); AD = 22 (4.3; 13-28) | Manual. MRI: 1T - slice thickness: 1.3 mm | Raw volumes (spatial normalization on original images) | HC > AD (26-28% loss in right and left, respectively) | HC > AD (19-24% loss in right and left, respectively) | Right: A < H Left: A = H | AD; H: no significant correlation (language, visuospatial, executive functions MMSE). A: correlation memory | AD + HC; *volumes and MMSE diagnosis as covariate:* no significant correlations | [27] |
| Mild | HC = 20; AD = 20. Age: HC = 66 (6.7); AD = 70 (8.6); MMSE: HC = 27.6 (2.06); AD = 23.3 (2.56; 20-29) | Manual. MRI: 1.5T - slice thickness: 2 mm | ICV-normalized volumes | HC > AD (30% loss) | HC > AD (29.5% loss) | A = H | AD; H and A: correlation memory | | [28] |
| Mild to moderate | HC = 15; AD = 12. Age: HC = 77 (10.6); AD = 78.4 (10); MMSE: AD = 20.8 (3.7) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes for mid-sagittal intracranial area | | HC > AD | | | | [86] |
| Mild to moderate | HC = 27; AD = 46; Age: HC = 71.1 (7.3); AD = 68.2 (7.9); MMSE: HC = 27.7 (2); 3 groups: AD 1 (CDR 0.5) MMSE = 23.2 (3.7); AD 2 (CDR 1) MMSE = 20.2 (2.7); AD 3 (CDR 2-3) MMSE = 12.2 (3.4) | Semi-automatic. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes; *age, sex, and education as covariate* | HC = AD (CDR 0,5); HC > AD (CDR 1; posterior hippocampus); HC > AD (CDR 1; anterior hippocampus) HC > AD (CDR 2-3) | HC > AD (CDR 0.5); HC > AD (CDR 1); HC > AD (CDR 2-3) | | | *Volumes as covariate:* AD (CDR 0, 5) + HC; A: correlations (verbal, visual, and Wechsler memory scores). AD (CDR 1) + HC; A and H correlations (verbal, visual, and Wechsler memory scores) | [4] |
| Mild to moderate | HC = 126; AD 1 = 36 AD 2 = 43; AD 3 = 15. Age: HC = 71.1 (7.3); AD 1 = 72.9; AD 2 = 73.5; AD 3 = 75.9. MMSE: HC = 28.6; AD 1 (CDR 0.5) = 21.7; AD 2 (CDR 1) = 18.9; AD 3 (CDR 2) = 16 | Manual. MRI: 1.5T - slice thickness: 1.6 mm | ICV-normalized volumes, then W scores (normal deviates: percentiles relative to HC adjusted for age, gender, education, and duration of disease) | | | | | AD + HC; *W scores volumes, age, sex, and education, diagnosis as covariates*. H correlation dementia scores Boston Naming Test, Wechsler, memory, verbal auditory learning A: no significant correlations. AD; H: correlation Wechsler, verbal auditory learning memory; A: no significant correlations | [10] |
| Mild to moderate | HC = 57; Mild = 66; Moderate = 79. Age: HC= 66.1 (8.3); Mild AD = 75.2 (7); Moderate AD = 73.4 (8.6). MMSE: HC = 29 (28-30); Mild AD = 23 (20-25); Moderate AD = 19 (16-22) | Automatic. MRI: 1.5T - slice thickness: 1.5 mm | Raw volumes - *sex, education, and ICV as covariate* | HC > mild > moderate | HC > mild = moderate | | AD + HC; H and A: correlation (attention, language, visuospatial, memory, executive functions, dementia scores) | AD + HC: *volumes, age, sex, education, and ICV as covariate:* H correlation (memory, visuospatial, and executive functions, dementia scores). A: no significant correlations | [23] |

*Note:* Disease severity was coded as follows: Mean MMSE between 21 and 26: Mild. Mean MMSE between 13 and 20: Moderate. AD = HC means that volumes between both groups are equivalent. HC > AD means that volumes of HC are higher than AD patients. H: hippocampal volume, A: amygdalar volume, HC: healthy control individuals, AD: Alzheimer's disease patients.

with mild to moderate disease (see Table **1**, MMSE scores ranging from 13 to 29 or CDR scores ranging from 0.5 to 1) [4, 10, 23, 25-28]. In particular, volume loss in mild to moderate AD patients varies from 15-16% [29, 30] to 33-37% [25, 31, 32].

The variation in findings may result from methodological issues related to amygdalar segmentation. Because of the numerous cortical and subcortical nuclei of the amygdala, its proximity to the hippocampus, and the similarity of neighboring tissues, the boundaries of the amygdala are difficult

