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Original

Tau Accumulation and Dopamine Transporter Availability in Elderly Adults with Depression

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Background: Depression in later life is associated with dopaminergic dysfunction and increased risk of neurodegenerative disorders, although the relationship between dopamine transporter (DAT) availability and tau accumulation remains unclear. Although previous studies have linked tau and DAT in neurodegenerative diseases, evidence related to depression is limited. Therefore, this study used positron emission tomography (PET) to investigate the association between tau pathology and DAT availability in elderly adults with depression.

Methods: Six patients diagnosed with depression according to ICD-10 criteria underwent PET scans with PET radioligands that enable accurate in vivo assessment, namely, florzolotau (18F) for tau and [^{18}F]FE-PE2I for DAT. Clinical assessments using the Mini-Mental State Examination (MMSE) and Hamilton Depression Rating Scale (HAM-D) were performed for all patients. Tau standardized uptake value ratios (SUVR) in the striatal and cortical regions and DAT binding potentials (BP_{ND}) in the striatum were calculated.

Results: Tau SUVR in all regions was negatively correlated with DAT BP_{ND} in the striatum, suggesting that greater tau burden may be linked to dopaminergic dysfunction. Tau SUVR in the striatum was negatively correlated with MMSE, indicating that tau accumulation may be related to subtle cognitive decline. DAT BP_{ND} in the striatum was not correlated with HAM-D.

Conclusions: These preliminary results suggest a link between tau pathology and dopaminergic dysfunction in elderly adults with depression.

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Keywords: aged, depressive disorder, dopamine transporter, tau proteins, positron-emission tomography

Introduction

Depression is one of the most common psychiatric illnesses worldwide and can significantly impair quality of life. However, the pathophysiology of depression remains insufficiently understood. To date, the most widely supported theoretical framework is the monoamine hypothesis[1], which posits that disturbances in serotonin, norepinephrine, and dopamine neurotransmission are implicated in the pathogenesis of depression. Accumulating evidence has also highlighted the role of dopaminergic dysfunction in depression[2,3].

Using positron emission tomography (PET), our research group previously found that elderly adults with depression had reduced dopamine transporter (DAT)

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binding in the striatum, particularly in the nucleus accumbens, which may be related to reward system dysfunction[4]. In fact, symptoms such as anhedonia and apathy, which are linked to reward system dysfunction, are frequently observed in older adults with depression[5], and numerous studies have documented impaired reward processing in depression[2,6,7]. Furthermore, age 60 years is a threshold at which the incidence of neurodegenerative diseases such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB) increases[8,9]. Such conditions are characterized by degeneration of the nigrostriatal system, and reduced striatal DAT binding is a neuroimaging hallmark[10]. In addition, depressive symptoms often precede cognitive and motor manifestations in prodromal stages of PD and DLB[11–13]. Such depressive symptoms in elderly adults may reflect underlying dopaminergic dysfunction, consistent with our prior findings of reduced DAT binding in the nucleus accumbens of elderly adults with depression[4].

Depression is associated with an increased risk of dementia[14–16], and up to 30% of elderly adults with dementia are also diagnosed with psychiatric disorders, most commonly depression[15]. This suggests a potential overlap of neuropathological mechanisms between depression and neurodegenerative diseases. One potential mechanism is tau accumulation in the brain. Using PET imaging, Moriguchi et al.[17] and Kurose et al.[18] reported greater cortical tau accumulation in elderly adults with depression than in healthy controls. These findings suggest that tau pathology is likely responsible for neuronal dysfunction in neurodegenerative diseases and may be important in the pathophysiology of late-life depression.

Regarding the relationship between tau pathology and dopaminergic dysfunction, a study of four-repeat tauopathies found that tau accumulation was associated with dopaminergic dysfunction. A study using PET with [^{18}F] PI-2620 for tau imaging and dopamine transporter single-photon emission computed tomography (DAT SPECT) with [^{123}I]-ioflupane reported a negative correlation between tau deposition and DAT binding in basal ganglia[19].

