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ORIGINAL ARTICLE

Cognitive components derived from traditional neuropsychological tests and their associations with plasma p-tau217 and p-tau181 in mild cognitive impairment: a multisite analysis

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Abstract

Background Currently, no single biomarker can reliably identify preclinical Alzheimer's disease (AD), particularly at or before the mild cognitive impairment (MCI) stage. Given the heterogeneity of MCI, integrative approaches are needed to improve early risk stratification.

Objectives (i) To derive robust latent cognitive components from a multicenter, clinically defined MCI cohort using principal component analysis (PCA); (ii) to investigate the associations between these components and plasma p-tau217 and p-tau181 levels.

Methods Data from 742 MCI participants in the AI-Mind cohort were analyzed. Cognitive domains were derived using PCA with varimax rotation and tested for associations with plasma p-tau biomarkers using site-specific linear regressions, adjusted for age, sex, and education.

Results A reproducible four-component cognitive structure emerged (memory, executive/processing

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speed, verbal fluency, visuospatial ability), with memory as the most p-tau-sensitive domain. The p-tau217 measure showed stronger associations with memory than p-tau181, though effects varied by site. *Conclusion* The findings indicate that a robust four-factor cognitive structure can be identified in clinically defined MCI cohorts without prior biological selection. The association between latent memory factors and plasma p-tau217, observed primarily in cohorts with higher biomarker burden or clearer amnestic profiles, highlights the potential for blood-based biomarkers to refine risk assessment in routine clinical practice.

Keywords Mild cognitive impairment, p-tau 217 · p-tau 181, principal component analysis · Alzheimer's disease · Plasma biomarkers

Introduction

Alzheimer's disease (AD) is undergoing a conceptual shift from a clinically defined syndrome to a biologically grounded entity, identified through in vivo biomarkers regardless of symptom severity. This transformation was formalized in the 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework, which introduced the A/T/N classification system encompassing amyloid pathology (A), tau pathology (T), and neurodegeneration (N) [1]. In 2024, the framework was updated to incorporate plasma biomarkers, facilitating broader clinical and research applicability, including earlier diagnosis and improved scalability [2].

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Among tau biomarkers, plasma phosphorylated tau at threonine 217 (p-tau217) and 181 (p-tau181) have shown high promise for early detection of AD pathology [3–6]. These markers correlate strongly with tau PET imaging, cerebrospinal fluid (CSF) p-tau levels, CSF amyloid biomarker ratios (e.g., Aβ42/40 and p-tau/Aβ42), longitudinal clinical outcomes, as well as neuropathology at autopsy [7–10]. With advances in immunoassay technologies, blood-based p-tau markers are increasingly integrated into diagnostic workflows, particularly in preclinical and prodromal populations, and may offer scalable solutions for population-level screening [11].

Despite this progress, accurately identifying individuals at high risk for progression to dementia remains challenging. Mild cognitive impairment (MCI) is a widely used clinical and research construct characterized by cognitive decline in the absence of functional dependence [12]. Although MCI is associated with an elevated risk of conversion to dementia, estimated at 10–15% per year [13], its clinical course is highly heterogeneous, with many individuals remaining stable or even reverting to normal cognition [14]. Operational neuropsychological definitions, such as those proposed by Petersen/Winblad [15] and Jak/Bondi [16], differ in sensitivity and specificity, which may limit their utility for individualized risk prediction.

Accordingly, current research highlights the need for integrative models that combine cognitive profiles, fluid biomarkers, genetic risk (e.g., *APOE* ε4 status) [17, 18] and neuroimaging [19, 20] to improve early detection and stratification [21–24]. Although neuropsychological testing remains essential for characterizing cognitive profiles in MCI, its utility is constrained by substantial interindividual variability, ceiling and floor effects, and inconsistencies in normative standards. Multivariate statistical techniques, such as principal component analysis (PCA), enable the reduction of complex cognitive test batteries into representative cognitive domains that may more accurately capture the major dimensions of variance rather than task-specific effects.

The present study, conducted within the AI-Mind project (Horizon 2020, Grant No. 964220), leverages the cognitive and plasma biomarker data collected at baseline across four European clinical sites. In line with the need for integrative, biologically informed risk models, our objectives were: (i) to derive robust latent cognitive components from a multicenter, clinically defined MCI cohort using Principal Component Analysis (PCA); and (ii) to investigate the associations between these cognitive components and plasma concentrations of p-tau217 and p-tau181. This work contributes to the field by demonstrating that multivariate cognitive components remain stable across heterogeneous cohorts, even when participants were recruited based on clinical criteria without prior biological stratification. More broadly, this work supports the use of a harmonized cognitive-biomarker framework for identifying AD-related decline in "real world" clinical settings.

