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Modeling the progression of neuropsychiatric symptoms in Alzheimer's disease with PET-based Braak staging

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ABSTRACT

In Alzheimer's disease (AD), neuropsychiatric symptoms (NPS) correlate with tau deposition in the brain. Here, we investigated the association of PET-based Braak stages with NPS and assessed whether they predict annual changes in NPS. We evaluated 231 individuals in the aging and AD continuum. Participants were assigned a Braak stage at baseline and followed for 1.97 (s.d. 0.62) years. NPS were investigated using the Mild Behavioral Impairment Checklist (MBI-C) and the Neuropsychiatric Inventory Questionnaire severity (NPI-Q-S) and distress (NPI-Q-D) scales. Multiple linear regressions (MLR) assessed the association of Braak stages with baseline NPS and the annual change in NPS scores. At baseline, stages I-II, III-IV, and V-VI were associated with higher MBI-C, NPI-Q-S, and NPI-Q-D scores. Stages V-VI were associated with a significant annual increase in MBI-C scores. These findings suggest that tau accumulation may manifest clinically with an increase in NPS, which seems to be an early event in AD pathophysiology. Moreover, PET-based Braak staging appears to be a good predictor of NPS severity progression.

1. Introduction

Neuropsychiatric symptoms (NPS) affect around 60–90 % of patients with dementia, being commonly present at the time of the diagnosis or even preceding cognitive symptoms (Devineni and Onyike, 2015; Lyketsos et al., 2000, 2002; Mega et al., 1996; Peters et al., 2006; Sink

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et al., 2004). They encompass disturbances in mood, anxiety, sleep, appetite, as well as behavioral changes such as disinhibition or aggression (Ballard et al., 2008). NPS are associated with faster progression of cognitive decline and dementia severity (Peters et al., 2015; Stern et al., 1994), as well as with increased functional impairment (Fischer et al., 2012a), caregiver burden (Fischer et al., 2012b), and institutionalization rates (Balestreri et al., 2000; Wiener et al., 2001). Moreover, NPS have been pointed out as possible predictors of the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia (Goukasian et al., 2019; McGirr et al., 2022). Mild behavioral impairment (MBI) has also been associated with a lower likelihood of reversion from MCI to unimpaired cognition (McGirr et al., 2022).

Pathologically, AD is characterized by the accumulation of amyloid-β (Aβ) and neurofibrillary tangles (NFT) in the brain (Bateman et al., 2012; Jack et al., 2013; Villemagne et al., 2013), whose association with NPS have been demonstrated in *post-mortem* studies (Guadagna et al., 2012; Rosenberg et al., 2015; Tekin et al., 2001). Moreover, MBI was found to be linked with the progression to pathologically-confirmed AD among cognitively unimpaired (CU) individuals (Ruthirakuhan et al., 2022). Clinico-pathological studies also show an association between NPS and Braak NFT staging (Ehrenberg et al., 2018; Gibson et al., 2023; Malpas et al., 2021), a scheme that describes the progression and indicates the severity of NFT accumulation (Braak and Braak, 1991; Braak et al., 2006). Positron emission tomography (PET) imaging with tau radiopharmaceuticals allowed for the translation of the Braak histopathological classification into a framework to be used in living humans, which has shown good reliability and correspondence with markers of clinical severity (Kreisl et al., 2022; Macedo et al., 2023, 2024a, 2024b; Pascoal et al., 2020, 2021a; Rullmann et al., 2022; Schöll et al., 2016; Schwarz et al., 2016; Therriault et al., 2022).

A literature review pointed out consistent evidence of the association between NPS and Aβ pathology (Ng et al., 2021). However, the relationship between tau deposition and NPS deserves further clarification, especially in preclinical populations (Ng et al., 2021). Recent studies with individuals in the aging and AD continuum demonstrated that NPS are associated with higher tau PET signal in Braak regions of interest (ROI) (Naude et al., 2024; Tissot et al., 2021; Yasuno et al., 2021). In these studies, however, no individual assignment of PET-based Braak stages or longitudinal analyses were conducted. Here, we aimed to track the progression of NPS, assessed with tools validated for both dementia and pre-dementia populations, through the aging and AD continuum using the PET-based Braak staging framework. Specifically, we investigated the association between individually-assigned PET-based Braak stages and NPS measures at baseline. We further assessed whether baseline PET-based Braak staging can predict annual change in NPS over two years. We hypothesize that NPS severity and burden will increase progressively with the advance of PET-based Braak stages.

2. Materials and methods

2.1. Participants

In this prospective cohort study, we included CU, MCI, and AD dementia individuals. All participants are part of the Translational Biomarkers of Aging and Dementia (TRIAD) cohort, recruited either from the community or the McGill Research Centre of Studies on Aging (MCSA) outpatient memory clinic between July 2016 to December 2021. The details of the TRIAD cohort have been described previously (Therriault et al., 2020). To be classified as CU, participants could not present with objective cognitive impairment. Following the evaluation of a multi-professional team including neurologists, neuropsychologists, and nurses, the diagnoses of participants with MCI or AD dementia were established respectively according to the National Institute on Aging - Alzheimer's Association (NIA-AA) criteria for MCI due to AD (Albert et al., 2011) and for probable AD dementia (McKhann et al., 2011). AD dementia encompassed both the amnestic and non-amnestic variants of the disease (behavioral/dysexecutive-variant AD (Ossenkoppele et al., 2022), logopenic-variant primary progressive aphasia (Gorno-Tempini et al., 2011), and posterior cortical atrophy (Crutch et al., 2017)). We employed [^{18}F]AZD4694 Aβ-PET to evaluate the Aβ status of all participants. Solely those MCI and AD individuals classified as Aβ+ were included in this study, as done in previous research focusing on the AD continuum (Jack et al., 2018). Both Aβ+ and Aβ- CU individuals were selected. However, while we included Aβ+ CU participants at any PET-based Braak stage, we only selected Aβ- CU individuals at PET-based Braak stage 0 to serve as a reference control group. All participants underwent baseline [^{18}F]MK6240 tau-PET, brain magnetic resonance imaging (MRI), and an extensive clinical and neuropsychological evaluation. The clinical battery included neurological examination and assessments for comorbidities, functionality, behavioral changes, sleep, nutritional status, and comprehensive laboratory workup. The neuropsychological assessment was administered by a trained psychometrist and included tests for global cognition, such as the Mini-Mental State Examination (MMSE), and tools for specific cognitive domains (e.g. Rey auditory verbal learning, for memory, and Boston naming tests, for language). Blood was collected from participants for apolipoprotein E (APOE) genotyping with the TaqMan allelic discrimination assay (Hixson and Vernier, 1990). APOE testing was performed since its ε4 variant is recognized as the most important genetic risk factor for sporadic AD (Farrer et al., 1997; Genin et al., 2011), being known to play a role in tau pathology (Ferrari-Souza et al., 2023; Therriault et al., 2020). Exclusion criteria were visual and auditory impairments hampering cognitive and neuropsychiatric assessments, inability to speak English or French, inability to provide a reliable informant (e.g. close friend, family member) for the NPS assessments, other neurological or psychiatric disorders that could be responsible for cognitive decline, inadequately controlled systemic disorders, recent major surgery or traumatic brain injury, and PET/MRI contraindications. A subsample of participants underwent a follow-up assessment. Approval for this study was granted by the Montreal Neurological Institute (MNI) PET working committee and the Douglas Mental Health University Institute Research Ethics Board (IUSMD 16–60). Participants were informed about all procedures involved in the research and signed a written informed consent form.

2.2. Neuroimaging acquisition and processing

We used a 3T Siemens Magnetom scanner with a standard head coil to obtain T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) structural brain MRI. The parameters were as follows: repetition time of 2300 ms, echo time of 2.96 ms, flip angle of 9°, coronal orientation perpendicular to the double spin echo sequence, with an in-plane resolution of 1×1 mm^2 and a slab thickness of 1 mm (Ferrari-Souza et al., 2022). T1-weighted MRI scans processing followed an in-house pipeline, which included non-uniformity correction, brain masking, and linear and non-linear transformation to the MNI reference space (Wu et al., 2012). A brain-dedicated Siemens high-resolution research tomograph was used to acquire PET scans. [^{18}F]MK6240 PET images were acquired following 90–110 min after intravenous bolus injection of the ligand. Reconstruction was performed using a sequential subset expectation-maximization algorithm on a 4D volume with four frames (4×300 s). [^{18}F]AZD4694 PET images acquisition happened after 40–70 min of the intravenous bolus injection of the ligand. Reconstruction of [^{18}F]AZD4694 PET images was performed with a sequential subset expectation-maximization algorithm on a 4D volume with three frames (3×600 s). A 6-min transmission scan with a rotating ^{137}Cs point source was done after each PET acquisition for attenuation correction. We also performed corrections for motion, dead time, decay, and random and scattered coincidences. Linear registration of PET images to T1-weighted image space was also accomplished, as well as linear and nonlinear registration to the MNI reference space. Spatial smoothing of PET images was conducted aiming at a full width of 8 mm

at a half-maximum resolution. Moreover, meninges stripping in native space was done for [^{18}F]MK6240 PET images before transformations and blurring to avoid meningeal spillover into neighboring brain regions (Pascoal et al., 2020). For [^{18}F]MK6240 PET, we used the cerebellar crus I gray matter as the reference region to calculate standardized uptake value ratios (SUVRs) (Cho et al., 2019; Jack et al., 2017, 2018; Macedo et al., 2024b; Therriault et al., 2022), according to the SUIT cerebellum atlas (Diedrichsen et al., 2009). For [^{18}F]AZD4694 SUVR calculation, the whole cerebellum gray matter was used as the reference region (Therriault et al., 2021). Amyloid positivity was considered as [^{18}F]AZD4694 SUVR>1.55 in a composite including the following regions: precuneus, prefrontal, orbitofrontal, parietal, temporal, and cingulate cortices (Jack et al., 2017; Therriault et al., 2021).

