Published in final edited form as:

Alzheimers Dement. 2018 August ; 14(8): 1005–1014. doi:10.1016/j.jalz.2018.02.020.

Imaging correlations of tau, amyloid, metabolism and atrophy in typical & atypical AD

Jennifer L. Whitwell, PhD¹, Jonathan Graff-Radford, MD², Nirubol Tosakulwong, BS³, Stephen D. Weigand, MS³, Mary Machulda, PhD⁴, Matthew L. Senjem, MS^{1,5}, Anthony J. Spychalla, BS¹, Prashanthi Vemuri, PhD¹, David T. Jones, MD², Daniel A. Drubach, MD², David S. Knopman, MD², Bradley F. Boeve, MD², Nilüfer Ertekin-Taner, MD, PhD^{6,7}, Ronald C. Petersen, MD, PhD², Val J. Lowe, MD¹, Clifford R. Jack Jr., MD¹, and Keith A. Josephs, MD, MST, MSc²

¹Department of Radiology, Mayo Clinic, Rochester, MN

²Department of Neurology, Mayo Clinic, Rochester, MN

³Department of Health Sciences Research, Mayo Clinic, Rochester, MN

⁴Department of Psychology and Psychiatry, Mayo Clinic, Rochester, MN

⁵Department of Information Technology, Mayo Clinic, Rochester, MN

⁶Department of Neurology, Mayo Clinic, Jacksonville, FL

⁷Department of Neuroscience, Mayo Clinic, Jacksonville, FL

Abstract

INTRODUCTION—Neuroimaging modalities can measure different aspects of the disease process in Alzheimer’s disease (AD), although the relationship between these modalities is unclear.

METHODS—We assessed subject-level regional correlations between tau on [¹⁸F]AV-1451 PET, beta-amyloid on Pittsburgh Compound-B PET, hypometabolism on [¹⁸F] fluorodeoxyglucose PET, and cortical thickness on MRI in 96 participants with typical and atypical AD presentations. We

Corresponding author: Jennifer L. Whitwell, PhD, Associate Professor of Radiology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, Tel: 507-284-5576, Fax: 507-284-9778, Whitwell.jennifer@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DECLARATION OF INTEREST

We have no conflicts of interest pertaining to this manuscript. Disclosures outside the submitted work: Matthew Senjem owns stocks in Align Technology, Inc., Gilead Sciences, Globus Medical Inc., Inovio Biomedical Corp., Johnson & Johnson, LHC Group, Inc., Medtronic, Inc., Mesa Laboratories, Inc., Natus Medical Incorporated, Oncocyte, Inc., Parexel International Corporation, and Varex Imaging Corporation. Dr. Ertekin-Taner has a patent “Human Monoclonal Antibodies Against Amyloid Beta Protein” issued, and a patent “Their Use as Therapeutic Agents Application” pending. Dr. Boeve receives grants from Cephalon, Inc., Allon Therapeutics, GE Healthcare, and Mangurian Foundation. Dr. Knopman receives grants from TauRx, Baxter Pharmaceuticals, Elan Pharmaceuticals and consults for Lundbeck Pharmaceuticals. Dr. Petersen consults for Roche, Inc., Merck, Inc., Genetech, Inc., Biogen, Inc., Eli Lilly and Company. Dr. Lowe consults for Bayer Schering Pharma, Piramal Life Sciences, and receives grants from GE Healthcare, Siemens Molecular Imaging, and AVID Radiopharmaceuticals. Dr. Jack consults for Janssen, Bristol-Meyer-Squibb, GE Healthcare, Johnson & Johnson, and receives grants from Allon and Baxter, Inc, and Pfizer, Inc.

also assessed how correlations between modalities varied according to age, presenting syndrome, tau-PET severity and asymmetry.

RESULTS—[¹⁸F]AV-1451 uptake showed the strongest regional correlation with hypometabolism. Correlations between [¹⁸F]AV-1451 uptake and both hypometabolism and cortical thickness were stronger in participants with greater cortical tau severity. In addition, age, tau asymmetry and clinical diagnosis influenced the strength of the correlation between [¹⁸F]AV-1451 uptake and cortical thickness.

DISCUSSION—These findings support a close relationship between tau and hypometabolism in AD, but show that correlations between neuroimaging modalities vary across participants.

Keywords

positron emission tomography; tau; beta-amyloid; cortical thickness; Alzheimer's disease; magnetic resonance imaging; posterior cortical atrophy; logopenic aphasia

1. INTRODUCTION

Neuroimaging modalities are now available that can measure many different aspects of the disease process in Alzheimer's disease (AD). Brain structure can be assessed using structural magnetic resonance imaging (MRI), brain metabolism can be assessed using [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET), and the presence in the brain of the two cardinal proteins typically associated with AD, i.e. tau and beta-amyloid, can also now be assessed using radioactive ligands and PET imaging.

