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Relevance of the interplay between amyloid and tau for cognitive impairment in early Alzheimer's disease

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ABSTRACT

Amyloid β (Aβ) and tau are key hallmark features of Alzheimer's disease (AD) neuropathology. The interplay of Aβ and tau for cognitive impairment in early AD was examined with cross-sectional analysis, measured by cerebrospinal fluid biomarkers ($Aβ_{1–42}$, total tau [t-tau], and phosphorylated tau [p-tau181P]), and on cognitive performance by the repeatable battery for assessment of neuropsychological status (RBANS). Participants (n = 246) included cognitively normal (Aβ−), mild cognitively impaired (Aβ−), preclinical AD (Aβ+), and prodromal AD (Aβ+). Overall, cognitive scores (RBANS total scale score) had a moderate negative correlation to t-tau (n = 246; r = −0.434; p < 0.001) and p-tau181P (r = −0.389; p < 0.001). When classified by Aβ status, this correlation to t-tau was applicable only in Aβ+ participants (n = 139; r = −0.451, p < 0.001) but not Aβ− participants (n = 107; r = 0.137, p = 0.16), with identical findings for p-tau. Both tau (p < 0.0001) and interaction of $Aβ_{1–42}$ with tau (p = 0.006) affected RBANS, but not $Aβ_{1–42}$ alone. Cognitive/memory performance correlated well with cerebrospinal fluid tau levels across early stages of AD, although the correlation is Aβ dependent.

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Availability of data and material: The data sharing policy of Janssen Research & Development, LLC is available at yoda.yale.edu. Requests for access to the study data can be submitted through that site.

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1. Introduction

The hallmark features of Alzheimer's disease (AD) neuropathology, amyloid-β (Aβ) plaques, and tau neurofibrillary tangles (NFT) are known to start accumulating years before the onset of clinical symptoms (Dubois et al., 2016; Villemagne et al., 2013), with a putative sequence of Aβ events preceding tau. With the molecular definition of the disease (Jack et al., 2018), the progressing clinical disorder of AD is considered a continuum with a seamless sequence of events from healthy elderly individuals with positive biomarker signature and impairments gradually increasing over time to progress from milder stages of cognitive deficits to functional impairment and dementia (Aisen et al., 2017; Jack et al., 2013). This interpretation of AD was enabled by advances in cerebrospinal fluid (CSF) and imaging biomarkers such as Aβ and tau to move from a clinically defined late stage disease to a biological definition of a disease process that starts many years before onset of clinical symptoms. These research advances have resulted in a new set of criteria for AD to define the earliest stages in the AD continuum, that is, cognitively normal individuals with an abnormal AD biomarker pattern, being preclinical AD (Dubois et al., 2014; Knopman and Caselli, 2012; Vos et al., 2013).

The amyloid cascade hypothesis brings forward the deposition of Aβ as a result of increased production and/or decreased clearance of Aβ from the central nervous system, as the initial pathological trigger in the disease continuum, interacting with the microtubule-binding protein tau, forming NFT leading to widespread neuronal degeneration and dysfunction, cognitive decline and dementia (Karran et al., 2011). Genetic evidence from rare familial forms of AD as well as mutations in amyloid-β precursor protein and presenilins 1 and 2 genes support the accumulation of Aβ as the causative factor for AD (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995).

Although genetic evidence points toward Aβ as the initiator of pathology, the eventual clinical syndrome appears to be more closely related to the progression of the tau pathology. The rate of cognitive impairment in AD and neuronal loss however strongly correlate spatially and temporally with the total tau burden and NFT formation (Nelson et al., 2012; Pontecorvo et al., 2017). Although Aβ pathology starts in the neocortical areas and spreads inwardly to the limbic regions, followed by the brainstem and cerebellum, tau pathology or NFTs topographically disconnect and spread in the opposite direction starting to accumulate first in the entorhinal cortex, before spreading into the hippocampal regions and lateral temporal cortex (Braak et al., 2006). In animal models, both Aβ and tau have shown self-propagation capabilities (Jucker and Walker, 2011, 2013), but whether this occurs in humans is not known. Extracellular phospho-tau (p-tau) seeds are known to induce tauopathy in neurons, supporting the hypothesis that tauopathy can spread in a prion-like fashion between neurons, a cascade that could potentially be initiated or accelerated by Aβ pathology (Goedert et al., 2017). Despite the prominent correlation of NFTs with cognitive impairment in AD, mutations in tau are not causative for AD but may result in dementia, without an AD clinical or neuropathological phenotype (Hardy and Selkoe, 2002).

Increasing preclinical evidence supports a possible interplay between Aβ and tau, whereby Aβ may exert its toxicity through tau by influencing or inducing the hyperphosphorylation, misfolding, and secretion of tau (Musiek and Holtzman, 2015; Nisbet et al., 2015), and tau may further enhance Aβ toxicity via a feedback loop. In addition, preclinical data demonstrate that tau is required for learning and memory deficits in the presence of Aβ (Roberson et al., 2007). Aβ is being proposed as the trigger to AD, which may induce the cascade of downstream events including tauopathy, and tau as the bullet, driving the neurodegeneration and cognitive deficits (Bloom, 2014). This potential interplay would further strengthen the interaction between both key features of the amyloid cascade hypothesis already at the start of the AD continuum, hypothesizing that the relation of CSF tau to cognitive performance is dependent on Aβ pathology as measured by CSF Aβ levels.

The interaction of Aβ and tau, measured by means of CSF biomarkers ($A\beta_{1-42}$, total tau [t-tau], and p-tau_{181P}), on cognitive performance as a clinical marker in normal participants, subjects with mild cognitive impairments (MCI) without biomarker evidence of AD pathology and those in the earliest stages of the AD continuum defined as preclinical and prodromal AD (pAD) was investigated.

2. Methods

2.1. Study population

Participants screened from 2 separate clinical trials in early AD (Study 1: NCT01978548 (Timmers et al., 2018); Study 2: NCT02260674) were included in this study. Both studies were conducted in sites across Europe in Caucasian participants between December 2013 and June 2016.

