Cross-sectional associations of tau protein biomarkers with semantic and episodic memory in older adults without dementia: A systematic review and meta-analysis

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A B S T R A C T

Pathological tau is suggested to play a role in cognitive deterioration in the preclinical phase of Alzheimer’s disease. We investigated cross-sectional associations of tau burden with episodic and semantic memory performance in older adults without dementia. A systematic search in MEDLINE (via PubMed), PsychINFO, and Embase resulted in 24 eligible studies for meta-analysis. Tau burden was assessed using CSF, PET, or histopathological measures. All studies evaluated associations of tau with episodic memory: weighted effect sizes were -0.46 (95% CI [-0.73; -0.20], \( p < .001 \)) for episodic composite scores, -0.19 ([-0.36; -0.03], \( p = .024 \)) for delayed word list recall, and -0.05 ([-0.14; 0.04], \( p = .257 \)) for logical memory. Fourteen studies evaluated associations of tau with semantic memory; weighted effect sizes were -0.28 ([-0.52; -0.04], \( p = .023 \)) for semantic composite scores, -0.06 ([-0.16; 0.03], \( p = .194 \)) for semantic fluency, and 0.06 ([-0.06; 0.18], \( p = .319 \)) for picture naming. Our findings indicate that tau burden related to both episodic and semantic memory impairment in older individuals without a diagnosis of mild cognitive impairment or manifest dementia, with episodic composite scores showing the strongest association with tau burden. Future potential lies in developing more sensitive scores to detect this subtle cognitive impairment, which could contribute to early identification of individuals in the preclinical phase of Alzheimer’s disease, thereby improving early diagnosis and timely intervention.

1. Introduction

Alzheimer’s disease is the most common neurodegenerative disease worldwide (Ferri et al., 2005). Before the onset of clinical dementia and manifest cognitive impairment, Alzheimer’s disease involves a long preclinical stage with various pathological changes and biomarker abnormalities (Holtzman et al., 2011). Among these, neurofibrillary tangles containing tau and amyloid β (Aβ) plaques are considered the most pathological hallmarks of Alzheimer’s disease (Mandellkow and Mandellkow, 1998; Olsson et al., 2016). Pathogenic tau is suggested to be one of the earliest pathophysiological changes in preclinical Alzheimer’s disease (Jack et al., 2013), making it a key biomarker and possible clinical target for early intervention.

Tau is a microtubule-associated protein and has an important function in the assembly and stabilization of microtubules in the brain (Mandellkow and Mandellkow, 1998). When hyperphosphorylated, however, tau detaches from the microtubes, leading to misfolding and accumulation of tau as it aggregates into neurofibrillary tangles (Arriagada et al., 1992; Mandellkow and Mandellkow, 1998; Villemagne et al., 2015). The pathological process of tau deposition is detectable in a preclinical stage of Alzheimer’s disease, long before the first clinical symptoms appear (Schmand et al., 2010). Tau pathology can be visualized using a variety of measurements, such as by analyzing abnormal composition of cerebrospinal fluid (CSF) (Olsson et al., 2016) or...
visualizing the distribution of these pathologies using positron emission tomography (PET) imaging (Oosenkoppete et al., 2015; Villedemagne et al., 2015). Previous studies have revealed that in contrast to a diffuse accumulation of Aβ in preclinical Alzheimer’s disease (Gordon et al., 2016; Ingelsson et al., 2004; Nordberg, 2004), tau accumulation occurs more focally, often starting from brain regions in the medial temporal lobe, including the anterolateral entorhinal cortex and the hippocampus (Braak and Braak, 1997). Tau pathology in these brain areas have been associated with episodic memory dysfunction in both Alzheimer’s disease (Reijis et al., 2017) and normal aging (Crary et al., 2014).

Even in absence of cognitive deterioration, an accumulation of tau is repeatedly detected in cognitively unimpaired individuals (Nelson et al., 2012; Zionsz et al., 2019). As tau pathology in cognitively normal adults starts in the entorhinal cortex and hippocampus (Braak and Braak, 1997), it is hypothesized that early tau deposition evokes hippocampal dysfunction, leading to the memory impairment prevalent in aging (Marks et al., 2017). Levels of entorhinal tau increase with age (Braak et al., 2011) and are found in individuals without any Aβ pathology (Braak et al., 2011; Nelson et al., 2012). Additionally, tau aggravation in the entorhinal cortex is also associated with memory impairment in healthy participants, independently of Aβ accumulation (Lowe et al., 2019; Maass et al., 2018). This observation suggests that Aβ-independent tau pathology is associated with memory decline in normal aging and localized in the medial temporal lobe (Zionsz et al., 2019). However, studies have also shown that Aβ is a promoter of endogenous tau hyperphosphorylation (Zempel and Mandelkow, 2012) and facilitates the distribution of tau outside the entorhinal cortex to other limbic areas and association cortices (Pooler et al., 2015). It is suggested that tau deposition outside the entorhinal cortex initiates memory decline in relation to Alzheimer’s disease pathology (Chen et al., 2020).

Memory domains affected in Alzheimer’s disease include episodic memory (the conscious recollection of specific events), semantic memory (the conceptual knowledge of facts) and working memory (temporal storage and manipulation of stimuli) (Hodges, 2000; Verma and Howard, 2012). Memory assessment is a useful and reliable tool in the early detection and tracking of disease progression of Alzheimer’s disease (Drago et al., 2011; Reijis et al., 2017). Many studies have shown that individuals in the preclinical phase of Alzheimer’s disease exhibit a profound deficit in episodic memory (Gallagher and Koh, 2011; Greene et al., 1996; Zakzanis, 1998) and, although to a lesser extent, a decline in semantic memory (Tchakoute et al., 2017; Vonk et al., 2019b). Recently, there has been a shift of focus in research from a decline in episodic memory towards semantic memory as a more reliable early biomarker for Alzheimer’s disease (Venneri et al., 2018), as the presence of semantic impairment is more restricted to the preclinical phase of Alzheimer’s disease (Lovden et al., 2004; Papp et al., 2016; Vonk et al., 2020a), whereas episodic memory decline is present in normal aging as well (Hänninen et al., 1996). Aβ burden has been associated, although relatively weakly, with both semantic and episodic memory in healthy aging (Baker et al., 2017; Hedden et al., 2013; Vonk et al., 2020b). However, the association between tau burden and these memory domains remains unclear. Assessing this relationship may offer insights for cognitive impairment in the presence of biomarkers as an early diagnostic target for Alzheimer’s disease.

