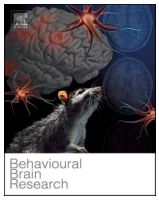
Behavioural Brain Research 498 (2026) 115889

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr



Research article

PET-measured tau deposition in emotion-related brain regions is differentially associated with depressive symptoms in individuals with versus without Alzheimer's disease pathology

Erika Glaubitz, Xiuyuan Hugh Wang, Ke Xi, Farnia Feiz, Silky Pahlajani, Tom Maloney, Emily Tanzi, Hani Hojjati, Liangdong Zhou, Lidia Glodzik, Gloria Chiang, Yi Li, Ray Razlighi, Mony de Leon, Tracy Butler *

Brain Health Imaging Institute, Department of Radiology, Weill Cornell Medicine, USA

ARTICLE INFO

Keywords:
Nucleus Accumbens
Ventral striatum, MK6240
Anhedonia
Late Life Depression
Neurogenesis

ABSTRACT

Depressive symptoms are common in patients diagnosed with Alzheimer's Disease (AD) and can also precede AD as a risk factor and/or prodrome. Brain deposition of hyper-phosphorylated tau is a hallmark pathology of AD. Tau deposition in brain regions involved in emotional processing is likely to be pathophysiologically relevant to these links between AD and depression. We used 18F-MK6240 PET to measure tau in amygdala, hippocampus, and nucleus accumbens—regions implicated in depression—in 141 participants with and without AD. In addition to tau PET, participants underwent amyloid-beta (Aβ) PET, MRI, and cognitive evaluation. Depressive symptoms were assessed with the Beck Depression Inventory (BDI). Multiple regression analyzed contributions of tau and Aβ status (positive vs. negative), depression (BDI > 13), cognition (impaired vs. normal), age and sex to tau burden in the three regions. A significant interaction between tau status and depression prompted subgroup analyses of tau-positive (n = 34) and tau-negative (n = 107) participants. Among tau-positive participants, depression was associated with greater tau in the nucleus accumbens, a region critical for reward processing and motivation. This finding suggests that tau-mediated accumbens dysfunction may contribute to anhedonia, a key symptom of depression that is particularly common in AD-related depression. In tau-negative participants, greater depression was associated with less tau in the medial temporal lobe. This unexpected finding requires confirmation through further research, but could reflect impaired neurogenesis in depression without AD pathology.

1. Background

AD and depression are prevalent and devastating conditions that frequently co-occur. Depressive symptoms are extremely common in patients with an established diagnosis of AD, [1,2] and depression often precedes an AD diagnosis. Depression preceding AD may represent a risk factor, a prodromal symptom, or both. [3–5] These observations indicate a complex and bidirectional relationship between AD and depression with depressive symptoms attributable to psychological responses to a diagnosis of dementia or its functional consequences as well as shared biology. Shared biological mechanisms linking depression and AD include neuroinflammation [6] and aberrant neurogenesis. [7–9] and shared neuroanatomy, with both depression and AD characterized by profound dysfunction of neural circuits underlying emotion and cognition.

Within these circuits, the hippocampus and amygdala in the medial temporal lobe and the nucleus accumbens in the basal forebrain play particularly critical roles. These regions are central to the pathophysiology of both AD and depression. The hippocampus is essential for memory functioning and one of the earliest regions of neurodegeneration in AD, with hippocampal atrophy serving as a key diagnostic biomarker for AD. [10–12] Hippocampal dysfunction and atrophy is also documented in chronic depression. [13–15] The amygdala is a key regulator of emotional processing implicated in animal models and human neuroimaging studies of psychiatric disorders including depression, [14] and also one of the earliest and most severely affected regions in AD. [16] The nucleus accumbens plays a critical role in motivation and reward processing, [17] and accumbens dysfunction is associated

* Correspondence to: Weill Cornell Medicine, 407 East 61st street, 2nd Floor, New York, NY 10065, USA.
E-mail address: tab2006@med.cornell.edu (T. Butler).

https://doi.org/10.1016/j.bbr.2025.115889
Received 7 April 2025; Received in revised form 17 October 2025; Accepted 20 October 2025
Available online 30 October 2025
0166-4328/© 2025 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

with the key depressive symptom of anhedonia – inability to derive pleasure from normally enjoyable activities. [18,19] In AD, degeneration of cholinergic neurons in the basal forebrain, most prominently in nucleus basalis of Meynert but also described in the nucleus accumbens, [20,21] is one of the earliest pathologic events, closely linked to cognitive impairment. [22,23] This cholinergic loss forms the rationale for the use of cholinesterase inhibitors—the most widely prescribed class of AD medications. [24] Notably, the depressive symptoms of anhedonia is particularly associated with depression in AD. [25]

While the underlying etiology for hippocampal, amygdala and nucleus accumbens dysfunction in depression remains uncertain, in AD, dysfunction and neurodegeneration of these regions is closely linked to deposition of hyperphosphorylated tau into tau tangles, which, along with amyloid-β (Aβ) plaques, are the hallmark neuropathologies of AD. These AD pathologies can be visualized using Positron Emission Tomography (PET), and prior studies have investigate whether the neuroanatomic location or quantity of these proteins is associated with depressive symptoms. Results of studies applying Aβ PET to individuals with and without AD and/or major depression have been variable, but in general, they indicate no or only a weak association between the degree of cortical Aβ and the severity of depression, with the anatomic location of Aβ not relevant. [26–29] This lack of correspondence between Aβ deposition and depressive symptoms mirrors results of multiple neuroimaging as well as autopsy studies showing only a weak association between cortical Aβ and cognitive symptoms, with little or no anatomic specificity. [30]

