

# Clinical Correlates of the PET-based Braak Staging Framework in Alzheimer's Disease

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## Abstract

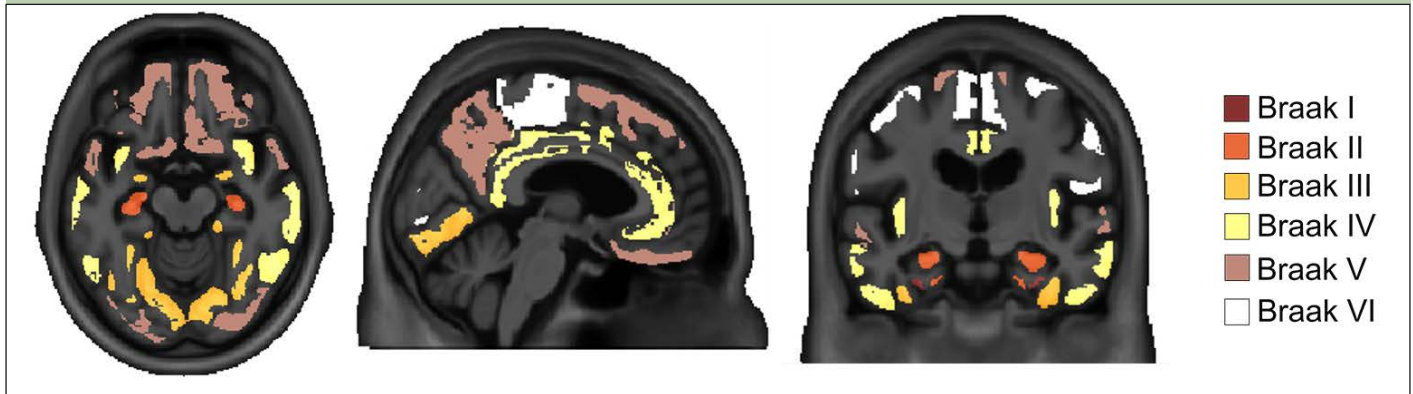
In vivo Alzheimer's disease diagnosis and staging is traditionally based on clinical features. However, the agreement between clinical and pathological Alzheimer's disease diagnosis, whose diagnosis assessment includes amyloid and Braak histopathological tau staging, is not completely convergent. The development of positron emission tomography (PET) tracers targeting neurofibrillary tangles offers prospects for advancing the staging of Alzheimer's disease from both biological and clinical perspectives. Recent advances in radiochemistry made it possible to apply the postmortem Braak staging framework to tau-PET images obtained in vivo. Here, our aim is to provide a narrative review of the current literature on the relationship between Alzheimer's disease clinical features and the PET-based Braak staging framework. Overall, the available studies support the stepwise increase in disease severity following the advance of PET-based Braak stages, with later stages being associated with worse cognitive and clinical symptoms. In line with this, there is a trend for unimpaired cognition, mild cognitive impairment, and Alzheimer's disease dementia to be compatible with early, intermediate, and late patterns of tau deposition based on PET-based Braak stages. Moreover, neuropsychiatric symptom severity seems to be linked to the extent of tau-PET signal across Braak areas. In sum, this framework seems to correspond well with the clinical progression of Alzheimer's disease, which is an indication of its potential utility in research and clinical practice, especially for detecting preclinical tau levels in individuals without symptoms. However, further research is needed to improve the generalizability of these findings and to better understand the applications of this staging framework.

*Key words: Alzheimer's disease, cognitive impairment, neurofibrillary tangles, Braak stages, positron emission tomography.*

## Introduction

In clinical practice, the diagnosis and staging of Alzheimer's disease (AD) dementia is traditionally based on clinical features. AD's first widely recognized and implemented diagnostic criteria, proposed in 1984, characterized it as an insidious-onset disease with progressive decline in memory and other cognitive domains with no considerable motor, sensory, or coordination deficits early in its course (1). Over the years, significant progress has been made in understanding the impact of AD pathophysiology in vivo using biomarkers. Researchers have developed several imaging and fluid biomarkers based on AD neuropathological hallmarks, including extracellular amyloid  $\beta$  (A $\beta$ ) plaques, neurofibrillary tangles (NFT), and neurodegeneration (2).

Following these advances, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed, in 2018, a research diagnostic framework integrating the results of biomarker assessment as part of AD diagnostic (3). This framework shifted the academic definition of AD in living individuals towards a biological conceptualization using the AT(N) system, which summarizes the status of individuals based on biomarker evidence of A $\beta$  (A), tau (T), and neurodegeneration (N) biomarkers (3). This AD reconceptualization became important considering those cases where there is a disagreement between the typical clinical presentation and the pathological definitions of AD: biological abnormalities appear in asymptomatic individuals and typical AD clinical features are manifested by patients without AD neuropathology (4, 5). Therefore, an in vivo biological staging system for AD would allow for a better selection of candidates for disease-modifying therapies and the possibility of tracking the progression of neuropathological changes.