Patterns of atrophy on MRI and hypometabolism on FDG-PET have been well described in AD, with involvement of the temporoparietal lobes shown to be a relatively specific biomarker to differentiate AD from other molecular pathologies[1, 2]. However, within the spectrum of AD patterns of atrophy on MRI and metabolism on FDG-PET have been shown to vary according to clinical presentation and also age. Participants who present with early and prominent memory impairment that is considered typical for AD[3], tend to show atrophy and hypometabolism in the medial temporal lobe and temporoparietal cortices[4–6]. However, participants with a young age at onset tend to show greater involvement of the isocortex than participants that present at an older age[7–12]. Striking isocortical atrophy and hypometabolism is also observed in participants with atypical clinical presentation of AD, such as logopenic progressive aphasia[13] and posterior cortical atrophy[14]. However, in contrast to typical AD, these participants tend to show relative sparing of the medial temporal lobe[15, 16] and the patterns of cortical involvement differ, with logopenic aphasia typically showing left-sided patterns of temporoparietal atrophy and hypometabolism[15, 17, 18] and posterior cortical atrophy showing striking involvement of temporal, parietal and occipital lobes[16, 19, 20]. There is some suggestion that the pattern of cortical atrophy may also differ by age at onset in atypical AD[21]. Molecular PET imaging has shown that the regional distribution of beta-amyloid deposition is relatively consistent regardless of clinical presentation[18], with deposition in AD differing from patterns of atrophy and observed predominantly in the prefrontal and parietal cortices[22]. In contrast, patterns of tau uptake on PET imaging appear to match well with regional patterns of atrophy and hypometabolism

across typical and atypical AD participants[23–28] and normal elderly[29], with tau uptake in the isocortex also greater in early-onset compared to late-onset AD[30].

Evidence from group-level studies, therefore, suggests good concordance between patterns of tau uptake on PET and patterns of atrophy and hypometabolism in AD. However, little is known about how well these imaging modalities correlate within individual participants, and whether concordance between metrics varies by clinical presentation, age or pattern or severity of tau uptake across the brain. In addition, it is unclear whether regional patterns of tau-PET uptake correlate better with regional patterns of atrophy or hypometabolism. In this study we used a large cohort of 96 typical and atypical AD participants who underwent tau-PET imaging with [¹⁸F]AV-1451, beta-amyloid PET with Pittsburgh Compound B (PiB), MRI and FDG-PET, to assess individual-level correlations between tau-PET and the other imaging metrics, and to determine the degree to which the strength of these correlations varies across participants. Determining the relationship between these different aspects of the disease will increase understanding of the disease process in AD. It will also help us understand whether MRI and FDG-PET measures of neurodegeneration are specific for the molecular pathologies underlying AD. Unlike tau-PET, MRI and FDG-PET are both widely available and hence could prove to be very valuable biomarkers of molecular pathology for centers that do not have access to tau PET. Measures of neurodegeneration are also already being used as outcome measures in clinical treatment trials, and hence it is critically important to understand how these measures relate to underlying molecular pathologies. This knowledge will help guide the inclusion and interpretation of biomarker findings in different populations of AD participants from clinical treatment trials, particularly those that assess therapies targeting tau or beta-amyloid.

2. METHODS

2.1. Participants

We identified all participants with a clinical diagnosis of typical or atypical AD who had elevated beta-amyloid deposition on PiB-PET and had undergone [¹⁸F]AV-1451 tau-PET and 3T MRI at Mayo Clinic, Rochester, MN between 2/25/2015 and 4/12/2017. Ninety-six patients were identified, of which 55 were diagnosed with typical Alzheimer's dementia[3] and 41 were diagnosed with atypical AD because the dominant cognitive deficit was in domains other than episodic memory[31]. Of the 41 atypical AD participants, 19 were diagnosed with posterior cortical atrophy[14], 16 were diagnosed with logopenic aphasia[13], and 6 were diagnosed with behavioral/dysexecutive AD[32]. Of the 96 participants, 80% had also undergone FDG-PET (47 typical AD and 30 atypical AD). These participants had been recruited as part of an NIH-funded grant studying atypical AD (PI Whitwell) or as part of the Mayo Clinic Alzheimer's Disease Research Center (PI Petersen). All participants, regardless of recruitment mechanism, underwent a detailed neurological examination by a behavioral neurologist and diagnoses were rendered based on established clinical criteria. Clinical and neuropsychological tests that were available for analysis across both cohorts included the Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR) scale to measure functional impairment, Trail Making Tests A and B to measure attention, processing speed and mental flexibility, letter (F) and animal fluency to

assess lexical and semantic access, Auditory Verbal Learning Test (AVLT) to assess memory, and the Rey-Osterrieth (Rey-O) Complex Figure Test – Copy Trial to assess visuospatial function. Apolipoprotein E (APOE) genotyping was also performed. Demographic and clinical features of the cohort are shown in Table 1.

The study was approved by the Mayo IRB. All participants consented to research in writing; in the situation of persons with dementia, a family informant also provided written consent.

2.2. Image acquisition

All PET scans were acquired using a GE PET/CT scanner. For tau-PET, participants were injected with approximately 370MBq (range 333–407 MBq) of [^{18}F]AV-1451, followed by a 20-minute PET acquisition performed 80 minutes after injection. For PiB-PET, participants were injected with PiB of approximately 628 MBq (range, 385–723 MBq) and after a 40-to-60-minute uptake period a 20-minute PiB scan was obtained. For FDG-PET, participants were injected with 18F-FDG of approximately 459 MBq (range 367–576 MBq) and after a 30-minute uptake period an 8-minute 18F-FDG scan was performed. Partial volume correction (PVC) was performed on all PET data using the two-compartment (Meltzer) method with an assumed point spread function of 6mm full width at half maximum[33]. Emission data was reconstructed into a 256×256 matrix with a 30-cm FOV (Pixel size=1.0mm, slice thickness=1.96mm). All participants underwent a 3T MPRAGE, as previously described[22].

