

Visual Functions Are Associated with Biomarker Changes in Alzheimer's Disease

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Abstract.

Background: While various biomarkers of Alzheimer's disease (AD) have been associated with general cognitive function, their association to visual-perceptive function across the AD spectrum warrant more attention due to its significant impact on quality of life. Thus, this study explores how AD biomarkers are associated with decline in this cognitive domain.

Objective: To explore associations between various fluid and imaging biomarkers and visual-based cognitive assessments in participants across the AD spectrum.

Methods: Data from participants ($N = 1,460$) in the Alzheimer's Disease Neuroimaging Initiative were analyzed, including fluid and imaging biomarkers. Along with the Mini-Mental State Examination (MMSE), three specific visual-based cognitive tests were investigated: Trail Making Test (TMT) A and TMT B, and the Boston Naming Test (BNT). Locally estimated scatterplot smoothing curves and Pearson correlation coefficients were used to examine associations.

Results: MMSE showed the strongest correlations with most biomarkers, followed by TMT-B. The p-tau181/A β_{1-42} ratio, along with the volume of the hippocampus and entorhinal cortex, had the strongest associations among the biomarkers.

Conclusions: Several biomarkers are associated with visual processing across the disease spectrum, emphasizing their potential in assessing disease severity and contributing to progression models of visual function and cognition.

Keywords: Alzheimer's disease, biomarkers, dementia, MRI, neuroimaging, visual processing

INTRODUCTION

Dementia is a debilitating clinical syndrome associated with memory impairments, as well as a decline in other areas of cognition such as visual processing, linguistic ability, and executive functions, leading to functional impairment [1, 2]. Alzheimer's disease (AD) is the most common type of dementia, affecting more than 25 million people globally [3]. AD is canonically defined by the presence of amyloid (A β) peptide-containing extracellular plaques

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and tau-containing neurofibrillary tangles [4]. This pathophysiology leads to progressive neuronal and synaptic loss [5]. Recently identified *in vivo* biochemical markers enable a quantification of these pathological processes, improving our understanding of AD, and aiding in its early detection and accurate diagnosis [6–8].

The A/T/N classification system proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) provides a framework for grouping biomarkers based on the biological definition of AD. It encapsulates the most accepted biomarkers for the disease: those that measure amyloid- β ("A") and tau ("T") pathology, and neurodegeneration ("N") [9]. These biomarkers can, for example, be measured through protein concentrations in cerebrospinal fluid (CSF), or via neuroimaging techniques [10]. More recently, plasma-based measures, such as plasma A β_{1-42} , phosphorylated tau181 (p-tau181), and neurofilament light chain (NfL), have been proposed as potential biomarkers that can be obtained by less invasive means [11–16].

Several of these biomarkers have been shown to be associated with clinical symptoms of AD. For example, it has been reported that CSF A β_{1-42} is positively associated with increasing scores on global cognitive assessments such as the Mini-Mental State Examination (MMSE) [17, 18]. Similarly, higher levels of p-tau181 and NfL in CSF have been shown to be associated with lower MMSE scores [17–19]. As AD constitutes a multidomain neurodegenerative disease, the assessment of domain-specific clinical severity through more targeted cognitive tests is crucial to fully characterize disease symptomatology. Doing so in conjunction with biomarkers may also help to determine whether specific pathophysiology is linked to declines in certain domains. Previous research has shown some of these associations [20–22].

Among the various cognitive and functional domains, visual-perceptive ability and its decline linked to AD warrant special attention due to the significant negative impact on a patient's quality of life [23–26]. Individuals with AD may present with deficits in visual acuity, as well as deterioration of aspects of higher-order visual processing, such as object recognition and visual attention [27, 28]. Notably, widely used visual-based cognitive assessments such as the Trail Making Tests (TMT) A and B, and the Boston Naming Test (BNT), offer valuable insights into disease progression. For instance, the BNT, which measures visual confrontation naming and recall, has been linked to atrophy in areas such as

the fusiform gyrus, which is functionally understood to be involved in processing visual information, along with areas of the brain involved in semantic memory [29–31]. Moreover, CSF NfL, a marker of global axonal degeneration, has been shown to be negatively correlated with the BNT, as well as the TMT-A and TMT-B, which evaluate visuospatial ability and executive function [32]. Alterations in lower-order visual processing in AD, such as decreased visual acuity and integration, as well as reduced contrast sensitivity and color perception, may underlie or exacerbate the deficits in higher-order visual processing observed in these patients [32–34]. To date, there is no comprehensive analysis investigating the association of the various AD biomarkers with assessments testing visuospatial ability and executive function in patients across the whole AD spectrum.

Thus, the purpose of this study was to examine the degree to which AD-specific and neurodegeneration biomarkers are associated with different domains of cognitive decline, with a particular focus on the visual-based cognitive assessments. The cognitive assessments used in this study were TMT A, TMT B, and BNT, which are all predominantly visual in nature and were chosen because they are commonly used and sensitive to clinical symptoms of AD [35, 36]. The MMSE was included as an additional score as a means of a baseline comparison. Overall, the results of this study can improve our understanding of the cognitive profile of the visual domain resulting from neurodegeneration. A deeper analysis of the association between visual-perceptive abilities and AD pathology may also inform the development of *in silico* models of neurodegenerative diseases [37].

METHODS

Dataset and participants

We examined associations between AD-related pathology and cognition using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Specifically, data used in this study were obtained from the LONI Image Data Archive (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI is to investigate whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments

can be combined to measure the progression of mild cognitive impairment (MCI) and early AD [38].

For this work, included were participants from all ADNI phases (ADNI1, ADNI GO, ADNI2 and ADNI3) who had completed the requisite four cognitive assessments and had available biomarker data at the ADNI baseline (i.e., participant first assessment). Our cohort included all participants across the AD continuum, that is, participants who were classified as cognitively normal (CN), MCI (including early and late MCI), or AD. Our goal was to quantify the extent of AD pathology and neurodegeneration as a continuum utilizing the full spectrum of biomarker values, rather than investigating group-wise differences of that pathology. Thus, the pooled sample was analyzed independent of diagnostic groups. Not all biomarker data were available for all ADNI participants at baseline. Therefore, to maximize the sample size in the study, we employed the complete dataset accessible for each biomarker, resulting in small variations in the composition of the participant groups across biomarkers. Similarly, not every participant completed each of the cognitive assessments at baseline. Hence, we only included participants who had completed all four assessments (Fig. 1).

For regional MRI biomarkers, we excluded participants from ADNI1. The majority of these participants were scanned using 1.5T MRI scanners, as opposed to 3T scanners for the remaining ADNI phases. This exclusion mitigates the influence of different scanner field strengths on volumetric measurements [39, 40], and allows direct comparisons between participants in the other three ADNI phases.

As per ADNI protocol, before conducting protocol-specific procedures, informed written consent was obtained from all ADNI participants. The ADNI protocol received approval from the ethics committees and Institutional Review Boards of participating institutions, a full list of which can be found in the Supplementary Material. This article does not contain studies performed on human participants by any of the authors.