2.2. Study participants

A total of 256 participants (Study 1: n = 112; Study 2: n = 144), aged 50–90 years inclusive, who completed a standardized 4-step screening process for either studies to assess their eligibility according to predefined inclusion and exclusion criteria (Supplemental Fig. S1), were included in this study (Timmers et al., 2018). Of the 256 participants who completed the screening process, a total of 10 participants were further excluded from final analysis due to incorrect, incomplete, or missing repeatable battery for the assessment of neuropsychological status (RBANS) data (n = 7), missing p-tau_{181P} data (n = 1), or no clinical dementia rating (CDR) scale data (n = 2) available, resulting in 246 evaluable participants.

Two paradigms were used to classify participants included (n = 246) as depicted in Supplemental Fig. S2.

2.2.1. Biomarker CSF $A\beta_{1-42}$ and cognitive status (CDR)

Participants were identified as "preclinical AD" (CDR = 0 and Aβ < 600 ng/L [A+] n = 33), prodromal Alzheimer's disease ([pAD]; CDR ≥0.5 but no dementia; CDR = 0.5 [n = 104] and 1.0 [n = 2], together with Aβ < 600 ng/L [A+], n = 106), "mild cognitive impairment" ([MCI]; CDR = 0.5 and normal Aβ levels [A−](≥600 ng/L), n = 38) or "control" (CDR = 0 and normal Aβ levels [A−], n = 69).

2.2.2. Biomarker status alone independent of clinical stage, that is, by Aβ (A-/A+) and tau (T-/T+) status

Participants were considered T+ if CSF t-tau and/or p-tau_{181P} were above the predefined cutoff (t-tau >350 ng/L; p-tau_{181p} >70 ng/L). All participants positive for p-tau_{181P} were positive for t-tau, given the strong correlation between both markers independent of Aβ status (A−: r = 0.95, $p < 0.001$; A+: r = 0.95, $p < 0.001$; Supplemental Fig. S3). Overall, n = 70 were A−/T−, n = 37 were A−/T+, n = 23 were A+/T−, and n = 116 were A+/T+.

2.3. Assessments

2.3.1. Mini-mental state examination (MMSE)

The MMSE (Folstein et al., 1975) was used during screening as a tool to screen dementia.

2.3.2. Clinical dementia rating scale (CDR)

The CDR scale, a semistructured interview of patients and informants, was used to measure a patient's current dementia status

Table 1
Demographics and biomarker summary by CDR and Aβ (A+ or A−) status

Baseline characteristics	Control (CDR = 0; A−) N = 69	Preclinical AD (CDR = 0; A+) N = 33	MCI (CDR≥0.5; A−) N = 38	Prodromal AD (CDR≥0.5; A+) N = 106	Total N = 246
Women, n (%)	37 (53.6)	14 (42.4)	19 (50)	57 (53.8)	127 (51.6)
Age, mean (SD), y	67.9 (5.62)	69.8 (5.54)	67.0 (6.77)	69.3 (7.08)	68.6 (6.49)
Age group, n (%)					
<65	18 (26.1)	7 (21.2)	12 (31.6)	26 (24.5)	63 (25.6)
≥65-<75	44 (63.8)	17 (51.5)	22 (57.9)	52 (49.1)	135 (54.9)
≥75	7 (10.1)	9 (27.3)	4 (10.5)	28 (26.4)	48 (19.5)
Race, n (%)					
White	68 (98.6)	33 (100)	38 (100)	103 (97.2)	242 (98.4)
Black or African-American	1 (1.4)	0	0	0	1 (0.4)
Other	0	0	0	3 (2.8)	3 (1.2)
Weight, mean (SD), kg	74.1 (14.28)	72.9 (11.86)	75.3 (16.69)	68.7 (12.26)[a]	71.8 (13.88)*
Height, mean (SD), cm	168.5 (9.87)	168.5 (9.43)	166.1 (11.24)	166.2 (10.16)	167.1 (10.08)
BMI, mean (SD), kg/m^2	26.0 (3.74)	25.6 (3.25)	27.2 (4.83)	24.8 (3.32)[b]	25.6 (3.84)**
MMSE total score					
Mean (SD)	28.3 (1.49)	28.3 (1.80)	27.3 (2.76)	25.3 (3.24)	26.8 (2.95)
Median (range)	29 (24; 30)	29 (21; 30)	28 (19; 30)	26 (14; 30)[c]	28 (14; 30)***
APOE ε4 carrier, n (%)					
Yes	0	17 (51.5)	0	58 (54.7)	75 (30.5)
Missing/unknown	69 (100)	5 (15.2)	38 (100)	10 (9.4)	122 (49.6)
CDR global score, n (%)					
0	69 (100)	33 (100)	0	0	102 (41.5)
≥0.5	0	0	38 (100)	106 (100)	144 (58.5)
RBANS total score					
Mean (SD)	102.0 (12.70)	97.5 (17.37)	84.4 (15.19)	73.5 (16.13)	86.4 (19.69)
Median (range)	102 (67; 136)	101 (57; 135)	87 (51; 114)[d]	74 (47; 124)[c]	87 (47; 136)***
Biomarkers					
Aβ 1−42 (innotest), ng/L					
Mean (SD)	860.9 (182.55)	416.5 (103.89)	840.4 (152.33)	390.8 (94.61)	595.6 (263.79)
Median (range)	860 (600; 1580)	395 (244; 590)[e]	815 (616; 1320)	384.5 (159; 586)[e]	526.5 (159; 1580)***
<600 ng/L, n (%)	0	33 (100)	0	106 (100)	139 (56.5)
T-tau, ng/L					
Mean (SD)	345.2 (135.65)	427.9 (192.57)	321.2 (137.53)	730.9 (333.26)	518.8 (309.06)
Median (range)	324 (152; 742)	404 (118; 1050)[f]	300 (100; 661)	644.5 (161; 1780)[g]	448 (100; 1780)***
>350 ng/L, n (%)	26 (37.7)	20 (60.6)	11 (28.9)	96 (90.6)	153 (62.2)
P-tau, ng/L					
Mean (SD)	53.4 (18.73)	62.2 (21.89)	48.9 (8.43)	90.0 (33.51)	69.7 (31.94)
Median (range)	50 (25; 116)	59 (23; 128)[f]	46 (20; 103)	86.5 (29; 197)[g]	64 (20; 197)***
>70 ng/L, n (%)	13 (18.8)	12 (36.4)	4 (10.5)	76 (71.7)	105 (42.7)