In contrast, autopsy studies and PET studies using recently available tau PET tracers show that the location and amount of tau deposition correlate closely with the severity and nature of cognitive dysfunction. [30,31] For example, greater tau in occipital-parietal regions is associated with visuospatial dysfunction in the posterior-cortical atrophy variant of AD [32]. Similar links between tau neuroanatomic location and psychiatric symptoms are beginning to be documented using tau PET: Using the first-generation radiotracer 18F-Flortaucipir, Gatchel et al. [33] found that higher depression scores on the Geriatric Depression Scale (GDS) were modestly associated with greater tau in inferior temporal and entorhinal cortices in cognitively normal older adults from the Harvard Aging Brain Study (n = 111). Babulal et al. [27] showed that tau positivity in a temporal meta-region was associated with the presence of depressive symptoms in cognitively normal individuals from the Knight ADRC (n = 301), with this relationship modified by antidepressant use. Gonzales et al. [26] reported that entorhinal tau was associated with depressive symptoms measured by the Center for Epidemiological Studies Depression Scale (CES-D) in cognitively normal individuals from the Framingham Heart Study (n = 201), although this effect was only significant among APOE ε4 carriers. In the ADNI cohort (n = 303), Talmasov et al. [34] found that GDS score was positively correlated with annualized tau accumulation rates in a temporal meta-region across participants with and without cognitive symptoms, but this effect was limited to amyloid-positive individuals. Li et al. [35] demonstrated that tau deposition in the amygdala, particularly the medial nuclei, was associated with depression in cognitively normal amyloid-positive participants from the A4 study (n = 598). Extending these findings with second-generation tau PET tracers, which have less off-target binding, Kurose et al. [36] showed that patients with late-life depression (n = 52) were more likely to be tau- and amyloid-positive than healthy controls when imaged with11C-PBB3, with the highest tau burden observed in psychotic depression. However, another study using the 2nd generation tracer 18F-MK-6240 did not find higher tau in late life major depression. [37] Tissot et al. [38] reported that tau, but not amyloid, was associated with neuropsychiatric symptoms on the Neuropsychiatric Inventory Questionnaire (NPI-Q) in individuals (n = 221) with and without AD, with depression linked to a pattern of elevated tau in parietal and superior temporal cortices.

These prior studies generally support an association between depressive symptoms and tau deposition, particularly in the temporal lobe, but are limited by small sample size and/or use of first generation tau tracers, which sometimes cannot accurately quantify tau in medial temporal lobe structures including the hippocampus due to strong off-target binding to choroid plexus in the adjacent temporal horn of the lateral ventricle. [39,40] Further, no prior studies assessed tau in nucleus accumbens. Therefore, it remains unclear whether tau accumulation in brain areas most implicated in emotional processing and depression is associated with depressive symptoms. To address this, we used the second-generation tau tracer ^{18}F-MK-6240, which does not bind to the choroid plexus, [39,40] to test the hypothesis that tau deposition in three emotion-related regions—the hippocampus, amygdala, and nucleus accumbens—is linked to depressive symptoms in a large, well-characterized cohort of community-dwelling participants with and without AD. Based on the replicated prior finding that links between regional tau deposition and depressive symptoms may be stronger, or only present in patient with amyloid deposition, [34,35] we specifically assess whether the presence of AD pathology (both amyloid and tau) affects the relation between depressive symptoms and tau in emotion-related brain regions.

2. Methods

2.1. Participants

Participants were recruited for several ongoing studies at the Brain Health Imaging Institute (BHII) of Weill Cornell Medicine. All studies were approved by the Weill Cornell Medicine IRB. All participants signed informed consent. Participants were either cognitively normal or diagnosed with Mild Cognitive Impairment (MCI) or early AD based on National Alzheimer's Coordinating Center (NACC) criteria. [41] Exclusion criteria included significant medical illness, neurological disorders other than the condition under study (AD), or clinically significant psychiatric disorders, including current major depression. Participants were selected for this analysis if they had undergone ^{18}F-MK-6240 tau PET, Aβ PET using 11C-PiB or 18F-florbetaben (FBB), 3 T MRI, and had completed the Beck Depression Inventory II (BDI). [42]

2.2. Beck Depression Inventory II

The BDI is a 21-item self-report questionnaire used to assess depressive symptoms with a possible score range of 0–63. Higher scores indicate increased depressive symptoms with 14 considered the minimum score for clinically significant depression. [42] We categorized participants as depressed or not based on this cut off. In addition, analyses were performed using BDI score.

2.3. Clinical/cognitive assessment

The majority of participants, including all participants with suspected or confirmed (based on clinical referral) MCI/AD, underwent detailed clinical and cognitive testing using the NACC assessment battery which includes multidomain neuropsychological testing, neurologic exam and Clinical Dementia Rating (CDR) interview by a board-certified cognitive neurologist. [41] After this assessment and review of all available information including PET, subjects were assigned a diagnosis of Normal Cognition, MCI due to AD, or AD in accord with NACC and National Institute on Aging criteria. [41] Participants who were cognitively impaired, but who did not have brain tau and Aβ deposition based on expert visual interpretation of PET, were determine to have a non-AD etiology for impairment and were therefore not included in this analysis. A portion of normal control subjects, including all subjects under age 40, underwent a screening questionnaire to confirm normal cognition, and a slightly different multidomain neuropsychological battery. These subjects were not formally evaluated by a cognitive neurologist, though their cognitive test scores were reviewed to confirm normal cognition prior to inclusion in this analysis.

2.4. PET imaging

2.4.1. Tau PET imaging

Tau PET images were acquired after IV bolus injection of ^{18}F-MK-6240 on a single, research-dedicated Siemens Biograph PET/CT. Images were acquired 0–60 and 90–120 min after injection of the tracer. Only 90–120 min images are analyzed and reported here. Images were pre-processed using validated methods including motion correction, co-registration to MRI and calculation of standardized uptake value ratio (SUVr) with reference to cerebellar grey matter. [43,44] To test study hypotheses concerning emotion-related brain regions, average SUVr was calculated in the three regions of interest (ROIs): bilateral hippocampi, amygdala, and nucleus accumbens as defined on MRI using FreeSurfer. In addition to quantitative analysis, tau PET scans co-registered to MRI were reviewed by an experienced neuroradiologist and interpreted as positive or negative, with tau deposition anywhere in cerebrum including medial temporal lobes considered positive. [45]

2.4.2. Aβ PET imaging

Aβ PET used either ^{11}C-PiB or Florbetaban (FBB). Scans were categorized as Aβ positive or negative based on visual review by an experienced neuroradiologist in accord with standard guidelines. [46]

2.5. Statistical analysis

SPSS 29.0 was used for all statistical analyses.

