Distinct White Matter Injury Associated with Medial Temporal Lobe Atrophy in Alzheimer's Versus Semantic Dementia

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Abstract: This study aims at further understanding the distinct vulnerability of brain networks in Alzheimer's disease (AD) versus semantic dementia (SD) investigating the white matter injury associated with medial temporal lobe (MTL) atrophy in both conditions. Twenty-six AD patients, twenty-one SD patients, and thirty-nine controls underwent a high-resolution T1-MRI scan allowing to obtain maps of grey matter volume and white matter density. A statistical conjunction approach was used to identify MTL regions showing grey matter atrophy in both patient groups. The relationship between this common grey matter atrophy and white matter density maps was then assessed within each patient group. Patterns of grey matter atrophy were distinct in AD and SD but included a common region in the MTL, encompassing the hippocampus and amygdala. This common atrophy was associated with alterations in different white matter areas in AD versus SD, mainly including the cingulum and corpus callosum in AD, while restricted to the temporal lobe — essentially the uncinate and inferior longitudinal fasciculi — in SD. Complementary analyses revealed that these relationships remained significant when controlling for global atrophy or disease severity. Overall, this study provides the first evidence that atrophy of the same MTL region is related to damage in distinct white matter fibers in AD and SD. These different

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patterns emphasize the vulnerability of distinct brain networks related to the MTL in these two disorders, which might underlie the discrepancy in their symptoms. These results further suggest differences between AD and SD in the neuropathological processes occurring in the MTL. *Hum Brain Mapp* 38:1791–1800, 2017. © 2016 Wiley Periodicals, Inc.

Key words: Alzheimer's disease; hippocampus; medial temporal lobe; primary progressive aphasia; semantic dementia; white matter

INTRODUCTION

Semantic dementia (SD), also called semantic variant of primary progressive aphasia [Gorno-Tempini et al., 2011], refers to a neurodegenerative condition characterized by progressive language deficits and bilateral but asymmetric anterior temporal atrophy [Agosta et al., 2012; Fletcher and Warren, 2011]. Intriguingly, day-to-day memory and laboratory tasks of episodic memory are relatively preserved in SD despite the marked atrophy of the medial temporal lobe grey matter (MTL) [Hornberger and Piguet, 2012]. This profile contrasts with Alzheimer's disease (AD) in which the early and major involvement of the MTL has been associated with manifest episodic memory deficits [Desgranges et al., 1998; Di Paola et al., 2007; Hirni et al., 2013; Leube et al., 2008; Sexton et al., 2010].

To account for this apparent paradox, it has been proposed that the two neurodegenerative disorders may disrupt distinct brain networks related to the MTL [La Joie et al., 2014; Ranganath and Ritchey, 2012]. This is in line with the idea that cumulative insult in episodic memory-related regions beyond the MTL (e.g., medial and lateral parietal cortex) might account for the different episodic memory profiles in AD versus SD [Irish et al., 2016; Nestor et al., 2006; Pleizier et al., 2012]. In support of the network degeneration hypothesis, a recent study showed that cortical regions more impaired in AD versus SD, or reversely, were all connected to the hippocampus in healthy controls [La Joie et al., 2014]. However, this connectivity was related with episodic memory performances only for the regions more impaired in AD than in SD. Furthermore, AD patients showed more damage than SD patients in regions with posterior greater than anterior hippocampal connectivity in controls, while a reverse pattern was observed in regions with anterior greater than posterior connectivity. These results suggest that the distinct profiles of memory impairment in AD versus SD despite common MTL alteration might reflect the involvement of different hippocampal networks. This interpretation fits with

growing evidence showing the existence of different brain networks functionally connected to the MTL, notably along the antero-posterior axis, and harboring distinct cognitive functions [Aggleton, 2012; Poppenk et al., 2013; Ritchey et al., 2015].