Key: Aβ, amyloid-β; AD, Alzheimer's disease; APOE, gene encoding for apolipoprotein E; BMI, body mass index; CDR, clinical dementia rating; MCI, mild cognitive impairment; MMSE, mini-mental state examination; P-tau, phospho tau; RBANS, repeatable battery for the assessment of neuropsychological status; SD, standard deviation; T-tau, total tau.
***, **, * indicates nominal p-value <0.001, <0.01, or <0.05, respectively, across groups.
[a] Nominal p-value <0.01 versus Control; <0.05 versus MCI.
[b] Nominal p-value <0.05 versus Control; <0.01 versus MCI.
[c] Nominal p-value <0.001 versus Control, versus Preclinical AD and versus MCI.
[d] Nominal p-value <0.001 versus Control, versus Preclinical AD and versus Prodromal AD.
[e] Nominal p-value <0.001 versus Control and versus MCI.
[f] Nominal p-value <0.05 versus Control; <0.01 versus MCI and <0.001 versus Prodromal AD.
[g] Nominal p-value < 0.001 versus Control, versus Preclinical AD and versus MCI.

(Morris et al., 1997). The CDR demonstrates good reliability (Burke et al., 1988) and has been validated against neuropathological findings (Berg et al., 1993).

2.3.3. Repeatable battery for the assessment of neuropsychological status (RBANS)

The RBANS is a brief standardized screening tool to measure neuropsychological status; it comprises 12 subtests that yield index scores (mean [SD]: 100 [30]) for 5 cognitive domains (neurocognitive status: immediate memory, visuospatial/constructional, language, attention, and delayed memory) and a total scale score (Randolph et al., 1998). The RBANS was performed twice by participants during screening (FORM A and FORM B) to explore test-retest reliability. For the purpose of this study, the first completion of the RBANS (either FORM A or B) was included in the analysis.

2.3.4. Collection and analysis of CSF $A\beta_{1-42}$, p-tau_{181p}, and t-tau levels

All participants had a baseline CSF sample (12 mL) collected during screening by single lumbar puncture between the L3 and L4 or L4 and L5 intervertebral space. CSF samples were collected in polypropylene tubes to avoid adsorbance of proteins to test tube walls. CSF samples were mixed to avoid possible gradient effects, aliquoted, frozen, and stored at −80 °C immediately after collection. All samples analyzed in this study had 1 freeze-thaw cycle.

CSF samples were analyzed at one central lab (Sahlgrenska University hospital, Sweden) for $A\beta_{1-42}$, phosphorylated tau at position threonine 181 (p-tau_{181P}) and total tau (t-tau) concentrations using the commercially available enzyme-linked immunosorbent assays (ELISA) that is, INNOTEST β-AMYLOID$_{1-42}$, INNOTEST Phospho-TAU$_{181}$ and INNOTEST hTAU Ag (Fujirebio, Ghent, Belgium) and the Luminex analytical platform (Luminex Corp., Austin, TX, USA) (Palmqvist et al., 2014; Timmers et al., 2018), following stringent protocols for quality control of analyses. Diagnostic threshold CSF concentrations for AD versus normal control for $A\beta_{1-42}$ (CSF $A\beta_{1-42}$ levels below cutoff value of 600 ng/L) were applied to the current sample set to assess the likelihood of having cerebral Aβ plaque deposition (A+) (Palmqvist et al., 2014; Timmers et al., 2018). In addition, elevated CSF t-tau (>350 ng/L) and/or p-tau181p levels

Table 2
Demographics and biomarker summary by Aβ (A+ or A−)/tau (T+ or T−) status

Baseline characteristics	Aβ/tau status				
	A−/T− N = 70	A−/T+ N = 37	A+/T− N = 23	A+/T+ N = 116	Total N = 246
Demographics					
Women, n (%)	38 (54.3)	18 (48.6)	8 (34.8)	63 (54.3)	127 (51.6)
Age, mean (SD), y	66.5 (5.90)[a]	69.6 (5.85)	68.6 (5.12)	69.6 (7.01)	68.6 (6.49)*
Age group, n (%)					
<65	23 (32.9)	7 (18.9)	7 (30.4)	26 (22.4)	63 (25.6)
≥65 − < 75	42 (60)	24 (64.9)	13 (56.5)	56 (48.3)	135 (54.9)
≥75	5 (7.1)	6 (16.2)	3 (13.0)	34 (29.3)	48 (19.5)
Race, n (%)					
White	69 (98.6)	37 (100)	22 (95.7)	114 (98.3)	242 (98.4)
Black or African-American	1 (1.4)	0	0	0	1 (0.4)
Other	0	0	1 (4.3)	2 (1.7)	3 (1.2)
Weight, mean (SD), kg	75.0 (16.45)	73.5 (12.37)	74.7 (10.34)	68.7 (12.40)[b]	71.8 (13.88)**
Height, mean (SD), cm	166.7 (10.56)	169.4 (9.99)	171.2 (9.91)	165.8 (9.82)	167.1 (10.08)
BMI, mean (SD), kg/m^2	26.8 (4.28)	25.7 (3.92)	25.4 (2.28)	24.9 (3.48)[c]	25.6 (3.84)*
MMSE total score					
Mean (SD)	28.0 (1.93)	27.8 (2.37)	28.0 (2.18)	25.6 (3.27)	26.8 (2.95)
Median (range)	28 (19; 30)	28 (21; 30)	28 (21; 30)	26 (14; 30)[d]	28 (14; 30)***
APOE ε4 carrier, n (%)					
Yes	0	0	11 (47.8)	64 (55.2)	75 (30.5)
No	0	0	10 (43.5)	39 (33.6)	49 (19.9)
Missing/unknown	70 (100)	37 (100)	2 (8.7)	13 (11.2)	122 (49.6)
CDR global score, n (%)					
0	43 (61.4)	26 (70.3)	13 (56.5)	20 (17.2)	102 (41.5)
≥0.5	27 (38.6)	11 (29.7)	10 (43.5)	96 (82.8)[d]	144 (58.5)***
RBANS total score					
Mean (SD)	94.8 (14.61)	97.5 (18.41)	93.6 (18.78)	76.4 (18.17)	86.4 (19.69)
Median (range)	94.5 (55; 125)	99 (51; 136)	100 (59; 124)	76 (47; 135)[d]	87 (47; 136)***
Biomarkers					
Aβ 1–42 (innotest), ng/L					
Mean (SD)	806.2 (137.15)	943.3 (195.94)	432.3 (110.96)	389.9 (93.07)	595.6 (263.79)
Median (range)	790 (600; 1180)[e]	903 (607; 1580)[f]	421 (259; 590)	381 (159; 587)	526.5 (159; 1580)***
<600 ng/L, n (%)	0	0	23 (100)	116 (100)	139 (56.5)
T-tau, ng/L					
Mean (SD)	257.1 (62.11)	487.3 (107.44)	257.5 (69.10)	738.6 (303.76)	518.8 (309.06)
Median (range)	264 (100; 350)	458 (353; 742)[f]	262 (118; 349)	637 (354; 1780)[g]	448 (100; 1780)***
>350 ng/L, n (%)	0	37 (100)	0	116 (100)	153 (62.2)
P-tau, ng/L					
Mean (SD)	41.5 (9.68)	71.5 (15.53)	41.8 (9.29)	91.7 (29.93)	69.7 (31.94)
Median (range)	42.5 (20; 62)	69 (46; 116) [f]	41 (23; 56)	85 (49; 197)[g]	64 (20; 197)***
>70 ng/L, n (%)	0	17 (45.9)	0	88 (75.9)	105 (42.7)