As demonstrated in the aforementioned studies, PET is a powerful, noninvasive tool for visualizing neurotransmitter systems and pathological protein aggregates in the brain. The development of radioligands that selectively target DAT and tau pathology has enabled detailed depression-related molecular imaging analyses. In this study, we used [^{18}F]FE-PE2I and florzolotau (18F) to assess DAT and tau aggregates, respectively. [^{18}F]FE-PE2I is a PET radioligand with high affinity and selectivity for DAT[20,21], making it one of the most suitable radioligands for DAT quantification in humans[22–24]. Its favorable binding properties also allow reliable quantification of DAT not only in the neostriatum but also in smaller regions[25] such as the nucleus accumbens. Accordingly, DAT was assessed in the caudate, putamen, globus pallidus, and nucleus accumbens, regions that are known to exhibit high DAT density[20] and have been commonly evaluated in previous PET studies of the dopaminergic system[25]. Florzolotau (18F) has been reported to detect diverse tau pathologies with high specificity, including not only Alzheimer's disease but also four-repeat tauopathies such as progressive supranuclear palsy and corticobasal degeneration[26,27].

Although previous studies focused on the relationship between tau accumulation and reduced DAT availability in neurodegenerative diseases[19], no study to date has examined this relationship in adults with depression. Therefore, the extent to which these processes contribute to the pathophysiology of depression remains unclear. Using PET imaging to assess both factors in the same individuals, we explored whether tau accumulation is associated with decreased DAT availability in elderly adults with depression.

Materials and Methods

Participants

Six patients (three men and three women; age range, 66-84 years; mean age ± SD, 77.3 ± 7.2 years) who had been diagnosed as having single-episode (F32) or recurrent (F33) depression according to the ICD-10 criteria of the Department of Neuropsychiatry, Nippon Medical School Hospital, were recruited. The patients' depressive symptoms were evaluated by psychiatrists using the 17-item Hamilton Rating Scale for Depression (HAM-D) at the time of DAT PET scanning, and their cognitive functions were assessed by the Mini-Mental State Examination (MMSE). Clinical observations and medical history reviews during outpatient visits showed that none of the patients exhibited any notable physical disease. Exclusion criteria were: (i) treatment with medications with obvious affinity to DAT, such as sertraline, bupropion, and methylphenidate; (ii) presence of dementia or other neurodegenerative disease, obvious brain injury, or substance use disorder. For clinical reasons, all patients were receiving medical treatment for depression at the time of PET scanning. Patient demographics, clinical assessments, and medication details are summarized in **Table 1**.

Table 1 Patient demographic characteristics, clinical assessments, and medications

No	Sex	Age	Diagnosis	Age at first episode	Number of episodes	Total disease duration (months)	Tau			DAT		
							Date	MMSE	Drug	Date	HAM-D	Drug
1	M	65	F33	57	3	20	2021-03-18	30	MIA 30 mg, FLU 2 mg, LEM 10 mg	2022-12-01	12	FLU 2 mg, LEM 10 mg
2	F	78	F33	55	3	Over 240	2021-06-24	29	NOR 75 mg, Li 600 mg, LRZ 3 mg	2022-01-27	20	NOR 75 mg, Li 600 mg, LRZ 2 mg
3	M	77	F32	63	1	6	2021-08-12	30	ZPD 5 mg, FLU 2 mg, ETZ 1 mg	2022-11-17	5	ZPD 5 mg, FLU 2 mg, ETZ 1 mg
4	F	81	F32	66	1	6	2022-03-10	26	DLX 60 mg, MIR 45 mg, ARI 3 mg, EST 2 mg	2023-03-09	10	DLX 40 mg, MIR 45 mg, ARI 3 mg, LEM 5 mg,
5	M	64	F32	63	1	18	2022-09-22	28	VTX 100 mg	2023-03-23	10	VEN 225 mg, ARI 1 mg
6	F	82	F33	75	3	19	2024-04-25	29	MIR 15 mg, VEN 150 mg	2023-03-09	23	MIR 30 mg, VEN 37.5 mg, LEM 5 mg, BRZ 6 mg

"Over 240" indicates a disease duration longer than 20 years, based on clinical records.
MMSE = Mini-Mental State Examination; HAM-D = Hamilton Depression Rating Scale; DAT = dopamine transporter; MIA = mianserin; FLU = flunitrazepam; LEM = lemborexant; NOR = nortriptyline; Li = lithium; LRZ = lorazepam; ZPD = zolpidem; ETZ = etizolam; DLX = duloxetine; MIR = mirtazapine; ARI = aripiprazole; EST = estazolam; VTX = vortioxetine; VEN = venlafaxine; BRZ = bromazepam.

MRI Procedures

All MRI scans were performed at the Clinical Imaging Center for Healthcare, Nippon Medical School, Tokyo, Japan, and were conducted before PET scanning at the same facility on the same day. MRI acquisition of the brain was performed for all patients with a 1.5-Tesla MRI system (Intera 1.5T Achieva Nova; Philips Medical Systems, Best, Netherlands). T1-weighted MR images were acquired at 1-mm slices to determine anatomical brain structure, and T2-weighted MR images were acquired to rule out any pathology.

