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Differentiating Treatment-Resistant Depression With and Without Parkinsonism in the Elderly From a Psychiatric Perspective by ^{99m}Tc-TRODAT-1 SPECT Imaging

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ABSTRACT

Objectives: Late-life depression often overlaps with neurodegenerative diseases leading to diagnostic and treatment challenges for neuropsychiatrists. This study aimed to differentiate elderly treatment-resistant depression (TRD) comorbid with parkinsonism from elderly TRD without Parkinsonism as well as elderly healthy controls using striatum dopamine transporter (DAT) imaging by ^{99m}Tc TRODAT-1 SPECT.

Methods: Three groups were enrolled, including patients with TRD, patients with TRD comorbid with parkinsonism, and healthy controls. To obtain the DAT availability, the specific uptake ratios of the bilateral striatum were evaluated. Linear regression analyses were performed to evaluate the relationship between age and DAT level in the subregions of the striatum. Machine learning was applied to categorize the three groups with 10-fold cross-validation.

Results: The study enrolled 32 patients with TRD (66.15 ± 6.82), 36 TRD patients with parkinsonism (70.27 ± 5.63), and 74 healthy elderly (66.95 ± 10.59). A normative DAT concentration by age was established, providing a reference for clinical use. DAT levels differed among groups (all pairwise $p < 0.01$), with healthy controls exhibiting the highest levels, followed by patients with TRD, and then TRD patients with parkinsonism. Further, the Fine k-NN classifier emerged as the top performer to achieve 85.7% accuracy.

Conclusions: Besides clinical assessment, dopaminergic assessment may help differentiate parkinsonism from TRD in old age. The findings of lower DAT availability in TRD suggest that TRD may be a prodromal symptom of Parkinson's disease. Psychiatrists should consider comorbid neurodegenerative disorders in elderly, depressed patients and use clinical assessment, neurological examination, and brain imaging for early Parkinson's Disease screening.

1 | Introduction

Late-life depression (LLD) is the second most common psychiatric disorder with high comorbidity and mortality [1]. It is characterized by its chronic course, with frequent relapses and recurrences. Global prevalence of LLD ranged from 12.9% to 35.1% estimated from different meta-analyses [2, 3]. Nearly one-third subpopulation of LLD meets for late-life treatment-

The first two authors contributed equally to this article.

Summary

- Depression may be a prodromal symptom of Parkinson's disease.
- A dataset of normative DAT availability, obtained using ^{99m}Tc-TRODAT-1 SPECT by age, was established for the elderly.
- The combination of age and dopaminergic assessment may differentiate parkinsonism from treatment-resistant depression.

resistant depression (TRD), defined as failure to respond to two or more adequate trials of antidepressant treatment [4]. Among multifactorial elements to account for the etiologies of LLD, the aging process is the imperative effect, which is often associated with neurodegenerative diseases such as Alzheimer's disease (AD), and Parkinson's disease (PD). Besides increased oxidative stress, neuroinflammatory events, and impaired neurotrophic support, over the past decades, neuroimaging findings have helped elucidate the structural and functional changes implicated in the relationship between depression and neurodegeneration, thus establishing a neuroanatomical signature to explain the comorbidity among LLD, AD, and PD [3] is very important.

Parkinson's disease is the second most common neurodegenerative disorder in aging and the most common movement disorder due to the loss of dopamine in the striatum [5, 6]. The diagnosis of PD is based on clinical criteria, such as tremor at rest, akinesia, rigidity, and postural instability. However, the motor phase of classical PD may take several years of prodromal period to appear. Those non-motor symptoms also occur during the progression of PD and significantly impact the quality of life [7]. Previous reports depicted Braak staging for Lewy body pathology in sporadic PD [8]. In that, the prodromal non-motor symptom phase (stages 1 and 2) had started 20 years before motor PD. A few non-motor symptoms of PD are highly similar to the criteria of depression, which may be attributed to decreased dopamine release in the brain [3] and early limbic microstructural alterations [9, 10]. Thus, there is a high degree of overlap between LLD and PD [11–16], posing a challenge for psychiatrists and neurologists in diagnosis and treatment. Will that be a misdiagnosis, leading to delayed provision of appropriate treatment?

Given that parkinsonism in Parkinson's disease (PD) emerges when > 50% of the striatal dopamine terminals are lost [17], DAT imaging is well suited to detect the motor and even the premotor/preclinical phases of this disease. Indeed, two major radiotracers for imaging the DAT, namely ^{18}F-FP-CIT and ^{123}I-FP-CIT, have provided viable biomarkers for early PD diagnosis [18], but these radiotracers are not available in Taiwan. However, the available ^{99m}Tc-TRODAT-1 Single Photon Emission Computed Tomography (SPECT) tool is a valuable alternative for evaluation of the DAT availability in the striatum. Its application extends beyond the detection of dopaminergic neurodegeneration for PD diagnosis [19], and may facilitate the identification of the prodromal phase of PD, which occurs many years before motor signs appear. PD screening by TRODAT imaging relies on radiologists' experience [19–21]. To establish a normative reference for the population, we created a TRODAT-SPECT imaging dataset for a cohort of healthy elderly aged between 50 and 95 years in this study. Second, we recruited elderly patients with TRD with/without parkinsonism to investigate the difference in dopamine levels in these patients, trying to separate the TRD patients with parkinsonism from patients with TRD. Finally, based on the power of efficient exploration and pattern discovery of machine learning, we also applied machine learning techniques to categorize the subjects of healthy elderly, patients with late-life TRD, and patients with TRD comorbid with parkinsonism.

