Published in final edited form as:

Neuroimage. 2017 August 15; 157: 612–622. doi:10.1016/j.neuroimage.2017.05.049.

The association between tau PET and retrospective cortical thinning in clinically normal elderly

Molly R. LaPoint^a, Jasmeer P. Chhatwal^a, Jorge Sepulcre^c, Keith A. Johnson^{a,b,c,*}, Reisa A. Sperling^{a,b,c}, and Aaron P. Schultz^a

^aDepartment of Neurology, Massachusetts General Hospital, Harvard Medical School, and the Martinos Center for Biomedical Imaging, 149/10.008 13th Street, Charlestown, MA 02129, USA

^bCenter for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 220 Longwood Ave, Boston, MA 02115, USA

^cDepartment of Radiology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02115, USA

Abstract

Tau pathology has been associated with neuronal loss at autopsy, but the temporal evolution of tau pathology and atrophy remains unclear. Here, we investigate the association between cross-sectional AV-1451-PET as a marker of tau pathology and cortical thickness cross-sectionally. We also investigated retrospective rates of cortical thinning over the three years preceding the AV-1451 scan in a clinically normal cohort of 103 older adults from the Harvard Aging Brain Study. Tau measurements were Geometric Transfer Matrix partial volume corrected standardized uptake value ratios (SUVRs) with a cerebellar gray reference region. Thirty-four FreeSurfer-defined cortical regions of interest (ROIs) were used for both thickness and AV-1451 in each hemisphere, with seven additional volumetric ROIs. We examined “local” relationships between AV-1451 and cortical thickness in the same ROI, as well as inferior temporal AV-1451 and all thickness ROIs. All models included baseline age and sex, both interacting with time in retrospective longitudinal models, as covariates. Cross-sectional models controlled for the number of days between the two

*Corresponding author at: Department of Neurology, Massachusetts General Hospital, Harvard Medical School, and the Martinos Center for Biomedical Imaging, 149/10.008 13th Street, Charlestown, MA 02129, USA. kjohnson@mgh.harvard.edu (K.A. Johnson).

Potential conflicts of interest

M. LaPoint has nothing to disclose.

J. Chhatwal received support from NIH K23 AG049087, American Brain Foundation/American Academy of Neurology Clinical Research Training Fellowship (C2013-334) and the BrightFocus Foundation (A2013003F).

J. Sepulcre received funding from NIH grant K23EB019023.

K. Johnson has served as paid consultant for Bayer, GE Healthcare, Janssen Alzheimer's Immunotherapy, Siemens Medical Solutions, Genzyme, Novartis, Biogen, Roche, ISIS Pharma, AZTherapy, GEHC, Lundberg, and Abbvie. He is a site coinvestigator for Lilly/Avid, Pfizer, Janssen Immunotherapy, and Navidea. He has spoken at symposia sponsored by Janssen Alzheimer's Immunotherapy and Pfizer. K. Johnson receives funding from NIH grants R01EB014894, R21 AG038994, R01 AG026484, R01 AG034556, P50 AG00513421, U19 AG10483, P01 AG036694, R13 AG042201174210, R01 AG027435, and R01 AG037497 and the Alzheimer's Association grant ZEN-10-174210.

R. Sperling has served as a paid consultant for Abbvie, Biogen, Bracket, Genentech, Lundbeck, Merck, Roche, and Sanofi. She has served as a co-investigator for Avid, Eli Lilly, and Janssen Alzheimer Immunotherapy clinical trials. She has spoken at symposia sponsored by Eli Lilly, Biogen, and Janssen. R. Sperling receives research support from Janssen Pharmaceuticals, and Eli Lilly and Co. These relationships are not related to the content in the manuscript. She also receives research support from the following grants: P01 AG036694, U01 AG032438, U01 AG024904, R01 AG037497, R01 AG034556, K24 AG035007, P50 AG005134, U19 AG010483, R01 AG027435, Fidelity Biosciences, Harvard NeuroDiscovery Center, and the Alzheimer's Association.

A. Schultz has been a paid consultant for Janssen Pharmaceuticals and Biogen.

scans. Cross-sectional local comparisons revealed significant associations between elevated AV-1451 and thinner cortical ROIs predominantly in temporal regions, while analyses associating inferior temporal AV-1451 with all cortical ROIs showed a widespread pattern of significant relationships, which was strongest in temporal and parietal cortices. In our retrospective longitudinal analyses, we saw significant relationships in temporal and parietal regions. Significant local relationships were seen in right superior temporal, middle temporal, temporal pole, and fusiform, as well as the left cuneus and banks of the left superior temporal sulcus. Significant relationships between inferior temporal AV-1451 and faster thinning were observed in right temporal regions (middle temporal and fusiform) and bilateral parahippocampal cortices. We observed significant negative relationships between local and inferior temporal AV-1451 signal and both cross-sectional cortical thickness and rates of thinning in lateral and medial temporal regions. This is an important early step toward elucidating the relationship between tau pathology and retrospective longitudinal atrophy in aging and preclinical AD.

Keywords

Tau; Atrophy; Neurodegeneration; Longitudinal; Aging; Alzheimer's disease

Introduction

Tau pathology in the form of neurofibrillary tangles (NFTs) is a pathological hallmark of Alzheimer's disease (AD). NFTs accumulate in a well-characterized progressive pattern. Tangles begin in the medial temporal lobe (MTL; Braak Stage I/II), spread to nearby neocortical regions predominantly in the lateral temporal lobe (Braak Stage III/IV), and then spread throughout the neocortex (Braak Stage V/VI) (Braak and Braak, 1991). Neuropathological research has shown a positive correlation in AD patients between NFT burden and disease severity, cognitive performance, and neuronal loss at autopsy (Arriagada et al., 1992; Bierer et al., 1995; Csernansky et al., 2004; Gómez-Isla et al., 1997; Mitchell et al., 2002; Nelson et al., 2012).

Tau accumulation is not unique to AD patients. Tangles in the MTL corresponding to Braak Stage I/II are widely observed in cognitively normal (CN) older adults and appear to develop independently of beta-amyloid plaques, a second hallmark of AD. Additionally, tangle density in the MTL, NFT spread to the neocortex (Braak Stage III/IV), and incidence of cognitive impairment all increase with advancing age (Braak and Braak, 1997; Knopman et al., 2003; Price and Morris, 1999). There is evidence that increased AD pathology at autopsy is related to subtle cognitive impairments in neuropsychological testing even in elderly with no history of clinical impairment, indicating that these molecular pathologies are likely present in preclinical AD (Guillozet et al., 2003; Hulette et al., 1998). Because autopsy studies are inherently cross-sectional, the temporal relationship between the development of tau pathology, changes in brain structure and function, and progression to AD remains unclear.