Key: Aβ, amyloid-β; *APOE*, gene encoding for E; BMI, body mass index; CDR, clinical dementia rating; MMSE, mini-mental state examination; P-tau, phospho tau; RBANS, repeatable battery for the assessment of neuropsychological status; SD, standard deviation; T-tau, total tau.
***, **, * indicates nominal *p*-value <0.001, <0.01, or <0.05, respectively, across groups.
[a] Nominal *p*-value <0.05 versus A−/T+; <0.01 versus A+/T+.
[b] Nominal *p*-value <0.05 versus A−/T+ and versus A+/T−; <0.01 versus A-/T-.
[c] Nominal *p*-value <0.01 versus A−/T−.
[d] Nominal *p*-value <0.001 versus A−/T−, versus A−/T+ and versus A+/T−.
[e] Nominal *p*-value <0.001 versus A−/T+, versus A+/T− and versus A+/T+.
[f] Nominal *p*-value <0.001 versus A−/T−, versus A+/T− and versus A+/T+.
[g] Nominal *p*-value <0.001 versus A−/T−, A−/T+ and versus A+/T−.

(>70 ng/L), respectively, (T+) as set by the analysis lab at the start of Studies 1 and 2 were applied to the current sample set to assess the likelihood of having neuronal injury and/or cerebral tau pathology (T+).

2.4. Statistical analyses

Statistical analyses were performed using SAS Software version 9.4 (SAS Institute). For categorical data, group differences were analyzed using Fisher's exact test. For numerical data when there were no clear departures from a normal distribution (age, height, weight, and body mass index), balance across groups was evaluated with an F-test and pairwise group comparisons were analyzed by Student's t-test (equal variances) or Satterthwaite test (unequal variances). Nonparametric statistics (Hollander and Wolfe, 1999) were used for skewed or truncated data ($A\beta_{1-42}$, t-tau, p-tau$_{181P}$, RBANS, and MMSE). Balance across groups was evaluated with a Kruskal-Wallis test. For pairwise comparisons, Hodges-Lehmann estimates for median differences between groups were calculated. Confidence intervals (CIs) and nominal *p*-values for the pairwise differences between groups were based on the Wilcoxon Rank Sum test. The choice of parametric versus nonparametric methods was driven by normality versus non-normality of data distributions. Spearman correlation coefficients were calculated to evaluate the strength of association between RBANS indexes and tau (t-tau and p-tau$_{181P}$). Multiple linear regression models were employed to explore the relationship between cognition (RBANS) and biomarkers ($A\beta_{1-42}$, t-tau, and the interaction of $A\beta_{1-42}$ with t-tau; variables were noncentered). Similar models using p-tau$_{181P}$ instead of t-tau were analyzed. Both t-tau and p-tau$_{181P}$ were not included together in the same model due to colinearity. Rank-transformed values were used for RBANS and biomarker variables in multiple regression models because assumptions for normality in the model residuals were not met.

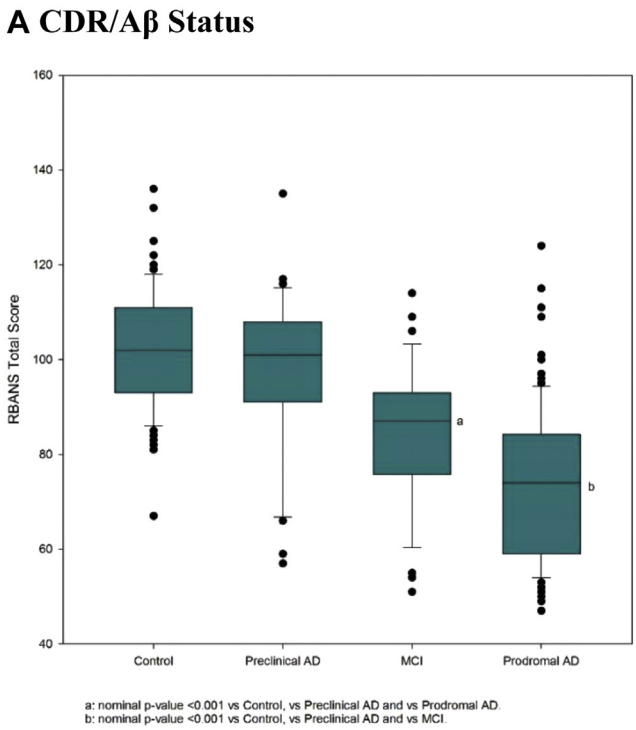

Fig. 1. RBANS Total Scale Score by CDR/Aβ Status (A) and Aβ (A+ or A−)/Tau (T+ or T−) Status (B) RBANS: repeatable battery for the assessment of neuropsychological status. Participants are considered Aβ+ (A+) if CSF $A\beta_{1-42} < 600$ ng/L and Tau+ (T+) if CSF T-Tau >350 ng/L or CSF p-$Tau_{181p} > 70$ ng/L. (A) Control (CDR 0; Aβ−; n = 69), pre-clinical AD (CDR 0; Aβ+; n = 33), MCI (CDR ≥0.5; Aβ−; n = 38), prodromal AD (CDR ≥0.5; Aβ+; n = 106); (B) A−/T− (n = 70), A−/T+ (n = 37), A+/T− (n = 23), A+/T+ (n = 116).