Three separate linear regression models were used to determine the relationship between depression and tau deposition in the three ROIs while accounting for relevant factors. The dependent variable was regional ^{18}F-MK-6240 SUVr and the predictors were: depression (binary presence or absence), tau status (visually tau-positive or tau-negative), Aβ status (visually Aβ-positive or Aβ-negative), cognitive status (cognitively normal or impaired), age and sex. We tested for interactions between depression and Aβ status and tau status. A significant interaction was observed between depression and tau status, prompting stratified analyses: separate regression models were conducted within tau-positive and tau-negative subgroups, and we compared characteristics (depression, age, sex, Aβ status) between tau-positive and tau-negative subgroups using *t*-tests for normally distributed continuous variables, Mann–Whitney tests for non-normally distributed continuous variables, and χ^2 tests for categorical variables. We also performed analyses using BDI score as a continuous measure of depressive symptoms. All model residuals were confirmed to be normal using the Shapiro-Wilk test of normality. We used 2-sided statistical tests and a significance level of $p \leq 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Participant characteristics are presented in Table 1**.** The study cohort comprised 141 participants with mean age of 58.8 (range: 20–86). 107 (75.9 %) identified as White, 14 (9.9 %) as Black or African American, 10 (7.1 %) as Asian, 8 (5.7 %) as Hispanic, and 2 (1.4 %) as other. Participants had an average of 16.5 years of education (SD = 2.34, range = 12–20). BDI scores were right-skewed (skewness = 1.68, SE = 0.20). Median BDI score (IQR) was 4 (1–7); range 0–31. Mean BDI score was 5.7 (SD = 6.1). Seventeen participants (12.1 %) were categorized as depressed based on a BDI score of 14 or greater. 12 participants (8.5 %) were diagnosed as cognitively impaired due to AD by a cognitive neurologist based on NACC criteria: [41] 7 had MCI due to AD with CDR of.5 and 5 had early AD with CDR of 1. All cognitively impaired subjects were positive for both amyloid and tau.

3.2. Associations between regional tau and depression

Results of multiple regression analyses predicting regional tau are presented in Table 2**.** All regression models were significant (amygdala R^2 =.601, adjusted R^2 =.580, F[7, 133] = 28.57, p < .001; hippocampus R^2 =.415, adjusted R^2 =.384, F[7, 133] = 13.67, p < .001; nucleus accumbens R^2 =.496, adjusted R^2 =.469, F[7, 133] = 18.67, p < .001). Across all three regions, higher tau PET SUVR was associated with cognitive impairment (ps <.001) and tau positivity based on visual interpretation (ps <.05). In hippocampus and nucleus accumbens, older age was also associated with higher tau (ps ≤.002). No other individual variables (depression, sex, Aβ status, sex) were significant predictors of tau in any of the three ROIs (lowest p = 0.052).

There was a significant tau status × depression interaction for predicting tau in amygdala (p = .031) and nucleus accumbens (p = .002), with a similar though nonsignificant trend in hippocampus (p = .076). In contrast, depression × amyloid interactions were not significant in any region (smallest p = .084). Scatterplots illustrating these divergent associations between depression and regional MK6240 PET SUVr in tau-positive versus tau-negative individuals are shown in Fig. 1**.**

Because of the significant depression × tau status interactions, participants were stratified into tau-positive (n = 34) and tau-negative (n = 107) groups and reanalyzed. Characteristics of tau positive and tau negative participants and results of statistical comparisons between them are presented in Table 1. Tau-positive subjects were significantly older (p < .001), more likely to be Aβ+ (p < .001), more likely to be cognitively impaired (p < .001), and had greater ^{18}F-MK-6240 SUVr in all three ROIs (p < .001); this is expected. Tau-positive and tau-negative subjects did not differ significantly by sex, presence of depression, or BDI score (ps>.50).

Table 1
Participant Characteristics.

Characteristic	Total	Tau+	Tau-	Tau+ vs Tau- Differences
Number of participants	141	34	107	
Age in years (SD, range)	58.8 (SD=19.6; 20–86)	71.2 (SD=7.8; 55–85)	54.8 (SD=20.6; 20–86)	t(134.8) = 6.851, p < .001
% Female (n)	62.4 % (88)	58.8 % (20)	63.6 % (68)	χ^2 (1, n = 141) = 0.246, p = .62
% Cognitively Impaired (n)	8.5 % (12; 7 with MCI, 5 with early AD)	35.3 % (12)	0	χ^2 (1, n = 141) = 41.278, p < .001
% Aβ Positive (n)	24.1 % (34)	70.6 % (24)	9.4 % (10)	χ^2 (1, n = 141) = 56.958, p < .001
% Depressed (n)	12.1 % (17)	11.8 % (4)	12.1 % (13)	χ^2 (1, n = 141) = 0.004, p = .952
BDI Score (SD, range)	5.7 (SD=6.1; 0–31)	5.1 (SD=5.2; 0–21)	5.9 (SD=6.4; 0–31)	U= 1739.50, p = .70
Amygdala MK6240 SUVr (SD, range)	0.853 (SD=0.36; 0.45–2.96)	1.2397 (SD=0.539)	0.7306 (SD=0.113)	t(139) = 9.200, p < .001
Hippocampal MK6240 SUVr (SD, range)	0.875 (SD=0.22; 0.48–1.97)	1.1170 (SD=0.291)	0.7983 (SD=0.124)	t(139) = 9.074, **p < .001**
Nucleus Accumbens MK6240 SUVr (SD, range)	0.713 (SD=0.16; 0.40–1.28)	0.8518 (SD=0.164)	0.6697 (SD=0.128)	t(139) = 6.723, **p < .001**

Abbreviations: SD = standard deviation, Aβ = amyloid-β, BDI = Beck Depression Inventory, SUVr = standardized uptake value ratio.

Table 2
Multiple Linear Regression Results Predicting Regional Tau Accumulation (MK6240 SUVr) in Amygdala, Hippocampus, and Nucleus Accumbens in 140 participants.