**Figure 1.** Regions of interest used to apply Braak staging with tau-PET

The different colors represent the topographical definitions of different Braak stages employed in three studies using [<sup>18</sup>F]MK6240 tau-PET [16,20,23]. PET - positron emission tomography.

Even though AD staging systems were already well-established in postmortem neuropathology, efforts to translate these to *in vivo* studies were only recently undertaken due to advancements in the field (6, 7) (Figure 1). The development of positron emission tomography (PET) tracers targeting NFT allowed for the translation, in 2016 (8), of the Braak NFT histopathological staging system for its use *in vivo*. Proposed in 1991, this histopathological classification describes the hierarchical and cumulative tau deposition in the brain into six stages, with the following topographic hallmarks: transentorhinal cortex (Braak I); entorhinal cortex and hippocampus CA1 sector (Braak II); hippocampus (extension of damage), amygdala, and adjacent neocortical areas (Braak III); associative neocortex (initial involvement; Braak IV); associative neocortex (extension of damage), notably in temporal, parietal, and occipital areas (Braak V); primary motor and sensory fields (Braak VI) (6). The Braak neuropathological stages are now integrated into the AD neuropathological diagnostic criteria (9–11). These stages coincide well with clinical manifestations: stages I–II correspond to preclinical AD, III–IV to prodromal dementia, and V–VI to fully installed dementia (6, 7).

Since 2016, several research groups have attempted to establish the clinical correlates of the Braak NFT staging framework as assessed with tau-PET, here termed PET-based Braak staging. This allows for the understanding of possible diagnostic and prognostic values of this framework, as well as its applicability in the selection of participants for clinical trials. Thus, our aim with this study is to provide a narrative review of studies assessing the relationship between classical clinical features of AD and the PET-based Braak staging framework, a promising candidate for biological staging system for AD.

## Methods

In May 2022, we performed a literature search on PubMed and Scopus combining the terms “Alzheimer” AND “Braak” AND (“positron emission tomography” OR “PET”), without restrictions for language or publication

date. We screened the search results for studies assessing the clinical correlates of Braak staging assigned with tau PET. Additionally, relevant reports published after the database search date were identified by experts in a non-systematic fashion.

## In-vivo braak staging using tau-PET

PET imaging makes it possible to map tau load across the whole human brain. Meanwhile, the Braak neuropathological staging is based on predefined sections of specific brain areas, limiting the identification of alternative NFT accumulation patterns highlighted in more recent neuropathologic observations (9). Indeed, although several studies show a high topographical correspondence between the tau deposition observed in PET and the Braak histopathological descriptions, Braak non-conformant patterns of accumulation have also been noted (10).

Another advantage of tau-PET as compared to neuropathology is the possibility of tracking changes in tau deposition in a longitudinal fashion, allowing the investigation of the relationship between tau accumulation and clinical performance over time. Neuropathological assessments, in turn, only allow for the establishment of cross-sectional associations with antemortem clinical measures. Furthermore, the Braak histopathological staging employs staining techniques that detect only NFT, one of the neurofibrillary changes underlying AD (11–14). Even though autoradiographic reports show a high affinity of tau-PET tracers to tau aggregates characteristic of AD (i.e., mixed 3-repeat/4-repeat tau isoforms) (15–20), the magnitude of the contribution of the tau species identified by different neuropathologic protocols to the signal detected by tau-PET remains to be elucidated. This should be taken into account when studying the clinical correlates of Braak stages assigned with PET.

Additionally, PET imaging is less sensitive and has a lower resolution than neuropathology, making it difficult to assess small brain regions such as those composing early Braak stages. Off-target binding to the choroid

plexus may also compromise the assessment of medial temporal structures with first-generation tau-PET ligands ( $^{18}\text{F}$ -AV1451 and  $^{18}\text{F}$ -THK5351) (16). In part, these limitations have been overcome by second-generation tau-PET ligands ( $^{18}\text{F}$ -MK6240,  $^{18}\text{F}$ -PI2620, and  $^{18}\text{F}$ -RO948) with greater sensitivity and reduced off-target binding (21-25). Nonetheless, the impact of the properties of different ligands for Braak staging using tau-PET remains to be elucidated (10).