3. Results

3.1. Demographic, biomarker, and cognitive characteristics

Two paradigms were used to classify participants as depicted in Supplemental Fig. S2, that is, by $A\beta_{1-42}$ and cognitive status (CDR) and by biomarker status alone independent of clinical stage, that is, by $A\beta_{1-42}$ and tau (T-/T+) status (see 2.2.1 and 2.2.2). For both classifications, the demographic, cognitive (RBANS, CDR, MMSE), and

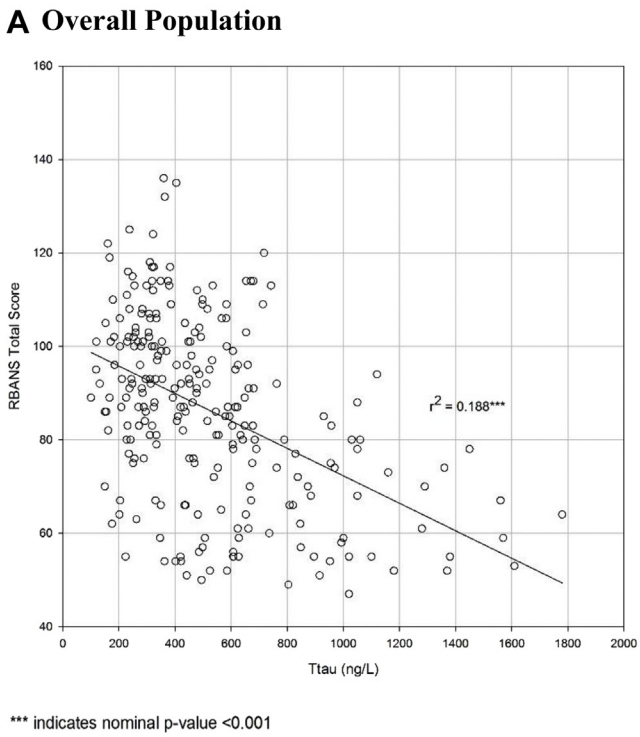

Fig. 2. Correlation RBANS Total Scale Score and T-tau for the Overall Population (A) and by Aβ Status (B) RBANS: repeatable battery for the assessment of neuropsychological status; T-tau: total tau. A Spearman correlation coefficient was calculated to evaluate the possible correlation between RBANS Total Scale Score and t-tau for the overall population (A) and by Aβ (amyloid) status (B). (A) $R^2 = 0.188$, rho = −0.434; $p < 0.001$. $n = 246$; B. Amyloid −: $R^2 = 0.019$, rho = 0.137, $p > 0.05$, n = 107; Amyloid +: $R^2 = 0.203$, rho = −0.451, $p < 0.001$, n = 139).

Table 3
Correlation of RBANS indexes versus T-tau and P-tau

RBANS indexes	All N = 246		Aβ− N = 107		Aβ+ N = 139	
	T-tau	P-tau	T-tau	P-tau	T-tau	P-tau
RBANS total score	−0.434***	−0.389***	0.137	0.173	−0.451***	−0.421***
RBANS sum of index	−0.433***	−0.391***	0.139	0.176	−0.449***	−0.422***
RBANS delayed memory	−0.433***	−0.377***	0.236*	0.310**	−0.431***	−0.406***
RBANS immediate memory	−0.368***	−0.329***	0.086	0.109	−0.327***	−0.307***
RBANS attention Index	−0.339***	−0.315***	0.119	0.120	−0.438***	−0.410***
RBANS language index	−0.321***	−0.311***	−0.052	−0.049	−0.261**	−0.275**
RBANS visuospatial index	−0.186**	−0.165**	0.063	0.069	−0.254**	−0.223**

Key: RBANS, repeatable battery for the assessment of neuropsychological status.
***, **, * indicates nominal *p*-value <0.001, <0.01, or <0.05, respectively.

biomarker characteristics ($A\beta_{1-42}$, p-tau_{181p}, t-tau) are summarized in Tables 1 and 2. The distribution of the overall population enrolled based on their Aβ and tau biomarker profiles is shown in Supplemental Fig. S3 (A: Aβ and t-tau; B: Aβ and p-tau_{181P}). Gender distribution was equal across groups independent of classification used (by $A\beta_{1-42}$ and cognitive status or biomarker only). A tendency toward higher representation of male subjects in the A+/T- versus the A+/T+ group was observed, which was in line with earlier reports (Paquet et al., 2018). Participants classified as pAD and A+/T+ had lower weight and BMI and participants classified as A−/T− were younger.

3.2. Prodromal AD, preclinical AD, control, and MCI groups

No differences in CSF $A\beta_{1-42}$ levels were observed among A+ groups (pAD vs. preclinical AD) or among A− groups (MCI vs. control). Tau levels (t-tau; p-tau_{181P}; median [range]) were significantly increased in both pAD (644.5 ng/L [161; 1780]; 86.5 ng/L [29; 197] vs. control and MCI $p < 0.001$) and preclinical AD (404 ng/L [118; 1050] vs. control $p < 0.05$, vs. MCI $p < 0.01$; and 59 ng/L [23; 128] vs. control $p < 0.05$, vs. MCI $p < 0.01$) compared with control (324 ng/L [152; 742]; 50 ng/L [25; 116]) and MCI groups (300 ng/L [100; 661]; 46 ng/L [20; 103]). No differences in CSF tau (t-tau or p-tau_{181P}) levels were observed between the control and MCI group (Table 1). The pAD group showed significantly increased tau levels compared with the preclinical AD group ($p < 0.001$ for both t-tau and p-tau_{181P}) (Table 1).

Overall, pAD participants presented with a lower median [range] global MMSE score (26 [14; 30], $p < 0.001$), and a lower RBANS total scale score (74 [47; 124], $p < 0.001$; Table 1, Fig. 1A) and significant impairment on all RBANS index scores (Supplemental Table S1; $p < 0.001$) compared with the control and preclinical AD groups, and for most of the RBANS index scores compared with the MCI group. The pAD participants showed highest impairment (lowest score) on the delayed memory index followed by the attention index, immediate memory index, language index, and visuospatial index. The preclinical AD group showed a normal cognitive profile on the RBANS total scale and index scores (Table 1, Fig. 1A, Supplemental Table S1), whereas the MCI group had a significantly ($p < 0.001$) lower RBANS total scale score (Table 1; Fig. 1A) and index scores (Supplemental Table S1) compared with the preclinical AD and control group. The MCI group showed the highest impairment on the attention index, followed by delayed memory, immediate memory, language, and visuospatial index.