**Table 2. Summary of research on amygdalar atrophy in moderate to severe AD.**

| Disease Severity | Population Characteristics | Segmentation Characteristics | Volume Data | Hippocampal Volume | Amygdalar Volume | Hippocampal vs. Amygdalar Atrophy | Correlation Analysis of Volumes with Cognitive Score | Regression Analysis of Volumes with Cognitive Score | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Moderate | HC = 42; AD = 56. Age: HC = 73.2 (6.7); AD = 71.2 (8.6); MMSE: HC = 29 (1); AD = 18.3 (4.3) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | HC > AD (17% loss) | HC > AD (23% loss) | A = H | AD; H: no correlation (language, memory, orientation, praxis, MMSE). A: correlation (memory, orientation, MMSE) | | [37] |
| Moderate | HC = 10; AD = 10. Age: HC = 56 (11); AD = 57 (9); MMSE: HC = 29 (1); AD = 15 (6) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | HC > AD (16.4% loss) | HC > AD (15% loss) | A = H | | | [29] |
| Moderate | HC = 19; AD = 19. Age: HC = 73.6 (5.5); AD = 76.1 (5.7); MMSE: HC = 28.6 (1.1; 27-30); AD = 13.1 (3.8; 5-21) | Manual. MRI: 3T - slice thickness: 1 mm | ICV-normalized volumes; *sex and education as covariate* | | HC > AD (22% loss) | | | | [21] |
| Moderate | HC = 18; AD = 27; Age: HC = 69.5 (6.4); AD = 71 (7.5); MMSE: HC = 30; AD = 19 (3.6) | Manual. MRI: 1.5T - slice thickness: 1 mm | ICV-normalized volumes | HC > AD (35% loss) | HC > AD (16% loss) | A < H | AD; H and A: correlation MMSE | | [38] |
| Moderate | HC = 126; AD = 94. Age: HC = 79 (6.73); AD = 73 (8); MMSE: HC = 28 (1.26); AD = 17.8 (4.94) | Manual. MRI: 1.5T - slice thickness: 1.6 mm | Raw volumes; *ICV as covariate* | HC > AD | HC > AD | A < H | | | [3] |
| Moderate | HC = 22; AD = 31; Age: HC = 67.7 (7.9); AD = 68 (6.8); MMSE: AD: 17.2 (3.2,14-23); HC: 28.8 (1.1, 25-30) | Manual. MRI: 0.5T - slice thickness: 5 mm | Normalized volumes | | HC > AD | | | AD; *age and A volume as covariate*: A: no significant correlation (MMSE, cognitive battery) | [87] |
| Moderate | HC = 12; AD = 46. Age: HC = 66.2 (4.9); AD = 70.3 (7.1); MMSE: HC = 28 (1); AD = 19.6 (3.5; 12-26) | Manual. MRI: 1.5T - slice thickness: 1.5 mm | Normalized volumes | HC > AD (15% loss) | HC > AD (18.5% loss) | | AD; H (right) and A: correlation (Wechsler visuo-spatial memory). A: correlation (Wechsler verbal memory) | AD; *volumes*, *age, sex, and education as covariates*: A correlation (Wechsler visuo-spatial and verbal memory subset). H: no significant correlation | [5] |
| Moderate | HC = 27; AD = 36. Age: HC = 72 (4.2); AD = 73 (8.9); MMSE: HC = 28; AD = 17.1 (5.2; 2-27) | Semi-automatic. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | HC > AD (24% loss) | HC > AD (21% loss) | | | | [22] |

**(Table 2) contd….**

| Disease Severity | Population Characteristics | Segmentation Characteristics | Volume Data | Hippocampal Volume | Amygdalar Volume | Hippocampal vs. Amygdalar Atrophy | Correlation Analysis of Volumes with Cognitive Score | Regression Analysis of Volumes with Cognitive Score | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Moderate | HC = 20; AD = 20; MMSE: MA = 18.8 (5.7; <26) | Manual. MRI: 1.5T - slice thickness: 2 mm | ICV-normalized volumes | HC > AD (20% loss) | HC > AD (33% loss) | | | AD; *volumes, age as covariate:* H no significant correlation; A (Right) correlation (ADAS non-cognitive score); AD; *cognitive scores, age as covariates:* H correlation (ADAS non-cognitive score); A correlation (ADAS-non-cognitive score, MMSE) | [88] |
| Moderate | HC= 17; AD = 20. Age: HC = 63.6 (10.5); AD = 63.8 (9.1); MMSE: HC = 28.9 (1.3); AD = 20.3 (5.1) | Semi-automatic. MRI: 1.5T - slice thickness: 1.5 mm | ICV-normalized volumes | | HC > AD (20.5% loss) | | | | [73] |
| Moderate to severe | HC = 57; Moderate = 79; Severe = 34. Age: HC= 66.1 (8.3); Moderate AD = 73.4 (8.6); Severe AD = 71.3 (9.6). MMSE: HC = 29 (28-30); Moderate AD = 19 (16-22); Severe AD = 12.5 (11-18) | Automatic. MRI: 1.5T - slice thickness: 1.5 mm | Raw volumes - *sex, education, and ICV as covariate* | HC > moderate > severe | HC > moderate = severe | | AD + HC; H and A: correlation (attention, language, visuo-spatial, memory, executive functions, dementia scores) | AD + HC: *volumes, age, sex, education, and ICV as covariate:* H correlation (memory, visuo-spatial, and executive functions, dementia scores). A: no significant correlations | [23] |

*Note:* Disease severity was coded as follows: Mean MMSE between 13 and 20: Moderate. Mean MMSE between 3 and 12: Severe. AD = HC means that volumes between both groups are equivalent. HC > AD means that volumes of HC are higher than AD patients. H: hippocampal volume, A: amygdalar volume, HC: healthy control individuals, AD: Alzheimer's disease patients.

to identify [33, 34]. Various approaches have been implemented to assess MTL atrophy in AD. One of these is based on voxel-based morphometry, which investigates amygdala volume change in AD within the MTL [35, 36]. While this technique allows group comparisons between AD and HC, it cannot provide the absolute volume of the structure at the individual level. The second technique uses manual segmentation of the amygdala on magnetic resonance imaging (MRI) [28, 31, 37, 38]. Although it remains the gold standard, this approach is impractical for cohorts beyond a certain size, because it requires a large amount of expert interaction for each image [33]. The third technique consists of semi-automatic (18) or automatic segmentation of the amygdala and hippocampus [26] on the basis of single-subject digital atlases. A limitation of these techniques is that single-subject atlases do not sufficiently take into account the neuroanatomical variation between subjects. This problem affects amygdala segmentation in particular, because the size and shape of the amygdala varies substantially even within demographically homogeneous groups of healthy subjects. This limitation can be addressed by probabilistic seeding followed by region-growing techniques [39] or by using multiple atlases [40, 41]. In combination with tissue probability maps to enhance registration, multi-atlas approaches are particularly suitable for subjects with neurodegenerative disease [42, 43]. We therefore used multi-atlas propagation with enhanced registration (MAPER) [42] to achieve the first objective of this study, which was to perform amygdalar volumetry in patients with mild to moderate AD.