2 | Materials and Methods

2.1 | Participants

The participating patients were assessed at the outpatient clinic of the Department of Psychiatry of Cheng-Hsin General Hospital in Taiwan. Sixty-eight patients with age over 50 years were recruited to meet the criteria of DSM-5 depression, which includes major depressive disorder, chronic dysthymia, and bipolar depression. Cases of severe physical diseases or substance/alcohol abuse, or using antipsychotic medications were excluded. Their Montgomery-Asberg Depression Rating Scale (MADRS) score was above mild degree ($\geq$ 12) and the average score was around 24–28 (Table 1). Meanwhile, all the study subjects took the Mini-Mental State Examination (MMSE) for cognitive evaluation. Further, to label treatment-resistant depression (TRD), their depression should not respond (reduction of depression less than 50% from baseline) to at least 2 antidepressants for more than 4 weeks. An eight-item version of the Unified Parkinson's Disease Rating Scale (UPDRS-8), which demonstrates a significant correlation with the complete UPDRS [22], was used to assess participants for Parkinson's disease. All cases with positive UPDRS-8 scores were referred to a board-certified neurologist to rule out the diagnosis of classical Parkinson's disease (who met the Triad criteria), drug-induced secondary parkinsonism, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and essential tremor. Patients with mild wrist rigidity, cogwheel rigidity in the elbows, slow movements, or a mask-like facial expression were included. All included patients were diagnosed with parkinsonism (PsD) and had a mean UPDRS-8 score of 9.56 $\pm$ 3.18 (Table 1). Finally, 32 patients with TRD (23 females, mean age 66.15 $\pm$ 6.82 years) and 36 TRD patients with parkinsonism (PsD, 22 females, mean age 70.27 $\pm$ 5.63 years) were enrolled in this study. Besides clinical history taking, mood rating, UPDRS-8 scoring, and neurologist confirmation, patients were required to undergo measurement of the striatum dopamine transporter (DAT) level in the brain using ^{99m}Tc-TRODAT-1 SPECT imaging. This procedure was also performed in the healthy control elderly from 50 to 95 years with around 10 subjects of nearly even gender for each 5-year level. Seventy-four elderly participants without a history of neurological and psychiatric diseases (HC, 34 males, mean age 66.95 $\pm$ 10.59) were recruited as the control group. The ethics committee of the Institutional Review Board of the Cheng Hsin General Hospital approved this study.

TABLE 1 | Demographic, clinical, and asymmetry index data by group.

		TRD comorbid with parkinsonism (PsD) ($N = 36$)	Treatment resistant depression (TRD) ($N = 32$)	Healthy control (HC) ($N = 74$)
Sex	M/F	14/22	23/9	34/40
Age	Years	70.27 ± 5.63	66.15 ± 6.82	66.95 ± 10.59
	(Mean ± SD)			
	Range	52.42–81.67	48.73–77.32	48.64–93.14
Onset age	—	62.19 ± 11.83†	55.94 ± 13.51	—
Range	Years	33–78	28–76	—
> 60	Cases (%)	24 (67)	16 (50)	—
[50–60]	Cases (%)	6 (16.5)	8 (25)	—
< 50	Cases (%)	6 (16.5)	8 (25)	—
Length of illness	year	7.54 ± 8.01	7.98 ± 8.38	—
UPDRS-8	—	9.56 ± 3.18††	2.72 ± 0.52	—
MADRS	—	24.06 ± 8.02†	28.06 ± 6.92	—
TDQ	—	—	—	3.48 ± 5.44
MMSE	—	25.50 ± 1.61**,†	26.56 ± 1.39**	28.22 ± 1.12
Antidepressant medications (percentage distribution between two TRD group patients: n.s.)				
SSRIs	%	36.3	40.4	
SNRIs	%	9.3	0	
NDRI	%	15.9	9.5	
CNS Stimulant	%	13.6	33.4	
Dopaminergic agent	%	4.5	16.7	
Agomelantine	%	13.6	7.1	
Antipsychotics	%	6.8	9.6	
Asymmetry index				
Striatum	% (mean ± SD)	16.58 ± 15.60**	12.95 ± 8.94*	7.33 ± 6.14
Putamen		16.55 ± 14.95**	13.31 ± 10.05*	7.64 ± 6.55
Caudate nucleus		14.64 ± 15.26	19.15 ± 23.22	11.30 ± 11.02

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini Mental Status Examination; NDRI, Norepinephrine Dopamine Reuptake Inhibitor; n.s., non-significance, using pair-t test for comparison percentage distributions of the two TRD group patients; SNRI, Selective Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TDQ, Taiwanese Depression Questionnaire; UPDRS-8, Unified Parkinson's Disease Rating Scale, a brief clinical assessment scale for Parkinson's disease (Hauser, Lyons et al. 2012).
**compared to HC, $p < 0.01$.
*compared to HC, $p < 0.05$.
††compared to TRD, $p < 0.01$.
†compared to TRD, $p < 0.05$.

