Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Quantified Striatal Dopaminergic Denervation as Predictor for Motor Outcomes in Parkinson's Disease

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ABSTRACT: Background: A hallmark of Parkinson's disease (PD) is progressive loss of dopamine terminals in the basal ganglia, with clinical symptoms including motor and non-motor manifestations such as bradykinesia, rigidity, and cognitive impairment. Dopamine transporter single-photon emission computed tomography (DaT-SPECT) can be used to assess dopaminergic denervation by detecting loss of striatal dopamine transporters (DaT).

Objective: We examined DaT binding scores' (DaTbs) association with motor outcomes in PD and explored its usefulness as a predictor of disease progression. Faster dopaminergic denervation in the basal ganglia was hypothesized to have stronger correlation and predictive value for poor motor outcomes.

Methods: Data was analyzed from the Parkinson's Progression Markers Initiative. DaTbs in the putamen and caudate nucleus were correlated with Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores for walking and balance difficulties, gait difficulties, and presence of dyskinesias. A predictive model using baseline speed of drop in DaT binding score was performed for each motor outcome.

Results: All motor outcomes had mild, significantly negative correlation with DaTbs in the putamen and caudate nucleus, with similar degree of correlation per region. Speed of drop was predictive of only substantial gait difficulties when evaluated in the putamen but not the caudate.

Conclusions: These findings suggest that analyzing speed of drop in DaTbs, which occurs early in the motor phase of the disease, may be helpful for predicting clinical outcomes in PD. Longer observation of this cohort may provide further data to investigate DaTbs as a prognostic marker in PD.

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases impacting elderly populations, affecting over 10 million people worldwide.[1] PD is characterized by progressive neurodegeneration, manifested in both motor and non-motor symptoms. Classical parkinsonian symptoms include bradykinesia, rigidity, and in some patients, resting tremor, with gait problems as disease progresses, and non-motor symptoms such as hyposmia, cognitive impairment, anxiety, depression and rapid eye movement (REM) sleep behavior disorder.[2] Manifestation and progression of symptoms differ greatly between patients, with some presenting only motor symptoms initially and others with preceding cognitive symptoms.[2] One of many neurodegenerative parkinsonisms, PD continues to present diagnostic challenges to physicians, despite progress in medical research. Patients in initial stages of parkinsonisms such as PD, multiple systems atrophy (MSA), and Progressive Supranuclear Palsy (PSP), often display similar symptoms, which causes difficulties differentiating between these diseases at an early disease stage.[1] Therefore, early and accurate diagnosis is critical in PD, especially since prognosis and related morbidity varies between parkinsonisms. To improve

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differential diagnosis and earlier treatment for PD patients, it is vital to determine distinct biological markers associated with PD that can distinguish the disease from other related parkinsonisms.

One of the hallmarks of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta projecting into the caudate and putamen, which is associated with the progressive decline seen in PD patients.[3] Loss of these neurons results in reduced dopamine (Da) in the striatum and subsequent reduction in striatal dopamine transporters (DaT), which reabsorb dopamine from the synaptic cleft.[4] This is thought to be in part responsible for the hypokinetic movements characteristic of PD.[5]

Dopamine transporter single-photon emission computed tomography (DaT-SPECT) is a useful imaging technique that allows for visualization of DaT in vivo in the striata through the use of ioflupane-123 ([123I]FP-CIT), a radiopharmaceutical tracer that binds to striatal DaT.[4] DaT-SPECT can be used as a surrogate marker of the amount of DaT present in the striata as it has been shown to correlate with degree of denervation of dopaminergic neurons in the nigrostriatal pathway.[4] On DaT-scan, bright areas which indicate bound striatal DaT are studied for shape, intensity, and symmetry.[1] To quantify [123I]FP-CIT accumulation, a software known as DaTQUANT can be used to calculate DaT binding scores (DaTbs) in various regions of the striatum.[1] Areas displaying lower amounts of [123I]FP-CIT indicate reduced levels of bound striatal DAT and thus less Da available in the striata. DaT-SPECT imaging can therefore be used to enhance differential diagnosis between essential tremor and parkinsonisms such as PD.[6] A direct association between degeneration of the substantia nigra and decrease in DaT has been disputed from previous imaging studies.[4] It is also thought that significant reduction in DaT is not displayed until 50% degeneration of the substantia nigra has occurred, causing difficulty in diagnosing PD patients in prodromal stages.[4] However, there is still significant evidence supporting the correlation between striatal DaT binding with post mortem substantia nigra cell counts.[7]