2.3. PET-based Braak staging methods

As reported by our group elsewhere, we adopted the following anatomical definitions of PET-based Braak stages: I (transentorhinal cortex), II (entorhinal cortex and hippocampus), III (amygdala, fusiform gyrus, lingual gyrus, and parahippocampal gyrus), IV (inferior parietal, inferior temporal, insula, lateral temporal, and posterior cingulate), V (anterior cingulate, cuneus, inferior frontal, lateral occipital, orbitofrontal, precuneus, rostromedial frontal, superior frontal, superior parietal, superior temporal, and supramarginal gyrus), and VI (paracentral, pericalcarine, postcentral, and precentral) (Macedo et al., 2024a; Pascoal et al., 2020, 2021a, 2021b; Therriault et al., 2022). We used the Desikan–Killiany–Tourville atlas to determine ROIs (Desikan et al., 2006). The transentorhinal cortex was segmented as described elsewhere, with no overlap between the transentorhinal and entorhinal cortices ROIs (Pascoal et al., 2020, 2021a, 2021b; Therriault et al., 2022).

Each participant was classified into a PET-based Braak stage according to the latest stage in which abnormality was found in tau-PET. We calculated the thresholds to define abnormal signals for each PET-based Braak region as 2.5 standard deviations (s.d.) higher than the mean SUVR of CU individuals younger than 26 years old, as previously reported (Pascoal et al., 2020, 2021b). Participants were grouped into five groups according to their PET-based Braak stage and their Aβ status: Aβ- Braak 0, Aβ+ Braak 0, Aβ+ Braak I-II, Aβ+ Braak III-IV, and Aβ+ Braak V-VI.

2.4. Neuropsychiatric assessment

All participants were assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q) (Kaufer et al., 2000) and the Mild Behavioral Impairment Checklist (MBI-C) (Ismail et al., 2017).

The NPI-Q, a brief form of the Neuropsychiatric Inventory (NPI), is an informant-based self-administered questionnaire that assesses 12 NPS: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating disturbances (Kaufer et al., 2000). In the event a given NPS has been present in the last month, the informant is asked to evaluate its severity from 1 (mild) to 3 (severe) and the caregiver distress it causes from 0 (not distressing at all) to 5 (extreme/very severe) (Kaufer et al., 2000). The total NPI-Q severity (NPI-Q-S) and NPI-Q caregiver distress (NPI-Q-D) scores range respectively from 0 to 36 and from 0 to 60. Higher scores mean more severity and caregiver distress, respectively (Kaufer et al., 2000).

The MBI-C is a 34-item questionnaire that identifies NPS that emerge in later life, represent a change from the patient's previous longstanding behavioral pattern, and persist for at least six months (Ismail et al., 2017). For NPS identified, raters (informants, in our study) assess the severity of the symptoms from 1 (mild) to 3 (severe) (Ismail et al., 2017). The MBI-C is divided into five domains with different score ranges: abnormal thought & perception (0−15), affective dysregulation (0−18), decreased motivation (0−18), impulse dyscontrol (0−36), and social inappropriateness (0−15) (Ismail et al., 2017). The sum of individual scores results in a total score ranging from 0 to 102. The objective of this tool is to measure behavioral manifestations that might precede the onset of dementia at preclinical and prodromal disease stages (Ismail et al., 2017), in accordance with the criteria for MBI (Ismail et al., 2016).

2.5. Statistical analyses

Statistical analyses were performed using R software version 3.5.3. Demographic data were compared with the Kruskal-Wallis for continuous variables and with contingency $\chi 2$ tests for categorical variables. Visual inspection of histograms and Shapiro–Wilk test results indicated that NPS scores and their rates of change had a non-parametric distribution. Baseline NPS scores and their rates of change were compared between PET-based Braak stage groups using the Kruskal-Wallis test, and *post hoc* comparisons were conducted with the Wilcoxon rank sum test. As a subgroup analysis, the Wilcoxon rank sum test also compared the baseline NPS scores of participants with MCI or AD dementia at similar Braak stages to assess the influence of the degree of cognitive impairment in the relationship between NPS and tau severity. We also compared the proportion of participants with at least one NPS (i.e. those with scores higher than zero in the NPS scales) at different Braak stages using the contingency $\chi 2$ test. Spearman's correlation assessed the relationship of baseline SUVR in Braak ROIs with NPS total scores and with the scores for specific domains. We also used Spearman's correlation to check whether baseline NPS scores changed following the increase of Braak staging groups in an ordinal fashion. For this, we considered the Braak stage grouping variable as an ordinal variable (Aβ- Braak 0 as 0, Aβ+ Braak 0 as 1, I-II as 2, III-IV as 3, and V-VI as 4). All Spearman's correlations were adjusted for age and sex.

Associations between individually-assigned PET-based Braak stages as the predictor and baseline NPS scores as the outcome were assessed through multiple linear regressions (MLR). NPS scores and their rates of change were log-transformed to approximate a parametric distribution. All MLR models were adjusted for age and sex. Exploratory analyses were performed with the stepwise inclusion of years of education, Aβ-PET neocortical SUVR and MMSE scores as covariates in the MLR models to investigate their roles in the relationship between PET-based Braak stages and baseline NPS. MLR was also used to evaluate the association between baseline PET-based Braak stages and the annual rate of change in the NPS measures, since the majority of participants had only one follow-up time point. The annual rate of change was calculated as the difference between the scores in the follow-up and baseline visits divided by the time, in years, between the visits. All MLR models for NPS rate of change were adjusted for age and sex. We conducted additional analyses adjusting for the MMSE rate of change to investigate the role of cognition in the relationship between baseline PET-based Braak stages and the progression of NPS. To investigate whether NPS predict tau accumulation in Braak regions, we also ran exploratory MLR models with baseline NPS scores as the independent variables and Braak SUVR as the dependent variables, adjusting for age and sex, with and without the inclusion of baseline MMSE as a covariate.

All MLR β coefficients were standardized. Statistical significance was considered if $p < 0.05$.

3. Results

We evaluated 231 participants grouped as follows: 87 Aβ- at Braak 0, 18 Aβ+ at Braak 0, 36 Aβ+ at Braak I-II, 27 Aβ+ at Braak III-IV, and 63 Aβ+ at Braak V-VI (Fig. 1). Participants' baseline demographic, clinical, and biomarker characteristics are summarized in Table 1. Significant differences between the groups were observed for age, clinical diagnoses, MMSE scores, APOE ε4 carriership, and neocortical [^{18}F]AZD4694 SUVR.

A total of 122 participants (49 Aβ- at Braak 0, 12 Aβ+ at Braak 0, 23

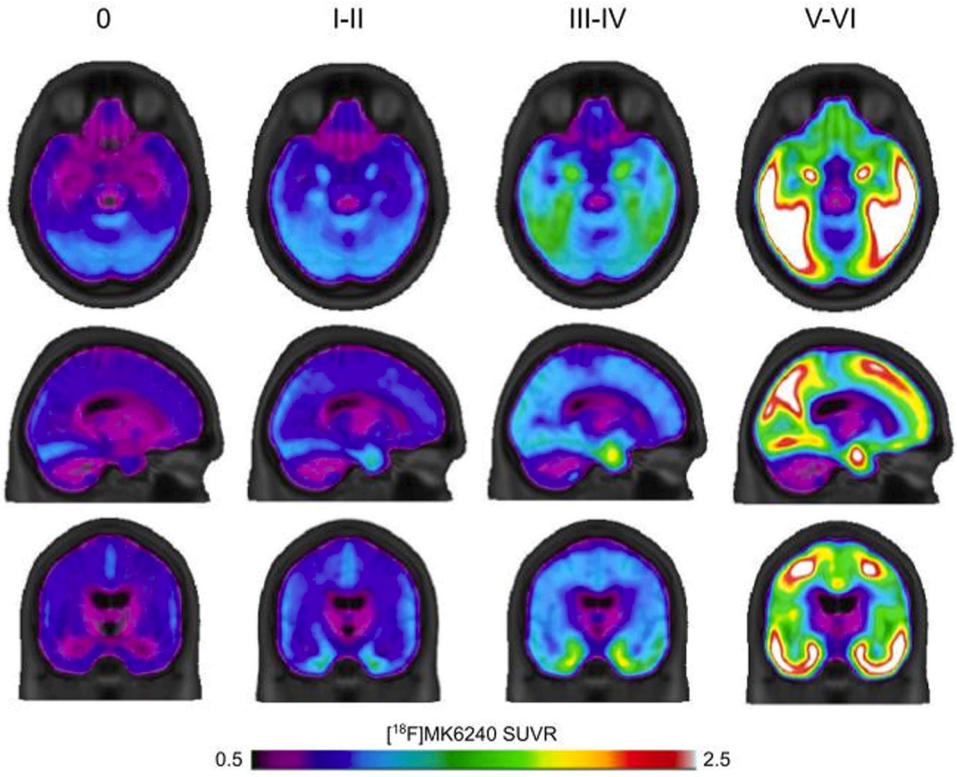

Fig. 1. Average [^{18}F]MK6240 SUVRs in the brain of participants at different PET-based Braak stages. At stage 0, no detectable tau abnormality is observed. Abnormalities at stages I-II are seen in the transentorhinal and entorhinal cortices and the hippocampus. At stages III-IV, there is a progression of the tau signal in the previously affected regions and an extension of the signal to adjacent neocortical areas. At stages V-VI, the images capture the extension of tau pathology to the whole neocortex, including primary sensory fields.

