Cross-sectional and longitudinal medial temporal lobe subregional atrophy patterns in semantic variant primary progressive aphasia

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\textbf{A B S T R A C T}

T1-magnetic resonance imaging (MRI) studies report early atrophy in the left anterior temporal lobe, especially the perirhinal cortex, in semantic variant primary progressive aphasia (svPPA). Improved segmentation protocols using high-resolution T2-MRI have enabled fine-grained medial temporal lobe (MTL) subregional measurements, which may provide novel information on the atrophy pattern and disease progression in svPPA. We aimed to investigate the MTL subregional atrophy pattern cross-sectionally and longitudinally in patients with svPPA as compared with controls and patients with Alzheimer’s disease (AD). MTL subregional volumes were obtained using the Automated Segmentation for Hippocampal Subfields software from high-resolution T2-MRIs in 15 svPPA, 37 AD, and 23 healthy controls. All MTL volumes were corrected for intracranial volume and parahippocampal cortices for slice number. Longitudinal atrophy rates of all subregions were obtained using an unbiased deformation-based morphometry pipeline in 6 svPPA patients, 9 controls, and 12 AD patients. Cross-sectionally, significant volume loss was observed in svPPA compared with controls in the left MTL, right cornu ammonis 1 (CA1), Brodmann area (BA)35, and BA36 (subdivisions of the perirhinal cortex). Compared with AD patients, svPPA patients had significantly smaller left CA1, BA35, and left and right BA36 volumes. Longitudinally, svPPA patients had significantly greater atrophy rates of left and right BA36 than controls but not relative to AD patients. Fine-grained analysis of MTL atrophy patterns provides information about the evolution of atrophy in svPPA. These results indicate that MTL subregional measures might be useful markers to track disease progression or for clinical trials in svPPA.

1. Introduction

Semantic variant primary progressive aphasia (svPPA), also referred to as semantic dementia, is a variant of frontotemporal dementia (Gorno-Tempini et al., 2011; Hodges, John R. and Patterson, 2007) that is characterized by progressive impairments in conceptual knowledge, naming, and word finding difficulties. Moreover, svPPA is characterized by volume loss particularly in the left anterior temporal lobe (Davies et al., 2009; Gorno-Tempini et al., 2011; Hodges et al., 1992; Tan et al., 2014), in the perirhinal cortex (PRC), entorhinal cortex (ERC), and hippocampus (Chan et al., 2001; Davies et al., 2004, 2009; Galton et al., 2001). Studies investigating longitudinal atrophy rates generally match these findings, reporting significantly greater atrophy rates in the anterior temporal lobes in svPPA than controls (Frings et al., 2012; Krueger et al., 2010; Lam et al., 2014; Rogalski et al., 2011; Rohrer et al., 2012), often more pronounced in the left hemisphere, although more pronounced atrophy rates in the right hemisphere have also been reported (Rohrer et al., 2008).

However, most of these studies, especially the longitudinal ones, report coarse, global measures using standard resolution T1-weighted MRI (~1 mm isotropic). T2-weighted MRI with high in-plane resolution enables better measurement of medial temporal...
lobe (MTL) regions than T1-weighted MRI because of the clear visualization of (1) the stratum radiatum lacunosum moleculare in the hippocampus which makes up a considerable portion of the subfield borders in the hippocampus which can rarely be visualized on standard resolution T1-weighted MRI and (2) the dura adjacent to the MTL cortices which can be difficult to separate from the cortex on T1-weighted MRI. We hypothesize that granular assessment of atrophy in subfields of MTL regions, such as hippocampal subfields and perirhinal subregions (BA35 and 36), using T2-weighted MRI can provide a better characterization of the topography and degree of subregional MTL atrophy in svPPA. Indeed, several previous studies indicated that high resolution T2-weighted MRI approached outperformed T1-weighted MRI approaches in the detection of early stage atrophy in AD, β-amyloid (Aβ) positivity, cognitive associations, and in sample size calculation for detecting change in patients’ atrophy rates compared with controls (Das et al., 2012, de Flores et al., 2015b, Mueller et al., 2018).

MTL atrophy patterns can potentially provide insight into the underlying pathology, as MTL subregions are thought to be differentially vulnerable to different pathologies such as 43-kDa TAR DNA-binding protein (TDP-43) (Brettschneider et al., 2014), which is thought to underlie svPPA in most cases (Bonner, M. F. et al., 2010; Grossman, 2010; Mesulam et al., 2014; Spinelli et al., 2017). A better characterization of the topography of atrophy in MTL subregions could thus potentially be helpful in detecting the presence of TDP-43 pathology in individuals with MTL atrophy without dementia or another neurodegenerative disease (Josephs et al., 2019; Nag et al., 2018; Nelson et al., 2019). Although MTL atrophy is often associated with neurofibrillary tangle (NFT) pathology in AD (Braak and Braak, 1991), recent autopsy studies of AD emphasize the important role of TDP-43 copathology in hippocampal volume loss even in individuals with significant AD pathology (Josephs et al., 2017; Nelson et al., 2013).

We are aware of only one previous study that assessed hippocampal subfield volumetry using T2-weighted MRI and showed that patients with svPPA have significantly smaller volumes of the subregions cornu ammonis (CA) 1 and subiculum (SUB) than controls, suggesting specificity for these subfields (La Joie et al., 2013). However, this study did not investigate adjacent MTL cortical regions (such as BA35 and BA36) or investigate longitudinal atrophy rates. Atrophy rates of MTL subfields could potentially provide better biomarkers to track disease progression or as end points in clinical trials. We therefore aim to investigate the MTL subregional atrophy pattern cross-sectionally and longitudinally in patients with svPPA as compared with controls and a dementia reference group, patients with AD. Besides hippocampal subfields CA1, SUB, and dentate gyrus (DG), we also interrogate aggregated anterior and posterior hippocampal regions. We hypothesize most pronounced atrophy, both cross-sectionally and longitudinally, in BA35 and BA36 in svPPA compared with controls and more so in the left than the right hemisphere, as well as more anterior than posterior hippocampal atrophy. Finally, we hypothesize that MTL atrophy in svPPA in the left hemisphere will be significantly greater than in AD.