The relation between amygdalar atrophy and the severity of the disease is still a matter of debate (see Tables **1** and **2**). A correlation between amygdalar atrophy and cognitive impairment in AD has been found in some studies [5, 26, 27, 37, 38], but not in others [25, 30, 31]. In most studies, the clinical significance of amygdalar atrophy in AD was estimated without controlling for hippocampal atrophy [25, 30, 31, 37, 38, 44, 45], which adds to the difficulty of interpreting the results. Considering the strong functional connectivity between the hippocampus and the amygdala, specifically in the context of memory [46, 47], it seems especially important to correct for hippocampal atrophy when assessing the specificity of the relationship between amygdalar atrophy and memory decline in AD. Furthermore, the majority of prior studies combined AD and HC groups for correlation

analysis [4, 10, 23], thus decreasing the sensitivity for detecting changes of anatomical and functional correlations. Finally, some of these studies investigated the correlation between region volumes and global cognitive scores [26, 38] rather than measures of specific cognitive functions. The use of global cognitive scores reduces the sensitivity toward specific functional changes correlated with atrophy.

In the present study, we used automated measurements of *in vivo* human brain volume obtained with MRI to evaluate amygdala and hippocampus volumes and investigated volumetric differences between AD patients and age-matched HC. To obtain automated segmentations of these structures, we used the MAPER approach, previously validated in neurodegenerative disease [42, 43]. The procedure uses 30 training data sets ("atlases," images with expert manual reference segmentations) [48, 49] to segment T1-weighted brain MR images. MAPER is the first automatic whole-brain multiregion segmentation method that has been shown to yield robust results in subjects with neurodegenerative disease [43]. The accuracy achieved with such multi-atlas segmentations is approximately equivalent to that of manual segmentation performed by trained operators (36). In addition, we aimed to explore how the neuropsychological test scores (assessing memory, language abilities, and executive functions) correlate with either amygdala or hippocampus volume. Our goal was to assess whether amygdalar atrophy is a good predictor of early AD. Consequently, we aimed to assess the linearity of the relationship between amygdalar volume and cognitive scores measured with clinical and neuropsychological tests. To determine the specificity of the relationship between amygdalar atrophy and cognitive functions, we performed multiple regression analysis, controlling for both demographic data and, more important, hippocampal volume. The main goal of this analysis was to determine whether amygdalar atrophy is a biomarker for AD independent of hippocampal atrophy.

## MATERIAL AND METHODS

### Participants

We recruited patients with memory complaints who consulted the Memory Center of the Grenoble University Hospital between October 2010 and February 2012. The diagnosis of probable AD was made according to the National Institute of Neurological, Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [50]. All patients were diagnosed after extensive clinical evaluation, including detailed history, physical and neurological examination, and extensive neuropsychological tests. Only patients who were more than 60 years old (mean age of the AD group: 75.3 years; SD = 5.7) and who were new referrals for evaluation of memory complaints were included. Exclusion criteria were current or past diagnosis of somatic, psychiatric, or neurological disorders such as stroke, head trauma, brain tumor, Parkinson's disease, or temporal lobe epilepsy. In addition, subjects with findings suggesting another neurodegenerative disease, such as primary progressive aphasia, fronto-temporal dementia, Lewy body dementia, or mixed forms, were excluded. A total of 48 subjects were selected for our study (33 women and 15 men).

Control subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI)[1]. The inclusion criteria for normal subjects were as follows:

1. No memory complaints aside from those common to other normal subjects of that age range
2. Normal memory function documented by scoring above specific cutoffs on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale – Revised[2] (the maximum score is 25). The cutoffs were as follows:
   a. 9 or higher for 16 or more years of education
   b. 5 or higher for 8-15 years of education,
   c. 3 or higher for 0-7 years of education,
3. MMSE score between 24 and 30 (inclusive)
4. Clinical Dementia Rating and Memory Box scores of zero
5. Absence of significant impairment of cognitive functions and activities of daily living
6. Absence of depression (scores lower than 6 on Geriatric Depression Scale)

Subjects were excluded if they were on current medication, except for vitamin E, estrogen, and estrogen-like compounds if the dose had been stable for at least four weeks before screening. Eighty-two ADNI control subjects (mean age 76.2 years; SD = 5.1) were compared with the study group. Control subjects and patients did not differ in terms of age and gender composition.

### AD Neuropsychological Examination

The neuropsychological examination of AD patients included tests that were standardized for French native speakers and that assessed (1) global cognitive functions (MMSE [51], French version [52]); (2) short-term memory (digit span forward and backward of the Wechsler Adult Intelligence Scale [53]); (3) long-term memory (*RL/RI16* [54], a word learning test based on the selective reminding procedure developed by Grober and Buschke [55]; *BEM 144 – figure learning*, part of the Memory Performance Battery of the BEM-144 [56]; *Doors and People Test* [57]); (4) language abilities (*Famous Faces Test*, an unpublished test de-

[1] ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership. The Principal Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research — approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years.

[2] Modified from Wechsler D. Wechsler Memory Scale-Revised. San Antonio, Texas: Psychological Corporation; 1987.

signed to assess recognition and naming of 30 monochrome pictures of famous faces; *Bachy-Langedock test*, in which subjects have to name 36 black-and-white drawings of ordinary objects; *Irregular word writing*, in which subjects have to write French words with unusual spelling); and (5) executive functions (*Literal and category fluency* – letter "p" and animals [58]; *Trail making test*, part A & B [59]).

### MRI Data Acquisition

Atlas data as required for MAPER consisted of 30 T1-weighted 3D image volumes acquired from healthy young adult volunteers at the National Society for Epilepsy at Chalfont, United Kingdom at 1.5 T. Detailed demographics, acquisition, and anatomical protocol information is available in Gousias *et al.,* Hammers *et al.,* and Niemann *et al.* [48, 49, 60]. Hand-drawn segmentations of 83 structures had been prepared according to the protocols described in these reports [48, 49, 60]. Segmentation protocols are also available at http://www.brain-development.org. We focused on four regions of interest, the left and right hippocampus, and the left and right amygdala.