This systematic review and meta-analysis aimed to summarize, compare, and contrast the available studies on the cross-sectional association between tau burden with episodic and semantic memory performance in older adults without the diagnosis dementia. Neuropsychological assessment of cognition in individuals without dementia is possible using well-validated clinical tasks (Wilson et al., 2011), but the wide variability in tasks available could lead to discrepancy in results (Vonk et al., 2020b). Therefore, we investigated the relation between tau burden and various tasks of episodic memory (e.g., delayed recall and complex figure tasks) and semantic memory (e.g., category fluency and picture naming tasks), as well as composite scores of these domains. We hypothesized to find negative associations of tau burden with both episodic and semantic task performance in older adults without dementia. As episodic memory impairment may be more common than semantic memory impairment in normal aging, we expected larger effect estimates for episodic tasks in relation to tau burden across these samples of individuals without dementia.

2. Methods

This systematic review was conducted in accordance with the PRISMA guidelines for systematic reviews (Moher et al., 2009). We registered the protocol of this systematic review on PROSPERO under registration number CRD42021224113 (see Supplementary Materials).

2.1. Literature searches

Three electronic databases—PubMed, PsychINFO, and Embase—were subjected to systematic searches on December 3rd, 2020. Search strategies were developed by two authors (JV and TP) in consultation with a professional librarian (PW, acknowledgments). The search string was built for PubMed and subsequently translated for PsychINFO and Embase. The full electronic search strings are outlined in Supplementary Table S1. The search was performed without date or language restrictions. We included peer-reviewed articles, while unpublished materials, conference abstracts, and grey literature were excluded.

Duplicates were removed in EndNote reference manager, then transferred into Rayyan (Ouzzani et al., 2016), where a final duplicate removal was performed. Screening was carried out using Rayyan, in which screening decisions were recorded. Two reviewers (MB and TP) independently screened all titles and abstracts for eligibility while being blinded from each other’s decisions. Differences in study selection were resolved by discussion between the reviewers. The full texts of the selected articles were extracted and independently examined by the two reviewers to confirm eligibility. Snowballing and reverse snowballing was performed to identify additional articles. The reference lists of the selected articles were searched for secondary references that might be of interest (i.e., snowballing) and articles that have cited the selected articles were screened using Scopus (i.e., reverse snowballing).

2.2. Study selection

Articles were included for this systematic review if (1) a cross-sectional or longitudinal observational design was used, (2) associations between tau pathology and episodic and semantic memory were reported, (3) tau pathology and memory tasks were measured within one year from each another, (4) information was reported for older participants without dementia with an average age of >50 years, and (5) sufficient information was provided to compute effect sizes. We were interested in investigating the cross-sectional relationship between memory performance and tau in older adults (>65 years) as opposed to mid-life. Pathogenic tau is suggested to be one of the earliest pathophysiological changes in preclinical Alzheimer’s disease (Jack et al., 2013), starting to accumulate approximately 10–15 years before symptom onset (Bateman et al., 2012). As such, we chose to include studies in which individuals had an average age of >50 years.

Studies were excluded if the study population was limited to participants with a diagnosis of neurodegenerative disease or mild cognitive impairment (MCI), or all participants were classified with the same tau status (i.e., either all tau positive or negative). Studies were excluded if only non-domain specific composite scores were reported (e.g., a score for cognition or multi-domain memory), as we aimed to investigate the role of specific memory domains (episodic and semantic) in relation to tau. We excluded articles that did not report scores of memory or tau for a cognitively normal group but only for a disease group, and articles that were written in any other languages than Dutch, English, or German. In
the case of multiple studies reporting the same tasks from the same cohort study, only the study with the largest sample was included to represent the data of a specific semantic or episodic task in order to avoid overestimation of effects due to inclusion of duplicated data (following e.g., Hedden et al., 2013).

2.3. Determinant and outcome measures

Tau burden, the determinant of interest, was defined in one of two ways; either as continuous (i.e., on a scale from no or low tau protein levels to high tau protein levels) or categorical variables (i.e., as a presence or absence of tau protein based on an established cut-off value). Tau levels were measured through CSF or blood plasma (total-tau, phosphorylated-tau), PET ligands, or via histopathology.

The outcome of interest was performance on episodic and/or semantic cognition tasks, defined as continuous outcome scores. Studies that assessed the following episodic tasks were included: (1) delayed recall on word-list learning tasks, including Rey Auditory Verbal Learning test (RAVLT), California Verbal Learning Test (CVLT), Auditory Verbal Learning Test (AVLT) and other word-list learning tasks, (2) delayed recall on the Rey-Osterrieth Complex Figure (RCFT), Benton Complex Figure (BCF), Benton Visual Retention Test and other complex figure tests, and (3) delayed recall on the Logical Memory (LM) subtest of the Wechsler Memory Scale (WMS), Craft Story 21, and other story memory tests. The following semantic tasks were included: (1) Boston Naming Test, Action Naming Test, and other picture naming tasks or object naming tasks, (2) category fluency, also called semantic fluency or animal fluency, and (3) WAIS Vocabulary or other vocabulary tasks. Besides individual task performance, we also considered studies that assessed composite scores of episodic and/or semantic memory, combining multiple different tasks of that memory domain. Outcome scores of task performance in cross-sectional studies and at baseline in longitudinal studies were included; however, change from baseline to follow-up (i.e., memory rate, decline) was not considered in this review.

2.4. Data extraction

Two reviewers (MB and TP) independently extracted and recorded the data from the eligible studies in an Excel spreadsheet. We extracted (1) information about study design and methodology, (2) study sample characteristics, (3) tau detection methods (PET, CSF, blood plasma, or histopathology), (4) tau levels, (5) performance on individual or composite episodic and/or semantic tasks, and (6) associations between tau and cognition tasks. Disagreements in data extraction were resolved by discussion between the reviewers. If studies reported both values corrected for demographic covariates and unadjusted values, we included the adjusted values. If PET studies reported associations with multiple brain regions, we included effect sizes for one of the following reported regions: the medial temporal lobe, Braak III/IV, or hippocampus. If CSF studies reported associations with total-tau (t-tau) and phosphorylated-tau (p-tau) levels, p-tau associations were included as this is more specific for neurofibrillary tangles than t-tau and more clinically relevant for Alzheimer’s disease (Thijssen et al., 2020).

2.5. Bias and quality assessment

The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was modified (see Vonk et al., 2020b) and used to assess the risk of bias of the included studies (Wells et al., 2014). The first six studies were independently assessed by two reviewers (MB and TP). Results were compared and Cohen’s kappa (κ) was computed to detect the inter-rater reliability. As there was very high agreement (Cohen’s κ = 0.959), the remaining studies were divided among reviewers. If a specific task had a sufficient number of studies (>10), publication bias was assessed using funnel plots, and significance of asymmetry was tested using Egger’s test.