3.3. A-/T-, A-/T+, A+/T-, A+/T+ groups

Although T+ subjects were observed in both A+ and A-groups, very high tau values (p-tau_{181p} >125 ng/L and t-tau >800 ng/L) were observed only in the A+ participants. Significantly ($p < 0.001$) higher t-tau and p-tau_{181P} levels (median [range]) were observed in the A+/T+ group (637 ng/L [354; 1780]; 85 ng/L [49; 197]) compared with the A−/T+ group (458 ng/L [353; 742]; 69 ng/L [46; 116]; Table 2). Aβ levels did not differ between the A+/T+ (381 ng/L [159; 587]) and A+/T− (421 ng/L [259; 590]) group. Slightly higher levels of Aβ were observed in the A-/T+ (903 ng/L [607; 1580]) versus the A-/T- (790 ng/L [600; 1180]) group ($p < 0.001$). Participants characterized as A−/T+ are considered participants with suspected non-Aβ pathophysiology (Supplemental Fig. S3A and S3B).

The A+/T+ participants presented with a significantly lower MMSE (26 [14; 30], $p < 0.001$) (Table 2), RBANS total scale score (76 [47; 135], $p < 0.001$; Table 2 and Fig. 1B), and RBANS index scores (except visuospatial index) compared with all the other groups ($p < 0.001$; Supplemental Table S2). The highest impairment (lowest score) was observed on delayed memory index, followed by attention, immediate memory, language index, and visuospatial index (no significant difference with the A+/T− group; Supplemental Table S2.) The A+/T−, A−/T+, or A−/T− group did not differ from each other based on the RBANS total scale score or RBANS index scores.

3.4. Correlation between CSF tau levels (t-tau and p-tau_{181P}) and cognitive scores

In the overall group, the RBANS total scale score showed a moderate negative correlation to t-tau (n = 246; r = −0.434; $p < 0.001$; Fig. 2A and Table 3) and p-tau_{181P} (n = 246; r = −0.389; $p < 0.001$ [Table 3]). However, when classified by Aβ status, the RBANS total scale score showed a moderate negative correlation to t-tau in the A+ participants (n = 139; r = −0.451, $p < 0.001$) and not in the A- participants (n = 107; r = 0.137, $p = 0.16$) (Fig. 2B). The individual RBANS index scores (Table 3) showed similar observations with only significant negative correlations with t-tau levels in

Table 4
Multiple regression results for RBANS total scale score versus biomarkers ($A\beta_{1-42}$ and t-tau)

Global test (*p*-value)	R-square	Variable	Parameter estimate (SE)	Test statistics	*p*-value
28.92 (<0.0001)	0.264	Intercept	178.019 (21.867)	8.14	<0.0001
		$A\beta_{1-42}$	−0.094 (0.141)	−0.67	0.5057
		t-tau	−0.649 (0.135)	−4.63	<0.0001
		$A\beta_{1-42}$*t-tau	0.003 (0.001)	2.51	0.0060

Key: Aβ, amyloid-β; RBANS, repeatable battery for the assessment of neuropsychological status; SE, standard error.

Table 5
Multiple regression results for RBANS total scale score versus biomarkers ($A\beta_{1-42}$ and t-tau), age and sex

Global test (*p*-value)	R-square	Variable	Parameter estimate (SE)	Test statistics	*p*-value
16.07 (<0.0001)	0.268	Intercept	127.324 (49.526)	2.57	0.0107
		$A\beta_{1-42}$	−0.069 (0.144)	−0.48	0.6294
		t-tau	−0.635 (0.137)	−4.63	<0.0001
		$A\beta_{1-42}$*t-tau	0.003 (0.001)	2.51	0.0127
		Age	0.693 (0.624)	1.11	0.2680
		Sex (0 = F, 1 = M)	2.380 (7.931)	0.30	0.7644

Key: Aβ, amyloid-β; RBANS, repeatable battery for the assessment of neuropsychological status; SE, standard error.

the A+ group and not in the A− group with the stronger negative correlation observed in the A+ group for the attention index ($r = -0.438$, $p < 0.001$) and delayed memory index ($r = -0.431$, $p < 0.001$), followed by the immediate memory index ($r = -0.327$, $p < 0.001$), language ($r = -0.261$, $p < 0.01$), and visuospatial index ($r = -0.254$, $p < 0.01$). Similar findings were observed for p-tau_{181P} (Table 3).

Both t-tau ($p < 0.0001$) and the interaction of $A\beta_{1-42}$ with t-tau ($p = 0.006$) were statistically significant in their effect on RBANS but not $A\beta_{1-42}$ (Table 4). When the regression included independent variables for age and sex (0 for female, 1 for male), again both t-tau ($p < 0.0001$), the interaction of $A\beta_{1-42}$ with t-tau was significant ($p = 0.0127$) but not the other variables (Table 5). *APOE* ε 4 carrier status was not included in the model because it was only available for the A+ participants. Similar findings were observed for p-tau_{181P} (Tables 6 and 7).

4. Discussion

We examined the role of tau and its possible interplay with Aβ, measured based on CSF biomarkers ($A\beta_{1-42}$, t-tau, and p-tau_{181P}), on cognitive performance (RBANS) as a clinical marker in normal participants, subjects with mild cognitive impairments (MCI) without biomarker evidence of AD pathology and those in the early AD continuum ranging from preclinical AD to pAD. Original screening paradigm allowed classification of participants based on their clinical function and evidence of Aβ pathology along the early stages of the AD continuum. In addition, across the early AD continuum, CSF Aβ levels were shown to plateau, whereas tau levels were higher with increased disease stage and cognitive impairment. In the present study, the correlation of cognitive/memory impairment with CSF tau was dependent on CSF Aβ levels indicative for Aβ pathology, suggesting the importance of an interplay between both hallmark features of AD neuropathology. In addition, both tau and the interaction of $A\beta_{1-42}$ with tau were significant in their effect on RBANS but not $A\beta_{1-42}$ alone.