For the matched control subjects, we selected the ADNI 1.5 T screening image and downloaded the pre-processed version (B1 non-uniformity correction, geometric distortion correction, bias field correction, and phantom scaling) as recommended by ADNI. The acquisition parameters for the various centers are available in Jack *et al.* [61].

MR images of patients were acquired on a 1.5 T Achieva MR scanner (Philips Healthcare) at Grenoble University Hospital, using a whole-body RF transmit coil and eight-channel head receive coils. Anatomical studies consisted of a 3D gradient recalled echo T1-weighted image (TR: 8.1 ms, TE: 3.8 ms, 1 × 1 × 1.3 mm voxel matrix, 256 mm field of view, 100 contiguous slices).

### Pre-Processing

Additional pre-processing of MR images was carried out to determine the intracranial volume (ICV) and to obtain tissue-class probability maps. ICV masks were determined for the control group using the procedure described in Heckemann *et al.* [42]. As this procedure relies on a semi-automatically generated white-and-grey matter mask, which was not available for the study group, we implemented [42] a multi-atlas label propagation procedure to generate ICV masks: a given study group (target) image was paired with each ADNI image and registered using non-rigid image registration. The resulting masks were added in the space of the target and thresholded at 50% to obtain an intracranial label for the target. The labels were visually reviewed for accuracy, and the threshold value modified to improve the ICV label if necessary. Probabilistic tissue-class maps were obtained using FSL FAST [62].

### Segmentation

The MAPER procedure has been described and validated previously in AD populations [42, 43]. Each target is paired with each of the 30 atlases to generate an individual atlas-based segmentation. This results in 30 segmentations for each target image, which are subsequently combined by using vote-rule decision fusion [41, 63].

### Masking Based on Tissue Class

We masked both regions (hippocampus and amygdala) by multiplication with a binary grey matter label generated as a maximum probability label with FSL FAST [62]. The analysis results reported in this work are based on the masked label sets.

### Visual and Statistical Analysis

Masked hippocampal and amygdalar volumes in each target subject were visually checked by an expert (RAH; see example in Fig. **1**). AD and HC were compared in terms of demographic and neuropsychological scores by using chi-square tests (categorical variables) or Student's *t* tests (continuous variables). Volumetric comparisons between groups were based on statistical analyses, including volumes normalized by ICV. The normalized volume was calculated for each individual and each structure, and expressed as a fraction of the total ICV, scaled by an arbitrary factor of $10^4$ [(masked volume/ICV) × $10^4$]. Analysis of volumetric differences between AD and HC groups (between-subject factor, the "Group" variable) was performed by using two within-subject factors: "Structure Volume" (ICV-normalized hippocampal and amygdalar volumes) and "Laterality" (right: R and left: L). Analysis of covariance (ANCOVA; General Linear Model [GLM]) was then used with ICV-normalized volumes as a dependent variable; "Group", "Structure Volume", and "Laterality" as independent variables, and "age", "gender", and "education" as covariates. Since previous work revealed substantial differences in the magnitude of the amygdalar and hippocampal volume loss (see Tables **1** and **2**), we additionally calculated an atrophy index for these structures, as follows: [1-(AD subject ICV-normalized volume / HC mean ICV-normalized volume)] [26].

To assess the relationship between AD patients' volumes and their cognitive scores (assessing memory, language abilities, and executive functions), we first analyzed whether the predictor variables (both hippocampal and amygdalar ICV-normalized volumes and age, sex, and education) were correlated with cognitive scores by using bivariate correlations (Pearson's *r*). Subsequently, we used multiple linear regressions to determine whether AD patients' volumes predict cognitive scores (dependent variables), for each cognitive score separately, considering the contribution of all predictor variables (i.e., age, gender, and education, as well as left and right hippocampal and amygdalar normalized volumes, all as independent variables)[3]. Multiple linear regression analysis then takes into account each variable of interest in the same analysis, and so controls the influence of both neuroanatomical structures.

## RESULTS

AD and HC groups did not differ significantly in age (AD range: 64-87; HC range: 65-87, t(1,128) = -0.92, p =

[3] Multiple regression analysis without the contribution of the demographic data age, gender, and education was also tested; the significance of the predicted hippocampus and amygdala volumes on cognitive scores remained the same whether they were considered or not. To control for demographic modulation, we decided to keep this factor in the statistical analysis.

0.3), gender ($\chi^2$: 1.67, df = 1, p = 0.19), or total ICV (AD range: 1.2 – 1.6 l; HC range: 1.1 – 1.7 l, t(1,128) = -0.61, p = 0.54). Compared with HC, patients had lower MMSE scores (AD range: 15-29; HC range: 26-30, t(1,128) = -14.5, p < 0.001) and a lower level of education (t(1,128) = -10.6, p < 0.001). MMSE scores of AD patients ranged from 15 to 29. Thirty-two patients (of 48) had mild AD severity (mean ± SD MMSE score 24.9 ± 2.3, range 21-29), and 16 of 48 had moderate AD severity (MMSE 18.1 ± 1.7, range 15-20). Subject characteristics are shown in Table **3**.