2.3. Image analysis

Regional metrics were calculated for each neuroimaging modality (tau-PET, PiB-PET, MRI and FDG-PET) for the same set of 74 cortical regions-of-interest (ROIs) covering all major lobes of the brain (see Supplementary Table 1 for full list) using the automated anatomical labelling (AAL)[34] atlas.

Each PET scan for a participant was co-registered to the participants MPRAGE using 6-degree-of-freedom rigid body registration. The AAL atlas was then transformed into the native space of each MPRAGE and used to calculate regional values. Median [^{18}F]AV-1451 uptake, PiB-PET uptake and FDG-PET metabolism were calculated across the grey and white matter in each ROI. [^{18}F]AV-1451 and PiB-PET values for each ROI were divided by uptake in the cerebellar crus, and FDG-PET values were divided by uptake in the pons, to create standard uptake value ratios (SUVRs). Regional data was generated from the PET scans both with and without PVC. For the MRI analysis, Freesurfer version 5.3.0[35, 36] was used to calculate cortical thickness for the 74 ROIs in the AAL atlas.

For inclusion in the study, participants were considered to have beta-amyloid deposition on PiB-PET if the global PiB SUVR, calculated as previously described[22], was greater than 1.42[37].

2.4. Statistical analyses

Participant characteristics and clinical features were compared between typical and atypical AD groups using Wilcoxon rank sum tests or Fisher exact tests as appropriate. All regional

neuroimaging data were Z scored using a reference data set of 105 amyloid-negative clinically unimpaired young participants (aged 30–49 with 41% female) recruited from the Mayo Clinic Study of Aging, as previously reported [38]. Z scores for an individual within an ROI were calculated in the usual manner as $Z = (\text{observed value} - \text{mean of reference data set}) / \text{standard deviation of reference data set}$. For each participant, we measured the strength of the association between a pair of imaging modalities by calculating within-participant Spearman rank correlations between an individual's Z scores across all ROIs for one modality versus the Z scores across all ROIs for another modality. With four modalities, we ended up with six correlation estimates for each individual which were then further analyzed. We note that since *higher* values of amyloid PET and tau PET indicate worse pathology while *lower* values of FDG PET and cortical thickness indicate worse pathology, we corrected for the resulting inverse associations by multiplying FDG and cortical thickness by -1 prior to calculating the rank correlations. We compared the strength of the associations in typical AD versus atypical AD using Wilcoxon rank sum/Mann-Whitney U tests. Within a group, we also compared modality pairs by estimating how often a participant's correlation estimate was higher for one modality pair versus another and performed a test of proportions under the null hypothesis of a 50% chance. Estimates, 95% confidence intervals, and hypothesis tests for these within-group comparisons were based on including one additional success and one addition failure to stabilize estimates and reduce the potential for artefactual findings[39]. We used a false discovery rate (FDR) adjustment to the resulting p-values. We performed a sensitivity analysis to determine the effects of the selection of brain regions on the correlations between tau-PET/FDG-PET, tau-PET/MRI-thickness, and tau-PET/PiB-PET by randomly removing 10 ROIs (5 left+5 right ROIs) and re-calculating the correlation estimates for each subject. The process was repeated 100 times and resulted in 100 estimates for each subject.

We were also interested in determining factors associated with stronger versus weaker associations for the three tau-PET modality pairs: tau-PET/MRI-thickness, tau-PET/FDG-PET, and tau-PET/PiB-PET. We treated the within-participant modality pair correlation as the dependent variable/response and considered the following primary predictors: (a) age at scan, (b) APOE $\epsilon 4$, (c) a participant's "tau severity" defined as the average of the individual's tau PET Z scores across ROIs; (d) a participant's "tau asymmetry" defined as the average absolute difference between left and right side tau Z scores across ROIs, and (e) clinical diagnosis. In each regression model, we rescaled covariates so that the regression coefficients were more interpretable and based on a clinically meaningful comparison. For example, rather than reporting the difference in mean correlation for a one-year difference in age, we report the effect for a 10-year difference in age. Since our severity and asymmetry measures are not in easily interpretable units, we report a difference based on contrasting individuals at the upper quartile (75th percentile) versus those at the lower quartile (25th percentile). As a secondary question, we assessed two clinical measures of disease severity (CDR-SB and MMSE) as predictors which were modeled separately. We report the effect of a 5-point difference in MMSE or a 5-point difference in CDR-SB.

All analyses were performed using PET data without PVC. However, a confirmatory analysis was performed using PET data that had undergone PVC. All analyses were

performed with R statistical software version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1. Comparison of the six modality-pair correlations

The strength of the correlations between modality pairs across typical and atypical AD participants are shown in Figure 1. The strongest correlation was observed between tau-PET and FDG-PET in both typical and atypical AD. The correlation between tau-PET and FDG-PET was significantly greater than the correlation between all other modality pairs in both typical and atypical AD (Table 2). Our sensitivity analysis assessing the influence of region selection showed that the probability [95% CI] of tau-PET having a stronger correlation to FDG-PET than MRI-thickness across the 100 repeats was 88% [88, 89%]. The poorest correlation was observed between PiB-PET and MRI-thickness, with this correlation being significantly lower than the correlations for nearly all other modality pairs in typical AD and atypical AD. MRI-thickness showed a stronger correlation with tau-PET than FDG-PET in typical AD. After PVC correction of the PET data, the tau-PET/FDG-PET correlation was still the strongest correlation, and was significantly greater than the tau-PET/MRI-thickness correlation in both typical and atypical AD (Supplementary Figure 1 and Supplementary Table 2).