In addition, previous studies of the basal ganglia have suggested that the putamen is associated with motor function and habitual movements, while the caudate nucleus is associated with cognitive and executive function.[8–10] Therefore, the objectives of this study were to (1) determine the degree of correlation between dopaminergic denervation measured by DaTbs and axial motor outcomes, (2) assess whether motor and cognitive outcomes show segregation between putaminal and caudate DaTbs decline, and (3) evaluate speed of dopaminergic denervation as a prognostic marker for PD. Based on the aforementioned studies, we hypothesized that DaTbs in the putamen are predicted to have stronger correlation with motor outcomes compared to DaT binding in the caudate nucleus. Putamen DaTbs could also be expected to be a stronger predictor for decline in motor function compared to that of the caudate nucleus, although correlation has not been strong in previous studies.[9,11]

Materials and Methods

The Parkinson's Progression Markers Initiative (PPMI) (https://www.ppmi-info.org/) database was used for this study. For our study we focused on the non-genetic cohort of PD patients. Subjects included for the PD group on PPMI were age 30 and older, diagnosed with PD for at most 2 years prior to screening, Hoehn and Yahr stage I or II at baseline, and presenting two or more of the following symptoms: resting tremor, bradykinesia or rigidity, or either asymmetric resting tremor or asymmetric bradykinesia, in addition to also having a DaTScan confirming dopamine denervation and not taking medications for their PD symptoms at least 60 days prior to baseline visit. Data were collected at baseline and follow-up visits every 3–6 months, with DaT-SPECT imaging taken during screening and follow-up visits every 12 months after baseline. Patients were allowed to initiate PD medications after baseline. The clinical motor assessment, the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was assessed 6 hours off PD medications. Data from the PPMI database available up to 2018 were used at the time this study was initiated.

Statistical Analysis

Variables chosen for this study include striatal DaTbs from DaT-SPECT imaging as an independent variable, and clinical measures related to gait and dyskinesias included in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were chosen as dependent variables. Clinical measures related to gait and dyskinesias were chosen as dependent variables due to their important role in morbidity and mortality in PD as well as being markers of disease progression.[2,12,13] Walking and balance difficulties in patient's daily living experience were assessed by analyzing scores on MDS-UPDRS II item 2.12 (labeled as NP2WALK in this analysis). MDS-UPDRS III item 3.10 (labeled as NP3GAIT) was used as a measure of gait difficulties as assessed by physician. MDS-UPDRS IV item 4.1 (labeled as NP4DYSKI) was used to assess development of dyskinesias. No post-hoc analysis was performed.

Correlation Analysis

Correlation analysis was performed to determine the relationship between DaTbs in regions of the striatum and MDS-UPDRS scores using repeated measures design and Pearson correlation. For all clinical measures NP2WALK, NP3GAIT, and NP4DYSKI, correlation analysis was conducted for DaTbs averaged in the left and right putamen and clinical motor scores in all PD patients. The same analysis for all variables was conducted for the caudate nucleus.

