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Contribution of Myelin Content to the PET-Measured Amyloid Burden

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Off-target binding to white matter myelin is well established in amyloid-β (Aβ) PET. Whether tracer binding to intracortical myelin influences cortical PET quantification remains unknown. We tested whether accounting for myelin water fraction (MWF), an MRI measure of myelin, improves the correlation between Aβ PET and the Alzheimer disease (AD) plasma biomarker phosphorylated tau 217 (p-tau217). **Methods:** This study included 114 participants with and without AD who underwent Aβ PET with ^{11}C-Pittsburgh compound B (n = 60) or ^{18}F-florbetaben (n = 54), multiecho fast T2 MRI to quantify MWF, and semiquantitative in vitro diagnostic immunoassay to measure plasma p-tau217 levels. Cortical Aβ burden was quantified using SUV ratio and Centiloids. Nested regression models predicted PET signal using age and p-tau217 level, with and without cortical MWF. **Results:** MWF independently predicted PET-measured Aβ signal and improved model fit by approximately 6% in both the combined and tracer-specific cohorts. **Conclusion:** Intracortical myelin contributes to Aβ PET signal. Incorporating MWF may improve Aβ PET quantification, with implications for AD diagnosis, patient selection, and monitoring response to anti-Aβ therapies.

Key Words: amyloid PET; cortical myelin; plasma biomarker; antiamyloid therapy; myelin water fraction

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Cortical amyloid-β (Aβ) accumulation is a defining pathologic feature of Alzheimer disease (AD) and the therapeutic target for newly Food and Drug Administration–approved monoclonal antibodies that remove Aβ. Eligibility for treatment with these agents requires confirmation of Aβ positivity, and continuation of treatment is dependent on quantification of Aβ reduction (*1*). Although estimates of cortical Aβ accumulation can be made on the basis of cerebrospinal fluid and, more recently, plasma assessments, PET is considered one of the most direct and accurate in vivo methods for assessing Aβ burden.

However, multiple studies have demonstrated that Aβ PET does not perfectly correlate with Aβ deposition measured at autopsy (*2–6*), as Aβ PET can both underestimate and overestimate regional Aβ plaque concentrations. This inaccuracy has important clinical consequences: overestimation may lead to inappropriate treatment with potentially harmful anti-Aβ agents, whereas underestimation could deny patients access to potentially beneficial therapies. Although some causes of Aβ PET–neuropathology mismatch (e.g., delays between imaging and autopsy, inherent technical differences between in vivo and postmortem methods) cannot easily be addressed, it is plausible that multimodal integration of Aβ PET with MRI could overcome limitations inherent to Aβ PET to improve the accuracy of Aβ burden quantification. Virtually all patients who undergo Aβ PET also undergo MRI.

In this study, we aimed to determine whether the well-established off-target binding of Aβ PET tracers to white matter (WM) could similarly affect Aβ quantification in the cortex. The basis of Aβ tracer signal in WM is incompletely understood but is considered to primarily reflect specific binding to myelin because of its β-sheet structure, as well as the delayed washout of nonspecifically distributed tracer within lipid-rich WM (*7*). Because of this strong signal in normal WM, Aβ tracers are commonly used to visualize and quantify WM lesions in diseases such as multiple sclerosis (*8–11*). In contrast, the potential contribution of myelin binding to cortical Aβ PET signal has been largely overlooked, despite the presence of substantial intracortical myelination, which varies across individuals and in association with aging and disease (*12*). Supporting the possibility that intracortical myelination contributes significantly to the Aβ PET signal, 2 prior studies have shown that regions with a high Aβ PET signal express high MRI measures of axonal and myelin integrity (*13*,*14*). Those studies interpreted these results as paradoxical, hypothesizing that the loss of myelin integrity, which is well-documented in AD (*15*), would be associated with worse AD pathology. However, the reported positive association between PET-measured Aβ deposition and MRI-measured myelin integrity is consistent with strong binding of Aβ PET tracers to myelin, including intracortical myelin.