Collectively, these previous studies suggest that MTL brain networks might be differently disturbed in AD versus SD. Differences in the memory profiles between these two neurodegenerative disorders might thus reflect the fact that MTL alteration is associated with the disruption of distinct connectivity pathway. The aim of the present study is to test this hypothesis directly in patients, assessing whether the MTL atrophy common to both AD and SD is associated with distinct white matter (WM) injury in each disorder. Based on the literature, we hypothesize that MTL atrophy will be related to damage in posterior temporo-parietal WM regions (e.g., cingulum bundle) in AD versus anterior temporal WM regions (e.g., uncinate fasciculus) in SD.

MATERIALS AND METHODS

Participants

In total, 26 patients with AD, 21 patients with SD and 39 older normal controls matched for age, sex and years of education were enrolled in the present study (for details about demographic data, see Table I). Part of these subjects were included in previous publications from our laboratory [Bejanin et al., 2016; La Joie et al., 2013, 2014]. The study was approved by regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and is registered with ClinicalTrials.gov (numbers NCT01638949 and NCT01962064). All participants gave written consent for participation before the scans.

Patients were recruited by senior neurologists in French expert centers (University Hospitals of Caen, Rennes and Rouen) and selected according to corresponding internationally agreed criteria [Gorno-Tempini et al., 2011; McKhann et al., 1984]. Among AD patients, all but three also underwent a Florbetapir-PET scan and were found to be amyloid-positive using previously published methods [La Joie et al., 2014], increasing therefore the likelihood of AD etiology [McKhann et al., 2011]. In agreement with previous demographical studies [Belliard et al., 2011; Hodges et al., 2010], the SD sample included 23% of patients ($n = 5$) with right-predominant atrophy.

Abbreviations

AD	Alzheimer's disease
MDRS	Mattis Dementia Rating Scale
MTL	medial temporal lobe grey matter
SD	semantic dementia
WM	white matter

TABLE I. Demographic data and selected neuropsychological features of patients with Alzheimer's disease, patients with semantic dementia, and normal controls

	Patients with AD	Patients with SD	Normal controls	P values		
				AD vs. NC	SD vs. NC	SD vs. AD
Gender (Male/Female)	13/13	9/12	19/20			
Age (years)	69.8 ± 10	67.2 ± 6.8	68.9 ± 7			
Education (years)	10.5 ± 3.3	11.4 ± 3.7	11.9 ± 3.9			
MDRS (/144)	115 ± 11.6 ^c	118.5 ± 11.6 ^c	141.9 ± 2.7	<0.001	<0.001	0.59
MDRS Episodic memory subscale (/25)	14.7 ± 2.9 ^c	18.8 ± 4.3 ^c	24.5 ± 0.9	<0.001	<0.001	<0.001
MDRS Concept subscale (/39)	33.2 ± 5.7 ^c	32.5 ± 3.7 ^c	38 ± 1.5	<0.001	<0.001	1
Picture naming (/80)	74.8 ± 6.5 ^b	36.1 ± 20.3 ^c	79.9 ± 0.3 ^a	.18	<0.001	<0.001
Semantic fluency (animals – 2 min)	14.7 ± 7.1	10.8 ± 7.6 ^a	33.1 ± 8.4	<0.001	<0.001	0.28
Phonemic fluency ("P" – 2 min)	12.6 ± 6.8	12 ± 4.2 ^a	22.4 ± 6.8	<0.001	<0.001	1
Copy of Rey complex figure (/36)	23.5 ± 12.2 ^c	34.9 ± 2	35.4 ± 1.2 ^a	<0.001	1	<0.001

Note: Unless otherwise indicated, values are mean ± standard deviation. P values refer to significant analysis of variance models, followed by post hoc pairwise comparisons with Bonferroni correction. AD: Alzheimer's disease; MDRS: Mattis dementia rating scale; NC: Normal controls; SD: Semantic dementia.

^aData missing for one subject.

^bData missing for two subjects.

^cData missing for three subjects.

All subjects underwent both a neuroimaging session and a standard neuropsychological battery including semantic and episodic memory tests (see Table I). Comparisons between the two patient groups revealed similar global cognitive decline (assessed with the Mattis Dementia Rating Scale [MDRS]) but different cognitive deficits. AD patients showed lower performances than SD in the MDRS episodic memory subtest. In contrast, SD patients had worse performance than AD in a naming task. Semantic fluency was not significantly different between the two patient groups, but this was due to one outlier within the SD group, with a right-predominant brain alteration and only subtle semantic impairment. The difference between both patient groups was significant when excluding this patient, with SD patients showing lower performance than AD patients ($P < 0.05$).