Methods

Study design and setting

The AI-Mind project is a five-year, multicenter, prospective observational cohort study conducted across four European countries: Norway, Italy, Finland, and Spain. Its overarching goal is to develop and validate AI-based tools to identify individuals with mild cognitive impairment (MCI) who are at high risk of progressing to dementia [25]. Recruitment strategies varied across sites, ranging from public advertisements targeting the general population to referrals from memory clinics. In Italy and Spain, participants were primarily recruited from clinical settings, whereas Finland employed a mixed strategy involving both clinical and community populations. In Norway, most participants were recruited from the general population. The study was conducted in accordance with the principles of the Declaration of Helsinki and has received approval from relevant ethics committees and national data protection authorities. All participants provided written informed consent prior to inclusion.

Inclusion criteria

Participants aged 60 to 80 years were eligible if they met diagnostic criteria for MCI based on either the Petersen/Winblad (PW) or Jak/Bondi (JB) frameworks [15, 16]. Individuals with a diagnosis of dementia, or with any neurological, psychiatric,

metabolic, or systemic condition capable of explaining cognitive impairment, were excluded. Healthy controls were not included.

In Finland, recruitment included 79 participants with subjective cognitive complaints (SCC) but without objective cognitive impairment (PW/JB), corresponding to 42.9% of the Finish cohort, and 10.6% of the total study sample, who were classified by a consensus diagnosis as representing the Subjective Cognitive Decline (SCD) stage within the MCI continuum.

Diagnostic decisions were made at each site by interdisciplinary consensus involving the examining physician, neuropsychologist, and study coordinator/principal investigator, with consideration of contextual factors such as education, occupational history, sensory deficits, and clinical presentation. For a complete description of the recruitment process, refer to the AI-Mind clinical study protocol [25].

Neuropsychological assessment

A structured and standardized neuropsychological test battery was administered to comprehensively assess cognitive function. The tests were selected for their sensitivity to early cognitive decline and alignment with international MCI diagnostic criteria. The assessment battery covered memory, language, processing speed, executive functioning, and visuospatial function.

While a harmonized protocol was implemented across all sites, some site-specific discrepancies were inevitable due to differences in availability of validated instruments, normative data, and clinical practice traditions across countries. To maximize comparability, we selected cognitive measures that were most consistently harmonized across sites.

For the present study, memory was assessed using the delayed recall trial of the Rey Auditory Verbal Learning Test (RAVLT) [26] and the delayed recall condition of the Rey–Osterrieth Complex Figure Test (ROCF) [27, 28]. Language was evaluated using semantic fluency (Category Fluency; CF) [29] and phonemic fluency tasks (Letter Fluency; LF) [30]**.** Processing speed and executive function were assessed via the Trail Making Test Part A (TMT-A) [31, 32], reflecting processing speed and attention, and Part B (TMT-B), measuring cognitive flexibility and set-shifting. Visuospatial function was assessed using the copy condition of the ROCF.

All assessments were conducted by trained neuropsychologists or clinical researchers following each site's national state of the art procedures for MCI diagnostics.

Blood sample collection

Plasma levels of phosphorylated tau proteins (p-tau217 and p-tau181), which serve as candidate biomarkers of neurodegenerative disease, were measured in all participants. Samples were collected and processed according to a harmonized protocol implemented across all participating sites to minimize pre-analytical variability. Blood was collected into K2-EDTA tubes, centrifuged at 2000 × g for 10 min at 4 °C, aliquoted into polypropylene cryovials, and stored at − 80 °C within 30–60 min of collection. Samples were transported on dry ice with temperature monitoring and stored at − 80 °C until analysis, in line with current recommendations for biofluid biomarker research [33].

Plasma p-tau217 concentrations were measured using the S-PLEX® Human Tau (pT217) Kit (Meso Scale Diagnostics, Rockville, MD, USA) on the MSD electrochemiluminescence platform according to the manufacturer's instructions and as previously described by Kivisäkk et al. [34]. Study samples were analyzed in singlicate in randomized order, whereas calibrators and quality-control samples (low, medium, and high controls) were measured in triplicate. Quantification was based on a seven-point calibration curve fitted using a four-parameter logistic (4-PL) regression model with $1/Y^2$ weighting. The assay has a reported lower limit of detection (LOD) of 880 fg/mL and a dynamic range of 880–3,590,000 fg/mL. Assay runs were accepted only when predefined quality criteria were met, including valid calibration curves, acceptable quality-control performance, and coefficients of variation below 20%.

Plasma p-tau181 concentrations were measured at the University of Gothenburg using the Roche NeuroToolKit electrochemiluminescence immunoassay (ECLIA) on the fully automated cobas e 801 analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). Calibration and analysis were

performed as specified in the assay method sheet [35]. Samples were analyzed in a pre-specified randomized order. The assay has a lower limit of quantification (LLOQ) of 0.300 pg/mL and a measuring range of 0.300–10.0 pg/mL. Reported intra-assay coefficients of variation ranged from 1.6% to 5.2%, whereas inter-assay coefficients of variation ranged from 2.0% to 5.5% across the measuring range. A valid instrument calibration and successful daily quality-control procedures were required prior to sample analysis.