Fluid biomarkers

Biochemical markers examined in this study were obtained from CSF and plasma fluid samples, comprising a total of 1,173 CSF samples for $A\beta_{42}$, t-tau, and p-tau181, along with 404 samples for CSF NfL, and 560 samples for plasma NfL (Fig. 1). CSF peptides $A\beta_{42}$, t-tau, and p-tau181 were

measured using Elecsys electrochemiluminescence (ECL) immunoassays using an automated Cobas e 601 analyzer (Roche Diagnostics International Ltd). Full details of the reagents and platforms used are provided in [41]. In brief, the assay process consists of two consecutive incubation steps. In the first step, the sample is incubated with two monoclonal antibodies that form a sandwich complex specific for the detection of the biomarker [41]. During the second incubation, after the addition of streptavidin-coated magnetic microparticles, this complex attaches to the solid phase. For detection, the reaction mixture is then drawn into a measuring cell, where the microparticles are magnetically captured on an electrode surface. After a washing step to remove unbound substances, a voltage is applied, inducing chemiluminescent emission measured by a photomultiplier to quantify the target biomarker [41]. This study included values of $A\beta_{1-42}$ above the upper technical limit of 1,700 pg/mL, which were based on the extrapolation of the calibration curve. CSF NfL was quantified using immunoassays specific for NfL [42]. Plasma NfL was quantified using the Single Molecule array (Simoa) technique, with an assay combining monoclonal antibodies and purified bovine NfL as a calibrator [19]. CSF NfL values were reported in ng/L, whereas the remaining biomarkers were reported in pg/mL. We also included the p-tau181- $A\beta_{1-42}$ ratio, which has been shown to be sensitive to AD pathology and to be associated with brain amyloid burden [43].

CSF $A\beta_{1-42}$, t-tau, and p-tau181 values were determined by the ADNI Biomarker Core laboratory at the University of Pennsylvania [41, 44]. Samples were obtained from participants enrolled in ADNI1, ADNI GO, and ADNI2. CSF and plasma NfL values were determined by the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden, with samples obtained from a subset of ADNI1 participants only [19, 42].

Image acquisition and processing

Structural MR brain images were acquired according to the ADNI protocol. A description of the protocol used for MRI acquisition can be found in [45]. All participants in this study were scanned using a 3T MRI scanner. Four specific subregions of the temporal lobe that are associated with amnesic AD were included for analysis: the hippocampus, entorhinal cortex, and fusiform and middle temporal gyri. These regions serve as powerful markers

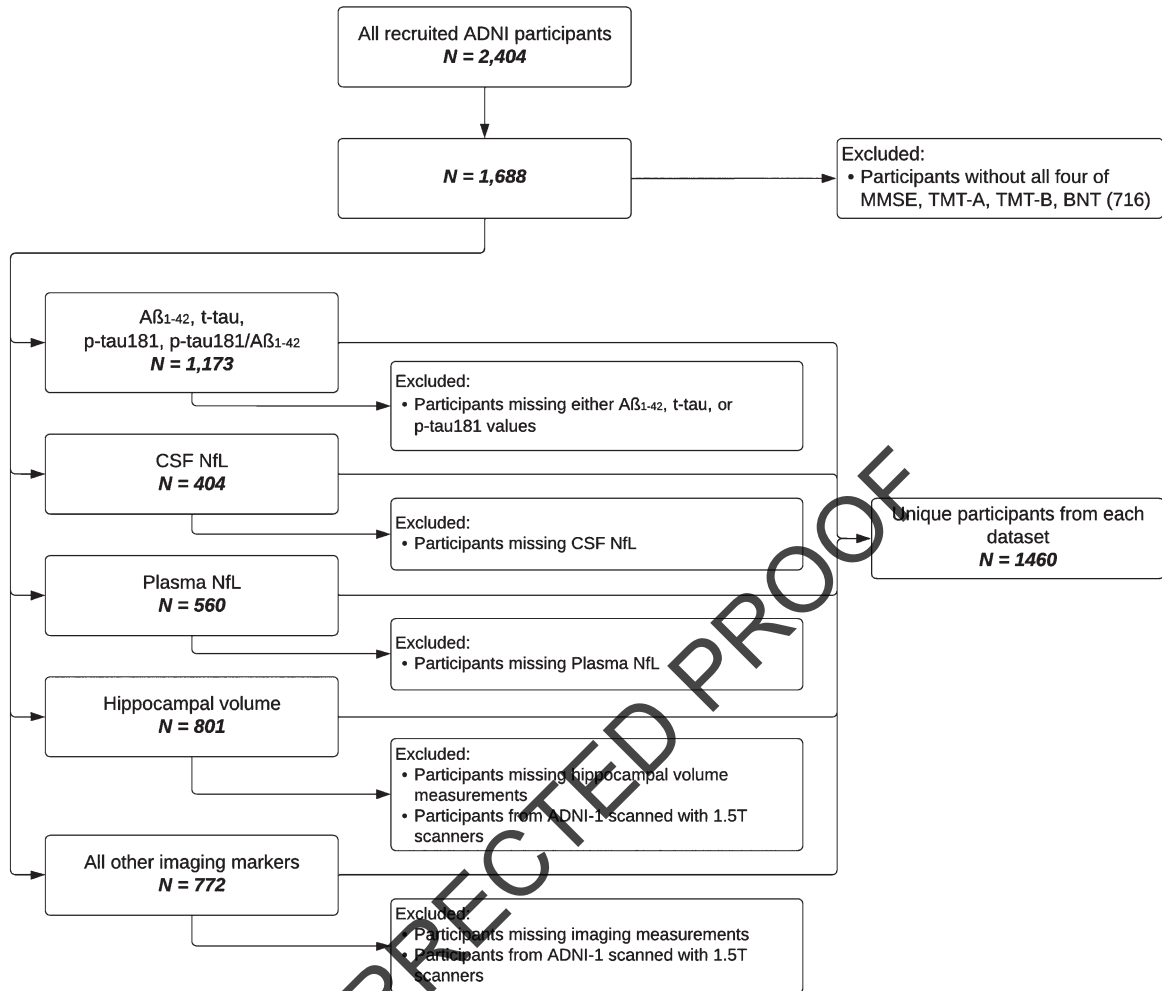


Fig. 1. PRISM flow diagram of participant inclusion in the final study sample. BNT, Boston Naming Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; MMSE, Mini-Mental State Exam.

for evaluating the severity of the disease, as they exhibit substantial rates of change in MCI and AD, as evidenced by postmortem examinations and MRI scans [46–49]. They are also thought to contribute to higher-order visual perception [50–52]. Furthermore, the measurements of these regions are readily accessible within ADNI. Volumetric and cortical thickness data were computed by the University of California, San Francisco (UCSF) based on the cross-sectional datasets. Cortical reconstruction and volumetric segmentation were performed using FreeSurfer. Additional details of the UCSF FreeSurfer methods used to analyze the MR images are described in [53]. To control for differences in overall brain size, each regional measurement was divided by the patient's full intracranial volume.

Neuropsychological assessments

Various global and domain-specific cognitive tests are available in the neuropsychological battery of ADNI; in this work, a subset consisting of MMSE, BNT, TMT-A, and TMT-B was used. We used the total scores for the MMSE and BNT for analysis and the completion times of TMT-A and TMT-B. The MMSE is used to assess global cognitive status, examining various cognitive domains, including attention, orientation, memory, registration, recall, and calculation [54]. It is scored on a scale of 0 to 30, with higher scores indicating better global cognitive functioning. The BNT is a visual confrontation naming test that measures word retrieval [54]. The ADNI study used the 30-item version of the BNT. Similar

to the MMSE, a score closer to 30 represents better domain-specific cognition. The TMT-A involves connecting numbered circles in ascending order from 1 to 25, and is a measure of visual search, attention, and speed [55, 56]. The TMT-B, which is a similar but slightly more challenging test that requires alternating between numbers and letters, measures the same cognitive abilities along with executive functions such as cognitive flexibility [55]. Both tests are scored based on the time it takes to complete the task, with faster completion times generally associated with better cognitive functioning and processing speed.

Statistical analyses

The aim of this analysis was to assess the strength and pattern of association between biomarkers for AD pathology and the four cognitive assessments, all of which contain a visual component. In this investigation, the cognitive test scores served as independent variables, while biomarkers were considered the dependent variables.