All pair-wise correlations were greater in atypical AD compared to typical AD ($p < 0.05$), except for the correlations between PiB-PET and both tau-PET and FDG-PET. These results were the same in the PVC analysis.

3.2. Multivariate associations with tau-PET modality-pair correlations

Age, tau severity, tau asymmetry, clinical diagnosis (typical vs. atypical AD), and APOE $\epsilon 4$ carrier status were entered into a multivariate model (Table 3). Younger age and greater tau severity were associated with higher tau-PET/MRI-thickness correlations, and greater asymmetry was associated with lower tau-PET/MRI-thickness correlations (Figure 2). The tau-PET/FDG-PET correlation was associated with tau severity, with greater tau severity associated with higher correlations between this modality pair (Figure 2). There was a trend for both the tau-PET/MRI-thickness and tau-PET/FDG-PET correlations to be associated with clinical diagnosis. Younger age was associated with higher correlations between tau-PET and PiB-PET. Neither CDR-SB nor MMSE were associated with any of the pair-wise correlations when they were each added separately to the models. These results were unchanged in the PVC analysis.

4. DISCUSSION

This study assessed correlations across a large number of brain ROIs between four different neuroimaging modalities in typical and atypical AD, and demonstrated that the regional distribution of tau-PET correlates better with the regional distribution of FDG-PET hypometabolism than with cortical thickness or beta-amyloid deposition on PiB-PET. However, we show that the strength of these correlations are not uniform across participants,

but vary by age as well as with the severity and asymmetry of tau deposition in individual participants.

The finding of a strong correlation between the regional patterns of tau uptake on [¹⁸F]AV-1451 PET and hypometabolism on FDG-PET concurs with two previous studies that have also shown strong regional correlations between these two metrics in AD[23, 27], and supports a relationship between these two processes. We also add to previous findings by demonstrating that the correlation between these metrics is strong in both typical and atypical AD. The fact that tau-PET uptake correlates better with hypometabolism compared to beta-amyloid deposition is also somewhat expected given that regional patterns of beta-amyloid deposition differ from regional patterns of tau deposition at autopsy[40]. However, a novel and surprising finding from our study was that the regional correlation between tau uptake and cortical thickness was poorer than the correlation between tau uptake and hypometabolism. This could be interpreted to indicate that cortical thickness is less sensitive than FDG-PET to the effects of tau pathology in AD. This is surprising since autopsy studies that have typically shown good correlations between tau measures and brain atrophy in typical and atypical AD[41–45]. A couple of previous studies have also observed good correlations between regional tau-PET uptake and atrophy [24, 25], although these correlations were only assessed in a small number of participants. Our findings may reflect differences in the ordering of biomarkers in AD. It has been suggested by some studies that abnormalities on FDG-PET may occur before structural changes in the brain in AD[46, 47], and hence potentially closer in time to the deposition of tau; perhaps relating to the better correlations observed in our study. Autopsy studies that have shown good correlations between tau burden and atrophy are typically assessing MRI performed at late stages of the disease. Given this hypothesis, it is possible that tau uptake may show better correlations to cortical thickness later in the disease in AD. However, we cannot rule out the possibility that methodological factors may be contributing; PET scans may share commonalities and regional sensitivities that make them inherently correlate better.

Importantly, we found that the correlations between regional tau-PET uptake and the other neuroimaging modalities were not consistent across participants. The overall severity of tau-PET uptake was an important factor in determining the strength of the correlations between tau uptake and both hypometabolism and cortical thickness, with stronger correlations observed in participants with greater tau severity. Conversely, participants with less cortical tau did not show good correlations between the regional distribution of tau uptake and hypometabolism or cortical thickness. This could suggest that there are some AD participants with atrophy or hypometabolism but little associated tau, or it could be because participants with little tau also have little neurodegeneration and then the observed correlations may be more affected by measurement noise. Participants with striking tau uptake likely also have striking hypometabolism and atrophy which appear to correlate topographically. The participant's age at PET scan was another important factor, with older participants showing poorer correlations between tau-PET and cortical thickness. This may be due to the contribution of other co-morbidities which occur in older participants and influence atrophy measures, such as vascular disease, grain's disease or possibly the presence of the protein TDP-43[48]. Our data suggest that tau may instead play a more direct role in determining atrophy in young-onset AD participants. Younger age was also

unexpectedly associated with higher correlations between tau and beta-amyloid uptake. It is possible that the topographic relationship between the two proteins was better in the younger subjects because these subjects are more likely to show tau in cortical regions[30] that may overlap with beta-amyloid distribution, such as parietal and frontal lobes.

We also analyzed the role of tau asymmetry given that asymmetric patterns of atrophy and hypometabolism can be observed in AD, and it is unknown whether this asymmetry correlates well across the different neuroimaging metrics. We found that asymmetry in tau uptake was only related to the strength of the regional correlation between tau uptake and cortical thickness, with greater asymmetry related to weaker correlations between these metrics. This finding may be telling us that asymmetry is not represented similarly in tau-PET and MRI-thickness; this was not the case for tau-PET and FDG-PET.