Amygdala Tau			
Predictor	**Full Sample**	**Tau+**	**Tau–**
Age	0.001 (0.001), β = .08, p = .185	−0.009 (0.010), β = −.13, p = .362	**0.002 (0.001), β = .44, p < .001**
Sex	−0.080 (0.041), β = −.11, p = .052	−0.275 (0.156), β = −.26, p = .089	−0.021 (0.021), β = −.09, p = .301
Depressed	−0.073 (0.069), β = −.07, p = .292	0.292 (0.243), β = .18, p = .240	**−0.063 (0.030), β = −.18, p = .042**
Amyloid status	0.084 (0.063), β = .10, p = .187	0.287 (0.190), β = .24, p = .142	−0.038 (0.036), β = −.10, p = .286
Cognitive impairment	**0.581 (0.091), β = .46, p < .001**	**0.557 (0.185), β = .50, p = .006**	—
Tau status	**0.192 (0.064), β = .23, p = .003**	—	—
Depressed × Tau Status	**0.320 (0.147), β = .15, p = .031**	—	—
Hippocampal Tau			
Predictor	**Full Sample**	**Tau+**	**Tau–**
Age	**0.002 (0.001), β = .20, p = .002**	−0.003 (0.006), β = −.09, p = .536	**0.003 (0.001), β = .46, p < .001**
Sex	−0.052 (0.027), β = −.11, p = .056	−0.148 (0.090), β = −.25, p = .112	−0.024 (0.022), β = −.09, p = .285
Depressed	−0.064 (0.046), β = −.09, p = .165	0.130 (0.140), β = .15, p = .359	−0.059 (0.033), β = −.16, p = .076
Amyloid status	−0.008 (0.042), β = −.02, p = .848	0.075 (0.109), β = .12, p = .499	−0.058 (0.039), β = −.14, p = .136
Cognitive impairment	**0.322 (0.061), β = .40, p < .001**	**0.318 (0.106), β = .53, p = .006**	—
Tau status	**0.154 (0.042), β = .30, p < .001**	—	—
Depressed × Tau Status	0.175 (0.098), β = .13, p = .076	—	—
Nucleus Accumbens Tau			
Predictor	**Full Sample**	**Tau+**	**Tau–**
Age	**0.003 (0.001), β = .36, p < .001**	0.000 (0.003), β = −.02, p = .905	**0.003 (0.001), β = .50, p < .001**
Sex	−0.027 (0.020), β = −.08, p = .181	−0.079 (0.044), β = −.24, p = .086	−0.012 (0.023), β = −.04, p = .605
Depressed	−0.053 (0.034), β = −.11, p = .124	**0.190 (0.069), β = .38, p = .010**	−0.051 (0.034), β = −.13, p = .135
Amyloid status	−0.035 (0.032), β = −.10, p = .267	−0.013 (0.054), β = −.04, p = .813	−0.048 (0.039), β = −.11, p = .227
Cognitive impairment	**0.175 (0.046), β = .31, p < .001**	**0.183 (0.053), β = .54, p = .002**	—
Tau status	**0.068 (0.032), β = .19, p = .033**	—	—
Depressed × Tau Status	**0.237 (0.073), β = .25, p = .002**	—	—

In tau-positive participants (n = 34), regression models were significant for all three regions: amygdala: $R^2 = .536$, adjusted $R^2 = .449$, $F(6, 27) = 6.16$, $p < .001$; hippocampus: $R^2 = .523$, adjusted $R^2 = .434$, $F(6, 27) = 5.89$, $p < .001$; nucleus accumbens: $R^2 = .632$, adjusted $R^2 = .565$, $F(6, 27) = 9.44$, $p < .001$.

Tau in nucleus accumbens was found to be significantly associated with presence of depression (p = 0.010). There was no significant association of depression with tau in the hippocampus or the amygdala (lowest p = .240). The effect of impaired cognition was significant for all three regions (ps<.001). No other variables (age, sex, Aβ status) were significant predictors of tau in the three ROIs in tau-positive participants (lowest p = .086).

In tau-negative participants (n = 107), regression models were also significant for all three regions: amygdala: $R^2 = .356$, adjusted $R^2 = .318$, $F(6, 100) = 9.27$, $p < .001$; Hippocampus: $R^2 = .363$, adjusted $R^2 = .325$, $F(6, 100) = 9.54$, $p < .001$; nucleus accumbens: $R^2 = .422$, adjusted $R^2 = .388$, $F(6, 100) = 12.36$, $p < .001$. Depression was a significant *negative* predictor of tau in amygdala (p = 0.042) with a similar though non-significant trend in hippocampus (p = 0.076), meaning that depressed subjects had *less* tau in these regions. The effect of age was significant for all three ROIs (ps<.001), with older age associated with greater tau in all three regions. No other variables were significant predictors of tau in any of the three ROIs in tau-negative participants (lowest p = .136). Note that there were no tau-negative cognitively impaired individuals so cognitive status was not included as a predictor in this model.

Results were not significant in any of the three ROIs when using BDI score rather than binary depressed/not depressed in analysis.

4. Discussion

This study examined the relationship between the level of tau deposition in three emotion-related brain regions (amygdala, hippocampus, nucleus accumbens) measured using ^{18}F-MK-6240 PET, and depressive symptoms, as measured by the BDI. We found intriguing differences in participants with versus without visually-detectable tau, reflected in a significant interaction between tau status and depression for 2 of the 3 regions (nucleus accumbens, amygdala) with a similar trend in hippocampus.

4.1. Greater nucleus accumbens tau in association with depression in participants with AD pathology

In tau-positive participants, the majority of whom were also Aβ+ , consistent with AD pathology, depression was associated with greater tau accumulation in the nucleus accumbens. The nucleus accumbens, a key component of the ventral striatum in the basal forebrain, plays a central role in reward processing, motivation, and reinforcement learning. [17–19] Dysfunction of this region has been implicated in core depressive symptoms such as anhedonia, apathy, and loss of motivation, [17–19] which are particularly relevant to the clinical presentation of AD [25] Our novel finding linking nucleus accumbens tauopathy to depression offers new insight into the pathophysiological links between depression and AD. Although our cross-sectional results cannot establish causality, they are consistent with the idea that tau in the nucleus accumbens contributes to dysfunction of this region and to depressive symptoms. This is analogous to prior studies linking specific cognitive deficits to tau deposition in corresponding brain regions, [30–32] and, for the first time, extends this relation from cognition to emotion.

Anatomically, the nucleus accumbens is highly interconnected with the dopaminergic ventral tegmental area and medial temporal lobe structures, serving as a crucial interface between cognition, emotion, and action. [17] It is divided into shell and core subregions. The shell receives strong inputs from the hippocampus, amygdala, and ventromedial/orbitofrontal prefrontal cortices and supports reward valuation and affective regulation, whereas the core integrates inputs from the dorsolateral prefrontal cortex and dorsal striatum to support goal-directed behavior and action selection. [17] Subregional variations in tau deposition could therefore give rise to different neuropsychiatric profiles in AD, with shell dysfunction linked to sadness and anhedonia, and core dysfunction linked to apathy, inertia, or executive deficits. Although differentiating accumbens subregions with PET remains challenging given spatial resolution limits, doing so will be important for testing whether subregional tau burden accounts for heterogeneity in AD-related neuropsychiatric features—analogous to emerging evidence linking tau deposition in amygdala subnuclei to specific mood symptoms in AD. [35]