### Relationship with cognitive measures

Schöll et al. (2016) evaluated the relationship of [ $^{18}\text{F}$ ]AV1451 tau-PET uptake in Braak regions of interests (ROIs) with cross-sectional and retrospective longitudinal (mean [SD] of 4.1 [2.2] years) cognitive measures in 33 cognitively unimpaired (CU) older adults (16 A $\beta$ +, 17 A $\beta$ -), employing least squares regressions adjusted for age and sex (8). They reported a significant association between tau-PET standardized uptake value ratio (SUVR) in Braak I/II ROIs and cross-sectional ( $\beta = -3.12$ ,  $p = 0.007$ ), as well as longitudinal ( $\beta = -0.06$ ,  $p = 0.006$ ) episodic memory impairment (8). Additionally, longitudinal but not cross-sectional decline in a global cognitive measure (a composite of episodic memory, working memory, and processing speed scores) was related to higher ligand uptake in all Braak ROIs (I/II:  $\beta = -0.013$ ,  $p = 0.009$ ; III/IV:  $\beta = -0.015$ ,  $p < 0.001$ ; V/VI:  $\beta = -0.07$ ,  $p = 0.007$ ) (8). However, [ $^{18}\text{F}$ ]AV1451 uptake had no association with cross-sectional or longitudinal working memory and processing speed performance (8). Interestingly, the average [ $^{18}\text{F}$ ]AV1451 uptake in all Braak ROIs correlated solely with longitudinal global cognitive worsening but not cross-sectional global cognitive decline or episodic memory (8). This suggests a better performance in the Braak ROI than the global approach in predicting cognitive performance (8). Most of these associations remained significant following the addition of cortical A $\beta$ -PET distribution volume ratio (DVR) to the models, except for the relationship between Braak V/VI ROI and longitudinal global cognitive decline (8).

In 2016, Schwarz et al. assessed 187 participants (14 young CU, 42 A $\beta$ - older CU, 87 with mild cognitive impairment [MCI; 40 A $\beta$ -, 47 A $\beta$ +]) and 44 with AD dementia [16 A $\beta$ -, 28 16 A $\beta$ +]) with [ $^{18}\text{F}$ ]AV1451 tau-PET (26). Using ordinal logistic regression models adjusted for age, sex and amyloid status, they observed that the estimated Braak stages were significantly associated with cross-sectional global cognitive impairment as assessed by the Mini-Mental State Examination (MMSE) ( $R^2 = 0.21$ ,  $p = 0.0005$ ) and the Alzheimer's Disease Assessment Scale-cognitive component (ADAS-Cog) ( $R^2 = 0.22$ ,  $p = 0.0007$ ) (26). In another study that followed 107 participants (45 A $\beta$ - CU, 7 A $\beta$ + CU, 31 A $\beta$ + MCI, and 24 A $\beta$ + AD dementia) for approximately 2 years, linear regressions adjusted for age, sex, education, and ApoE  $\epsilon 4$  status demonstrated a relationship between the progression of cognitive decline and tau propagation to

higher Braak ROIs as indexed by [ $^{18}\text{F}$ ]AV1451 PET (27).

Another cross-sectional study, including A $\beta$ - and A $\beta$ + participants from two different cohorts, used the Spearman rank test with Bonferroni correction to investigate the correlation of cognition with Braak ROIs SUVR and with individually assigned Braak stage (28). In both samples, increasing SUVR in all Braak ROIs and increasing Braak stage correlated with poorer MMSE scores. Differences between the cohorts were observed regarding verbal recall performance. In sample 2, only Braak I/II SUVR correlated with worse verbal recall, while in sample 1, all Braak ROIs and Braak stages demonstrated significant associations (28). This could be an indication of an increased sensitivity of Braak I/II regions to early clinical manifestations of AD. However, clinical and demographic differences between the samples could also be contributing factors. For instance, sample 2 is smaller and most of its participants presented only amnesic mild cognitive deficits. In contrast, sample 1 included participants with different AD clinical variants, most of them having an early age of symptom onset.