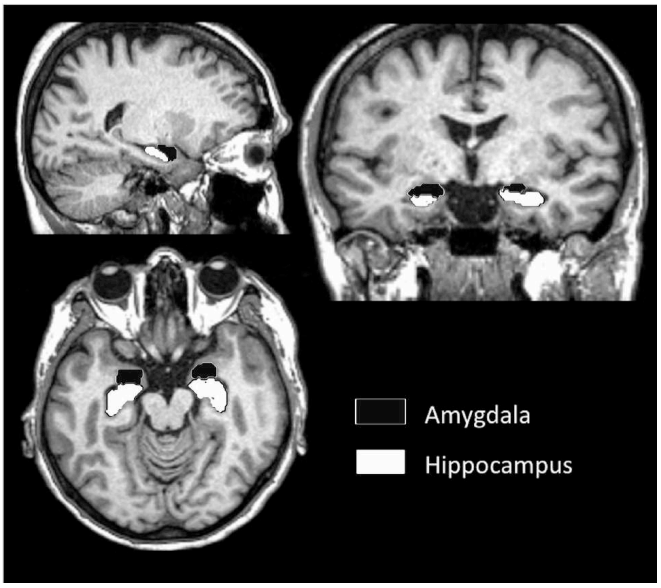


**Fig. (1).** Example of brain segmentations from a subject with AD.

**Table 3. Healthy control and AD patient group characteristics.**

| | HC (n=82) | AD (n=48) |
|---|---|---|
| Age (years; mean ± SD) | 76.2 ± 5.1 | 75.3 ± 5.7 |
| **Gender (W:M)** | 47 : 35 | 33 : 15 |
| Education (years; mean ± SD) | 15.6 ± 3.2 | 8.1 ± 4.7 |
| MMSE (score; mean ± SD) | 29.1 ± 0.9 | 22.6 ± 3.9 |
| ICV (L; mean ± SD) | 1.36 ± 1.2 | 1.35 ± 1.19 |

***Note*. W = women, M = men**, MMSE = Mini-Mental State Examination, ICV = total intracranial volume, n = number of subjects, SD = standard deviation, HC = healthy controls, AD = Alzheimer's disease.

### Amygdalar and Hippocampal ICV-Normalized Volumes

A significant main effect of Structure Volume (F(1,125) = 21.67; p < 0.001) and Group (F(1,125) = 131.7; p < 0.001) was observed. Moreover, we observed a significant interaction of Structure Volume × Group (F(1,125) = 16.01; p < 0.001). Planned comparisons demonstrated a significant effect of Group for the hippocampus (F(1,125) = 93.4; p < 0.001) and the amygdala (F(1,125) = 113.3; p < 0.001) (Fig. **2**), indicating that, compared with HC, AD patients showed significantly smaller volumes of both hippocampus and amygdala. The effect of age (F(1,125) = 16.96; p < 0.001) and gender (F(1,125) = 5.41; p = 0.02) suggests that the amygdalar and hippocampal volumes decrease with age and are larger in women than in men. Education level (F(1,125) = 1.33; p = 0.24) had no significant effect on structure volumes.

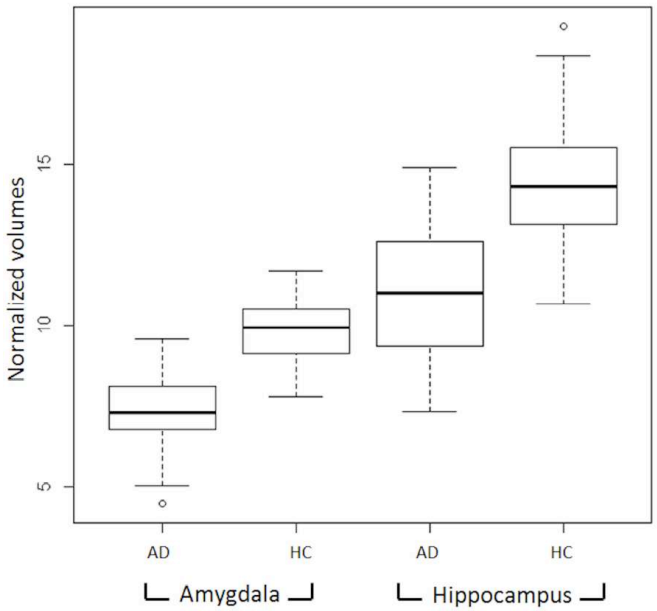


**Fig. (2).** Box plot of the normalized hippocampal and amygdalar volumes in AD patients and HC. The center line shows the median, boxes capture the 25%-75% quantile range, and whiskers indicate 1.5 interquartile ranges. The ring denotes an outlier. Normalized volumes represent gray-matter masked volumes in $mm^3$, divided by total intracranial volume and scaled (arbitrarily) by $10^4$. AD = Alzheimer's disease, HC = healthy controls. The volumes differed significantly between AD and HC subjects (p < 0.05).

No main effect of Laterality (F(1,125) = 1.84; p = 0.17), Laterality × Group (AD patients' right hemisphere volumes: mean ± SD 9.43 ± 2.84; AD patients' left hemisphere volumes: mean ± SD 8.95 ± 2.15; HC right hemisphere volumes: mean ± SD 12.36 ± 3.09; HC left hemisphere volumes: mean ± SD 11.85 ± 2.32; F (1,125) = 1.15; p = 0.69), and Structure Volume × Laterality × Group (F(1,128) = 0.56; p = 0.45) wasobserved in the full model (the physiological R>L asymmetry (e.g., [60]) was observed when age was removed from the model). For subsequent analyses, left and right volumes of each structure (i.e., hippocampus and amygdala) were averaged.

To assess whether the magnitude of the atrophy was similar across structures in AD patients, we included the magnitude index of (R+L) hippocampal and (R+L) amygdalar volumes into the ANCOVA analysis, controlling for age, gender and education. Results revealed no significant effect of the magnitude of the volume loss (amygdalar volume loss: mean ± SD 25.4 ± 11.5 %; hippocampal volume loss mean ± SD 23.2 ± 14.2 %; F(1, 44) = 2.29; p = 0.13, representation as a percentage in Fig. **3**). The volume loss for both structures was thus similar in AD patients. The effect of age (F(1, 44) = 5.27; p=0.02) was statistically significant, but that of gender (F(1, 44) = 1.92; p = 0.17) or of education level (F(1, 44) = 1.13; p = 0.71) was not.