PET Procedures

PET scans for DAT and tau imaging were performed on separate days. The procedures for each radioligand are described separately below.

Imaging with [^{18}F]FE-PE2I for Dopamine Transporter

[^{18}F]FE-PE2I, a radioligand targeting DAT, was synthesized according to a previously published method[20]. PET scans were acquired using an Eminence SET3000GCT-X scanner (Shimadzu Corp., Kyoto, Japan). All patients were placed in a supine position in the scanner with head fixation devices to minimize movement. After a bolus injection of [^{18}F]FE-PE2I into an antecubital vein, a 60-minute dynamic PET scan was conducted. The injected radioactivity was 185.63 ± 6.86 MBq, and the specific radioactivity was 862.55 ± 399.39 GBq/μmol.

Imaging with Florzolotau (18F) for Tau Deposition

Florzolotau (18F), a radioligand targeting tau aggregates, was synthesized according to a previously published method[28]. PET scans were acquired using a Biograph Vision scanner (Siemens Healthineers, Erlangen, Germany). After a bolus injection of florzolotau (18F) under dimly lit conditions to avoid photoracemization, a 20-minute static PET scan was conducted during a 90- to 110-minute interval. The injected radioactivity was 193.73 ± 7.06 MBq, and the specific radioactivity was 524.59 ± 110.57 GBq/μmol.

Data Analysis

For each participant, regions of interest (ROIs) were drawn automatically by FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) on T1-weighted MR images. ROIs were defined for the striatum (caudate and putamen), four cortical regions (frontal, temporal, parietal, and occipital cortices), and the cerebellar cortex. Left and right ROIs were combined. PET images acquired with [^{18}F]FE-PE2I and florzolotau (18F) were co-registered onto the T1-

Table 2 SUVR, BP_{ND}, and correlations across the striatum and cortical ROIs

	Striatum	Frontal cortex	Temporal cortex	Parietal cortex	Occipital cortex
Tau SUVR	0.86 ± 0.15	0.87 ± 0.19	1.03 ± 0.23	0.88 ± 0.12	0.94 ± 0.10
DAT BP_{ND}	1.58 ± 0.17				
r (p) (SUVR–BP_{ND})	–0.84 (0.04)	–0.83 (0.04)	–0.85 (0.03)	–0.73 (0.10)	–0.73 (0.10)
r (p) (SUVR–MMSE)	–0.59 (0.22)	–0.28 (0.59)	–0.12 (0.82)	–0.28 (0.59)	–0.41 (0.42)
r (p) (BP_{ND}–HAM-D)	0.38 (0.46)				

Depression Rating Scale. Data are means ± standard deviation.
SUVR = standardized uptake value ratio; BP_{ND} = binding potential; MMSE = Mini-Mental State Examination; HAM-D = Hamilton.

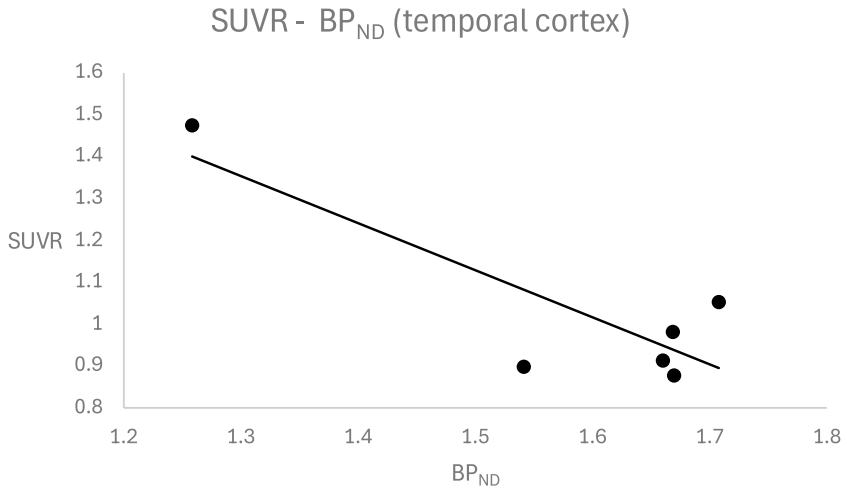

Figure 1 Scatter plot showing the negative correlation between tau SUVR and DAT BP_{ND} in the temporal cortex (r = –0.85, p = 0.03)

weighted MRI images by using PMOD (Version 4.1; PMOD Technologies Ltd., Zurich, Switzerland). Binding potentials (BP_{ND}) for [^{18}F]FE-PE2I in the striatum were calculated using the simplified reference tissue model with the cerebellum as reference region. Standardized uptake value ratios (SUVR) for florzolotau (18F) in the striatum and the four cortical regions were calculated by dividing each ROI SUV by the cerebellar SUV.