Negative correlations (assessed with Bonferroni-corrected Pearson's test) between MMSE scores and [ $^{18}\text{F}$ ]THK5351 signal in Braak ROIs (I/II:  $r = -0.57$ ,  $p < 0.0001$ ; III/IV:  $r = -0.59$ ,  $p < 0.0001$ ; V/VI:  $r = -0.50$ ,  $p < 0.0001$ ) were also observed in another cross-sectional study with older A $\beta$ - CU participants and A $\beta$ + participants in the AD continuum (29). Similarly, tau signal in PET-based Braak stages I/II ( $r = 0.55$ ,  $p < 0.0001$ ), III/IV ( $r = 0.67$ ,  $p < 0.0001$ ), and V/VI ( $r = 0.60$ ,  $p < 0.0001$ ) was correlated with ADAS-Cog scores (15). Tau-PET SUVR also correlated negatively with episodic memory immediate recall in Braak I/II ( $r = -0.57$ ,  $p < 0.0001$ ), III/IV ( $r = -0.56$ ,  $p < 0.0001$ ), and V/VI ( $r = -0.56$ ,  $p < 0.0001$ ) ROIs as well as with delayed recall in Braak I/II ( $r = -0.58$ ,  $p < 0.0001$ ), III/IV ( $r = -0.51$ ,  $p < 0.0001$ ), and V/VI ( $r = -0.49$ ,  $p < 0.0001$ ) ROIs (29). However, the interpretation of these findings should take into account that [ $^{18}\text{F}$ ]THK5351 presents important off-target binding to monoamine oxidase B, a marker linked to neural degeneration and inflammation (30-32).

Using [ $^{18}\text{F}$ ]MK6240 tau-PET, Pascoal et al. (2020) assessed 30 A $\beta$ - young CU, 138 A $\beta$ - and A $\beta$ + older CU, 67 A $\beta$ - and A $\beta$ + MCI, and 54 A $\beta$ + typical and atypical AD dementia participants in a cross-sectional study (25). They applied ordinal logistic regression and observed that the six-stage PET-Braak model was significantly associated with poorer MMSE scores ( $R^2 = 0.51$ ,  $p < 0.0001$ ). Braak V-VI stages were invariably linked to cognitive impairment, even though the isolated increased tau-PET signal in Braak I ROIs was also associated with a higher prevalence of cognitive impairment ( $p < 0.0001$ ) (25). Of note, 2% of the participants of this study showed patterns of NFT deposition in tau-PET that differed from the stereotypical patterns described by Braak & Braak.

Another study reported that [ $^{18}\text{F}$ ]MK6240 uptake was cross-sectionally associated with poorer performance in

the MMSE in a sample of 101 participants (33). Across all participants, higher [ $^{18}\text{F}$ ]MK6240 uptake in all Braak ROIs was associated with lower MMSE scores, in linear regression models including age, sex, and education as covariates, even after false discovery rate (FDR) correction ( $r = -0.59$  to  $-0.47$ ,  $p < 0.0001$ ) (33). Among  $\text{A}\beta^+$  participants, higher uptake in all Braak ROIs was also associated to lower MMSE scores, surviving FDR correction ( $r = -0.63$  to  $-0.36$ ;  $p = 1\text{E-}6$  to  $0.007$ ) (33). In  $\text{A}\beta^-$  participants, the only associations surviving FDR correction were between poorer MMSE scores and Braak I, III and V SUVR (33).

A cross-sectional study published in 2021 investigated the association of MMSE scores with [ $^{18}\text{F}$ ]AV1451 PET SUVR in Braak ROIs with FDR-corrected Pearson correlation adjusted for age and gender (34). Among 32 MCI (13  $\text{A}\beta^+$ , 19  $\text{A}\beta^-$ ) participants, MMSE scores were significantly correlated with SUVR in areas corresponding to Braak stages I-IV, including the entorhinal cortex, the hippocampus, the amygdala, the parahippocampal gyri, and most of the temporal lobe (34). Interestingly, significant correlations between Braak ROIs SUVR and MMSE scores were not observed in the AD group, which included 20  $\text{A}\beta^+$  and 6  $\text{A}\beta^-$  participants (34). Nonetheless, these results should be interpreted carefully given the limited sample size and the fact that  $\text{A}\beta^-$  cognitively impaired participants were analyzed along with  $\text{A}\beta^+$  subjects.

Rullmann et al. (2022) employed Pearson's correlation to investigate the relationship between the DVR signal of [ $^{18}\text{F}$ ]PI2620 tau-PET and MMSE in a study including 26 CU ( $\text{A}\beta$  status not reported) and 38  $\text{A}\beta^+$  AD individuals (35). When correcting for age, a higher DVR signal was associated with worse MMSE scores in all PET-based Braak stages, except stage VI, a finding that was suggested by the authors to be related to floor effects of MMSE scores with the progression of AD (35). No association, however, was found between the assigned PET-based Braak stage and MMSE scores ( $r = 0.24$ ,  $p = 0.2$ ). Statistical power issues or the fact that only 13% of the studied sample was classified as PET-based Braak stage VI may partially account for these findings.