While our article is mainly focused on svPPA, we also interrogate cross-sectional and longitudinal MTL atrophy patterns in amnesic AD patients. It should be noted that approximately 80% of our AD patients had an early onset (i.e., before 65 years), to match the age of the svPPA patients. While MTL atrophy has been well demonstrated in late-onset AD (de Flores et al., 2015a), there have been few studies examining MTL atrophy that focus on AD patients with an earlier onset (Phillips et al., 2018), and we are unaware of investigations of MTL subfield atrophy in early-onset AD using T2-weighted imaging. It has been hypothesized that tau pathology may originate in a different location in some nonamnesic cases of early AD, however, all AD patients included in this study had amnesic AD. Moreover, a recent neuropathologic study showed that the subset of AD patients with an amnesic syndrome who on average had an age of onset of 62.6 years, had a median Braak stage of VI and significantly more NFT pathology in the SUB compared with the cognitively impaired/mild dementia cases (Petersen et al., 2019), indicating that these cases harbor MTL NFT pathology. Our expectation is therefore that we will see neurodegeneration in the typical Braak regions in these early-onset amnesic cases of AD, including BA35 (approximates the transenthorctal cortex), ERC, and CA1 (Braak and Braak, 1997). We do not expect any differences between the hemispheres and in anterior versus posterior hippocampal atrophy in AD.

2. Methods

2.1. Participants

Patients were recruited at the Penn Frontotemporal Degeneration Center and Cognitive Neurology Clinic at the University of Pennsylvania. For the present study, only patients with a diagnosis of svPPA or early-onset AD and with available T1- and T2-weighted MRI scans were selected. A diagnosis of svPPA was established by a board-certified neurologist based on published criteria (Gorno-Tempini et al., 2011) and a neuropsychological profile consistent with svPPA. The clinical diagnosis was based on clinical criteria and then image-supported when clinical imaging was available (note that the high resolution T2-weighted MRI scans were not used to support the clinical diagnosis). Of 15 svPPA patients, 14 had available cerebrospinal fluid (CSF) measures of tau and Aβ. Most showed a tau-to-Aβ ratio of <0.34 consistent with non-AD pathology (Irwin et al., 2012), although 2 patients with svPPA had a CSF tau-to-Aβ ratio which was marginally above the cutoff (>0.34 (0.38 and 0.41). Many patients underwent neuropsychological examination with the Unified Data Set-2 and more recent cases also underwent the frontotemporolobar degeneration (FTLD)-National Alzheimer’s Coordination Center protocol which also included the neuropsychiatric inventory (see more details in the section Cognitive tasks). Moreover, all patients were evaluated for extrapyramidal and behavioral symptoms at every valuation. Demographically matched patients with a clinical diagnosis of AD were also recruited. The clinical diagnosis of AD was established as per the McKhann criteria (McKhann et al., 2011). All AD patients had an amnesic AD phenotype. Of 59 patients with AD, 6 showed a tau-to-Aβ ratio of <0.34 and were excluded, 13 did not have available CSF measures, and 2 had CSF measures but more than 1.5 years after the MRI scan and were excluded, resulting in a cohort of 38 AD patients with CSF evidence of AD pathology obtained either close in time to the MRI scan or before the MRI scan. Additional exclusion criteria were any evidence of vascular disease, hydrocephalus, head trauma, or other neurological disorder or medical illness that could affect cognition or a medication regimen that could affect cognition. In addition, 24 cognitively normal older adults of similar age were selected from a panel of cognitively healthy volunteers, with no history of a medical condition or neurologic disorder that could affect cognition. After quality assessment of the MRI scans and segmentations (see section Medial temporal lobe segmentation below), data from 15 patients with svPPA, 37 patients with early-onset AD, and 23 healthy controls were available. Of 37 patients with AD, 30 (81.1%) had an estimated age of onset 65 years or younger and are therefore traditionally considered early-onset AD or EOAD. Moreover, most of the patients in the AD group had dementia, however, 8 had mild cognitive impairment (MCI).

A subset of patients, including 6 svPPA patients, 12 AD patients, and 9 healthy controls, returned for a follow-up MRI scan within 600 days after the initial scan. There were no significant differences between the patients and controls included in the longitudinal
analyses as compared with those not included on age, sex, education, disease duration, and Mini Mental Status Examination (MMSE) (p > 0.05). Of 12 patients with AD with longitudinal data, 10 (83.3%) had an estimated age of onset 65 years or younger and are therefore considered EOAD. In addition, of 12 patients with AD, 7 had MCI.

2.2. Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Board from the University of Pennsylvania and all participants provided written informed consent.

2.3. Data availability

Anonymized data will be shared by request with any qualified investigator for purposes of validation and/or replication using our center’s established methods for sharing data.

2.3.1. Cognitive tasks

While all patients underwent cognitive testing, only a subset of the patients underwent cognitive testing within 6 months of MRI scanning. Note that the data were collected over many years and as a result, different subsets of patients completed each neuropsychological test. We chose to present neuropsychological tests that were available in most of the patients and that were most relevant for the 2 included patient groups, svPPA and amnestic AD. The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was obtained as well as specific tests for semantic and episodic memory. To assess semantic knowledge, the Boston Naming Task (BNT) (Kaplan et al., 1983) and the Pyramids and Palm Trees (PPT) test (Howard and Patterson, 1992) were used. For memory, delayed recall of the Philadelphia Verbal Learning Test (Libon et al., 1996) and the 15-minute delayed recall of the Rey figure (Osterrieth, 1944) were obtained. To equate for differences in the total number of correct items across the BNT, PPT, delayed recall of the Philadelphia Verbal Learning Test, and Rey figure, the percentage of correct answers was calculated.

2.3.2. MR imaging

MRI scans were acquired at a 3T Siemens Tim Trio scanner. A high-resolution T2-weighted MRI scan, specialized for imaging the MTL, was acquired perpendicular to the long axis of the hippocampus with partial coverage, with a repetition time of 5310 ms, echo time of 68 ms, a flip angle of 150°, a matrix size of 448x448, a voxel size of 0.4 × 0.4 × 2 mm³ and a 0.6 mm gap, and an acquisition time of 7:01 minutes. In addition, a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) scan was obtained with a repetition time of 1620 ms, an echo time of 3.09 ms, a flip angle of 15°, a matrix size of 192 × 256, a voxel size of 0.97 × 0.97 × 1 mm³, and an acquisition time of 5:11 minutes.