For both biomarkers, measurements were performed in a single round of experiments using one batch of reagents. Analyses were conducted by board-certified laboratory technicians who were blinded to all clinical information throughout the study. Detailed analytical characteristics and available reference values for the plasma p-tau assays are provided in Supplementary Table S5.

The full AI-Mind cohort comprised of 1,022 participants recruited across four European sites. For the present analysis, we included 742 participants from the AI-Mind cohort. A reserved hold-out test set of 281 participants was excluded from the present analysis and will be used as an independent sample for unbiased evaluation and validation of the AI-Mind artificial intelligence tools. All included participants completed neuropsychological testing. Availability of samples for biomarker analysis differed slightly by site. In Norway, all 171 participants had valid measurements for both p-tau217 and p-tau181. In Finland, p-tau217 data were available for 182 of 184 participants, and p-tau181 for 181 of 184. In Italy, both biomarkers were available for 183 of 184 participants. In Spain, 181 of 185 participants had valid measurements for both markers.

Statistical analysis

Raw cognitive test scores were used rather than site-specific normative values to ensure consistency across sites, preserve the full range of performance variability, and minimize bias introduced by heterogeneous normative datasets. For PCA, raw scores were subsequently standardized within each site (z-transformed; mean = 0, standard deviation = ± 1) so that variables with larger numeric ranges would not disproportionately influence component extraction. Sociodemographic variables (age, sex, and education level) were included as covariates to account for cultural, educational, and socioeconomic differences that may influence cognitive performance. Education level was assessed on a six-point ordinal scale, with higher values indicating higher educational attainment (1 = left school before age 16; 6 = PhD or equivalent). For all cognitive measures, higher numerical values were coded to indicate better performance (e.g., higher scores, faster completion times, fewer errors). Site differences in mean values in neuropsychological test performance, sociodemographic variables, and plasma p-tau measures were assessed with one-way ANOVAs for continuous variables and chi-squared tests for categorical variables.

Intercorrelations among standardized cognitive variables were examined using Pearson correlation coefficients. To account for multiple testing, p-values were adjusted using the Benjamini–Hochberg procedure to control the false discovery rate (FDR) [36] (see Supplementary materials Fig. 1–4).

PCA [37] was conducted separately for each site on the correlation matrix of standardized cognitive variables to reduce dimensionality and identify cognitive components capturing the largest proportion of total variance. To account for potential site-specific differences in recruitment, assessment context, and cohort composition, separate PCAs were conducted for each country. This ensured that site-to-site variation did not distort the latent cognitive structure and allowed us to analyze consistency prior to any pooled analysis. The number of retained components was determined by inspection of the scree plot and eigenvalues greater than one, resulting in a four-component solution across sites. To enhance interpretability, varimax orthogonal rotation was applied [38]. Individual component scores were computed by projecting standardized cognitive data onto the rotated eigenvector matrix and were used as independent variables in subsequent analyses.

Linear regression models were then fitted at each site to evaluate associations between plasma p-tau217 and p-tau181 concentrations as dependent variables and PCA-derived cognitive component scores as independent variables. All statistical analyses were conducted independently by the academic study team.

This work was performed on the TSD (Tjenester for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo IT-Department (UiO IT; tsd-drift@usit.uio.no). The statistical analyses were conducted in the software R version 4.5.0 [39]. The principal component analyses were conducted using the R package psych [40].

Results

Sociodemographic, cognitive, and biomarker characteristics by site are presented in Table 1. One-way ANOVAs indicated significant inter-site differences in age and education ($p < 0.001$), with Spanish participants being the oldest on average and Finnish participants the youngest. Educational attainment was highest in Norway and lowest in Spain, while sex distribution remained consistent across all cohorts (χ^2 test, $p = 0.287$). Cognitive performance differed across all domains; Norwegian participants showed the highest RAVLT delayed recall scores and the fastest performance on processing speed and executive measures (TMT-A and TMT-B), whereas Italian participants showed the lowest memory scores and Spanish participants the slowest completion times (all $p < 0.001$). Plasma biomarker concentrations also differed significantly: Norwegian participants exhibited lower levels of both p-tau217 ($p = 0.005$) and p-tau181 ($p = 0.003$) relative to the other cohorts. These differences remained statistically significant after adjustment for age, sex, and education (p-tau217: $p < 0.001$; p-tau181: $p = 0.004$). The distributions of plasma p-tau217 and p-tau181 concentrations across study sites are shown in Supplementary Figures S5 and S6.