Prediction Model

To determine whether DaTbs in the putamen and caudate can predict various clinical outcomes, a prediction model was designed to analyze whether the speed of the first-year drop in DaTbs could predict relevant clinical outcomes in the following years. The goal was to capture speed of neurodegeneration, predicting that a faster decline would lead to worse outcomes sooner. The rationale is based on studies showing the correlation

between DaT and loss of dopamine-producing cells.[7] Baseline speed of drop in DaTbs was calculated by dividing the difference in DaTbs by the difference in time between first and second DaT-SPECT, which were performed at baseline visit and 12 months later, respectively. For each clinical measure, PD subjects were categorized into three event groups: event diagnosis at baseline, event diagnosis at follow-up, and no event diagnosis. Events chosen were as above. Cutoffs for events were as follows. NP2WALK score >0, NP3GAIT score >1, NP4DYSKI score >0. These are the scores at which onset of walking and balance difficulties; substantial change in gait; and onset of dyskinesias occur, respectively. The baseline drop speed distribution in the putamen and caudate nucleus were compared among the three event groups using one-way ANOVA model. Subjects with only one visit were excluded from the test. The total number of subjects that could be analyzed was 371.

Results

Correlation Analysis

Correlation Between DaTbs and NP2WALK

There was a significant negative correlation between DaTbs averaged in the left and right putamen and NP2WALK ($P < 0.0001$). Degree of correlation was small at $R = -0.23$, 95% CI [−0.30, −0.16] (Fig. 1A). Correlation analysis between DaTbs averaged in the left and right caudate nucleus and NP2WALK also indicated significant negative correlation ($P < 0.0001$). Degree of correlation was also small for caudate nucleus at $R = -0.29$, 95% CI [−0.35, −0.23] (Fig. 1B).

Correlation Between DaTbs and NP3GAIT

There was a significantly negative correlation between DaTbs averaged in the left and right putamen and scores on NP3GAIT ($P < 0.0001$). Degree of correlation in the putamen was small at $R = -0.20$, 95% CI [−0.27, −0.15] (Fig. 1C). Correlation between DaTbs averaged in the left and right caudate nucleus and NP3GAIT scores also demonstrated significantly negative correlation ($P < 0.0001$). Correlation magnitude in the caudate nucleus was similar to that of the putamen at $R = -0.21$, 95% CI [−0.27, −0.15] (Fig. 1D).

Correlation Between DaTbs and NP4DYSKI

There was a significantly negative correlation between DaTbs averaged in the left and right putamen and scores on NP4DYSKI ($P < 0.001$). Degree of correlation was small at $R = -0.10$, 95% CI [−0.16, −0.05] (Fig. 1E). Correlation between DaTbs averaged in the left and right caudate nucleus and NP4DYSKI scores was also significantly negative ($P < 0.001$). Correlation magnitude for caudate nucleus was similar to that of the putamen at $R = -0.12$, 95% CI [−0.17, −0.08] (Fig. 1F).

Prediction Model

Prediction Model for NP2WALK

Comparison of baseline drop speed in DaT binding in the putamen indicated no significant differences among patients who developed NP2WALK event at baseline, at follow-up, or those who never suffered an event ($P = 0.80$, ANOVA) (Fig. 2A). Similar findings were obtained for caudate. ($P = 0.17$, ANOVA) (Fig. 2B).

Prediction Model for NP3GAIT

Baseline drop speed in the putamen was significantly higher in PD patients with NP3GAIT event occurrence at follow-up compared to PD patients who never suffered an event ($P = 0.024$, ANOVA). There was no significant difference in baseline drop speed in the putamen between PD patients who suffered events at baseline compared to those who never suffered an event ($P = 0.96$, ANOVA) (Fig. 2C). However, comparison of baseline drop speed in the caudate nucleus indicated no significant differences among the three event groups ($P = 0.25$, ANOVA) (Fig. 2D).