Studies of *in vivo* NFT pathology have been ongoing, but have previously relied on cerebrospinal fluid (CSF) measures, which correlate with NFT pathology in AD (Tapiola et

al., 1997), as well as PET measures (Brier et al., 2016; Chhatwal et al., 2016; Gordon et al., 2016), but which lack information regarding the topology of tau pathology as it relates to neurodegeneration. The recent advent of tau-PET imaging ligands, in particular ^{18}F AV-1451-PET (^{18}F T807-PET) (Xia et al., 2013), allows us to examine both the spatial pattern of tau pathology *in vivo* and the relationship between NFTs and other markers of neurodegeneration. Early imaging results showed that AV-1451 signal was elevated in individuals with mild cognitive impairment (MCI) and AD compared to healthy elderly controls (Chien et al., 2013) and a preliminary autoradiography study in individuals who had previously received AV-1451 scans found that the ligand held promise as a marker of AD-like tau pathology (Marquie et al., 2015). Subsequent studies have shown a positive relationship between AV-1451 signal and older age, worsening clinical diagnosis, and greater cognitive impairment (Jack et al., 2016; Johnson et al., 2016; Schöll et al., 2016; Villemagne and Okamura, 2016; Wang et al., 2016).

The present study seeks to elucidate the relationship between AV-1451 signal as a measure of tau pathology and brain atrophy, as assessed by longitudinal MRI. Using data from cognitively normal older adults from the Harvard Aging Brain Study (HABS), we investigated the relationship between tau pathology and atrophy using both concurrent cross-sectional cortical thickness measured within a year of AV-1451 imaging (mean 139 days), and longitudinal measures of cortical thinning over the three years preceding AV-1451 imaging. We hypothesized that participants with higher tau pathology would show both thinner cortical regions cross-sectionally, and a faster rate of longitudinal cortical thinning, examined retrospectively. Lastly, we examined associations between tau burden and local cortical thinning, as well as distributed patterns of cortical atrophy.

Materials and methods

Participants

Data from 103 participants in HABS, a longitudinal study of normal aging and preclinical Alzheimer's disease at the Massachusetts General Hospital (Dagley et al., 2015), were included in the present study. Here we refer to preclinical AD in the sense of a cognitively normal elderly cohort that can be characterized in terms of NIA-AA criteria (Jack et al., 2012; Sperling et al., 2011) and recently updated to include tau-PET imaging (Jack et al., 2016). All participants provided informed consent and were studied under protocols approved by the Partners Human Research Committee. All participants underwent a comprehensive evaluation to ensure they had no medical or neurological disorders that might contribute to cognitive dysfunction. At study entry, all participants were assessed as clinically normal (CDR = 0, MMSE > 25, and performance within 1.5 standard deviations of age- and education-adjusted norms on the Logical Memory Delayed Recall), without current clinical depression (Geriatric Depression Scale < 11) or active psychiatric illness (Folstein et al., 1975; Morris, 1993; Wechsler, 1987; Yesavage et al., 1983). Participants were also excluded from the study if they had a history of alcoholism, drug abuse, or head trauma. As AV-1451 PET was added to the study protocol after the start of the study, 10 participants had progressed to a global CDR of 0.5 by the time of AV-1451 imaging. Notably, the presented analyses were conducted both with and without including these 10 mildly impaired

participants, and the pattern of results remained largely the same. Accordingly, all 103 participants were retained in the final analyses. A schematic of the study's progression from baseline to the time of the AV-1451 scan can be found in Supplementary Fig. 1. Participant demographic data is shown in Table 1.

Image acquisition and processing

As described previously (Johnson et al., 2016), AV-1451-PET (^{18}F T807-PET) was prepared at Massachusetts General Hospital in Boston, MA with a radiochemical yield of $14 \pm 3\%$ and specific activity of $216 \pm 60\text{GBq}/\mu\text{mol}$ at the end of synthesis (60 min), and validated for human use (Shoup et al., 2014). Data were acquired using a Siemens/CTI ECAT HR+ scanner (3-dimensional mode, 63 image planes, 15.2 cm axial field of view, 5.6 mm transaxial resolution, and 2.4 mm slice interval), and acquisition took place 80–100 min after a 9.0–11.0Ci bolus injection in 4×5 min frames. PET data were reconstructed and attenuation corrected, and each frame was evaluated to verify adequate count statistics and absence of head motion.

Magnetic resonance imaging was performed on two matched 3.0 T Tim Trio Siemens scanners at the Athinoula A. Martinos Center for Biomedical Imaging in Charlestown, MA, and included a multi-echo MPRAGE processed with FreeSurfer (FS) version 5.1 to identify gray-white and pial surfaces to permit automatic region of interest (ROI) parcellation (Fischl, 2012). Following previously-described cross-sectional quality control measures (Dagley et al., 2015), each subjects' MRIs were run through the FS longitudinal processing stream (Reuter et al., 2012). In the longitudinal processing stream, a temporally-unbiased template is created for each subject based on all MR time points; next, each time point is resampled to this median template space, with the intention of reducing random variability between subject time points and improving sensitivity of analyses. Identical manual quality control of FS recons processed through the longitudinal pipeline was repeated to ensure accuracy of data, including skullstripping, white matter edits, and placement of control points in the templates and longitudinally-processed scans as needed. All 34 cortical thickness ROIs produced by FS using the Desikan-Killiany cortical atlas were utilized in each hemisphere in our analyses, for a total of 68 regions (Desikan et al., 2006). Further analyses utilized seven volumetric ROIs from the automatic FS segmentation: cortex (total neocortical gray matter), left and right hippocampus, as well as all left and right lateral and inferior lateral ventricles (temporal horn; Fischl et al., 2002).

To evaluate the anatomy of cortical AV-1451 binding, PET scans were rigidly coregistered to the individual's MPRAGE images using SPM8 (Function Imaging Laboratory, Wellcome Department of Cognitive Neurology, London, UK). The ROIs defined by the cross-sectional FS analysis at the MRI time point closest to the AV-1451 scan were transformed into the PET native space. AV-1451 data were partial-volume corrected using the Geometric Transfer Matrix (GTM) method (Rousset et al., 1998) using the recently-developed FS implementation (Greve et al., 2016). AV-1451 signal was expressed in FS ROIs as the standardized uptake value ratio (SUVR), using the FS cerebellar gray ROI as the reference.

Statistical analyses

Statistical analyses were performed in MATLAB R2015A (MathWorks, Inc., Natick, MA) using linear models for cross-sectional analyses and linear mixed-effects models for retrospective longitudinal analyses with subject as a random factor. Thickness was the dependent variable in all analyses. All statistical models included baseline age and sex (interacted with time in retrospective longitudinal analyses) as covariates. Cross-sectional models utilized the longitudinally-processed FS data from the time point closest to the AV-1451 scan for consistency and, additionally, controlled for the temporal lag between the MRI and PET scan. All results were reported at a threshold of $p < 0.05$, uncorrected, to investigate the pattern of the relationships across the cortex, and FDR-corrected in the tables to confirm which associations survive correction for multiple comparisons.