Table 1
Baseline demographic, clinical and biomarker characteristics of the study sample.

	Aβ- Braak 0 (N = 87)	Aβ+ Braak 0 (N=18)	Aβ+ Braak I-II (N=36)	Aβ+ Braak III-IV (N=27)	Aβ+ Braak V-VI (N=63)	p-value
Age (years), mean (s.d.)	69.13 (7.7)	72.63 (6.4)	72.81 (5.6)	72.20 (4.7)	68.43 (9.1)	**0.02**
Female, n (%)	49 (56.3 %)	13 (72.2 %)	23 (63.9 %)	17 (63.0 %)	34 (54.0 %)	0.60
Clinical diagnosis, n (%)	87 (100 %) CU, 0 (0 %) MCI, 0 (0 %) AD	14 (77.8 %) CU, 4 (22.2 %) MCI, 0 (0 %) AD	16 (44.4 %) CU, 18 (50.0 %) MCI, 2 (5.6 %) AD	7 (25.9 %) CU, 11 (40.7 %) MCI, 9 (33.3 %) AD	1 (1.6 %) CU, 23 (36.5 %) MCI, 39 (61.9 %) AD	**< 0.001**
Years of education, mean (s.d.)	15.83 (3.9)	14.00 (3.1)	15.19 (4.2)	15.63 (4.0)	14.67 (3.8)	0.22
MMSE, mean (s.d.)[#]	29.15 (0.9)	28.83 (1.6)	28.69 (1.3)	26.96 (3.9)	21.74 (6.9)	**< 0.001**
APOE ε4 carriers, n (%)[$]	18 (20.7 %)	4 (22.2 %)	14 (38.9 %)	17 (63.0 %)	35 (55.6 %)	**< 0.001**
Neocortical [^{18}F] AZD4694 SUVR, mean (s.d.)	1.28 (0.1)	1.88 (0.3)	2.15 (0.4)	2.28 (0.5)	2.61 (0.5)	**< 0.001**

AD: Alzheimer's disease; CU: cognitively unimpaired; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; ROI: region of interest; s.d.: standard deviation; SUVR: standardized uptake value ratio. Statistical significance was considered if $p < 0.05$ (results in bold).
#2 missing values
$19 missing values

Aβ+ at Braak I-II, 15 Aβ+ at Braak III-IV, and 23 Aβ+ at Braak V-VI) returned for a follow-up visit in a mean (s.d.) of 1.97 (0.62) years (Supplementary Table 1). The minimum and maximum time of follow-up were respectively 0.89 and 4.07 years. No significant difference in the follow-up time was observed between groups.

At baseline, significant differences, compared to Aβ- participants at Braak 0, started to be observed at Braak III-IV, for the NPI-Q-S and the NPI-Q-D, and at Braak I-II for the MBI-C (Fig. 2A-C). When subgrouping participants based on their degree of cognitive impairment (i.e. MCI vs AD dementia), we observed significantly higher NPI-Q-S and NPI-Q-D scores in AD compared to MCI participants at stages III-IV and V-VI and higher MBI-C scores in AD than in MCI individuals at stages V-VI (Supplementary Figures 1A-C). Baseline NPS scores in all tools correlated positively and significantly with the advance of Braak stages from 0 to V-VI (Fig. 2A-C). Participants at stages III-IV and V-VI showed significantly higher annual rates of change in MBI-C scores than Aβ- individuals at Braak 0 (Fig. 2D-F). Meanwhile, significant differences in the rates of change were observed only between Braak V-VI and Aβ+ Braak 0 participants, for the NPI-Q-S, and between individuals at Braak III-IV and Aβ- Braak 0, for the NPI-Q-D.

Furthermore, the Braak III-IV and V-VI groups had higher proportions (compared to Braak 0) of participants with at least one NPS than those at earlier Braak stages (Fig. 3). In Spearman's correlations adjusted for age and sex, the total scores in all NPS tools showed significant positive correlations with SUVR values in Braak ROIs (all $p < 0.001$; Fig. 4A-C). All MBI-C domains were significantly correlated with

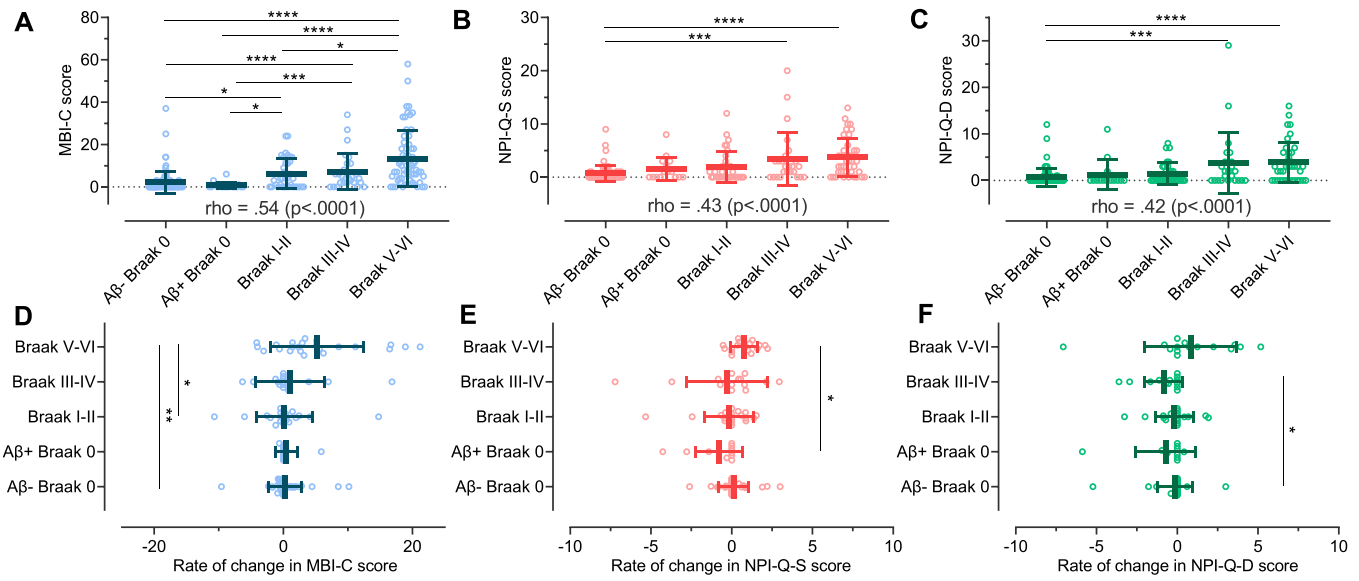

Fig. 2. Progression of baseline neuropsychiatric scores and their annual rates of change across PET-based Braak stages. Fig. 2A-F depict the mean (s.d.) of the MBI-C (A), NPI-Q-S (B), and NPI-Q-D (C) baseline scores per PET-based Braak stage. Fig. 2D-F display the mean (s.d.) rates of change in the scores of the MBI-C (D), NPI-Q-S (E), and NPI-Q-D (F). Scores were compared with the Kruskal-Wallis test, and *post hoc* comparisons were conducted with the Wilcoxon rank sum test. The displayed rho coefficients indicate whether or not the scores changed in an ordinal fashion following the advance of Braak staging groups, from Aβ- 0 to V-VI. Statistical significance is assigned as follows: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Legend: MBI-C: Mild Behavioral Impairment Checklist; NPI-Q-D: Neuropsychiatric Inventory Questionnaire Distress; NPI-Q-S: Neuropsychiatric Inventory Questionnaire Severity; PET: positron emission tomography.

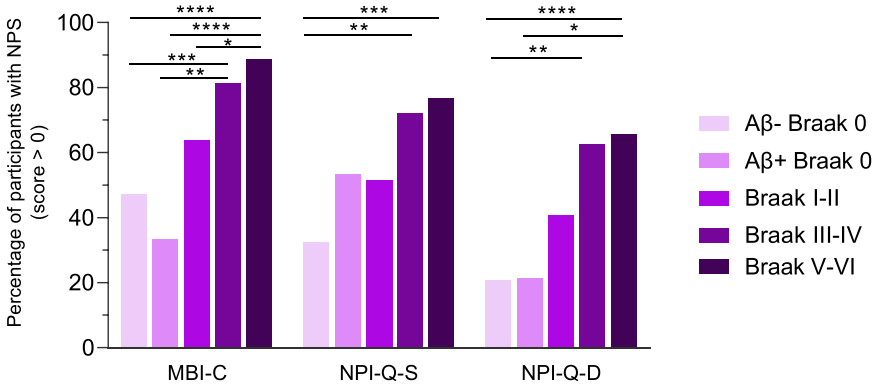

Fig. 3. The proportion of participants presenting neuropsychiatric symptoms across PET-based Braak stages. The graphs display the percentage of participants with at least one neuropsychiatric symptom (i.e. with a score higher than zero) according to the MBI-C, NPI-Q-S, and NPI-Q-D. Statistical significance is assigned as follows: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Legend: MBI-C: Mild Behavioral Impairment Checklist; NPI-Q-D: Neuropsychiatric Inventory Questionnaire Distress; NPI-Q-S: Neuropsychiatric Inventory Questionnaire Severity; PET: positron emission tomography.

tau-PET SUVR in at least one Braak ROI. "Agitation/aggression", "anxiety", "apathy/indifference", "appetite/eating disturbances", "dysphoria/depression" and "irritability/lability" presented significant correlations with tau-PET signal in at least one Braak ROI for both the NPI-Q-S and the NPI-Q-D. "Aberrant motor behaviors" in the NPI-Q-D but not in the NPI-Q-S was significantly correlated with Braak V-VI SUVR.

