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Atrophy in Alzheimer's Disease and Semantic Dementia: An ALE Meta-Analysis of Voxel-Based Morphometry Studies

Marianne Chapleau[a,b], Joséphine Aldebert[a], Maxime Montembeault[a,b] and Simona M. Brambati[a,b]
[a]*Département de Psychologie, Université de Montréal, Montréal, Québec, Canada*
[b]*Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada*

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Abstract.
Background/Objectives: Alzheimer's disease (AD) and semantic dementia (SD) have distinct episodic memory profiles despite the hippocampal atrophy that characterizes both diseases. The aim of this study was to delineate the pattern of gray matter (GM) atrophy associated with AD and SD as well as any differences in these patterns by pooling together the results of previous voxel-based morphometry (VBM) studies.
Methods/Overview: We conducted a meta-analysis of VBM studies that investigated GM atrophy in AD patients versus controls (CTRLs) and in SD patients versus CTRLs using the activation likelihood estimation (ALE) approach. Our systematic review allowed us to identify 63 VBM studies.
Results: The results confirmed that in addition to the classical cortical pattern of atrophy involving posterior medial and lateral regions in AD and the anterior lateral temporal lobes in SD, both AD and SD patients are characterized by bilateral atrophy of the hippocampus. Furthermore, in SD, the hippocampal atrophy was limited to the anterior portion of the hippocampus, while in AD, both the anterior and posterior parts of the hippocampus exhibited atrophy. When we compared the foci identified in the studies that compared AD patients versus CTRLs with those identified in the studies that compared SD patients versus CTRLs, we observed that the atrophy in the posterior hippocampus and precuneus was more severe in AD.
Conclusion: These results support theories that propose that the deficits observed in AD result from damage to the episodic memory network, which involves the posterior hippocampus and posterior medial brain regions. However, sparing of the posterior hippocampus in SD could explain the absence of episodic memory deficits in this population.

Keywords: Alzheimer's disease, episodic memory, gray matter, meta-analysis, semantic dementia, semantic memory, semantic variant of primary progressive aphasia, voxel-based morphometry

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive decline that begins with episodic memory impairment and progressively disrupts patients' cognitive capacities. Several structural neuroimaging studies have been conducted to characterize brain atrophy in AD patients *in vivo*. The majority of these studies have used voxel-based morphometry (VBM), a whole-brain volumetric technique based on high-definition magnetic resonance (MR) images. In this approach, differences in brain tissue volume between patient populations and normal controls (CTRLs) are assessed on a voxel-

*Correspondence to: Simona Maria Brambati, PhD, Centre de Recherche de l'IUGM, 4565, Chemin Queen Mary, Montréal QC H3W 1W5, Canada. Tel.: +1 514 340 3540/Ext. 4147; Fax: +1 514 340 3548; E-mail: simona.maria.brambati@umontreal.ca.

by-voxel basis after the brain images are normalized to a standard space [1]. VBM studies have consistently demonstrated a pattern of gray matter (GM) atrophy in early AD; this pattern primarily involves the medial temporal lobe (including the hippocampus, the parahippocampal gyrus, and the entorhinal cortex), the inferior temporal lobes, the posterior cingulate, parietal regions, and the thalami [2–4].

Over the last couple of decades, hippocampal atrophy has received considerable attention as a possible early anatomical hallmark of AD. The crucial role of hippocampal atrophy in current AD research is highlighted by the fact that evidence of such atrophy obtained via structural magnetic resonance imaging (MRI) is a key supportive marker of AD according to recently revised diagnostic criteria [5, 6] and is one of the main outcome in tests of disease-modifying therapies. Atrophy in this region has been reported in AD using not only voxel-based whole-brain imaging methods but also hippocampal volumetry approaches. With hippocampal volumetry approaches, the study of brain tissue volume is limited to the hippocampus and its components, which are manually or automatically traced on MR brain images, and is not extended to the rest of the brain. Evidence based on both whole-brain and hippocampal volumetric studies converge, indicating that compared to age-matched CTRLs, individuals with AD present a 10–30% loss of hippocampal volume. Furthermore, the severity of hippocampal atrophy correlates with episodic memory deficits [7, 8].

The specificity of hippocampal atrophy and its relationship to the development of episodic memory deficits in AD has been recently questioned due to evidence in patients with semantic dementia (SD). SD, which is also referred to as a semantic variant of primary progressive aphasia (svPPA), is a neurodegenerative disease characterized by progressive deterioration of semantic memory and atrophy in the anterior temporal lobes [9–13]. The presence of episodic memory deficits in the early phases of the disease is considered an exclusion criterion for a diagnosis of SD [12, 13]. However, early hippocampal atrophy has been consistently reported in anatomical studies comparing SD patients to cognitively unimpaired age-matched individuals [11, 14–21].

The absence of major episodic memory symptoms in SD, despite significant atrophy of the hippocampus, has been described as a paradox for which several anatomical hypotheses have been proposed (for a more cognitive perspective, see [22–24]).

According to some authors, this paradox could be related to the laterality of the hippocampal atrophy in AD and SD. More specifically, the hippocampal atrophy is symmetrical (i.e., affecting the hippocampus bilaterally) in AD, while it is asymmetrical (i.e., limited to one hemisphere, usually the left one) in SD [15]. The atrophic asymmetry in SD could thus be indicative of the presence of compensatory mechanisms that could contribute to the preservation of episodic memory [17].