We first inspected the univariate distribution of each biomarker and cognitive exam, and assessed normality with the Shapiro-Wilk test for each plot of association between biomarker and cognitive assessment. After that, the TMT A and TMT B scores were log-transformed to achieve normality. All CSF and plasma biomarkers, including the p-tau181/A β ₁₋₄₂ ratio, were also log-transformed.

To assess visual patterns of cognitive decline, we plotted each biomarker against each cognitive assessment using locally estimated scatterplot smoothing (LOESS) (Figs. 2 and 3). We used LOESS in the study due to its non-parametric nature, which does not require making any underlying assumptions about the distributions of biomarker or cognitive assessment data. The goal was to take an exploratory approach to investigate these relationships. The smoothing parameter for all LOESS curves in this study was set to $\alpha = 0.75$. The plots were stratified by sex (reported in ADNI as gender) to limit confounding effects. Pearson correlation coefficients were calculated to assess the degree of association between biomarkers and cognitive assessments, and their absolute values taken to simplify comparison (Fig. 4). Raw Pearson's correlation coefficients (without the absolute value) are included in the Supplementary Material (see Supplementary Figure 1). For clarity in our discussion, we categorized the strength of each association according to its correlation coefficient. Consequently,

associations within the range of 0.2 to 0.39 were characterized as weak, those between 0.4 and 0.59 as moderate, and those with a correlation coefficient greater than 0.6 were denoted as strong.

All statistical analyses were performed with the R software (version 4.2.1) [57].

RESULTS

Demographic information and cognitive scores

The final subject sample used in this study comprised of 1460 unique participants. Among these participants, the mean age at baseline was 73.64 years (SD = 7.15), ranging from 54.4 to 91.4 years (45.48% female). On average, participants had 15.98 years of education (SD = 2.81). Detailed information on cohort-specific demographics and mean test scores is shown in Table 1.

Fluid biomarkers

An examination of the correlation coefficients comparing the degrees of association between the four cognitive tests and six fluid biomarkers (p-tau181, t-tau, A β ₁₋₄₂, CSF NfL, plasma NfL, and p-tau181/A β ₁₋₄₂ ratio) revealed that the MMSE consistently showed the strongest correlation with most fluid biomarkers (Fig. 4). Depending on sex, these correlations were either moderate or weak for p-tau181 (0.429 for females and 0.316 for males), t-tau (0.423 for females and 0.297 for males), and plasma NfL (0.359 for females and 0.304 for males). Notably, exceptions were found for A β ₁₋₄₂ and CSF NfL, where TMT-B, instead of MMSE, demonstrated a stronger, albeit still weak to moderate, correlation with these biomarkers. Specifically, among males, the coefficient was 0.408 for A β ₁₋₄₂ and 0.264 for CSF NfL, while among females, it was 0.391 for A β ₁₋₄₂ and 0.222 for CSF NfL. The cognitive assessment showing the lowest correlation with fluid biomarkers was either BNT or TMT-A, depending on the biomarker and sex studied.

Among the fluid biomarkers, the p-tau181/A β ₁₋₄₂ ratio demonstrated the highest associations with MMSE. Both, male and female participants, exhibited moderate negative correlation coefficients of -0.453 and -0.495, respectively. This finding suggests that a higher p-tau181/A β ₁₋₄₂ ratio was associated with lower MMSE scores. Analyzing the visual relationship between cognitive test scores

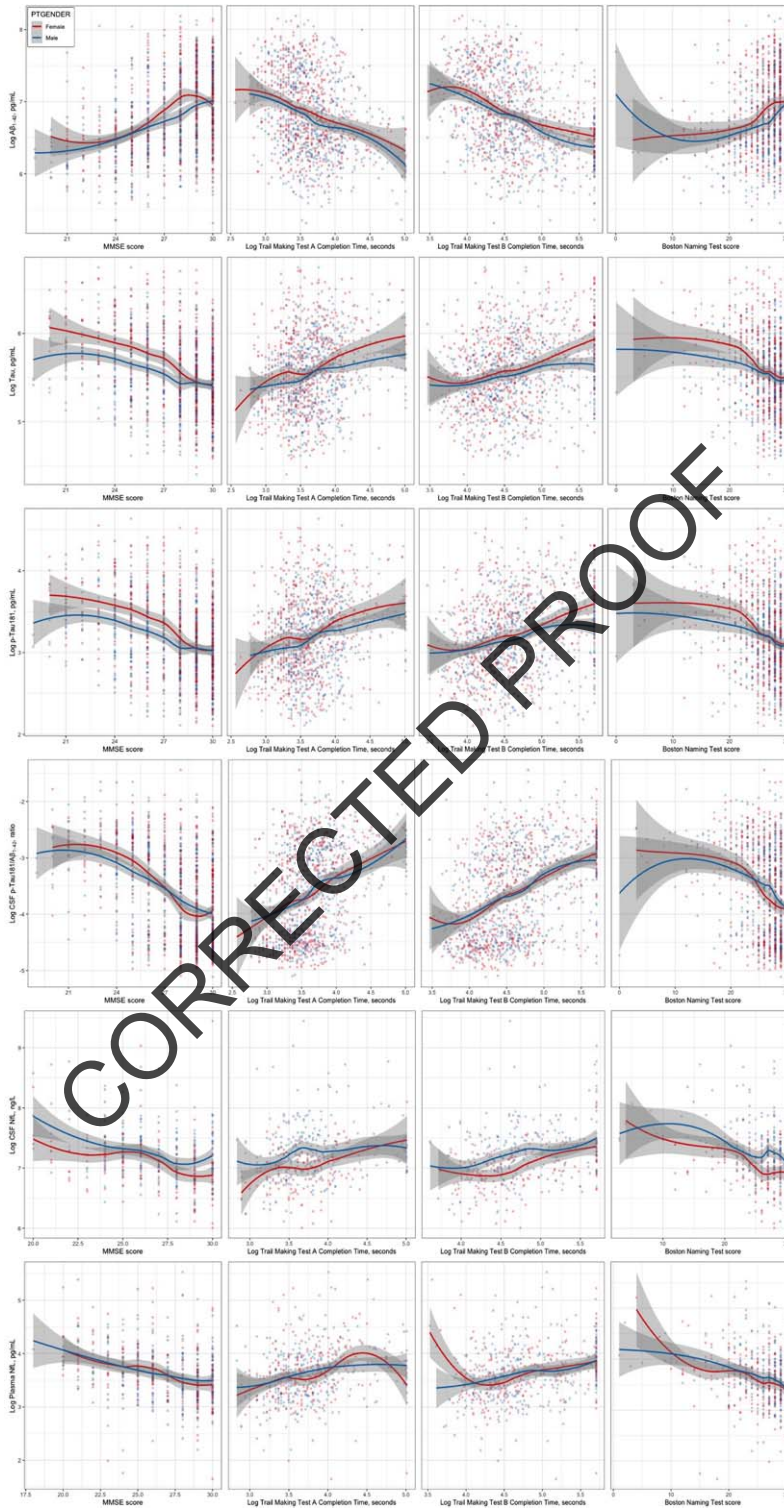


Fig. 2. Panel of scatterplots for fluid biomarkers versus cognitive assessments with fitted LOESS curves. LOESS curves were computed with a smoothing parameter of 0.75. Error bands represent 95% confidence intervals. MMSE, Mini-Mental State Exam.