Statistical Analysis

Pearson's correlation coefficient was used to evaluate the relationships between tau SUVR in each ROI and DAT BP_{ND} in the striatum, tau SUVR and MMSE, and DAT BP_{ND} and HAM-D. Correlation strength was interpreted according to Cohen's guidelines, which describe Pearson's r values of approximately 0.10, 0.30, and 0.50 as small, medium, and large, respectively[29]. In this study, correlations with $r > 0.50$ or $r < -0.50$ were interpreted as strong, and statistical significance was defined as a p value of <0.05.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Nippon Medical School Hospital (approval No. IRB20170525). All participants provided written informed consent prior to participation. Consent for publication is not applicable.

Results

The DAT BP_{ND} and tau SUVR values for the six patients with depression are summarized in **Table 2**.

Correlation between Tau SUVR and DAT BP_{ND}

Tau SUVR in all regions was negatively correlated ($r < -0.50$) with DAT BP_{ND} in the striatum, and the correlation was significant for several cortical regions (**Table 2**). The correlation coefficients are summarized in **Table 2**, and the trendline for the temporal cortex is shown in **Figure 1** as an example.

Correlation between Tau SUVR and MMSE

Tau SUVR in the striatum was negatively correlated ($r < -0.50$) with MMSE, but the correlation was not signifi-

cant (**Table 2**).

Correlation between DAT BP_{ND} and HAM-D

No significant correlation was observed between DAT BP_{ND} in the striatum and HAM-D (**Table 2**).

Discussion

This is the first study to use tau PET with florzolotau (18F) and DAT PET with [^{18}F]FE-PE2I to investigate the relationship between tau accumulation and DAT availability in elderly adults with depression. A main finding of this study was the negative correlation ($r < -0.50$) between tau SUVR in the four cortical regions and DAT BP_{ND} in the striatum. Although the precise mechanisms remain unclear, this association may partially explain why depressive symptoms and apathy are frequently observed in neurodegenerative disorders such as Alzheimer's disease. Moriya et al.[4] reported reduced DAT availability in the nucleus accumbens of elderly adults with depression, implicating reward system dysfunction in anhedonia and apathy. In addition, Moriguchi et al.[17] and Kurose et al.[18] found greater cortical tau accumulation in elderly adults with depression than in healthy controls. Taken together, past and present findings suggest that the overlap of tau accumulation and dopaminergic dysfunction could contribute to mood and motivational disturbances in late-life depression. Additionally, we observed a negative correlation ($r < -0.50$) between tau SUVR and DAT BP_{ND} in the striatum, which is consistent with the findings of Ferschmann et al.[19], who demonstrated a similar association in patients with four-repeat tauopathies. Our finding extends this evidence to elderly adults with depression, suggesting that similar pathophysiological mechanisms may be involved in depression.

A negative correlation ($r < -0.50$) was observed between tau SUVR in the striatum and MMSE scores, suggesting an association between tau accumulation and cognitive decline. This finding implies that tau pathology may contribute to cognitive changes even in elderly patients with depression. Although our results suggest a potential link between tau accumulation in the striatum and cognitive changes, the MMSE scores of all participants in this study were higher than 26, indicating no obvious cognitive impairment. Thus, the observed negative correlation may reflect mild cognitive fluctuations consistent with early-stage decline, such as those seen in mild cognitive impairment, rather than dementia-level symptoms. Since MMSE is a general screening tool and may not detect such subtle changes, this limitation should be considered when interpreting the present findings, and future studies should incorporate neuropsychological tests targeting specific domains such as attention, executive function, and episodic memory.