In MLR models adjusted for age and sex, PET-based Braak stages I-II (β=0.61, 95 % CI 0.28–0.94, p < 0.001), III-IV (β=0.84, 95 % CI 0.47–1.20, p < 0.0001), and V-VI (β=1.28, 95 % CI 1.01–1.55, p < 0.0001) were associated with higher baseline MBI-C scores (Fig. 5A). Similarly, PET-based Braak stages I-II (β=0.49, 95 % CI 0.11–0.87, p < 0.05), III-IV (β=0.89, 95 % CI 0.47–1.31, p < 0.0001) and V-VI (β=1.07, 95 % CI 0.71–1.43, p < 0.0001) were associated with higher baseline NPI-Q-S scores (Fig. 5A). We also observed associations between Braak I-II (β=0.40, 95 % CI 0.01–0.79, p < 0.05), III-IV (β=0.90, 95 % CI 0.47–1.33, p < 0.0001) and V-VI (β=1.04, 95 % CI 0.68–1.41, p < 0.0001) and higher NPI-Q-D scores (Fig. 5A).

Baseline PET-based Braak stages V-VI predicted a significantly higher annual rate of increase in MBI-C scores (β=0.94, 95 % CI 0.46–1.42, p < 0.001; Fig. 5B), in models adjusted for age and sex. No associations were found between PET-based Braak stages and the NPI-Q-S or NPI-Q-D rates of change.

3.1. *Exploratory analyses*

The associations of PET-based Braak stages I-II, III-IV, and VI with baseline NPS scores of all tools remained significant, even after stepwise adjustment for years of education, Aβ-PET neocortical SUVR, and MMSE scores (Supplementary Figure 2A-C). Moreover, after correction for MMSE rate of change, baseline Braak V-VI was associated with significantly higher rates of increase in both the MBI-C (β=0.83, 95 % CI 0.22–1.44, p < 0.01) and the NPI-Q-D (β=0.72, 95 % CI 0.04–1.40, p < 0.05; Supplementary Figure 3). We also tested whether baseline NPS scores were associated with the annual change in tau-PET signal in Braak ROIs. In models adjusted for age and sex, baseline NPI-Q-S and

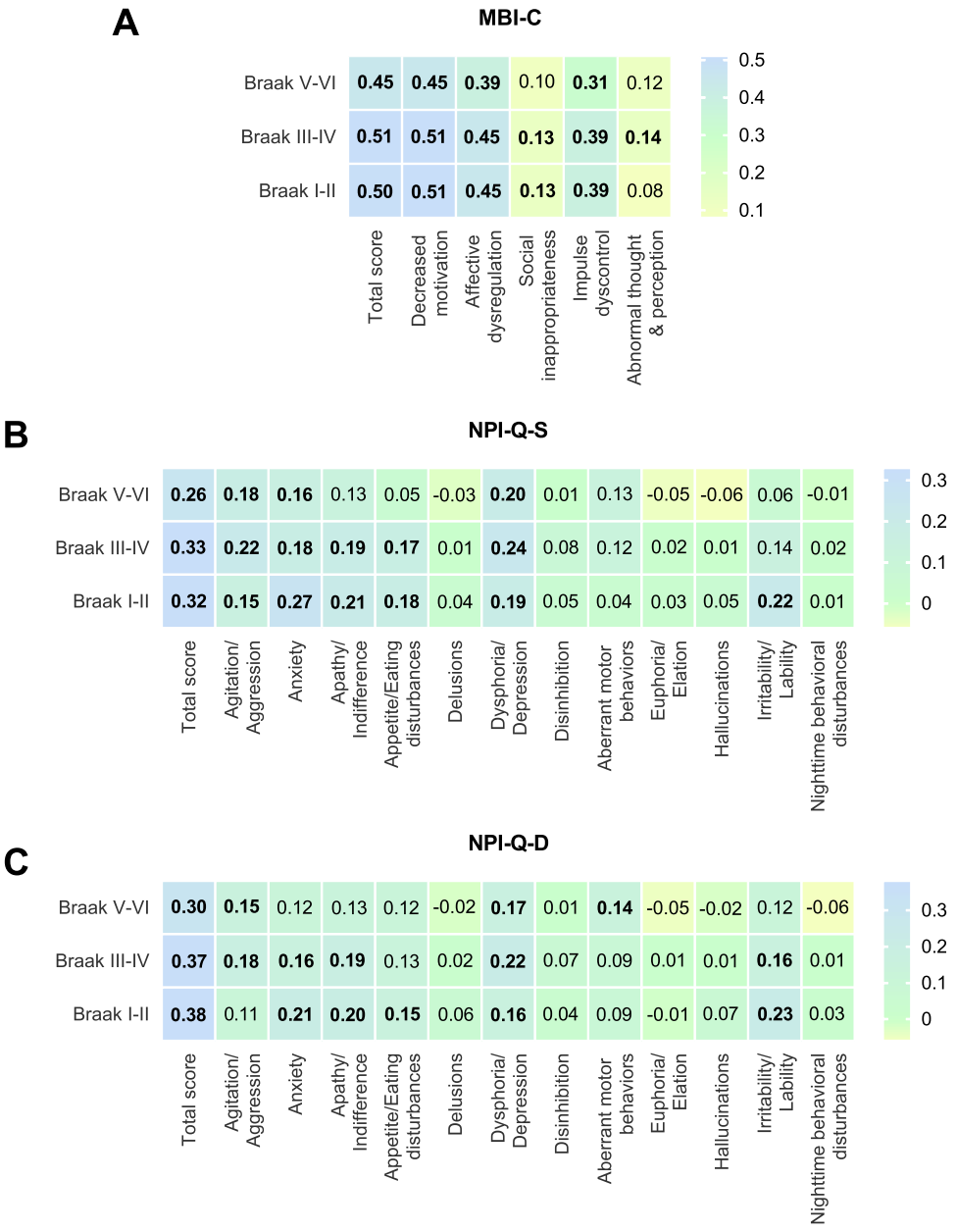

Fig. 4. Correlation between SUVR in Braak ROIs and NPS scores. The heatmaps show Spearman's rho coefficients of the correlations between SUVR values from Braak-like ROIs and baseline total scores and the scores for the domains of the MBI-C (A), NPI-Q-S (B), and NPI-Q-D (C). Coefficients in **bold** represent those with statistical significance ($p < 0.05$). Legend: MBI-C: Mild Behavioral Impairment Checklist; NPI-Q-D: Neuropsychiatric Inventory Questionnaire Distress; NPI-Q-S: Neuropsychiatric Inventory Questionnaire Severity; NPS: neuropsychiatric symptoms; ROI: region of interest; SUVR: standardized uptake value ratio.

NPI-Q-D scores were associated with higher rates of change in Braak III-IV and V-VI SUVR (Supplementary Figure 4A-C). Following the inclusion of baseline MMSE scores as a covariate, only the association between baseline NPI-Q-S scores and increased rates of change in Braak III-IV and V-VI SUVR remained significant (Supplementary Figure 4D-F).

4. Discussion

In this study, we investigated the relationship between NPS and Braak stages assigned *in vivo* with tau-PET at an individual level. Our results demonstrate associations between early, middle, and late Braak stages with NPS burden and severity as well as the increase of NPS with the advance of Braak stages. Moreover, participants at late PET-based Braak stages presented with greater increases in NPS as measured in a follow-up visit happening on average two years after baseline. These results indicate that tau accumulation may precede the onset and progression of NPS, suggesting NPS may present as a sequelae of progressing tauopathy. Our study also adds to the previous literature showing that the progression of PET-based Braak stages parallels and predicts clinical worsening in AD (Kreisl et al., 2022; Macedo et al., 2023, 2024a, 2024b; Pascoal et al., 2020, 2021a; Rullmann et al., 2022; Schöll et al., 2016; Schwarz et al., 2016; Therriault et al., 2022).