2.6. Data synthesis

To evaluate the effects of tau on our outcome of interest, we computed effect sizes using the statistics reported in the included studies (e.g., mean and standard deviation or standard error, or results from analyses including t-tests, analysis of variance, correlations, regressions, and linear mixed effects models). We transformed effect sizes into standardized mean differences (Cohen’s d), i.e., the mean difference/ pooled standard for dichotomous variables and standardized regression coefficients for continuous variables. Greater tau pathology associated with lower episodic or semantic cognitive performance was coded as a negative effect size. Studies that evaluated semantic or episodic cognition in individuals with high levels of tau protein (categorized as tau-positive) were contrasted to individuals with low levels of tau protein (categorized as tau-negative subjects). We computed pooled estimates using random-effects models with inverse variance weighting if a specific cognitive task was reported in 5 or more studies. If between 2 and 4 studies were identified for a task, we applied a fixed-effects model with inverse variance weighting, although we recognize the result may be too optimistic when using the fixed-effects model (Vonk et al., 2020b).

Heterogeneity of the results were examined using Cochran’s Q test, visual inspection of confidence intervals in the forest plots, and I-squared statistic. The models used a DerSimonian-Laird estimator for τ2, in order to detect between-study variance. Heterogeneity was investigated by performing subgroup analyses. These subgroup analyses were performed to detect effects of method of tau assessment (PET, CSF, plasma, or histopathology), mean sample age above or below 70 years, studies controlling for demographic data (e.g., age, sex/gender, or other covariates), studies using continuous or categorical scales of tau, and studies only including participants with subjective cognitive complaints (SC). To investigate whether there are differences in strength of associations across tasks, we included subgroup analyses comparing pairs of episodic and semantic tasks. We evaluated the difference in strength between all episodic and all semantic tasks, between episodic and semantic composites, and between word list learning and semantic fluency, as the number of studies of these tasks were sufficient.

P-values below .05 were considered as statistically significant. For subgroup analyses, p-value threshold of the Q-test was set at p = .10 (Pereira et al., 2010). All analyses and subsequent generation of figures were conducted in R Version 4.0.2 (Rstudio, 2020), using the meta, metafor and dplyr packages (Balduzzi et al., 2019; Viechtbauer, 2010; Wickham et al., 2021).

3. Results

3.1. Data collection process

The results of our literature search and screening process are depicted in the PRISMA flowchart in Fig. 1. We retrieved a total of 4271 titles from MEDLINE, PsychINFO, and Embase databases, followed by the removal of 1631 duplicates. During the first screening, 2425 articles were excluded based on title and abstract, leaving 215 articles for full-text evaluation. During full-text screening, studies were omitted for the following reasons: no semantic or episodic tasks, no association between tau and cognition reported, no tau or cognition metrics reported for cognitively healthy participants, period between tau and cognitive assessment >1 year, only longitudinal associations reported, part of a series of publications from the same cohort, mean sample age <50 years, or insufficient information reported for effect size computation. After excluding 192 studies during the full-text screening, 24 studies met the inclusion criteria for the meta-analysis.

3.2. Study characteristics

Study characteristics are presented in Table 1. Articles originated from publications between 2012 (Bennett et al., 2012) to 2021 (Radestig...
et al., 2021). Of these selected studies, the sample size ranged between 10 (Villemagne et al., 2014) and 579 individuals (Lowe et al., 2019), and the total number of included participants was 4,466. In 18 studies (75.0%), the sample size included 50 or more participants, which increased power to detect the presence of an association. Mean age ranged from 57.4 years (Li et al., 2014) to 85.0 years (Bennett et al., 2012), and the percentage female participants ranged from 46.0% (Lowe et al., 2019) to 73.9% (McSweeney et al., 2020). The association between tau and cognition was controlled for age, sex/gender, education, and/or other variables in 19 studies (79.2%). Tau was analyzed as a continuous determinant in 19 studies (79.2%). Thirteen studies (54.2%) used CSF measures to detect tau burden, ten studies (41.7%) used PET ligands, and one study via histopathology (4.2%; Bennett et al., 2012). None of the included studies measured tau levels in blood plasma. Almost all CSF studies evaluated levels of p-tau (n = 12/13, 92.3%), except one study that solely investigated levels of t-tau (n = 1/13, 7.7%). The study that measured tau burden using histopathology used antibodies for p-tau (Bennett et al., 2012). Eight of ten PET studies (80.0%) targeted tau using [18 F] AV-1451, one study (10.0%) used [18 F] THK53511, and one study (10.0%) [18 F] THK523 as PET ligands. Of these, two studies assessed tau retention in Braak stage III/IV (Maass et al., 2018; Snitz et al., 2020), three studies the medial temporal lobe (which corresponds to Braak III/IV; Groot et al., 2020; Kang et al., 2017; Weigand et al., 2020), one study limbic regions (Wolters et al., 2020), and one study the entorhinal region (Lowe et al., 2019).

Of 24 included studies, all incorporated episodic memory tasks and 14 studies (58.3%) additionally included tasks of semantic memory. All tasks are presented in Table 1. Most studies that evaluated episodic tasks involved, either individual or as part of domain scores, delayed recall on various word-lists tasks, generally the Rey Auditory Verbal Learning test (RAVLT; n = 6/24; 25.0%), or the California Verbal Learning Test (CVLT; n = 6/24; 25.0%). Story memory tests used the Logical Memory subtest of the Wechsler Memory Scale (WMS; n = 13/24; 54.2%). One study assessed individual scores of the Rey Complex Figure Task (Kang et al., 2017). The most evaluated semantic tasks were semantic fluency (predominantly Animal Fluency, n = 13/14; 92.9%) and naming tasks (Boston Naming Test; n = 8/14; 57.2%). Twelve studies computed episodic composite scores (n = 12/24, 50.0%) and seven computed semantic composite scores (n = 7/14, 50.0%). Tasks incorporated in domain scores varied between studies. Higher scores reflected better cognitive function for all tasks.

3.3. Publication bias

Using an adjusted version of the Newcastle-Ottawa Quality Assessment Scale, quality assessment for risk of bias for included studies was performed (Table 2). Twelve studies (48%) lost stars on account of using a non-representative sample, as they only included volunteers or individuals with subjective cognitive complaints. Only a few studies (n = 5; 20%) lost stars as a result of not controlling for age, sex/gender, education and/or other covariates in their analyses. Three studies lost stars because they categorized tau on non-established cut-offs. Every study received the maximum number of stars on the assessment of outcome, as we only included studies that assessed cognition using independent neuropsychological tasks.