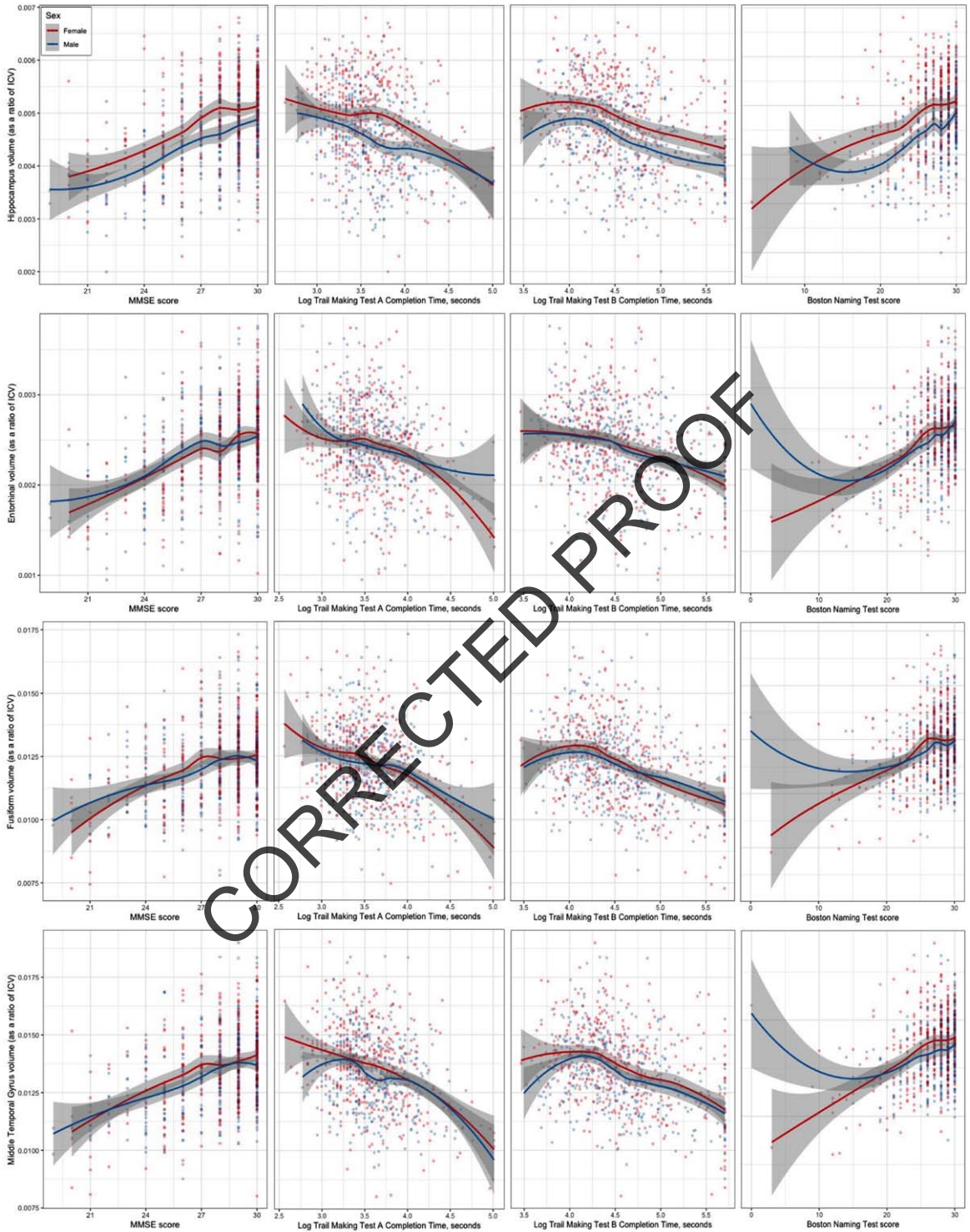


Fig. 3. Panel of scatterplots for imaging biomarkers vs. cognitive assessments with fitted LOESS curves. LOESS curves were computed with a smoothing parameter of 0.75. Error bands represent 95% confidence intervals. MMSE, Mini-Mental State Exam.

and the p-tau181/ $A\beta_{1-42}$ ratio showed that the MMSE and the BNT exhibited a tail-ended drop,

whereby even small decreases in these cognitive test scores were reflected by sharp increases in



Fig. 4. Absolute Pearson's correlation coefficient matrix of biomarkers and cognitive assessments. Correlation coefficients represent the association level between each biomarker and cognitive assessment, separated by sex. The first four columns correspond to imaging biomarkers, and the last six columns correspond to fluid biomarkers. BNT, Boston Naming Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; MMSE, Mini-Mental State Exam.

the p-tau181/Aβ₁₋₄₂ ratio (Fig. 2). In contrast, the association between the p-tau181/Aβ₁₋₄₂ ratio and completion times for TMT-A and TMT-B appeared more linear (Fig. 2).

Individually, p-tau181 and Aβ₁₋₄₂, along with t-tau, showed similar tail-ended changes as the p-tau181/Aβ₁₋₄₂ ratio when plotted against the MMSE and to a lesser degree against the BNT (Fig. 2). Biomarker associations with TMT-A and TMT-B completion times also appeared more linear.

The correlation coefficients between plasma or CSF NfL and each of the cognitive assessments (with the exception of BNT) were comparatively lower compared to other fluid biomarkers (Fig. 4). Notably, both CSF and plasma NfL exhibited a consistent and linear decline in association with improving cognitive scores (Fig. 2). When examining the relationship between fluid biomarkers and the BNT, both CSF and plasma NfL, also exhibited the highest correlation coefficients with BNT (0.246 and 0.351 for CSF NfL, and 0.302 and 0.286 for plasma NfL, for males and females respectively), followed by the p-tau181/Aβ₁₋₄₂ ratio and Aβ₁₋₄₂ (Fig. 4). The BNT showed the lowest correlation coefficients with p-tau181 and t-tau (0.204 and 0.274 for p-tau181, and 0.195 and 0.273 for t-tau, among males and females respectively). These findings indicate weaker associations between p-tau181, t-tau, and the BNT, compared to other fluid biomarkers.

Imaging biomarkers

The MMSE demonstrated the highest degree of association with most regional brain volume biomarkers, indicating a moderate relationship with cognitive performance (Fig. 4). The only exception was the fusiform gyrus, which exhibited a stronger association with TMT-B than with MMSE (0.327 for males and 0.44 for females compared to 0.303 for males and 0.351 for females). The entorhinal cortex and hippocampus showed stronger associations with the MMSE (0.360 and 0.437 for the entorhinal cortex, and 0.473 and 0.424 for the hippocampus, among males and females respectively) and BNT (0.367 and 0.383 for the entorhinal cortex, and 0.395 and 0.308 for the hippocampus, among males and females respectively), while the fusiform gyrus and middle temporal gyrus exhibited stronger associations with TMT-A (0.238 and 0.344 for the fusiform gyrus, and 0.254 and 0.381 for the middle temporal gyrus, among males and females respectively) and TMT-B (0.327 and 0.440 for the fusiform gyrus, and 0.351 and 0.379 for the middle temporal gyrus, among males and females respectively).