No correlation was observed between DAT BP_{ND} in the striatum and HAM-D, although previous studies have reported inconsistent findings regarding this association. While not directly comparable to our findings based on HAM-D scores, Moriya et al.[4] reported a positive correlation of DAT BP_{ND} in the nucleus accumbens with the number of depressive episodes and illness duration in patients with depression. In contrast, other studies reported a negative correlation between DAT BP_{ND} and number of depressive episodes in the putamen[30]. These discrepancies may reflect differences in factors such as participant age, depression severity, illness duration, medication effects, and methodological variations, including radioligands and ROI settings[4]. In addition, HAM-D primarily reflects the severity of current depressive symptoms, whereas DAT availability may represent longer-term neurobiological alterations. This difference in temporal characteristics between clinical symptom ratings and dopaminergic measures may partly explain the absence of a significant correlation in the present cohort. Given the small sample size and cross-sectional design of the present study, drawing definitive conclusions about the relationship between DAT BP_{ND} and depressive symptoms remains a challenge.

Taken together, the observed association between increased tau accumulation, reduced DAT availability, and lower cognitive performance may indicate that dopaminergic dysfunction and tau pathology jointly affect the neural circuits underlying depressive symptoms in late life.

This study has several limitations. First, the interval between PET imaging with [^{18}F]FE-PE2I and florzolotau (18F) ranged from 182 to 623 days, during which interval changes in clinical status or brain pathology may have occurred. In particular, DAT is known to gradually decline with age, with previous PET studies using [^{18}F]FE-PE2I reporting reductions of approximately 7.6% per decade in the caudate and 7.7% in the putamen[23]. These estimates indicate that the expected change in DAT availability over an interval of up to 2 years would be modest, suggesting that the impact of the scan interval on the present results is likely limited. However, differences in scan timing may have influenced DAT measurements, potentially affecting the observed correlations. To im-

prove the accuracy and interpretability of such analyses, future studies should aim to minimize the interval between PET scans.

Second, some participants in this study were taking antidepressants or antipsychotics, which may have influenced DAT availability and tau accumulation. Previous studies have shown that antidepressants and antipsychotics may increase, decrease, or have no effect on DAT availability[31–37], making the results inconsistent. Likewise, the present study cannot rule out the possibility that medication affected DAT availability. Moriguchi et al.[17] did not arrive at definitive conclusions regarding the impact of antidepressants on tau pathology in elderly depression. Moreover, previous research has reported that citalopram may affect amyloid-β (Aβ) metabolism, raising the possibility that such mechanisms might also influence tau accumulation indirectly[38,39]. The present study did not assess the effects of individual medications, making it difficult to determine their influence on tau accumulation and DAT availability. However, the pharmacological profiles of the medications used in the present cohort suggest that serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine primarily inhibit serotonin and noradrenaline reuptake and generally exhibit low affinity for DAT, suggesting that their direct effects on DAT availability are likely limited. Similarly, antipsychotics such as aripiprazole mainly exert their effects through dopamine receptor modulation rather than by direct interaction with DAT. Regarding tau pathology, the effects of antidepressants and antipsychotics remain unclear, and thus the potential influence of pharmacological treatment cannot be completely excluded. Data from experimental and preclinical studies suggest that some antidepressants may modulate tau-related pathways; however, clinical evidence remains limited[40].

Third, the sample size was small (n = 6), limiting the generalizability of the findings. However, despite the small sample size, the observed cortical SUVR values were in a range similar to those reported by Kurose et al.[18], who also used florzolotau (18F) in elderly patients with depression, supporting the validity of our PET findings. Larger-scale studies will be necessary to confirm the observed correlations.

Fourth, the present study did not include a healthy control group. Because this study examined the correlation between DAT availability and tau accumulation in the same individuals, it is difficult to draw conclusions about potential reductions in DAT availability or increases in tau accumulation based on comparisons with healthy controls, and the present findings should instead be interpreted in terms of relative differences within the cohort.

Conclusion

This study demonstrated a negative correlation between tau accumulation and DAT availability in elderly adults with depression. These findings suggest that tau pathology may be associated with dopaminergic dysfunction and may contribute to the underlying pathophysiology of late-life depression.

Author Contributions: R.A. and A.T. designed the study and wrote the study protocol. S.U., T.O., T.S., and T.N. contributed to data acquisition and clinical evaluation. S.U. and R.A. performed the data analysis. S.U. drafted the initial manuscript. R.A., A.T., and M.H. critically revised the manuscript for important intellectual content. All authors contributed to and approved the final version of the manuscript.

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Conflict of Interest: Makoto Higuchi holds patents on compounds related to the present report (JP 5422782/EP 12884742.3/CA2894994/HK1208672).

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: Generative AI and AI-assisted technologies (ChatGPT) were used for language editing and improvement of clarity during manuscript preparation.

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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