As the number of studies was too small to compute the Egger’s test for asymmetry for each individual task, all tasks were pooled for each cognitive domain. Funnel plots for both episodic tasks and semantic tasks indicated asymmetry (Fig. 2A-B). The Egger’s t statistic confirmed this asymmetry for episodic tasks (b for bias = -1.801, SE = 0.806; t(22)
### Table 1

Study characteristics of included studies. Population characteristics (cognitive distribution, sample size, cohort); sex/gender; age; education; tau measures (method, definition of tau burden); neuropsychological assessments (domain, tasks).

| Study                             | Population | Sex/gender | Age | Education | Tau | Cognition |
|-----------------------------------|------------|------------|-----|-----------|-----|-----------|
|                                   | N or SCD   | % female   | Mean±SD | Mean±SD   | Method | Domain | Tasks |
|-----------------------------------|------------|------------|--------|-----------|-------|---------|
| Alam et al. (2020)                | NC 109     | 60.6%      | 69.2 ±6.8 | 17.5 ±1.2 | CSF   | t-tau   | Episodic |
| Healthy Aging and Senile Dementia (HADL) study and Adult Children Study (ACS) | NC 255     | 62.0%      | 66.2 ±5.5 | 16.1 ±1.5 | CSF   | p-tau   | Episodic |
| Bennett et al. (2012)             | NC 296     | 62.2%      | 85.0 ±6.6 | 16.5 ±1.3 | histopathology | p-tau_f | Episodic & Semantic |
| Bruno et al. (2019)               | NC 110     | 72.0%      | 62.5 ±8.9 | 16.1 ±1.5 | CSF   | p-tau   | Episodic |
| Casaletto et al. (2017)           | NC 132     | 65.2%      | 64.5 ±7.4 | 16.0 (14–18) | CSF   | p-tau   | Episodic |
| Groot et al. (2020)               | NC 47      | 53.2%      | 73.3 ±5.5 | 13.0 ±1.5 | PET   | [18 F] AV-1451 | Episodic |
| Ho and Nation (2018)              | NC 518     | 51.2%      | 71.3 ±6.9 | 16.3 ±1.5 | CSF   | p-tau   | Episodic & Semantic |
| Ifara et al. (2018)               | NC 12      | 48.9%      | 67.81 ±13.4 | 13.4 ±1.5 | CSF   | p-tau   | Episodic |
| Insel et al. (2015)               | NC 220     | 47.7%      | 75.2 ±5.5 | 16.1 ±1.5 | CSF   | p-tau   | Delayed recall on LM |
| Kang et al. (2017)                | NC 43      | 68.6%      | 66.4 ±7.9 | 11.1 ±1.5 | PET   | [18 F] THK5351 | Episodic & Semantic |
| Li et al. (2014)                  | NC 315     | 54.0%      | 57.4 ±18.1 | 16.1 ±1.5 | CSF   | p-tau   | Delayed recall on LM; CAT-A |
| Lowe et al. (2019)                | NC 579     | 46.0%      | 70± (63, 79) | 16± (13, 16) | PET   | [18 F] AV-1451 | Episodic & Semantic |
| Maas et al. (2018)                | NC 83      | 58.0%      | 77 ±6 | 17 ±2.0 | PET   | [18 F] AV-1451 | Episodic & Semantic |
| Matura et al. (2019)              | NC 30      | 63.0%      | 66.4 ±4.1 | 15.2 ±1.5 | CSF   | p-tau   | Episodic |
| McSweeney et al. (2020)           | NC 119     | 73.9%      | 67.5 ±4.8 | 15.1 ±1.2 | PET   | [18 F] AV-1451 | Episodic & Semantic |

(continued on next page)
### Table 1 (continued)

| Study                  | Population   | Cohort/Sample origin | Sex/ age | Age | Education | Tau | Cognition | Domain | Tasks                              |
|------------------------|--------------|-----------------------|----------|-----|-----------|-----|-----------|--------|-----------------------------------|
| Radestig et al. (2021) | NC 259       | Gothenburg H70 Birth Cohort Studies | 49.8 %   | 70.6 | 13.1      | CSF | p-tau     | Episodic & Semantic               |
| Schindler et al. (2017) | NC 233       | Adult Children Study (ACS) | 64.0 %   | 60.7 | 16.1      | CSF | p-tau     | Delayed recall on LM; CAT-A       |
| Snitz et al. (2020)   | NC 118       | Monongahela-Youighiobgeny Healthy Aging Team Neuroimaging (MYHAT-NI) and Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) parent study | 57.6 %   | 76.3 | t         | PET | [18 F] AV-1451 | Delayed recall on LM; CAT-A       |
| Verberk et al. (2020)  | SCD 241      | SCIENCE project and Amsterdam Dementia Cohort Australia community | 40.0 %   | 61.0 | 5.0       | CSF | p-tau     | Delayed recall on RAVLT; BNT; CAT-A |
| Villemagne et al. (2014) | NC 10        | 70.0 %   | 77.4 | ±10.0 | 14.7     | PET | [18 F] THK523 | Delayed recall on CVLT, RCFT, and LM |
| Weigand et al. (2020)  | NC 209       | Alzheimer’s Disease Neuroimaging Initiative (ADNI) Cohort | 51.4 %   | 75.1 | ±0.5      | PET | [18 F] AV-1451 | Delayed recall on LM; SC = BNT and CAT-A |
| Wolfgruber et al. (2020) | SCD 449     | German Center for Neurodegenerative Diseases (DZNE) and Longitudinal Cognitive Impairment and Dementia Study (DELCODE) | 53.7 %   | 70.0 | ±5.6      | CSF | p-tau     | Episodic & Semantic               |
| Wolters et al. (2020)  | SCD 25       | Amsterdam Dementia Cohort | 60.0 %   | 65.0 | ±6.0      | PET | [18 F] AV-1451 | Episodic & Semantic               |
| Zionist et al. (2019)  | NC 54        | Baltimore Longitudinal Study of Aging (BLSA) | 55.5 %   | 77.4 | ±8.9      | PET | [18 F] AV-1451 | Episodic & Semantic               |

Note. a = range; b = not specified; c = not specified for p-tau group, as all p-tau participants (n = 12) were amyloid \( \beta \) positive, we used the mean for amyloid \( \beta \) group; \( \gamma \) = education was specified as high school or less (25.6%), some college (24.8%), 4-year college (18.8%), greater than college (30.8%); f = study used antibodies for phosphorylated tau.

**Abbreviations:** NC = normal cognition; SCD = subjective cognitive decline; SD = standard deviation; PET = positron emission tomography; CSF = cerebrospinal fluid; t-tau = total tau; p-tau = phosphorylated tau; EC = episodic composite score; SC = semantic composite score; BNT = Boston Naming Test; CAT = Category Fluency; CAT-A = Category Fluency Animals; CAT-G = Category Fluency Groceries; CVLT = California Verbal Learning Test; RCFT = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; LM = Wechsler Logical Memory; VR = Virtual Reality; SVLT = Seoul verbal learning test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WMS-R = Wechsler Memory Scale-Revised; FCSRT = free and cued selective reminding test; FNART = Face Name Associative Recognition Test; SDMT = Symbol Digits Modality Test; VAT-A = Visual Association Test version A.

