adjustment, suggesting potential sensitivity to detecting transitional cognitive decline in preclinical AD. Measures emphasizing learning should be given equal consideration as measures of delayed memory in AD-focused studies, particularly in the preclinical phase.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: computerized neuropsychological testing
Keyword 2: technology
Keyword 3: memory disorders
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4 Evaluating Plasma GFAP for the Detection of Alzheimer's Disease Dementia

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Objective: Blood-based biomarkers represent a scalable and accessible approach for the detection and monitoring of Alzheimer's disease (AD). Plasma phosphorylated tau (p-tau) and neurofilament light (NfL) are validated biomarkers for the detection of tau and neurodegenerative brain changes in AD, respectively. There is now emphasis to expand beyond these markers to detect and provide insight into the pathophysiological processes of AD. To this end, a reactive astrocytic marker, namely plasma glial fibrillary acidic protein (GFAP), has been of interest. Yet, little is known about the relationship between plasma GFAP and AD. Here, we examined the association between plasma GFAP, diagnostic status, and neuropsychological test performance. Diagnostic accuracy of plasma GFAP was compared with plasma measures of p-tau$_{181}$ and NfL.
Participants and Methods: This sample included 567 participants from the Boston University (BU) Alzheimer's Disease Research Center (ADRC) Longitudinal Clinical Core Registry, including individuals with normal cognition (n=234), mild cognitive impairment (MCI) (n=180), and AD dementia (n=153). The sample included all participants who had a blood draw. Participants completed a comprehensive neuropsychological battery (sample sizes across tests varied due to missingness). Diagnoses were adjudicated during multidisciplinary diagnostic consensus conferences. Plasma samples were analyzed using the Simoa platform. Binary logistic regression analyses tested the association between GFAP levels and diagnostic status (i.e., cognitively impaired due to AD versus unimpaired), controlling for age, sex, race, education, and *APOE e4* status. Area under the curve (AUC) statistics from receiver operating characteristics (ROC) using predicted probabilities from binary logistic regression examined the ability of plasma GFAP to discriminate diagnostic groups compared with plasma p-tau$_{181}$ and NfL. Linear regression models tested the association between plasma GFAP and neuropsychological test performance, accounting for the above covariates.
Results: The mean (SD) age of the sample was 74.34 (7.54), 319 (56.3%) were female, 75 (13.2%) were Black, and 223 (39.3%) were *APOE e4* carriers. Higher GFAP concentrations were associated with increased odds for having cognitive impairment (GFAP z-score transformed: OR=2.233, 95% CI [1.609, 3.099], p<0.001; non-z-transformed: OR=1.004, 95% CI [1.002, 1.006], p<0.001). ROC analyses, comprising of GFAP and the above covariates, showed plasma GFAP discriminated the cognitively impaired from unimpaired (AUC=0.75) and was similar, but slightly superior, to plasma p-tau$_{181}$ (AUC=0.74) and plasma NfL (AUC=0.74). A joint panel of the plasma markers had greatest discrimination accuracy (AUC=0.76). Linear regression analyses showed that higher GFAP levels were associated with worse performance on neuropsychological tests assessing global cognition, attention, executive functioning, episodic memory, and language abilities (ps<0.001) as well as higher CDR Sum of Boxes (p<0.001).

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Conclusions: Higher plasma GFAP levels differentiated participants with cognitive impairment from those with normal cognition and were associated with worse performance on all neuropsychological tests assessed. GFAP had similar accuracy in detecting those with cognitive impairment compared with p-tau$_{181}$ and NfL, however, a panel of all three biomarkers was optimal. These results support the utility of plasma GFAP in AD detection and suggest the pathological processes it represents might play an integral role in the pathogenesis of AD.

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Keyword 1: dementia - Alzheimer's disease
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5 Antemortem Plasma GFAP Predicts Alzheimer's Disease Neuropathological Changes

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Objective: Blood-based biomarkers offer a more feasible alternative to Alzheimer's disease (AD) detection, management, and study of disease mechanisms than current *in vivo* measures. Given their novelty, these plasma biomarkers must be assessed against post-mortem neuropathological outcomes for validation. Research has shown utility in plasma markers of the proposed AT(N) framework, however recent studies have stressed the importance of expanding this framework to include other pathways. There is promising data supporting the usefulness of plasma glial fibrillary acidic protein (GFAP) in AD, but GFAP-to-autopsy studies are limited. Here, we tested the association between plasma GFAP and AD-related neuropathological outcomes in participants from the Boston University (BU) Alzheimer's Disease Research Center (ADRC).
Participants and Methods: This sample included 45 participants from the BU ADRC who had a plasma sample within 5 years of death and donated their brain for neuropathological examination. Most recent plasma samples were analyzed using the Simoa platform. Neuropathological examinations followed the National Alzheimer's Coordinating Center procedures and diagnostic criteria. The NIA-Reagan Institute criteria were used for the neuropathological diagnosis of AD. Measures of GFAP were log-transformed. Binary logistic regression analyses tested the association between GFAP and autopsy-confirmed AD status, as well as with semi-quantitative ratings of regional atrophy (none/mild versus moderate/severe) using binary logistic regression. Ordinal logistic regression analyses tested the association between plasma GFAP and Braak stage and CERAD neuritic plaque score. Area under the curve (AUC) statistics from receiver operating characteristics (ROC) using predicted probabilities from binary logistic regression examined the ability of plasma GFAP to discriminate autopsy-confirmed AD status. All analyses controlled for sex, age at death, years between last blood draw and death, and *APOE e4* status.
Results: Of the 45 brain donors, 29 (64.4%) had autopsy-confirmed AD. The mean (SD) age of the sample at the time of blood draw was 80.76 (8.58) and there were 2.80 (1.16) years between the last blood draw and death. The sample included 20 (44.4%) females, 41 (91.1%) were White, and 20 (44.4%) were *APOE e4* carriers. Higher GFAP concentrations were associated with increased odds for having autopsy-confirmed AD (OR=14.12, 95% CI [2.00, 99.88], p=0.008). ROC analysis showed plasma GFAP accurately discriminated those with and without autopsy-confirmed AD on its own (AUC=0.75) and strengthened as the above covariates were added to the model (AUC=0.81). Increases in GFAP levels corresponded to increases in Braak stage (OR=2.39, 95% CI [0.71-4.07], p=0.005), but not CERAD ratings (OR=1.24, 95% CI [0.004, 2.49], p=0.051). Higher GFAP levels were associated with greater temporal lobe atrophy (OR=10.27, 95% CI [1.53 ,69.15],

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