Human neuroimaging studies have demonstrated nucleus accumbens atrophy [47,48] and abnormal functional connectivity in AD [49] and autopsy studies confirm tau pathology in this region. [20,21] However, whether tau deposition here is an early or late event in AD, or how it relates to premorbid neuropsychiatric symptoms, remains uncertain. Given its strong connectivity with medial temporal lobe structures that are early sites of tau accumulation, [22] it has been suggested that tau in the accumbens may arise via transsynaptic spread from these regions. [20,21] Alternatively, animal studies suggest that dopaminergic

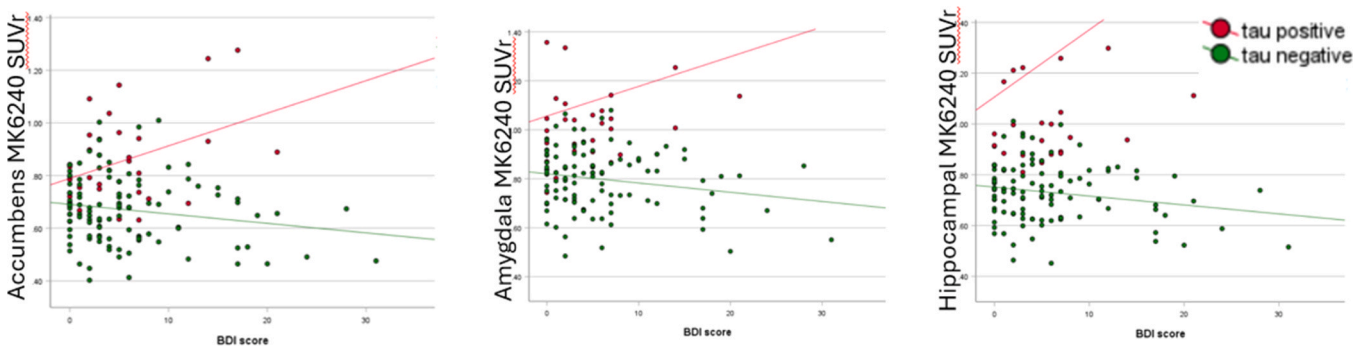


Fig. 1. Scatter plots depicting the relationship between PET-measured ^{18}F-MK-6240 SUVr and Beck Depression Inventory (BDI) scores across three emotion-related regions (nucleus accumbens, amygdala, hippocampus) in 141 participants. In tau-positive participants (red), regional tau burden correlates positively with depression, whereas in tau-negative participants (green)—who lack visually detectable tau at standard viewing thresholds—regional tau shows an inverse relationship with depression. These plots are provided for visualization purposes; associations between BDI score and regional tau were not significant in multiple regression analysis. However, as described in the text, there was a significant interaction between binarized depression status (BDI > 13) and tau deposition in the nucleus accumbens and amygdala, with a similar trend in the hippocampus. These divergent associations suggest distinct neurobiological mechanisms underlying depression depending on whether or not it is associated with Alzheimer's disease pathology.

deficits and accumbens dysfunction may represent early events in AD pathogenesis, preceding amyloid plaque formation. [50,51] This raises the possibility that such dysfunction could underlie early and disabling neuropsychiatric symptoms of AD such as depression and amotivation. Additional research in animal models and humans is needed to clarify mechanisms and clinical associations of nucleus accumbens tauopathy, including its role in patients who develop late-life depression as the initial manifestation of AD. This line of research has the potential to deepen understanding of the neurobiology underlying AD and guide earlier diagnosis and targeted interventions for its neuropsychiatric manifestations.

4.2. Failure to replicate prior findings of greater medial temporal tau in association with depression

We did not replicate prior findings of greater medial temporal tau in association with greater depression [26,27,33–35,52,53] in our full sample or in the subgroup of amyloid-positive subjects. This could relate to our relatively small sample size and restricted range of depressive symptoms. Our use of a second generation tau tracer may also be relevant, as other studies using second-generation tau tracers also have not reported greater medial temporal tau associated with psychiatric symptoms. [36–38] This raises the possibility that results using first-generation flortaucipir could be affected by known, off-target binding to the choroid plexus and skull that can confound medial temporal signal. [39,40] Continued application of second generation tau PET tracers to studying neuropsychiatric symptoms in AD will clarify this issue.

4.3. Inverse association of medial temporal tau PET signal with depression in participants without AD pathology

After demonstrating a statistically significant interaction between tau status and depression in amygdala (with a similar trend in hippocampus), which motivated stratification by tau status, we found that in subjects without any visually detectable tau in their brains, there was a significant *negative* association between depressive symptoms and PET signal in the amygdala (with a similar trend in hippocampus). This was an unexpected finding. However, it is similar to unexpected findings from other studies: Gonzales et al. [26] found an inverse association between depressive symptoms and PET-measured hippocampal tau in cognitively normal participants who were not carriers of the APOE ε4 allele, while in APOE ε4 carriers, the association was positive. Naude et al. [53] found that in amyloid-negative participants, severity of mild behavioral impairment (MBI), which quantifies depressive and other psychiatric symptoms, was inversely associated with tau in Braak III regions consisting of medial temporal (amygdala and parahippocampus) and cortical regions, while in amyloid-positive participants, they found the opposite. Other studies have shown an association between depressive symptom and medial temporal tau *only* in amyloid-positive individuals. [34,35]

We believe our finding of an inverse correlation between medial temporal tau and depression in tau-negative subjects is broadly consistent with these prior similar findings in amyloid-negative subjects [53] and in APOE ε4-negative cognitively normal middle-aged subjects [26] (who are likely to be amyloid-negative). Taken together, these results suggest a qualitative difference in the relationship between medial temporal tau and depression that depends upon the presence versus absence of AD pathology, whether AD pathology is defined by tau status (as we have done here) or by amyloid status (as done in prior studies [26,34,35]). To further evaluate this idea, we performed a supplemental analysis in which we defined AD clinically. In this analysis, we examined whether clinical status (MCI/AD vs. cognitively normal), depression, and their interaction, as well as age and sex, predicted amygdala tau. The interaction was significant ($\beta = 2.565$, $p = 0.011$; see Supplementary Materials for details of analysis and results), again suggesting that the association between medial temporal tau and depression diverges according to the presence of AD pathology. Specifically, a positive association between tau and depressive symptoms is present only in subjects with AD pathology (whether defined by tau, amyloid, or cognition), whereas in individuals without AD pathology, medial temporal tau is not pathological and may in fact be associated with better psychiatric status.