Table 1 Sociodemographic, cognitive, and biomarker characteristics by site. The values in each cell show the mean and standard deviations (in parenthesis). The *p* value column indicates if there was a significant effect of site on the variable

Domain/Variable	Norway	Finland	Italy	Spain	Effect of site *p*
Sociodemographic					
Age (years)	69.39 (5.19)	67.86 (4.81)	70.44 (5.79)	71.68 (5.24)	**< 0.001***
Sex, male n (%)	78 (45.6%)	90 (48.9%)	90 (48.9%)	66 (35.7%)	0.287
Educational level	3.93 (0.99)	3.86 (1.02)	3.64 (1.39)	3.12 (1.47)	**< 0.001***
Memory tests					
RAVLT Delayed Recall	7.24 (3.42)	7.01 (3.83)	5.36 (2.77)	6.51 (3.73)	**0.001***
RAVLT Recognition_FP	−3.57 (4.10)	−5.28 (5.20)	−2.95 (3.43)	−1.25 (2.24)	**< 0.001***
ROCF Delayed Recall	11.29 (5.55)	10.15 (4.90)	11.63 (5.87)	12.19 (6.97)	**0.036***
Language tests					
Category Fluency	19.31 (5.30)	19.96 (5.78)	15.24 (4.07)	17.17 (5.28)	**< 0.001***
Category Fluency Errors	−0.06 (0.55)	−0.65 (1.03)	−0.01 (0.08)	−0.86 (1.23)	**< 0.001***
Letter Fluency	39.78 (11.21)	46.66 (14.26)	35.23 (11.39)	40.19 (12.72)	**0.017***
Letter Fluency Errors	−0.39 (0.97)	−2.09 (0.21)	−0.06 (0.37)	−3.46 (0.37)	**< 0.001***
Processing speed/executive function tests					
TMT-A Time (sec)	−36.85 (11.81)	−43.97 (18.29)	−49.44 (21.13)	−54.29 (23.11)	**< 0.001***
TMT-A Errors	−0.21 (0.51)	−0.12 (0.36)	−0.04 (0.25)	−0.16 (0.51)	0.096
TMT-B Time (sec)	−106.80 (54.89)	−118.39 (60.42)	−130.68 (62.48)	−148.80 (69.55)	**< 0.001***
TMT-B Errors	−0.82 (1.39)	−0.78 (1.05)	−0.54 (1.51)	−1.41 (2.11)	**0.005***
Visuospatial tests					
ROCF Copy	30.58 (3.89)	25.30 (5.12)	30.76 (4.99)	30.79 (5.88)	**< 0.001***
Biomarkers					
Plasma p-tau217 (pg/mL)	4.58 (3.86)	6.25 (5.26)	6.55 (5.86)	6.10 (4.62)	**0.005***
Plasma p-tau181 (pg/mL)	0.87 (0.40)	1.03 (0.53)	1.05 (0.53)	1.06 (0.74)	**0.003***

Negative values reflect score inversion for harmonization (higher values = better performance)

Principal cognitive components

To identify stable cognitive domains within the heterogeneous MCI continuum, PCA were conducted independently for each of the four clinical sites. Across all cohorts, scree plots consistently suggested a four-component solution, explaining between 53 and 62% of the total variance in cognitive performance. Although exact loading patterns differed somewhat between sites, the resulting components showed strong conceptual convergence and mapped onto comparable cognitive domains across cohorts.

Despite the statistically sociodemographic and biomarker differences in mean values between sites, the PCA yielded a highly interpretable and broadly stable component structure consisting of four primary domains: Memory (Verbal and Visuospatial), Executive Function/Processing Speed, Verbal Fluency, and Error Monitoring. Model adequacy was confirmed across all sites, with comparable item complexity (mean = 1.6) and acceptable fit indices (RMSR range: 0.09–0.11; see Supplementary materials (Tables S1–S4 for full PCA outputs).

Cross-site consistency of cognitive domains

Factor loadings revealed substantial cross-site consistency in the tests defining each component, supporting the use of these components as harmonized cognitive measures.

Memory Domain:

Across all four sites, this component was anchored by RAVLT Delayed Recall (loadings 0.62–0.82) and RAVLT Recognition (loadings 0.54–0.78). In Finland and Italy, this component merged verbal and visuospatial memory (including ROCF Delayed Recall), while in Norway and Spain, visuospatial memory emerged as a more distinct component.

Executive Function & Processing Speed: This domain was consistently defined primarily by TMT-B completion time (loadings 0.74–0.91) and TMT-B errors. In Norway and Spain, TMT-A performance also contributed significantly to this factor, reflecting the underlying requirement for processing speed.

Verbal Fluency: Across all sites, a distinct fluency-related component was identified, characterized by strong loadings from Letter Fluency (LF) and Category Fluency (CF) scores (loadings 0.52–0.82).

Error Monitoring: A recurring component in the Finnish, Italian, and Spanish cohorts captured task accuracy or error monitoring, with high loadings from TMT-A/B errors and Fluency errors.