According to other authors, the paradox could be explained by the differential roles of the anterior and posterior regions of the hippocampus in the neural networks that support episodic and semantic memory [25] In fact, neuroimaging data in healthy participants have shown that the anterior part of the hippocampus is functionally and anatomically connected to the anterior temporal lobes and is part of the brain network that underlies the semantic memory system [25]. On the other hand, the posterior part of the hippocampus is functionally and anatomically connected to the posterior cingulate, parietal regions, and the thalamus and is part of the brain network that supports the episodic memory system [26–28]. Consequently, AD patients should present more posterior hippocampal atrophy, which would explain the presence of episodic memory deficits. On the other hand, hippocampal atrophy in SD patients should be limited to anterior hippocampal regions, which would justify the presence of semantic deficits and the absence of episodic memory deficits.

Other authors seem to diminish the role of the hippocampus within the episodic memory system by taking a 'network' perspective. In fact, growing evidence suggests that cognitive symptoms in neurodegenerative diseases derive from brain network dysfunction rather than isolated regional atrophy [29, 30]. In this framework, the paradox could be explained by the fact that the episodic memory impairment that is observed in AD does not solely depend on the integrity of the hippocampus but rather depends on the integrity of a more extended brain network, including the parahippocampal gyrus, the entorhinal cortex, the dorsomedial thalamus, and the posterior cingulate gyrus [17, 20, 21]. These regions are usually atrophied in early AD patients but not in SD patients [21].

Each of these hypotheses has been only partially supported by structural neuroimaging studies using hippocampal volumetric and voxel-based whole-brain approaches, and conclusive evidence has yet to be reported. In addition, few studies have directly

compared the pattern of atrophy in AD and SD. Indeed, most studies have compared each patient population to cognitively unimpaired age-matched CTRLs to delineate the pattern of atrophy associated with each disease. Notably, the vast majority of these studies have relied on a relatively small sample of patients (approximately 10–20). Findings based on small samples are often difficult to reproduce across studies, and the results are hard to interpret in isolation. To better elucidate this paradox, researchers would benefit from pooling evidence from different studies, both to overcome the problem of the small sample size of individual studies and to be able to generalize the results.

The goal of the present study was to test the different anatomical hypotheses that have been proposed to account for the paradox of the presence of hippocampal atrophy in SD despite the absence of major episodic memory deficits, as reported above. To achieve this aim, we conducted a meta-analysis by pooling together studies that have investigated the pattern of atrophy in AD and SD using VBM. Although the hippocampus is certainly one of the main focuses of our study, we were interested in delineating the pattern of atrophy at the whole-brain level. For this reason, we included studies that used VBM, the most widely used voxel-based whole-brain volumetric approach, in our meta-analysis. Volumetric studies limited to the hippocampus were not included but are presented and discussed in the discussion section. Furthermore, because of the very limited number of studies that have directly compared AD and SD, only studies that compared each patient population to CTRLs were considered for the present meta-analysis. The meta-analysis was based on a coordinate-based activation likelihood estimation (ALE) approach, which is considered the most sophisticated and validated meta-analysis technique for neuroimaging studies [31].

MATERIALS AND METHODS

Search strategy

The review process was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [32]. The PubMed database was used to perform a systematic online search. The keywords "semantic dementia voxel-based morphometry"; "semantic variant primary progressive aphasia voxel-based morphometry"; "fluent variant primary progressive aphasia voxel-based morphometry"; "frontotemporal lobar degeneration voxel-based morphometry"; and "temporal variant frontotemporal dementia voxel-based morphometry" were used to identify studies of SD, and "Alzheimer's disease voxel-based morphometry" was used to identify studies related to AD (Fig. 1). The search was limited to publications in English. Two independent evaluators selected the studies to be included using steps that allow greater objectivity (the first evaluator completed this process in July 2014, while the second evaluator completed it in January 2015). The first evaluator verified the eligibility of the studies based primarily on the article titles and abstracts, followed by the full text. To ensure that no papers were erroneously rejected based on the content of the abstract or title, the second evaluator applied the exclusion criteria based on full-text articles only. The final consensus for the selection of studies was established by a third person who assessed the relevance of the articles that had not been selected by either evaluator.

Inclusion criteria

The studies identified through the systematic online search were reviewed if they met the following inclusion criteria: 1) GM locations reported in Talairach/Tournoux or Montreal Neurological Institute (MNI) coordinates; 2) use of VBM, as it is one of the most prevalent techniques used to evaluate the cerebral GM volume [33]; 3) use of whole-brain analyses (studies based on regions of interest were rejected); 4) cross-sectional studies; 5) employment of comparisons between patients with the amnestic variant of AD and healthy subjects or employment of comparisons between SD patients and healthy subjects.

Studies directly comparing both groups were not included in the study but were reviewed (see Table 6). However, not all of these studies were based on VBM methods.

Exclusion criteria

The following types of studies were excluded: 1) studies that were published before the 2000 s, as the VBM technique has drastically improved since then [34]; 2) correlational studies; 3) case studies; 4) longitudinal studies; 5) studies comparing patients with the language or visual variant of AD and CTRLs, 6) studies comparing patients with the right variant of SD and CTRLs. Studies from the same group of