The reason for this divergent relationship between medial temporal tau and depression in subjects with versus without AD pathology will require further study, but one intriguing potential explanation relates to neurogenesis, which is known to occur in the adult human hippocampus [54] and amygdala, [55] with impaired neurogenesis considered to play an important role in the pathophysiology of depression. [7,8] Phosphorylated tau –the target of tau PET tracers– is not always pathological; it is a normal component of dividing cells including neurons, [56] and can be used as a marker of newborn neurons. [57] It is conceivable, though unproven, that tau PET may be sensitive to this normal, expected level of phosphorylated tau present in dividing cells in neurogenic brain regions, with abnormally low levels in depressed participants reflecting impaired neurogenesis. [7,8] Attempts to image neurogenesis in vivo have previously met with little success. [58] Additional study is clearly needed to confirm these findings, including tissue studies to determine whether MK6240 binds to normally phosphorylated tau outside of neurofibrillary tangles.

Whether or not tau PET can detect neurogenesis, our findings in tau-negative participants emphasize the importance of not assuming a consistent relationship between tau deposition and symptoms in participants with versus without AD pathology. This could be relevant to results of prior studies that included participants with the full range of tau deposition, including those with no visibly detectable tau, and failed to demonstrate expected associations between medial temporal tau and impaired cognition, [59] or found associations in an unexpected direction (more tau in association with better cognition). [60] This is an important methodologic consideration in all tau PET studies that include participants with low or no tau deposition.

4.3.1. Limitations

Our study has several limitation. The current analysis uses only cross-sectional data, and it would be valuable to incorporate longitudinal follow up in future research. The majority of participants were white and highly educated, which may limit generalizability; future studies including more diverse populations are essential. We had only 34 tau positive participants, and only 12 of them were cognitively impaired. Results need to be verified in larger numbers of participants with greater variability of tau deposition and wider range of cognitive function. A significant limitation is our use of BDI as a self report measure of depression without clinician verified diagnosis. Related to this, analyses using BDI score, rather than binarization into depressed and non-depressed, did not produce significant results. This may relate to the limited range and skewed distribution of depressive symptoms severity in our sample, with 26 participants with a BDI score of zero and only 6 with a score above 20. Future studies should employ more detailed assessments of depressive symptoms, and include participants with a wider range of symptoms severity, including those with clinically diagnosed major depression, to capture a more comprehensive understanding of the relationship between depression and tau pathology.

5. Conclusion

We found that tau deposition in emotion-related regions is differentially associated with depressive symptoms in patients with versus without AD pathology. In patients with visually detectable tau deposition, greater tau in nucleus accumbens was associated with greater depressive symptoms. This implicates tau-mediated dysfunction of this region as an explanation for strong links between depression and AD, especially neuropsychiatric symptoms like anhedonia, apathy and amotivation, which are common in AD. [25]

In participants who had no visually detectable tau, we unexpectedly found the opposite relationship: less tau in medial temporal lobe regions in association with depression. We speculate this could relate to impaired neurogenesis in depression. Specifically, it is possible that variations in medial temporal ^{18}F-MK-6240 PET signal, though not visually detectable using typical thresholding, may reflect levels of phospho-tau normally present in dividing cells and newborn neurons.

By linking depression to regional tau burden in individuals with preclinical or overt AD, our findings shed light on the biological underpinnings of non-cognitive manifestations of AD. This work may ultimately help unravel the complex interplay between depression and AD and inform the development of novel treatment strategies targeting both cognitive and psychiatric symptoms. Overall, these results advance our understanding of the shared and distinct pathophysiological mechanisms of depression and AD, with potential important clinical implications for both conditions.

Author contributions

EG and TB devised the main conceptual ideas and drafted the manuscript; SP, ET, YL, RR, ET, FF, MdL and TB contributed to clinical assessment and neuroimage data collection; EG, XHW, KX, TM, HH, LZ, RR and TB performed data analysis; all authors contributed to data interpretation and manuscript revisions.

Data statement

These data were previously presented as a poster at the 2025 American Neuropsychiatric Association Annual Meeting in Houston, Texas, USA.

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with wording, grammar checking and formatting of tables. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Tracy Butler: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiuyuan Hugh Wang:** Writing – review & editing, Formal analysis. **Erika Glaubitz:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Farnia Feiz:** Writing – review & editing, Project administration, Data curation. **Ke Xi:** Writing – review & editing, Formal analysis. **Emily Tanzi:** Writing – review & editing, Data curation. **Silky Pahlajani:** Writing – review & editing, Investigation. **Lidia Glodzik:** Writing – review & editing, Data curation. **Thomas Maloney:** Writing – review & editing, Conceptualization. **Liangdong Zhou:** Writing – review & editing, Methodology, Data curation. **Hani Hojjati:** Writing – review & editing, Formal analysis. **Yi Li:** Writing – review & editing, Investigation, Funding acquisition, Data curation. **Gloria Chiang:** Writing – review & editing, Methodology, Investigation. **Ray Razlighi:** Writing – review & editing, Funding acquisition, Data curation. **Mony de Leon:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The following NIH grants supported data acquisition for this project: R01AG057962. R01AG057848. RF1AG057570. R56NS111052

References

[1] C.G. Lyketsos, J. Olin, Depression in Alzheimer's disease: overview and treatment, Biol. Psychiatry 52 (3) (2002) 243–252.
[2] G.S. Zubenko, W.N. Zubenko, S. McPherson, et al., A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease, Am. J. Psychiatry 160 (5) (2003) 857–866.
[3] R.L. Ownby, E. Crocco, A. Acevedo, et al., Depression and Risk for Alzheimer Disease: Systematic Review, Meta-analysis, and Metaregression Analysis, Arch. Gen. Psychiatry 63 (5) (2006) 530–538, https://doi.org/10.1001/archpsyc.63.5.530.
[4] J.S. Saczynski, A. Beiser, S. Seshadri, et al., Depressive symptoms and risk of dementia, Neurology 75 (1) (2010) 35–41, https://doi.org/10.1212/WNL.0b013e3181e62138.
[5] R.C. Green, L.A. Cupples, A. Kurz, et al., Depression as a Risk Factor for Alzheimer Disease: The MIRAGE Study, Arch. Neurol. 60 (5) (2003) 753–759, https://doi.org/10.1001/archneur.60.5.753.
[6] F. Caraci, A. Copani, F. Nicoletti, et al., Depression and Alzheimer's disease: neurobiological links and common pharmacological targets, Eur. J. Pharmacol. 626 (1) (2010) 64–71.
[7] A.J. Eisch, D. Petrik, Depression and Hippocampal Neurogenesis: A Road to Remission? Science 338 (6103) (2012) 72–75, https://doi.org/10.1126/science.1222941.
[8] A. Sahay, R. Hen, Adult hippocampal neurogenesis in depression, Nat. Neurosci. 10 (9) (2007) 1110–1115, https://doi.org/10.1038/nn1969.
[9] B. Winner, Z. Kohl, F.H. Gage, Neurodegenerative disease and adult neurogenesis, Eur. J. Neurosci. 33 (6) (2011) 1139–1151.