We evaluated the association of cortical thickness and tau pathology in two ways: locally, *i.e.*, with both measures obtained from the same ROI, and by comparing a single proxy AV-1451 ROI measure to each of cortical thickness measures. We chose the inferior temporal gyrus AV-1451 FS ROI as a proxy for neocortical tau deposition based on previous work with AV-1451-PET (Chhatwal et al., 2016; Johnson et al., 2016; Mormino et al., 2016; Sepulcre et al., 2016) and neuropathological studies suggesting that inferior, neocortical regions of the temporal lobe are the initial site of tau spread into the neocortex during Braak Stage III (Braak et al., 2006). Tau pathology increases with advancing age, but autopsy evidence suggests that the spread from MTL to neocortex is associated with the early cognitive impairment of AD (Braak and Braak, 1997; Hulette et al., 1998; Price and Morris, 1999). Furthermore, *in vivo* inferior temporal AV-1451 elevation is associated with clinical symptoms in MCI and AD, and has sufficient variability in the cognitively normal HABS cohort to enable assessment of its relationship with atrophy (Johnson et al., 2016; Sepulcre et al., 2016). In addition to our two main analyses with local and inferior temporal tau, we have included a supplemental figure and table exploring the relationship between atrophy and entorhinal tau. Elevated AV-1451 in the medial temporal lobes has previously been related to increasing age by other research groups (Brier et al., 2016; Gordon et al., 2016; Jack et al., 2016; Pontecorvo et al., 2017; Schöll et al., 2016), and there is some research indicating that entorhinal tau may be more closely associated with higher levels of amyloid than inferior temporal tau burden (Vemuri et al., 2017). Fig. 1, *Panel A* shows the non-partial volume corrected SUVR distribution of AV-1451 across the cortex and Fig. 1, *Panel B* shows the relationship between cortical amyloid burden, measured with PiB-PET, and AV-1451 signal in each cortical ROI, and reaffirms our use of inferior temporal AV-1451 as an ROI with variability in this sample that is related to AD pathology.

Results

Relevance for preclinical AD

We observed that tau signal was most elevated, as expected, in temporal regions (Fig. 1, Panel A). We were also interested in the relationship between AV-1451 and amyloid burden, measured with PiB-PET (Fig. 1, Panel B). The strongest associations were seen between cortical amyloid burden and tau in medial and lateral temporal regions. This figure presents

evidence that individuals with highly elevated tau also have elevated amyloid consistent with clinical AD.

Cross-sectional analyses

We observed significant negative relationships between local AV-1451 and concurrent cortical thickness predominantly in medial, inferior, and lateral temporal regions, with weaker but still significant relationships in the cingulate cortex and parietal lobe. (Fig. 2A), mirroring our earlier report (Sepulcre et al., 2016). All significant relationships are listed in Table 2, column 1. The strongest local relationships were observed in the right fusiform ($t(98)=-4.97$, $p < 0.00001$) and inferior temporal cortex ($t(98)=-3.92$, $p < 0.001$), and bilateral middle temporal cortices (left: $t(98)=-3.71$; $p < 0.001$; right: $t(98)=-4.14$; $p > 0.0001$), entorhinal cortices (left: $t(98)=-4.18$, $p < 0.0001$; right: $t(98)=-3.96$, $p < 0.001$) and temporal poles (left: $t(98)=-4.24$, $p < 0.0001$; right: $t(98)=-6.40$, $p < 0.00001$).

Next, we investigated the association between inferior temporal AV-1451 signal and cortical thickness across all ROIs. We observed widespread negative relationships across the cortex, indicating that thinner cortical regions were significantly associated with increased inferior temporal tau pathology, especially in regions within the temporal and parietal lobes. (Fig. 2B). The strongest relationships were found in regions relatively close to the inferior temporal ROI, including the right fusiform ($t(98)=-5.53$, $p < 0.00001$), inferior temporal ($t(98)=-3.61$, $p < 0.001$), middle temporal ($t(98)=-4.96$, $p < 0.00001$), and right inferior parietal ($t(98)=-3.82$, $p < 0.001$). Cross-sectional relationships between entorhinal tau and cortical thickness across the cortex looks relatively similar to, though less robust than, this inferior temporal tau figure and can be seen in Supplementary Fig. 2A.

Volumetric analyses found a significant association between temporal AV-1451 and total cortical gray matter volume controlling for intracranial volume ($t(97)=-2.93$, $p=0.0042$). No significant associations were found between AV-1451 and hippocampal volume, lateral ventricular volume or inferior lateral ventricular volume (temporal horn). All regions exhibiting a significant relationship with inferior temporal AV-1451 are shown in Table 2, column 3.

Retrospective longitudinal analyses

We began retrospective longitudinal analyses by looking at the relationship between local AV-1451 and the rate of retrospective longitudinal thinning in the same region. Significant associations between a faster rate of thinning and increased AV-1451 signal were observed in right temporal regions (superior temporal – $t(228)=-2.85$, $p < 0.01$, estimate= -0.040 mm/year; middle temporal – $t(228)=-3.66$, $p < 0.001$, estimate= -0.043 mm/year; temporal pole – $t(228)=-3.74$, $p < 0.001$ estimate= -0.063 mm/year; right fusiform – $t(228)=-2.22$, $p < 0.05$, estimate= -0.031 mm/year), with additional significant associations with the left cuneus ($t(228)=-2.14$, $p < 0.05$ estimate= -0.019 mm/year) and left banks of the superior temporal sulcus ($t(228)=-2.01$, $p < 0.05$, estimate= -0.032 mm/year) (Fig. 2C). These results are also shown in Table 2, column 2. The right middle temporal and right temporal pole associations survive an FDR correction for multiple comparisons ($p = 0.00090$).

Next, we investigated the relationship between inferior temporal AV-1451 and retrospective thinning across the cortex. Longitudinally, faster retrospective thinning and increased inferior temporal AV-1451 were significantly associated predominantly in right temporal regions (middle temporal – $t(228)=-2.18$, $p < 0.05$ estimate $=-0.029$ mm/year; right fusiform – $t(228)=-3.82$, $p < 0.001$, estimate $=-0.052$ mm/year), as well as bilateral parahippocampal cortices (left: $t(228)=-2.60$, $p < 0.01$, estimate $=-0.049$ mm/year; right: $t(228)=-1.99$, $p < 0.05$, estimate $=-0.041$ mm/year). (Fig. 2D). Only the association with the right fusiform survived FDR correction for multiple comparisons ($p = 0.00017$). Supplementary Fig. 2B shows the retrospective longitudinal associations between entorhinal tau and cortical thickness; again, these relationships are largely observed in the medial and lateral temporal cortices.

Volumetric analyses, controlling for intracranial volume, revealed a significant association between higher AV-1451 and faster expansion of the left inferior lateral ventricle (temporal horn; $t(226)=2.14$, $p < 0.05$, estimate $=525.77$ mm³/year) and left lateral ventricle ($t(226)=2.22$, $p < 0.05$, estimate $=57.879$ mm³/year). No significant associations were found between inferior temporal AV-1451 and rate of total cortical volume loss, hippocampal volume loss, or expansion of the inferior lateral ventricles. All significant results from retrospective longitudinal analyses with inferior temporal AV-1451 are included in Table 2, column 4.

Following ROI analyses, we wanted to further characterize the relationship between thinning and inferior temporal tau pathology. To do this, we graphed the expected pattern of bilateral parahippocampal thinning at three different levels of inferior temporal AV-1451 signal based on linear mixed model fit (Fig. 3). This analysis suggests that individuals with higher inferior temporal AV-1451 signal at year 3 of the study had both thinner parahippocampal cortices at study entry and a faster rate of parahippocampal thinning over the first three years of the study.