Among imaging biomarkers, the entorhinal cortex had the strongest association with MMSE (0.36 for males and 0.436 for females), along with the hippocampus (0.473 for males and 0.424 for females). However, these associations were relatively weaker

Table 1
Demographic and cognitive data for 1460 ADNI participants by biomarker cohort

Group		Biomarker cohorts				
		A β ₁₋₄₂ , t-tau, p-tau181, p-tau181/A β ₁₋₄₂	CSF NfL	Plasma NfL	Hippocampus	Entorhinal cortex, Middle temporal gyrus, Fusiform gyrus
Demographic						
Number of subjects		1,173	404	500	801	772
Mean age in years (SD)		73.28 (7.24)	74.89 (6.94)	75.55 (6.67)	72.60 (7.18)	72.01 (6.99)
Percent female		44.59	39.36	41.79	48.19	49.22
Mean education in years (SD)		16.09 (2.73)	15.69 (2.95)	15.55 (2.98)	16.22 (2.66)	16.31 (2.61)
Participants in each diagnostic group (%)	CN	362 (30.86)	116 (28.71)	192 (34.29)	269 (33.58)	265 (34.33)
	MCI	607 (51.75)	195 (48.27)	198 (35.36)	419 (52.31)	412 (53.37)
	AD	204 (17.39)	93 (23.02)	170 (30.36)	113 (14.11)	95 (12.31)
Mean cognitive test scores (SD)						
MMSE	CN	29.04 (1.16)	29.08 (1.03)	29.09 (0.99)	29.02 (1.20)	29.02 (1.24)
	MCI	27.74 (1.81)	26.93 (1.80)	26.90 (1.79)	28.10 (1.67)	28.10 (1.68)
	AD	23.46 (1.93)	23.33 (1.86)	23.33 (2.00)	23.24 (1.96)	23.29 (1.98)
TMT-A	CN	34.17 (11.92)	36.80 (13.52)	36.53 (13.23)	33.74 (11.40)	33.17 (10.91)
	MCI	40.61 (18.94)	44.94 (23.26)	45.40 (24.11)	38.36 (15.59)	38.43 (15.69)
	AD	61.52 (33.89)	67.81 (37.28)	65.06 (34.16)	59.11 (31.67)	58.88 (32.86)
TMT-B	CN	84.59 (42.49)	89.59 (41.81)	89.78 (42.95)	84.21 (43.39)	81.95 (42.17)
	MCI	113.40 (63.56)	131.92 (72.43)	133.86 (73.21)	104.84 (56.81)	103.72 (55.18)
	AD	196.28 (87.87)	204.49 (86.35)	198.24 (87.32)	196.56 (85.61)	196.60 (84.15)
BNT	CN	28.04 (2.24)	27.55 (2.47)	27.83 (2.39)	28.19 (2.13)	28.20 (2.14)
	MCI	26.46 (3.74)	25.67 (4.00)	25.46 (4.00)	26.99 (2.96)	26.88 (3.39)
	AD	21.77 (5.82)	23.02 (6.20)	22.41 (6.31)	22.23 (5.60)	22.42 (5.38)

t-tau, total tau; p-tau, phosphorylated tau; CSF, cerebrospinal fluid; NfL, neurofilament light chain; CN, cognitive normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; BNT, Boston Naming Test; SD, standard deviation.

compared to the association between MMSE and p-tau181/A β ₁₋₄₂ ratio. When examining the association with BNT, the imaging biomarkers demonstrated higher correlation coefficients compared to most fluid biomarkers (Fig. 4). Only CSF and plasma NfL exhibited stronger associations.

All imaging biomarkers showed an approximate linear LOESS curve when analyzed in relation to cognitive test scores, although the relationship between each of the imaging biomarkers and BNT appeared to have a slight concave downward trend (Fig. 3).

DISCUSSION

The primary objective of this study was to investigate and compare the associations between specific biomarkers and visual-perceptive cognitive abilities in participants across the whole AD spectrum. In doing so, we investigated the visual pattern of cognitive decline in terms of changes in biomarkers. Several fluid and structural MR biomarkers were included in this study and analyzed in conjunction with four cognitive assessments: the MMSE, TMT-A, TMT-B, and BNT. The MMSE, a measure of global cognitive functioning, exhibited the strongest associations with most biomarkers, indicating that it is more sensitive to variations in biological pathophysiology when compared to domain-specific cognitive assessments (Fig. 4). This observation is consistent with existing literature, where the MMSE demonstrates higher reported sensitivities than TMT and BNT in classifying subjects into AD diagnostic groups [58–60, 35]. This finding may be attributed to the fact that the assessment of multiple cognitive domains in the MMSE enhances sensitivity to AD-related brain changes. As a result, even if AD pathology affects specific cognitive domains, it is more likely to be detected by a generalized cognitive assessment such as the MMSE because it is more robust than many domain-specific assessments alone. It is likely for similar reasons that the MMSE outperformed its individual components in the diagnosis of AD in previous studies [61, 62]. The brain regions involved in higher-order visual processing, such as the fusiform gyrus, as well as the middle temporal gyrus involved in semantic memory, showed significant associations with TMT-A and TMT-B, which measure visuospatial abilities and symbol recognition, among other cognitive functions [63, 64]. Furthermore, poorer performance on the BNT, a measure of confrontational recall, was strongly associated with atrophy

in memory-related brain regions, specifically the entorhinal cortex and hippocampus. This observation aligns well with the existing literature that highlights the involvement of these regions in memory processes [65].

Among the biomarkers studied, the p-tau181/A β ₁₋₄₂ ratio had the strongest correlations with all cognitive assessments, the only exception being the BNT (Fig. 4). Previous research has shown an inverse correlation of the p-tau181/A β ₁₋₄₂ ratio with visual-spatial abilities, such as the clock drawing test, in patients with AD, which emphasizes the ratio's potential as a marker of visual-spatial cognitive impairment [66]. These results further contribute to existing research that has demonstrated the potential of this biomarker for diagnostic assistance, screening purposes, and prognostic evaluation [67, 68]. Additionally, while p-tau181 and A β ₁₋₄₂ individually have been shown to be strong biomarkers for AD pathology, this result suggests that considering both, tau and amyloid pathology, simultaneously better reflects cognitive decline [69]. The superior correlation of p-tau181/A β ₁₋₄₂ compared to p-tau181 and A β ₁₋₄₂ alone can be attributed to several possible reasons. For example, combining measures of two distinct pathological processes of AD into a single diagnostic biomarker may enhance its effectiveness [44]. Additionally, utilizing ratios of one protein to other brain-derived proteins may normalize natural fluctuations in protein concentration [44].

Furthermore, these findings are complemented by research demonstrating that tauopathy, including elevated phosphorylated tau, is associated with impairments in visuospatial episodic memory, aligning with our observations of the p-tau181/A β ₁₋₄₂ ratio's cognitive correlations [70–72]. This supports the notion that tau pathology may have a pronounced impact on certain cognitive domains, particularly visuospatial aspects of functioning, in the continuum of AD.

Elevated levels of NfL, a marker of axonal degeneration, have been consistently associated with poorer performance on cross-sectional cognitive tests [73]. In our study, we observed weak associations between higher plasma and CSF NfL levels and lower cognitive test scores (Fig. 4). However, in particular, NfL exhibited a stronger association with the BNT compared to other fluid biomarkers. Given that the BNT primarily measures confrontational recall and was previously shown to be associated with atrophy in the entorhinal cortex and hippocampus, these findings

may suggest that axonal-predominant degeneration in these specific regions may contribute to recall deficits. While recent research in other neurodegenerative diseases lends some credence to this hypothesis [74], further investigations on regional neuroaxonal degeneration in patients would be required to establish direct evidence for this assumption. The correlation coefficients for CSF and plasma NfL were similar, showing slight variations between different cognitive assessments and with respect to sex (Fig. 4). However, no consistent trend was discernible in relation to sex. These results support the use of plasma NfL as a biomarker that can be obtained through less invasive methods while providing comparable information to CSF NfL.