Generally we found that relationships across the different modality correlations were similar in atypical and typical variants of AD, despite the fact that they typically show different patterns of brain atrophy, hypometabolism and tau-PET uptake[23]. However, clinical diagnosis was related to the strength of the correlations, with regional correlations between tau uptake and both cortical thickness and hypometabolism stronger in atypical AD compared to typical AD. Clinical diagnosis was significant at trend level in the multi-variate models when other factors, such as age, tau severity and tau asymmetry were taken into account, demonstrating that differences in correlation strength between clinical diagnoses was not driven solely by differences in these other variables. We did not find any evidence that the strength of the modality correlations were associated with general clinical disease severity, despite the fact that typical AD participants performed worse on measures of disease severity.

An issue to consider when interpreting our findings is that the identification of a correlation between modalities may allow us to generate hypotheses, but does not allow us to draw conclusions on causation. For example, we cannot address the hypothesis that tau deposition causes hypometabolism, which later results in reductions in cortical thickness; as the data may suggest. Longitudinal study designs assessing regional patterns of abnormalities and correlations between these modalities starting at the very earliest stage of the disease may be needed to help understand the course of events in AD.

The strength of our study was the large number of participants and individual-level design which allowed us to assess the factors underlying variability in neuroimaging correlations. In addition, we performed analyses both with and without partial volume correction, and performed a sensitivity analysis to show that our findings are not driven by the selection of ROIs. A limitation was that not all our participants underwent FDG-PET scanning, although the proportion of participants with FDG-PET did not differ between typical and atypical AD and age, tau severity and tau asymmetry were quantitatively similar between the FDG-only cohort and the full cohort. Another potential limitation is that our measure of tau severity was calculated across all the ROIs in the study and hence may not be sensitive to capture severity in subjects with very focal patterns of [¹⁸F]AV-1451 uptake. We would also like to point out that our analysis was focused on assessing correlations across regions within-participants and hence we cannot draw any conclusions about which regions of the brain

showed the strongest correlations between metrics. A previous study in 10 subjects with AD observed similar correlations between FDG-PET and [^{18}F]AV-1451 across all four lobes of the brain[27].

In summary, the findings of this study suggest that the deposition of hyperphosphorylated tau in the brain of patients with AD is more closely related to hypometabolism than reductions in cortical thickness. However, the strength of the relationship between tau deposition and the other metrics, particularly MRI thickness, depends on the patient's age, the degree of tau deposition and asymmetry and the clinical syndrome. These findings have implications for the utility of FDG-PET and MRI thickness as indicators of tau pathology in AD and the results should be taken into consideration when planning outcome measures for clinical treatment trials in AD, particularly those using therapies that target tau.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health (grant numbers R01-AG50603, R21-NS94684, P50 AG16574, U01 AG006786, R01 AG11378, R01 AG041851, RF1 AG051504, U01 AG046139, and R01 NS080820) and the Elsie and Marvin Dekelboum Family Foundation. The sponsors played no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

We would like to acknowledge AVID Radiopharmaceuticals for provision of AV-1451 precursor, chemistry production advice and oversight, and FDA regulatory cross-filing permission and documentation needed for this work.

References

1. Whitwell JL, Jack CR Jr, Przybelski SA, Parisi JE, Senjem ML, Boeve BF, et al. Temporoparietal atrophy: a marker of AD pathology independent of clinical diagnosis. *Neurobiol Aging*. 2011; 32:1531–41. [PubMed: 19914744]
2. Lehmann M, Rohrer JD, Clarkson MJ, Ridgway GR, Scallan RI, Modat M, et al. Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease. *J Alzheimers Dis*. 2010; 20:587–98. [PubMed: 20182057]
3. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:263–9. [PubMed: 21514250]
4. Whitwell JL, Shiung MM, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, et al. MRI patterns of atrophy associated with progression to AD in amnesic mild cognitive impairment. *Neurology*. 2008; 70:512–20. [PubMed: 17898323]
5. Foster NL, Chase TN, Mansi L, Brooks R, Fedio P, Patronas NJ, et al. Cortical abnormalities in Alzheimer's disease. *Ann Neurol*. 1984; 16:649–54. [PubMed: 6335378]
6. Baron JC, Chetelat G, Desgranges B, Percey G, Landeau B, de la Sayette V, et al. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage*. 2001; 14:298–309. [PubMed: 11467904]
7. Dickerson BC, Brickhouse M, McGinnis S, Wolk DA. Alzheimer's disease: The influence of age on clinical heterogeneity through the human brain connectome. *Alzheimers Dement (Amst)*. 2017; 6:122–35. [PubMed: 28239637]