Discussion

This study explored the association in cognitively normal elderly individuals between cortical thickness and tau pathology, measured *in vivo* with AV-1451-PET. We examined the relationship between cross-sectional AV-1451 and retrospective longitudinal thinning during the three years preceding AV-1451 imaging. We also examined “local” relationships between AV-1451 signal and cortical thickness in the same FreeSurfer-defined ROI and the broader relationship between inferior temporal AV-1451 and atrophy patterns across the brain.

The cross-sectional analyses indicate a widespread negative relationship between AV-1451 signal and thickness, with significant “local” relationships between PET signal and thickness observed primarily in the temporal lobe, similar to what has been seen in previous analyses (Sepulcre et al., 2016). As expected, extensive relationships between tau pathology and thickness outside the medial temporal lobes and surrounding neocortex were relatively uncommon in our non-demented participants. Therefore, the lack of variance in AV-1451 signal in more distal regions likely precludes the ability to detect strong relationships between thickness and tau pathology in these areas. These results mirror earlier autopsy

studies which found a relationship between NFTs and neurodegeneration in AD patients (Csernansky et al., 2004; Gómez-Isla et al., 1997).

The aim of using inferior temporal AV-1451 was to test the relationship between cortical thickness throughout the brain and tau pathology in a proxy region of early neocortical tau spread previously shown to be associated with cognitive impairment (Braak and Braak, 1991; Johnson et al., 2016). We found widespread significant associations between increased inferior temporal AV-1451 signal and thinner cortical ROIs. This relationship was strongest in temporal and parietal regions, in a pattern similar to the atrophy typically seen in AD (Buckner et al., 2005; Dickerson et al., 2009; Sabuncu and Konukoglu, 2014; Thompson et al., 2003). Furthermore, increased inferior temporal AV-1451 signal was associated with a smaller left hippocampal volume.

These results are largely consistent with similar cross-sectional studies using CSF tau measures, which have demonstrated associations between CSF tau and cortical atrophy measures, including precuneus and AD signature thickness (Alcolea et al., 2015; Wang et al., 2015), hippocampal volume and radial distance (Apostolova et al., 2010; de Souza et al., 2012; Herukka et al., 2008) and gray matter density in the hippocampus and middle temporal lobe (Thomann et al., 2009). However, it is noteworthy that many of these studies included participants both with and without impairment, and not all studies reported significant relationships in all clinical groups. Additionally, other studies have failed to find a significant relationship between cross-sectional thickness and CSF tau measures (Ossenkoppele et al., 2015; Tosun et al., 2011). Broadly, the findings here do support a negative association between cross-sectional cortical thickness and cross-sectional PET-based measurements of tau pathology.

Unlike the effects for cross-sectional thickness, we did not observe widespread relationships between longitudinal rates of retrospective cortical thinning and inferior temporal AV-1451 binding. Local relationships between faster thinning and higher PET signal were seen in right lateral temporal lobe regions, as well as in the left cuneus and the banks of the left superior temporal sulcus. Inferior temporal AV-1451 was related to retrospective thinning in right temporal regions and bilateral parahippocampal cortices. The most robust association between inferior temporal AV-1451 and retrospective longitudinal cortical thinning was observed in the right fusiform, which survives an FDR comparison for multiple corrections. Somewhat surprisingly, parahippocampal AV-1451 did not significantly predict retrospective longitudinal parahippocampal thinning. However, this may be due to a mixture of weaker AV-1451 signal properties in the parahippocampus relative to the inferior temporal cortex and a more complex pathological picture of tau pathology due to both AD and non-AD sources. Consistent with this, inferior temporal AV-1451 was associated with rates of parahippocampal thinning retrospectively. It will be interesting to see if this pattern holds up, and if tau in later Braak stages predicts atrophy in earlier Braak stages.

Longitudinal imaging studies using CSF tau have found similar results. They have shown a relationship between baseline CSF tau measures and rates of hippocampal atrophy in AD, MCI, and CN groups (Hempel et al., 2005; Henneman et al., 2009), and in MCI subjects, between baseline CSF tau and rates of thinning in medial and lateral temporal regions

(Tosun et al., 2011). These anatomical regions are consistent with the findings of the present study.

The retrospective nature of the longitudinal analyses and the limited length of follow-up may help explain the observation that tau burden and cortical thickness were more robustly associated in cross-sectional as compared to retrospective longitudinal analyses. Perhaps cross-sectional thickness is indicative of many years of slow or nonlinear atrophy collapsed into a single measure, but it is also possible that certain subjects have simply had a thinner cortex their entire lives, making them more susceptible to tau pathology. Overall, however, these results show that smaller cortical ROIs cross-sectionally are not always indicative of a faster rate of change in these regions over three years, at least in relation to regional tau pathology. We cannot yet tell if tau is reflective of atrophy and/or driving atrophy. If tau pathology precedes (and perhaps drives) atrophy, we would expect that longitudinal analyses using prospective longitudinal structural MR data would be more robust than the retrospective effects reported here. If thinning precedes tau pathology, we would have expected to see stronger relationships between retrospective thinning and AV-1451 signal, but given the presence of some modest effects and without prospective data to compare against, it is difficult to speculate. Questions regarding the simultaneous longitudinal trajectories of atrophy and tau will necessitate longitudinal AV-1451 imaging, and we are planning future investigations into this question once longitudinal AV-1451 data is available in this sample.

Additionally, because all participants began the study cognitively normal, in this context it is perhaps not surprising that highly elevated AV-1451 signal and/or steep decreases in thickness were not observed over the three-year follow-up period. In general, the less robust findings between retrospective longitudinal and cross-sectional analyses does serve as a caution against labeling cross-sectional anatomical measures as “atrophy” or “neurodegeneration,” particularly in datasets comprised of relatively unimpaired individuals with putatively low pathologic burdens.

Furthermore, as the AV-1451 PET data used here are cross-sectional and concurrent with the last MRI, tau burden at study entry is not known, nor is the rate of tau accumulation in the years preceding AV-1451 imaging. Longitudinal CSF studies have used prospective MR data relative to baseline CSF tau, and have found associations with similar regions in the temporal lobe (Hampel et al., 2005; Henneman et al., 2009; Tosun et al., 2011), but the association between atrophy and baseline regional tau pathology remains to be investigated. Such prospective assessments will be particularly critical in determining the temporal relationship between tau accumulation and atrophy, and the extent to which high AV-1451 signal is predictive of impending local and global neurodegeneration.

Notably, the analyses presented here used partial-volume corrected AV-1451 data, and the use of partial volume correction was necessary to observe robust, significant associations between AV-1451 binding and atrophy. We propose that this is due to the measurement properties of PET data, as a higher degree of PET signal loss to adjacent CSF likely leads to underestimates of tau pathology in individuals with thinner cortical ROIs, and *vice versa*. Partial volume correction seeks to improve assignment of PET signal to its proper tissue

type, mitigating this confound and allowing us to observe a relationship between higher tau pathology and faster temporal thinning. This study also examines a limited range of tau pathology as our cohort includes only cognitively intact participants. Though it is notable that such relationships can be seen between atrophy and tau in a cognitively normal cohort, further follow-up to compare progressors to AD dementia *versus* non-progressors is necessary to elucidate the relationship between tau, longitudinal atrophy, and progression to a clinical diagnosis.