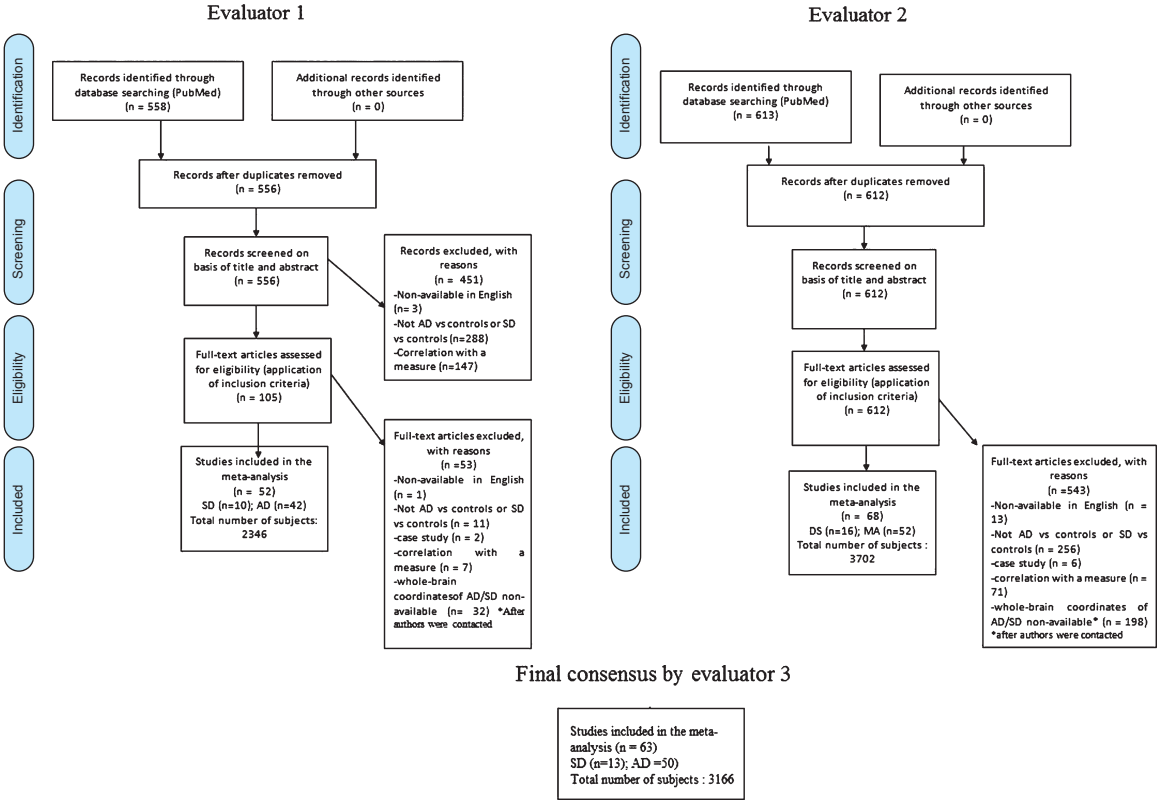

Fig. 1. PRISMA flow diagrams of both evaluators for the selection of studies.

authors were rejected if the sample included the same patients.

Activation likelihood estimation (ALE) meta-analysis

We used a quantitative, random-effects meta-analytic method known as ALE, which we implemented using the software program GingerALE 2.3.5 (UT Health Science Center Research Imaging Institute, San Antonio, TX) [35–37].

The objective of this ALE meta-analysis of VBM studies was to systematically analyze the coordinates reported in each selected study to obtain the precise locations of significant changes in the whole-brain GM volume of AD and SD patients. To achieve this, the coordinates of the brain atrophy reported in the studies were saved in a file (Notepad format) and entered into the GingerAle software (https://brainmap.org/ale/). The statistical analysis allowed us to determine areas where the overlap between the peak coordinates of atrophied regions reported across studies was more significant than expected if the results of the studies were taken separately. To reflect the spatial uncertainty of the different foci, ALE treats each VBM focus as a Gaussian probability distribution. The width of the distribution was determined by the number of subjects in the study. First, the distributions were compared within the experimental contrasts. Then, across-group contrasts were used to create a whole-brain ALE map that assigned each voxel a different ALE value that represented the likelihood of GM atrophy in that voxel [35, 38, 39].

Statistical P-maps were obtained using the following analysis: 1) *Single dataset analysis based on AD versus CTRLs foci:* this analysis was based on the foci (i.e., result coordinates) extracted from the articles that compared AD patients versus CTRLs; 2) *Single dataset analysis based on SD versus CTRLs foci:* this analysis was based on the foci (i.e., result coordinates) extracted from the articles that compared SD patients versus CTRLs; 3) *Contrast analysis: (AD versus CTRLs) foci versus (SD versus CTRLs) foci*: this analysis compared and contrasted the foci extracted from the articles that compared AD patients versus CTRLs and those extracted from the studies that compared SD versus CTRLs; and 4) *Contrast*

analysis: (SD versus CTRLs) foci versus (AD versus CTRLs) foci: this analysis compared and contrasted the foci extracted from the articles that compared SD patients versus CTRLs and those extracted from those that compared AD patients versus CTRLs. A cluster-level corrected value of $p < 0.05$ was used for the single dataset analyses (#1 and 2). A more permissive threshold of $p < 0.001$, uncorrected was used for the contrast analyses (#3 and 4). Additionally, there were no limits in terms of cluster size because the hippocampus is relatively small.

The results were visualized using Mango software (http://www.nitrc.org/projects/mango), and the anatomical locations of the resulting coordinates were then determined using an anatomical atlas [40].

RESULTS

A total of 63 studies were included in the meta-analysis, including 13 on SD and 50 on AD. A total of 3,166 SD, AD, and CTRL subjects were included (513 for SD versus CTRL studies, 2653 for AD versus CTRL studies). The characteristics of the studies included in the meta-analysis are detailed in Table 1.

Analysis #1: Single dataset analysis based on AD versus CTRLs foci

The clusters of significant atrophy in AD are reported in Table 2. The largest area of consistent GM atrophy in AD was centered in the anterior portion of the right hippocampus and included the right posterior hippocampus and the right superior temporal pole. The second cluster was centered in the anterior portion of the left hippocampus and included the left posterior hippocampus, the left anterior fusiform gyrus, and the left middle hippocampus. Other clusters included the bilateral middle and inferior temporal lobe, the middle occipital gyrus, the angular gyrus, the insula, the left inferior parietal lobe, the precuneus, the thalamus, the inferior frontal gyrus, the right posterior cingulum, the fusiform gyrus, and the straight rectus (Fig. 2).