Prediction Model for NP4DYSKI

By the end of the observation period, approximately 80% of PD patients were taking levodopa carbidopa. Comparison of baseline drop speed in the putamen indicated no significant differences between PD patients who suffered NP4DYSKI event (dyskinesias) at baseline, at follow-up, or never ($P = 0.30$, ANOVA) (Fig. 2E). Comparison of baseline drop speed in the caudate nucleus also indicated no significant differences between the three event groups for NP4DYSKI ($P = 0.96$, ANOVA) (Fig. 2F).

Discussion

Based on the findings, DaT binding in the putamen and caudate nucleus were significantly but weakly correlated with all clinical measures of motor functions. DaT binding in the putamen and caudate nucleus negatively correlated with clinical measures for walking ability, gait, and dyskinesias. As expected, lower striatal DaT binding was associated with higher scores on NP2WALK, NP3GAIT, and NP4DYSKI, indicating that less available dopamine was related to greater motor difficulties. Although significant, the negative correlations were small, as indicated by the low magnitude of correlation coefficients for each clinical measure. Small correlations between DaTbs and MDS-UPDRS scores were also found in another study using the same database.[14] Correlation studies by Marek et al on DaTbs in the putamen and MDS-UPDRS baseline scores also demonstrated significant yet weak negative correlation.[15] Similar findings were published by Chahine et al.[11]