### 3.4. Meta-analysis of association tau and cognition

Analysis of the pooled cognitive tasks of episodic and semantic cognitive domain revealed that an increased tau burden is associated with lower performance on both episodic tasks (overall effect size = -0.27, 95% CI [-0.41, -0.13], \( p < .001 \)) and semantic tasks (overall...
The effect sizes for semantic tasks were -0.28 (95% CI [-0.52; -0.04], learning and -0.05 (95% CI [-0.14; 0.04], semantic fluency) and composite scores of the episodic and semantic domain were 0.319 for picture naming. These effect sizes are considered to be between small and medium, as effect sizes of d = 0.194) for semantic fluency, and 0.06 (95% CI [-0.06; 0.18], for logical memory) and composite scores of the episodic and semantic domain compared to all tasks of the semantic domain (Q = 11.18, df = 1, p = .001), had a mean sample age above 70 years (14 vs. 10 studies; Q = 3.05, df = 1, p = .083) and studies using PET tracers to detect tau burden (13 vs. 10 vs. 1 studies; Q = 9.43, df = 2, p = .009). The association was similarly moderated by method of tau burden for semantic tasks, as the association was greater when PET was used (8 vs. 8 vs. 1 studies; Q = 5.94, df = 2, p = .051).

For episodic composite scores, the association between tau and cognition was stronger in studies using categorical tau measures (1 vs. 11 studies; Q = 145.93, df = 1, p < .001) and studies using PET, as opposed to CSF or histopathology, as tau method (3 vs. 8 vs. 1 studies; Q = 6.09, df = 2, p = .048). The association between tau and delayed recall on word lists was stronger when studies used categorical measures of tau (2 vs. 5 studies; Q = 5.76, df = 1, p = .016), had a mean sample age above 70 years (14 vs. 2 vs. 1 studies; Q = 5.76, df = 1, p = .016), and in study samples who were not selected on subjective cognitive complaints (6 vs. 6 vs. 1 studies; Q = 12.37, df = 1, p < .001). For semantic cognition, we found that the association between tau and semantic composite scores was greater in studies using categorical tau (1 vs. 6; Q = 18.19, df = 1, p < .0001) and in studies using PET as tau measurement (1 vs. 5 vs. 1 studies; Q = 12.47, df = 2, p < .001). The association between tau and semantic fluency was stronger in study samples who were not selected on subjective cognitive complaints (5 vs. 1 studies; Q = 10.84, df = 1, p = .001). Subgroup results are depicted in forest plots in Supplementary Figures. However, these results should be interpreted with caution due to sample size as subgroup analyses were performed among a

3.5. Subgroup analyses

To address the heterogeneity within our results, we included subgroup analyses investigating the role of age, method of tau assessment, controlling for demographics, using either continuous or categorical tau scales, and studies including only participants with subjective cognitive complaints (Table 4). The number of studies for picture naming (n = 3) and logical memory (n = 5) was too low to allow for a stratified analysis.

When combining all tasks for each domain, we found an effect of tau method for both episodic and semantic tasks, as well as an effect of age for episodic tasks. The association between tau and episodic tasks was greater when studies had a mean sample age above 70 years (14 vs. 10 studies; Q = 12.47, df = 1, p = .005) and studies using categorical tau scales, and studies including only participants with subjective cognitive complaints (Table 4). The number of studies for picture naming (n = 3) and logical memory (n = 5) was too low to allow for a stratified analysis.
additionally examined its relation to semantic tasks. We found that
and semantic fluency. Large heterogeneity was found within the results,
on word-list delayed recall, but not on logical memory, picture naming,
depiction of the largest effect sizes in the association with tau burden.
subjective cognitive impairment. Our findings indicate that tau-associated memory impairment is already present and detectable in
increased tau levels were associated with lower performance on episodic tasks. These findings resonate with longitudinal studies reporting associations between an increase of tau levels and decline in episodic performance over time (Aschenbrenner et al., 2018; Mitchell et al., 2002; Ziontz et al., 2019). Episodic composite scores had a medium-sized effect estimate, whereas smaller effect sizes were found for individual episodic tasks, like delayed recall on word lists and logical memory. While the effect was present for episodic domain scores and delayed recall on word lists, no effect was found for logical memory. This finding could be attributed to the low number of studies evaluating logical memory tasks (n = 5). Although most studies (n = 19) reported negative effect estimates, the vast majority of these (n = 14) were not significant. This discrepancy between the pooled overall effect sizes and effect sizes reported by individual studies might result from high variance between-studies and poor statistical power within individual studies. When pooling effect sizes, the high variance between studies is reduced, thus generating more statistical power to detect smaller effect estimates, as shown in the meta-analysis. The lack of study results could also be attributed to low sample sizes in some of the studies. Another explanation may be possible ceiling effects, due to a generally high cognitive performance in a cognitively normal population.
We also observed a cross-sectional association between tau and semantic memory, as higher levels of tau were associated with lower performance on semantic memory tasks. In line with our hypothesis, we found a smaller effect between tau and semantic cognition compared to episodic cognition, and the effect was only observed for semantic domain scores but not for individual tasks of semantic fluency and picture naming. These findings suggest that these individual tasks may not be sensitive enough to detect the subtle semantic impairment that is expected in a cognitively healthy older population, indicating that the traditional metrics of semantic tasks are too coarse to measure subtle semantic impairment cross-sectionally (Vonk et al., 2020b). As relatively few studies have evaluated tau burden in relation to semantic composite scores (n = 7), semantic fluency (n = 6), and picture naming (n = 3), more studies are needed to qualify these observations. Our results indicate that semantic cognition is associated with increased tau accumulation in healthy aging and emphasizes the need for more sensitive neuropsychological tasks to detect these subtle cognitive effects.
For both episodic and semantic memory, domain composite scores depicted the largest effect sizes in the association with tau burden. Composite scores are suggested to be useful as cognitive measures, assuming that the individual tasks of a certain cognitive domain measure similar aspects of that specific domain (Hedden et al., 2013). However, this premise is difficult to uphold as the neuropsychological tasks that are used to compute composite scores for each cognitive domain vary between studies, and not all tasks may be equally related to a specified cognitive domain (Vonk et al., 2020b). Additionally, composite scores may include tests that do not measure that specific cognitive domain; for example, one study included measures of working memory (i.e., digit-span task) as part of their semantic composite score (Ketten et al., 2012). Nonetheless, we found the domain scores of episodic and semantic memory were able to detect an effect between tau burden and memory performance, in contrast to individual tasks that had lower effect sizes (e.g., word-list delayed recall) or non-significant effect sizes (e.g., logical memory, semantic fluency and picture naming). The diversity in tasks that are included in composite scores makes it difficult to pinpoint which types of tasks may be more sensitive than others to capture early cognitive impairment that tracks with biomarkers of Alzheimer’s disease. For this reason, we investigated both
depicted the largest effect sizes in the association with tau burden.
impact that is expected in a cognitively healthy older population, indicating that the traditional metrics of semantic tasks are too coarse to measure subtle semantic impairment cross-sectionally (Vonk et al., 2020b). As relatively few studies have evaluated tau burden in relation to semantic composite scores (n = 7), semantic fluency (n = 6), and picture naming (n = 3), more studies are needed to qualify these observations. Our results indicate that semantic cognition is associated with increased tau accumulation in healthy aging and emphasizes the need for more sensitive neuropsychological tasks to detect these subtle cognitive effects.
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domain composite scores as well as separate tasks. Based on our results, we did not find a semantic memory measure that seems particularly sensitive, but among the episodic memory measures the word list learning tasks seems to be more strongly associated with tau than the logical memory tasks. It is important to note that the number of studies evaluating these individual tasks were also lower than studies investigating domain scores, thus possessing less power to detect an effect. Our findings indicate that the literature on preclinical Alzheimer’s disease biomarkers and cognition is posed to publication bias, suggesting that non-significant findings are less likely to be published in this field. Publication bias poses a threat to the validity of meta-analyses, as it potentially leads to overestimation of effect sizes (Van Aert et al., 2019). In order to diminish this overestimation, we contacted authors of studies that did not report the statistical data of non-significant associations. Although we were able to include two additional studies in this manner, the risk of bias is still present and should be taken into account when evaluating our findings.