8. Frisoni GB, Testa C, Sabattoli F, Beltramello A, Soininen H, Laakso MP. Structural correlates of early and late onset Alzheimer's disease: voxel based morphometric study. *J Neurol Neurosurg Psychiatry*. 2005; 76:112–4. [PubMed: 15608008]
9. Moller C, Vrenken H, Jiskoot L, Versteeg A, Barkhof F, Scheltens P, et al. Different patterns of gray matter atrophy in early- and late-onset Alzheimer's disease. *Neurobiol Aging*. 2013; 34:2014–22. [PubMed: 23561509]
10. Kim EJ, Cho SS, Jeong Y, Park KC, Kang SJ, Kang E, et al. Glucose metabolism in early onset versus late onset Alzheimer's disease: an SPM analysis of 120 patients. *Brain*. 2005; 128:1790–801. [PubMed: 15888536]
11. Mosconi L, Herholz K, Prohovnik I, Nacmias B, De Cristofaro MT, Fayyaz M, et al. Metabolic interaction between ApoE genotype and onset age in Alzheimer's disease: implications for brain reserve. *J Neurol Neurosurg Psychiatry*. 2005; 76:15–23. [PubMed: 15607989]
12. Ishii K, Kawachi T, Sasaki H, Kono AK, Fukuda T, Kojima Y, et al. Voxel-based morphometric comparison between early- and late-onset mild Alzheimer's disease and assessment of diagnostic performance of z score images. *AJNR Am J Neuroradiol*. 2005; 26:333–40. [PubMed: 15709131]
13. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011; 76:1006–14. [PubMed: 21325651]
14. Crutch SJ, Schott JM, Rabinovici GD, Murray M, Snowden JS, van der Flier WM, et al. Consensus classification of posterior cortical atrophy. *Alzheimers Dement*. 2017; 13:870–84. [PubMed: 28259709]
15. Madhavan A, Whitwell JL, Weigand SD, Duffy JR, Strand EA, Machulda MM, et al. FDG PET and MRI in Logopenic Primary Progressive Aphasia versus Dementia of the Alzheimer's Type. *PLoS One*. 2013; 8:e62471. [PubMed: 23626825]
16. Whitwell JL, Jack CR Jr, Kantarci K, Weigand SD, Boeve BF, Knopman DS, et al. Imaging correlates of posterior cortical atrophy. *Neurobiol Aging*. 2007; 28:1051–61. [PubMed: 16797786]
17. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004; 55:335–46. [PubMed: 14991811]
18. Rabinovici GD, Jagust WJ, Furst AJ, Ogar JM, Racine CA, Mormino EC, et al. Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol*. 2008; 64:388–401. [PubMed: 18991338]
19. Singh TD, Josephs KA, Machulda MM, Drubach DA, Apostolova LG, Lowe VJ, et al. Clinical, FDG and amyloid PET imaging in posterior cortical atrophy. *J Neurol*. 2015; 262:1483–92. [PubMed: 25862483]
20. Whitwell JL, Graff-Radford J, Singh TD, Drubach DA, Senjem ML, Spychalla AJ, et al. 18F-FDG PET in Posterior Cortical Atrophy and Dementia with Lewy Bodies. *J Nucl Med*. 2017; 58:632–8. [PubMed: 27688479]
21. Suarez-Gonzalez A, Lehmann M, Shakespeare TJ, Yong KXX, Paterson RW, Slattery CF, et al. Effect of age at onset on cortical thickness and cognition in posterior cortical atrophy. *Neurobiol Aging*. 2016; 44:108–13. [PubMed: 27318138]
22. Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain*. 2008; 131:665–80. [PubMed: 18263627]
23. Ossenkoppele R, Schonhaut DR, Scholl M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*. 2016; 139:1551–67. [PubMed: 26962052]
24. Xia C, Makaretz SJ, Caso C, McGinnis S, Gomperts SN, Sepulcre J, et al. Association of In Vivo [18F]AV-1451 Tau PET Imaging Results With Cortical Atrophy and Symptoms in Typical and Atypical Alzheimer Disease. *JAMA Neurol*. 2017; 74:427–36. [PubMed: 28241163]
25. Nasrallah IM, Chen YJ, Hsieh MK, Philips JS, Ternes K, Stockbower G, et al. 18F-Flortaucipir PET-MRI correlations in non-amnesic and amnesic variants of Alzheimer Disease. *J Nucl Med*. 2017

26. Day GS, Gordon BA, Jackson K, Christensen JJ, Rosana Ponisio M, Su Y, et al. Tau-PET Binding Distinguishes Patients With Early-stage Posterior Cortical Atrophy From Amnesic Alzheimer Disease Dementia. *Alzheimer Dis Assoc Disord*. 2017; 31:87–93. [PubMed: 28394771]
27. Bischof GN, Jessen F, Fliessbach K, Dronse J, Hammes J, Neumaier B, et al. Impact of tau and amyloid burden on glucose metabolism in Alzheimer's disease. *Ann Clin Transl Neurol*. 2016; 3:934–9. [PubMed: 28097205]
28. Dronse J, Fliessbach K, Bischof GN, von Reutern B, Faber J, Hammes J, et al. In vivo Patterns of Tau Pathology, Amyloid-beta Burden, and Neuronal Dysfunction in Clinical Variants of Alzheimer's Disease. *J Alzheimers Dis*. 2017; 55:465–71. [PubMed: 27802224]
29. Hanseeuw BJ, Betensky RA, Schultz AP, Papp KV, Mormino EC, Sepulcre J, et al. Fluorodeoxyglucose metabolism associated with tau-amyloid interaction predicts memory decline. *Ann Neurol*. 2017; 81:583–96. [PubMed: 28253546]
30. Cho H, Choi JY, Lee SH, Lee JH, Choi YC, Ryu YH, et al. Excessive tau accumulation in the parieto-occipital cortex characterizes early-onset Alzheimer's disease. *Neurobiol Aging*. 2017; 53:103–11. [PubMed: 28254589]
31. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014; 13:614–29. [PubMed: 24849862]
32. Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, et al. The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. *Brain*. 2015; 138:2732–49. [PubMed: 26141491]
33. Meltzer CC, Leal JP, Mayberg HS, Wagner HN Jr, Frost JJ. Correction of PET data for partial volume effects in human cerebral cortex by MR imaging. *J Comput Assist Tomogr*. 1990; 14:561–70. [PubMed: 2370355]
34. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 2002; 15:273–89. [PubMed: 11771995]
35. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97:11050–5. [PubMed: 10984517]
36. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999; 9:195–207. [PubMed: 9931269]
37. Jack CR Jr, Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement*. 2017; 13:205–16. [PubMed: 27697430]
38. Vemuri P, Lowe VJ, Knopman DS, Senjem ML, Kemp BJ, Schwarz CG, et al. Tau-PET uptake: Regional variation in average SUVR and impact of amyloid deposition. *Alzheimers Dement (Amst)*. 2017; 6:21–30. [PubMed: 28138510]
39. Agresti A, Coull BA. Approximate is better than 'exact' for interval estimation of binomial proportions. *The American Statistician*. 1998; 52:119–26.
40. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta neuropathologica*. 1991; 82:239–59. [PubMed: 1759558]
41. Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, et al. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. *Neurology*. 2008; 71:743–9. [PubMed: 18765650]
42. Josephs KA, Dickson DW, Murray ME, Senjem ML, Parisi JE, Petersen RC, et al. Quantitative neurofibrillary tangle density and brain volumetric MRI analyses in Alzheimer's disease presenting as logopenic progressive aphasia. *Brain Lang*. 2013
43. Whitwell JL, Dickson DW, Murray ME, Weigand SD, Tosakulwong N, Senjem ML, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurol*. 2012; 11:868–77. [PubMed: 22951070]
44. Gefen T, Gasho K, Rademaker A, Lalehzari M, Weintraub S, Rogalski E, et al. Clinically concordant variations of Alzheimer pathology in aphasic versus amnesic dementia. *Brain*. 2012; 135:1554–65. [PubMed: 22522938]