[10] M.J. de Leon, A.E. George, L.A. Stylopoulos, et al., Early marker for Alzheimer's disease: the atrophic hippocampus, Lancet 2 (8664) (1989) 672–673, https://doi.org/10.1016/s0140-6736(89)90911-2.
[11] P. Scheltens, D. Leys, F. Barkhof, et al., Atrophy of medial temporal lobes on MRI in probable Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates, J. Neurol. Neurosurg. Psychiatry 55 (10) (1992) 967–972.
[12] C.R. Jack, R.C. Petersen, Y.C. Xu, et al., Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease, Neurology 49 (3) (1997) 786–794, https://doi.org/10.1212/WNL.49.3.786.
[13] S. Campbell, G. MacQueen, The role of the hippocampus in the pathophysiology of major depression, J. Psychiatry Neurosci. 29 (6) (2004) 417–426.
[14] J.P. Hamilton, M. Siemer, I.H. Gotlib, Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies, Mol. Psychiatry 13 (11) (2008) 993–1000, https://doi.org/10.1038/mp.2008.57.
[15] P. Videbech, B. Ravnkilde, Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies, Am. J. Psychiatry 161 (11) (2004) 1957–1966, https://doi.org/10.1176/appi.ajp.161.11.1957.
[16] L.K. Vogt, B. Hyman, G. Van Hoesen, et al., Pathological alterations in the amygdala in Alzheimer's disease, Neuroscience 37 (2) (1990) 377–385.
[17] S.B. Floresco, The nucleus accumbens: an interface between cognition, emotion, and action, Annu. Rev. Psychol. 66 (1) (2015) 25–52.
[18] E.J. Nestler, Role of the brain's reward circuitry in depression: transcriptional mechanisms, Int. Rev. Neurobiol. 124 (2015) 151–170.
[19] J. Epstein, H. Pan, J.H. Kocsis, et al., Lack of ventral striatal response to positive stimuli in depressed versus normal subjects, Am. J. Psychiatry 163 (10) (2006) 1784–1790, https://doi.org/10.1176/ajp.2006.163.10.1784.
[20] I. Kawakami, M. Hasegawa, T. Arai, et al., Tau accumulation in the nucleus accumbens in tangle-predominant dementia, Acta Neuropathol. Commun. 2 (1) (2014) 40.
[21] N. Selden, M.-M. Mesulam, C. Geula, Human striatum: the distribution of neurofibrillary tangles in Alzheimer's disease, Brain Res. 648 (2) (1994) 327–331.
[22] H. Braak, E. Braak, J. Bohl, Staging of Alzheimer-Related Cortical Destruction, Eur. Neurol. 33 (6) (2008) 403–408, https://doi.org/10.1159/000116984.
[23] J.L. Cantero, M. Atienza, C. Lage, et al., Atrophy of Basal Forebrain Initiates with Tau Pathology in Individuals at Risk for Alzheimer's Disease, Cereb. Cortex 30 (4) (2019) 2083–2098, https://doi.org/10.1093/cercor/bhz224.
[24] H. Hampel, M.-M. Mesulam, A.C. Cuello, et al., The cholinergic system in the pathophysiology and treatment of Alzheimer's disease, Brain 141 (7) (2018) 1917–1933, https://doi.org/10.1093/brain/awy132.
[25] J.R. Lee, S.W. Suh, J.W. Han, et al., Anhedonia and dysphoria are differentially associated with the risk of dementia in the cognitively normal elderly individuals: a prospective cohort study, Psychiatry Investig. 16 (8) (2019) 575.
[26] M.M. Gonzales, J. Samra, A. O'Donnell, et al., Association of Midlife Depressive Symptoms with Regional Amyloid-β and Tau in the Framingham Heart Study, J. Alzheimers Dis. 82 (1) (2021) 249–260, https://doi.org/10.3233/jad-210232.
[27] G.M. Babulal, C.M. Roe, S.H. Stout, et al., Depression is Associated with Tau and Not Amyloid Positron Emission Tomography in Cognitively Normal Adults, J. Alzheimers Dis. 74 (4) (2020) 1045–1055, https://doi.org/10.3233/jad-191078.
[28] Z.T. Wang, X.N. Shen, Y.H. Ma, et al., Associations of the Rate of Change in Geriatric Depression Scale with Amyloid and Cerebral Glucose Metabolism in Cognitively Normal Older Adults: A Longitudinal Study, J. Affect Disord. 280 (Pt A) (2021) 77–84, https://doi.org/10.1016/j.jad.2020.10.078.
[29] S.T. Chen, P. Siddarth, N.Y. Saito, et al., Psychological well-being and regional brain amyloid and tau in mild cognitive impairment, Am. J. Geriatr. Psychiatry 22 (4) (2014) 362–369, https://doi.org/10.1016/j.jagp.2012.09.002.
[30] R. Ossenkoppele, D.R. Schonhaut, M. Schöll, et al., Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease, Brain 139 (5) (2016) 1551–1567, https://doi.org/10.1093/brain/aww027.
[31] A. Bejanin, D.R. Schonhaut, R. La Joie, et al., Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease, Brain 140 (12) (2017) 3286–3300, https://doi.org/10.1093/brain/awx243.
[32] G.S. Day, B.A. Gordon, K. Jackson, et al., Tau-PET Binding Distinguishes Patients With Early-stage Posterior Cortical Atrophy From Amnestic Alzheimer Disease Dementia, Alzheimer Dis. Assoc. Disord. 31 (2) (2017) 87–93, https://doi.org/10.1097/wad.0000000000000196.
[33] J.R. Gatchel, N.J. Donovan, J.J. Locascio, et al., Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: a pilot study, J. Alzheimer'S. Dis. 59 (3) (2017) 975–985.
[34] D. Talmasov, A.S. Johnson, P.J. Brown, et al., Depressive Symptoms Correlate With Tau Accumulation Rates in Amyloid Positive Adults, Am. J. Geriatr. Psychiatry (2025).
[35] J.S. Li, S.M. Tun, B. Ficek-Tani, et al., Medial amygdalar tau is Associated with Mood symptoms in preclinical Alzheimer's Disease, Biological Psychiatry Cognitive Neuroscience Neuroimaging 9 (12) (2024) 1301–1311.