Analysis #2: Single dataset analysis based on SD versus CTRLs foci

The clusters of significant atrophy in SD are reported in Table 3. The largest area of consistent GM atrophy in SD was centered in the anterior portion of the left hippocampus and included the left anterior fusiform gyrus and the left middle fusiform gyrus. The second cluster was centered in the anterior portion of the right hippocampus and included the right anterior temporal lobe. Other clusters included the left anterior fusiform gyrus; the right middle and superior temporal pole; the left inferior, middle and superior temporal lobe; the left superior temporal pole; the right anterior fusiform gyrus; and the right insula (Fig. 2).

Analysis #3: Contrast analysis: (AD versus CTRLs) foci versus (SD versus CTRLs) foci

The clusters that showed a more severe pattern of atrophy in the comparison (AD versus CTRLs) foci versus (SD versus CTRLs) foci are reported in Table 4. The ALE analysis revealed two significant clusters. The first cluster was centered in the posterior portion of the right hippocampus, while the second was centered in the left posterior precuneus (Fig. 3).

Analysis #4: Contrast analysis: (SD versus CTRLs) foci versus (AD versus CTRLs) foci

The clusters that showed more severe atrophy in the comparison (SD versus CTRLs) foci versus (AD versus CTRLs) foci are reported in Table 5. Comparing the patterns of atrophy in SD and AD revealed more significant atrophy in the lateral portion of the anterior temporal lobe in SD. More specifically, significant clusters were centered in the right and left superior temporal pole, the left middle and inferior temporal lobe, the right inferior and superior temporal lobe, and the right middle temporal pole (Fig. 3).

DISCUSSION

In the present study, we performed a meta-analysis of VBM studies that evaluated the pattern of GM atrophy in patients with AD by comparing AD patients versus CTRLs and in patients with SD by comparing SD patients versus CTRLs. The meta-analysis was conducted using the ALE approach, which is considered the most sophisticated and validated meta-analysis technique based on the coordinates obtained in VBM studies [31]. By pooling the data from studies that investigated the pattern of atrophy in AD patients compared to CTRLs, we observed that AD is characterized by a pattern of atrophy that mainly involves the bilateral medial temporal lobe. Other regions of atrophy were observed bilaterally, including in the middle and inferior temporal lobe,