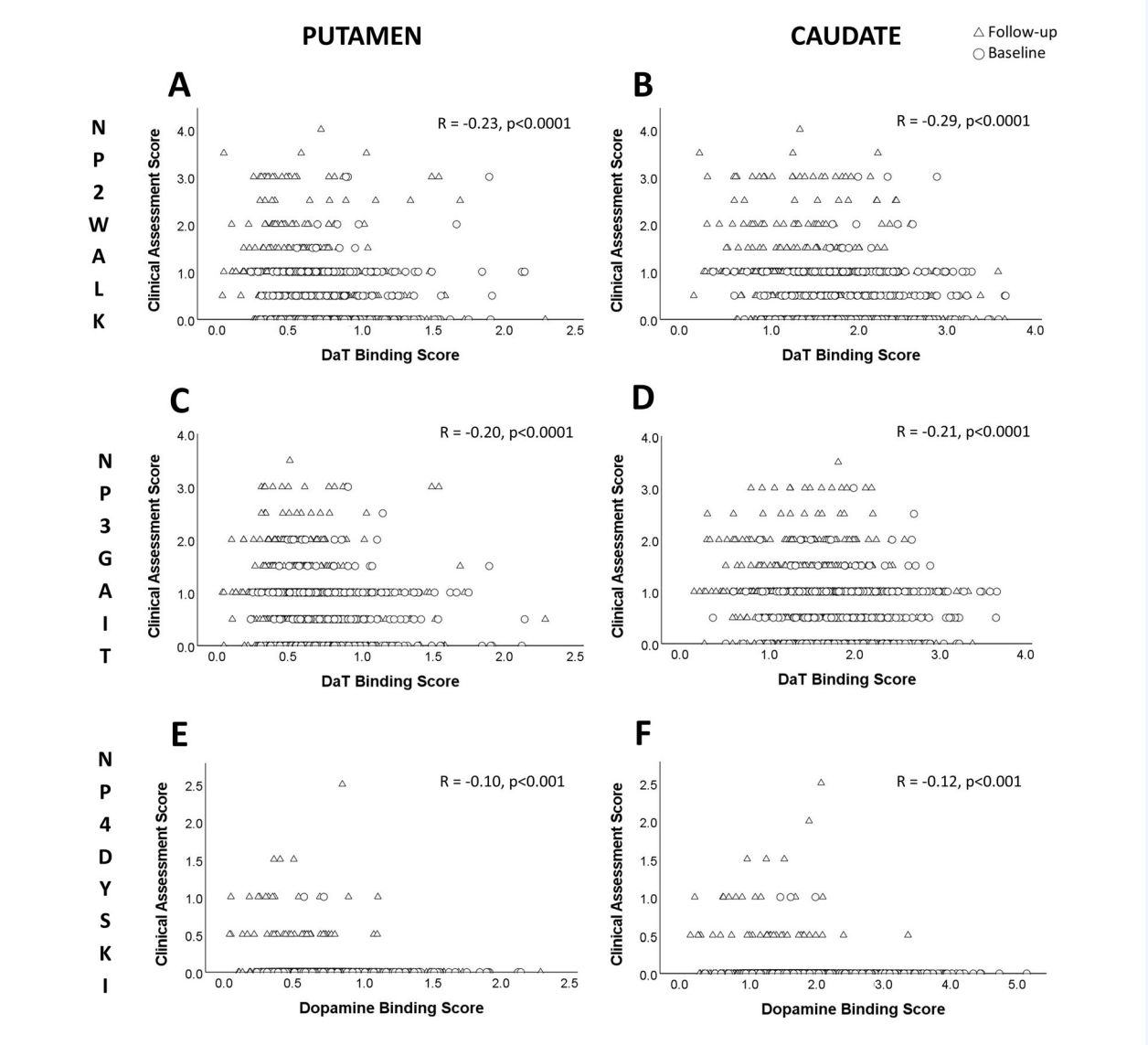

Figure 1. Correlation analyses of striatal DaTbs and MDS-UPDRS item scores in PD patients (n = 410). DaTbs had significantly negative correlation with scores on NP2WALK for the (**A**) putamen ($R = -0.23$, $P < 0.0001$) and (**B**) caudate nucleus ($R = -0.29$, $P < 0.0001$). DaTbs had significantly negative correlation with scores on NP3GAIT for the (**C**) putamen ($R = -0.20$, $P < 0.0001$) and (**D**) caudate nucleus ($R = -0.21$, $P < 0.0001$). DaTbs had significantly negative correlation with scores on NP4DYSKI for the (**E**) putamen ($R = -0.10$, $P < 0.001$) and (**F**) caudate nucleus ($R = -0.12$, $P < 0.001$)

A possible explanation to the weak correlation between motor outcomes and DaTbs may be the role of other (non-dopaminergic) systems (eg, serotonin and acetylcholine) in the pathogenesis of motor PD which is not assessed by an only dopamine marker diagnostic study (namely DaT-SPECT).[16] These other systems role in PD has been documented. A SPECT imaging study by Nicastro et al examined extrastriatal serotonergic transporters (SERT) in the PPMI cohort and found that PD patients had a significant decrease in serotonin uptake in the caudate nucleus, putamen, and extrastriatal regions compared to healthy controls.[17] Results from another imaging study indicate a possible link between β-amyloid plaques and postural instability and gait difficulty in PD as well.[18] Other imaging studies have even implicated the role of cholinergic denervation in PD, suggesting that multiple neuronal systems may interact to cause the manifestation of motor and non-motor symptoms seen in PD patients.[19,20]

In addition, regulatory mechanisms compensating for the loss of dopamine in early disease stages may also explain why a stronger correlation is not presented between motor outcomes and DaT binding. One possible mechanism is downregulation of DaT during early stages to retain dopamine in the synapse and promote normal dopamine levels in the basal ganglia.[4,21,22] However, previous studies on whether this compensatory