In this study, we assessed participants with three NPS tools widely used in clinical practice and research. These three outcomes offer distinct perspectives on the NPS burden and severity in preclinical and clinical AD populations. We found that baseline scores of all NPS tools were associated with PET-based Braak stages I-II, III-IV, and V-VI. However, the MBI-C seems to add value in distinguishing the presence of NPS and their severity between participants at different stages of tau accumulation, possibly because it evaluates milder NPS over a broader

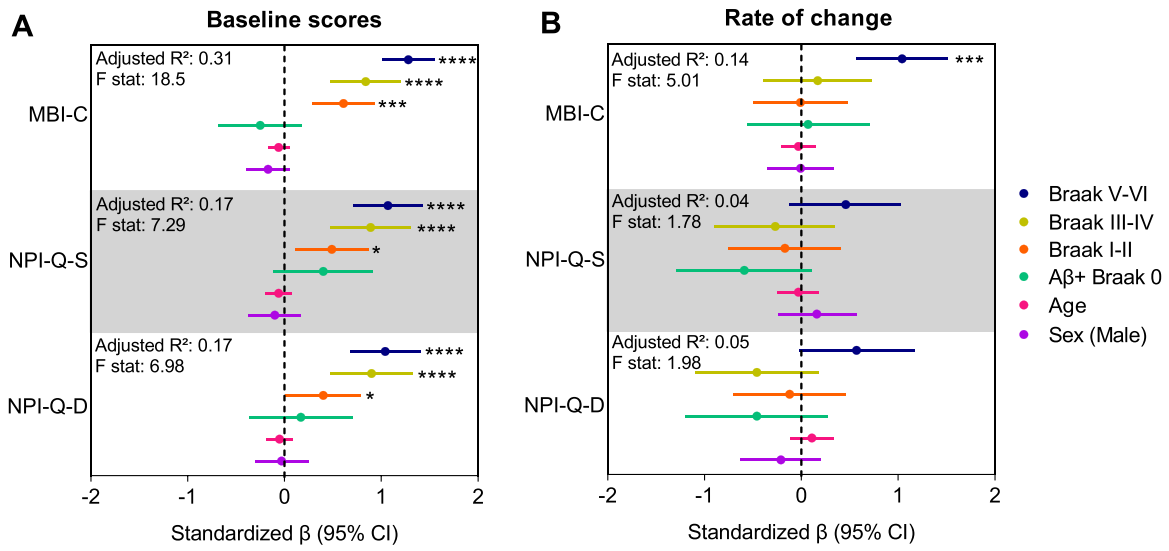

Fig. 5. Regression coefficients of the association between PET-based Braak stages and NPS in models adjusted for age and sex. The figures display the standardized β coefficients and 95 % confidence intervals of multiple linear regression models testing the association of PET-based Braak stages with baseline NPS scores (A) and the rates of change in NPS scores (B). Statistical significance is assigned as follows: *p < 0.05, ***p < 0.001, ****p < 0.0001. Legend: CI: confidence interval; MBI-C: Mild Behavioral Impairment Checklist; NPI-Q-D: Neuropsychiatric Inventory Questionnaire Distress; NPI-Q-S: Neuropsychiatric Inventory Questionnaire Severity.

time frame (Ismail et al., 2017). Furthermore, the fact that we observed higher MBI-C scores in individuals at Braak I-II stages lends preliminary support to the "transitional decline" clinical stage proposed in the recent Alzheimer's Association Workgroup research criteria (Jack et al., 2024). Notably, all MBI-C domains but not all NPI-Q-S and NPI-Q-D domains were significantly correlated with tau-PET signal in at least one Braak ROI. Previous studies have described the tau-PET correlates of NPI-Q-S domains, indicating distinct topographies for different NPS (Tissot et al., 2021). Our study builds on these findings by supporting that PET-based Braak staging might reflect the progression of global NPS severity and burden, particularly of affective domains (Pichet-Binette et al., 2021; Yasuno et al., 2021).

The literature on the relationship of global NPS burden and severity with AD biological staging is emerging. Previous post-mortem observations support our findings showing associations of higher Braak stages with increased NPI-Q-S scores (Malpas et al., 2021) and number of NPS (Gibson et al., 2023). Another histopathological study reported higher odds for NPS at Braak I-II, but not at III-IV and V-VI, compared to Braak 0, which could be due to the adjustments performed for Aβ pathology and functional cognitive status (Ehrenberg et al., 2018). Indeed, in our study, correction for MMSE scores influenced the associations between NPS and Braak stages, probably due to the collinearity between tau severity and cognitive function. We also observed differences in NPS scores between MCI and AD participants at the same Braak stage, highlighting the influence of the degree of cognitive impairment in the relationship between tau and NPS.

Recent evidence also highlights a relationship between global NPS severity and tau accumulation in Braak-like ROIs as assessed by tau-PET. In the aging and AD continuum, higher NPI-Q-S scores were found to be correlated with increased [^{18}F]MK6240 SUVR in Braak I-II, III-IV, and V-VI ROIs (Tissot el al., 2021). In a study with [^{18}F]AV1451 PET including CU, Aβ+ MCI, and Aβ+ AD individuals, Braak I-II but not III-IV and V-VI SUVR was significantly correlated with NPI global severity (Yasuno et al., 2021). In Naude et al. (2024), Aβ+ but not Aβ- CU and MCI individuals with MBI (i.e., NPS meeting MBI criteria) showed increased [^{18}F]AV1451 tau-PET uptake in Braak I and III regions, in models adjusted for age, sex, education, and cognitive status. In fact, among Aβ- participants, the presence of MBI was negatively associated with SUVR in Braak III (Naude et al., 2024). Moreover, Aβ status was found to moderate the association between MBI presence and tau-PET uptake in Braak I and III ROIs (Naude et al., 2024), which underscores the intricate relationship between Aβ and tau pathology in the context of NPS in AD. This might also indicate a complex interplay of other pathological factors, such as neurodegeneration (Matuskova et al., 2021), neuroinflammation (Aguzzoli et al., 2023), and comorbid pathologies.

In two studies investigating the tau-PET correlates of NPS in Aβ+ and Aβ- preclinical subjects, no significant associations were found between MBI-C scores and [^{18}F]MK6240 at global or at voxel level (Lussier et al., 2020) nor between [^{18}F]AV1451 tau positivity and NPI-Q scores (Babulal et al., 2020). Meanwhile, [^{18}F]RO948 PET signal in the entorhinal cortex/hippocampus (correspondent to Braak II in our study) was associated with higher MBI-C scores in another study including only Aβ+ CU subjects (Johansson et al., 2021). The integration of these findings with our results supports the idea that the presence and severity of NPS in AD are influenced by a combination of Aβ and tau pathology, with tau pathology possibly exerting its influence even in the early stages of tau accumulation. This underscores the importance of considering both Aβ and tau pathology in understanding and managing NPS in AD patients. Further research exploring the mechanistic underpinnings of this relationship is warranted to inform targeted therapeutic interventions for improving patient outcomes.

Our exploratory analyses also indicated that more severe baseline behavioral manifestations are consistent with higher rates of tau accumulation in AD-related brain regions. A similar dynamic of progression has been described regarding cognitive performance (Macedo et al., 2024a). Individuals with higher degree of cognitive impairment present greater longitudinal tau accumulation in the brain (Cho et al., 2019; Pascoal et al., 2021b), and tau deposition in AD-related regions is associated with future clinical deterioration (Macedo et al., 2024b; Schöll et al., 2016). Taken together, these findings indicate a concomitant progression of biological and clinical AD markers. Here, we anchor ourselves in the principle that symptoms follow pathological changes (and not the opposite; Jack et al., 2024) to support the possible value of PET-based Braak staging as a prognostic tool for use in clinical practice or recruitment in clinical trials.

This study has some limitations. First, no confirmation of our findings was done with autopsies, which is still considered the gold standard method to diagnose and stage individuals with the Braak histopathological scheme. Second, our study cohort does not include patients living in nursing homes, where the prevalence of NPS is known to be higher (Selbæk et al., 2013), or individuals with CDR>2, which is indicative of severe dementia. Third, the NPS tools were answered by an informant,

which produced a bias that we sought to diminish by selecting reliable informants. However, using this type of questionnaire when dealing with cognitively impaired subjects may be more trustworthy due to their lack of awareness of their illness. The MBI-C has been validated for self-report, and in CU participants, self-report may offer additional or complementary information to informant reports, which are more reliable in later disease stages (Creese et al., 2020; Ismail et al., 2023). In addition, although highly accurate, the NPI-Q is a concise and less complete version of the NPI (Kaufer et al., 2000). Another caveat is that our participants had a single follow-up visit, occurring at varying times from baseline. This is particularly noteworthy given the common fluctuating course of NPS in the progression of AD (Poulin et al., 2017). Finally, due to our limited sample of participants with follow-up data, we could not reproduce the exact same models of our cross-sectional exploratory analyses in the longitudinal analyses. We suggest that future studies include more elaborate models accounting for other variables that potentially interfere with the progression of NPS, including measures of cognitive reserve, amyloid burden, and neuroinflammation markers.

5. Conclusions

In conclusion, our study suggests that the global NPS severity and burden in the aging and AD continuum is associated with early to late PET-based Braak stages and increases with the severity of tau accumulation. Our findings also indicate that the PET-based Braak staging framework may have prognostic value in predicting future NPS burden and severity in AD. This study also adds to previous research stating the clinical significance of the PET-based Braak staging framework. This may be useful to define recruitment strategies for trials investigating disease-modifying therapies or targeting behavioral manifestations of AD. Future research should investigate the longitudinal progression of NPS for a longer period, replicate our findings with other tau-PET ligands and methods of NPS assessment (e.g. self-report), examine the contribution of other pathological and psychosocial factors to NPS, and assess the progression of specific NPS or NPS patterns in relation to tau severity.