Image Acquisition and Preprocessing

All participants underwent a high-resolution T1-weighted anatomical image, using a 3D fast field echo sequence (3D-T1-FFE sagittal, SENSE factor = 2, time of repetition (TR) = 20 ms, time of echo (TE) = 4.6 ms, flip angle = 10°, 180 slices, no gap, slice thickness = 1 mm, field of view (FOV) = 256 × 256 mm², in-plane resolution = 1 × 1 mm²). All the MRI data sets were acquired on the same scanner (Philips Achieva 3.0 T scanner) at the CYCERON Centre (Caen, France).

Neuroimaging data processing was performed using the Statistical Parametric Mapping Version 8 (SPM8) software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) implemented in MATLAB 7.4. Using the VBM8 toolbox, T1-MRI were segmented and

spatially normalized to the MNI space. Grey matter maps were then modulated to correct for nonlinear warping effects. Finally, both grey matter volume and WM density maps were smoothed using an 8 mm full-width at half-maximum Gaussian kernel.

Statistical Analysis

First, an analysis of covariance (ANCOVA) was performed voxel-wise throughout the whole grey matter to identify regions of grey matter atrophy in each patient group (see the covariates below). Second, a conjunction analysis was conducted to identify the areas of common atrophy (i.e., reduced grey matter volume compared with normal controls) in both AD and SD patients. We used a conjunction analysis based on the proposed "valid conjunction inference with the minimum statistic" [Nichols et al., 2005] which corresponds to the valid test for a "logical AND" (i.e., all the comparisons in the conjunction are individually significant). Finally, in order to test whether the common MTL grey matter atrophy would be related to distinct WM alterations, the volume of the MTL included in the statistical conjunction was extracted for each patient. These values were then introduced in an ANCOVA to assess voxel-wise, in each patient group, the relationship with WM density maps. Thus, both group and grey matter volume in the MTL were included as between-subjects factors in the model and covariates (see below) as within-subjects factors.

To prevent any overlap between voxels included in analyses with grey matter and those with WM, two distinct explicit masks were used to perform the statistical models: a grey matter mask including the voxels of the group template with a grey matter probability higher than

0.3 and than both WM and cerebrospinal fluid probabilities (grey matter > 0.3 $\cap$ grey matter > WM $\cap$ grey matter > cerebrospinal fluid) and a WM mask including the voxels of the group template with a WM probability higher than 0.3 and than both grey matter and cerebrospinal fluid probabilities (WM > 0.3 $\cap$ WM > grey matter $\cap$ WM > cerebrospinal fluid).

A stringent threshold (family-wise error (FWE)-corrected $P < 0.05$ with cluster extent $k > 1,000 \text{ mm}^3$) was used for grey matter analyses in order to isolate the MTL atrophy (common to both patient groups) from other regions of common atrophy. The threshold of significance was then set at $P < 0.005$ uncorrected, together with a FWE corrected threshold ($P < 0.005$) at cluster level, to assess the relationship with WM density. A more liberal threshold was selected as (i) the controls were not included in these analyses (i.e., smaller sample size and therefore lower statistical power), (ii) more subtle effects were expected, and (iii) we wanted to highlight the whole pattern of WM related to MTL atrophy in each group. Age, sex, and years of education were regressed out in all statistical models. Anatomical grey matter labels were determined with reference to the Automated anatomical labeling (AAL) [Tzourio-Mazoyer et al., 2002] and Harvard-Oxford atlases. White-matter atlases provided with FSL (JHU ICBM-DTI-81 white-matter labels and JHU white-matter tractography atlases) and the second edition of the MRI Atlas of Human White Matter [Oishi et al., 2010] were used to determine the anatomical WM labels.