Earlier publications have suggested that tau correlates with and is predictive of clinical function and cognitive impairment (Nelson et al., 2009). In the present study, clinical function aligned with cognitive performance (Hobson et al., 2010). The pAD group presented an RBANS total scale score and RBANS index scores in line with AD pathology (Randolph et al., 1998), whereas the preclinical AD group presented a normal cognitive profile, confirming the usability of the RBANS as a cognitive screening tool in AD (Duff et al., 2008).

CSF tau levels (t-tau and p-tau_{181P}) were higher across stages in the early AD continuum (preclinical and pAD) with the pAD group showing highest tau levels. In the early AD stages, CSF Aβ levels were lower but did not differ between preclinical and pAD, suggesting that CSF Aβ levels may plateau early, whereas CSF tau levels do not and may drive lower cognitive scores (Andersson et al., 2008; Buchhave et al., 2012). High CSF levels of t-tau and p-tau_{181P} have been associated with a distinct cognitive profile with more severe impairment of memory and mental speed, and executive functions, not explained by disease severity (van der Vlies et al., 2009). In contrast, the amount of Aβ accumulation or its removal by immunotherapy has not yet been shown to correlate with cognitive performance (Giannakopoulos et al., 2003; Salloway et al., 2014). In addition, substantial Aβ deposition may also occur without affecting cognitive performance overall (Perez-Nievas et al., 2013). Based on the aforementioned, Aβ pathology appears to be an early marker of incident disease.

The observation of elevated CSF tau levels already in the preclinical AD stage is in line with previous studies (Hoglund et al., 2017; Mattsson et al., 2017; Toledo et al., 2013; Vos et al., 2013) and similar as to further elevated CSF tau levels along to early AD continuum (Andersson et al., 2008; Stefani et al., 2006; Toledo et al., 2013). However, this finding is not observed in some studies (Insel et al., 2018). The CSF tau elevations may indicate that the preclinical and pAD groups are already in a state of neuronal injury/degeneration.

CSF Aβ levels did not significantly differ between A+ populations, despite the fact that pAD participants presumably have more accumulated brain Aβ pathology compared to preclinical AD participants. CSF Aβ and Aβ PET measures do not change precisely in parallel as they measure different aspects of the AD amyloid pathology (Toledo et al., 2015). CSF Aβ significantly decreases early in preclinical AD and then remains rather stable, whereas the Aβ PET signal would continuously increase in the nondemented AD stages, lowering again in the symptomatic stage of the disease (Kadir et al., 2012). In contrast to the pAD group, the MCI group presented with a less severe and slightly distinct cognitive profile from the pAD group. The overall MCI group presented normal CSF tau levels indicating that the cognitive impairment may have another etiology than AD.

When classifying participants solely based on their CSF biomarker profile, it became apparent that CSF Aβ or tau levels alone did not result in significant cognitive changes compared with the participants having normal CSF levels (Pascoal et al., 2017). This

Table 6
Multiple regression results for RBANS total scale score versus biomarkers ($A\beta_{1-42}$ and p-tau_{181P})

Global test (*p*-value)	R-square	Variable	Parameter estimate (SE)	Test statistics	*p*-value
25.84 (<0.0001)	0.243	Intercept	169.015 (22.222)	7.61	<0.0001
		$A\beta_{1-42}$	−0.065 (0.143)	−0.46	0.6477
		p-tau_{181P}	−0.603 (0.138)	−4.37	<0.0001
		$A\beta_{1-42}$*p-tau_{181P}	0.003 (0.001)	2.74	0.0066

Key: Aβ, amyloid-β; RBANS, repeatable battery for the assessment of neuropsychological status; SE, standard error.

Table 7
Multiple regression results for RBANS total scale score versus biomarkers ($A\beta_{1-42}$ and p-tau_{181P}), age and sex

Global test (*p*-value)	R-square	Variable	Parameter estimate (SE)	Test statistics	*p*-value
15.68 (<0.0001)	0.246	Intercept	124.111 (49.541)	2.51	0.0129
		$A\beta_{1-42}$	−0.045 (0.145)	−0.31	0.7570
		p-tau_{181}	−0.590 (0.139)	−4.24	<0.0001
		$A\beta_{1-42}$*p-tau_{181P}	0.003 (0.001)	2.54	0.0117
		Age	0.599 (0.627)	0.96	0.3402
		Sex (0 = F, 1 = M)	3.881 (8.025)	0.48	0.6291

Key: Aβ, amyloid-β; RBANS, repeatable battery for the assessment of neuropsychological status; SE, standard error.

suggests that elevated CSF tau levels are essential for learning and memory deficits in the presence of decreased CSF Aβ levels indicative of amyloid pathology in AD (Desikan et al., 2012; Roberson et al., 2007). Although T+ participants were observed in both A+ and A-groups, very high CSF tau levels (>800 ng/L) were only observed in A+ participants, suggesting that Aβ pathology may further drive or advance CSF tau levels resulting in synergistic rather than additive effects (Pascoal et al., 2017). Recent in vivo labeling data suggest that neurons may respond to Aβ pathology by increasing their secretion of both total and phosphorylated tau (Sato et al., 2018). Such neurons may be at increased risk of developing tangles and eventually degenerate but this may be downstream of the tau dysmetabolism that the biomarkers reflect. On the contrary, a weak positive association between tau and the RBANS delayed memory was observed only in Aβ-individuals, which is surprising and warrants further investigation.

In the current analysis, cognitive/memory performance is correlated with CSF tau levels (t-tau and p-tau_{181P}) in the early stages of the AD continuum (Rami et al., 2011; Reijs et al., 2017). However, the correlation observed is Aβ dependent and only present in the Aβ positive group. This correlation with CSF tau levels (t-tau and p-tau_{181P}) was also observed for all relevant RBANS subdomains, delayed memory, attention, and immediate memory on the background of Aβ. A recent meta-analysis of preclinical data in transgenic mice further supports a primary role for tau in cognitive decline in preclinical AD, whereas Aβ may rather play an indirect role in the development of NFT (Huber et al., 2018). In contrast, other groups have observed the opposite, showing a correlation of cognitive impairment with Aβ on the backbone of tau in preclinical AD and MCI (Desikan et al., 2012; Haldenwanger et al., 2010).