The meta-analysis indicated substantial heterogeneity across tasks between studies investigating the relationship between tau burden and cognition. Subgroup analyses identified various moderators that influenced the meta-analytic results. A mean sample age of >70 years seemed to influence the results of delayed recall on word lists, suggesting that the effect of tau-associated cognitive impairment is stronger in older populations. We did not find this effect for the other cognitive tasks, and as a large proportion of studies corrected for age in their analysis, this effect may be diminished. For word-list learning and semantic fluency, the inclusion of individuals with subjective cognitive complaints moderated the meta-analytic results. A smaller effect size was found.

**Fig. 3.** Forest plots of association between tau burden and pooled tasks of the (A.) episodic domain and (B.) semantic domain. Greater tau burden associated with lower task performance is represented by negative effect sizes. Study weight is represented by size of the squares.
### Table 3
Study analytic specifications (effect sizes with standard error).

| Author                          | N   | Tau metric | Tau method | SCD only | Covariates | Semantic composite | Semantic fluency | Picture naming task | Episodic composite | Delayed recall word list | Delayed recall complex figure task | Logical memory |
|---------------------------------|-----|------------|------------|----------|------------|-------------------|-----------------|--------------------|--------------------|-----------------------|-------------------------------|-----------------|
| Alm et al. (2020)               | 109 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Aschenbrenner et al. (2020)     | 255 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Bennett et al. (2012)           | 296 | con        | histo      | no       | yes        | 0.001 (0.011)     | –               | –                  | –                  | –                     | –                            | –               |
| Bruno et al. (2019)             | 110 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Canaleto et al. (2017)          | 132 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Groot et al. (2020)             | 47  | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Ho and Nation (2018)            | 518 | cat        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Ihara et al. (2018)             | 12  | cat        | CSF        | no       | no         | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Intel et al. (2015)             | 220 | cat        | CSF        | no       | no         | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Kang et al. (2017)              | 43  | con        | PET        | no       | no         | 0.215 (0.306)     | –               | –                  | –                  | –                     | –                            | –               |
| Li et al. (2014)                | 315 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Lowe et al. (2019)              | 579 | cat        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Maas et al. (2018)              | 83  | con        | PET        | no       | no         | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Matura et al. (2019)            | 30  | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| McSweeney et al. (2020)         | 119 | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Radvog et al. (2021)            | 259 | cat        | CSF        | no       | no         | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Schindler et al. (2017)         | 233 | con        | CSF        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Snitz et al. (2020)             | 118 | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Verberk et al. (2020)           | 241 | con        | CSF        | yes      | yes        | 0.020 (0.08)      | 0.120 (0.060)   | –                  | –                  | –                     | –                            | –               |
| Villemagne et al. (2014)        | 10  | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Weigand et al. (2020)           | 209 | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Wolfragrau et al. (2020)        | 449 | con        | CSF        | yes      | no         | –                 | –               | –                  | –                  | –                     | –                            | –               |
| Wolters et al. (2020)           | 25  | con        | PET        | yes      | yes        | 0.110 (0.232)     | –               | –                  | –                  | –                     | –                            | –               |
| Ziontz et al. (2019)            | 54  | con        | PET        | no       | yes        | –                 | –               | –                  | –                  | –                     | –                            | –               |

Note. Cohen’s D (Standard Error).
Abbreviations: con = continuous; cat = categorical.
when solely individuals with subjective cognitive complaints were included. When all participants have subjective cognitive complaints, instead of only part of the study sample, it is more difficult to detect a cross-sectional association because the distribution of the subject population is less variable which may explain these findings. However, as only one study evaluated individuals with subjective complaints for semantic fluency and delayed recall on word lists (Verberk et al., 2020), more studies are needed to substantiate this finding. Another factor that moderated the results was using categorical versus continuous metrics for tau burden, as the effect was stronger when categorical metrics were used for episodic domain scores, word-list learning and semantic domain scores. When using continuous metrics, a linear relationship with cognitive impairment is expected, which might suggest that the relationship between tau accumulation and cognitive deterioration is non-linear. The results of the subgroup analyses should be interpreted with caution, as smaller subsets of studies were compared.

The method of tau assessment influenced the meta-analytic results, as PET studies reported greater effect estimates compared to CSF or histopathology. Tau accumulates locally, starting in the mesial temporal lobe, including the anterolateral entorhinal cortex and then spreading to other regions, such as the hippocampus (Braak and Braak, 1997). In contrast to CSF studies, PET studies have the capacity to assess focal tau concentrations, as the retention of tau ligands are measured in specific, pre-determined brain areas (Ossenkoppele et al., 2015; Villemagne et al., 2015). Our findings resonate with previous findings of an aggravation of tau in these specific areas that is associated with memory dysfunction in individuals without dementia (Crary et al., 2014), and also individuals with Alzheimer’s disease (Reijs et al., 2017). As CSF methods are limited to measuring only global levels of tau, the assessment of tau through CSF may not be sensitive enough to detect the more localized elevations of tau, and thus unable to examine its relation with cognition. Future studies should measure tau burden using tau PET tracers when assessing its relation to cognition, as this is more sensitive to the focal characteristic of tau accumulation. This regional accumulation may be more sensitive to some cognitive domains than others, depending on the localization. For example, our focus on medial temporal and limbic regions in the current analysis may be more sensitive to episodic memory than semantic memory, as semantic memory has been linked more strongly to temporal-parietal regions and the anterior temporal lobe (Binder et al., 2009; Vonk et al., 2019a). As such, future work should investigate if the differential strength of associations of tau with episodic versus semantic memory changes depending on the progression of tau accumulation towards temporal-parietal regions in individuals without dementia.