2.3.3. Medial temporal lobe subregion segmentation

The ASHS software (Yushkevich et al., 2015) was used to obtain volumes CA1, CA2, CA3, DG, subiculum (SUB), ERC, and BA35 and 36, which are subregions of the PRC and the parahippocampal cortex (PHC) and an estimate of intracranial volume (ICV). The Dice similarity coefficient comparing ASHS against the manual segmentation was higher than 0.70 for most of the subregions (Yushkevich et al., 2015), except CA2 (0.552) and CA3 (0.525). For this reason, CA2 and CA3 were excluded from all analyses. Moreover, an anterior and posterior hippocampal region was created by merging all hippocampal subfield labels from ASHS and using the uncus as the border between anterior and posterior hippocampus (Malykhin et al., 2008). The volumes of cortical regions (ERC, BA35, BA36, and PHC) were normalized by number of slices as recommended in (Yushkevich et al., 2015). ICV was regressed out for all volumes, based on the regression coefficients of the control group.

2.3.3.1. Quality assessment. All MRI scans and segmentations were visually inspected, and the segmentations were edited if necessary. Decisions on quality of the segmentations were made separately for the left and the right hemisphere as well as separately for the hippocampus and the extrahippocampal regions to preserve as much data as possible. The quality assessment led to the exclusion of 3 left hemispheres and one right hemisphere for different svPPA patients, the left and right hemisphere of one healthy control patient, and 2 left and one right hemisphere for AD patients as well as 2 left and right hippocampi and one left extrahippocampal region for AD patients. This leaves 15 svPPA patients (left: 12; right: 14), 38 AD patients (left: 36 (hippocampus: 34 and extrahippocampal regions: 35); right: 37 (hippocampus: 35 and extrahippocampal regions: 37)) and 23 cognitively normal controls (left: 23; right: 23). Segmentations were excluded when the segmentation was clearly inaccurate and could not be edited because the borders could not be identified either because of poor image quality or too severe atrophy.

2.3.3.2. Hemispheric asymmetry Index (HAI). For all patients, a HAI (La Joie et al., 2013) was calculated by the following formula: HAI = ((Hippocampus_right–Hippocampus_left)/(Hippocampus_left + Hippocampus_right)) × 100%. Positive values indicated smaller volumes in the left hemisphere than the right hemisphere. All svPPA patients had more pronounced left than right hemispheric atrophy, except for one patient. For the AD patients and elderly controls, this was more of a mix, whereas on average these groups also had slightly smaller left than right hippocampal volumes. See Table 1 for the average HAI in each of the groups.

2.3.3.3. Anterior-to-posterior ratio. An anterior to posterior ratio was calculated as the percentage of the total hippocampus that is made up by the anterior hippocampus ([anterior hippocampal volume/total hippocampal volume] × 100%) (La Joie et al., 2013).

2.3.3.4. Longitudinal analyses. An unbiased deformation-based morphometry pipeline was used to estimate longitudinal change in MTL subregions (Das et al., 2012). This method is specifically optimized for measuring the change from anisotropic T2-weighted MRI scans. All patients passed quality assessment. First, percentage volume loss was calculated as follows: (Follow-Up Subfield Volume–Baseline Subfield Volume)/Baseline Subfield volume × 100%. Second, to obtain annualized percentage volume loss, a correction was made for the slightly differing follow-up times as follows: (Percentage volume change/follow up time in days)×365. The average time between the 2 scans was 382±151 days for the svPPA patients, 341±80 days for the AD patients, and 399±52 days for the elderly controls (see also Supplementary Table 1).

2.4. Statistical analyses

Mann-Whitney U tests were performed to compare MTL subregion volumes and atrophy rates of the svPPA group with the healthy control group and the AD group, for the left and right hemisphere separately. No covariates were included as there were no significant differences between the groups in the potential confounder’s age, sex, disease duration (Table 1), and time difference between scans (Supplementary Table 1). A Wilcoxon rank test was used to compare subregion volumes and atrophy rates between the left and the right hemisphere. Note that in the analyses looking at longitudinal atrophy rates or when comparing left and right hemispheres, MTL measures are not corrected for ICV as these are within-subject comparisons.
For each of the analyses, we performed a multiple comparison correction using the Holm-Bonferroni method.

3. Results

3.1. Demographics

3.1.1. Cross-sectional data set

The demographics of the groups are displayed in Table 1. There were no significant differences in age, sex, and education between svPPA and the other groups and no difference for disease duration between the 2 patient groups. None of the svPPA patients was an APOE-4 carrier, which was significantly different from the AD patients and at a trend level from the healthy controls. Compared with the healthy controls, patients with svPPA had significantly decreased scores on the BNT, PPT, and verbal delayed recall. Compared with the AD group, the svPPA group had significantly worse performance on the BNT but significantly better performance on the delayed recall task of the Rey figure. svPPA and AD groups were similarly impaired in their verbal delayed memory performance. Compared with the elderly controls, the AD group was impaired on all cognitive tests except the Rey figure recall. These findings are consistent with the clinical diagnoses of svPPA and AD.

3.1.2. Longitudinal dataset

Demographics of the longitudinal data set are shown in Supplementary Table 1. There were no significant differences in age, sex, education, and follow-up time between the 3 groups and no difference for disease duration between the 2 patient groups. The only observed difference was a significantly lower MMSE score in the AD group than the elderly control group and a qualitatively lower MMSE score in the svPPA group than the elderly control group.

3.2. Anterior and posterior hippocampal analyses

3.2.1. Cross-sectional analyses

Both left anterior and posterior hippocampal volumes are smaller in svPPA than controls, and left anterior hippocampal volumes are also smaller than AD patients (Table 2). The left anterior-to-posterior ratio is also significantly different in svPPA compared with the other groups, indicating that the anterior hippocampus is relatively more affected than the posterior hippocampus in svPPA compared with the other groups.

In AD, both left and right anterior and posterior hippocampal volumes are smaller than those of healthy controls, however, the ratio is not significantly different from that of healthy controls.

3.2.2. Longitudinal analyses

No significant differences were observed in anterior or posterior hippocampal atrophy rates for any of the group comparisons, after Holm-Bonferroni correction (Table 3). However, qualitatively left anterior and posterior hippocampal atrophy rates were more pronounced in the svPPA group, and posterior atrophy rates in the svPPA group were qualitatively slightly larger than anterior hippocampal atrophy rates.