The data presented in this study are suggestive of an interplay between Aβ and tau in relation to cognitive impairment/decline in AD. Both are required to induce the impairment, whereas tau pathology is driving the level of impairment. Supportive hereof is that widespread cortical tau pathology (Braak stage≥3) has commonly been observed in patients with Aβ plaques, although not in patients without plaques, supporting the hypothesis that Aβ aggregation is required for the appearance of high cortical tau pathology (Knopman et al., 2003; Petersen et al., 2006; Price and Morris, 1999). In addition, significant interactions between CSF Aβ and CSF p-tau levels have been shown to affect brain structure (MRI) only in preclinical patients with AD positive for both CSF Aβ and tau. This interaction is suggestive of a 2-phase phenomenon of pathological cortical thickening associated with low Aβ, followed by atrophy and cognitive decline associated with abnormal (high) CSF p-tau levels (Fortea et al., 2014).

Recent preclinical studies have highlighted several possible pathways by which Aβ could directly and indirectly influence the levels of tau and induce hyperphosphorylation of tau and the formation of neurofibrillary tangles (Gotz et al., 2001; Nisbet et al., 2015). In in vitro and in vivo (transgenic mice) models, inhibition of Aβ production by beta and gamma secretases elicits Aβ aggregation and subsequent tau pathology (incl. CSF tau) suggesting tau to be downstream effect of Aβ pathology (Choi et al., 2014; Schelle et al., 2017), hence preventing Aβ aggregation may directly affect tau pathology. On the other hand, both Aβ and tau have shown self-propagation capabilities in animal models (Jucker and Walker, 2011). Extracellular p-tau seeds can induce tauopathy in neurons, supporting the hypothesis that tauopathy can spread in a prion-like fashion between neurons, a cascade that could be potentially initiated or accelerated by Aβ pathology (Goedert et al., 2017; Nussbaum et al., 2013). In such a case, optimal treatment to prevent cognitive decline/impairment should ideally start before tau reaching pathological (high) levels in CSF or before reaching levels associated with cognitive decline, hence in preclinical AD stage 1 or 2 (Sperling et al., 2011), highlighting the importance for the inclusion of biomarkers in the diagnosis of preclinical AD. Current ongoing studies in preclinical AD targeting Aβ (e.g., BACE inhibitor studies) will provide further insight into this possible interaction between Aβ and tau and the ability to prevent cognitive decline and increases in tau pathology by Aβ inhibition.

As all participants were screened in light of an AD clinical trial, the population included may not be representative for the overall continuum as some patients may have presented with subjective memory complaints. However, data presented clearly demonstrated that based on the screening paradigm applied, different population groups could be identified from normal controls to preclinical AD and pAD and even MCI. Secondly, this study only reports cross-sectional data, and longitudinal data further supporting the hypothesis that tau pathology correlates to cognitive decline on the backbone of Aβ (CSF) are needed. Furthermore, although similar correlations between CSF tau and cognitive impairment have been reported before, opposite results have also been reported, still describing an interaction between Aβ and tau in the opposite direction (Desikan et al., 2012). These differences may be explained by the application of different cognitive measures. Where most studies opted for the classical clinical and cognitive measures such as MMSE, CDR, and ADAS-cog, we applied, next to the CDR and MMSE, the RBANS as a sensitive and specific measure for cognitive function, currently applied in several multicentre trials in AD, which may clarify some of the differences observed.

5. Conclusion

Across the early stages of the AD continuum, cognitive/memory performance correlated well with CSF tau levels. However, the observed correlation is Aβ-dependent and only present in the Aβ-positive group indicating the importance of a possible interplay between both neuropathological hallmarks of AD.

Disclosure

Drs. Maarten Timmers, Ina Tesseur, Luc Tritsmans and Luc Van Nueten and Ms. Bogert are employees of Janssen Research & Development and hold stock in the company. The study site received research grant from Janssen Research & Development. Dr Streffer is a former employee of Janssen Pharmaceutica N. V. and is currently affiliated with University of Antwerp with a research

advisory role at Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium, and collects no consulting fees and receives no research funding. Dr Engelborghs is employed at the Department of Biomedical Sciences, University of Antwerp, 2610 Antwerp and at the Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, 2020 Antwerp, Belgium, and reports research funding from Janssen Pharmaceutica N.V. and ADx Neurosciences (paid to institution). Dr Miquel Baquero is an employee of Hospital Universitari i Politecnic La Fe, Valencia, Spain, and has no disclosures to declare. Dr Börjesson-Hanson is employed at Sahlgrenska University Hospital, Mölndal, Sweden, and has no disclosures to declare. Dr Mercè Boada is an employee of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain, consulting for Araclon, AstraZeneca, Grifols, Janssen, Kyowa Kirin, Lilly, MSD, Nutricia, Roche, Schwabe and Servier. She received fees for lectures from Araclon Biotech, Biogen, Grifols, KRKA, Nutricia, Roche and Schawe, and reports research funding from Araclon Biotech, Bioiberica, Grifols, KRKA, Lilly, Merck, Piramal, Nutricia, Roche, Fundació Bancaria la Caixa, ISCIII, EC-H2020, IMI-EFPIA, and ERANET. Dr Blennow has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Merck, Novartis, Pfizer, and Roche Diagnostics, and is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. Dr Henrik Zetterberg has served at scientific advisory boards for Eli Lilly, Roche Diagnostics and Wave, has received travel support from Teva and is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. Dr Christopher Randolph is the author of the RBANS and receives royalties from the copyright holder, Pearson. Dr Anne Börjesson-Hanson is employed at Sahlgrenska University Hospital, Mölndal, Sweden, and has no disclosures to declare.

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Authors' contributions: MT, LT, IT, and LVN were responsible for study design, data collection, and interpretation. JS was the clinical leader and study medical officer who participated in the study design and conduct of the trial, data analysis plan, and interpretation. JB was the project statistician who made contribution to study design, data analysis, and interpretation of the results. SE, ABH, MB, and MB were clinical investigators and were involved in patient recruitment, study operation, study management, data collection and interpretation and review and finalization of the study report. KB and HZ were involved in biomarker analysis, data analysis, sample analysis, and interpretation. CR was involved in cognitive data collection, analysis, and interpretation. All authors participated in interpretation of the data, drafting, and reviewing of the article. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the article, made the final decision about where to publish these data, and approved submission to the journal.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.03.016.

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