This study shows that retrospective rates of neurodegeneration in right middle temporal, right fusiform, and bilateral parahippocampus as well as ventricular expansion in the left lateral ventricle and left inferior lateral ventricle (temporal horn) are related to concurrent inferior temporal AV-1451 signal, though only right fusiform survives multiple comparison correction. In terms of local AV-1451 signal, retrospective neurodegeneration was observed in the left banks of the superior temporal sulcus, left cuneus, right fusiform, right middle temporal, right superior temporal, and right temporal pole, though only right middle temporal and right temporal pole survived correction for multiple comparisons. These findings are an important first step toward elucidating the anatomic and temporal evolution of tau pathology and atrophy in aging and preclinical AD, and reveal the presence of modest relationship between regional retrospective cortical thinning and concurrent AV-1451 signal. This was largely impossible prior to the advent of *in vivo* tau imaging methods, and can now be studied further. Additional studies will be needed to see how this relationship may change with prospective data, and how this relationship may be changed relative to cognitive impairment. Looking forward, there may be implications for clinical trials. If this relationship is borne out in prospective studies, this may indicate that being able to decrease the accumulation of tau pathology may be able to halt or slow cortical thinning, and, in turn, perhaps prevent or slow cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the participants of the Harvard Aging Brain Study for their dedication. Data collection for this project was supported by the National Institute on Aging (NIA) and National Institutes of Health *via* P01 AG36694 and K24 AG035007, respectively, as well as R01 AG046396, the Massachusetts Alzheimer's Disease Research Center (P50 AG005134), and Shared Instrumentation Grants S10RR023401 and S10OD010364. Additional support was provided by the Harvard NeuroDiscovery Center, the Martinos Center for Biomedical Imaging, Fidelity Biosciences, and Alzheimer's Association.

References

- Alcolea D, Vilaplana E, Pegueroles J, Montal V, Sánchez-Juan P, González-Suárez A, Fortea J. Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease. *Neurobiol Aging*. 2015; 36(6):2018–2023. <http://dx.doi.org/10.1016/j.neurobiolaging.2015.03.001>. [PubMed: 25865441]
- Apostolova LG, Hwang KS, Andrawis JP, Green AE, Babakchanian S, Morra JH, Thompson PM. 3D PIB and CSF biomarker associations with hippocampal atrophy in ADNI subjects. *Neurobiol Aging*. 2010; 31(8):1284–1303. <http://dx.doi.org/10.1016/j.neurobiolaging.2010.05.003>. [PubMed: 20538372]

- Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*. 1992; 42(3):631–639. <http://dx.doi.org/10.1212/WNL.42.3.631>. [PubMed: 1549228]
- Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol*. 1995; 52(1):81–88. <http://dx.doi.org/10.1001/archneur.1995.00540250089017>. [PubMed: 7826280]
- Braak H, Alafuzo I, Arzberger VT, Kretschmar H, Del K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006; 112(4):389–404. <http://dx.doi.org/10.1007/s00401-006-0127-z>. [PubMed: 16906426]
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991; 82(4):239–259. <http://dx.doi.org/10.1007/BF00308809>. [PubMed: 1759558]
- Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997; 18(4):351–357. [PubMed: 9330961]
- Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Ances BM. Tau and A β imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med*. 2016; 8(338):1–10. <http://dx.doi.org/10.1126/scitranslmed.aaf2362>.
- Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Mintun MA. Molecular, Structural, and Functional Characterization of Alzheimer's Disease: evidence for a Relationship between Default Activity, Amyloid, and Memory. *J Neurosci*. 2005; 25(34):7709–7717. <http://dx.doi.org/10.1523/JNEUROSCI.2177-05.2005>. [PubMed: 16120771]
- Chhatwal, JP., Schultz, AP., Marshall, GA., Boot, B., Isla, TG., Dumurgier, J., Bradley, T. Temporal T807 binding correlates with CSF tau and phosphotau in normal elderly. *Neurology*. 2016. <http://dx.doi.org/10.1212/WNL.0000000000003050>
- Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY, Kolb HC. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimer's Dis*. 2013; 34(2):457–468. <http://dx.doi.org/10.3233/JAD-122059>. [PubMed: 23234879]
- Csernansky JG, Hamstra J, Wang L, McKeel D, Price JL, Gado M, Morris JC. Correlations between antemortem hippocampal volume and postmortem neuropathology in AD subjects. *Alzheimer Dis Assoc Disord*. 2004; 18(4):190–195. (<http://doi.org/00002093-200410000-00006>)(pii). [PubMed: 15592129]
- Dagley, Alexander, LaPoint, Molly, Huijbers, Willem, Chhatwal, Jasmeer P., Papp, Kathryn V., Amariglio, Rebecca E., Blacker, Deborah, Rentz, Dorene M., Johnson Keith, A., Sperling, Reisa A., Schultz, AP. Harvard Aging Brain Study: dataset and accessibility. *Neuroimage*. 2015
- de Souza LC, Chupin M, Lamari F, Jardel C, Leclercq D, Colliot O, Sarazin M. CSF tau markers are correlated with hippocampal volume in Alzheimer's disease. *Neurobiol Aging*. 2012; 33(7):1253–1257. <http://dx.doi.org/10.1016/j.neurobiolaging.2011.02.022>. [PubMed: 21489655]
- Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006; 31(3):968–980. <http://dx.doi.org/10.1016/j.neuroimage.2006.01.021>. [PubMed: 16530430]
- Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Buckner RL. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex*. 2009; 19(3):497–510. <http://dx.doi.org/10.1093/cercor/bhn113>. [PubMed: 18632739]
- Fischl B. FreeSurfer. *Neuroimage*. 2012; 62:774–781. <http://dx.doi.org/10.1016/j.neuroimage.2012.01.021>. [PubMed: 22248573]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, Dale AM. Whole Brain Segmentation: neurotechnique Automated Labeling of Neuroanatomical Structures in the Human Brain. *Neuron*. 2002; 33(3):341–355. [http://dx.doi.org/10.1016/S0896-6273\(02\)00569-X](http://dx.doi.org/10.1016/S0896-6273(02)00569-X). [PubMed: 11832223]
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–198. [http://dx.doi.org/10.1016/0022-3956\(75\)90026-6](http://dx.doi.org/10.1016/0022-3956(75)90026-6). [PubMed: 1202204]