2.2 | SPECT Imaging and Analysis

TRD participants with and without parkinsonism were off antidepressant medications 24 h before SPECT scanning. Brain SPECT imaging was performed 4 h after the intravenous injection of 740 MBq (20 mCi) of ^{99m}Tc –TRODAT-1 [23]. The detailed of radiopharmaceutical preparation are provided in the Supplementary materials. SPECT imaging was conducted using a dual-head camera equipped with a low-energy-high-resolution collimator (Bright View XCT, Philip, Netherlands). Data were acquired in a 128 × 128 matrix with a 2.19 zoom through a 360° rotation (180° for each head) at 3° intervals for 30 s per angle step. Images were reconstructed using a standard iterative (Astonish) method with a Hanning filter. Automatic semi-quantification of striatal dopamine transporter activity was conducted using a developed analytic package (Q striatum) [20]. In brief, the reconstructed SPECT images were spatially resampled to obtain 1 mm^3-thick slices. Four regions of interest (ROIs) with fixed dimensions were then set corresponding to the left and right caudate nucleus and putamen (striatum). Finally, the mean value of counts in each ROI was calculated to obtain the specific uptake ratio (SUR), which value was defined as dopamine transporter activity. An anatomical parcellation of the spatially normalized single-subject high-resolution T1 volume provided by the Montreal Neurological Institute (MNI) was employed as a normal template for setting ROI on the striatum

[24]. After whole-brain scaling and warping of the normal template set, the warped ROIs are mapped to the striatum on the SPECT images. The SPECT images were then resampled to a 1-mm^3 isotropic resolution (image size of 256 × 256 × 256 voxels), and the ROIs for the left and right caudate nucleus and putamen (striatum) and the whole brain without the striatum were automatically defined for each subject. The striatal SUR was described as:

$$\mathrm{SUR} = \frac{\mathrm{ROI}_{Target} - \mathrm{DAT}_{Reference}}{\mathrm{DAT}_{Reference}}$$

where ROI_{Target} was the mean activity concentration in the striatal region (caudate nucleus and putamen) and $\mathrm{DAT}_{Reference}$ was the mean value of the voxels with the 75th percentile activity concentration of the whole brain excluding the striatum to reduce the influence of brain atrophy and infarction as well as statistical noise associated with the estimation of non-striatal uptake [20]. The percentage of the asymmetry index was calculated as:

$$\text{Asymmetry index} = \left|\frac{SUR_{right} - SUR_{left}}{SUR_{right} + SUR_{left}}\right| \times 2 \times 100$$

where SUR_{right} and SUR_{left} are the average value of the ROI striatum on the right and left sides, respectively. Asymmetry was considered to be an absolute value [20].

2.3 | Conventional Statistical Analysis

One-way ANOVA and two-sample *t*-tests were employed to compare demographic characteristics, SUR scores, and asymmetry index among three groups and two patient groups, respectively. Bonferroni post hoc tests were conducted to identify pairwise differences. The Shapiro-Wilk test was used to assess the normality of SUR scores and clinical response. Statistical analyses were conducted using SPSS 23 (IBM Corp., Armonk, NY; Version 23).

We employed a two-step approach to identify the potential inflection point in age-related dopamine transporter availability decline. First, we performed a linear regression analysis on the entire dataset (age 50–95). Second, we applied a piecewise linear model to explore different linear trends and breakpoints.

2.4 | Machine Learning

2.4.1 | Data Preparation

The features consisted of the age and SUR scores at the bilateral striatum, caudate nucleus, and putamen. Z-transformation was applied to reduce the scale discrepancies between the age and SUR scores. The dataset was divided into two subsets using a 90%–10% split, with 128 participants allocated for training and 14 for testing. Data augmentation was employed to address issues of small sample size and imbalanced data, expanding the training set to around 320 instances for each of the PsD, TRD, and HC groups through the application of an anti-aliasing FIR filter with 5 neighbor terms and a Kaiser window with a value of 0.8 [25].

2.5 | Classification Model

A total of 24 machine learning models were applied for three-class classification. The classifiers include types of decision tree (DT), discriminant analysis (DA), naive Bayes, k-nearest neighbor (k-NN), support vector machines (SVM), and neural network (NN). All models were implemented using the MATLAB Classification Learners App [26]. To further validate the contribution of age, we performed an ablation experiment using the image features with/without age. The detailed parameters for each model are provided in the Supplementary materials. Default classifier parameters and the 10-fold cross-validation were applied to evaluate the performance of various classifiers. Classification performance was assessed based on accuracy, precision, sensitivity, specificity, F1-score, and the area-under-curve of the receiver operating characteristic curve (AUROC).

3 | Results

3.1 | Demographic Characteristics and SUR Scores

Table 1 presents the demographic characteristics of the three groups. The mean ages of the PsD, TRD, and HC groups were 70.3, 66.2, and 67.0 years ($F_{(2,139)} = 2.29$, $p = 0.10$), respectively. Patients with TRD exhibited more severe depression symptoms ($t_{(66)} = -2.19$, $p < 0.05$) and had an earlier onset of depression than those with PsD ($t_{(66)} = 2.04$, $p < 0.05$), while PsD patients had significantly greater UPDRS-8 score than the TRD patients ($t_{(37.1)} = 12.69$, $p < 0.01$). Cognitive function by MMSE ($F_{(2,139)} = 55.63$, $p < 0.01$) revealed slightly lower scores in the PsD and TRD patients than healthy controls ($p < 0.01$) and lower scores seen in PsD than in TRD patients ($p < 0.01$), suggesting mild cognitive dysfunction in PsD and TRD patients, albeit the differences are small. However, there were no significant differences in age and gender among the three groups. Of note was no significant difference in the percentage distribution of antidepressant medications use between PsD and TRD patients (Table 1).