Table 1
Articles included in the meta-analysis

Publication	Age (SD)	MMSE	Subjects (patients)	Comparison	Disease duration (Y)	Reference	MNI scanner strength
Brambati et al., 2009 [55]	62.1 (6.0)	22.0 (6.9)	38 (13)	SD versus CTR	3.2	MNI	1.5
Gorno Tempini et al., 2004 [11]	67.62 (8.2)	23.8 (5.1)	74 (10)	SD versus CTR	4.5 (1.8)	MNI	1.5
Agosta et al., 2012 [56]	65 (4)	24.2 (4.0)	32 (7)	SD versus CTR	5.6 (1.5)	MNI	3
Irish et al., 2012 [57]	62.1 (5.5)	NM	21 (11)	SD versus CTR	3.3 (2.5)	MNI	3
Irish et al., 2014 [58]	63.4 (6.0)	NM	24 (11)	SD versus CTR	5.2 (1.8)	MNI	3
Wilson et al., 2010 [59]	66.7 (6.0)	22.0 (6.2)	35 (25)	SD versus CTR	8.9 (3.1)	MNI	1.5 or 4
Libon et al., 2009 [60]	67.87 (9.69)	23.07 (5.40)	52 (41)	SD versus CTR	3.5 (3.4)	MNI	3
Ash et al., 2009 [61]	66.8 (7.3)	22.5 (8.2)	22 (12)	SD versus CTR	5.2 (2.3)	MNI	1.5
Pereira et al., 2009 [62]	63.8 (7.2)	29.3 (0.84)	33 (13)	SD versus CTR	5.0 (2.5)	MNI	1.5
Adlam et al., 2006 [63]	62.8 (5.8)	NM	54 (7)	SD versus CTR	NA	MNI	1.5
Desgranges et al., 2007 [64]	68.3 (4.7)	22.6 (5.9)	48 (10)	SD versus CTR	3.3 (2.5)	MNI	1.5
Boxer et al., 2003 [65]	56.2 (9.8)	21.7 (7.1)	26 (11)	SD versus CTR	NA	MNI	1.5
Wilson et al., 2009 [66]	61.4 (4.8)	24.2 (4.8)	14 (5)	SD versus CTR	5.0 (1.7)	MNI	3
Imabayashi et al., 2013 [67]	73.8 (20.7)	NM	12 (5)	AD versus CTR	NA	MNI	1.5
Canu et al., 2013 [68]	75.4 (4.6)	19.5 (3.9)	51 (35)	AD versus CTR	3.2 (2.0)	MNI	3
Brambati et al., 2009 [4]	74.2 (4.3)	20.1 (3.5)	23 (9)	AD versus CTR	NA	MNI	3
Mok et al., 2012 [69]	69.3 (10.1)	NM	45 (22)	AD versus CTR	NA	MNI	1.5
Tondelli et al., 2012 [70]	79.4 (5.0)	27.6 (1.1)	48 (8)	AD versus CTR	NA	MNI	1.5
Kim et al., 2011 [71]	73.0 (7.94)	17.5 (4.0)	94 (51)	AD versus CTR	NA	MNI	3
Bozzali et al., 2012 [72]	72.8 (6.8)	17.8 (4.2)	45 (31)	AD versus CTR	NA	MNI	3
Rami et al., 2012 [73]	75.5 (5.5)	22.5 (3.3)	56 (32)	AD versus CTR	NA	MNI	3
Gili et al., 2011 [74]	71.9 (7.9)	19.7 (4.5)	21 (11)	AD versus CTR	NA	MNI	3
Whitwell et al., 2011 [2]	67.4 (12.7)	18.8 (6.1)	34 (14)	AD versus CTR	NA	TALAIRACH	1.5
Loskutova et al., 2009 [75]	74.3 (6.3)	26.2 (3.7)	138 (61)	AD versus CTR	NA	MNI	3
Rami et al., 2009 [76]	76.4 (6.8)	22.3 (2.9)	61 (34)	AD versus CTR	NA	TALAIRACH	1.5
Shiino et al., 2008 [77]	74.2 (3.4)	21.3 (2.7)	77 (50)	AD versus CTR	NA	MNI	1.5
Kanda et al., 2008 [78]	65 (*NM*)	17.5 (NM)	40 (20)	AD versus CTR	NA	MNI	1.5
Rabinovici et al., 2007 [79]	64.5 (9.7)	19.9 (6.9)	51 (11)	AD versus CTR	6.0 (4.6)	TALAIRACH	1.5
Di Paola et al. 2007 [80]	72.3 (6.8)	19.3 (4.5)	36 (18)	AD versus CTR	NA	MNI	1.5
Hämäläinen et al., 2007 [81]	73.1 (6.7)	21.7 (3.7)	36 (15)	AD versus CTR	NA	TALAIRACH	1.5
Shiino et al., 2006 [82]	71.1 (9.7)	18.03 (3.91)	168 (40)	AD versus CTR	NA	TALAIRACH	1.5
Brenneis et al., 2004 [83]	73.1 (7.6)	17.4 (7.9)	20 (10)	AD versus CTR	NA	MNI	1.5
Testa et al., 2004 [84]	74.0 (9.0)	21.0 (4.0)	52 (27)	AD versus CTR	NA	MNI	1.5
Frisoni et al., 2002 [85]	76.0 (8.0)	21.1 (2.3)	56 (28)	AD versus CTR	NA	TALAIRACH	1.5
Baron et al., 2001 [86]	74.1 (6.5)	19.1 (3.4)	35 (19)	AD versus CTR	NA	TALAIRACH	3
Ishii et al., 2005 [87]	66.8 (7.0)	24.0 (2.2)	60 (30)	AD versus CTR	NA	MNI	1.5
Colloby et al., 2014 [88]	79.0 (8.8)	20.8 (4.0)	87 (48)	AD versus CTR	NA	MNI	3
Irish et al., 2014 [58]	65.8 (6.8)	NM	37 (18)	AD versus CTR	4.3 (2.5)	MNI	3
Kim et al., 2013 [89]	64.3 (6.7)	19.3 (2.4)	27 (17)	AD versus CTR	NA	MNI	1.5
Feldman et al., 2008 [90]	68.1 (3.4)	18.3 (3.2)	26 (16)	AD versus CTR	3.4 (2.1)	TALAIRACH	1.5
Koenig et al., 2008 [91]	74.0 (8.4)	21.6 (3.3)	15 (6)	AD versus CTR	NA	TALAIRACH	4
Mazère et al., 2008 [92]	80.0 (6.8)	23.8 (1.6)	16 (8)	AD versus CTR	NA	MNI	1.5
Matsunari et al., 2007 [93]	68.6 (6.8)	22.0 (3.3)	151 (61)	AD versus CTR	2.4 (1.9)	MNI	1.5
Bozzali et al., 2006 [94]	67.9 (7.6)	19.8 (4.1)	42 (22)	AD versus CTR	2	MNI	1.5
Xie et al., 2006 [95]	71.7 (6.7)	21.1 (NM)	29 (13)	AD versus CTR	NA	MNI	1.5
Hirata et al., 2005 [96]	70.6 (8.4)	26.0 (1.5)	71 (30)	AD versus CTR	NA	MNI	1.0
Frisch et al., 2013 [97]	60.89 (6.94)	NM	32 (19)	AD versus CTR	NA	MNI	3
Wang et al., 2012 [98]	67.2 (5.6)	22.4 (3.5)	56 (26)	AD versus CTR	NA	MNI	1.5
Dashjamts et al., 2011 [99]	65.3 (2.3)	NM	46 (23)	AD versus CTR	NA	MNI	1.5
Agosta et al., 2011 [100]	74.6 (8.6)	19.5 (5.9)	38 (23)	AD versus CTR	2.7 (1.6)	MNI	1.5
Dos Santos et al., 2011 [101]	70.3 (5.7)	21.4 (2.2)	66 (34)	AD versus CTR	NA	MNI	1.5
Takahashi et al., 2010 [102]	68.4 (3.5)	23.1 (4.3)	91 (41)	AD versus CTR	NA	MNI	1.5
Guo et al., 2010 [103]	72.1 (6.5)	18.5 (3.5)	27 (17)	AD versus CTR	NA	MNI	3
Raji et al., 2009 [104]	82.8 (5.16)	NM	202 (33)	AD versus CTR	NA	MNI	1.5
Brys et al., 2009 [105]	70.3 (8.3)	24.9 (2.7)	29 (8)	AD versus CTR	NA	MNI	1.5
Caroli et al., 2007 [106]	69.0 (3.4)	26.8 (1.8)	26 (9)	AD versus CTR	2.5 (1.4)	TALAIRACH	NM
Zahn et al., 2005 [107]	66.5 (8.9)	23.6 (2.8)	20 (10)	AD versus CTR	NA	MNI	1.5
Boxer et al., 2003 [65]	69.6 (8.2)	20.2 (7.3)	26 (11)	AD versus CTR	NA	MNI	1.5
Kanda et al., 2008 [78]	65.9 (NM)	17.5 (*NM*)	50 (20)	AD versus CTR	NA	MNI	1.5

NA, non apparent; NM, not mentioned.