CRediT authorship contribution statement

Nesrine Rahmouni: Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Jaime Fernandez-Arias:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Firoza Z. Lussier:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Yi-Ting Wang:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Kok Pin Ng:** Writing – review & editing, Visualization, Formal analysis. **Marie Vermeiren:** Writing – review & editing, Investigation, Formal analysis. **Gleb Bezgin:** Writing – review & editing, Investigation, Formal analysis. **Kely Quispialaya Socualaya:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Jenna Stevenson:** Writing – review & editing, Project administration, Formal analysis, Data curation. **Seyyed Ali Hosseini:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Mira Chamoun:** Writing – review & editing, Project administration, Funding acquisition, Data curation. **João Pedro Ferrari-Souza:** Writing – review & editing, Investigation, Formal analysis. **Pâmela C.L. Ferreira:** Writing – review & editing, Investigation, Formal analysis. **Bruna Bellaver:** Writing – review & editing, Investigation, Formal analysis. **Douglas Teixeira Leffa:** Writing – review & editing, Investigation, Formal analysis. **Paolo Vitali:** Writing – review & editing, Investigation, Formal analysis. **Arthur C. Macedo:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eduardo R. Zimmer:** Writing – review & editing, Investigation, Formal analysis. **Zahinoor Ismail:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Tharick A. Pascoal:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Joseph Therriault:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Serge Gauthier:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation. **Cécile Tissot:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pedro Rosa-Neto:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Étienne Aumont:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Stijn Servaes:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis.

Submission declaration and verification

We declare that the present work has not been published previously (except in the form of an abstract) and is not under consideration for publication elsewhere. We also declare that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Data statement

All requests for raw and analyzed data and materials will be promptly reviewed by McGill University to verify if the request is subject to any intellectual property or confidentiality obligations. Anonymized data will be shared upon request to the study's senior author from a qualified academic investigator for the sole purpose of replicating the procedures and results presented in this article. Any data and materials that can be shared will be released via a material transfer agreement. Data are not publicly available due to information that could compromise the privacy of research participants. Related documents, including study protocol and informed consent forms, can similarly be made available upon request.

Declaration of Interest

E.R.Z. serves on the scientific advisory board of Next Innovative Therapeutics. Z.I. has served as an advisor/consultant to CADTH, Eisai, Eli Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche. S.G. has served as a scientific advisor to Cerveau Therapeutics. Outside the work presented in this paper, P.R.N. provides consultancy services for Roche, Cerveau Radiopharmaceuticals, Lilly, Eisai, Pfizer, and Novo Nordisk. P.R.N. also

serves as a clinical trials investigator for Biogen and Novo Nordisk. The other authors declare that they have no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.09.009.

References

Aguzzoli, C.S., Ferreira, P.C.L., Povala, G., Ferrari-Souza, J.P., Bellaver, B., Soares Katz, C., Zalzale, H., Lussier, F.Z., Rohden, F., Abbas, S., Leffa, D.T., Scop Medeiros, M., Therriault, J., Benedet, A.L., Tissot, C., Servaes, S., Rahmouni, N., Cassa Macedo, A., Bezgin, G., Kang, M.S., Stevenson, J., Pallen, V., Cohen, A., Lopez, O.L., Tudorascu, D.L., Klunk, W.E., Villemagne, V.L., Soucy, J.P., Zimmer, E. R., Schilling, L.P., Karikari, T.K., Ashton, N.J., Zetterberg, H., Blennow, K., Gauthier, S., Valcour, V., Miller, B.L., Rosa-Neto, P., Pascoal, T.A., 2023. Neuropsychiatric Symptoms and Microglial Activation in Patients with Alzheimer Disease. JAMA Netw. Open 6 (11) e2345175.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 270–279.

Babulal, G.M., Roe, C.M., Stout, S.H., Rajasekar, G., Wisch, J.K., Benzinger, T.L.S., Morris, J.C., Ances, B.M., 2020. Depression is associated with tau and not amyloid positron emission tomography in cognitively normal adults. J. Alzheimers Dis. 74, 1045–1055.

Ballard, C., Day, S., Sharp, S., Wing, G., Sorensen, S., 2008. Neuropsychiatric symptoms in dementia: importance and treatment considerations. Int. Rev. Psychiatry 20, 396–404.

Balestreri, L., Grossberg, A., Grossberg, G.T., 2000. Behavioral and psychological symptoms of dementia as a risk factor for nursing home placement. Int. Psychogeriatr. 12, 59–62.

Bateman, R.J., Xiong, C., Benzinger, T.L., Fagan, A.M., Goate, A., Fox, N.C., Marcus, D.S., Cairns, N.J., Xie, X., Blazey, T.M., Holtzman, D.M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P.S., Ghetti, B., Klunk, W.E., McDade, E., Martins, R. N., Masters, C.L., Mayeux, R., Ringman, J.M., Rossor, M.N., Schofield, P.R., Sperling, R.A., Salloway, S., Morris, J.C., Dominantly Inherited Alzheimer Network, 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med. 367, 795–804.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., Del Tredici, K., 2006. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 112, 389–404.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Cho, H., Choi, J.Y., Lee, H.S., Lee, J.H., Ryu, Y.H., Lee, M.S., Jack, C.R., Jr, Lyoo, C.H., 2019. Progressive Tau accumulation in alzheimer disease: 2-year follow-up study. J. Nucl. Med. 60, 1611–1621.

Creese, B., Griffiths, A., Brooker, H., Corbett, A., Aarsland, D., Ballard, C., Ismail, Z., 2020. Profile of mild behavioral impairment and factor structure of the Mild Behavioral Impairment Checklist in cognitively normal older adults. Int. Psychogeriatr. 32 (6), 705–717.

Crutch, S.J., Schott, J.M., Rabinovici, G.D., Murray, M., Snowden, J.S., van der Flier, W. M., Dickerson, B.C., Vandenberghe, R., Ahmed, S., Bak, T.H., Boeve, B.F., Butler, C., Cappa, S.F., Ceccaldi, M., de Souza, L.C., Dubois, B., Felician, O., Galasko, D., Graff-Radford, J., Graff-Radford, N.R., Hof, P.R., Krolak-Salmon, P., Lehmann, M., Magnin, E., Mendez, M.F., Nestor, P.J., Onyike, C.U., Pelak, V.S., Pijnenburg, Y., Primativo, S., Rossor, M.N., Ryan, N.S., Scheltens, P., Shakespeare, T.J., Suárez González, A., Tang-Wai, D.F., Yong, K.X.X., Carrillo, M., Fox, N.C., 2017. Alzheimer's Association ISTAART Atypical Alzheimer's Disease and Associated Syndromes Professional Interest Area. Consensus classification of posterior cortical atrophy. Alzheimers Dement 13, 870–884.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.

Devineni, B., Onyike, C.U., 2015. Young-onset dementia epidemiology applied to neuropsychiatry practice. Psychiatr. Clin. N. Am. 38, 233–248.

Diedrichsen, J., Balsters, J.H., Flavell, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. Neuroimage 46, 39–46.

Ehrenberg, A.J., Suemoto, C.K., França Resende, E.P., Petersen, C., Leite, R.E.P., Rodriguez, R.D., Ferretti-Rebustini, R.E.L., You, M., Oh, J., Nitrini, R., Pasqualucci, C.A., Jacob-Filho, W., Kramer, J.H., Gatchel, J.R., Grinberg, L.T., 2018. Neuropathologic correlates of psychiatric symptoms in alzheimer's disease. J. Alzheimers Dis. 66, 115–126.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R. H., Pericak-Vance, M.A., Risch, N., van Duijn, C.M., 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278 (16), 1349–1356.

Ferrari-Souza, J.P., Bellaver, B., Ferreira, P.C.L., Benedet, A.L., Povala, G., Lussier, F.Z., Leffa, D.T., Therriault, J., Tissot, C., Soares, C., Wang, Y.T., Chamoun, M., Servaes, S., Macedo, A.C., Vermeiren, M., Bezgin, G., Kang, M.S., Stevenson, J., Rahmouni, N., Pallen, V., Poltronetti, N.M., Cohen, A., Lopez, O.L., Klunk, W.E., Soucy, J.P., Gauthier, S., Souza, D.O., Triana-Baltzer, G., Saad, Z.S., Kolb, H.C., Karikari, T.K., Villemagne, V.L., Tudorascu, D.L., Ashton, N.J., Zetterberg, H., Blennow, K., Zimmer, E.R., Rosa-Neto, P., Pascoal, T.A., 2023. APOEε4 potentiates amyloid β effects on longitudinal tau pathology. Nat. Aging 3 (10), 1210–1218.

Ferrari-Souza, J.P., Ferreira, P.C.L., Bellaver, B., Tissot, C., Wang, Y.T., Leffa, D.T., Brum, W.S., Benedet, A.L., Ashton, N.J., De Bastiani, M.A., Rocha, A., Therriault, J., Lussier, F.Z., Chamoun, M., Servaes, S., Bezgin, G., Kang, M.S., Stevenson, J., Rahmouni, N., Pallen, V., Poltronetti, N.M., Klunk, W.E., Tudorascu, D.L., Cohen, A. D., Villemagne, V.L., Gauthier, S., Blennow, K., Zetterberg, H., Souza, D.O., Karikari, T.K., Zimmer, E.R., Rosa-Neto, P., Pascoal, T.A., 2022. Astrocyte biomarker signatures of amyloid-β and tau pathologies in Alzheimer's disease. Mol. Psychiatry 27 (11), 4781–4789 (Nov).

Fischer, C.E., Ismail, Z., Schweizer, T.A., 2012. Delusions increase functional impairment in Alzheimer's disease. Dement Geriatr. Cog Dis. 33, 393–399 (a).