[36] S. Kurose, S. Moriguchi, M. Kubota, et al., Diverse tau pathologies in late-life mood disorders revealed by PET and autopsy assays, Alzheimer's. Dement. 21 (6) (2025) e70195.
[37] T. Vande Casteele, M. Laroy, M. Van Cauwenberge, et al., Late life depression is not associated with Alzheimer-type tau: Preliminary evidence from a next-generation tau ligand PET-MR study, Am. J. Geriatr. Psychiatry 33 (1) (2025) 47–62.
[38] C. Tissot, J. Therriault, T.A. Pascoal, et al., Association between regional tau pathology and neuropsychiatric symptoms in aging and dementia due to Alzheimer's disease, Alzheimer's. Dement. Transl. Res. Clin. Interv. 7 (1) (2021) e12154.
[39] A. Leuzy, K. Chiotis, L. Lemoine, et al., Tau PET imaging in neurodegenerative tauopathies—still a challenge, Mol. Psychiatry 24 (8) (2019) 1112–1134, https://doi.org/10.1038/s41380-018-0342-8.
[40] I. Ozsahin, E.P. Onakpojeruo, B. Uzun, et al., A Multi-Criteria Decision Aid Tool for Radiopharmaceutical Selection in Tau PET Imaging, Pharmaceutics 15 (4) (2023), https://doi.org/10.3390/pharmaceutics15041304.
[41] D.L. Beekly, E.M. Ramos, W.W. Lee, et al., The National Alzheimer's Coordinating Center (NACC) Database: The Uniform Data Set, Alzheimer Dis. Assoc. Disord. 21 (3) (2007) 249–258, https://doi.org/10.1097/WAD.0b013e318142774e.
[42] A.T. Beck, R.A. Steer, G.K. Brown, Beck depression inventory-II, San. Antonio 78 (2) (1996) 490–498.
[43] M. Tahmi, W. Bou-Zeid, Q.R. Razlighi, A Fully Automatic Technique for Precise Localization and Quantification of Amyloid-β PET Scans, J. Nucl. Med. 60 (12) (2019) 1771–1779, https://doi.org/10.2967/jnumed.119.228510.
[44] S. Hani Hojjati, T.A. Butler, G.C. Chiang, et al., Distinct and joint effects of low and high levels of Aβ and tau deposition on cortical thickness, Neuroimage Clin. 38 (2023) 103409, https://doi.org/10.1016/j.nicl.2023.103409.
[45] J.P. Seibyl, J.M. DuBois, A. Racine, et al., A Visual Interpretation Algorithm for Assessing Brain Tauopathy with 18F-MK-6240 PET, J. Nucl. Med. 64 (3) (2023) 444–451, https://doi.org/10.2967/jnumed.122.264371.
[46] S. Minoshima, A.E. Drzezga, H. Barthel, et al., SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0, J. Nucl. Med. 57 (8) (2016) 1316–1322, https://doi.org/10.2967/jnumed.116.174615.
[47] M. Pievani, M. Bocchetta, M. Boccardi, et al., Striatal morphology in early-onset and late-onset Alzheimer's disease: a preliminary study, Neurobiol. Aging 34 (7) (2013) 1728–1739.
[48] X. Nie, Y. Sun, S. Wan, et al., Subregional structural alterations in hippocampus and nucleus accumbens correlate with the clinical impairment in patients with Alzheimer's disease clinical spectrum: parallel combining volume and vertex-based approach, Front. Neurol. 8 (2017) 399.
[49] L. Yu, M. Feng, Y. Shang, et al., Reduced Functional Connectivity in Nucleus Accumbens Subregions Associates With Cognitive Changes in Alzheimer's Disease, Brain Behav. 15 (3) (2025) e70440.
[50] P. Krashia, E. Spoleti, M. D'Amelio, The VTA dopaminergic system as diagnostic and therapeutical target for Alzheimer's disease, Front. Psychiatry 13 (2022) 1039725.
[51] E. Fernández-Pérez, S. Gallegos, L. Armijo-Weingart, et al., Changes in neuronal excitability and synaptic transmission in nucleus accumbens in a transgenic Alzheimer's disease mouse model, Sci. Rep. 10 (1) (2020) 19606.
[52] A.S. Johnson, G. Ziaggi, A.C. Smith, et al., Psychotic symptoms are associated with elevated tau PET signal in the amygdala independent of Alzheimer's disease clinical severity and amyloid burden, medRxiv (2024).
[53] J. Naude, M. Wang, R. Leon, et al., Tau-PET in early cortical Alzheimer brain regions in relation to mild behavioral impairment in older adults with either normal cognition or mild cognitive impairment, Neurobiol. Aging 138 (2024) 19–27.
[54] P.S. Eriksson, E. Perfilieva, T. Björk-Eriksson, et al., Neurogenesis in the adult human hippocampus, Nat. Med. 4 (11) (1998) 1313–1317, https://doi.org/10.1038/3305.
[55] S.S. Roeder, P. Burkardt, F. Rost, et al., Evidence for postnatal neurogenesis in the human amygdala, Commun. Biol. 5 (1) (2022) 366, https://doi.org/10.1038/s42003-022-03299-8.
[56] Y. Wang, E. Mandelkow, Tau in physiology and pathology, Nat. Rev. Neurosci. 17 (1) (2016) 22–35, https://doi.org/10.1038/nrn.2015.1.
[57] X.P. Hong, C.X. Peng, W. Wei, et al., Essential role of tau phosphorylation in adult hippocampal neurogenesis, Hippocampus 20 (12) (2010) 1339–1349, https://doi.org/10.1002/hipo.20712.
[58] Simard S., Matosin N., Mechawar N. Adult Hippocampal Neurogenesis in the Human Brain: Updates, Challenges, and Perspectives. The Neuroscientist 0(0): 10738584241252581, doi:10.1177/10738584241252581.
[59] N. Krishnadas, V. Doré, C. Groot, et al., Mesial temporal tau in amyloid-β-negative cognitively normal older persons, Alzheimer's. Res. Ther. 14 (1) (2022) 51.
[60] V.J. Lowe, T.J. Bruinsma, H.J. Wiste, et al., Cross-sectional associations of tau-PET signal with cognition in cognitively unimpaired adults, Neurology 93 (1) (2019) e29–e39.