Significant group effects were observed for SUR scores in both left and right striatum ($F_{(2,139)} = 53.75/62.34$, $p < 0.01$), caudate nucleus ($F_{(2,139)} = 46.72/49.17$, $p < 0.01$), and putamen ($F_{(2,139)} = 50.02/60.53$, $p < 0.01$). Bonferroni post-hoc tests revealed significant differences among all groups ($p < 0.01$). Patients with PsD had the lowest scores in all regions compared to both TRD and control groups. Similarly, patients with TRD had significantly lower SUR scores than controls in all regions, as shown in Figure 1.

Additionally, ANOVA revealed significant differences in the asymmetry indices of the striatum ($F_{(2,139)} = 10.80$, $p < 0.01$), putamen ($F_{(2,139)} = 10.11$, $p < 0.01$), and caudate nucleus ($F_{(2,139)} = 2.89$, $p = 0.05$), among the three groups. The highest absolute value was observed in PsD groups followed by the TRD

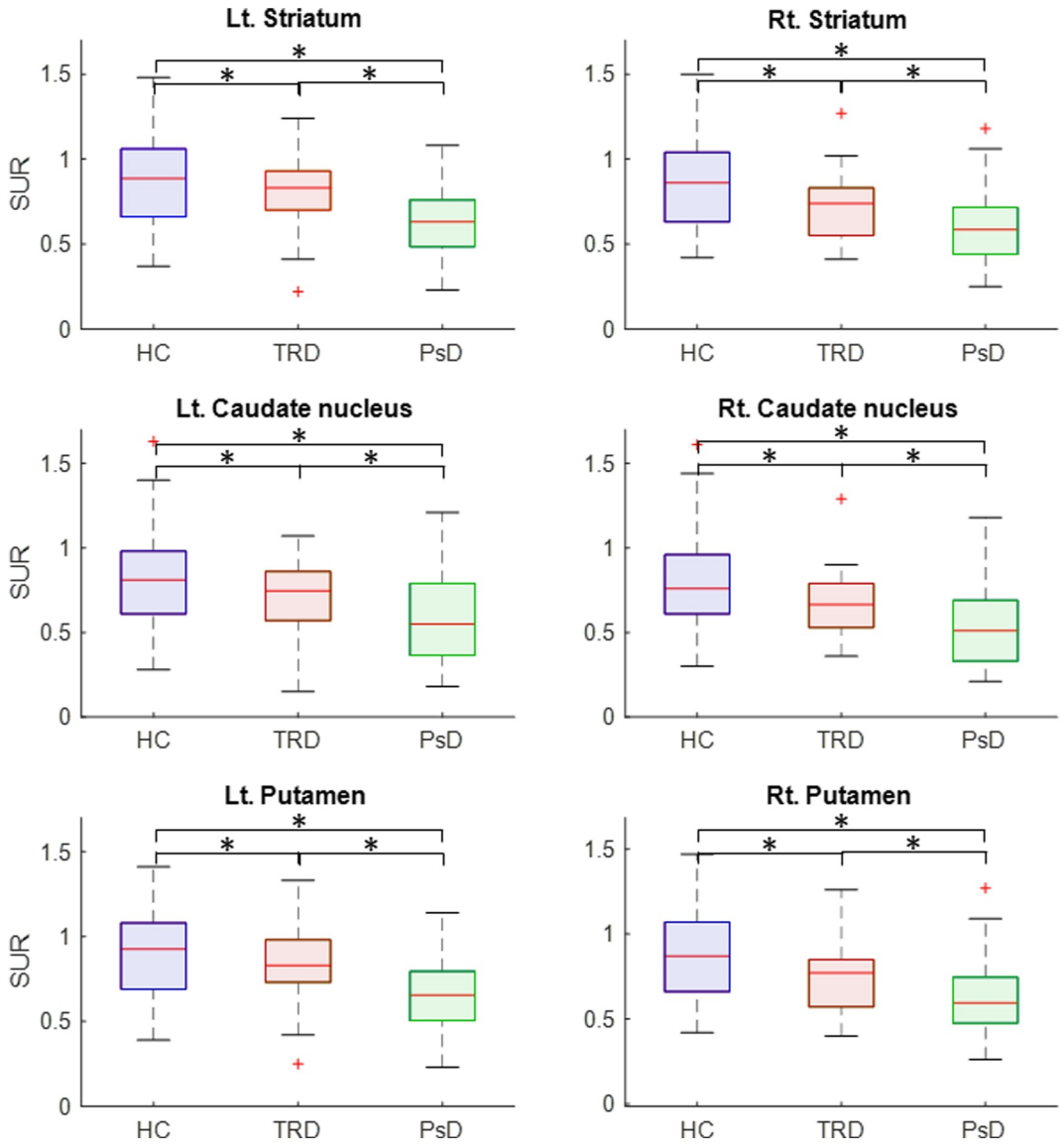

FIGURE 1 | The comparison results of the specific uptake ratio (SUR) scores at the bilateral striatum, caudate nucleus, and putamen in the TRD patients with parkinsonism (PsD), the patients with treatment-resistant depression (TRD), and the healthy control elderly group (HC). Data is presented as the median with an interquartile range. *$p < 0.01$.

group with the lowest value in the healthy elderly (Table 1). Post-hoc tests revealed significantly greater striatum asymmetry in the PsD and TRD groups compared to the healthy elderly ($p < 0.01$ and $p < 0.05$, respectively). Similar results were observed for putamen asymmetry. There was no significant difference in asymmetry index between the TRD and PsD groups. Although TRD is slightly lower than PsD.

