

# White matter <sup>18</sup>F-florbetapir retention predicts cognitive decline and treatment response in Alzheimer’s disease

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| INTRODUCTION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | METHODS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | RESULTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | CONCLUSIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <ul style="list-style-type: none"><li>• Cortical Aβ PET is the core AD biomarker, but anti-Aβ therapies show modest benefits → need for additional markers.</li><li>• <sup>18</sup>F-Florbetapir (FBP) retention in normal-appearing white matter (NAWM) is traditionally dismissed as nonspecific.</li><li>• <b>Hypotheses:</b> NAWM FBP retention (1) follows a stage-specific trajectory distinct from cortical Aβ; (2) predicts cognitive decline and treatment response; (3) correlates with fluid biomarkers.</li><li>• <b>Objective:</b> Evaluate NAWM FBP retention as a novel PET biomarker across the AD continuum.</li></ul> | <ul style="list-style-type: none"><li>• <b>Participants:</b> 672 (ADNI n=546; Chinese cohorts n=126) – CN–, CN+, MCI+, AD+. Longitudinal data n=205.</li><li>• <b>Imaging:</b> FBP PET + 3T MRI (T1, T2-FLAIR). NAWM defined after WMH exclusion; RBV partial volume correction. SUVRs from 6 meta-regions (frontal, parietal, temporal, occipital, cingulate, limbic).</li><li>• <b>Fluid biomarkers:</b> CSF Aβ42, p-tau, t-tau (Elecsys); plasma p-tau217, Aβ42/40, GFAP, NfL (Simoa).</li><li>• <b>Treatment:</b> Lecanemab group (n=12) vs. controls (n=18), pre-post PET.</li><li>• <b>Statistics:</b> ANOVA, paired t-tests, ROC, Cox regression, Kaplan-Meier, mediation (5,000 bootstraps), adjusted for age/sex.</li><li>• <b>Post-mortem validation:</b> 9 AD, 4 controls – 4G8 IHC for Aβ plaques in GM and WM.</li></ul> | <ul style="list-style-type: none"><li>1. <b>Distinct trajectory:</b> NAWM retention increases early (CN→CN+) then plateaus in symptomatic stages, unlike cortical Aβ which rises continuously (p&lt;0.0001).</li><li>2. <b>Predicts decline:</b> In CN+ with identical cortical SUVR (1.14), higher NAWM predicted 2-point MMSE/MoCA drop over 24 months; lower remained stable. Cox HR: NAWM high-risk vs. low-risk, p&lt;0.0001 (comparable to CSF p-tau/Aβ42 and plasma p-tau217).</li><li>3. <b>Treatment response:</b> Lecanemab significantly reduced NAWM SUVR globally and in frontal/parietal/temporal/occipital regions (p&lt;0.05) vs. controls.</li><li>4. <b>Diagnostic gain:</b> Cortical + NAWM achieved AUC=0.988 for CN– vs. CN+ (vs. 0.975/0.976 alone); validated in Chinese cohorts with 92% accuracy.</li><li>5. <b>Fluid correlations:</b> NAWM correlated with plasma p-tau217, CSF Aβ42, CSF p-tau/Aβ42 (r=0.31–0.56) in CN+/MCI+. Mediation: these biomarkers significantly mediated NAWM–cognition associations.</li></ul> | <ul style="list-style-type: none"><li>• <b>NAWM FBP retention is not nonspecific noise</b> – it reflects early white matter pathology and is a clinically meaningful biomarker.</li><li>• <b>Clinical utility:</b> Enhances early amyloid detection (especially near thresholds), predicts progression, and monitors anti-Aβ therapy response.</li><li>• <b>Mechanism:</b> Likely reflects Aβ at the axon-myelin interface, neuroinflammation, or impaired clearance, triggering tau cascades.</li><li>• <b>Future directions:</b> Larger cohorts, multimodal imaging (myelin, inflammation) to disentangle signal; caution on using white matter as reference in longitudinal SUVR.</li><li>• <b>Take-home:</b> NAWM FBP PET should be integrated into AD biomarker frameworks for preclinical detection, risk stratification, and therapeutic monitoring.</li></ul> | <ul style="list-style-type: none"><li>1. Jack CR, et al. Revised criteria for diagnosis and staging of AD. <i>Alzheimers Dement</i> (2024).</li><li>2. Depp C, et al. Myelin dysfunction drives amyloid-beta deposition. <i>Nature</i> (2023).</li><li>3. Moscoso A, et al. Florbetapir PET as a marker of myelin integrity. <i>Eur J Nucl Med Mol Imaging</i> (2022).</li></ul> <div><div>CONTACT</div><div><div><p>广东 广州</p><p>扫二维码，添加我为朋友。</p></div><div><p>Corresponding author:<br/>Chuantao Zuo,</p><p>Email:<br/>zuochuantao@fudan.edu.cn.</p></div></div><div><div>ALZHEIMER'S ASSOCIATION</div><div>AAIC&gt;26</div></div></div> |