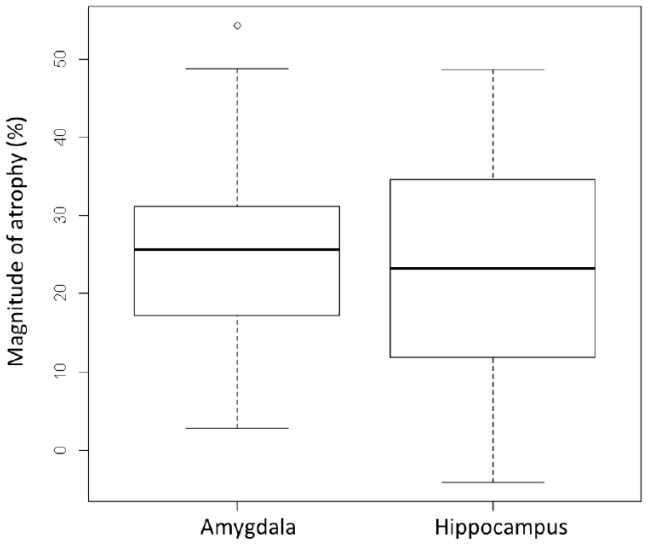


**Fig. (3).** Magnitude of the reduction of hippocampal and amygdalar volume in AD patients relative to healthy controls. The center line shows the median, boxes capture the 25%-75% quantile range, and whiskers indicate 1.5 interquartile ranges. The ring denotes an outlier. The magnitude of atrophy is expressed as a percentage.

### Correlations Between ICV-Normalized Volumes and Neuropsychology Scores

Bivariate correlations indicated that the ICV-normalized hippocampal and amygdalar volumes in AD patients were significantly and positively correlated. In addition, the ICV-normalized hippocampal volume of AD patients was negatively correlated with age (Table **4**). MMSE scores were strongly correlated with gender and level of education, indicating that higher MMSE scores were related to a higher level of education and that women had higher scores than men. Significant correlations were found between memory scores and amygdalar volume, whereas language abilities (naming of famous faces and irregular word writing tests) were correlated with hippocampal volume (Table **4**).

Multiple linear regression analysis (Table **5**) was performed to determine whether volumes in AD patients were predictive of cognitive decline. Age, gender, and education level were additionally included into the regression model as covariates. The amygdalar volume was correlated with memory performance (Grober & Buschke memory test) after we controlled for demographic variables and, of importance, after we controlled for hippocampal volume, indicating that amygdalar atrophy contributes to memory decline independently from hippocampal volume loss. Hippocampus or amygdala volumes did not predict scores for executive functions. The amygdala volume was predictive of naming scores (Bachy-Langedock object naming test).

## DISCUSSION

Hippocampal atrophy is considered the hallmark of AD. However, hippocampal volume loss is associated with many other diseases, including Parkinson's disease [12], frontotemporal lobar degeneration [64], vascular dementia [13, 14], and schizophrenia [15]. Moreover, researchers have detected substantial hippocampal volume loss in cognitively intact individuals [65]. Although hippocampal atrophy has strong sensitivity for AD, several studies showed that its specificity is low. To attempt to improve the identification of this disease by using neuroimaging markers, we evaluated the volume of two limbic structures, the hippocampus and the amygdala. We were also interested in evaluating the relationship between their volumes and neuropsychological test scores.

A critical factor for sensitively in detecting the correlations described in this work was the accuracy of the volumetry method used. Manual image segmentation, while considered the gold standard, is impractical for studies of this size, and the quality of the segmentations depends on many methodological details, e.g., slice thickness [33, 66, 67]. Conventional automatic segmentation approaches frequently fail when the target image is affected by changes typical of neurodegenerative disease, such as ventriculomegaly [43]. We used MAPER [42] and the largest single-investigator atlas database currently available, consisting of 30 manually segmented atlases [48, 49]. This combination eliminates idiosyncrasies typically associated with single-atlas methods and entails high accuracy as well as robustness toward atrophy-related segmentation failures. MAPER has been extensively validated [42] and used [43] for target images acquired from patients with AD.

Amygdalar atrophy was previously regarded as typical for moderate and late AD stages. We report here that it also occurs in early stages. The amount of volume loss is comparable to that seen in the hippocampus. In addition, we observed that amygdala volume predicts cognitive scores even after hippocampal volume is controlled for. This suggests that as a biomarker for early AD, amygdalar volume may be at least as important as hippocampal volume.

A crucial question is whether regional atrophy predicts memory impairment. Contrary to recent findings [26, 37, 38], our results have not revealed any significant correlation between a global index of clinical severity assessed with MMSE and the amygdalar and hippocampal volume. This may be due to the average MMSE score in our study being higher than in previous studies [37, 38]. For early disease, the MMSE scale may not be sensitive enough to reflect a relationship with atrophic regions [25, 31]. In addition, even when strong correlations between volumes and MMSE scores have been found [23, 26, 68] they did not remain statistically significant after factoring out other structure volumes in a linear regression model. In this respect, our results are in agreement with other studies [25, 27, 30, 31, 45].

While significant correlations with MMSE were absent, more specific clinical indices of the disease, such as declarative memory performance (Grober & Buschke test), did correlate with amygdalar volume. Other authors have suggested that such a correlation is explained by the strong correlation between the amygdala and the hippocampus [46, 47]. We performed multiple regression analysis to evaluate amygdalar atrophy and cognitive scores independently of variations of hippocampal volume. We therefore posit that the amygdala has stronger relevance than previously acknowledged.