Site-specific variations in model fit

While the overall conceptual structure remained stable, the explained variance and fit varied slightly by site, reflecting the unique characteristics of each clinically defined sub-cohort. Spain showed the strongest model fit (RMSR = 0.09; 62% variance explained). Finland and Italy demonstrated similar adequacy (60% and 58% variance explained, respectively). Norway, which exhibited the lowest mean p-tau levels and different recruitment characteristics, showed 53% explained variance with a moderate fit (RMSR = 0.11).

Associations between plasma p-tau and cognitive components

Linear regression analyses were conducted to assess associations between site-specific PCA-derived cognitive components and plasma p-tau217 (Table 2) and p-tau181 (Table 3).

In the Norwegian cohort, neither biomarker was significantly associated with any component; the model explained variance was negligible (< 1%). Trends were noted for p-tau217 with *fluency and processing speed* component ($p = 0.115$) and for p-tau181 with *verbal memory* component ($p = 0.067$).

For the Finnish site, both biomarkers showed robust negative associations with cognition. For p-tau217, the model explained 18.8% of the variance, and for p-tau181, 16.8%. For both biomarkers, stronger associations were observed for the *verbal memory* component ($p < 0.001$), with an additional association for the *executive functioning with visuospatial involvement* component ($p = 0.015$).

For the Italian site, significant negative associations were observed between both biomarkers and the combined *memory (visual and verbal)* component ($p < 0.001$). Variance explained was 11.5% for the p-tau217 model and 10.0% for the p-tau181 model. No other components showed significant associations.

For the Spanish site, no significant associations were detected for either biomarker; the model

Table 2 Linear regression models: Associations between plasma p-tau217 and principal components across sites. Significant predictors in bold

Site	Predictor	Estimate (B)	SE	t	p-value
Norway	Intercept	4.90	0.51	9.57	<.001
Component 1	Executive functioning	0.31	0.51	0.60	.547
Component 2	Verbal fluency/processing speed	0.81	0.51	1.59	.115
Component 3	Verbal memory component	–0.67	0.51	–1.30	.196
Component 4	Visuospatial memory	0.30	0.51	0.58	.563
Finland	**Intercept**	**6.30**	0.36	17.33	<.001
Component 1	**Verbal memory**	**–2.26**	0.36	–6.19	<.001
Component 2	**Executive functioning/visuospatial**	**–0.89**	0.36	–2.45	.015
Component 3	Verbal fluency	–0.38	0.36	–1.03	.304
Component 4	Error monitoring	–0.17	0.36	–0.47	.642
Italy	Intercept	6.57	0.42	15.59	<.001
Component 1	**Memory (visual and verbal)**	**–2.05**	0.42	–4.85	<.001
Component 2	Verbal fluency	–0.29	0.42	–0.68	.498
Component 3	Fluency-related error monitoring	–0.31	0.42	–0.74	.459
Component 4	Executive error monitoring	–0.62	0.42	–1.46	.147
Spain	Intercept	6.13	0.36	16.83	<.001
Component 1	Executive functioning/verbal fluency	–0.26	0.37	–0.72	.471
Component 2	Verbal memory	–0.72	0.37	–1.97	.051·
Component 3	Fluency-related error monitoring	–0.20	0.37	–0.55	.586
Component 4	Visuospatial memory	–0.32	0.37	–0.87	.388

Linear regression models were estimated separately for each site and adjusted for age, sex, and education. Model fit statistics: Norway ($R^2 = 0.029$, adj. $R^2 = 0.005$), Finland ($R^2 = 0.206$, adj. $R^2 = 0.188$), Italy ($R^2 = 0.135$, adj. $R^2 = 0.115$), Spain ($R^2 = 0.032$, adj. $R^2 = 0.009$)

Table 3 Linear regression models: Associations between plasma p-tau181 and principal components across sites. Significant predictors in bold

Site	Predictor	Estimate (B)	SE	t	p-value
Norway	Intercept	0.87	0.03	27.98	<.001
Component 1	Executive functioning	–0.02	0.03	–0.51	.607
Component 2	Verbal fluency/processing speed	–0.01	0.03	–0.17	.862
Component 3	Verbal memory component	–0.06	0.03	–1.85	.067·
Component 4	Visuospatial memory	0.01	0.03	0.26	.792
Finland	Intercept	1.03	0.04	28.66	<.001
Component 1	**Verbal memory**	**–0.20**	0.04	–5.54	<.001
Component 2	**Executive functioning/visuospatial**	**–0.11**	0.04	–3.01	.003
Component 3	Verbal fluency	–0.03	0.04	–0.77	.444
Component 4	Error monitoring	–0.00	0.04	–0.03	.974
Italy	Intercept	1.05	0.04	27.70	<.001
Component 1	**Memory (visual and verbal)**	**–0.17**	0.04	–4.46	<.001
Component 2	Verbal fluency	–0.01	0.04	–0.35	.728
Component 3	Fluency-related error monitoring	–0.01	0.04	–0.22	.826
Component 4	Executive error monitoring	–0.07	0.04	–1.82	.071·
Spain	Intercept	1.06	0.06	18.50	<.001
Component 1	Executive functioning/verbal fluency	0.05	0.06	0.83	.406
Component 2	Verbal memory	–0.03	0.06	–0.49	.628
Component 3	Fluency-related error monitoring	–0.06	0.06	–1.09	.279
Component 4	Visuospatial memory	0.04	0.06	0.73	.468