With respect to the visual analysis of patterns related to the changes in imaging biomarkers and cognition, our findings suggest that the regional variation in brain volumes correlates with cognitive performance (Fig. 3). In contrast, the patterns of change in fluid biomarkers and cognition exhibited greater variability. These findings are consistent with the existing body of knowledge suggesting that different biomarkers reflect distinct mechanisms of damage [75]. For instance, similar patterns of diminished task performance have been observed in artificial neural networks when synaptic damage occurs, as opposed to neuronal damage [37]. Variations in patterns between biomarkers may also be explained by our understanding that changes in different biomarkers occur at different stages of the disease continuum [75].

Close inspection of the observed patterns also revealed that even minor declines in cognition were accompanied by sharp changes in some fluid biomarker values, especially p-tau181/A β_{1-42} (Fig. 2). This finding suggests that subtle changes in cognitive function beyond a certain threshold are associated with significant changes in fluid biomarkers. One possible explanation for this phenomenon is the presence of a cognitive reserve, which allows the brain to withstand limited damage before cognitive deficits become more pronounced [76, 77]. In contrast, the presence of a linear relationship between cognitive assessments and various imaging and fluid biomarkers indicates heterogeneity between markers that warrants further investigation. The findings presented here provide a more detailed picture of specific patterns of degeneration with biomarkers and subsequent cognitive decline, specifically visual processing. This will help future studies to develop more precise models of disease progression, which

may lead to the investigation of optimal intervention strategies.

The present study has several limitations that should be acknowledged. First, the data used in this work are subject to considerable variance from confounding factors, such as participant age, education, ailment condition, carrier status of *APOE* $\epsilon 4$, or variables such as body mass index and creatinine, which are known to affect plasma biomarker values [78]. The design of the study, namely our reliance on a visual analysis of trends, posed challenges in controlling for these factors. Although further stratification of the graphs beyond sex could potentially mitigate this issue, it would introduce complexity to the analysis. Second, visual analysis of trends introduces other inherent limitations. Describing these trends in a manner that allows for direct comparisons is challenging, and even when attempted, the subjective nature of those descriptions persists. We made a deliberate choice to utilize LOESS over other general multivariate regression models to better observe the intrinsic behavior of the data and account for its natural variations without making any strict assumptions. Moreover, it is important to acknowledge that the study population consisted of ADNI participants, who tend to have higher levels of education and may not be fully representative of the general population. Finally, it should be noted that the comparison of results between different biomarkers should be interpreted cautiously due to the utilization of different cohorts for each biomarker, thereby adding another degree of variability that limits direct comparisons.

In conclusion, this study investigated biomarker associations with the decline of visual processing, providing valuable insights into the intricate relationship between biomarkers and cognition across the AD spectrum. Relevant correlations were observed between biomarkers and cognitive performance, highlighting their potential value in assessing disease severity. Brain regions associated with visual processing and memory showed significant associations with corresponding cognitive assessments. Overall, these findings contribute to our understanding of the complex interplay between biomarkers and cognitive decline of the visual domain in patients along the AD spectrum.

AUTHOR CONTRIBUTIONS

Ashar Memon (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visu-

alization; Writing – original draft; Writing – review & editing); Jasmine A Moore (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing); Chris Kang (Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing); Zahinoor Ismail (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing); Nils D. Forkert (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing).

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CONFLICT OF INTEREST

Zahinoor Ismail has received personal fees for consulting/advisory boards for Otsuka/Lundbeck and consulting fees paid to institution by Biogen and Roche. Zahinoor Ismail is an Editorial Board Member of this journal but was not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available in the ADNI dataset, which can be accessed by approved users on <https://adni.loni.usc.edu>.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-231084>.

REFERENCES

- [1] Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA (2009) The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* **66**, 200-208.
- [2] Hennekes C, Reed C, Chen YF, Dell'Agnello G, Lebec J (2016) Describing the sequence of cognitive decline in Alzheimer's disease patients: Results from an observational study. *J Alzheimers Dis* **52**, 1065-1080.
- [3] Qiu C, Kivipelto M, von Strauss E (2009) Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci* **11**, 111-128.

- [4] Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement* **8**, 1-13.
- [5] Wilson DM, 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I (2023) Hallmarks of neurodegenerative diseases. *Cell* **186**, 693-714.
- [6] Fortea J, Garcia-Arcelay E, Terrance A, Galvez B, Diez-Carreras V, Rebollo P, Maurino J, Garcia-Ribas G (2023) Attitudes of neurologists toward the use of biomarkers in the diagnosis of early Alzheimer's disease. *J Alzheimers Dis* **93**, 275-282.
- [7] Bocchetta M, Galluzzi S, Kehoe PG, Aguera E, Bernabei R, Bullock R, Ceccaldi M, Dartigues JF, de Mendonca A, Didic M, Eriksdotter M, Felician O, Frolich L, Gertz HJ, Hallikainen M, Hasselbalch SG, Hausner L, Heuser I, Jessen F, Jones RW, Kurz A, Lawlor B, Lleo A, Martinez-Lage P, Mecocci P, Mehrabian S, Monsch A, Nobili F, Nordberg A, Rikkert MO, Orgogozo JM, Pasquier F, Peters O, Salmon E, Sanchez-Castellano C, Santana I, Sarazin M, Traykov L, Tsolaki M, Visser PJ, Wallin AK, Wilcock G, Wilkinson D, Wolf H, Yener G, Zekry D, Frisoni GB (2015) The use of biomarkers for the etiologic diagnosis of MCI in Europe: An EADC survey. *Alzheimers Dement* **11**, 195-206 e191.
- [8] Schweda M, Kogel A, Bartels C, Wiltfang J, Schneider A, Schickanz S (2018) Prediction and early detection of Alzheimer's dementia: Professional disclosure practices and ethical attitudes. *J Alzheimers Dis* **62**, 145-155.
- [9] Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, Hampel H, Jagust WJ, Johnson KA, Knopman DS, Petersen RC, Scheltens P, Sperling RA, Dubois B (2016) A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* **87**, 539-547.
- [10] Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, Nixon RA, Jones DT (2021) Alzheimer disease. *Nat Rev Dis Primers* **7**, 33.
- [11] Teunissen CE, Chiu MJ, Yang CC, Yang SY, Scheltens P, Zetterberg H, Blennow K (2018) Plasma amyloid-beta (Abeta42) correlates with cerebrospinal fluid Abeta42 in Alzheimer's disease. *J Alzheimers Dis* **62**, 1857-1863.
- [12] Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, Airey DC, Knopman DS, Roberts RO, Machulda MM, Jack CR, Jr., Petersen RC, Dage JL (2018) Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement* **14**, 989-997.
- [13] Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K (2019) Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurol* **76**, 791-799.
- [14] Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Dore V, Fowler C, Li QX, Martins R, Rowe C, Tomita T, Matsuzaki K, Ishii K, Ishii K, Arahata Y, Iwamoto S, Ito K, Tanaka K, Masters CL, Yanagisawa K (2018) High performance plasma amyloid-beta biomarkers for Alzheimer's disease. *Nature* **554**, 249-254.
- [15] Naude JP, Gill S, Hu S, McGirr A, Forkert ND, Monchi O, Stys PK, Smith EE, Ismail Z, Alzheimer's Disease Neuroimaging Initiative (2020) Plasma neurofilament light: A marker of neurodegeneration in mild behavioral impairment. *J Alzheimers Dis* **76**, 1017-1027.
- [16] Ghahremani M, Wang M, Chen HY, Zetterberg H, Smith E, Ismail Z, Alzheimer's Disease Neuroimaging Initiative (2023) Plasma phosphorylated tau at threonine 181 and neuropsychiatric symptoms in preclinical and prodromal Alzheimer disease. *Neurology* **100**, e683-e693.
- [17] Skillback T, Farahmand BY, Rosen C, Mattsson N, Nagga K, Kilander L, Religa D, Wimo A, Winblad B, Schott JM, Blennow K, Eriksdotter M, Zetterberg H (2015) Cerebrospinal fluid tau and amyloid-beta1-42 in patients with dementia. *Brain* **138**, 2716-2731.
- [18] Jiao F, Yi F, Wang Y, Zhang S, Guo Y, Du W, Gao Y, Ren J, Zhang H, Liu L, Song H, Wang L (2020) The validation of multifactor model of plasma Abeta (42) and total-tau in combination with MoCA for diagnosing probable Alzheimer disease. *Front Aging Neurosci* **12**, 212.
- [19] Mattsson N, Andreasson U, Zetterberg H, Blennow K, Alzheimer's Disease Neuroimaging Initiative (2017) Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol* **74**, 557-566.
- [20] Armstrong NM, An Y, Shin JJ, Williams OA, Doshi J, Erus G, Davatzikos C, Ferrucci L, Beason-Held LL, Resnick SM (2020) Associations between cognitive and brain volume changes in cognitively normal older adults. *Neuroimage* **223**, 117289.
- [21] Xiao Z, Wu X, Wu W, Yi J, Liang X, Ding S, Zheng L, Luo Y, Gu H, Zhao Q, Xu H, Ding D (2021) Plasma biomarker profiles and the correlation with cognitive function across the clinical spectrum of Alzheimer's disease. *Alzheimers Res Ther* **13**, 123.
- [22] Ismail Z, Leon R, Creese B, Ballard C, Robert P, Smith EE (2023) Optimizing detection of Alzheimer's disease in mild cognitive impairment: A 4-year biomarker study of mild behavioral impairment in ADNI and MEMENTO. *Mol Neurodegener* **18**, 50.
- [23] Tyler SL, Maltby J, Paterson KB, Hutchinson CV (2022) Reduced vision-related quality of life in dementia: A preliminary report. *J Alzheimers Dis* **87**, 239-246.
- [24] Kirby E, Bandelow S, Hogervorst E (2010) Visual impairment in Alzheimer's disease: A critical review. *J Alzheimers Dis* **21**, 15-34.
- [25] Glosser G, Gallo J, Duda N, de Vries JJ, Clark CM, Grossman M (2002) Visual perceptual functions predict instrumental activities of daily living in patients with dementia. *Neuropsychiatry Neuropsychol Behav Neurol* **15**, 198-206.
- [26] Ocal D, McCarthy ID, Poole T, Primativo S, Suzuki T, Tyler N, Frost C, Crutch SJ, Yong KXX (2023) Effects of the visual environment on object localization in posterior cortical atrophy and typical Alzheimer's disease. *Front Med (Lausanne)* **10**, 1102510.
- [27] Brewer AA, Barton B (2014) Visual cortex in aging and Alzheimer's disease: Changes in visual field maps and population receptive fields. *Front Psychol* **5**, 74.
- [28] Wu SZ, Masurkar AV, Balcer LJ (2020) Afferent and efferent visual markers of Alzheimer's disease: A review and update in early stage disease. *Front Aging Neurosci* **12**, 572337.
- [29] Kang SH, Park YH, Lee D, Kim JP, Chin J, Ahn Y, Park SB, Kim HJ, Jang H, Jung YH, Kim J, Lee J, Kim JS, Cheon BK, Hahn A, Lee H, Na DL, Kim YJ, Seo SW (2019) The cortical neuroanatomy related to specific neuropsychological deficits in Alzheimer's continuum. *Dement Neurocogn Disord* **18**, 77-95.
- [30] Bruffaerts R, Schaeveerbeke J, De Weer AS, Nelissen N, Dries E, Van Bouwel K, Sieben A, Bergmans B, Swinnen