In turn, Therriault et al. (2022) assigned an individual PET-based Braak stage to 324  $\text{A}\beta^-$  and  $\text{A}\beta^+$  participants based on their [ $^{18}\text{F}$ ]MK6240 tau-PET SUVR (36). In this study, the progression of cognitive decline was cross-sectionally modeled by grouping participants according to their assigned Braak stage. Group comparisons were established with ANOVA adjusted for multiple comparisons with the Dunnett's T3 test (36). Participants were assessed in the following cognitive domains: global cognition, executive function, language, memory, and visuospatial abilities. A significant decline in global cognitive scales was seen in participants at PET-based Braak stages IV-VI when compared to controls at Braak 0 (36). Nearly no variation was observed in MMSE scores between participants classified as PET-based Braak stages 0 to III, with impairments starting at stage IV (36).

Memory dysfunction was observed starting at Braak stage II and worsening across groups with higher Braak stages (36). Executive function, language, or visuospatial domains were impaired solely at late PET-based Braak stages. Importantly, all participants at stages V or VI displayed some degree of cognitive impairment (36). It should be noted, however, that these analyses were not adjusted for potential confounders (e.g. age and sex).

Fernández-Arias et al. (2023) compared the verbal memory performance of  $\text{A}\beta^-$  and  $\text{A}\beta^+$  individuals in the aging and AD continuum grouped according to their individually assigned [ $^{18}\text{F}$ ]MK6240 PET-based Braak stage (37). Group comparisons were performed using the Kruskal-Wallis test and post hoc analyses using the Mann-Whitney U-tests with FDR correction (37). While delayed recall was significantly affected in participants classified as PET-Braak stage II and above, as compared to individuals at stage 0, recognition memory impairment started only at PET-Braak stage IV (37). No adjustments were done for possible confounders.

Overall, these findings support the stepwise decline in cognition following the advance of PET-based Braak stages, with later stages being compatible with worse cognitive performance. Several studies also observed an association between worse cognitive performance and higher tau accumulation in Braak regions. Furthermore, these results indicate that this framework is capable of modeling the sequential decline of different cognitive domains that is characteristic of AD dementia. Supplementary Table 1 depicts the features of these studies.

## Relationship with global disease severity measures

King-Robson et al. (2021) also investigated the association between Clinical Dementia Rating sum of boxes (CDR-SB; i.e. the raw sum of its domains' scores) performance and [ $^{18}\text{F}$ ]AV1451 tau-PET SUVR in Braak ROIs using Pearson's correlation controlling for age and gender with FDR correction (34). Worse CDR-SB scores correlated significantly with higher SUVR in Braak stages I-IV, in the MCI group (13  $\text{A}\beta^+$ , 19  $\text{A}\beta^-$ ), and in ROIs reflecting Braak stages III-VI, in the AD group (20  $\text{A}\beta^+$ , 6  $\text{A}\beta^-$ ) (34).

In Pascoal et al. (2020), ordinal logistic regressions accounting for age and gender showed that PET-based Braak stages were significantly associated with a poorer performance in the Clinical Dementia Rating (CDR; calculated through an algorithm using its domains' scores) ( $r = 0.73$ ,  $p < 0.0001$ ) (25). Similarly, in Therriault et al. (2022), stages 0-II were compatible with the absence of dementia (CDR=0), whereas most individuals at PET-based Braak stages III-IV had a CDR of 0.5, indicating either very mild dementia or MCI (36). All participants at Braak stages V or VI presented a CDR > 0, with the majority of participants at stage VI presenting with a CDR of 1 or 2 (36).

In sum, these findings are in line with the idea that higher Braak stages represent a more severe stage of AD. PET-based Braak staging seems to be able to model the increase in clinical severity across the aging and AD continuum. Supplementary Table 2 summarizes these studies' characteristics.

### Relationship with clinical diagnosis

In Schwarz et al. (2016), 92% of A $\beta$ - CU older participants were classified as being at PET-based Braak stage 0 assigned with [<sup>18</sup>F]AV1451 PET, with the remaining 8% classified as being at Braak stages I, V, and VI (26). Overall, A $\beta$ + MCI and A $\beta$ + AD participants had a significantly higher estimated Braak stage than A $\beta$ - MCI and A $\beta$ - AD participants, respectively (26). While 61% of A $\beta$ + MCI participants were classified at a higher PET-based Braak stage, 81% of A $\beta$ + AD participants were estimated to be at stages V or VI (26). Even when controlling for age and sex, ordinal logistic regressions showed a significant association between PET-based Braak staging and the diagnostic group ( $r = 0.22$ ,  $p = 0.0002$ ) (26).

In Maass et al. (2017), [<sup>18</sup>F]AV-1451 SUVR at Braak ROIs showed a stepwise increase across diagnostic groups in two different samples (28). They were higher among A $\beta$ + participants with AD dementia followed by A $\beta$ + MCI, A $\beta$ + CU, A $\beta$ - CU, and young CU individuals (28). Braak ROI SUVR showed adequate to excellent power to discriminate between A $\beta$ + MCI/AD and A $\beta$ - CU individuals (28). Depending on the sample and on whether partial volume correction was performed, the area under the curve (AUC) values ranged from 0.8-0.92 for Braak I/II, 0.78-0.97 III/IV, and 0.76-0.95 for V/VI (28).