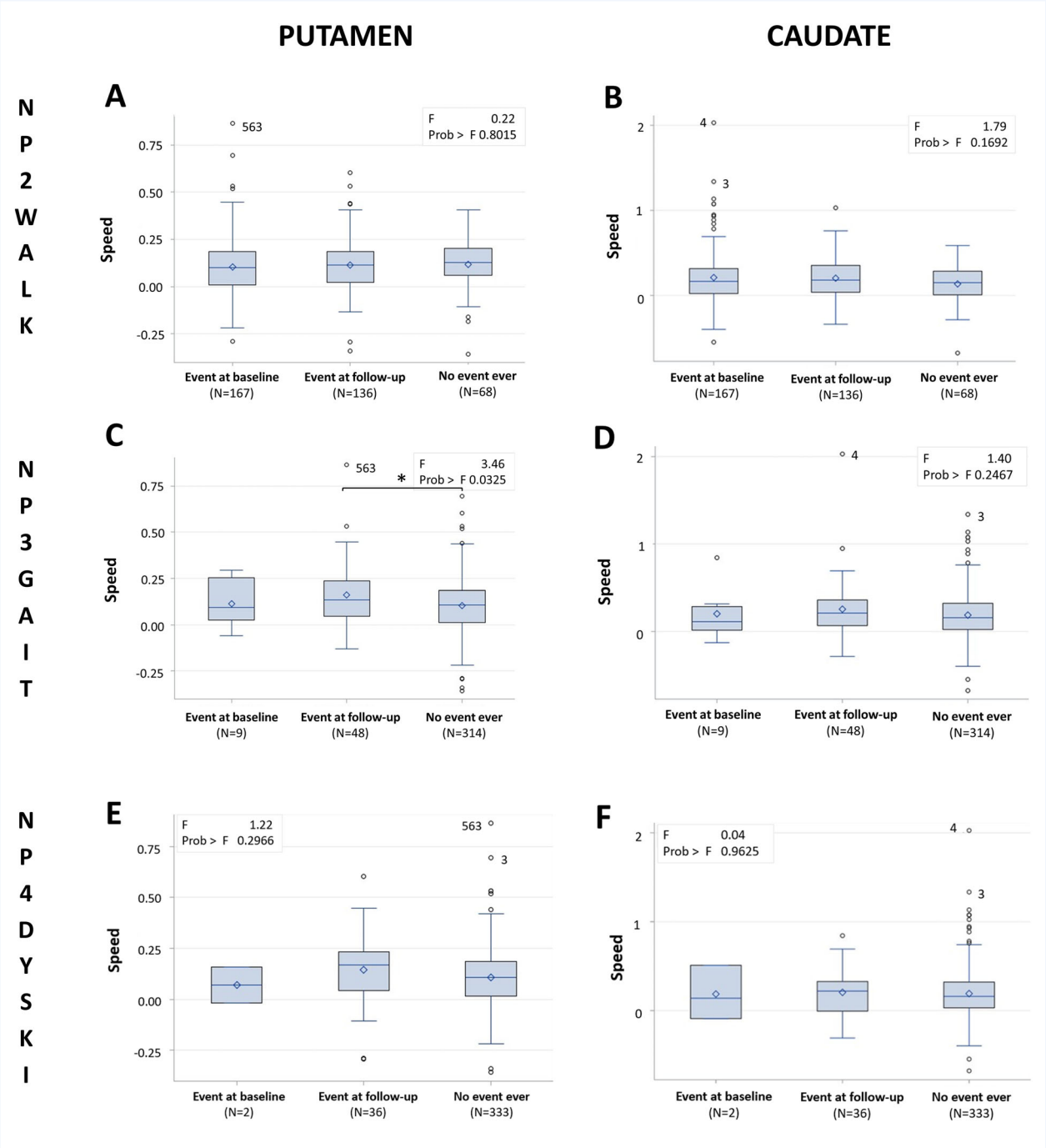

Figure 2. Baseline speed distribution for DaT binding among event groups: event at baseline, event at follow-up, and no event ever. NP2WALK event observed in (**A**) putamen and (**B**) caudate nucleus. No significant differences in baseline speed of drop in DaTbs among event groups for both putamen and caudate. NP3GAIT event observed in (**C**) putamen and (**D**) caudate nucleus. (**C**) For NP3GAIT event, baseline speed of drop in DaTbs in the putamen was significantly higher in PD patients who developed event at follow-up compared to those who never developed event ($P = 0.024$, ANOVA). NP4DYSKI event observed in (**E**) putamen and (**F**) caudate nucleus. No significant differences in speed of drop among event groups for putamen and caudate. * represents $P < 0.05$

mechanism plays a role have shown mixed findings.[23] Upregulation of dopamine receptors as a compensatory mechanism during early pre-symptomatic disease stages, causing an increase in dopamine binding, has also been implicated in a previous study.[23]