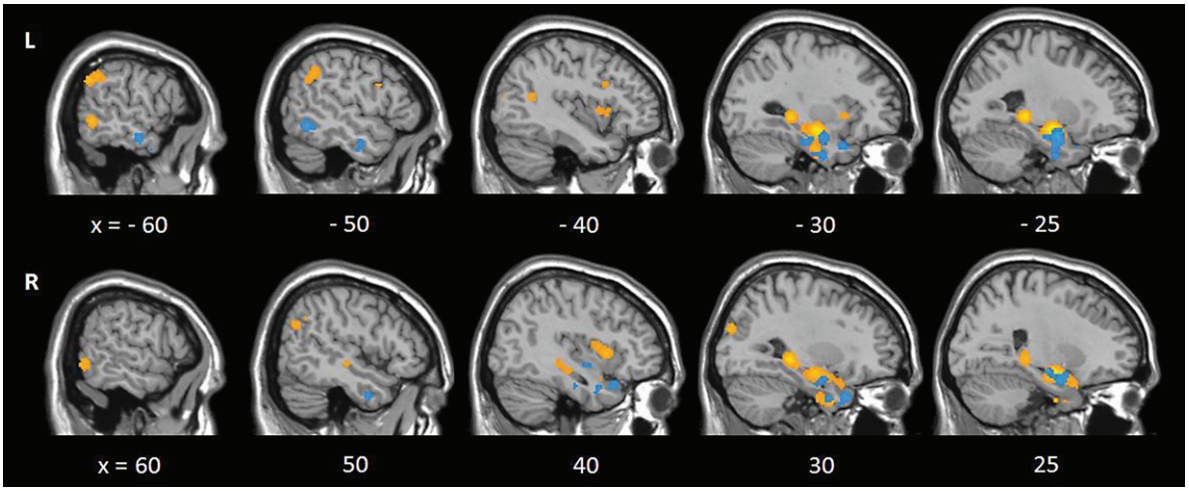

Fig. 2. Significant gray matter atrophy from the results of single dataset analysis based on AD versus CTRL foci (orange; Analysis #1) and SD versus CTRLs foci (blue; Analysis #2).

Table 2
Results of Analysis #1: Single dataset analysis based on AD versus CTRL foci

Cluster #	Extrema Value	x	y	z	Label
1	0.0690	24	–8	–16	Right Anterior Hippocampus
	0.0582	30	–34	–4	Right Posterior Hippocampus
	0.0293	26	10	–26	Right Superior Temporal Pole
	0.0252	36	–24	–14	Right Posterior Hippocampus
	0.0190	36	6	–20	Right Superior Temporal Pole
2	0.0900	–24	–8	–16	Left Anterior Hippocampus
	0.0649	–26	–36	–2	Left Posterior Hippocampus
	0.0461	–32	–14	–32	Left Anterior Fusiform Gyrus
	0.0325	–34	–26	–12	Left Middle Hippocampus
3	0.0364	–58	–58	30	Left Angular Gyrus
	0.0356	–54	–50	36	Left Inferior Parietal Lobe
4	0.0397	–2	–58	26	Left Precuneus
	0.0326	4	–52	32	Right Posterior Cingulum
5	0.0399	36	12	2	Right Insula
6	0.0275	2	–16	10	Left Thalamus
	0.0190	–4	–6	0	Left Thalamus
7	0.0343	–34	12	–2	Left Insula
	0.0212	–42	4	2	Left Insula
8	0.0375	28	2	–42	Right Anterior Fusiform Gyrus
	0.0283	28	–8	–40	Right Posterior Fusiform Gyrus
9	0.0402	58	–62	–8	Right Inferior Temporal Lobe
10	0.0387	–58	–54	–6	Left Inferior Temporal Lobe
11	0.0330	52	–68	28	Right Middle Occipital Lobe
	0.0209	52	–58	32	Right Angular Gyrus
12	0.0354	–46	–82	14	Left Middle Occipital Lobe
13	0.0379	30	–88	24	Right Middle Occipital Lobe
14	0.0234	–48	8	26	Left Inferior Frontal Operculum
15	0.0307	–44	–56	16	Left Middle Temporal Lobe
16	0.0268	52	–22	–8	Right Middle Temporal Lobe
17	0.0295	0	24	–14	Right Straight Rectus

the angular gyrus, the insula, the left inferior parietal lobe, the precuneus, the thalamus, the inferior frontal gyrus, the right posterior cingulum, and the fusiform gyrus. Analyzing the foci identified in studies that compared SD patients and CTRLs revealed a pattern of atrophy that mainly involved the anterior lateral temporal lobe and the anterior hippocampus bilaterally.

Table 3
Results of Analysis #2: Single dataset analysis based on SD versus CTRL foci

Cluster #	Extrema Value	x	y	z	Label
1	0.0255	–26	–6	–22	Left Anterior Hippocampus
	0.0175	–34	–16	–38	Left Anterior Fusiform Gyrus
	0.0152	–28	–6	–38	Left Anterior Fusiform Gyrus
	0.0142	–30	–22	–26	Left Middle Fusiform Gyrus
2	0.0220	26	–2	–22	Right Anterior Hippocampus
	0.0155	24	–12	–16	Right Anterior Hippocampus
3	0.0156	48	–2	–36	Right Anterior Temporal Lobe
	0.0136	30	0	–40	Right Anterior Fusiform Gyrus
	0.0119	38	4	–30	Right Middle Temporal Pole
4	0.0165	44	20	–26	Right Superior Temporal Pole
	0.0159	38	18	–26	Right Superior Temporal Pole
5	0.0175	–58	–12	–22	Left Superior Temporal Lobe
	0.0120	–52	–8	–28	Left Inferior Temporal Lobe
	0.0104	–56	–2	–32	Left Inferior Temporal Lobe
6	0.0208	30	16	–38	Right Middle Temporal Pole
7	0.0213	–50	–58	–12	Left Inferior Temporal Lobe
8	0.0156	–30	12	–30	Left Superior Temporal Pole
	0.0152	–36	16	–28	Left Superior Temporal Pole
9	0.0202	–48	12	–16	Left Superior Temporal Pole
10	0.0150	–34	–6	0	Left Middle Temporal Lobe
11	0.0143	42	–18	–28	Right Anterior Fusiform Gyrus
12	0.0134	40	–6	–8	Right Insula