- Gómez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol*. 1997; 41(1):17–24. <http://dx.doi.org/10.1002/ana.410410106>. [PubMed: 9005861]
- Gordon, BA., Friedrichsen, K., Brier, M., Blazey, T., Su, Y., Christensen, J., Benzinger, TLS. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging; *Brain*. 2016 Sep. p. 139 <http://dx.doi.org/10.1093/brain/aww139>
- Greve DN, Salat DH, Bowen SL, Izquierdo-Garcia D, Schultz AP, Catana C, Johnson KA. Different partial volume correction methods lead to different conclusions: an 18F-FDG-PET study of aging. *NeuroImage*. 2016; 132:334–343. <http://dx.doi.org/10.1016/j.neuroimage.2016.02.042>. [PubMed: 26915497]
- Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol*. 2003; 60(5):729–736. <http://dx.doi.org/10.1001/archneur.60.5.729>. [PubMed: 12756137]
- Hampel H, Bürger K, Pruessner JC, Zinkowski R, DeBernardis J, Kerkman D, Teipel SJ. Correlation of cerebrospinal fluid levels of tau protein phosphorylated at threonine 231 with rates of hippocampal atrophy in Alzheimer disease. *Arch Neurol*. 2005; 62(5):770–773. <http://dx.doi.org/10.1001/archneur.62.5.770>. [PubMed: 15883264]
- Henneman WJP, Vrenken H, Barnes J, Sluimer IC, Verwey NA, Blankenstein MA, Van Der Flier WM. Baseline CSF p-tau levels independently predict progression of hippocampal atrophy in Alzheimer disease. *Neurology*. 2009; 73(12):935–940. <http://dx.doi.org/10.1212/WNL.0b013e3181b879ac>. [PubMed: 19770469]
- Herukka SK, Pennanen C, Soininen H, Pirttilä T. CSF Aβ42, tau and phosphorylated tau correlate with medial temporal lobe atrophy. *J Alzheimer's Dis*. 2008; 14(1):51–57. [PubMed: 18525127]
- Hulette, CM., Welsh-Bohmer, Ka, Murray, MG., Saunders, AM., Mash, DC., McIntyre, LM. Neuropathological and Neuropsychological Changes in “Normal” Aging: evidence for Preclinical Alzheimer Disease in Cognitively Normal Individuals. *J Neuropathol Exp Neurol*. 1998. <http://dx.doi.org/10.1097/00005072-199812000-00009>
- Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, Dubois B. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016 Aug. 87:539–547. [PubMed: 27371494]
- Jack CR, Knopman DS, Weigand SD, Heather J, Vemuri P, Lowe V, Petersen RC. An operational Approach to NIA-AA Criteria for Preclinical Alzheimer's Disease. *Ann Neurol*. 2012; 71(6):765–775. <http://dx.doi.org/10.1002/ana.22628>. [PubMed: 22488240]
- Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, Sperling R. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann Neurol*. 2016; 79(1): 110–119. <http://dx.doi.org/10.1002/ana.24546>. [PubMed: 26505746]
- Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, Petersen RC. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol*. 2003; 62(11):1087–1095. <http://dx.doi.org/10.1016/j.jalz.2008.05.2215>. [PubMed: 14656067]
- Marquie M, Normandin MD, Vanderburg CR, Costantino IM, Bien EA, Rycyna LG, Gómez-Isla T. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. *Ann Neurol*. 2015; 78(5):787–800. <http://dx.doi.org/10.1002/ana.24517>. [PubMed: 26344059]
- Mitchell TW, Mufson EJ, Schneider JA, Cochran EJ, Nissanol J, Han LY, Arnold SE. Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Ann Neurol*. 2002; 51(2):182–189. <http://dx.doi.org/10.1002/ana.10086>. [PubMed: 11835374]
- Mormino, EC., Papp, KV., Rentz, DM., Schultz, AP., Lapoint, M., Amariglio, R., Sperling, RA. Heterogeneity in suspected non-alzheimer disease pathophysiology among clinically normal older individuals. *JAMA Neurol*. 2016. <http://dx.doi.org/10.1001/jamaneurol.2016.2237>
- Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993; 43(11):2412–2414. <http://dx.doi.org/10.1212/WNL.43.11.2412-a>.
- Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Beach TG. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol*

Exp Neurol. 2012; 71(5):362–381. <http://dx.doi.org/10.1097/NEN.0b013e31825018f7>. [PubMed: 22487856]

Ossenkoppele R, Mattsson N, Teunissen CE, Barkhof F, Pijnenburg Y, Scheltens P, Rabinovici GD. Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. *Neurobiol Aging*. 2015; 36(8):2340–2347. <http://dx.doi.org/10.1016/j.neurobiolaging.2015.04.011>. [PubMed: 25990306]

Pontecorvo MJ, Devous MD, Navitsky M, Lu M, Salloway S, Schaerf FW, Mintun MA. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain*. 2017; 140(3):748–763. <http://dx.doi.org/10.1093/brain/aww334>. [PubMed: 28077397]

Price JL, Morris JC. Tangles and plaques in nondemented aging and “preclinical” alzheimer's disease. *Ann Neurol*. 1999; 45(3):358–368. [http://dx.doi.org/10.1002/1531-8249\(199903\)45:3<358::AID-ANA12>3.0.CO;2-X](http://dx.doi.org/10.1002/1531-8249(199903)45:3<358::AID-ANA12>3.0.CO;2-X). [PubMed: 10072051]

Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*. 2012; 61(4):1402–1418. [PubMed: 22430496]

Rousset OG, Ma Y, Evans AC. Correction for partial volume effects in PET: principle and validation. J Correction for Partial Volume Effects in PET: Principle and Validation. *J Nucl Med*. 1998; 39(5): 904–911. [PubMed: 9591599]

Sabuncu MR, Konukoglu E. Clinical prediction from Structural brain MRI scans: a large-scale empirical study. *Neuroinformatics*. 2014; 13:31–46. <http://dx.doi.org/10.1007/s12021-014-9238-1>.

Schöll M, Lockhart SN, Schonhaut DR, O'Neil JP, Janabi M, Ossenkoppele R, Jagust WJ. PET imaging of tau deposition in the aging human Brain. *Neuron*. 2016; 89(5):971–982. <http://dx.doi.org/10.1016/j.neuron.2016.01.028>. [PubMed: 26938442]

Sepulcre J, Schultz AP, Sabuncu M, Gomez-Isla T, Chhatwal X, Becker A, Johnson KA. In Vivo tau, amyloid, and gray matter profiles in the aging brain. *J Neurosci*. 2016; 36(28):7364–7374. <http://dx.doi.org/10.1523/JNEUROSCI.0639-16.2016>. [PubMed: 27413148]

Shoup TM, Yokell DL, Rice PA, Jackson RN, Livni E, Johnson A, Vasdev N. A concise radiosynthesis of the tau radiopharmaceutical, [(18)F]T807. *J Label Compd Radiopharm*. 2014; 56(14):736–740. <http://dx.doi.org/10.1002/jlcr.3098.A>.