In Pascoal et al. (2020), [<sup>18</sup>F]MK6240 tau-PET assigned Braak stages showed significant associations with clinical diagnosis (CU, MCI, AD) ( $r = 0.61$ ,  $p < 0.0001$ ) in ordinal logistic regressions adjusted for age and gender (25). Furthermore, the combination of PET-based Braak staging and [<sup>18</sup>F]AZD4694 A $\beta$ -PET neocortical SUVR demonstrated a high accuracy to distinguish A $\beta$ + AD from CU (AUC = 98%) and MCI (AUC = 86%). These tools also had adequate accuracy to distinguish MCI from CU (AUC = 78%) (25).

In a cross-sectional study published in 2020, Leuzy et al. assessed 257 CU (98 A $\beta$ +, 159 A $\beta$ -), 154 MCI (96 A $\beta$ +, 58 A $\beta$ -), 100 A $\beta$ + AD subjects, and 102 individuals with non-AD neurodegenerative disorders (42 A $\beta$ +, 60 A $\beta$ -) (38). They observed that [<sup>18</sup>F]RO948 tau-PET uptake in Braak ROIs could effectively distinguish participants with AD dementia from participants with no cognitive impairment or with non-AD disorders (38). Even though better AUC results were observed when employing Braak I-IV ROI to differentiate AD from CU (AUC = 0.98) and from non-AD (AUC = 0.97) individuals, SUVR in Braak I-II, III-IV and V-VI ROIs also showed high accuracy (38). Lower AUC values were observed when using Braak ROIs to distinguish between MCI and non-AD disorders,

but Braak I-IV ROIs still showed the most promising results (AUC = 0.73) (38).

Pascoal et al. (2021) followed 125 participants across the aging and AD continuum (17 A $\beta$ + AD, 21 A $\beta$ + MCI, 22 A $\beta$ + CU, and 65 A $\beta$ - CU) for a mean (SD) of 1.16 (0.33) years and assessed the increase of tau signal in Braak ROIs per diagnostic group (39). Interestingly, A $\beta$ - CU and A $\beta$ + CU groups demonstrated a trend of SUVR increase limited to ROIs corresponding to Braak I-II and I-III, respectively (39). On the other hand, A $\beta$ + MCI participants had increases in tau-PET signal particularly in Braak IV-V ROIs and A $\beta$ + AD participants in Braak V-VI ROIs (39). Another study with a 2-year follow-up found that [<sup>18</sup>F]AV1451 SUVR in A $\beta$ + participants with MCI or dementia increased mainly in ROIs corresponding to Braak I-IV, with the maximal increase in Braak I-II and III-IV regions belonging respectively to the MCI and the dementia groups (27). In A $\beta$ - and A $\beta$ + CU individuals, the maximal SUVR progression was observed in Braak I-II ROIs (27).