Another possible confounder of these results may be attributed to long-duration response to levodopa in PD subjects, which can last up to 2 weeks after drug withdrawal.[14,24–27] MDS-UPDRS was assessed in patients in the "off-state," which was defined in the PPMI protocol as refraining from levodopa/dopamine

agonists for at least 6 hours. However, in this early PD cohort, 6 hours may have not been enough to truly assess the degree of progression in the true off-state which may be more reflective of raw dopaminergic denervation.

In addition, correlation between DaT binding in the putamen and motor outcomes were expected to have a stronger correlation compared to that of the caudate nucleus.[8–10] However, contrary to the hypothesis, magnitude of correlation between DaT binding and motor outcomes were relatively similar between the putamen and caudate nucleus, with even a slightly higher correlation coefficient for the caudate nucleus ($R = -0.29$) compared to the putamen ($R = -0.23$) in the correlation analysis conducted for NP2WALK. Previous imaging studies examining striatal DaT binding and motor function found mixed results for the role of dopamine deficit in the caudate and motor decline in PD. A similar correlation analysis also reported significant negative correlation between DaT binding in the caudate and UPDRS motor scores with similar correlation coefficients between the putamen and caudate.[28] Other imaging studies examining DaT binding and motor outcomes also found similar correlation coefficients between the putamen and caudate nucleus.[28,29] In addition, caudate DaT binding analysis by Pasquini et al indicated greater gait impairment in PD patients with dopamine uptake deficit in the bilateral caudate than patients with deficit in the unilateral caudate or no caudate deficit at all, suggesting that dopamine deficit in the caudate may be related to gait impairment in PD.[10] However, in contrast to our findings and the ones discussed above, Moccia et al. found significant negative correlation between DaT binding in the putamen and various motor scores on MDS-UPDRS part III but not in the caudate nucleus.[9] Whether differences in methodology underlay these opposing findings remains to be assessed.

The prediction model tested using baseline drop speed in DaTbs only demonstrated significant results when examining gait difficulties (NP3GAIT) in the putamen. Significant difference was found between PD patients who developed substantial gait difficulties at follow-up and PD patients who did not develop substantial gait difficulties ever. This was consistent with the hypothesis that DaTbs in the putamen would be a stronger predictor for motor outcomes than that of the caudate nucleus. However, DaTbs was not a significant predictor for other motor outcomes. As mentioned before, these results may have also been affected by long-duration response to levodopa and early disease stage of the patients.[14] For example, many patients in this population did not yet develop dyskinesias, resulting in smaller sample sizes for event group at baseline and at follow-up. Other prediction analyses by Chahine et al also found that mean striatal DaTbs was a significant predictor for changes in total MDS-UPDRS scores as well as changes in MDS-UPDRS part III subscores. Although significant, mean striatal DaTbs held low predictive value.[11] It is possible that further monitoring for development of dyskinesias as the PPMI cohort progresses to later stages may provide stronger significance in predicting motor outcomes using baseline drop speeds.

Overall, significant correlations between striatal DaT binding and motor outcomes as well as ability of DaTbs to predict gait outcomes provide some support for the clinical usefulness of quantified DaT binding in predicting clinical outcomes in PD patients. As the PPMI study is ongoing, and more patients develop clinically significant outcomes, further analysis using similar methodology may yield more significant results.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

I.T.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

A.M.: 1A, 1B, 3B

J.Y.: 1A, 1B, 3B

N.P.: 1A, 1B, 1C, 2A, 2C, 3B.

Disclosures

Ethical Compliance Statement: This study was approved by the University of California, Irvine Institutional Review Board.

Informed patient consent was not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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