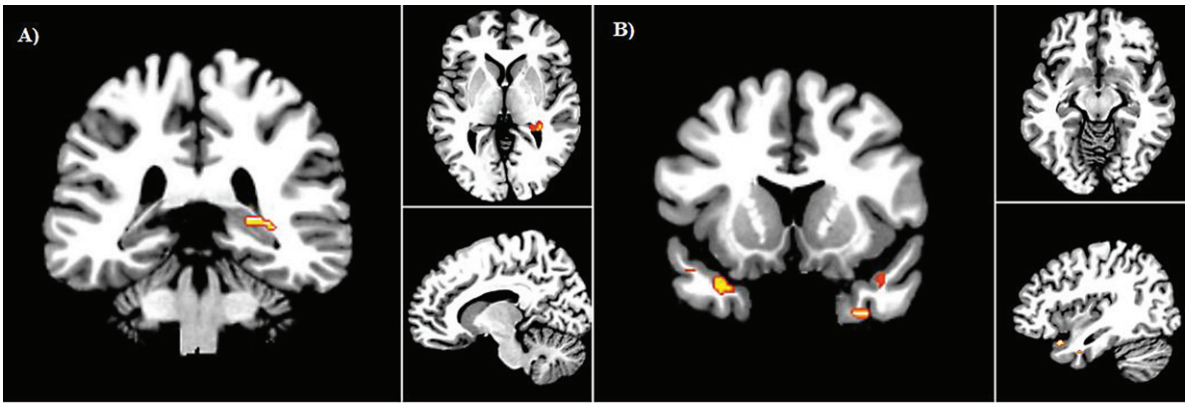

Fig. 3. Significant gray matter atrophy from the contrast analysis; Analysis #3: (AD versus CTRLs) foci versus (SD versus CTRLs) foci (A) and Analysis #4: (SD versus CTRLs) foci versus (AD versus CTRLs) foci (B).

While the cortical results seem to confirm the pattern that has been observed in previous structural imaging studies, the hippocampal results that were obtained by pooling together all the published VBM studies seem to provide important new information. In fact, the results revealed that not only AD patients but also SD patients exhibit bilateral hippocampal atrophy. More importantly, the results showed that in the SD patients, the atrophy was mainly limited to the anterior portion of the hippocampus, whereas in the AD patients, a more global atrophy involving both the anterior and posterior portions of the hippocampus was observed. Direct comparisons of the foci identified in the studies that compared AD patients and CTRLs versus those that compared SD patients and CTRLs indicated that the posterior hippocampus, both left and right, was more atrophic in AD than in SD. Outside the hippocampal regions, AD atrophy is to be more severe in the left posterior precuneus. On the other hand, direct comparisons of the foci identified in the studies that compared SD patients and CTRLs versus those that compared AD patients and CTRLs indicated no difference at the level of the hippocampus but more severe atrophy in the lateral anterior temporal lobe bilaterally in SD. No laterality effect on hippocampal atrophy in AD and SD was observed.

Table 4
Results of Analysis #3: Contrast analysis: (AD versus CTRLs) foci versus (SD versus CTRLs) foci

Cluster #	Extrema Value	x	y	z	Label
1	3.2905	28	–35	3	Right Posterior Hippocampus
	3.0902	31	–30	0	Right Posterior Hippocampus
2	3.0902	–6	–58	26	Left Precuneus

Our results seem to provide critical evidence that both AD and SD are characterized by bilateral hippocampal atrophy. However, the hippocampal atrophy is limited to the anterior portion in SD, whereas it is more global (anterior and posterior atrophy) in AD. Consistently, we found more severe posterior hippocampal atrophy in AD when we compared the pattern of atrophy in the two clinical populations.

Although some evidence based on previous isolated VBM studies has suggested a dissociation between anterior and posterior hippocampal atrophy [19], this result has not been consistently replicated across studies [18, 20, 41]. Inconsistent results were also obtained by studies using volumetric hippocampal approaches in these two patient populations. While some studies report more severe anterior hippocampal atrophy or more severe anterior-posterior asymmetry in SD compared to AD [14, 15, 25], these results have not been replicated in other studies [16, 17, 42, 43]. The results of all volumetric hippocampal studies that compared AD and SD are reported in Table 6.

However, the lack of clear evidence that the posterior hippocampus is more atrophic in AD is even more surprising. In fact, the hypothesis that differential damage of the anterior and posterior hippocampi may be associated with cognitive differences between SD and AD is based on the observation that the anterior and posterior portions of the hippocampus are involved in different memory systems. This hypothesis, which was initially proposed by Ranaganath & Richey (2012), has been supported by a series of independent studies. For instance, resting-state fMRI studies of healthy subjects [28, 44] have demonstrated that the anterior portion of the hippocampus is involved in the semantic memory system. Such studies have also implicated the anterior lateral temporal lobes in this system. In contrast, the episodic memory system appears to involve posterior medial brain regions and the thalami. Based on this evidence, SD patients should show an absence of or less severe atrophy of the posterior portion of the hippocampus, which would explain the preservation of episodic memory functions during the early stages of the disease. However, previous studies have failed to report this difference, probably because many of the structural imaging studies, especially those involving SD patients, were underpowered, with the sample size typically ranging between 10 and 20 patients (see Table 1). Our study, by pooling together different studies, has demonstrated that the hippocampal atrophy in SD is limited to the anterior portion of the hippocampus and that the pattern of atrophy found in AD is characterized by more severe posterior hippocampal atrophy than that found in SD. In our study, increased anterior hippocampal atrophy was not observed in SD compared to AD. This result is not surprising from a cognitive perspective, as it is increasingly accepted that semantic deficits can be present in AD patients even in the very early stages of the disease [45–50]. Some authors have even suggested that subtle semantic memory deficits can be observed up to several years prior to disease onset [51].