These results could also reflect an increased sensitivity owing to the accuracy of the MAPER method. Mori *et al.* [5] stressed that the correlation between hippocampal volume

**Table 4. Bivariate correlational analysis of the associations between predictor variables (demographic data and normalized volumes of the hippocampus and amygdala) and neuropsychological tests in patients with mild to moderate Alzheimer's disease.**

| Variables | 1 – Age | 2 – Sex | 3 – Education | 4 – Normalized Hippocampus Volume | 5 – Normalized Amygdala Volume |
|---|---|---|---|---|---|
| | Pearson's *r* | | | | |
| 1 – Age | _ | -0.14 | 0.30* | -0.37** | -0.25 |
| 2 – Sex | -0.14 | _ | -0.24 | 0.21 | 0.22 |
| 3 – Education | 0.30* | -0.24 | _ | -0.18 | 0.03 |
| 4 - Normalized hippocampus volume | -0.37** | 0.21 | -0.18 | _ | 0.69** |
| 5 - Normalized amygdala volume | -0.25 | 0.22 | 0.03 | 0.69** | _ |
| MMSE | -0.04 | -0.28* | 0.49** | -0.01 | -0.08 |
| *Memory* | | | | | |
| WAIS : Digit span forward | 0.16 | -0.21 | 0.20 | -0.22 | -0.21 |
| WAIS : Digit span backward | 0.10 | -0.3 | 0.29 | -0.27 | -0.22 |
| RL-RI 16: Immediate recall | 0.22 | -0.25 | -0.18 | 0.08 | 0.12 |
| RL-RI 16: Free recall | 0.08 | -0.03 | -0.22 | 0.22 | 0.36* |
| RL-RI 16: Total recall | 0.03 | 0.10 | -0.32 | 0.30 | 0.39* |
| RL-RI 16: Delayed free recall | 0.02 | 0.01 | -0.26 | 0.28 | 0.44** |
| RL-RI 16: Delayed total recall | 0.10 | -0.01 | -0.34* | 0.29 | 0.35* |
| BEM 144: Immediate recall | -0.18 | -0.30 | 0.01 | 0.27 | 0.24 |
| BEM 144: Delayed recall | -0.15 | -0.32 | 0.00 | 0.28 | 0.33* |
| Doors and People Tests (set A+ B) | -0.31 | -0.08 | -0.12 | 0.25 | 0.09 |
| *Language abilities* | | | | | |
| Naming of famous faces | 0.04 | -0.02 | 0.02 | 0.50* | 0.38 |
| Bachy-Langedock test | 0.14 | -0.04 | 0.15 | -0.08 | -0.03 |
| Irregular words writing | 0.14 | 0.03 | 0.32 | 0.41* | -0.23 |
| *Executive functions* | | | | | |
| VF: Literal | 0.06 | 0.18 | 0.39* | -0.10 | 0.09 |
| VF: Category | -0.20 | -0.09 | 0.11 | 0.20 | 0.20 |
| TMT: A | 0.01 | 0.07 | -0.18 | 0.17 | 0.26 |
| TMT: B | 0.37* | 0.03 | -0.15 | 0.06 | 0.03 |

*Note*: MMSE = Mini-Mental State Examination, WAIS = Wechsler Adult Intelligence Scale, RL-RI 16 = Rappel libre – Rappel Indicé of the Gröber & Buschke test, BEM 144 = Batterie d'Efficience Mnésique (Memory Performance Battery), VF = Verbal Fluency, TMT = Trail Making Test. Positive correlation for the sex variable means that females have higher scores than males. Negative correlation for the sex variable means that males have higher scores than females. Significant correlations are marked with asterisks: * $p<0.05$; ** $p<0.01$.

and memory scores depends on whether the hippocampal segmentation encompassed the subiculum region. Critically, AD pathology affects numerous structures that surround the hippocampus, such as the subiculum, parahippocampal gyrus, and entorhinal cortex [69]. Anatomical connections between the subiculum and the hippocampus are particularly important in supporting memory functions [70]. Therefore, additional MTL structures not considered in our study (e.g., subiculum, entorhinal, perirhinal, or parahippocampal cortices) may explain memory impairment beyond the hippocampus. Consistent with this possibility in this framework is that the hippocampus shows evidence for plasticity in dementia. In fact, Dickerson *et al.* [71] demonstrated that compensatory hippocampal mechanisms are activated during the earliest stages of the atrophy process. Moreover, Jin *et al.* [72] showed that neurogenesis in the hippocampus occurs even in the context of AD. Taken together, these studies support the view that correlations between hippocampal volume, hippocampal function, and memory impairment in AD are highly non-linear.

Overall, our results demonstrate that MAPER-based amygdalar volumetry can show major neuroanatomical

**Table 5. Multiple linear regression analyses of the associations between volumes of the hippocampus and amygdala and neuropsychological tests in patients with mild to moderate Alzheimer's disease.**