Linear regression models were estimated separately for each site and adjusted for age, sex, and education. Model fit statistics: Norway ($R^2 = 0.022$, adj. $R^2 = -0.001$), Finland ($R^2 = 0.186$, adj. $R^2 = 0.168$), Italy ($R^2 = 0.120$, adj. $R^2 = 0.100$), Spain ($R^2 = 0.016$, adj. $R^2 = -0.008$)

explained variance was negligible (< 1%). A near-significant trend was observed for p-tau217 with *verbal memory* component (p = 0.051), and no associations were observed for p-tau181.

Discussion

In this multicenter study of clinically defined MCI, we observed a four-component cognitive structure that remained broadly consistent across the four studied European cohorts, despite variations in recruitment strategies, levels of cognitive decline and biomarker profiles. Across sites, a memory-related component emerged as the cognitive domain most consistently associated with plasma tau biomarkers, particularly p-tau217. Importantly, these associations were detectable even in cohorts recruited without prior biological stratification, supporting the value of data-driven cognitive domains combined with blood-based biomarkers for identifying AD-related cognitive decline in real-world clinical populations.

Cohort characteristics

We observed significant effects of site on both cognitive performance and plasma p-tau burden. Although these differences were statistically significant, overall cohort characteristics remained broadly comparable; mean values across sites generally fell within less than one standard deviation of each other, indicating that these differences were minor relative to the substantial within-site variability. The Norwegian cohort showed broadly preserved cognitive performance, the highest mean education level, and the lowest p-tau217 and p-tau181 concentrations, a pattern compatible with lower pathological burden and the higher reversion potential often observed in community-based MCI samples, (while still carrying increased dementia risk compared with cognitively normal individuals) [14, 41, 42]. The Finnish cohort, the youngest and second most educated cohort, performed strongest on verbal fluency and showed on average preserved memory and executive abilities despite elevated p-tau levels. This profile may reflect cognitive reserve buffering cross-sectional deficits despite the presence of underlying pathology. Such reserve may delay but does not eliminate clinical progression risk, as longitudinal studies demonstrate that individuals with elevated p-tau remain at increased risk even when baseline cognition appears preserved [43]. The Italian cohort exhibited the lowest verbal memory performance alongside the highest plasma p-tau levels, consistent with an amnestic MCI phenotype at elevated progression risk, consistent with prior findings linking plasma p-tau to memory impairment and AD conversion [44]. The Spanish cohort, the oldest and least educated cohort, showed slower executive performance and more fluency errors together with elevated p-tau181, a profile that may be compatible with mixed or vascular contributions to cognitive impairment [45]. Together, these findings indicate that, within a shared diagnostic MCI label, clinical expression and biomarker burden vary across sites. This highlights the importance of site-aware analyses and warrant caution when pooling multicenter data.

Principal components of cognitive test performance

Across sites, PCA consistently supported a four-component structure with acceptable psychometric fit (variance explained 53–62%; mean item complexity ≈1.6), indicating a coherent but moderately differentiated cognitive structure in MCI. Despite some site-specific differences in loading patterns and terminology, the extracted components showed strong conceptual convergence, supporting the presence of broadly replicable underlying cognitive structures.

A memory-related component emerged consistently across sites, most often defined by RAVLT delayed recall and recognition FP. This verbal memory construct, which showed partial overlap with visual memory at some sites, was the most consistently replicated across sites, consistent with extensive evidence identifying delayed recall as a core marker of amnestic MCI and prodromal AD [46–48]. Executive functioning, predominantly represented by TMT-B, emerged consistently as a cognitive component, corroborating its established role in indexing set-shifting and cognitive control [49]. However, its structure varied across sites: in Finland, executive measures overlapped with visuo-constructive abilities, whereas in Italy, executive functioning was expressed more clearly through error-monitoring variables. These differences suggest that executive processes may

fractionate depending on sample composition, task variability, or underlying neuropathology. Verbal fluency also showed notable cross-site variability. While LF and CF scores formed a robust fluency component in several sites, they frequently overlapped with processing speed or error variables, consistent with literature showing that fluency tasks rely on multiple cognitive resources, including lexical retrieval, working memory, and executive control [50]. Visuospatial memory and construction showed greater cross-site variability. ROCF Delayed Recall contributed meaningfully at most sites, whereas ROCF Copy often demonstrated weaker communalities, likely reflecting additional perceptual–motor and strategic demands inherent to the task [51]. Error monitoring emerged as a distinct component across sites, although its strength and composition varied. In Spain, fluency errors alone defined a specific error-monitoring component, whereas in Italy, fluency and executive errors clustered separately. Although error variables exhibited higher item complexity and lower communalities, their repeated emergence suggests that they capture meaningful dimensions of executive control and self-monitoring, functions known to be sensitive to early cognitive decline [52, 53].