Here, we aimed to determine whether accounting for cortical myelin content would improve the biologic validity of PET-measured cortical Aβ burden. Cortical Aβ burden was measured using either ^{18}F-florbetaben (^{18}F-FBB) or ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET. A validated multiecho fast T2 MRI sequence with an ultrashort echo time, sensitive to myelin water fraction (MWF) (*16–18*), was used to estimate cortical myelin content on a voxelwise basis.

Because neuropathologic confirmation is not available in living participants, plasma phosphorylated tau 217 (p-tau217), a biomarker strongly associated with cerebral Aβ deposition, was used as an independent measure of AD pathology (*19*). We tested whether the inclusion of MWF in regression models predicting PET-measured Aβ burden (Centiloid or regional SUV ratio [SUVR]) from plasma p-tau217 levels, would improve model fit. If accounting for intracortical myelin strengthened the relationship between plasma and PET

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biomarkers, this would support the hypothesis that variability in intracortical myelin contributes to Aβ PET signal and that MRI-based correction could improve the accuracy of Aβ PET quantification.

MATERIALS AND METHODS

Participants

This retrospective analysis of prospectively collected data included 114 individuals (43 men and 71 women; mean age ± SD, 68.82 ± 7.87 y) who underwent Aβ PET (^{18}F-FBB or ^{11}C-PiB) and multiecho fast T2 MRI between February 2020 and April 2025 at Weill Cornell Medicine. All participants underwent standardized National Alzheimer's Coordinating Center–based clinical and cognitive assessments and were classified by consensus diagnosis as cognitively normal, having mild cognitive impairment (MCI), or having AD (MCI/AD). All participants provided informed consent for participation in this institutional review board–approved study.

MRI and PET Acquisition

MRI was performed on a 3T Prisma scanner with a 64-channel head–neck coil (Siemens Healthineers). To estimate myelin content, multiecho fast T2 data were acquired with established parameters (*16*,*17*). T1-weighted images, used for coregistration and segmentation of regions of interest, were acquired using a magnetization-prepared rapid acquisition gradient-echo sequence (*17*).

A research-dedicated 64-slice PET/CT scanner (Biograph mCT-S; Siemens Healthineers) was used to acquire images 90–110 min after intravenous injection of approximately 301 MBq of ^{18}F-FBB or 50–70 min after intravenous injection of approximately 555 MBq of ^{11}C-PiB. ^{18}F-FBB PET images were reconstructed into a 400 × 400 × 55 matrix with a voxel size of 2.036 × 2.036 × 3 mm. ^{11}C-PiB PET images were reconstructed into a 512 × 512 × 74 matrix with a voxel size of 0.8 × 0.8 × 3 mm.

Neuroimage Processing and Analysis

Processing followed our established pipeline and included realignment, motion correction, T1-weighted MRI coregistration, segmentation, and regional PET signal quantification in subject-native space (*20*). Defined regions of interest included the bilateral cerebellar cortex (as the reference for SUVR) and a composite region (ADmask) consisting of the posterior cingulate, precuneus, and bilateral frontal, parietal, and temporal cortices—regions known to be vulnerable to Aβ deposition in AD (*21*). To reduce partial-volume effects, regions of interest were eroded by 1 voxel using a 3-dimensional spheric kernel. MWF was reconstructed from 6-echo fast T2 data, restricting T2 relaxometry to 0–20 ms using a previously reported 3-pool water compartment model (*16*,*18*). The mean PET SUVR and MWF were calculated within the ADmask.

Centiloids were calculated using established methods (*22*,*23*) and carefully calibrated for ^{11}C-PiB data using Equation 1, and ^{18}F-FBB data were calibrated to ^{11}C-PiB data using Equation 2:

$$\text{Centiloid} = 100 \times (^{11}\text{C-PiB\_SUVR\_CTX} - 1.014513)/1.092145, \quad \text{Eq. 1}$$

$$\text{PiB\_SUVR\_CTX} = (^{18}\text{F-FBB\_SUVR\_CTX} - 0.5147)/0.5936, \quad \text{Eq. 2}$$

where PiB_SUVR_CTX is the ^{11}C-PiB SUVR measured in the cortex, and FBB_SUVR_CTX is the ^{18}F-FBB SUVR measured in the cortex.