Figure 2 illustrates the age-related dopamine transporter availability in the health control, as indicated by SUR scores, which decreases with age by linear regression (Figure 2a) and piecewise linear model (Figure 2b). A significant decrease of approximately 0.01 SUR units per year is observed in the bilateral striatum of the control elderly, as shown in Figure 2a (left, $r^2 = 0.25$, $p < 0.01$; right, $r^2 = 0.30$, $p < 0.01$). The SUR scores of the control elderly over the 10-year and 20-year age brackets are shown in Supporting Information S1: Table 1.

As shown in Figure 2b, the piecewise linear model revealed distinct age-related trends in SUR scores for the bilateral striatum. An age-related decline was observed before age of 65.8 in the left striatum ($r^2 = 0.11$, $p < 0.05$); whereas, the age-related decline was observed after age of 60.4 in the right striatum ($r^2 = 0.12$, $p < 0.01$). These results demonstrated different effects of aging on the dopamine transporter availability in the left and right striatum.

3.2 | Performance of Classification

In most models, we found that the features with the age outperformed the features without the age, implicating the importance of age in differentiating groups. The top six classifiers were chosen based on the accuracy of validation and testing, as outlined in Table 2. The cross-validation performance

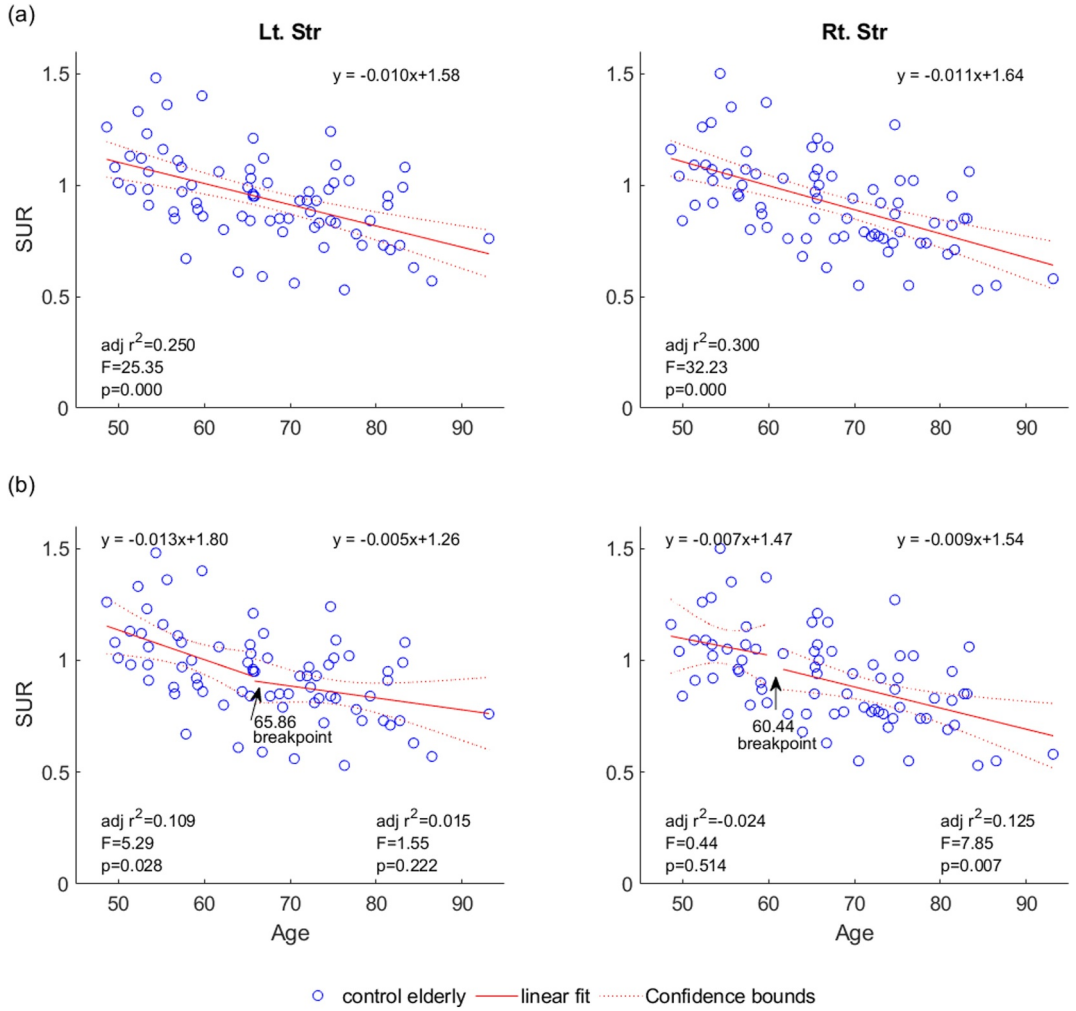

FIGURE 2 | Age-related decline in dopamine transporter availability in the control group. Panel (a) shows a significant linear decrease in SUR with age in both the left and right striatum (Str), as indicated by the negative slopes of the regression lines. Panel (b) reveals a nonlinear decline, with a steeper decline in the left striatum before age 65.8. The blue circles represent the SUR scores of healthy elderly controls. Solid lines indicate the linear fits. Lt., left; Rt., right; SUR, specific uptake ratio.