Cognitive-biomarker associations

Phosphorylated tau proteins, particularly p-tau217, have emerged as highly sensitive and specific plasma biomarkers for AD, demonstrating strong correlations with tau PET and CSF p-tau concentrations, and amyloid pathology measures such as amyloid PET and CSF Aβ42/40 [6, 54]. In the present study, associations between plasma p-tau and PCA-derived cognitive components varied across sites. Associations emerged primarily in cohorts with higher biomarker burden or clearer amnestic profiles, whereas cohorts with lower p-tau levels or greater cognitive heterogeneity showed negligible associations.

In Finland, both p-tau217 and p-tau181 were significantly associated with poorer performance in verbal memory and p-tau217 was additionally associated with the executive/visuospatial component. In Italy significant negative associations were observed specifically for the combined memory component. In contrast, no significant associations were detected in the Norwegian or Spanish cohorts, although trends were evident for verbal memory and fluency.

This cross-site heterogeneity may reflect differences in p-tau burden, stage of cognitive impairment, assay completeness, or recruitment and logistics strategies. The Italian cohort, recruited through clinical pathways, likely represents individuals with more advanced impairment, which may enhance the detection of biomarker–cognition relationships. In Finland, however, the sample also included a subgroup with subjective cognitive complaints (SCC), who were clinically classified within the MCI continuum as representing the SCD stage. The emergence of significant biomarker–cognition associations in this cohort is therefore particularly noteworthy, suggesting that plasma p-tau markers may be sensitive to cognitive decline even in earlier or subtler stages of impairment.

In the Norwegian and Spanish cohorts, restricted biomarker variance, range limitation, or reduced statistical power may also have attenuated detectable associations, in addition to potential differences in underlying pathologies.

Although cohort heterogeneity may reduce direct comparability across sites, it reflects the conceptual diversity inherent to the MCI spectrum and may enhance the ecological validity and translational relevance of the findings.

These findings support the potential of plasma tau biomarkers to track cognitive changes across the full continuum of preclinical and clinical Alzheimer's disease. Longitudinal follow-up will be critical to determining whether early biomarker elevations in these individuals predict future cognitive decline or conversion to more advanced clinical stages, and the rate at which this progression occurs.

The present approach used PCA to derive cognitive components and examine their associations with plasma p-tau217 and p-tau181, thereby offering insights that go beyond traditional, single-domain scores. While prior work using latent composites or standard scoring has consistently linked p-tau217 and p-tau181 to episodic memory and executive function (3–6) our empirical approach extends these observations. Specifically, we demonstrate that (i) PCA-derived domains yield relatively stable cognitive structures across multiple European sites, and (ii) that biomarker–cognition associations may be contingent

on cohort-specific characteristics. These results support recent arguments for more data-driven and harmonized approaches to biomarker validation in multicenter cohorts [55, 56].

Clinically, our results reinforce plasma p-tau, particularly p-tau217, as a promising and scalable marker of cognitive impairment, especially in domains most vulnerable to early AD. By applying PCA-derived cognitive domains within a harmonized analytic framework, this study contributes to improving the reproducibility, cross-site comparability, and translational value of plasma p-tau biomarkers across diverse populations.

Although site-specific differences in recruitment and biomarker levels were observed, the relationship between p-tau related biomarker burden and memory remained detectable through multivariate modeling. By identifying stable latent memory components that correlate with p-tau markers in specific cohorts with distinct clinical profiles, this study suggests that biological signals can be isolated from a noisy, clinically defined MCI cohort. This highlights the potential utility of translating biomarker research into real-world clinical practice where biological status is initially unknown.

Limitations

Several limitations should be acknowledged. Despite harmonization efforts, site-specific differences in recruitment, clinical practice, and testing environments may have influenced both cognitive and biomarker measures. Moreover, differences in demographic composition, baseline biomarker burden, and inclusion criteria across sites may have reduced direct comparability between cohorts and contributed to the observed variability in biomarker-cognition associations. However, such heterogeneity reflects the conceptual diversity inherent to the MCI spectrum and may therefore enhance the ecological validity of the findings. In addition, the absence of a cognitively healthy control group limits our ability to determine whether the identified cognitive structure is specific to MCI or reflects broader patterns of normal aging.