^{11}C-PiB SUVR was directly converted to Centiloids, whereas ^{18}F-FBB SUVR was converted to ^{11}C-PiB SUVR first and then to Centiloids using these formulas.

p-tau217 Measurement

Plasma concentrations of p-tau217 were measured at the Weill Cornell Brain Health Imaging Institute biomarker laboratory using the Simoa HD-X platform (Quanterix) in accordance with the manufacturer's protocols, using the AlzPATH p-tau 217 Advantage Plus assay (Quanterix) for HD-X. All samples were analyzed without knowledge of clinical status through comparison with internal calibrator curves.

Statistical Analysis

Multiple linear regression was used to determine whether accounting for cortical myelin content improved prediction of PET-measured Aβ burden. PET Centiloid or SUVR served as the dependent variable. Plasma p-tau217 was entered in the base model, with age included as a covariate in primary analyses. Cortical MWF was then added to evaluate incremental improvement in model fit. Improvement was assessed using change in R^2 (ΔR^2), and likelihood ratio test was used to evaluate significant differences between nested models. Standardized β-coefficients defined relative contributions, and collinearity diagnostics were inspected using variance inflation factor.

RESULTS

Demographics and Key Measurements

Participant demographics and key measures are summarized in Table 1. The cohort included 114 participants (27 MCI/AD, 87

TABLE 1
Demographics and Key Measurements

Variable	Overall	Cognitively normal	MCI/AD	*P*
n	114	87	27	
Age (y)	68.82 ± 7.87	68.53 ± 7.57	69.74 ± 8.84	0.524*
Male	43 (37.7)	32 (36.8)	11 (40.7)	0.886†
Aβ positive	44 (38.6)	17 (19.5)	27 (100)	<0.001†
Centiloids	26.06 ± 45.43	5.79 ± 23.17	91.38 ± 37.26	<0.001‡
p-tau217	0.48 ± 0.55	0.34 ± 0.33	0.95 ± 0.81	<0.001‡
^{11}C-PiB	60 (52.6)	42 (48.3)	18 (66.7)	0.256†

*Determined using *t*-test.
†Determined using χ^2 test.
‡Determined using Wilcoxon rank sum test.
Qualitative data are expressed as number and percentage; continuous data are expressed as mean ± SD.

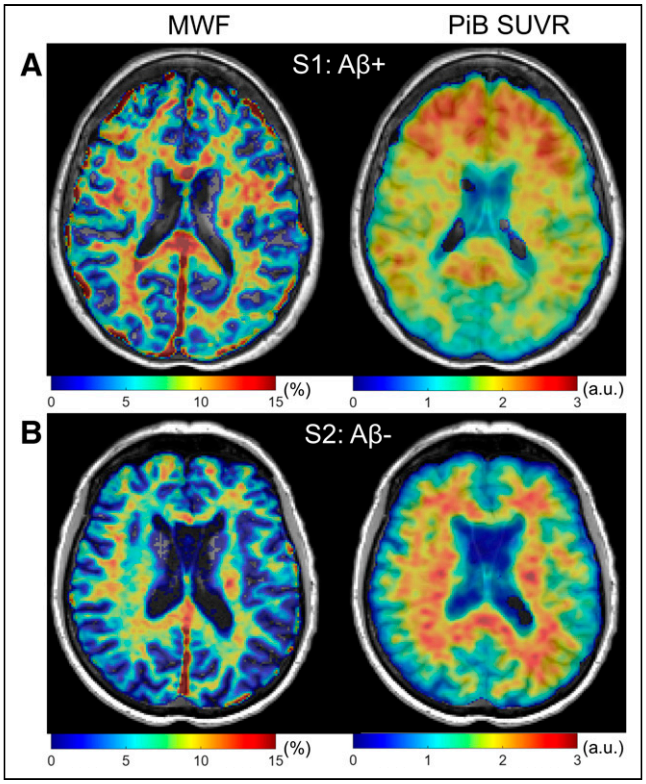

FIGURE 1. Representative images of MWF and Aβ PET SUVR in Aβ-positive patient (62-y-old woman with MCI/AD; A) and Aβ-negative patient (65-y-old, cognitively normal man; B) in Montreal Neurological Institute space.

cognitively normal), with no between-group differences in age or sex. As expected, diagnostic groups differed in Aβ PET positivity, Centiloid burden, and plasma p-tau217 (all $P < 0.001$).