RESULTS

Grey Matter Loss

Whole-brain analyses revealed distinct pattern of grey matter atrophy in each patient group (see Supporting Information Fig. 1 and Supporting Information Table 1). As compared with controls, AD patients displayed typical grey matter loss in the MTL, medial and lateral parietal regions and temporo-occipital areas. Patients with SD showed bilateral, albeit predominantly left, anterior temporal lobe atrophy encompassing the MTL, inferior, middle, and superior temporal gyri, and medial prefrontal cortex.

The statistical conjunction of significant atrophy in both AD and SD patients revealed common grey matter loss in two MTL clusters (left and right MTL, see Fig. 1 and Table II), including mainly the amygdala and hippocampus, and extending into the anterior parahippocampal cortex and ventral temporal pole. A cluster in the left posterior temporal neocortex also showed significant volume loss in both patient groups.

Relationship Between Medial Temporal Lobe Atrophy and White Matter Density Maps

To assess the WM regions associated with the common MTL atrophy within each patient group, we tested the relationship between the grey matter volume from both

left and right MTL clusters included in the statistical conjunction and the WM density maps. As depicted in Figures 1 and 2, our results highlighted different patterns of relationship with the common MTL atrophy in AD versus SD (see Table II for peak details).

In AD, the left MTL volume was positively associated with WM density mainly in medial WM fibers (anterior and posterior portions of the cingulum bundle and corpus callosum) as well as the left inferior longitudinal fasciculus and posterior thalamic radiation. Similarly, the right MTL volume was associated with bilateral WM fibers, comprising essentially the splenium and body of the corpus callosum, the posterior and middle cingulum, and the posterior thalamic radiation.

Regarding SD, the WM regions showing a significant positive relationship with the left MTL volume were restricted within the left temporal lobe. They predominated in the anterior temporal WM, mainly comprised the inferior longitudinal, uncinata, and inferior fronto-occipital fasciculi and also included a portion of the cingulum bundle. The right MTL volume was associated with the same regions but in the right hemisphere, extending more posteriorly in the right posterior thalamic radiation.

MTL volumes were related with the cingulum bundle in both AD and SD, but the relationships mainly concerned distinct parts of this structure (Fig. 2). The relationship involved the medial (cingulate) portion in AD versus the lateral (parahippocampal) portion in SD, with only limited overlap.

Complementary Analyses

Several complementary analyses were then conducted to support the interpretation of our results.

Do WM regions associated with MTL grey matter atrophy show decreased density in AD and SD?

First, we aimed at assessing whether the WM regions found to be related to MTL atrophy in each patient group were atrophied in patients with AD and SD compared with controls.

Between-group differences in the mean WM density in the regions related to the common MTL atrophy were examined using ANCOVAs controlling for age, sex, and education. Results are illustrated with histograms in Figure 1. Essentially, these comparisons yielded a significant effect of group for all WM regions ($P < 0.05$). Bonferroni post hoc test indicated that the WM areas related to MTL atrophy in AD showed decreased density in AD compared with controls (and compared with SD patients for the WM areas associated with the right MTL atrophy). Similarly, the WM regions associated with MTL atrophy in SD showed decreased density in SD compared with controls (and compared with AD patients for the WM regions associated with left MTL atrophy).

Figure 1.

Significant relationships between the common medial temporal lobe atrophy (center panel) and whole-brain white matter density maps in patients with Alzheimer's disease (top panel) and semantic dementia (bottom panel). The left panels show white matter regions associated with the right medial temporal lobe volume and the right panels show white matter regions

associated with the left medial temporal lobe volume. The histograms depict the mean density of the corresponding white matter regions per group and between-group comparisons. AD, Alzheimer's disease; L, left; NC, normal controls; R, right; SD, semantic dementia. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Voxel-based morphometry results showing the white matter regions significantly associated with left and right medial temporal lobe grey matter volume in Alzheimer's disease and semantic dementia