- C, Pijnenburg Y, Snaert S, Vandenbulcke M, Vandenbergh R (2020) Multivariate analysis reveals anatomical correlates of naming errors in primary progressive aphasia. *Neurobiol Aging* **88**, 71-82.
- [31] Weiner KS, Zilles K (2016) The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia* **83**, 48-62.
- [32] Sanchez-Valle R, Heslegrave A, Foiani MS, Bosch B, Antonell A, Balasa M, Llado A, Zetterberg H, Fox NC (2018) Serum neurofilament light levels correlate with severity measures and neurodegeneration markers in autosomal dominant Alzheimer's disease. *Alzheimers Res Ther* **10**, 113.
- [33] Salobar-Garcia E, de Hoz R, Rojas B, Ramirez AI, Salazar JJ, Yubero R, Gil P, Trivino A, Ramirez JM (2015) Ophthalmologic psychophysical tests support OCT findings in mild Alzheimer's disease. *J Ophthalmol* **2015**, 736949.
- [34] Salobar-Garcia E, de Hoz R, Ramirez AI, Lopez-Cuenca I, Rojas P, Vazirani R, Amarante C, Yubero R, Gil P, Pinazo-Duran MD, Salazar JJ, Ramirez JM (2019) Changes in visual function and retinal structure in the progression of Alzheimer's disease. *PLoS One* **14**, e0220535.
- [35] Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA (2008) Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Arch Clin Neuropsychol* **23**, 129-137.
- [36] Hirsch JA, Cuesta GM, Jordan BD, Fonzeiti P, Levin L (2016) The auditory naming test improves diagnosis of naming deficits in dementia. *Sage Open* **6**, 2158244016665693.
- [37] Moore JA, Tuladhar A, Ismail Z, Mouches P, Wilms M, Forkert ND (2023) Dementia in convolutional neural networks: Using deep learning models to simulate neurodegeneration of the visual system. *Neuroinformatics* **21**, 45-55.
- [38] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jr., Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology* **74**, 201-209.
- [39] Chow N, Hwang KS, Hurtz S, Green AE, Somme JH, Thompson PM, Elashoff DA, Jack CR, Weiner M, Apostolova LG, Alzheimer's Disease Neuroimaging Initiative (2015) Comparing 3T and 1.5T MRI for mapping hippocampal atrophy in the Alzheimer's Disease Neuroimaging Initiative. *AJNR Am J Neuroradiol* **36**, 653-660.
- [40] Jovicich J, Czanner S, Han X, Salat D, van der Kouwe A, Quinn B, Pacheco J, Albert M, Killiany R, Blacker D, Maguire P, Rosas D, Makris N, Gollub R, Dale A, Dickerson BC, Fischl B (2009) MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths. *Neuroimage* **46**, 177-192.
- [41] Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Jr., Militello M, Andreasson U, Hubeek I, Gibson D, Chu DC, Eichenlaub U, Heiss P, Kobold U, Leinenbach A, Madin K, Manuilova E, Rabe C, Blennow K (2016) Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement* **12**, 517-526.
- [42] Zetterberg H, Skillback T, Mattsson N, Trojanowski JQ, Portelius E, Shaw LM, Weiner MW, Blennow K, Alzheimer's Disease Neuroimaging Initiative (2016) Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. *JAMA Neurol* **73**, 60-67.
- [43] Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S (2017) CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev* **3**, CD010803.
- [44] Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, Lifke V, Corradini V, Eichenlaub U, Batrla R, Buck K, Zink K, Rabe C, Blennow K, Shaw LM, Swedish Bio Fsg, Alzheimer's Disease Neuroimaging I (2018) CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement* **14**, 1470-1481.
- [45] Jack CR, Jr., Barnes J, Bernstein MA, Borowski BJ, Brewer J, Clegg S, Dale AM, Carmichael O, Ching C, DeCarli C, Desikan RS, Fennema-Notestine C, Fjell AM, Fletcher E, Fox NC, Gunter J, Gutman BA, Holland D, Hua X, Insel P, Kantarci K, Killiany RJ, Krueger G, Leung KK, Mackin S, Maillard P, Malone JB, Mattsson N, McEvoy L, Modat M, Mueller S, Nosheny R, Ourselin S, Schuff N, Senjem ML, Simonson A, Thompson PM, Rettmann D, Vemuri P, Walhovd K, Zhao Y, Zuk S, Weiner M (2015) Magnetic resonance imaging in Alzheimer's Disease Neuroimaging Initiative 2. *Alzheimers Dement* **11**, 740-756.
- [46] Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259.
- [47] Holland D, Brewer JB, Hagler DJ, Fennema-Notestine C, Dale AM, Alzheimer's Disease Neuroimaging I (2009) Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci U S A* **106**, 20954-20959.
- [48] Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttman CR, Blacker D, Hyman BT, Albert MS, Killiany RJ (2008) MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Neurology* **71**, 819-825.
- [49] Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckner RL (2009) 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* **19**, 497-510.
- [50] Lee AC, Yeung LK, Barense MD (2012) The hippocampus and visual perception. *Front Hum Neurosci* **6**, 91.
- [51] Grill-Spector K, Weiner KS (2014) The functional architecture of the ventral temporal cortex and its role in categorization. *Nat Rev Neurosci* **15**, 536-548.
- [52] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
- [53] Hartig M, Truran-Sacrej D, Raptentsetsang S, Simonson A, Mezher A, Schuff N, Weiner M, (2014) *UCSF FreeSurfer Methods*. ADNI Alzheimer's Disease Neuroimaging Initiative: San Francisco, CA, USA.
- [54] Calero MD, Arnedo ML, Navarro E, Ruiz-Pedrosa M, Carnero C (2002) Usefulness of a 15-item version of the Boston Naming Test in neuropsychological assessment of low-educational elders with dementia. *J Gerontol B Psychol Sci Soc Sci* **57**, P187-191.
- [55] Smith Watts AK, Ahern DC, Jones JD, Farrer TJ, Correia S (2019) Trail-Making Test Part B: Evaluation of the effi-