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011; 7:280–292. <http://dx.doi.org/10.1016/j.jalz.2011.03.003>. [PubMed: 21514248]

Tapiola T, Overmyer M, Lehtovirta M, Helisalmi S, Ramberg J, Alafuzoff I, Soininen H. The level of cerebrospinal fluid tau correlates with neurofibrillary tangles in Alzheimer's disease. *Neuroreport*. 1997; 8(18):3961–3963. <http://dx.doi.org/10.1097/00001756-199712220-00022>. [PubMed: 9462474]

Thomann PA, Kaiser E, Schönknecht P, Pantel J, Essig M, Schröder J. Association of total tau and phosphorylated tau 181 protein levels in cerebrospinal fluid with cerebral atrophy in mild cognitive impairment and Alzheimer disease. *J Psychiatry Neurosci*. 2009; 34(2):136–142. [PubMed: 19270764]

Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, Toga AW. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci*. 2003; 23(3):994–1005. (<http://doi.org/23/3/994>)(pii). [PubMed: 12574429]

Tosun D, Schuff N, Shaw LM, Trojanowski JQ, Weiner MW. Relationship between CSF biomarkers of Alzheimer's disease and rates of regional cortical thinning in ADNI data. *Adv Alzheimer's Dis*. 2011; 26:77–90. <http://dx.doi.org/10.3233/978-1-60750-793-2-127>.

Vemuri P, Lowe VJ, Knopman DS, Senjem ML, Kemp BJ, Schwarz CG, Jack CR. Tau-PET uptake: regional variation in average SUVR and impact of amyloid deposition. *Alzheimer's Dement: Diagn, Assess Dis Monit*. 2017; 6:21–30. <http://dx.doi.org/10.1016/j.dadm.2016.12.010>.

Villemagne VL, Okamura N. Tau imaging in the study of ageing, Alzheimer's disease, and other neurodegenerative conditions. *Curr Opin Neurobiol*. 2016. <http://dx.doi.org/10.1016/j.conb.2015.09.002>

- Wang L, Benzinger TL, Hassenstab J, Blazey T, Owen C, Liu J, Ances BM. Spatially distinct atrophy is linked to β -amyloid and tau in preclinical Alzheimer disease. *Neurology*. 2015; 84(12):1254–1260. <http://dx.doi.org/10.1212/WNL.0000000000001401>. [PubMed: 25716355]
- Wang L, Benzinger TL, Su Y, Christensen J, Friedrichsen K, Aldea P, Ances BM. Evaluation of tau imaging in staging Alzheimer disease and Revealing interactions Between β -amyloid and Tauopathy. *JAMA Neurol*. 2016
- Wechsler, D. Manual for Wechsler memory scale - Revised. Psychol Corp. 1987. (<http://doi.org/PCA-Converted#56>)
- Xia CF, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D, Kolb HC. [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. *Alzheimer's Dement: J Alzheimer's Assoc*. 2013; 9(6):666–676. <http://dx.doi.org/10.1016/j.jalz.2012.11.008>.
- Yesavage J, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1983; 17(1):37–49. [http://dx.doi.org/10.1016/0022-3956\(82\)90033-4](http://dx.doi.org/10.1016/0022-3956(82)90033-4).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.neuroimage.2017.05.049.

Fig. 1.

Panel A shows the distribution of AV-1451 SUVRs (non partial-volume corrected) across the brain, indicating that the highest SUVRs are seen in medial and lateral temporal regions. Panel B shows the relationship between PIB-PET and AV-1451 signal across the brain at a threshold of $p < 0.05$, uncorrected. The areas with the strongest relationships are, as expected, in the medial temporal lobe, fusiform, and inferior temporal cortex.

Fig. 2.

Significant relationships between AV-1451 signal and cortical thickness. All associations $p < 0.05$ uncorrected are shown in the figure. All models controlled for age and sex. Cross-sectional models additionally controlled for the date difference between the MRI and PET sessions, while longitudinal models controlled for the interactions of age and sex with time. *Panel A* shows the significant local associations between cross-sectional cortical thickness and AV-1451 signal, which were observed most strongly in the temporal lobe. *Panel B* shows the significant associations between cross-sectional cortical thickness and inferior temporal AV-1451 signal. Widespread negative relationships were observed, with the strongest associations in temporal regions. *Panel C* shows significant local relationships between retrospective longitudinal cortical thinning and AV-1451 signal. Faster retrospective thinning was observed in the presence of higher AV-1451 in the left cuneus and banks of the left superior temporal sulcus, as well as the right superior temporal, middle temporal, fusiform, and temporal pole. Negative relationships surviving FDR correction ($p < 0.00090$) are observed in the right middle temporal and temporal pole. *Panel D* shows significant relationships between retrospective longitudinal cortical thinning and inferior temporal AV-1451 signal. Faster retrospective thinning was observed in the presence of higher AV-1451 in the right middle temporal, right fusiform, and bilateral parahippocampal cortices. The relationship in the right fusiform survives FDR correction ($p < 0.00017$).

Fig. 3.

This graph maps the rate of retrospective thinning expected in the bilateral parahippocampal cortices based on linear mixed-effects models, controlling for age and sex, both interacted with time, for three levels of inferior temporal AV-1451 signal (1.00, 1.45, and 1.9 in partial volume corrected units). With increasing levels of AV-1451, we would expect a participant to have both a faster rate of retrospective thinning and thinner cortices at baseline.

Table 1

Demographics of participants in the present study. (*) There is one case of missing APOE status. N denotes the number of participants. BL denotes baseline. M and F represent male and female, respectively, and AMNART-VIQ indicates the Verbal Intelligence Quotient from the American National Adult Reading Test, MMSE is the Mini-Mental State Examination, and CDR is the Clinical Dementia Rating.

N	103
Age (BL)	73.93 $\pm$ 6.18
Number of follow-up visits	2: N=73 3: N=30
Days between MR & AV-1451 scans	139.48 $\pm$ 161.27
Years follow-up	2.72 $\pm$ 0.74
Sex (M/F)	47/56 (54.3% F)
APOE ϵ 4 status*	ϵ 4+: N=31 ϵ 4-: N=71
Years of Education	16.10 $\pm$ 3.01
AMNART VIQ	122.86 $\pm$ 7.33
Logical Memory Delayed Recall (BL)	13.99 $\pm$ 3.42
MMSE (BL)	29.08 $\pm$ 0.96
CDR Progression	Stable CDR 0: N=93 Progressors to CDR 0.5: N=10

Table 2

Significant relationships between cortical thickness and AV-1451 signal.