Cluster size	Region	MNI			T
		x	y	z	
Patients with Alzheimer's Disease					
Correlation with left MTL					
16,568	L Inferior longitudinal fasciculus	-39	-25	-15	5.73
	L Cingulum (hippocampus)	-38	-13	-23	5.47
	L Body of the corpus callosum	-6	16	19	4.70
Correlation with right MTL					
18,839	R Splenium of the corpus callosum	3	-36	16	4.57
	L Posterior thalamic radiation	-36	-58	1	4.30
	R Body of the corpus callosum	3	4	22	4.30
Patients with semantic dementia					
Correlation with left MTL					
7,655	L Inferior longitudinal fasciculus	-36	-10	-26	9.44
	L Uncinate fasciculus	-36	-1	-26	8.50
	L Inferior longitudinal fasciculus	-39	-24	-15	7.28
Correlation with right MTL					
13,659	R Inferior longitudinal fasciculus	32	2	-30	12.30
	R Inferior longitudinal fasciculus	33	-6	-21	6.68
	R Inferior longitudinal fasciculus	38	-22	-18	6.36

Cluster size is indicated in mm^3 . L, left; MTL, medial temporal lobe; R, right; WM, white matter.

Figure 2.

Illustration of the overlap (in red) of the relationships, in patients with Alzheimer's disease (purple) and semantic dementia (cyan), between the common left medial temporal lobe atrophy and whole-brain white matter density maps. Similar results were obtained with the right medial temporal lobe (data not shown). [Color figure can be viewed at wileyonlinelibrary.com]

Does the relationship between MTL atrophy and WM regions merely reflect co-atrophy within each disease?

We aimed at assessing whether the associations found between MTL grey matter atrophy and WM regions reflected specific links between MTL volume and WM

Figure 3.

White matter regions in patients with Alzheimer's disease and with semantic dementia showing significant atrophy as compared with controls (red), significant relationship with the left medial temporal lobe atrophy (blue) or both (purple). Results are displayed at the same threshold of $P < 0.005$ uncorrected at voxel level and FWE-corrected ($P < 0.005$) at cluster level. MTL, medial temporal lobe; WM, white matter. [Color figure can be viewed at wileyonlinelibrary.com]

density within each disease, or whether they mainly reflected the effects of each disease on both MTL volume and WM density. To address this issue (i) we compared the WM regions associated with MTL atrophy with the whole brain profile of WM density loss within each disease to examine how much they overlap; (ii) we checked whether the relationships between MTL atrophy and WM regions within each disease remained significant when controlling for global grey matter volume, global WM density, and global cognitive decline using the MDRS score as a reflect of disease severity.

An ANCOVA was performed throughout the whole WM to assess the regions of decreased WM density in each patient group compared with controls. For the sake of comparison, results of WM density loss depicted in Figure 3 were superimposed on the results of the relationships between left MTL volume and WM density for each patient group. Both results partly overlapped (in purple) but they also showed specificities with WM areas showing decreased density but no relationship with MTL atrophy (in red) and reversely (in blue).

Then, we extracted in each patient the mean grey matter volume in the common MTL atrophy and the mean WM density in the regions related to this common atrophy, and performed partial correlations between both, introducing the whole grey matter volume, the whole WM density, or the global MDRS score as confounding variables. The relationships between

MTL volume and WM density remained significant in both AD and SD in all these analyses (for all correlations, $r > 0.61$, $P < 0.005$; see Supporting Information Table 2).

DISCUSSION

In line with the idea that neurodegenerative syndromes target distinct neural networks [Seeley et al., 2009], we directly tested in patients the hypothesis that the common MTL atrophy in AD and SD is associated with the damage of distinct WM regions. We showed that the MTL region atrophied in both diseases was mainly related to the atrophy of medial WM fibers in AD versus temporal WM fibers in SD. These specific relationships did not simply reflect the distinct WM atrophy profile of each disease and were found to be independent from global atrophy or disease severity. Together, these results corroborate the hypothesis of distinct vulnerability of brain networks related to MTL in AD and SD.