Myelin Contributes to PET-Measured Aβ Burden

Figure 1 shows representative images of MWF and Aβ PET SUVR from Aβ-positive and Aβ-negative subjects in Montreal Neurological Institute space.

For the combined sample ($n = 114$) and separately for the ^{11}C-PiB ($n = 60$) and ^{18}F-FBB ($n = 54$) cohorts, we compared a full regression model (PET_Amyloid ~ Age + MWF + p-tau217) with a nested model (PET_Amyloid ~ Age + p-tau217) to estimate the additional variance explained by MWF. MWF was associated with regional PET Aβ deposition (^{11}C-PiB/^{18}F-FBB SUVR) in AD-vulnerable cortex and with global Centiloid values, consistent with prior reports (*13*,*14*).

In the combined cohort ($n = 114$), Aβ burden was harmonized to Centiloids. The full model (Centiloid ~ Age + p-tau217+ MWF) explained more variance ($R^2 = 0.328$) than the nested model (Centiloid ~ Age + p-tau217; $R^2 = 0.271$), with both p-tau217 ($t = 5.70$, $P < 0.001$; Fig. 2A) and MWF ($t = 3.22$, $P = 0.002$; Fig. 2B) independently associated with Centiloids. Adding MWF increased the explained variance ($\Delta R^2 = 0.056$) and significantly improved fit (likelihood ratio test: $\chi^2 = 10.63$, $P = 0.001$).

Stratified analyses using the ADmask SUVR showed consistent results. In the ^{11}C-PiB PET group ($n = 60$), R^2 increased from 0.347 to 0.403 ($\Delta R^2 = 0.056$), with significant effects of age ($t = 2.65$, $P = 0.011$), p-tau217 ($t = 4.48$, $P < 0.001$; Fig. 2C), and MWF ($t = 2.51$, $P = 0.015$; Fig. 2D) (likelihood ratio test: $\chi^2 = 6.41$, $P = 0.011$). In the ^{18}F-FBB PET group ($n = 54$), R^2 increased from 0.165 to 0.231 ($\Delta R^2 = 0.066$), with significant effects of p-tau217 ($t = 3.31$, $P = 0.002$; Fig. 2E) and MWF ($t = 2.31$, $P = 0.025$; Fig. 2F) (likelihood ratio test: $\chi^2 = 5.48$, $P = 0.019$).

Overall, adding MWF improved model fit by approximately 6% across cohorts.

DISCUSSION

Aβ PET tracers have transformed AD research and clinical care by enabling in vivo visualization of Aβ deposition. In addition, their strong off-target binding to WM, thought to primarily reflect binding to myelin, has led to their use as markers of myelin integrity in multiple sclerosis and other WM diseases (*8*–*11*). However, despite the presence of substantial and variable intracortical myelin (*12*), the potential contribution of myelin binding to cortical Aβ PET signal has received little attention. Here, by quantifying intracortical myelin using MWF, a highly specific MRI measure acquired using a clinically feasible rapid MRI sequence (*16*–*18*), we showed that this well-known myelin-binding property also influences the quantification of cortical Aβ burden.

We replicated prior unexplained findings that cortical MWF correlates with PET-measured cortical Aβ deposition (*13*,*14*) and, by referencing an independent measure of AD pathology (plasma p-tau217), showed that this association is not explained by true Aβ burden. Instead, our findings suggest that off-target tracer binding to intracortical myelin contributes a non-Aβ component to the PET signal, reducing the accuracy of PET-measured cortical Aβ burden. Consistent with this interpretation, accounting for MRI-measured intracortical myelin content improved the association between PET-measured Aβ burden and plasma p-tau217 by approximately 6%. Although modest, this effect was statistically significant and consistent across PiB, FBB, and Centiloid analyses, suggesting that intracortical myelin is a reproducible and previously unrecognized source of variance in Aβ PET quantification. Given the increasing importance of Aβ PET for diagnosis, prognosis, and treatment selection in AD, and the fact that most patients undergoing Aβ PET also undergo MRI, the integration of MRI-derived measures of cortical myelin into PET analysis may represent a feasible strategy to improve the accuracy of Aβ quantification. In practice, MRI-derived MWF could be incorporated into voxelwise or regional correction models to generate a myelin-adjusted measure of Aβ burden.