Strengths of this study include identification of risk of bias using a validated quality assessment tool, consideration of publication bias, investigation of individual task effects, and exploration of potential moderator factors. We also acknowledge several limitations of this systematic review and meta-analysis. We limited our inclusion criteria to cross-sectional associations; as exposure and outcome are
Fig. 5. Forest plots of association between tau burden and episodic memory tasks, (A.) episodic composite scores, (B.) delayed recall on word lists, and (C.) delayed recall on Logical Memory tasks. Greater tau burden associated with lower task performance is represented by negative effect sizes. Study weight is represented by size of the squares.

Table 4

Subgroup analyses.

| Moderators                  | Mean sample age <70 vs. >70 years | CSF vs. PET vs. histopathology | Q, df, P value |
|-----------------------------|-----------------------------------|-------------------------------|----------------|
| All episodic tasks, n       | 14 vs. 10                         | 13 vs. 10 vs. 1               | 5 vs. 19       |
| Episodic composite, n       | 6 vs. 6                           | 3 vs. 8 vs. 1                 | 5 vs. 19       |
| Word-list learning, n       | 1.59, 1, 0.2079                   | 6.09, 2, 0.0477               | 154.93, 1, <0.0001 |
| All semantic tasks, n       | 0.41, 1, 0.5207                   | 5.94, 2, 0.0512               | 1.89, 1, 0.1885 |
| Semantic composite, n       | 3 vs. 4                           | 1 vs. 5 vs. 1                 | 0.79, 1, 0.3738 |
| Semantic fluency, n         | 0.06, 1, 0.8078                   | 12.47, 2, 0.0020              | 18.19, 1, 0.0001 |
| All episodic tasks, n       | 1.20, 1, 0.2736                   | 0.02, 1, 0.8936               | 0.89, 1, 0.3446 |

Note. Bold indicates statistically significant findings (p < 0.10).
simultaneously assessed, it is challenging to determine their temporal relationship. Longitudinal studies could offer more insight into cognitive deterioration over time and may elaborate on disease outcome. The low number of studies that evaluated individual tasks in the association between tau and episodic (logical memory, n = 5) and semantic cognition (semantic composite scores, n = 7; semantic fluency, n = 6; and picture naming, n = 3) limited our ability to assess the sensitivity of these tasks with more conclusive observations. A third limitation arose from excluding 24 studies that did not provide sufficient information to compute effect sizes, leading to poorer statistical power and possible overestimation of the results. Lastly, we found that the risk of bias within studies mostly stemmed from non-representative samples used in cohort studies, as they were often not truly representative of the average older adult in the community, but a selected group of individuals (often volunteers). Additionally, study samples may not be racially and ethnically diverse, as the majority of participants are often well-educated white individuals.

Various directions for future research can be identified. When measuring subtle cognitive impairment, the focal aspect of tau accumulation should be taken into account by measuring tau burden through the retention of tau tracers using PET. Future work should also investigate the role of race/ethnicity in the association between tau and cognition, as Black individuals depict lower levels of CSF-tau but higher levels of postmortem neurofilibrillary tangles (Zintz et al., 2019). The role of Aβ on the mechanism through which tau mediates its effects on cognition should be further investigated (Weigand et al., 2020), by assessing the association of tau and cognition in Aβ-positive and Aβ-negative cognitively unimpaired individuals. We found no eligible studies that investigated tau burden using blood plasma, probably due to the relative novelty of assays that are sensitive enough for plasma tau detection (Ding et al., 2021). To address this gap in literature, future research should investigate the association of plasma tau to episodic and semantic memory performance. Plasma tau combined with other biomarkers has shown to accurately predict the conversion to Alzheimer’s disease and the use of plasma tau also offers a less invasive alternative to detect tau burden (Palmqvist et al., 2021). Finally, future research should investigate and increase sensitivity of existing and new neuro-psychological tasks to detect subtle cognitive effects in older populations without dementia.

Our findings demonstrated that tau burden relates to both episodic and semantic memory impairment in older individuals without a diagnosis of MCI or manifest dementia. Sensitive metrics of neuropsychological tasks are needed to better detect these subtle cognitive effects to investigate episodic and semantic memory as cognitive markers in the preclinical stage. Future studies should investigate tau burden with methods that take the focal aspect of tau accumulation into account (i.e., using PET imaging opposed to CSF). Investigating the relationship of tau in older individuals without dementia with episodic and semantic impairment at baseline, decline over time, and development of incident dementia is important as these factors may predict the conversion towards Alzheimer’s disease. Aggregating a robust body of evidence consistent with the current results would propose a role for tau in combination with cognitive biomarkers as a biomarker for early clinical diagnosis and possible clinical target for timely intervention.

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**CRediT authorship contribution statement**

Teuntje A.D. Pelgrim: Data curation, Formal analysis, Investigation, Writing - original draft, Visualization, Writing - review & editing. Magdalena Beran: Data curation, Writing - review & editing. Emma L. Twait: Methodology, Writing - review & editing. Mirjam I. Geerlings: Writing - review & editing. Jet M.J. Vonk: Conceptualization, Methodology, Writing - review & editing, Supervision.

**Declaration of Competing Interest**

None declared.

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**Appendix A. Supplementary data**

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101449.

**References**

Alm, K.H., Faria, A.V., Moghekar, A., Petittrew, C., Soldan, A., Mori, S., Albert, M., Bakker, A., 2020. Medial temporal lobe white matter hyperintensities are associated with individual differences in episodic memory in cognitively normal older adults. Neurobiol. Aging 87, 78–88. https://doi.org/10.1016/j.neurobiaging.2019.11.011.

Arragada, P.V., Growdon, J.H., Hedley-Whyte, E.T., Hyman, B.T., 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer’s disease. Neurology 42, 631–639. https://doi.org/10.1212/wnl.42.3.631.

Auchensreiter, A.J., Gordon, B.A., Benzinger, T.L.S., Morris, J.C., Hassenstab, J.J., 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. Neurology 91. https://doi.org/10.1212/ WNL.0000000000006075.

Auchensreiter, A.J., Gordon, B.A., Fagan, A.M., Schindler, S.E., Balota, D.A., Morris, J.C., Hassenstab, J.J., Tales, A., 2020. Neurofilament light predicts decline in attention but not episodic memory in preclinical alzheimer’s disease. J. Alzheimers Dis. 74, 1119–1129. https://doi.org/10.3233/JAD-200018.

Baker, J.E., Lim, Y.Y., Pietrzak, R.H., Hassenstab, J., Snyder, P.J., Masters, C.L., Maruff, P., 2017. Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: a meta-analysis. Alzheimer’s Dement. Diagnosis, Assess. Dis. Monit. https://doi.org/10.1016/j.jalz.2016.09.002.