3.3. MTL subregional analyses

3.3.1. Cross-sectional analyses

Representative cases of MTL subregional imaging in svPPA, healthy controls, and AD are illustrated in Fig. 1. Compared with healthy controls, svPPA patients had significantly smaller volumes of all left MTL regions and right CA1, BA35, and BA36. Other MTL regions in the right hemisphere were smaller than in healthy controls but not to a significant extent (Table 4). Compared with the AD group, patients with svPPA had significantly smaller left CA1, BA35, and left and right BA36 volumes. There were no MTL subregions that were significantly smaller in AD than svPPA. Fig. 2A illustrates that BA35 and BA36 show qualitatively the most pronounced atrophy, followed by CA1 in the right hemisphere. Fig. 2B shows that the right hemisphere matches this pattern, although with less pronounced atrophy in BA35. Compared with the elderly control group, AD has significantly smaller left and right CA1, DG, BA35, and PHC volumes. Other regions are also qualitatively smaller but not to a significant degree.

Comparisons of MTL subregion volumes between the left and right hemisphere showed that every left hemisphere subregion was noticeably and significantly smaller than its right hemisphere homologue in the svPPA group. However, this did not survive Holm-Bonferroni correction. The lack of significant differences in the

Table 1 Demographic and clinical features of svPPA, healthy controls, and AD

|                  | svPPA Mean ± SD | Healthy control Mean ± SD | svPPA vs. control p-value | AD Mean ± SD | svPPA vs. AD p-value | AD vs. control p-value |
|------------------|-----------------|---------------------------|---------------------------|--------------|---------------------|------------------------|
| N                | 15              | 23                        |                           | 37           |                     |                        |
| Age (y) (range) | 63.1 ± 7.3 (49-75) (15) | 63.7 ± 6.4 (55-76) (23) | 0.836                     | 61.6 ± 8.2 (49-82) (37) | 0.368               | 0.204                  |
| Sex (% male)     | 66.7 (15)       | 60.9 (23)                 | 0.717                     | 48.6 (37)    | 0.238               | 0.356                  |
| Education (y)    | 17.2 ± 2.5 (14) | 16.0 ± 2.3 (23)          | 0.313                     | 15.9 ± 2.7 (36) | 0.145               | 0.733                  |
| Disease duration (y) (total n) | 2.6 ± 1.9 (15) | -                         |                           | 2.9 ± 2.3 (37) | 0.842               | -                      |
| APOE-4 status (%) (total n) | 0 (11)         | 13 (10)                  | 0.050                     | 54.1 (37)    | 0.001               | 0.177                  |
| One allele (%) of APOE-4 | 0              | 66.7                      |                           | 80.0         |                     |                        |
| Two alleles (%) of APOE-4 | 0              | 33.3                      |                           | 20.0         |                     |                        |
| CSF tau-to-abeta ratio (total n) | 0.022 ± 0.09 (14) | -                        |                           | 0.83 ± 0.41 (37) | -0.001             | -                      |
| HAI (total n)    | 10.05 ± 9.74 (11) | 1.43 ± 2.35 (23)        | <0.001                    | 2.37 ± 5.99 (33) | <0.001             | 0.335                  |
| MMSE (total n)   | 22.9 ± 8.7 (14) | 29.4 ± 0.8 (14)          | 0.004                     | 18.8 ± 5.3 (33) | 0.026               | <0.001                 |
| BNT (% correct) (total n) | 24.5 ± 22.7 (12) | 96.2 ± 42.18 (12)       | <0.001                    | 66.4 ± 25.3 (31) | <0.001             | <0.001                 |
| PPT (% correct) (total n) | 75.2 ± 14.9 (6)   | 98.6 ± 2.4 (7)             | 0.001                     | 89.4 ± 7.6 (13) | 0.029               | 0.001                  |
| PVTL 9 (% correct) (total n) | 32.2 ± 25.4 (10) | 88.9 ± 15.7 (5)           | 0.001                     | 22.6 ± 22.7 (27) | 0.286               | <0.001                 |
| Rey Recall (% correct) (total n) | 45.8 ± 25.5 (10) | 53.1 ± 32.8 (5)           | 0.394                     | 16.1 ± 15.5 (25) | 0.001               | 0.031                  |

Bolded values are significant after the Holm-Bonferroni correction.

Key: AD, Alzheimer’s disease; BNT, Boston naming task; CSF, cerebrospinal fluid; HAL, Hemispheric Asymmetry Index; MMSE, mini mental state examination; PPT, Pyramids and Palm Trees Test; PVTL, Pennsylvania verbal learning task; svPPA, semantic variant Primary Progressive Aphasia.

* Number alleles were displayed for descriptive purposes, no statistics were performed.
svPPA group is likely due to a lack of power. Left and right hemisphere subregions were much more comparably sized in AD and control groups, except for significantly smaller left than right CA1 in the AD group (this survived Holm-Bonferroni correction).

3.3.2. Longitudinal analyses

Exploratory longitudinal analyses were performed in the smaller subset with available longitudinal data. Comparing atrophy rates in MTL regions of svPPA patients with the other groups, we found significantly increased longitudinal atrophy rates in left and right BA36 in svPPA patients compared with healthy controls (Table 5). However, qualitatively all regions showed noticeably greater atrophy rates in svPPA than healthy controls. Fig. 2C and D show a fairly similar pattern longitudinally compared with the cross-sectional atrophy pattern for both hemispheres, although left SUB shows a more pronounced atrophy rate in svPPA. No significant differences in atrophy rates were found between patients with svPPA and patients with AD, although the atrophy rates were qualitatively greater in the svPPA group than the AD group for all but 2 regions. Left and right atrophy rates were not significantly different in any of the groups (data not shown). Again, this is likely due to a lack of power.

The AD group showed most pronounced atrophy rates in BA35 compared with the elderly control group which reached significance for the right hemisphere. Moreover, right BA36 atrophy rates were also significantly larger in AD patients than controls.

3.4. Additional analyses

Excluding the 2 svPPA patients with a CSF tau-to-abetra ratio >0.34 did not change the results. Moreover, one svPPA patient had relatively more pronounced right-sided atrophy, and excluding this patient did not change the results.

We also repeated the analyses without the AD patients with an estimated onset after 65 years, and this did not change the results. Finally, we repeated the analyses for the AD group without the MCI patients, and this did also not notably change the results.