Cortical region	Concurrent Cross-Sectional Cortical Thickness		Retrospective Longitudinal Cortical Thinning	
	Local tau	Inferior temporal tau	Local tau	Inferior temporal tau
lh bankssts	t(98)=-2.32 p=0.022 [#] e=-0.205	t(98)=-2.60 p=0.011 [#] e=-0.265	t(228)=-2.01; p=0.046 [#] e=-0.032	-
rh bankssts	-	t(98)=-2.59 p=0.011 [#] e=-0.251	-	-
rh caudal anterior cingulate	-	-	t(228)=-2.31; p=0.022 [#] e=0.044	-
lh caudal anterior cingulate	t(98)=-3.14 p=0.0023 ^{##} e=-0.492	-	-	-
lh caudal middle frontal	t(98)=-2.27 p=0.025 [#] e=-0.193	t(98)=-2.90; p=0.0047 ^{##} e=-0.232	-	-
rh caudal middle frontal	-	t(98)=-3.13 p=0.0023 ^{##} e=-0.214	-	-
lh cuneus	-	-	t(228)=-2.14 p=0.033 [#] e=-0.019	-
lh entorhinal	t(98)=-4.18 p=0.000064 [*] e=-0.440	t(98)=-2.22 p=0.029 [#] e=-0.502	-	-
rh entorhinal	t(98)=-3.96 p=0.00014 e=-0.438	t(98)=-3.01 p=0.0034 ^{##} e=-0.708	-	-
lh frontal pole	t(98)=3.30 p=0.0013 ^{##} e=0.301	-	-	-
lh fusiform	t(98)=-3.36 p=0.0011 ^{##} e=-0.283	t(98)=-2.66 p=0.0091 [#] e=-0.229	-	-
rh fusiform	t(98)=-4.97 p=0.0000029 ^{**} e=-0.448	t(98)=-5.531; p=0.00000027 ^{**} e=-0.494	t(228)=-2.22; p=0.027 [#] e=-0.031	t(228)=-3.82 p=0.00017 [*] e=-0.052
lh inferior parietal	t(98)=-2.32 p=0.023 [#] e=-0.212	t(98)=-2.36; p=0.020 [#] e=-0.172	-	-
rh inferior parietal	t(98)=-2.73 p=0.0075 [#] e=-0.202	t(98)=-3.82 p=0.00023 [*] e=-0.265	-	-
lh inferior temporal	t(98)=-2.67 p=0.0090 [#] e=-0.210	-	-	-
rh inferior temporal	t(98)=-3.92 p=0.00016 ^{**} e=-0.325	t(98)=-3.61; p=0.00048 [*] e=-0.326	-	-

	Concurrent Cross-Sectional Cortical Thickness		Retrospective Longitudinal Cortical Thinning	
Cortical region	Local tau	Inferior temporal tau	Local tau	Inferior temporal tau
lh insula	t(98)=-2.81 p=0.0060 ^{##} e=-0.395	-	-	-
rh insula	t(98)=-2.30 p=0.023 [#] e=-0.270	t(98)=-2.22 p=0.029 [#] e=-0.216	-	-
lh lateral occipital	-	t(98)=-2.29; p=0.024 [#] e=-0.196	-	-
rh lateral occipital	t(98)=-2.09 p=0.039 [#] e=-0.104	t(98)=-3.15 p=0.0022 ^{##} e=-0.235	-	-
rh lateral orbitofrontal	t(98)=-2.15 p=0.034 [#] e=-0.207	t(98)=-2.44; p=0.017 [#] e=-0.226		
rh lingual	t(98)=-3.30 p=0.0014 ^{##} e=-0.178	-	-	-
lh middle temporal	t(98)=-3.71 p=0.00034 [*] e=-0.354	t(98)=-3.10 p=0.0025 ^{##} e=-0.269	-	-
rh middle temporal	t(98)=-4.14 p=0.000075 ^{**} e=-0.278	t(98)=-4.96 p=0.0000029 ^{**} e=-0.357	t(228)=-3.66 p=0.00032 [*] e=-0.043	t(228)=-2.18 p=0.030 [#] e=-0.029
rh paracentral	t(98)=-2.39 p=0.019 [#] e=-0.201	-	-	-
lh parahippocampal	t(98)=-2.71 p=0.0079 [#] e=-0.377	t(98)=-2.77; p=0.0066 [#] e=-0.577	-	t(228)=-2.60 p=0.0099 [#] e=-0.049
rh parahippocampal	-	t(98)=-2.47 p=0.015 [#] e=-0.411	-	t(228)=-1.99 p=0.048 [#] e=-0.041
lh pars opercularis	t(98)=-2.80 p=0.0061 [#] e=-0.219	-	-	-
lh pars orbitalis	t(98)=-2.91 p=0.0045 ^{##} e=-0.239	-	-	-
rh pars orbitalis	t(98)=-2.12 p=0.037 [#] e=-0.207	-	-	-
lh pars triangularis	-	-	-	t(228)=1.98 p=0.049 [#] e=0.036
rh pars triangularis	t(98)=-2.52 p=0.013 [#] e=-0.203	-	-	t(228)=2.15 p=0.033 [#] e=0.036
lh precentral	-	t(98)=-2.05 p=0.043 [#] e=-0.167	-	-

	Concurrent Cross-Sectional Cortical Thickness		Retrospective Longitudinal Cortical Thinning	
Cortical region	Local tau	Inferior temporal tau	Local tau	Inferior temporal tau
rh precentral	-	t(98)=-2.31 p=0.023 [#] e=-0.190	-	-
rh precuneus	-	t(98)=-2.78 p=0.0066 [#] e=-0.213	-	-
lh rostral anterior cingulate	-	-	-	-
lh rostral middle frontal	-	-	-	-
rh rostral middle frontal	-	-	t(228)=3.37; p=0.00090 ^{##} e=0.041	t(228)=2.61 p=.0098 [#] e=0.034
rh superior frontal	-	t(98)=-3.12 p=0.0024 ^{##} e=-0.208	-	-
lh superior parietal		t(98)=-2.12 p=0.037 [#] e=-0.179	-	-
Rh superior parietal		t(98)=-2.24 p=0.027 [#] e=-0.175	-	-
lh superior temporal	-	t(98)=-3.23 p=0.0017 ^{##} e=-0.288	-	-
rh superior temporal	-	t(98)=-2.46 p=0.016 [#] e=-0.192	t(228)=-2.85 p=0.0047 ^{##} e=-0.040	-
lh supramarginal	t(98)=-2.20; p=0.030 [#] e=-0.222	t(98)=-2.53 p=0.013 [#] e=-0.191	-	-
rh supramarginal	t(98)=1.98; p=0.050 [#] e=-0.207	t(98)=-2.67 p=0.0089 [#] e=-0.220	-	-
lh temporal pole	t(98)=-4.24; p=0.000051 ^{**} e=-0.535	-	-	-
rh temporal pole	t(98)=-6.40; p=0.000000061 ^{**} e=-0.640	t(98)=-3.46 p=0.00080 ^{##} e=-0.661	t(228)=-3.74 p=0.00023 [*] e=-0.063	-
lh transverse temporal	t(98)=-2.13 p=0.036 [#] e=-0.241	-	-	-
rh transverse temporal	-	-	t(228)=2.37; p=0.018 [#] e=0.036	-
lh hippocampus	-	-	-	-
lh lateral ventricle	-	-	-	t(226)=2.22 p=0.027 [#] e=525.77
lh inferior lateral ventricle (temporal horn)	-	-	-	t(226)=2.14 p=0.034 [#] e=57.879

	Concurrent Cross-Sectional Cortical Thickness		Retrospective Longitudinal Cortical Thinning	
Cortical region	Local tau	Inferior temporal tau	Local tau	Inferior temporal tau
Total cortical gray matter volume	-	t(97)=-2.93; p=0.0042 ^{##} e=-37295	-	-

Cortical regions are listed in the first column. Left and right hemispheres are abbreviated as lh and rh, respectively. Bankssts is the banks of the superior temporal sulcus.

Significance is denoted with the following symbols:

[#]
p 0.05

^{##}
p 0.005

^{*}
p 0.0005

^{**}
p 0.00005 (all uncorrected); gray shading – survives FDR correction (local and inferior temporal cross-sectional: p 0.013; local longitudinal: p 0.00090; inferior temporal longitudinal: p 0.00017).