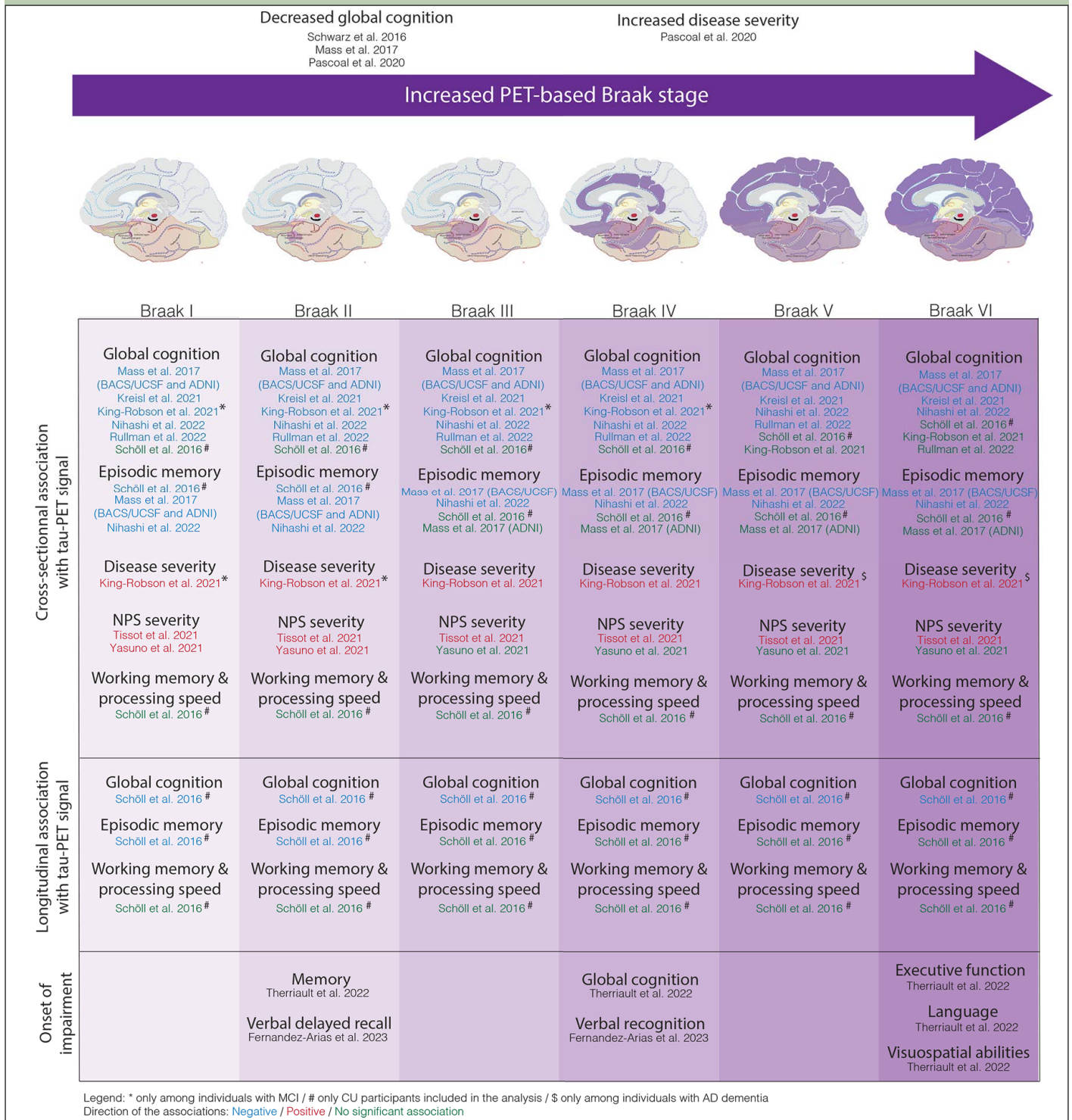
Across the literature and following what is observed in neuropathological studies, there is a trend for unimpaired cognition, MCI, and AD dementia to be compatible with lower, intermediate, and higher PET-based Braak stages, respectively. Supplementary Table 3 displays the characteristics of these studies.

### Relationship with neuropsychiatric symptoms (NPS)

In a cross-sectional study, Pichet-Binette et al. (2021) evaluated 115 CU participants (A $\beta$  status not reported) from the Pre-symptomatic Evaluation of Experimental or Novel Treatments for AD (PREVENT-AD) cohort, all of which had a high risk of sporadic AD (40). They investigated the univariate parametric correlations of [<sup>18</sup>F]AV1451 tau-PET SUVR in ROIs representing Braak stages I, III and IV with the following behavioral features: NPS (apathy, anxiety, depression, stress), cognitive lifestyle factors (lifetime cognitive activity, years of education), and personality traits (agreeableness, conscientiousness, extraversion, neuroticism, openness) (40). Braak I ROIs SUVR was significantly associated to apathy ( $r = 0.24$ ,  $p < 0.01$ ), depression ( $r = 0.23$ ,  $p < 0.05$ ), lifetime cognitive activity ( $r = -0.29$ ,  $p < 0.001$ ), as well as the conscientiousness ( $r = -0.21$ ,  $p < 0.05$ ), extraversion ( $r = -0.22$ ,  $p < 0.05$ ), neuroticism ( $r = 0.24$ ,  $p < 0.01$ ), and openness ( $r = -0.34$ ,  $p < 0.001$ ) personality traits. PET-based Braak stages III ( $r = -0.21$ ,  $p < 0.05$ ) and IV ( $r = -0.19$ ,  $p < 0.05$ ) were related only to lifetime cognitive activity, but the associations did not survive FDR correction (40). Since this study was conducted with highly educated individuals with a family history of AD, caution should be taken when generalizing these findings.