TABLE 2 | Classification accuracy of top six machine learning models with and without age feature.

		Accuracy			
		With age		Without age	
	Classifier model	Validation	Testing	Validation	Testing
1	Fine k-NN	84.9	85.7	79.2	57.1
2	Wide neural network	88.7	78.6	83.5	78.6
3	Fine Gaussian SVM	87.8	78.6	80.7	64.3
4	Weighted k-NN	85.6	78.6	80.3	64.3
5	Trilayered neural network	83.3	78.6	79.1	71.4
6	Narrow neural network	82.9	78.6	79.8	78.6

Abbreviations: k-NN, k-nearest neighbor; SVM, support vector machines.

of all the models adopted in this study was provided in Supporting Information S1: Table 2. The confusion matrix of the top two classifiers is shown in Supporting Information S1: Figure 1.

Table 3 presents the performance of the top six classifiers using the testing dataset. The fine k-NN classifier emerged as the top performer, achieving an accuracy of 85.7%, a macro-average sensitivity of 77.78%, a specificity of 91.41%, a F1 score of 80.26, and a Cohen's kappa of 0.74. As shown in Figure 3, there were instances of misclassification in the two patient groups, especially among patients with TRD. The performance of the top six classifiers using the training dataset was provided in

TABLE 3 | The performance from test dataset.

	Precision	Sensitivity	Specificity	F1-score	AUROC	Accuracy
Testing						
Fine K-NN						
HC	88.89	100.00	83.33	94.12	91.67	85.71
TRD	66.67	66.67	90.91	66.67	78.79	
PsD	100.00	66.67	100.00	80.00	83.33	
macro AVG	85.19	77.78	91.41	80.26		
Wide neural network						
HC	88.89	100.00	83.33	94.12	91.67	78.57
TRD	50.00	33.33	90.91	40.00	57.58	
PsD	66.67	66.67	90.91	66.67	75.76	
macro AVG	68.52	66.67	88.38	66.93		
Fine Gaussian SVM						
HC	88.89	100.00	83.33	94.12	97.92	78.57
TRD	50.00	33.33	90.91	40.00	87.88	
PsD	66.67	66.67	90.91	66.67	96.97	
macro AVG	68.52	66.67	88.38	66.93		
Weighted KNN						
HC	88.89	100.00	83.33	94.12	87.50	78.57
TRD	50.00	33.33	90.91	40.00	65.15	
PsD	66.67	66.67	90.91	66.67	93.94	
macro AVG	68.52	66.67	88.38	66.93		
Trilayered neural network						
HC	80.00	100.00	66.67	88.89	87.50	78.57
TRD		0.00	100.00		42.42	
PsD	75.00	100.00	90.91	85.71	92.42	
macro AVG		66.67	85.86			
Narrow neural network						
HC	88.89	100.00	83.33	94.12	83.33	78.57
TRD	50.00	33.33	90.91	40.00	42.42	
PsD	66.67	66.67	90.91	66.67	93.94	
macro AVG	68.52	66.67	88.38	66.93		

Abbreviations: AUROC, the area under curve of the receiver operating characteristic curve; HC, the elderly control; k-NN, k-nearest neighbor; macro AVG, macro average; PsD, the TRD patients with parkinsonism; SVM, support vector machines; TRD, the patients with treatment-resistant depression.

Supporting Information S1: Table 3. The distribution of training dataset was show in Supporting Information S1: Figure 2.

4 | Discussion

This study aims to differentiate treatment-resistant depression comorbid with parkinsonism from treatment-resistant depression in elderly individuals through dopamine transporter (DAT) imaging of the striatum using ^{99m}Tc TRODAT-1 SPECT. Firstly, we established a normative dataset for individuals aged 50 and above, revealing a non-linear age-related decline in left striatal DAT availability, with a steeper decline observed before age 65.8. Second, patients with TRD exhibit DAT availability intermediate between those of the elderly controls and TRD patients with parkinsonism, suggesting that depression symptoms may precede motor symptoms in the trajectory of parkinsonism. Further, we utilize machine learning techniques to tackle the challenge of diagnosing the pre-motor stage of Parkinson's disease, which frequently includes affective problems, vegetative symptoms, and insomnia. The findings strongly suggest that affective mood complaints in the elderly may serve as potential early signs of neuropsychiatric symptoms or neurodegenerative disorders.

Age-related reductions in brain volume [27] and the brain's dopamine system [28] are associated with impaired motor function, cognitive, and emotion. As the aging population