4. Discussion

This study has several key findings. First, we found that svPPA has significant atrophy in all left and several right MTL subregions compared with healthy controls. Moreover, svPPA has significantly smaller left CA1, BA35, and left and right BA36 than AD, and all other left MTL regions were smaller than those in AD, although not to a significant extent. We also found more pronounced cross-sectional anterior than posterior hippocampal atrophy in svPPA compared with both AD and control comparison groups. Longitudinal analyses revealed that svPPA has a significantly faster rate of decline than healthy controls in left and right BA36 and had relatively more rapid decline in all other regions. Indeed, in all but 2 subregions, svPPA had a rate of declining atrophy that was more rapid than in AD, although not to a significant extent.

4.1. Strengths and limitations

The strength of our study is that we used high resolution T2-weighted images which allowed us to measure hippocampal subregions and to account for confounders such as the dura, which can be easily separated from gray matter on T2-weighted images but not on the more commonly used T1-weighted images. Moreover, we used a well-validated automated segmentation method with a segmentation scheme that was developed together with a neuroanatomist. Another strength of our study is its comparative design, using T2-weighted imaging to evaluate relative MTL atrophy in svPPA compared with AD. Finally, in the small number of cases with

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Table 2
Comparison of svPPA with healthy controls and AD on anterior and posterior hippocampal volumes (in mm³; ICV is regressed out for all variables)

| Left | svPPA | Control | svPPA vs. control | AD | AD vs. control |
|------|-------|---------|-------------------|----|---------------|
| N    | 12    | 23      |                   | 36 |               |
| Left ant H | 832 ± 99 | 1325 ± 192 | 62.8 | <0.001 | 1101 ± 260 | 83.1 | 0.002 | 0.002 |
| Left post H | 1071 ± 153 | 1356 ± 101 | 79.0 | <0.001 | 1080 ± 196 | 79.7 | 0.484 | <0.001 |
| Left ant/post ratio | 43.4 ± 4.2 | 49.2 ± 4.4 | – | 0.001 | 50.4 ± 5.5 | 80.6 | <0.001 | 0.603 |
| N    | 14    | 23      |                   | 37 |               |
| Right ant H | 1242 ± 253 | 1484 ± 247 | 83.7 | 0.006 | 1196 ± 234 | 80.6 | 0.535 | <0.001 |
| Right post H | 1138 ± 213 | 1276 ± 172 | 89.2 | 0.039 | 1070 ± 204 | 83.8 | 0.341 | <0.001 |
| Right ant/post ratio | 51.9 ± 6.1 | 53.5 ± 6.8 | – | 0.360 | 53.2 ± 5.4 | 80.6 | 0.452 | 0.893 |

B Bolded p-values are significant after the Holm-Bonferroni correction.

Key: AD, Alzheimer’s disease; Ant, anterior; H, hippocampus; post, posterior; svPPA, semantic variant Primary Progressive Aphasial.
available data, we performed longitudinal analyses in svPPA as well as AD and controls. Several limitations should be taken into account when interpreting these findings. While our sample size for svPPA falls well within the range of those of previous studies (Davies et al., 2009; Galton et al., 2001; Krueger et al., 2010; Rogalski et al., 2011), the first limitation is the relatively small sample size of rare svPPA patients. This limited our power to detect group differences, and this was most apparent in our comparisons of left versus right MTL regions in svPPA, where all left hemisphere subregions were noticeably smaller than the right hemisphere homologues although not after Bonferroni correction. Second, the time between the 2 MRI scans was relatively short (~1 year) which may have made our atrophy rate estimations less stable and may have limited our power to detect significant differences in atrophy rates between the groups. Third, there was sometimes limited gray-white matter contrast in the MRI scans of the svPPA patients, especially in the more severe cases. We mitigated this as much as possible by careful quality assessment of the MRI scans and segmentations and careful editing using both the T1- and T2-weighed MRI if needed. Fourth, in most of the healthy controls, no CSF biomarkers of AD pathology were available. It is therefore possible that cross-sectional and longitudinal atrophy in the healthy controls may have been influenced by AD pathology. However, this likely would have led to an underestimation of the actual group differences and we believe that the results would likely have been stronger if the healthy controls are limited to an Aβ-negative group only. Fifth, our patient groups had on average 3 years of disease duration when first seen, and we were therefore not able to measure changes in the earliest stages of

Fig. 1. T2-weighted MRI (lower panel) and accompanying MTL subregion segmentation (upper panel) for a representative svPPA, healthy control, and AD case. Abbreviation: ASHS, Automated Segmentation of Hippocampal Subfields; BA, Brodmann area; CA, cornu ammonis; DG, dentate gyrus; ERC, entorhinal cortex; MISC, miscellaneous PHC, parahippocampal cortex; SUB, subiculum.
the disease. Moreover, estimates of disease duration have limitations related to the sensitivity of family members and loved ones to the presence of word-finding problems and comprehension difficulties, and it is therefore possible that some patients were in more advanced stages of the disease.

4.2. MTL atrophy patterns in svPPA

The cross-sectional findings are consistent with previous studies showing anterior MTL atrophy in svPPA using traditional T1-weighted imaging (Davies et al., 2009, Gorno-Tempini et al., 2011, Hodges et al., 1992, Tan et al., 2014), with most pronounced atrophy in the PRC (note that what we call BA35 and BA36 is sometimes included in the fusiform gyrus and the parahippocampal gyrus [Davies et al., 2009; Davies et al., 2004; Galton et al., 2001]) and more pronounced atrophy in the anterior rather than the posterior hippocampus (Chapleau et al., 2016; Davies et al., 2005; La Joie et al., 2013; Tan et al., 2014). Note that our longitudinal data revealed more pronounced atrophy in the posterior than anterior hippocampus, although not to a significant extent, potentially indicating plateauing of the atrophy rates of the anterior hippocampus.