- ciency score for assessing floor-level change in Veterans. *Arch Clin Neuropsychol* **34**, 243-253.
- [56] Spreen O, Strauss E (1998) *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. Oxford University Press, USA.
- [57] R Core Team (2015) *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing.
- [58] Abramson DA, Resch ZJ, Ovsiew GP, White DJ, Bernstein MT, Basurto KS, Soble JR (2022) Impaired or invalid? Limitations of assessing performance validity using the Boston Naming Test. *Appl Neuropsychol Adult* **29**, 486-491.
- [59] Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJ, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton GF, Neale BE, Watton ME, Cullum S (2016) Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev* **2016**, CD011145.
- [60] Tariq SH, Tumosa N, Chibnall JT, Perry MH, 3rd, Morley JE (2006) Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder—a pilot study. *Am J Geriatr Psychiatry* **14**, 900-910.
- [61] Braekhus A, Laake K, Engedal K (1992) The Mini-Mental State Examination: Identifying the most efficient variables for detecting cognitive impairment in the elderly. *J Am Geriatr Soc* **40**, 1139-1145.
- [62] Fillenbaum GG, Wilkinson WE, Welsh KA, Mohs RC (1994) Discrimination between stages of Alzheimer's disease with subsets of Mini-Mental State Examination items: An analysis of Consortium to Establish a Registry for Alzheimer's Disease data. *Arch Neurol* **51**, 916-921.
- [63] Palejwala AH, O'Connor KP, Milton CK, Anderson G, Pelargos P, Briggs RG, Conner AK, O'Donoghue DL, Glenn CA, Sughrue ME (2020) Anatomy and white matter connections of the fusiform gyrus. *Sci Rep* **10**, 3449.
- [64] Levy DA, Bayley PJ, Squire LR (2004) The anatomy of semantic knowledge: Medial vs. lateral temporal lobe. *Proc Natl Acad Sci U S A* **101**, 6710-6715.
- [65] Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS (2002) MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology* **58**, 1188-1196.
- [66] de Oliveira FF, Miraldo MC, de Castro-Neto EF, de Almeida SS, Matas SLA, Bertolucci PHF, Naffah-Mazzacoratti MDG (2023) Differential associations of clinical features with cerebrospinal fluid biomarkers in dementia with Lewy bodies and Alzheimer's disease. *Aging Clin Exp Res* **35**, 1741-1752.
- [67] Campbell MR, Ashrafzadeh-Kian S, Petersen RC, Mielke MM, Syrjanen JA, van Harten AC, Lowe VJ, Jack CR, Jr., Bornhorst JA, Algeciras-Schimnich A (2021) P-tau/Abeta42 and Abeta42/40 ratios in CSF are equally predictive of amyloid PET status. *Alzheimers Dement (Amst)* **13**, e12190.
- [68] Fowler CJ, Stoops E, Rainey-Smith SR, Vanmechelen E, Vanbrabant J, Dewit N, Mauroo K, Maruff P, Rowe CC, Frripp J, Li QX, Bourgeat P, Collins SJ, Martins RN, Masters CL, Doecke JD (2022) Plasma p-tau181/Abeta(1-42) ratio predicts Abeta-PET status and correlates with CSF-p-tau181/Abeta(1-42) and future cognitive decline. *Alzheimers Dement (Amst)* **14**, e12375.
- [69] Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M, Rich K, Kaiser E, Verbeek M, Tsolaki M, Mulugeta E, Rosen E, Aarsland D, Visser PJ, Schroder J, Marcussen J, de Leon M, Hampel H, Scheltens P, Pirtila T, Wallin A, Jonhagen ME, Minthon L, Winblad B, Blennow K (2009) CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* **302**, 385-393.
- [70] Okafor M, Nye JA, Shokouhi M, Shaw LM, Goldstein F, Hajjar I (2020) 18F-Flortaucipir PET associations with cerebrospinal fluid, cognition, and neuroimaging in mild cognitive impairment due to Alzheimer's disease. *J Alzheimers Dis* **74**, 589-601.
- [71] Pettigrew C, Soldan A, Moghekar A, Wang MC, Gross AL, O'Brien R, Albert M (2015) Relationship between cerebrospinal fluid biomarkers of Alzheimer's disease and cognition in cognitively normal older adults. *Neuropsychologia* **76**, 63-72.
- [72] Seo EH, Lim HJ, Yoon HJ, Choi KY, Lee JJ, Park JY, Choi SH, Kim H, Kim BC, Lee KH (2021) Visuospatial memory impairment as a potential neurocognitive marker to predict tau pathology in Alzheimer's continuum. *Alzheimers Res Ther* **13**, 167.
- [73] He L, Morley JE, Aggarwal G, Nguyen AD, Vellas B, de Souto Barreto P, MAPT/DSA Group (2021) Plasma neurofilament light chain is associated with cognitive decline in non-dementia older adults. *Sci Rep* **11**, 13394.
- [74] Frigerio I, Laansma MA, Lin CP, Hermans EJM, Bouwman MMA, Bol J, Galis-de Graaf Y, Hepp DH, Rozemuller AJM, Barkhof F, van de Berg WDJ, Jonkman LE (2023) Neurofilament light chain is increased in the parahippocampal cortex and associates with pathological hallmarks in Parkinson's disease dementia. *Transl Neurodegener* **12**, 3.
- [75] Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.
- [76] Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* **11**, 1006-1012.
- [77] Esiri MM, Chance SA (2012) Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease. *Alzheimers Res Ther* **4**, 7.
- [78] Pichet Binette A, Janelidze S, Cullen N, Dage JL, Bateman RJ, Zetterberg H, Blennow K, Stomrud E, Mattsson-Carlsson N, Hansson O (2023) Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement* **19**, 1403-1414.