Our findings are consistent with previous studies in AD that explored the relationship between grey matter loss in MTL structures and WM integrity. Hippocampal atrophy has been associated with density loss [Villain et al., 2008] and micro-structure alteration [Agosta et al., 2011; Xie et al., 2005] in the cingulum, corpus callosum and inferior longitudinal fasciculus in AD patients. Particular attention has been paid to the cingulum bundle given its involvement in the Papez circuit [Shah et al., 2012]. The alteration of this bundle has been consistently found in AD and seems to occur early in the disease process, that is, in the prodromal stages of the disease [Clerx et al., 2012; Sexton et al., 2011]. Its dysfunction has been associated with episodic memory impairment in AD patients and mild cognitive impairment [Choo et al., 2010; Sexton et al., 2010]. Furthermore, atrophy of the caudal cingulate WM region (in very similar regions than those obtained in the present study) was found to be related to glucose hypometabolism in Papez circuit nodes in AD [Villain et al., 2008]. Together with longitudinal evidence [Villain et al., 2010], this points out that MTL atrophy may lead, via the disruption of the posterior cingulum bundle, to the disruption of a memory network in AD. Our findings reinforce this view and provide novel evidence of the specificity of this relationship in AD compared with SD.

Indeed, in SD, atrophy in the same MTL region was not associated with medial posterior WM fibers — the involvement of the cingulum bundle being restricted to its lateral/parahippocampal part. Instead, MTL atrophy was related to temporal WM fibers, predominating in the anterior portion and mostly including the inferior longitudinal and uncinate fasciculi. To our knowledge, this is the first study exploring the relation between atrophy in the MTL (or any grey matter region) and WM injury specifically in SD. However, previous studies exploring WM structural changes in SD have shown that the inferior longitudinal and uncinate fasciculi are particularly vulnerable, especially in their anterior temporal part

[Agosta et al., 2010, 2011; Galantucci et al., 2011; Mahoney et al., 2013]. These fasciculi connect respectively the occipital [Catani et al., 2003; Latini, 2015] and frontal [Von Der Heide et al., 2013] lobes to MTL structures. The inferior longitudinal fasciculus projections are predominantly afferent while uncinate fasciculus originates from MTL structures and temporal pole. Their disruption might thus reflect distinct mechanisms, with inferior longitudinal fasciculus impairment mainly resulting from the progressive degeneration of feedback neurons [Acosta-Cabronero et al., 2011] while uncinate bundle alteration would be due to neuronal cell body degeneration in anterior temporal regions.

The originality of the present study relies on the direct comparison of the relationships between MTL atrophy and WM integrity in AD versus in SD. Ranganath and Ritchey (2012) have suggested the existence of two separate neocortical networks interacting with hippocampal formation and involving different MTL regions (see also [Ritchey et al., 2015]). The *posterior medial system* would include the parahippocampal cortex and cortical regions connected via the cingulum bundle such as the retrosplenial, medial parietal and prefrontal cortices. This system would be particularly involved in episodic memory processes. Conversely, the *anterior temporal system* would comprise the perirhinal, ventral temporopolar, and lateral orbitofrontal cortices connected by the uncinate fasciculus and support semantic memory. Recent data in healthy subjects supported this model and suggested a specific vulnerability of the posterior medial system in AD versus anterior temporal system in SD [La Joie et al., 2014]. Here we provide direct evidence in patients showing that the common MTL atrophy is essentially associated with WM fiber alterations of the posterior medial system in AD versus anterior temporal system in SD. The dichotomy in the role of these two systems in episodic versus semantic memory was not extensively assessed in this study as very few cognitive tests were performed in both patient groups. Yet, we found a significant relationship between the WM regions associated with the left MTL atrophy and semantic deficits in SD ($P < 0.05$) but not in AD (data not shown). No relationship was observed in AD with performance in other cognitive domains (e.g., episodic memory), which might be explained by the restricted number of measurements and/or the fact that the WM regions associated with MTL atrophy were very extended in this disease so that relationships with cognition might be less specific.