Several limitations should be considered. Because our analyses used SUVR rather than fully quantitative PET measures, some myelin-related signal may have been reduced through reference-region normalization. However, complete cancelation is unlikely given differences in myelin content and tracer kinetics between cortical target and cerebellar reference regions. This normalization may explain both the modest (~6%) improvement in model fit and the similar effects observed across tracers despite known differences in WM-binding properties (*23*). Future studies using quantitative PET approaches will be important for determining the true magnitude of the myelin contribution to Aβ PET signal and tracer-specific effects.

Further, our cohort contained relatively few participants with advanced AD and a large proportion of cognitively normal and Aβ-negative individuals. This restricted range of pathology likely contributed to the modest PET–p-tau217 correlations observed and may have limited our ability to detect stronger effects.

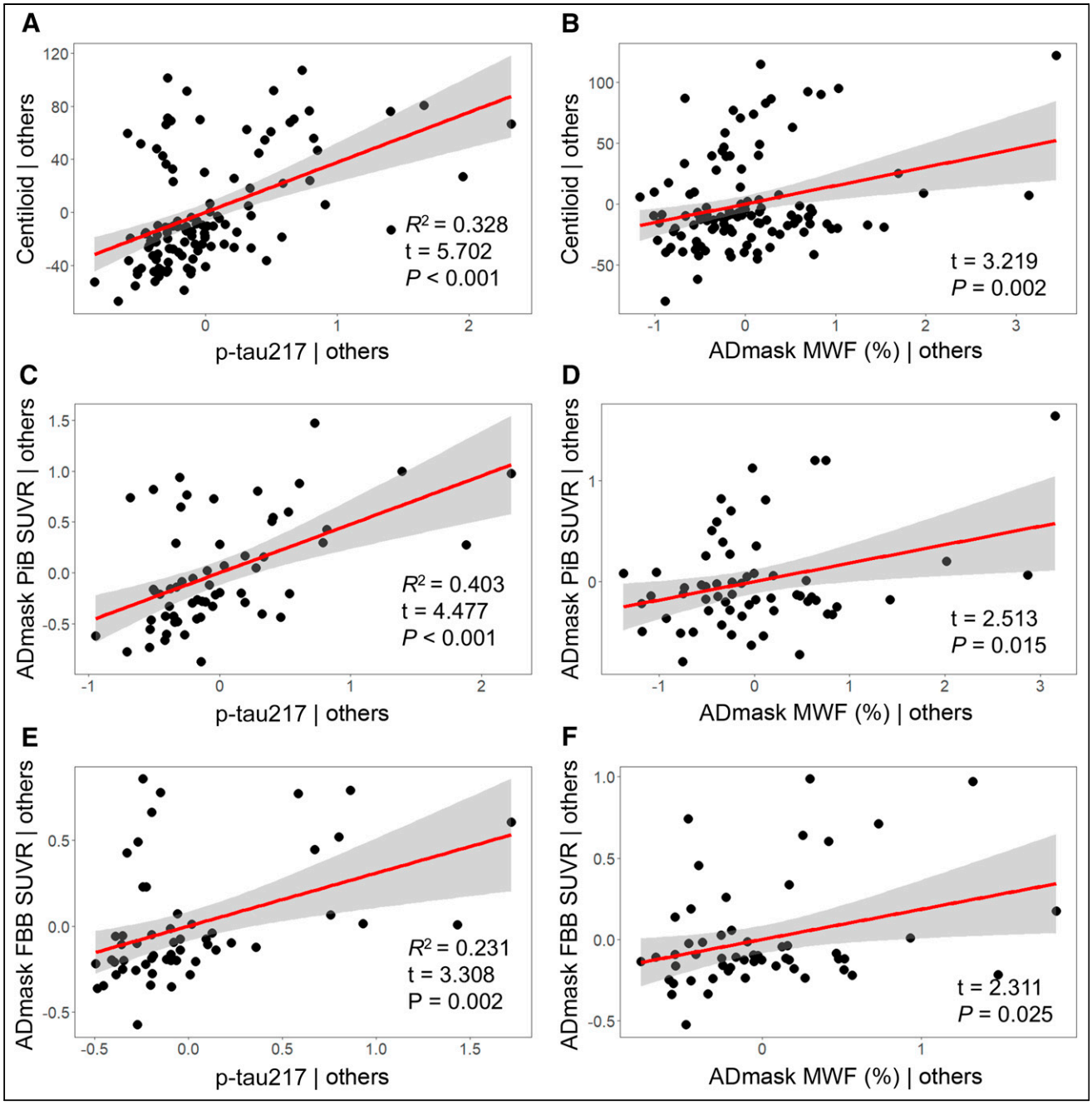

FIGURE 2. Partial regression plots of full models showing associations of PET-measured Aβ burden with p-tau217 and MWF in combined cohort (A and B), ^{11}C-PiB PET cohort (C and D), and ^{18}F-FBB PET cohort (E and F). Across all 3 cohorts, MWF remained significant independent predictor of Aβ burden after adjusting for p-tau217.

Additional limitations relate to interpretation of the underlying biology. Improved correspondence between Aβ PET and plasma p-tau217 after accounting for MWF cannot be interpreted as definitive evidence of improved Aβ quantification, as these biomarkers reflect related but distinct aspects