Fischer, C.E., Ismail, Z., Schweizer, T.A., 2012. Impact of neuropsychiatric symptoms on caregiver burden in patients with Alzheimer's disease. Neurodegener. Dis. Manag 2, 269–277 (b).

Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., Bullido, M.J., Engelborghs, S., De Deyn, P., Berr, C., Pasquier, F., Dubois, B., Tognoni, G., Fiévet, N., Brouwers, N., Bettens, K., Arosio, B., Coto, E., Del Zompo, M., Mateo, I., Epelbaum, J., Frank-Garcia, A., Helisalmi, S., Porcellini, E., Pilotto, A., Forti, P., Ferri, R., Scarpini, E., Siciliano, G., Solfrizzi, V., Sorbi, S., Spalletta, G., Valdivieso, F., Vepsäläinen, S., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossù, P., Hanon, O., Piccardi, P., Annoni, G., Seripa, D., Galimberti, D., Licastro, F., Soininen, H., Dartigues, J.F., Kamboh, M.I., Van Broeckhoven, C., Lambert, J.C., Amouyel, P., Campion, D., 2011. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. Mol. Psychiatry 16 (9), 903–907.

Gibson, L.L., Grinberg, L.T., Ffytche, D., Leite, R.E.P., Rodriguez, R.D., Ferretti-Rebustini, R.E.L., Pasqualucci, C.A., Nitrini, R., Jacob-Filho, W., Aarsland, D., Suemoto, C.K., 2023. Neuropathological correlates of neuropsychiatric symptoms in dementia. Alzheimers Dement 19 (4), 1372–1382.

Goukasian, N., Hwang, K.S., Romero, T., Grotts, J., Do, T.M., Groh, J.R., Bateman, D.R., Apostolova, L.G., 2019. Association of brain amyloidosis with the incidence and frequency of neuropsychiatric symptoms in ADNI: a multisite observational cohort study. BMJ Open 9, e031947.

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. Neurology 76, 1006–1014.

Guadagna, S., Esiri, M.M., Williams, R.J., Francis, P.T., 2012. Tau phosphorylation in human brain: relationship to behavioral disturbance in dementia. Neurobiol. Aging 33, 2798–2806.

Hixson, J.E., Vernier, D.T., 1990. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with *Hha*I. J. Lipid Res. 31 (3), 545–548.

Ismail, Z., Agüera-Ortiz, L., Brodaty, H., Cieslak, A., Cummings, J., Fischer, C.E., Gauthier, S., Geda, Y.E., Herrmann, N., Kanji, J., Lanctôt, K.L., Miller, D.S., Mortby, M.E., Onyike, C.U., Rosenberg, P.B., Smith, E.E., Smith, G.S., Sultzer, D.L., Lyketsos, C., Professional Interest Area, N.P.S., 2017. of the International Society of to Advance Alzheimer's Research and Treatment (NPS-PIA of ISTAART). The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. J. Alzheimers Dis. 56, 929–938.

Ismail Z., Guan D., Vellone D., Ballard C., Creese B., Corbett A., Pickering E., Bloomfield A., Hampshire A., Sekhon R., Roach P., Smith E.E. The Canadian platform for research online to investigate health, quality of life, cognition, behaviour, function, and caregiving in aging (CAN-PROTECT): study protocol, platform description, and preliminary analyses. medRxiv 2023. doi: 10.1101/2023.12.16.23300094.

Ismail, Z., Smith, E.E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., Agüera-Ortiz, L., Sweet, R., Miller, D., Lyketsos, C.G., 2016. ISTAART Neuropsychiatric Symptoms Professional Interest Area. Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 12 (2), 195–202.

Jack Jr., C.R., Andrews, J.S., Beach, T.G., Buracchio, T., Dunn, B., Graf, A., Hansson, O., Ho, C., Jagust, W., McDade, E., Molinuevo, J.L., Okonkwo, O.C., Pani, L., Rafii, M.S., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Teunissen, C.E., Carrillo, M.C., 2024. Revised criteria for diagnosis and staging of Alzheimer's disease. Alzheimer's Association Workgroup. Alzheimers Dement. 20, 5143–5169.

Jack, C.R., Jr, Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216.

Jack, C.R., Jr, Wiste, H.J., Schwarz, C.G., Lowe, V.J., Senjem, M.L., Vemuri, P., Weigand, S.D., Therneau, T.M., Knopman, D.S., Gunter, J.L., Jones, D.T., Graff-Radford, J., Kantarci, K., Roberts, R.O., Mielke, M.M., Machulda, M.M., Petersen, R.