Table 4

Comparison of svPPA with healthy controls and AD on MTL subregional volumes (in mm³; parahippocampal subregions are corrected for slice number; ICV is regressed out for all variables)

|                | svPPA       | Control     | svPPA vs control | AD           | AD vs control |
|----------------|-------------|-------------|------------------|--------------|--------------|
|                | Mean±SD     | Mean±SD     | % Of control     | p-value      | p-value      |
| Left           |             |             |                  |              |              |
| N              | 12          | 23          | 36               |              |              |
| CA1            | 831±129     | 1328±126    | −37.4            | <0.001       | 0.002        |
| DG             | 612±72      | 826±107     | −25.9            | <0.001       | 0.001        |
| SUB            | 460±44      | 496±44      | −15.2            | <0.001       | 0.012        |
| ERC            | 157±3.4     | 211±2.5     | −25.9            | <0.001       | 0.012        |
| BA35           | 98±3.9      | 212±4.0     | −53.8            | <0.001       | <0.001       |
| BA36           | 330±10.6    | 715±12.2    | −53.8            | <0.001       | 0.007        |
| PHC            | 42.1±9.1    | 55.3±9.6    | −23.9            | 0.001        |              |
| Right          |             |             |                  |              |              |
| N              | 14          | 23          | 37               |              |              |
| CA1            | 1157±208    | 1399±138    | −17.3            | <0.001       | 0.001        |
| DG             | 747±126     | 851±94      | −12.2            | 0.010        |              |
| SUB            | 403±50      | 438±42      | −8.1             | 0.013        | 0.003        |
| ERC            | 94.4±4.8    | 22.2±3.4    | −12.6            | 0.024        | 0.001        |
| BA35           | 16.9±5.9    | 21.3±2.6    | −20.6            | 0.002        | 0.001        |
| BA36           | 46.3±16.4   | 69.4±11.7   | −33.2            | <0.001       | 0.194        |
| PHC            | 55.2±12.9   | 62.2±9.7    | −9.2             | 0.156        | 0.001        |

Bolded p-values are significant after the Holm-Bonferroni correction.

Key: AD, Alzheimer’s disease; BA, Brodmann area; CA, cornu ammonis; DG, dentate gyrus; ERC, entorhinal cortex; PHC, parahippocampal cortex; SUB, subiculum; svPPA, semantic variant Primary Progressive Aphasia.

Fig. 2. Cross-sectional (A, B) and longitudinal (C, D) atrophy patterns in the MTL in patients with svPPA and AD. Cross-sectional atrophy is expressed as percentage volume loss compared with the healthy controls. Abbreviation: AD, Alzheimer’s disease; BA, Brodmann area; CA, cornu ammonis; DG, dentate gyrus; ERC, entorhinal cortex; PHC, parahippocampal cortex; SUB, subiculum; svPPA, semantic variant Primary Progressive Aphasia.
While svPPA atrophy was more pronounced qualitatively in the PRC, atrophy was relatively widespread throughout the MTL in part because the svPPA patients included in this study had on average a disease duration of 3 years. It is likely that more specificity would be observed in earlier stages of the disease. Atrophy was more pronounced in every left hemisphere subregion compared with its right hemisphere homologue, although this is not significant after correction for multiple comparisons. While svPPA is typically characterized by more pronounced atrophy in the left hemisphere (Davies et al., 2009; Gorno-Tempini et al., 2011; Hodges et al., 1992; Tan et al., 2014), our study included one patient with more pronounced right hemispheric atrophy (see also Josephs et al., 2008; Thompson et al., 2003). Additional studies are needed to understand these atypical cases.

At first sight, our results regarding hippocampal subfields seem to partly contrast with the only other study investigating these atrophy differences in segmentation protocols may have caused these differences. Interestingly, several regions including left BA35 showed significantly more pronounced atrophy cross-sectionally in svPPA than AD, even though BA35, which approximates the entorhinal cortex, is the earliest site of NFT (NF pathology (Braak and Braak, 1991). While it is possible that the less pronounced atrophy in the AD group is due to the inclusion of several patients with MCI, this does not seem likely as the disease duration in both groups is similar and the MMSE score in the AD group is actually lower than the svPPA group. Moreover, repeating the analyses without the MCI patients did not change the results. In addition, it should be noted that most patients with AD included in this study had early-onset AD, who, while showing MTL atrophy compared with healthy controls, tend to have less MTL involvement compared with late-onset AD (Cavedo et al., 2014, Cho et al., 2013, Frisoni et al., 2005). The difference in BA35 atrophy between patients with AD and svPPA was most apparent in the left hemisphere, potentially reflecting the significantly greater naming impairment in svPPA than AD. Detailed clinical-anatomical studies have also associated the specific semantic impairment profile in svPPA for concrete object concepts with significant atrophy in these anterior temporal regions (Bonner, Michael et al., 2016; Cousins et al., 2016, 2017). Likewise, visual memory was significantly less impaired in svPPA than AD, potentially reflecting a relatively spared right MTL in svPPA. The larger visual memory recall impairments in AD than svPPA could potentially be the result of more pronounced baseline atrophy in the right posterior hippocampus and PHC (significantly different from controls but not svPPA). In combination with other regions such as the posterior cingulate, typically atrophied in AD, these MTL regions together make up the posterior temporal system which is thought to subserve episodic recollection (Ranganath and Ritchey, 2012). Regardless of the consequences of lateralized disease in svPPA, the presence of significant MTL atrophy in association with TDP-43 pathology is consistent with the AT(N) (deposition, pathological tau, and neurodegeneration) framework that neurodegenerative measures such as MRI atrophy have limited specificity to underlying molecular pathology (Jack et al., 2018; Knopman et al., 2018). We observed most pronounced longitudinal atrophy rates in svPPA in left BA36 and right BA35 and BA36 reaching between 8.52%–9.02% volume loss/year. These rates of decline for these fine-

| Left | svPPA Means±SD Control Means±SD svPPA vs. control p-value | AD Means±SD p-value | svPPA vs. AD p-value | AD vs. control p-value |
|------|--------------------------------------------------------|---------------------|---------------------|-----------------------|
| CA1  | −5.21 ± 4.48                                          | −0.98 ± 1.98        | 0.066               | −0.65 ± 3.46          | 0.053               | 1.000               |
| DG   | −3.52 ± 2.42                                          | 0.39 ± 1.98         | 0.012               | −1.25 ± 4.26          | 0.102               | 0.422               |
| SUB  | −6.72 ± 4.80                                          | −1.21 ± 2.06        | 0.036               | −2.26 ± 3.25          | 0.067               | 0.422               |
| ERC  | −3.92 ± 4.55                                          | −0.54 ± 2.17        | 0.181               | −3.34 ± 2.79          | 0.964               | 0.015               |
| BA35 | −2.11 ± 7.44                                          | −1.53 ± 2.36        | 0.689               | −4.06 ± 6.62          | 0.682               | 0.277               |
| BA36 | −8.57 ± 5.63                                          | −0.36 ± 1.46        | <0.001              | −3.90 ± 3.40          | 0.041               | 0.004               |
| PHC  | −5.01 ± 3.92                                          | 0.42 ± 2.06         | 0.012               | −3.03 ± 3.13          | 0.151               | 0.009               |