The cross-sectional design precludes causal inference, and longitudinal follow-up is required to assess predictive validity for clinical progression. The present findings should be interpreted as evidence of cross-sectional associations rather than prognostic relationships. The lack of a healthy control group limits comparisons with normative aging. Although PCA provides a data-driven approach to deriving cognitive domains, results are dependent on the test battery used and may not capture all relevant dimensions of cognition. In addition, PCA identifies components that maximize explained variance and may not map directly onto latent neurocognitive constructs in the psychometric sense. Plasma p-tau levels may be influenced by unmeasured biological factors, and the predominantly European sample may limit generalizability. Finally, the absence of amyloid status and imaging data, together with potential residual confounding (e.g., vascular risk, depression), constrains interpretation of biological heterogeneity.

Future directions

Building on the present findings, future research should adopt multimodal, longitudinal approaches that combine plasma p-tau with additional biomarkers such as amyloid measures, expanded neurodegeneration markers, and electrophysiological indicators (e.g., EEG) to more accurately track progression from MCI to dementia. Digital cognitive platforms may further improve harmonization, scalability, and repeated testing across sites. Within this landscape, synaptic biomarkers such as EEG are particularly promising, as they provide non-invasive indices of synaptic dysfunction, network connectivity, and functional integration, processes closely linked to both cognitive performance and AD pathophysiology.

Conclusions

Across four European MCI cohorts, we identified a four-component cognitive structure, encompassing memory, executive functioning/processing speed, verbal fluency, and visuospatial ability, that remained broadly stable despite some site-level heterogeneity. Our findings demonstrate that even in clinically defined cohorts recruited without prior biological stratification, a latent memory-related component emerges as the most tau-sensitive domain, with p-tau217 showing greater sensitivity to cognitive profiles compared to p-tau181.

By demonstrating that significant memory-biomarker associations can be detected in cohorts with distinct clinical profiles, this study highlights the feasibility of utilizing a harmonized cognitive-biomarker framework to isolate biological signals from the noise of real-world clinical practice. Integrating empirically derived cognitive domains with scalable plasma p-tau markers may improve the identification of individuals at risk of progression within the heterogeneous MCI continuum.

Author contributions *Conceptualization:* Ana Perez, Hugo Lewi Hammer. *Data curation:* Ana Perez, Christoffer Hatlestad-Hall, Vebjørn Andersson, Guido Maria Giuffrè, Soraya Alfonsín, Timo Saarinen. *Formal analysis:* Ana Perez, Hugo Lewi Hammer. *Funding acquisition:* Ira H. Haraldsen, Fernando Maestú, Hanna Renvall, Camillo Marra, Paolo M. Rossini. *Investigation:* Ana Perez, Hugo Lewi Hammer, Christoffer Hatlestad-Hall, Vebjørn Andersson, Timo Saarinen, Soraya Alfonsín, Guido Maria Giuffrè, Naike Caraglia, Noemi Martellacci, Federico Ramírez-Toraño, Thomas Tveitstøl, Antti Kinnunen, Mia Liljeström, Jaakko Hotta, Anne M. Koivisto, Davide Quaranta. *Methodology:* Hugo Lewi Hammer, Ana Perez, Christoffer Hatlestad-Hall. *Project administration:* Ira H. Haraldsen, Fernando Maestú, Hanna Renvall, Camillo Marra, Paolo M. Rossini. *Resources:* Erik Christensen, Clara Quijano-Rubio, Gwendlyn Kollmorgen, Henrik Zetterberg. *Supervision:* Hugo Lewi Hammer, Christoffer Hatlestad-Hall, Ira H. Haraldsen. *Writing – original draft:* Ana Perez. *Writing—review & editing:* All authors.

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Data availability The dataset presented in this article is not readily available because it forms part of an ongoing multicenter study and is subject to ethical and data protection restrictions. Requests to access the data on which the analyses in this article are based should be directed to the corresponding author.

Declarations

Role of the funders The funders had no role in study design, data collection, statistical analysis, interpretation of results, manuscript preparation, or the decision to submit the manuscript for publication.

Ethical approval The study was approved by the ethics committees at all participating sites and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to inclusion after receiving information about the study procedures, risks, and benefits. Informed consent was obtained in accordance with national regulations and AI-Mind-specific ethical guidelines. All data were handled in compliance with the European Union General Data Protection Regulation (GDPR).

Disclosures Roche product disclosure: The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders. It is intended for research use only and is not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).

Competing interests G.K. is a full-time employee of Roche Diagnostics GmbH, Penzberg, Germany. C.Q.-R. is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland, and a shareholder (non-voting equity securities) of F. Hoffmann-La Roche Ltd. E.C. is co-founder, stockholder and employed by Pre Diagnostics AS. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp \& Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs,

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