45. Jack CR Jr, Dickson DW, Parisi JE, Xu YC, Cha RH, O'Brien PC, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology*. 2002; 58:750–7. [PubMed: 11889239]
46. Insel PS, Ossenkoppele R, Gessert D, Jagust W, Landau S, Hansson O, et al. Time to Amyloid Positivity and Preclinical Changes in Brain Metabolism, Atrophy, and Cognition: Evidence for Emerging Amyloid Pathology in Alzheimer's Disease. *Front Neurosci*. 2017; 11:281. [PubMed: 28567001]
47. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–28. [PubMed: 20083042]
48. Josephs KA, Whitwell JL, Weigand SD, Murray ME, Tosakulwong N, Liesinger AM, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. *Acta Neuropathol*. 2014; 127:811–24. [PubMed: 24659241]
49. Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimers Dement*. 2013; 9:529–37. [PubMed: 23260866]

HIGHLIGHTS

- Regional AV-1451 uptake correlates better with hypometabolism than atrophy in AD
- Correlations between AV-1451 and the other metrics varied across participants
- Age, tau severity, tau asymmetry and clinical syndrome influenced correlation strength

RESEARCH IN CONTEXT

Systemic review

The authors reviewed literature using PubMed that had assessed correlations between tau PET uptake and other neuroimaging modalities in Alzheimer's disease (AD). A few publications have suggested close concordance between tau uptake on PET imaging and both hypometabolism on FDG-PET and atrophy on MRI. However, little is known about how these imaging modalities correlate within individual participants, and whether concordance varies across participants.

Interpretation

Our findings show that tau uptake correlates best with hypometabolism but that concordance between metrics varies across participants; with correlation strength varying by age, clinical diagnosis and tau severity.

Future directions

These findings have implications for the utility of FDG-PET and MRI as indicators of tau pathology in AD and for the inclusion of these imaging metrics as outcome measures in clinical trials. Future work will be needed to characterize the longitudinal relationship between these neuroimaging metrics at different stages of the disease.

Figure 1.
Box-plots showing the group-level strength of the correlations between each modality pair

Figure 2.

Scatter-plots showing the relationship between pair-wise modality correlations and age, tau severity and tau asymmetry

Table 1

Demographic and clinical features of the typical and atypical AD cohorts

	Typical AD (n = 55)	Atypical AD (n = 41)	P-values
No. Female, n (%)	28 (51%)	26 (63%)	0.30
APOE ε4 carrier	38 (75%)	14 (48%)	0.03
Age at PET, yrs	71.6 [63.4, 78.2]	63.8 [58.8, 71.5]	0.01
Age at onset, yrs	64.0 [56.3, 70.6]	60.1 [56.0, 65.0]	0.09
Disease duration, yrs	5.5 [4.0, 7.2]	3.8 [2.0, 5.0]	<0.001
Montreal Cognitive Assessment Battery	13.0 [9.0, 17.0]	18.0 [10.0, 22.0]	0.02
Mini-Mental State Examination	21 [16, 24]	24 [18, 26]	0.03
Clinical Dementia Rating Scale Sum of Boxes	5.8 [3.1, 9.0]	3.0 [1.5, 4.8]	0.005
Letter fluency (F)	10.0 [6.0, 16.0]	11.0 [8.0, 13.2]	0.80
Animal fluency	11.0 [8.0, 17.0]	13.0 [8.0, 17.5]	0.74
Trail Making Test A MOANS	9.0 [7.0, 10.0]	6.0 [2.0, 8.0]	0.01
Trail Making Test B MOANS	7.0 [2.0, 8.0]	5.0 [2.0, 8.0]	0.51
AVLT Delayed % Recall MOANS	4.0 [3.0, 5.2]	7.0 [5.0, 9.8]	<0.001
Rey-Osterrieth Complex Figure Test MOANS	7.0 [2.0, 10.0]	2.5 [2.0, 6.8]	0.050
Global PiB SUVRs	2.61 [2.37, 2.81]	2.37 [2.14, 2.57]	0.001
No. with FDG-PET	47 (85%)	30 (73%)	0.20

Data shown are n (%) or median [IQR]. P-values are from Fisher's Exact Test or Wilcoxon Rank Sum Test. Neuropsychological test scores are shown as Mayo's Older Americans Normative (MOANS) age-adjusted scores which are constructed to have a mean of 10 and standard deviation of 3 among cognitively healthy participants. APOE = apolipoprotein E; AVLT = Auditory Verbal Learning Test; SUVR = standard uptake value ratio

Montreal Cognitive Assessment Battery data of 20 atypical AD were converted into MMSE using measures based upon equipercntile equating in 321 AD, 126 MCI and 140 older adults with healthy cognition[49]. Equivalent scores were derived from equipercntile equating with log-linear smoothing.