Although the present results are consistent with the anterior-posterior dissociation hypothesis, they are also compatible with the hypothesis that the episodic memory deficits observed in AD are not determined by hippocampal atrophy alone but also by the atrophy

Table 5
Results of Analysis #4: Contrast analysis: (SD versus CTRLs) foci versus (AD versus CTRLs) foci

Cluster #	Extrema Value	x	y	z	Label
1	3.2905	45	21	–24	Right Superior Temporal Pole
2	3.2905	–59	–10	–22	Left Middle Temporal Lobe
	3.0902	–54	–14	–24	Left Inferior Temporal Lobe
3	3.2905	–33	14	–29	Left Superior Temporal Pole
4	3.0902	32	15	–42	Right Middle Temporal Pole
5	3.2905	42	–2	–34	Right Inferior Temporal Lobe
	3.0902	37	1.5	–33	Right Middle Temporal Pole
6	3.0902	50	–4	–38	Right Inferior Temporal Lobe
7	3.0902	48	–4	–36	Right Superior Temporal Lobe

Table 6
Summary of the hippocampal volumetric studies that compared hippocampal atrophy in AD and SD

Publication	Age (SD) AD patients	Age (SD) SD patients	MMSE AD	MMSE SD	Subjects (AD patients)	Hippocampal differences AD versus SD	Years of disease duration (SD) AD patients	Years of disease duration (SD) SD patients
Nestor et al., 2006 [17]	62.5 (5.5)	63.4 (7.0)	26.8 (3.0)	25.8 (3.3)	37 (14)	No differences were found between AD and SD patients	3.1 (1.4)	3.6 (2.1)
Chan et al., 2001 [14]	N/A	N/A	N/A	N/A	20 (10)	Bilateral and global hippocampal atrophy in AD, left anterior atrophy in SD (more extensive than AD)	N/A	N/A
Galton et al., 2001 [15]	69.1 (7.6)	62.7 (7.1)	22.5 (3.2)	21.2 (6.9)	44 (26)	Bilateral and global hippocampal atrophy in AD, left anterior atrophy in SD (more extensive than AD)	4.8 (3.0)	4.0 (2.4)
Davies et al., 2004 [16]	64.9 (4.6)	60.9 (8.1)	23.0 (2.5)	25.9 (2.7)	16 (8)	Left anterior hippocampal atrophy in AD (more extensive than SD)	N/A	N/A
La Joie et al., 2013 [25]	66.0 (3.0)	62.5 (3.0)	20.5 (1.5)	N/A	26 (18)	No different found between AD and SD patients, however, anterior-posterior asymmetry more marked in SD compared to AD	N/A	N/A
Barnes et al., 2006 [42]	57.0 (9.0)	56.0 (10.0)	15.0 (6.0)	22.0 (6.0)	27 (10)	Smaller volume in SD than AD patients	3.1 (0.7)	3.5 (2.0)
Lehmann et al., 2010 [43]	60.0 (7.6)	63.5 (5.8)	20.4 (5.8)	21.8 (5.4)	20 (10)	Smaller volume in AD than SD patients	N/A	N/A
Van de Pol et al., 2006 [108]	65.0 (7.0)	71.0 (9.0)	N/A	N/A	145 (103)	Bilateral atrophy in AD and SD (volume left side SD less than left side AD, right side SD greater than right side AD)	N/A	N/A

of many brain regions that are spared in SD [17]. More specifically, according to Nestor and colleagues [17], the loss of episodic memory in AD may not be caused only by the degeneration of the hippocampus but also by degeneration of the mammillary bodies, the dorsomedial thalamus and the posterior cingulate gyrus. In a previous study, they noted atrophy of the precuneus cortices as well [52]. Consistently, in our meta-analysis, we observed that the AD patients presented a pattern of atrophy that included, among other regions, the thalamus bilaterally and the precuneus. These regions were not atrophied in the SD patients. Additionally, comparisons of the foci identified in the studies that compared AD patients and CTRLs and those that compared SD patients and CTRLs revealed more severe atrophy in the left precuneus in AD.

Not surprisingly, and in line with the single studies included in the meta-analysis, the SD patients presented more severe atrophy in the lateral anterior temporal cortex. This region plays a key role in the semantic memory system [53], consistent with the fact that semantic deficits are the most prominent clinical symptoms of the disease.

CONCLUSIONS

Altogether, our findings seem to be consistent with the hypothesis that neurodegenerative diseases are disconnection syndromes and that the cognitive symptoms may emerge from variation or dysfunction in specific large-scale brain networks rather than from neural loss in focal brain regions [30]. Our findings are also consistent with the idea that the semantic and episodic memory networks could differentially involve the anterior and posterior portion of the hippocampus.

According to the revised criteria for the diagnosis of AD, hippocampal atrophy, as assessed via structural MRI, is a key supportive markers of the disease [5, 45, 54]. Better understanding of the specificity of this atrophy and its relationship to different cognitive functions represents a crucial issue in this field. Our study suggests that the posterior portion of the hippocampus could be a key region of atrophy in AD that is associated with the episodic memory deficits present in this population. Nonetheless, better understanding of the roles of the networks associated with different portions of the hippocampus could be indispensable for the monitoring of disease symptoms and for tracking the effects of potential therapies.

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