Balduzzi, S., Rücker, G., Schwarzer, G., 2019. How to perform a meta-analysis with R: A practical tutorial. Evid. Based. Ment. Health 22, 153–160. https://doi.org/10.1136/ EBMENTAL-2019-300117.

Bateman, R., Xiong, C., Benzinger, T., Fagan, A., Goate, A., Fox, N., Marcus, B., Cairns, N., Xie, Z., Blazey, T., Holtzman, D., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P., Ghetti, B., Klink, W., Mcrae, D., Martins, R., Masters, C., Mayeux, R., Ringman, J., Rossor, M., Schofield, P., Sperling, R., Salloway, S., Morris, J.C., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. N. Engl. J. Med. 367, 795–804. https://doi.org/10.1056/ NEJMoa1202753.

Bennett, D.A., Wilson, R.S., Boyle, P.A., Buchman, A.S., Schneider, J.A., 2012. Relation of neuroopathology to cognition in persons without cognitive impairment. Ann. Neurol. 72, 599–609. https://doi.org/10.1002/ana.23654.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb. Cortex 19, 2767–2796. https://doi.org/10.1093/CEREBOR/BIP055.

Braak, H., Braak, E., 1997. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol. Aging 18, 351–357. https://doi.org/10.1016/S0197-4580(97)00056-X.

Braak, H., Thal, D.R., Ghebremedhin, E., Del Tredici, K., 2011. Stages of the pathologic process in alzheimer disease: age categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70, 960–969. https://doi.org/10.1093/jenepath/eln009.

Bruno, D., Gleason, C.E., Koscik, R.L., Pomara, N., Zetterberg, H., Blennow, K., Johnson, S.C., 2019. The recency ratio is related to CSF amyloid beta 1–42 levels in MCI-AD. Int. J. Geriatr. Psychiatry 34, 415–419. https://doi.org/10.1002/gps.3502.

Casaleto, K.B., Elahi, F.M., Betcher, B.M., Neuhaus, J., Bendlin, B.B., Asthana, S., Johnson, S.C., Yaffe, K., Carlson, C., Blennow, K., Zetterberg, H., Kramer, J.H., 2017. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. Neurology 89, 1782–1788. https://doi.org/10.1212/WNL.0000000000004569.

Chen, X., Cassady, K., Adams, J.N., Harrison, T.M., Baker, S.L., Jagust, W.J., 2020. Regional tau effects on prospective cognitive change in cognitively normal older adults. J. Neurosci. 42, 639. https://doi.org/10.1212/JN.0000000000008260.

Cohen, J., 1988. The Effect Size Index: D: in: Statistical Power Analysis for the Behavioral Sciences.
measures that detect early impairment and decline in preclinical Alzheimer disease. Neurobiol. Aging 56, 25–32. https://doi.org/10.1016/j.neurobiolaging.2017.04.004.
Schmand, B., Huizenga, H.M., Van Gool, W.A., 2010. Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer’s disease. Psychol. Med. (Paris) 40, 135–145. https://doi.org/10.1016/j.aip.2009.09.016.
Snitz, B.E., Tudorascu, D.L., Yu, Z., Campbell, E., Lopresti, B.J., Layon, C.M., Minhas, D.S., Nadkarni, N.K., Aizenstein, H.J., Klink, W.E., Weintraub, S., Gershon, R.C., Cohen, A.D., 2020. Associations between NIH Toolbox Cognition Battery and in vivo brain amyloid and tau pathology in non-demented older adults. Alzheimer’s Dement. Diagnosis. Assess. Dis. Mot. 12. https://doi.org/10.1002/dad.212018.
Tchakoute, C.T., Sainani, K.L., Henderson, V.W., 2017. Semantic memory in the clinical progression of Alzheimer disease. Cogn. Behav. Neurol. 30, 81–89. https://doi.org/10.1007/s00259-019-00131.
Thijssen, E.H., La Joie, R., Wolf, A., Strom, A., Wang, P., Iaccarino, L., Bourakova, V., Kudo, Y., Rowe, C.C., Okamura, N., 2014. In vivo evaluation of a novel tau imaging tracer for Alzheimer disease. J. Neurosci Methods 242, 376–382. https://doi.org/10.1016/j.jneumeth.2013.12.012.
Teunissen, C.E., Scheltens, P., van Berckel, B.N.M., 2020. Regional [18F]flortaucipir PET is more closely associated with disease severity than CSF p-tau in Alzheimer’s disease. J. Nucl. Med. Imaging 56, 259–269. https://doi.org/10.2967/jnumed.120.083589.
Wolfsgruber, S., Kleinendiam, L., Guskii, J., Polcher, A., Frommann, I., Roeseke, S., Spruth, E.J., Franke, C., Grillo, M., Kilianm, I., Teipel, S., Buerger, K., Janowitz, D., Bartels, C., Dieder, E., Metzger, C., Glanz, W., Thelen, M., Spotke, A., Ramirez, A., Koffer, B., Fleischbach, K., Schneider, A., Heneka, M.T., Grosser, M., Meibert, D., Jessen, F., Wagner, M., Mann, W., 2020. Minor neuropsychological deficits in patients with subjective cognitive decline. Neurology 95, e1134–e1143. https://doi.org/10.1212/WNL.000000000001043.
Wolters, E.E., Osnenkopp, E., Verfaillie, S.C.J., Coomans, E.M., Timmers, T., Visser, D., Tuncel, H., Golla, S.S.V., Windhorst, A.D., Boellaard, R., van der Flier, W.M., Teunissen, C.E., Scheltens, F., van Berckel, B.N.M., 2020. Regional [18F]fotaurcipir PET is more closely associated with disease severity than CSF p-tau in Alzheimer’s disease. Eur. J. Nucl. Med. Mol. Imaging 47, 2866–2878. https://doi.org/10.1007/s00259-020-04758-2.
Zakransky, K., 1998. Quantitative evidence for neuroanatomic and neuropsychological markers in dementia of the Alzheimer’s type. J. Clin. Exp. Neuropsychol. 20, 259–269. https://doi.org/10.1076/1464-0640.19.2.259.1174.
Zempel, H., Mandelkow, E.-M., 2012. Linking Amyloid-β and tau: Amyloid-β induced synaptic dysfuncion via local wreckage of the neuronal cytoskeleton. Neurodegener. Dis. 10, 64–72. https://doi.org/10.1159/000328216.
Zioz, J., Bilgel, M., Shafer, A.T., Moghekar, A., Elkins, W., Helsphey, J., Gomez, G., June, D., McDonald, M.A., Dzawo, R.F., Azzad, B.B., Ferrucci, L., Wong, D.F., Resnick, S.M., 2019. Tau pathology in cognitively normal older adults. Alzheimer’s Dement. Diagnosis. Assess. Dis. Mot. 11, 637–645. https://doi.org/10.1016/j.jadm.2019.07.007.