of AD biology. It is a limitation that plasma p-tau217 and Aβ PET were the only AD biomarkers available in this cohort; cerebrospinal fluid or additional plasma biomarkers could provide a more accurate assessment of underlying AD pathology. An alternative explanation for our findings, which we cannot refute on the basis of our current data, is that iron deposition near Aβ plaques influences the T2 signal, producing an association between MWF and PET-measured Aβ independent of intracortical myelin (*24*). Distinguishing between these possibilities and confirming the biologic basis of our findings will require tissue studies. More broadly, longitudinal studies incorporating both in vivo neuroimaging and postmortem neuropathologic assessment are essential for validating and refining biomarker-based measures of AD pathology.

CONCLUSION

Accounting for MRI-measured intracortical myelin improved the association between Aβ PET and plasma p-tau217, indicating

that off-target binding to intracortical myelin influences PET-measured Aβ burden.

DISCLOSURE

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KEY POINTS

QUESTION: Is the cortical Aβ PET signal contaminated by off-target binding to intracortical myelin?

PERTINENT FINDINGS: Accounting for MRI-measured intracortical myelin improved the association between Aβ PET and plasma p-tau217, indicating that off-target binding to intracortical myelin influences PET-measured Aβ burden.

IMPLICATIONS FOR PATIENT CARE: A framework for myelin-informed adjustment of PET measured Aβ burden may guide clinical care, including anti-Aβ therapy, by providing more accurate quantification of Aβ burden for treatment initiation and monitoring.