| Neuropsychological Variable | | | | Hippocampus | | | | Amygdala | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Range | β* | t | Df | p | β* | t | df | P |
| MMSE | 22.6 | 3.9 | (15-29) | 0.06 | 0.29 | 42 | 0.77 | -0.16 | -0.88 | 42 | 0.38 |
| *Memory* | | | | | | | | | | | |
| WAIS : Digit span forward | 5.3 | 0.9 | (3-7) | -0.08 | -0.32 | 29 | 0.75 | -0.09 | -0.39 | 29 | 0.69 |
| WAIS : Digit span backward [4] | 4.1 | 0.7 | (3-5) | 0.03 | 0.13 | 22 | 0.89 | -0.07 | -0.34 | 22 | 0.73 |
| RL-RI 16: Immediate recall [2] | 13.4 | 2.2 | (8-16) | -0.32 | -1.2 | 26 | 0.24 | 0.58 | 2.29 | 26 | 0.03* |
| RL-RI 16: Free recall [1,2] | 11.4 | 6.9 | (0-27) | -0.28 | -1.28 | 25 | 0.21 | 0.83 | 3.84 | 25 | <0.01** |
| RL-RI 16: Total recall | 31.1 | 11 | (3-48) | -0.09 | -0.39 | 29 | 0.69 | 0.63 | 2.92 | 29 | <0.01** |
| RL-RI 16: Delayed free recall [1] | 3.6 | 3.6 | (0-12) | -0.28 | -1.39 | 29 | 0.17 | 0.86 | 4.27 | 29 | <0.01** |
| RL-RI 16: Delayed total recall | 10.1 | 4 | (1-16) | -0.03 | -0.17 | 29 | 0.86 | 0.59 | 2.82 | 29 | <0.01** |
| BEM 144: Immediate recall [3] | 5.2 | 2.1 | (1.5-11) | 0.1 | 0.46 | 29 | 0.65 | 0.08 | 0.36 | 29 | 0.71 |
| BEM 144: Delayed recall [1, 3] | 4.4 | 2.7 | (0-10.5) | 0.12 | 0.55 | 29 | 0.58 | 0.24 | 1.07 | 29 | 0.28 |
| Doors and People Tests (set A+ B) [3] | 12 | 5.3 | (1-22) | -0.02 | -0.07 | 23 | 0.93 | -0.03 | -0.16 | 23 | 0.87 |
| *Language abilities* | | | | | | | | | | | |
| Naming of famous faces | 55.9 | 23 | (12-93) | 0.49 | 1.64 | 17 | 0.11 | 0.18 | 0.57 | 17 | 0.57 |
| Bachy-Langedock test [1, 5] | 34.1 | 1.6 | (30-36) | -0.26 | -0.99 | 23 | 0.33 | 0.74 | 2.82 | 23 | 0.01* |
| Irregular words writing [1, 5] | 9.4 | 0.7 | (8-10) | 0.08 | 0.29 | 21 | 0.77 | -0.44 | -1.38 | 21 | 0.18 |
| *Executive functions* | | | | | | | | | | | |
| VF: Literal | 17 | 6.4 | (5-28) | -0.16 | -0.71 | 30 | 0.48 | 0.14 | 0.6 | 30 | 0.55 |
| VF: Category [3] | 16.8 | 5.9 | (4-27) | 0.05 | 0.19 | 29 | 0.85 | 0.08 | 0.33 | 29 | 0.74 |
| TMT: A [1] | 81.4 | 58.2 | (26-310) | -0.11 | -0.47 | 30 | 0.63 | 0.36 | 1.49 | 30 | 0.14 |
| TMT: B [1] | 202.8 | 120.4 | (62-538) | 0.05 | 0.21 | 26 | 0.83 | 0.31 | 1.35 | 26 | 0.18 |

*Note:* Cognitive tests were entered as dependent variables; hippocampal volumes, amygdalar volumes, age, sex, and education were entered as independent variables. MMSE = Mini-Mental State Examination, WAIS = Wechsler Adult Intelligence Scale, RL-RI 16 = Rappel libre – Rappel Indicé of the Gröber & Buschke test, BEM 144 = Batterie d'Efficience Mnésique (Memory Performance Battery), VF = Verbal Fluency, TMT = Trail Making Test, SD = Standard Deviation, df = degrees of freedom. The reported mean, standard deviation, and range were calculated after correcting for outliers (Stevens, 1984[a]). [1] The original data were transformed to the logarithmic function. [2] Two outliers on the Cook criterion were excluded. [3] One outlier on the Cook criterion was excluded. [4] Two outliers were excluded: one on the Cook criterion, one on the studentized residuals (SDR) criterion. [5] Three outliers were excluded on the SDR criterion. Significant associations are marked with asterisks: * p<0.05. ** p<0.01.

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differences between AD patients and HC. Amygdalar atrophy and its association with memory decline in the early stages of AD may be a useful marker for clinical diagnosis. However, additional studies are needed to assess in more detail the clinical relevance of investigating this structure. In particular, amygdalar atrophy patterns in AD could be compared with those occurring in other types of neurodegenerative disease. One study reported more severe amygdala atrophy in fronto-temporal dementia than in AD [73], but further work is needed to develop differential diagnostic criteria. Future studies should also investigate whether substantial amygdala volume change occurs in more cognitively intact persons, including patients with mild cognitive impairment (MCI). To clarify the potential role of the amygdala as an early AD biomarker, it may be relevant to assess whether the association between cognitive abilities and amygdala volume in cognitively intact persons is dissimilar to that obtained in AD patients. In addition, correlations reported between amygdalar volume and cognitive scores are not proof of any mechanism of causation. The fact that the level of volume reduction in this structure can predict several types of cognitive decline, even after hippocampal volume is controlled for, may appear surprising, since the amygdala's primary role is emotion processing and not memory or language processing. However, the amygdala is intricately connected with the four lobes of the brain (i.e., occipital, temporal, parietal, frontal) [74], leading to its indirect implication in a vast range of cognitive functions, including perception, attention, and declarative memory [75]. Regarding memory function, the amygdala is able to modulate the encoding and consolidation of information when it pertains to emotional stimuli [76-79]. In a recent functional MRI study on MCI and AD [80], authors found that functional connectivity was notably decreased (according to disease severity) between the amygdala and structures of the default mode

network (e.g., hippocampus, parahippocampal gyrus, superior frontal gyrus, medial frontal gyrus), an ensemble of regions implicated in an array of cognitive functions, notably episodic memory [80]. This decrease in functional connectivity between the amygdala and structures of the default mode network is suggested to underlie the memory deficits observed in MCI and AD. Through its various connections, the amygdala may have a role in modulating numerous cognitive functions, including those that are affected in dementia. Taken together, these studies show that the amygdala is not only an emotion-processing structure, but rather an essential part of a large network of structures that is able to adapt its activity as changes occur throughout the network. Further research is needed to assess the specific amygdalar compensatory mechanisms that take place throughout the course of dementia. If amygdalar volume loss is indeed predictive of cognitive decline and dementia, then affective disorders will most likely ensue, as the amygdala remains the key structure in processing emotions. Affective disorders have been previously observed in MCI and mild AD [81-83], yet whether these disturbances occur systematically and in parallel with amygdalar atrophy remains unknown.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Amorfix Life Sciences Ltd.; AstraZeneca; Bayer HealthCare; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514, and by Region Rhône-Alpes, Cluster 11: Handicap, Vieillissement & Neurosciences. RAH was supported by a research grant from the Dunhill Medical Trust, London, UK.

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**Received:** ???????????????? **Revised:** ???????????????? **Accepted:** ????????????????