In 99 A $\beta$ + participants across the AD continuum, Yasuno et al. (2021) employed Spearman's correlation with Bonferroni correction to evaluate the association between [<sup>18</sup>F]AV1451 SUVR in Braak ROIs and

**Figure 2.** The relationship of different clinical markers of Alzheimer’s disease with PET-based Braak stages



The figure summarizes the findings presented in different studies assessing the clinical correlates of Braak staging assigned with tau positron emission tomography. AD - Alzheimer’s disease; CU - cognitively unimpaired; MCI - mild cognitive impairment; PET - positron emission tomography. Adapted with permission of Macedo et al., 2023 (10)

the presence of neuropsychiatric symptoms (NPS) (41). Briefly, NPS were assessed with the 12-item neuropsychiatric inventory (NPI) severity scale, whose domains were grouped into four composite domains based on a factor analysis conducted by Aalten et al. (42): a) hyperactivity (including agitation, euphoria, disinhibition, irritability, and aberrant motor behavior);

b) psychosis (including delusions, hallucinations, and night-time behavior); c) affective (including depression and anxiety); and d) apathy (including apathy and eating abnormalities). The SUVR in Braak I/II ROIs was significantly correlated with both the NPI total score ( $r = 0.43, p < 0.001$ ) and with the NPI affective score ( $r = 0.31, p = 0.002$ ) (41). No significant correlations were found

between Braak III-IV and V-VI ROIs SUVR and NPS (41). Of note, participants with affective symptoms presented a significantly higher tau signal in Braak I-II ROIs, which was indicated to have a potential role in discriminating the presence of affective symptoms consequent to AD pathology (41).

Another study by Tissot et al. (2021), evaluated A $\beta$ <sup>+</sup> and A $\beta$ <sup>-</sup> individuals in the aging and AD continuum with [<sup>18</sup>F]MK6240 and observed a significant correlation (as assessed by Spearman's correlation analysis) between the SUVR at PET-based Braak stages I-II ( $r = 0.27$ ,  $p < 0.001$ ), III-IV ( $r = 0.31$ ,  $p < 0.001$ ), and V-VI ( $r = 0.3$ ,  $p < 0.001$ ) and Neuropsychiatric Inventory Questionnaire (NPI-Q) global severity scores (43). The different results compared to Yasuno et al. (2021) may be explained by the higher sensitivity of [<sup>18</sup>F]MK6240 as compared to [<sup>18</sup>F]AV1451, a possible under- or overestimation of NPS severity by the NPI-Q in relation to the NPI, and by the fact that, in Tissot et al. (2021), A $\beta$ <sup>-</sup> individuals were also included.

Taking these results together, we have an indication of a relationship between PET-based Braak stages with neuropsychiatric symptoms. The results of these studies are summarized in Supplementary Table 4. We can speculate that the global neuropsychiatric severity is linked to tau-PET signal in Braak ROIs, but the correspondence with specific NPS remains to be elucidated, especially considering that their prevalence varies with the progression of AD (44, 45). Besides, the onset of NPS was suggested to precede tau accumulation and to be related to A $\beta$ -PET but not with tau-PET in A $\beta$ -CU older adults (46). Thus, even though NPS were shown to be associated with tau accumulation in the aging and AD continuum, the direction of this association remains to be fully elucidated (43).

The relationship of different clinical markers of AD with PET-based Braak stages is summarized in Figure 2.

## Limitations

Some limitations in the currently available literature on the issue should be considered. Firstly, most studies do not provide the clinical variants of participants with AD dementia, which is a crucial piece of information for their interpretation, since different AD clinical phenotypes present not only with distinct symptomatology but also with diverse tau propagation profiles (47). Moreover, there is a lack of studies conducted in low, lower-middle, or upper-middle-income countries, hampering the generalizability of the currently available findings. Most of the evidence also comes from studies using [<sup>18</sup>F]AV1451, a first-generation tau-PET ligand, with other ligands being underrepresented in the literature. For instance, the use of second-generation ligands showing greater sensitivity and less off-target binding is expected to provide more accurate information regarding tau accumulation in earlier Braak stages (25, 20-23). Additionally, since the majority of studies focus on global cognition, future studies should investigate further the

links with specific cognitive domains (e.g. language or executive function), subtypes of memory (e.g. semantic or spatial memory), neuropsychiatric symptoms (e.g. psychosis, agitation), and performance in activities of daily living. Longer times to follow-up are also needed to have a better picture of the temporal associations of PET-based Braak stages with clinical features of AD.

## Conclusions

The PET-based Braak staging framework, a promising biological staging system for AD, seems to correspond well with the clinical severity of the disease. Deterioration in different clinical markers (i.e. cognitive, disease severity, and neuropsychiatric, as well as diagnostic category) show associations with PET-based Braak staging. This is an indication that this framework may be useful in research (e.g. in the selection of participants in clinical trials) and in clinical practice (e.g. as a prognostic tool). However, further research is needed to improve the generalizability of the current findings and to better understand the applicability of this staging framework.

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