REFERENCES

1. Rafii MS, Aisen PS. Amyloid-lowering immunotherapies for Alzheimer disease: current status and future directions. *Nat Rev Neurol.* 2025;21:490–498.
2. Clark CM, Pontecorvo MJ, Beach TG, et al.; AV-45-A16 Study Group. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. *Lancet Neurol.* 2012;11:669–678.
3. Sojkova J, Driscoll I, Iacono D, et al. In vivo fibrillar β-amyloid detected using [^{11}C]PiB positron emission tomography and neuropathologic assessment in older adults. *Arch Neurol.* 2011;68:232–240.
4. La Joie R, Ayakta N, Seeley WW, et al. Multisite study of the relationships between antemortem [^{11}C]PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. *Alzheimers Dement.* 2019;15:205–216.
5. Murray ME, Lowe VJ, Graff-Radford NR, et al. Clinicopathologic and ^{11}C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain.* 2015;138:1370–1381.
6. Thal DR, Poesen K, Vandenberghe R, De Meyer S. Alzheimer's disease neuropathology and its estimation with fluid and imaging biomarkers. *Mol Neurodegener.* 2025;20:33.
7. Fodero-Tavoletti MT, Rowe CC, McLean CA, et al. Characterization of PiB binding to white matter in Alzheimer disease and other dementias. *J Nucl Med.* 2009;50:198–204.
8. Glodzik L, Rusinek H, Li J, et al. Reduced retention of Pittsburgh compound B in white matter lesions. *Eur J Nucl Med Mol Imaging.* 2015;42:97–102.
9. van der Weijden CW, Biondetti E, Gutmann IW, et al. Quantitative myelin imaging with MRI and PET: an overview of techniques and their validation status. *Brain.* 2023;146:1243–1266.
10. Stankoff B, Freeman L, Aigrot MS, et al. Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-^{11}C]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole. *Ann Neurol.* 2011;69:673–680.
11. Veronese M, Bodini B, García-Lorenzo D, et al. Quantification of [^{11}C]PIB PET for imaging myelin in the human brain: a test–retest reproducibility study in high-resolution research tomography. *J Cereb Blood Flow Metab.* 2015;35:1771–1782.
12. Grydeland H, Walhovd KB, Tamnes CK, Westlye LT, Fjell AM. Intracortical myelin links with performance variability across the human lifespan: results from T1-and T2-weighted MRI myelin mapping and diffusion tensor imaging. *J Neurosci.* 2013;33:18618–18630.
13. Pelkmans W, Dicks E, Barkhof F, et al. Gray matter T1-w/T2-w ratios are higher in Alzheimer's disease. *Hum Brain Mapp.* 2019;40:3900–3909.
14. Yasuno F, Kazui H, Morita N, et al. Use of T1-weighted/T2-weighted magnetic resonance ratio to elucidate changes due to amyloid β accumulation in cognitively normal subjects. *Neuroimage Clin.* 2017;13:209–214.
15. Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. *Acta Neuropathol Commun.* 2018;6:22.
16. Nguyen TD, Deh K, Monohan E, et al. Feasibility and reproducibility of whole brain myelin water mapping in 4 minutes using fast acquisition with spiral trajectory and adiabatic T2prep (FAST-T2) at 3T. *Magn Reson Med.* 2016;76:456–465.
17. Zhou L, Nguyen TD, Chiang GC, et al. Brain glymphatic fluid mapping in Alzheimer's disease: a human MRI and PET study. *Brain Commun.* 2025;7:fcaf200.
18. Zhou L, Li Y, Sweeney EM, et al. Association of brain tissue cerebrospinal fluid fraction with age in healthy cognitively normal adults. *Front Aging Neurosci.* 2023;15:1162001.
19. Khalafi M, Dartora WJ, McIntire LBJ, et al. Diagnostic accuracy of phosphorylated tau217 in detecting Alzheimer's disease pathology among cognitively impaired and unimpaired: a systematic review and meta-analysis. *Alzheimers Dement.* 2025;21:e14458.
20. Tahmi M, Bou-Zeid W, Razlighi QR. A fully automatic technique for precise localization and quantification of amyloid-β PET scans. *J Nucl Med.* 2019;60:1771–1779.
21. Mosconi L, Rinne JO, Tsui WH, et al. Increased fibrillar amyloid-β burden in normal individuals with a family history of late-onset Alzheimer's. *Proc Natl Acad Sci USA.* 2010;107:5949–5954.
22. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement.* 2015;11:1–15.e1–4.
23. Khalafi M, Hojjati SH, Wang XH, et al. Concordance between Centiloid quantification and visual interpretation of amyloid PET scans across the Alzheimer disease continuum. *AJNR.* 2025;46:1884–1892.
24. Zhao Z, Zhang L, Wen Q, et al. The effect of beta-amyloid and tau protein aggregations on magnetic susceptibility of anterior hippocampal laminae in Alzheimer's diseases. *Neuroimage.* 2021;244:118584.