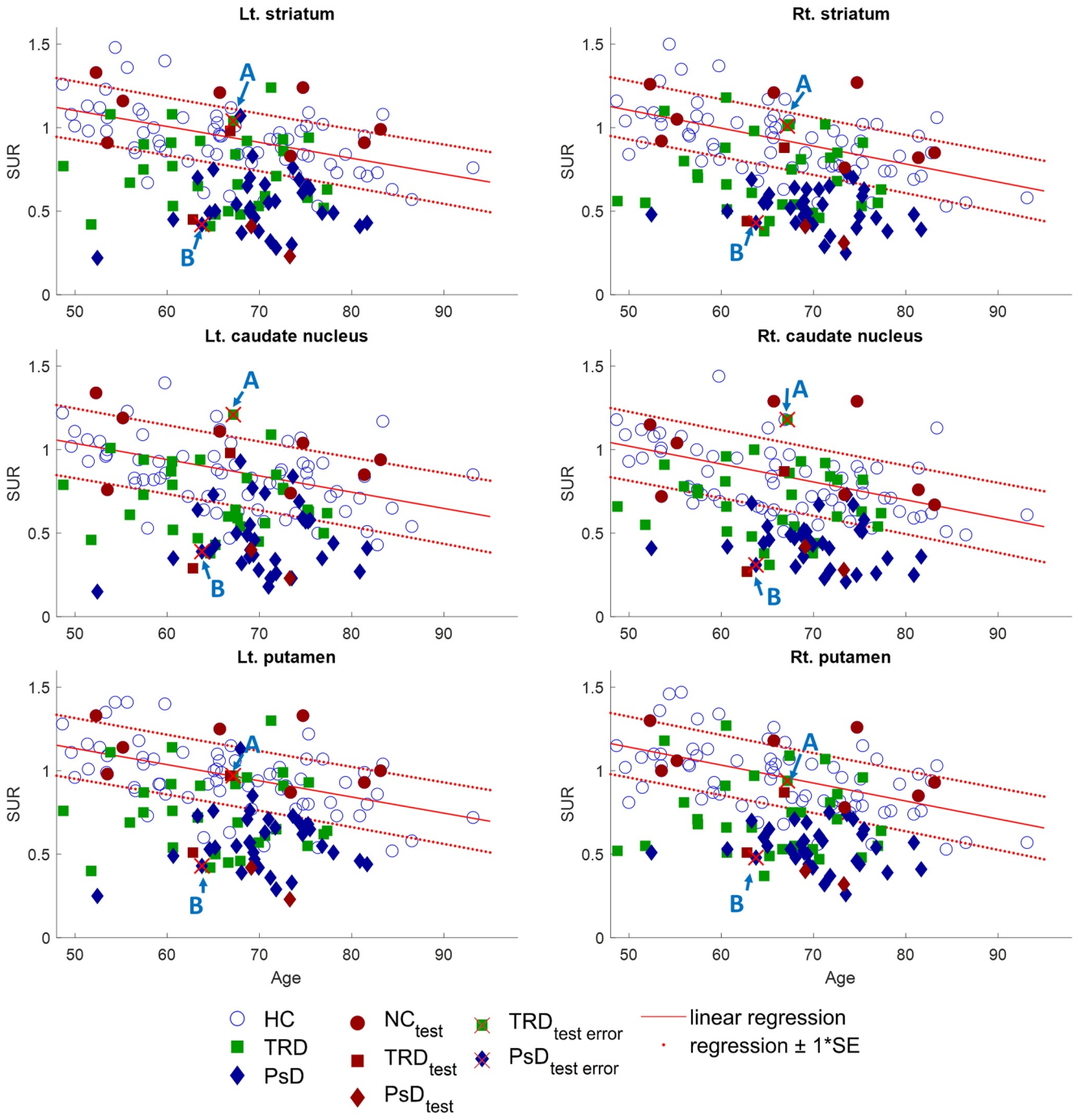

FIGURE 3 | The classification results by using the fine k-NN model. The SUR scores from the dataset are represented as follows: blue hollow circles for HC, green squares for TRD, and blue diamonds for PsD. The test data are shown in red. The regression results of HC are superimposed on the graph for reference. Solid lines indicate the linear fits of the HC group, while dotted lines represent one standard error. Point A: A patient with TRD who was misclassified as an elderly control. Point B: A patient with PsD who was incorrectly classified as having treatment-resistant depression. HC, the healthy control elderly; k-NN, k-nearest neighbor; Lt., left; PsD, the TRD patients with parkinsonism; Rt., right, TRD, the patients with treatment-resistant depression.

grows, reliable reference values for disease screening are crucial. Given the complex nature of human aging, we developed a dataset to characterize the age-related decline of DAT availability in the elderly population. Our results align with previous studies [21, 29–32], suggesting the decline is not significantly influenced by ethnicity. We also found the age-related decline in the elderly is nonlinear, with a different decline observed in the left and right striatum. Two linear models were found to best capture the nonlinear trend [29, 32–34]. Maintaining brain health through lifestyle factors, such as physical activity,

cognitive engagement, and diet, is particularly important during the early stages of aging [35, 36]. To the best of our knowledge, this is among a large norm datasets of DAT density using ^{99m}Tc-TRODAT-1 SPECT, with a relatively even age distribution of healthy elderly controls, which will provide a valuable reference for comparison in ^{99m}Tc-TRODAT-1 SPECT studies for late-life depression, Parkinson's, or other neurodegenerative diseases.

Patients with major depressive disorder have a higher risk of developing Parkinson's disease (PD) later in life [37–40]. This study takes a unique approach by recruiting elderly patients with TRD from the psychiatric outpatient clinic, rather than focusing on patients with clinically diagnosed PD. These patients do not exhibit classic PD triad motor symptoms, such as tremor, rigidity, and dyskinesia, which appear later in the pathological process when about 50% of the dopaminergic neurons in the substantia nigra have been lost. The asymmetry index is an important reference for PD diagnosis. Our data show that the index in patient with TRD is more closely aligned with that observed in TRD patients with parkinsonism, indicating TRD could represent a prodromal stage within the PD spectrum. That is consistent with Kazmi et al.'s findings that late-onset depression increases the risk for developing PD [40]. Also, although in our study a clinical diagnosis of PD (or another α-synucleinopathy) was excluded as best as possible on neurological examination, we cannot exclude that some of the included elderly depressed patients, and particularly those with parkinsonism, were already an early manifestation of an α-synucleinopathy. While symptomatic treatments are available, there are currently no drugs that can slow disease progression [41]. Identifying individuals in the early stage of the disease would facilitate clinical trials of new drugs to prevent/delay progression to clinically manifest PD.