| Right | svPPA Means±SD Control Means±SD svPPA vs. control p-value | AD Means±SD p-value | svPPA vs. AD p-value | AD vs. control p-value |
|-------|--------------------------------------------------------|---------------------|---------------------|-----------------------|
| CA1  | −2.08 ± 4.61                                          | −0.04 ± 1.17        | 0.113               | −1.56 ± 3.13          | 0.616               | 0.219               |
| DG   | −3.14 ± 4.29                                          | 0.07 ± 2.50         | 0.181               | −0.59 ± 7.27          | 0.616               | 0.277               |
| SUB  | −4.33 ± 3.58                                          | −1.05 ± 2.47        | 0.113               | −2.45 ± 3.10          | 0.437               | 0.219               |
| ERC  | −2.17 ± 3.87                                          | −0.03 ± 2.41        | 0.181               | −4.02 ± 3.82          | 0.437               | 0.023               |
| BA35 | −8.52 ± 5.74                                          | 0.46 ± 1.61         | 0.008               | −6.05 ± 3.78          | 0.385               | <0.001              |
| BA36 | −9.02 ± 3.22                                          | 0.12 ± 1.79         | <0.001              | −3.86 ± 2.62          | 0.003               | 0.001               |
| PHC  | −3.89 ± 4.39                                          | −0.36 ± 1.71        | 0.145               | −3.29 ± 3.10          | 1.000               | 0.049               |

Bolded p-values are significant after the Holm-Bonferroni correction.

Key: AD, Alzheimer’s disease; BA, Brodmann area; CA, cornu ammonis; DG, dentate gyrus; ERC, entorhinal cortex; PHC, parahippocampal cortex; SUB, subiculum; svPPA, semantic variant Primary Progressive Aphasia.
grained MTL subregions are much larger than those reported for more global measures (1.6%–2.6% volume loss/years (Gordon et al., 2010; Knopman et al., 2009) but are more similar to those reported for the temporal lobe (Frings et al., 2012; Krueger et al., 2010; Rogalski et al., 2014; Rohrer et al., 2012). Similar to previous longitudinal studies (Czarnecki et al., 2008; Frings et al., 2012; Krueger et al., 2010; Rogalski et al., 2014; Rohrer, Jonathan D. et al., 2012), the present study showed somewhat more pronounced atrophy in the left hemisphere (but note Rohrer et al. [Rohrer et al., 2008] who reported more pronounced atrophy rates in the right hemisphere). We also observed considerable atrophy rates in the right hemisphere. This fits with the general notion that atrophy in svPPA spreads from the left to the right hemisphere over time (Marshall et al., 2018), potentially showing early involvement in the amygdala and the temporal pole in the MTL (Bocchetta et al., 2019). Another notable finding is that there are considerable differences in atrophy rates between the different MTL subregions. This indicates that subregion-specific information is lost in more global measures such as the temporal lobe or hippocampus and those subregional measures of decline might provide more sensitive and specific biomarkers for clinical trials, especially in the early stages when atrophy might still be very localized. Some evidence for this comes from detailed longitudinal clinical-anatomic studies of the declining semantic memory profile in svPPA, where a specific decline in concrete object knowledge is associated with progressive atrophy in the anterior temporal region (Cousins et al., 2018).

However, our longitudinal analyses of MTL subfields using T2-weighted MRI need to be replicated in a larger sample.

4.3. MTL atrophy pattern in amnesic AD

While this study was mainly focused on MTL atrophy patterns in svPPA, we also investigated MTL atrophy patterns in a group of amnesic AD patients, of whom the majority had early-onset AD. We found significant cross-sectional atrophy, bilaterally, in BA35 and CA1 but also in DG and PHC. Moreover, longitudinally, progressive atrophy was most pronounced in BA35 in both hemispheres in AD compared with healthy controls, even though this comparison only reached significance for the right hemisphere. In addition, right BA36 atrophy rates were also larger in AD patients than healthy controls. While atrophy in BA35 and CA1 is in line with the expectations as early loci for NFT pathology (Braak and Braak, 1991), cross-sectional volume loss in the DG and PHC and longitudinal atrophy rates in BA36 is perhaps less expected. It should be noted that these patients already had evidence of clinical AD for 3 years and perhaps NFT pathology had already spread to other MTL regions. A possible explanation for more pronounced atrophy rates in BA36 is that the boundaries with BA35 are difficult to determine and BA36 may have included some portion of BA35. However, as BA35 is smaller than BA36, this can likely not fully explain this finding. A possible explanation for the DG atrophy is that this label actually includes the stratum radiatum lacunosum moleculare (SRLM) in this atlas set (Yushkevich et al., 2015), and SRLM is actually an early target of NFT pathology (Adler et al., 2018; Braak and Braak, 1997; Kerchner et al., 2010; Thal et al., 2000). This inclusion of SRLM in the DG label perhaps partially explains the atrophy effects in the DG. A possible explanation for the atrophy observed in PHC is that PHC is part of the posterior MTL network (Ranganath and Ritchey, 2012), which is also thought to be affected in the early stages of AD (Das et al., 2015) and especially by Aβ pathology (Schöll et al., 2016). As Aβ pathology has accrued over the years preceding the diagnosis in the posterior MTL network, this pathology may have indirectly affected the integrity of the PHC. As noted, atrophy in the posterior MTL network likely contributes in part to the episodic memory impairments, observed in this group.

Although limited information is available about MTL subregional atrophy patterns in early amnesic AD, these findings are in line with previous studies reporting both cross-sectional and longitudinal atrophy in gross MTL regions in early- and late-onset AD with memory impairments (Cho et al., 2013; Frisoni et al., 2007).

5. Conclusions

This study revealed MTL subfield atrophy patterns in svPPA, with most pronounced atrophy in the PRC, in anterior regions of the MTL, and in the MTL of the left hemisphere. Significant progressive atrophy in BA36, part of the PRC, was observed over time. The considerable differences in atrophy rates between the different MTL subregions indicate that subregional measures of decline might provide more sensitive and specific biomarkers for clinical trials, especially in the early stages when atrophy might still be very localized. However, this should be further explored in future studies in larger sample sizes.