C., 2018. Longitudinal tau PET in ageing and Alzheimer's disease. Brain 141, 1517–1528.
Jack, C.R., Jr, Wiste, H.J., Weigand, S.D., Therneau, T.M., Lowe, V.J., Knopman, D.S., Gunter, J.L., Senjem, M.L., Jones, D.T., Kantarci, K., Machulda, M.M., Mielke, M.M., Roberts, R.O., Vemuri, P., Reyes, D.A., Petersen, R.C., 2017. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement. 13, 205–216.
Johansson, M., Stomrud, E., Insel, P.S., Leuzy, A., Johansson, P.M., Smith, R., Ismail, Z., Janelidze, S., Palmqvist, S., van Westen, D., Mattsson-Carlgren, N., Hansson, O., 2021. Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. Transl. Psychiatry 11 (1), 76.
Kaufer, D.I., Cummings, J.L., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., Lopez, O. L., DeKosky, S.T., 2000. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J. Neuropsychiatry Clin. Neurosci. 12, 233–239.
Kreisl, W.C., Lao, P.J., Johnson, A., Tomljanovic, Z., Klein, J., Polly, K., Maas, B., Laing, K.K., Chesebro, A.G., Igwe, K., Razlighi, Q.R., Honig, L.S., Yan, X., Lee, S., Mintz, A., Luchsinger, J.A., Stern, Y., Devanand, D.P., Brickman, A.M., 2022. Patterns of tau pathology identified with 18F-MK-6240 PET imaging. Alzheimers Dement. 18, 272–282.
Lussier, F.Z., Pascoal, T.A., Chamoun, M., Therriault, J., Tissot, C., Savard, M., Kang, M. S., Mathotaarachchi, S., Benedet, A.L., Parsons, M., Qureshi, M.N.I., Thomas, É.M., Shin, M., Dion, L.A., Massarweh, G., Soucy, J.P., Tsai, I.H., Vitali, P., Ismail, Z., Rosa-Neto, P., Gauthier, S., 2020. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. Alzheimers Dement. 16, 192–199.
Lyketsos, C.G., Lopez, O., Jones, B., Fitzpatrick, A.L., Breitner, J., DeKosky, S., 2002. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 288, 1475–1483.
Lyketsos, C.G., Steinberg, M., Tschanz, J.T., Norton, M.C., Steffens, D.C., Breitner, J.C., 2000. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am. J. Psychiatry 157, 708–714.
Macedo, A.C., Durço, D.F.P.A., Tissot, C., Therriault, J., Vilela de Faria, A.O., Aumont, É., Servaes, S., Rahmouni, N., Fernandez-Arias, J., Wang, Y.T., Lussier, F.Z., Bieger, A., Zimmer, E.R., Pascoal, T.A., Gauthier, S., Rosa-Neto, P., 2024a. Clinical Correlates of the PET-based braak staging framework in alzheimer's disease. J. Prev. Alzheimers Dis. 11 (2), 414–421 (a).
Macedo, A.C., Therriault, J., Tissot, C., Fernandez-Arias, J., Ferreira, P.C.L., Vitali, P., Servaes, S., Rahmouni, N., Vermeiren, M., Bezgin, G., Lussier, F.Z., Stevenson, J., Wang, Y.T., Socualaya, K.Q., Kunach, P., Nazneen, T., Hosseini, S.A., Pallen, V., Stevenson, A., Ferrari-Souza, J.P., Bellaver, B., Leffa, D.T., Ng, K.P., Zimmer, E.R., Pascoal, T.A., Gauthier, S., Rosa-Neto, P., 2024b. Predicting functional decline in aging and Alzheimer's disease with PET-based Braak staging. Brain Commun. 6 (2), fcae043 (b).
Macedo, A.C., Tissot, C., Therriault, J., Servaes, S., Wang, Y.T., Fernandez-Arias, J., Rahmouni, N., Lussier, F.Z., Vermeiren, M., Bezgin, G., Vitali, P., Ng, K.P., Zimmer, E.R., Guiot, M.C., Pascoal, T.A., Gauthier, S., Rosa-Neto, P., 2023. The Use of Tau PET to stage alzheimer disease according to the braak staging framework. J. Nucl. Med. 64 (8), 1171–1178.
Malpas, C.B., Sharmin, S., Kalincik, T., 2021. The histopathological staging of tau, but not amyloid, corresponds to antemortem cognitive status, dementia stage, functional abilities and neuropsychiatric symptoms. Int. J. Neurosci. 131, 800–809.
Matuskova, V., Ismail, Z., Nikolai, T., Markova, H., Cechova, K., Nedelska, Z., Laczó, J., Wang, M., Hort, J., Vyhnalek, M., 2021. Mild behavioral impairment is associated with atrophy of entorhinal cortex and hippocampus in a memory clinic cohort. Front. Aging Neurosci. 13, 643271.
McGirr, A., Nathan, S., Ghahremani, M., Gill, S., Smith, E.E., Ismail, Z., 2022. Progression to dementia or reversion to normal cognition in mild cognitive impairment as a function of late-onset neuropsychiatric symptoms. Neurology 98 (21), e2132–e2139.
McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Jr, Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 263–269.
Mega, M.S., Cummings, J.L., Fiorello, T., Gornbein, J., 1996. The spectrum of behavioral changes in Alzheimer's disease. Neurology 46, 130.
Naude, J., Wang, M., Leon, R., Smith, E., Ismail, Z., 2024. Tau-PET in early cortical Alzheimer brain regions in relation to mild behavioral impairment in older adults with either normal cognition or mild cognitive impairment. Neurobiol. Aging 138, 19–27.
Ng, K.P., Chiew, H., Rosa-Neto, P., Kandiah, N., Ismail, Z., Gauthier, S., 2021. Associations of AT(N) biomarkers with neuropsychiatric symptoms in preclinical Alzheimer's disease and cognitively unimpaired individuals. Transl. Neurodegener. 10 (1), 11.
Ossenkoppele, R., Singleton, E.H., Groot, C., Dijkstra, A.A., Eikelboom, W.S., Seeley, W. W., Miller, B., Laforce, R.J., Scheltens, P., Papma, J.M., Rabinovici, G.D., Pijnenburg, Y.A.L., 2022. Research criteria for the behavioral variant of alzheimer disease: a systematic review and meta-analysis. JAMA Neurol. 79, 48–60.
Pascoal, T.A., Benedet, A.L., Ashton, N.J., Kang, M.S., Therriault, J., Chamoun, M., Savard, M., Therriault, F.Z., Tissot, C., Karikari, T.K., Ottoy, J., Mathotaarachchi, S., Stevenson, J., Massarweh, G., Schöll, M., de Leon, M.J., Soucy, J.P., Edison, P., Blennow, K., Zetterberg, H., Gauthier, S., Rosa-Neto, P., 2021a. Microglial activation and tau propagate jointly across Braak stages. Nat. Med. 27, 1592–1599 (a).
Pascoal, T.A., Benedet, A.L., Tudorascu, D.L., Therriault, J., Mathotaarachchi, S., Savard, M., Lussier, F.Z., Tissot, C., Chamoun, M., Kang, M.S., Stevenson, J., Massarweh, G., Guiot, M.C., Soucy, J.P., Gauthier, S., Rosa-Neto, P., 2021b. Longitudinal 18F-MK-6240 tau tangles accumulation follows Braak stages. Brain 144, 3517–3528 (b).
Pascoal, T.A., Therriault, J., Benedet, A.L., Savard, M., Lussier, F.Z., Chamoun, M., Tissot, C., Qureshi, M.N.I., Kang, M.S., Mathotaarachchi, S., Stevenson, J., Hopewell, R., Massarweh, G., Soucy, J.P., Gauthier, S., Rosa-Neto, P., 2020. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. Brain 143, 2818–2830.
Peters, K.R., Rockwood, K., Black, S.E., Bouchard, R., Gauthier, S., Hogan, D., Kertesz, A., Loy-English, I., Beattie, B.L., Sadovnick, A.D., Feldman, H.H., 2006. Characterizing neuropsychiatric symptoms in subjects referred to dementia clinics. Neurology 66, 523–528.
Peters, M.E., Schwartz, S., Han, D., Rabins, P.V., Steinberg, M., Tschanz, J.T., Lyketsos, C. G., 2015. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache Country dementia progression study. Am. J. Psychiatry 172, 460–465.
Pichet-Binette, A., Vachon-Presseau, É., Morris, J., Bateman, R., Benzinger, T., Collins, D. L., et al., 2021. Amyloid and tau pathology associations with personality traits, neuropsychiatric symptoms, and cognitive lifestyle in the preclinical phases of sporadic and autosomal dominant Alzheimer'S disease. Biol. Psychiatry 89, 776–785.
Poulin, S.P., Bergeron, D., Dickerson, B.C., Alzheimer's Disease Neuroimaging Initiative, 2017. Risk factors, neuroanatomical correlates, and outcome of neuropsychiatric symptoms in alzheimer's disease. J. Alzheimers Dis. 60 (2), 483–493.
Rosenberg, P.B., Nowrangi, M.A., Lyketsos, C.G., 2015. Neuropsychiatric symptoms in Alzheimer's disease: what might be associated brain circuits? Mol. Asp. Med. 43–44, 25–37.
Rullmann, M., Brendel, M., Schroeter, M.L., Saur, D., Levin, J., Perneczky, R.G., Tiepolt, S., Patt, M., Mueller, A., Villemagne, V.L., Classen, J., Stephens, A.W., Sabri, O., Barthel, H., On Behalf Of The German Imaging Initiative For Tauopathies Gii, T., 2022. Multicenter 18F-PI-2620 PET for in vivo braak staging of tau pathology in alzheimer's disease. Biomolecules 12 (3), 458.
Ruthirakuhan, M., Ismail, Z., Herrmann, N., Gallagher, D., Lanctôt, K.L., 2022. Mild behavioral impairment is associated with progression to Alzheimer's disease: a clinicopathological study. Alzheimers Dement. 18 (11), 2199–2208.
Schöll, M., Lockhart, S.N., Schonhaut, D.R., O'Neil, J.P., Janabi, M., Ossenkoppele, R., Baker, S.L., Vogel, J.W., Faria, J., Schwimmer, H.D., Rabinovici, G.D., Jagust, W.J., 2016. PET imaging of tau deposition in the aging human brain. Neuron 89, 971–982.
Schwarz, A.J., Yu, P., Miller, B.B., Shcherbinin, S., Dickson, J., Navitsky, M., Joshi, A.D., Devous, M.D., Sr, Mintun, M.S., 2016. Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. Brain 139, 1539–1550.
Selbæk, G., Engedal, K., Bergh, S., 2013. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. J. Am. Med. Dir. Assoc. 14, 161–169.
Sink, K.M., Covinsky, K.E., Newcomer, R., Yaffe, K., 2004. Ethnic differences in the prevalence and pattern of dementia-related behaviors. J. Am. Geriatr. Soc. 52, 1277–1283.
Stern, Y., Albert, M., Brandt, J., Jacobs, D.M., Tang, M.X., Marder, K., Bell, K., Sano, M., Devanand, D.P., Bylsma, F., Lafleche, G., 1994. Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease Prospective analyses from the Predictors Study. Neurology 44, 2300–2307.
Tekin, S., Mega, M.S., Masterman, D.M., Chow, T., Garakian, J., Vinters, H.V., Cummings, J.L., 2001. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. Ann. Neurol. 49, 355–361.
Therriault, J., Benedet, A.L., Pascoal, T.A., Mathotaarachchi, S., Chamoun, M., Savard, M., Thomas, E., Kang, M.S., Lussier, F., Tissot, C., Parsons, M., Qureshi, M.N. I., Vitali, P., Massarweh, G., Soucy, J.P., Rej, S., Saha-Chaudhuri, P., Gauthier, S., Rosa-Neto, P., 2020. Association of apolipoprotein e ϵ4 with medial temporal tau independent of amyloid-β. JAMA Neurol. 77, 470–479.
Therriault, J., Benedet, A.L., Pascoal, T.A., Savard, M., Ashton, N.J., Chamoun, M., Tissot, C., Lussier, F., Kang, M.S., Bezgin, G., Wang, T., Fernandes-Arias, J., Massarweh, G., Vitali, P., Zetterberg, H., Blennow, K., Saha-Chaudhuri, P., Soucy, J. P., Gauthier, S., Rosa-Neto, P., 2021. Determining amyloid-B positivity using 18F-AZD4694 PET imaging. J. Nucl. Med. 62, 247–252.
Therriault, J., Pascoal, T.A., Lussier, F.Z., Tissot, C., Chamoun, M., Bezgin, G., Servaes, S., Benedet, A.L., Ashton, N.J., Karikari, T.K., Lantero-Rodriguez, J., Kunach, P., Wang, Y.T., Fernandez-Arias, J., Massarweh, G., Vitali, P., Soucy, J.P., Saha-Chaudhuri, P., Blennow, K., Zetterberg, H., Gauthier, S., Rosa-Neto, P., 2022. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. Nat. Aging 2, 526–535.
Tissot, C., Therriault, J., Pascoal, T.A., Chamoun, M., Lussier, F.Z., Savard, M., Mathotaarachchi, S.S., L Benedet, A., Thomas, E.M., Parsons, M., Nasreddine, Z., Rosa-Neto, P., Gauthier, S., 2021. Association between regional tau pathology and neuropsychiatric symptoms in aging and dementia due to Alzheimer's disease. Alzheimers Dement (N. Y) 7, e12154.
Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C. L., 2013. Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group. Amyloid-β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 12, 357–367.

Wiener, P.K., Kiosses, D.N., Klimstra, S., Murphy, C., Alexopoulos, G.S., 2001. A short-term inpatient program for agitated demented nursing home residents. Int. J. Geriatr. Psychiatry 16, 866–872.
Wu, L., Rowley, J., Mohades, S., Leuzy, A., Dauar, M.T., Shin, M., Fonov, V., Jia, J., Gauthier, S., Rosa-Neto, P., Alzheimer's Disease Neuroimaging Initiative, 2012. Dissociation between brain amyloid deposition and metabolism in early mild cognitive impairment. PLoS One 7 (10), e47905.
Yasuno, F., Minami, H., Hattori, H., 2021. Relationship between neuropsychiatric symptoms and Alzheimer's disease pathology: An in vivo positron emission tomography study. Int J. Geriatr. Psychiatry 36, 598–605.