Braak proposed six pathways of α-synuclein propagation in PD, starting in the medulla and spreading upwards [7, 8]. Clinically, the Movement Disorder Society (MDS) categorizes PD into three stages: preclinical, prodromal, and clinical [41]. Our elderly patients with TRD or Parkinsonism likely fall within stages 2–3 of Braak's model or the prodromal phase of the MDS classification. The latency period between non-motor symptoms (NMS), such as hyposmia, RBD, constipation, depression, and anxiety, and the onset of motor symptoms can vary from 5 to 20 years. Early detection of NMS, particularly depression, is crucial for slowing disease progression. The neurodegenerative process in PD involves multiple neurotransmitter systems, not just dopamine. However, dopamine system dysfunction, as measured by TRODAT-SPECT imaging, is a clinically available biomarker for early PD detection. Early diagnosis and intervention can improve mood, facilitate recovery, and enhance quality of life for patients [42–44].

While this study is cross-sectional, the mean duration of depression is 7.54 years in the TRD patient with parkinsonism and 7.98 years in the TRD group. Although we cannot definitively determine the time it takes for depression to develop Parkinsonism symptoms, data from Taiwan's National Health Insurance Research Database (NHIRD) suggests a link. NHIRD data showed that patients with difficult-to-treat major depressive disorder [37] or bipolar disorder [38] had a greater risk of developing Parkinsonism/Parkinson's disease (PD) compared to healthy controls (hazard ratio 3.34 and 6.78 with 95% CI, 1.99–5.95 and 5.74–8.02, respectively). The calculated mean duration from TRD onset to PD onset was approximately 6.5–-6.7 years after excluding cases of drug-induced parkinsonism and recent onset of PD (< 3 years) [37, 38]. Particularly, the former MDD [37] study revealed a higher risk of PD development in the 50 to 65 group compared to the > 65 age group (hazard ratios of 7.03 vs. 2.89, with 95% CI 2.95–16.76, 1.26–6.65, respectively). These longitudinal findings are compatible with our current data, indicating that our patients with parkinsonism might have experienced a prolonged period of depression before the onset of motor symptoms, despite the insidious nature of the disease.

Molecular imaging, which quantitatively measures biological processes in vivo, is a valuable tool for screening and early diagnosis [45]. Machine learning, a valuable pattern recognition technique, is applied to medical images [46, 47]. By combining molecular imaging with machine learning, physicians can identify subtle symptoms that may not be readily apparent. Our findings demonstrate that integrating demographic information with image examination data improved classification accuracy, highlighting that a subset of patients with depression have a risk of developing Parkinson's disease. The fine k-NN model exhibited the best performance with minimal misclassifications.

This study has several limitations that should be considered. First, while we established a normative data for striatal DAT availability in the elderly population, the sample size was relatively small. Second, the overlapping symptomatology between PD and depression, including symptoms like fatigue, sleep disturbances, and cognitive impairment, made it challenge to differentiate between the two conditions. Third, the cross-sectional design of the study limits our ability to directly link depression to the development of Parkinsonism. However, longitudinal studies, such as the Taiwan's NHIRD analysis [37, 38], indirectly support a potential association between the two. Fourth, as both patient groups were difficult-to-treat, there are no differences in medication use, suggesting that medications effects did not influence the TRODAT-SPECT imaging results. Fifth, our study focused on patients with treatment-resistant depression, and, regrettably, we did not include elderly depressed patients responding to treatment, which restricted the generalizability of our findings to the broader population of late-onset depression. Finally, neurodegenerative processes affect multiple brain areas; and incorporating additional factors into the classification model may improve its performance. Our results suggest that a subset of TRD patients with lower DAT availability might be in the early stages of PD, as these patients were often misclassified by the models.

In conclusion, this study represents a unique and pioneering effort to investigate non-motor symptoms of potential PD in elderly patients with treatment-resistant depression within a psychiatric outpatient setting in Taiwan. Our findings suggest that TRD in older adults may be a prodromal phase of Parkinson's disease, prompting psychiatrists to consider comorbid neurodegenerative disorders in elderly depressed patients. Early detection through demographic information, neurological examination, and brain imaging may aid in the early identification of individuals at risk for PD.

Author Contributions

Tung-Ping Su: study conception, investigation, resources, interpretation of data, writing, supervision, **Chiu-Jung Huang:** analysis and interpretation of data, draft manuscript preparation, **Wei-Chung Mao:** investigation, resources, **Yu-Hsien Chiu:** analysis, draft manuscript preparation, **Ren-Shyan Liu:** imaging acquisition and analysis, draft manuscript preparation, **Li-Fen Chen:** interpretation of data, supervision.

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Ethics Statement

The ethics committee of the Institutional Review Board of the Cheng Hsin General Hospital approved this study (approval number (718) 108A-34).

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

A poster including partial data was presented at the 29th Annual Meeting of the Organization for Human Brain Mapping in 2023. The datasets generated and analyzed in this study are not publicly available. However, data can be obtained from the corresponding author upon reasonable request and with the necessary ethical approval.

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Supporting Information

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