The differences between both disorders in terms of targeted WM fibers might result from differences in the specific portion of the MTL that is altered. Indeed, MTL atrophy is known to show more anterior-posterior asymmetry in SD than AD [Chan et al., 2001; Davies et al., 2004; La Joie et al., 2013]. While atrophy is relatively homogeneous along the hippocampus in AD [Davies et al., 2004; Jack et al., 1997], it strongly predominates in the head of the hippocampus in SD [La Joie et al., 2013; Tan et al., 2014]. Interestingly, several studies have

highlighted that the connectivity of hippocampus [Aggleton, 2012; Poppenk et al., 2013] but also entorhinal [Maass et al., 2015; Navarro Schröder et al., 2015] and perirhinal [Zhuo et al., 2016] cortices varies along the anterior–posterior axis. It is thus possible that the earliest MTL lesions occur in distinct regions in AD versus SD and that the pathology then spreads across distinct sub-MTL networks. In agreement with this hypothesis, the connectivity of the posterior versus anterior hippocampus in healthy controls was shown to match with the regions specifically altered in AD versus SD [La Joie et al., 2014].

The distinct pathology underlying the MTL neurodegeneration in AD versus SD may also account for the different relationships with WM integrity. While tau is the primary cause of MTL neurodegeneration in AD [Braak and Braak, 1991], TDP-43 Type C is the most common histopathological substrate of SD [Hodges et al., 2010]. Growing evidence suggests that both misfolded proteins propagate in a prion-like manner, from one neuron to the next [Brettschneider et al., 2015]. It is nevertheless possible that these pathologies target different neuronal populations within the MTL [Galton et al., 2001]. For instance, granule cells of the dentate gyrus have generally been found to be spared until late stages of AD [Ohm, 2007] while they often showed cytoplasmic inclusions in patients with TDP-43 Type C [Kao et al., 2015; Mackenzie et al., 2006; Rossor et al., 2000; Sampathu et al., 2006]. MTL atrophy may therefore reflect, at least partly, loss of different cell populations that present with distinct connectivity. The additional presence of amyloid- β ($A\beta$) pathology in AD can also contribute to the distinct patterns of relationship in AD versus SD. $A\beta$ has been hypothesized to increase the accumulation of tau aggregates and accelerate the spread of tau both within and beyond the MTL [Sperling et al., 2014]. In agreement with this hypothesis, recent evidence have shown *in vivo* that increasing $A\beta$ burden predicted tau spread outside MTL regions [Johnson et al., 2016; Schöll et al., 2016]. It is thus possible that the interaction between tau and $A\beta$ pathologies leads to a specific disruption of MTL connectivity pathway in AD.

This study has some limitations that suggest directions for future works. First, T1-weighted MRI was used to assess WM structural changes. While previous studies assessing the relationship between MTL atrophy and WM changes in AD have obtained comparable results using either T1-weighted MRI [Villain et al., 2008] or diffusion tensor imaging [Agosta et al., 2011; Xie et al., 2005], the latter is more sensitive to subtle WM microstructural changes. Therefore, it would be interesting to confirm and refine current findings with diffusion tensor imaging. Second, due to the cross-sectional nature of this study, causal relationships between grey matter and WM could not be explored. A previous longitudinal study has shown that hippocampal atrophy progressively leads to disruption of the cingulum bundle in AD [Villain et al., 2010]. Similar longitudinal studies would be necessary to specify the dynamic of grey matter and WM losses in SD and to

assess whether the increased alteration over time in inferior longitudinal and uncinate fasciculi [Lam et al., 2014] results, at least partially, from increased neuronal loss in MTL structures. Comparison with AD patients will also be required to further confirm different profiles in this causal relationship.

Notwithstanding these limitations, our study is the first to demonstrate directly in patients that the common MTL atrophy in AD and SD is related to the disruption of distinct WM fibers. These fibers belong to different brain networks which might be the reason for the differences in the clinical manifestation between the two degenerative diseases. Neuropathological studies might help further understanding the reasons for the distinct MTL-related WM pathway disruption in AD versus SD.

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AUTHOR CONTRIBUTIONS

A.B. study design, analysis and interpretation of data, drafting the manuscript. B.D. study concept and design. R.L.J. analysis and interpretation of the data. B.L. analysis of the data. A.P. analysis of the data. F.M. analysis of the data. S.B. study concept. V.d.L.S. study concept. F.E. study concept. G.C. study design, interpretation of data, revising the manuscript for content.

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