Table 2

Probability that the correlations between one modality pair are greater than another modality pair

Correlations being compared Correlation 1	Correlation 2	Typical AD		Atypical AD	
		Probability (95% CI)	FDR adjusted P-value	Probability (95% CI)	FDR adjusted P-value
Tau-PET vs. FDG-PET	Tau-PET vs. MRI-thickness	0.81 (0.67, 0.90)	<0.001	0.94 (0.80, 0.98)	<0.001
Tau-PET vs. FDG-PET	FDG-PET vs. MRI-thickness	0.94 (0.83, 0.98)	<0.001	0.97 (0.85, 0.99)	<0.001
Tau-PET vs. FDG-PET	Tau-PET vs. PiB-PET	0.87 (0.74, 0.94)	<0.001	0.94 (0.80, 0.98)	<0.001
Tau-PET vs. FDG-PET	FDG-PET vs. PiB-PET	0.80 (0.67, 0.89)	<0.001	0.91 (0.76, 0.97)	<0.001
Tau-PET vs. FDG-PET	PiB-PET vs. MRI-thickness	0.93 (0.82, 0.98)	<0.001	0.97 (0.85, 0.99)	<0.001
Tau-PET vs. MRI-thickness	FDG-PET vs. MRI-thickness	0.66 (0.52, 0.78)	0.04	0.58 (0.41, 0.73)	0.44
Tau-PET vs. MRI-thickness	Tau-PET vs. PiB-PET	0.50 (0.37, 0.63)	>0.99	0.58 (0.43, 0.72)	0.43
Tau-PET vs. MRI-thickness	FDG-PET vs. PiB-PET	0.32 (0.20, 0.47)	0.02	0.52 (0.35, 0.67)	0.86
Tau-PET vs. MRI-thickness	PiB-PET vs. MRI-thickness	0.81 (0.68, 0.89)	<0.001	0.93 (0.81, 0.98)	<0.001
FDG-PET vs. MRI-thickness	Tau-PET vs. PiB-PET	0.45 (0.32, 0.60)	0.59	0.52 (0.35, 0.67)	0.86
FDG-PET vs. MRI-thickness	FDG-PET vs. PiB-PET	0.27 (0.16, 0.42)	0.004	0.42 (0.27, 0.59)	0.44
FDG-PET vs. MRI-thickness	PiB-PET vs. MRI-thickness	0.64 (0.49, 0.76)	0.08	0.82 (0.66, 0.91)	<0.001
Tau-PET vs. PiB-PET	FDG-PET vs. PiB-PET	0.26 (0.16, 0.40)	0.002	0.42 (0.27, 0.59)	0.44
Tau-PET vs. PiB-PET	PiB-PET vs. MRI-thickness	0.73 (0.60, 0.83)	0.002	0.74 (0.60, 0.85)	0.003
FDG-PET vs. PiB-PET	PiB-PET vs. MRI-thickness	0.95 (0.85, 0.99)	<0.001	0.73 (0.56, 0.85)	0.02

Table 3

Linear regression analysis investigating factors that are associated with the strength of the within-participant regional correlation between tau-PET and the other neuroimaging modalities

Effects	Tau-PET vs. MRI-thickness		Tau-PET vs. FDG-PET		Tau-PET vs. PIB-PET	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age at PET	-0.06 (-0.11, -0.007)	0.03	0.01 (-0.05, 0.08)	0.74	-0.09 (-0.17, -0.003)	0.04
APOE ε4 carrier	-0.02 (-0.10, 0.05)	0.55	-0.05 (-0.15, 0.05)	0.30	-0.02 (-0.14, 0.10)	0.78
Average Tau Severity / (Q3 vs Q1) *	0.12 (0.05, 0.18)	<0.001	0.11 (0.03, 0.20)	0.01	0.003 (-0.11, 0.11)	0.96
Average Tau Asymmetry / (Q3 vs Q1) *	-0.05 (-0.10, -0.01)	0.01	0.03 (-0.02, 0.09)	0.19	0.03 (-0.04, 0.09)	0.43
Clinical diagnosis	0.08 (-0.004, 0.15)	0.06	0.09 (-0.01, 0.19)	0.08	-0.03 (-0.16, 0.09)	0.62

* The difference in mean correlation comparing individuals at the third quartile versus individuals at the first quartile of the distribution of severity or asymmetry.

Age at PET is centered at mean 68 and divided by 10. Clinical diagnosis = atypical versus typical AD. Estimates and 95% CIs are for the regression coefficients from a linear regression model and can be interpreted as the estimated difference in mean within-subject correlation coefficient. Positive regression coefficients indicate an increase in the covariate is associated with a stronger relationship between the modalities.