CRediT authorship contribution statement

Laura E.M. Wisse: Conceptualization, Visualization, Writing - original draft, Writing - review & editing. Molly B. Ungrady: Data curation, Writing - review & editing. Ranjit Ittyerah: Data curation, Writing - review & editing. Sydney A. Lim: Data curation, Writing - review & editing. Paul A. Yushkevich: Software, Writing - review & editing. David A. Woll: Writing - review & editing. David J. Irwin: Writing - review & editing. Sandhitsu R. Das: Conceptualization, Software, Writing - review & editing. Murray Grossman: Conceptualization, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2020.11.012.

References

Adler, D.H., Wisse, L.E., Ittyerah, R., Pluta, J.B., Ding, S., Xie, L., Wang, J., Kadivar, S., Robinson, J.L., Schuck, T., 2018. Characterizing the human hippocampus in aging and Alzheimer's disease using a computational atlas derived from ex vivo MRI and histology. Proc. Natl. Acad. Sci. U. S. A. 115, 4252–4257.

Bocchetta, M., Iglesias, J.E., Russell, L.L., Greaves, C.V., Marshall, C.R., Scelsi, M.A., Cash, D.M., Ourselin, S., Warren, J.D., Rohrer, J.D., 2019. Segmentation of medial temporal subregions reveals early right-sided involvement in semantic variant PPA. Alzheimers Res. Ther. 11, 41.

Bonner, M.F., Ash, S., Grossman, M., 2010. The new classification of primary progressive aphasia into semantic, logopenic, or nonfluent/agragrammatic variants. Curr. Neurol. Neurosci. Rep. 10, 484–490.

Bonner, M.F., Price, A.R., Peelle, J.E., Grossman, M., 2016. Semantics of the visual environment encoded in parahippocampal cortex. J. Cogn. Neurosci. 28, 361–378.
Nelson, P., Dickson, D., Trokanowski, J., Jack Jr., C., Boyle, P., Arfanakis, K., Rademakers, R., Alafuzoff, I., Attems, J., Brayne, C., 2019. Limbic-predominant age-related TDP-43 Encephalopathy (LATE): consensus working group report. Brain 142, 1503–1527.

Osterrieth, P.A., 1944. Filetest de copie d’une figure complex: contribution a l’etude de la perception et de la memoire. Arch. de Psychol. 30, 286–305.

Petersen, C., Nolan, A.J., Resende, Elisa de Paula FranÃ, Miller, Z., Ehrenberg, A.J., Gorno-Tempini, M.L., Rosen, H.J., Kramer, J.H., Spina, S., Rabinovici, G.D., 2019. Alzheimer’s disease clinical variants show distinct regional patterns of neuro-fibrillary tangle accumulation. Acta Neuropathol. 138, 597–612.

Phillips, J.S., Da Re, F., Dratch, L., Xie, S.X., Irwin, D.J., McMillan, C.T., Vaishnavi, S.N., Ferrarese, C., Lee, E.B., Shaw, L.M., 2018. Neocortical origin and progression of gray matter atrophy in nonamnestic Alzheimer’s disease. Neurobiol.Aging. 63, 75–87.

Ranganath, C., Ritchey, M., 2012. Two cortical systems for memory-guided behaviour. Nat. Rev. Neurosci. 13, 713–726.

Rogalski, E., Cobia, D., Harrison, T.M., Wieneke, C., Weintraub, S., Mesulam, M., 2011. Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. Neurology 76, 1804–1810.

Rogalski, E., Cobia, D., Martersteck, A., Rademaker, A., Wieneke, C., Weintraub, S., Mesulam, M., 2014. Asymmetry of cortical decline in subtypes of primary progressive aphasia. Neurology 83, 1184–1191.

Rohrer, J.D., McNaught, E., Foster, J., Clegg, S.L., Barnes, J., Omar, R., Warrington, E.K., Rossor, M.N., Warren, J.D., Fox, N.C., 2008. Tracking progression in fronto-temporal lobar degeneration: serial MRI in semantic dementia. Neurology 71, 1445–1451.

Rohrer, J.D., Clarkson, M.J., Kittus, R., Rossor, M.N., Durselin, S., Warren, J.D., Fox, N.C., 2012. Rates of hemispheric and lobar atrophy in the language variants of frontotemporal lobar degeneration. J. Alzheimers Dis. 30, 407–411.

Schöll, M., Lockhart, S.N., Schonhaut, D.R., Oâ’Neil, J.P., Janabi, M., Ossenkoppele, R., Baker, S.L., Vogel, J.W., Faria, J., Schwimmer, H.D., 2016. PET imaging of tau deposition in the aging human brain. Neuron 89, 571–582.

Spinelli, E.G., Mandelli, M.L., Miller, Z.A., Santos-Santos, M.A., Wilson, S.M., Agosta, F., Grinberg, L.T., Huang, E.J., Trojanowski, J.Q., Meyer, M., 2017. Typical and atypical pathology in primary progressive aphasia variants. Ann. Neurol. 81, 430–443.

Tan, R.H., Wong, S., Kril, J.J., Piguet, O., Hornberger, M., Hodges, J.R., Halliday, G.M., 2014. Beyond the temporal pole: limbic memory circuit in the semantic variant of primary progressive aphasia. Brain 137, 2065–2076.

Thal, D.R., Holzer, M., Rub, U., Waldmann, G., Gunzel, S., Zedlick, D., Schober, R., 2000. Alzheimer-related tau-pathology in the perforant path target zone and in the hippocampal stratum oriens and radiatum correlates with onset and degree of dementia. Exp. Neurol. 163, 98–110.

Thompson, S.A., Patterson, K., Hodges, J.R., 2003. Left/right asymmetry of atrophy in semantic dementia: behavioral–cognitive implications. Neurology 61, 1196–1203.

Wolk, D.A., Dickerson, B.C., Alzheimerâ€’s Disease Neuroimaging Initiative, 2010. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimerâ€’s disease. Proc. Natl. Acad. Sci. U. S. A. 107, 10256–10261.

Yushkevich, P.A., Pluta, J.B., Wang, H., Xie, L., Ding, S.L., Gertje, E.C., Mancuso, L., Kliot, D., Das, S.R., Wolk, D.A., 2015. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum. Brain Mapp. 36, 258–287.