RESEARCH ARTICLE

Selective Effects of Substantia Nigra and Locus Coeruleus Degeneration on Cognition in Parkinson's Disease

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ABSTRACT: Background: The substantia nigra (SN) and locus coeruleus (LC) are among the first brain regions to degenerate in Parkinson's disease (PD). This has important implications for early cognitive deficits because these nuclei are sources of ascending neuromodulators (i.e., dopamine and noradrenaline) that support various cognitive functions such as learning, memory, and executive function.
Objective: Our aim was to investigate the selective and independent contributions of SN and LC degeneration to cognitive deficits in PD.
Methods: We ran a cross-sectional study testing patients with PD and older adults on tasks of positive reinforcement learning, attention/working memory, executive function, and memory to measure cognitive performance in domains thought to be related to dopaminergic and noradrenergic function. Participants also underwent neuromelanin-sensitive magnetic resonance imaging as a measure of degeneration.
Results: Reduced SN neuromelanin signal in PD was independently associated with impaired positive reinforcement learning ($\beta = 0.41$, 95% confidence interval [CI]: 0.08, 0.74) controlling for changes in the LC. In contrast, reduced LC neuromelanin signal was independently associated with impairments in attention/working memory ($\beta = 0.20$, 95% CI [−0.47, −0.10]) and executive function ($\beta = 0.22$, 95% CI: −0.57, −0.24), controlling for changes in the SN.
Conclusions: These results suggest that SN and LC degeneration may contribute to different cognitive deficits, potentially explaining the heterogeneity that exists in the cognitive manifestations of PD. These results also highlight the potential value of leveraging brain-behavior relationships to develop performance-based measures of cognition that could be used to characterize the phenotypic differences associated with underlying patterns of neurodegeneration.

Key Words: reinforcement learning; attention; executive function; neuromelanin; locus coeruleus; substantia nigra

The catecholaminergic substantia nigra (SN) and locus coeruleus (LC) play crucial roles in modulating a wide range of cognitive processes.[1,2] In Parkinson's disease (PD), SN and LC degeneration starts early.[3] For instance, studies using magnetic resonance imaging (MRI) sensitive to neuromelanin,[4,5] a by-product of catecholamine metabolism, have shown that neuromelanin in the SN and LC is already significantly reduced in the early stages of PD.[6,7] Correspondingly, impairments of the cognitive processes that depend on dopaminergic

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and noradrenergic signalling are also often already present in this early period.[8] However, whether specific aspects of early cognitive dysfunction in PD can be selectively attributed to degeneration in either one or both of these systems is less clear because they have largely been studied in isolation of one another and typically in association with singular domains of cognitive performance rather than with the range of domains they are known to modulate. Meanwhile, delineating their independent contributions to cognition in PD is essential for understanding the heterogeneity that exists in the cognitive phenotype of PD and for developing methods to track clinical outcomes associated with early neurodegeneration.

The idea that degeneration of dopaminergic neurons in the SN plays a critical role in early cognitive deficits observed in PD is supported by studies showing that dopamine replacement remediates certain cognitive deficits, including working memory, executive function, and reinforcement learning.[9-15] Although pharmacological studies demonstrate the importance of dopamine in cognitive functioning, they do not account for individual variability in severity of SN degeneration. Meanwhile, attempts to directly correlate the severity of SN degeneration with cognitive deficits (i.e., attention, working memory, executive function) have produced surprisingly mixed results,[16-18] especially in contrast with the clearer relationship observed with measures of motor disease severity.[16,18,19] One explanation may be that standard neuropsychological testing fails to capture one of the most extensively studied dopamine-dependent processes: reinforcement learning, the ability to update expectations on the basis of feedback.[1,15,20] Reinforcement learning is believed to be impaired in PD on the basis that positive feedback signals, carried by dopamine,[21] are dampened,[15] but whether reduced positive reinforcement learning is associated with the severity of SN degeneration in PD is unknown.

Another explanation for the mixed results linking SN degeneration with cognition is that there may be confounding effects of degeneration in other neurotransmitter systems that also modulate cognition as well as of the effects of age. Indeed, there is an important overlap in the cortical regions receiving projections from dopaminergic, noradrenergic, cholinergic, and serotonergic nuclei, which are all regions known to degenerate in PD, in the cognitive functions reported to be sensitive to modulation by these neurotransmitters (including attention, working memory, and executive function) and, more generally, in the effects of age and PD on cognition.[1,2,22-24] It is particularly important to consider the possible confounding effects of degeneration in the noradrenergic LC because the LC has direct and indirect connections with the SN (via the thalamus and striatum), because levodopa is a precursor to both noradrenaline and dopamine, and because LC terminals have been shown to release both catecholamines.[25-27] These observations raise the possibility that results from pharmacological studies examining the effect of dopamine replacement on cognition may not necessarily reflect the sole contribution of SN degeneration to cognitive deficits. Therefore, it remains unclear to what degree SN and LC degeneration distinctly contribute to cognitive deficits in PD and to what degree these relationships are unique to the disease.

The objective of this study was to determine whether SN and LC neurodegeneration in PD are independently and selectively associated with cognitive deficits. In a large sample of people with PD and older adults, we measured cognitive processes known to be related to these nuclei: positive reinforcement learning for the SN and executive function, attention/working memory, and memory for the LC. A subset of these participants also underwent neuromelanin MRI to extract measures of SN and LC neurodegeneration. First, we predicted that people with PD would be impaired across all cognitive measures. Second, we predicted that SN neurodegeneration would be selectively associated with impaired learning from positive feedback while controlling for effects of LC degeneration and of aging, and, conversely, that LC degeneration would be selectively associated with impairments in attention/working memory, executive function, and memory.

Subjects and Methods

Participants

A total of 135 patients with PD were recruited from the Quebec Parkinson Network (QPN),[28] a registry of patients referred by their neurologist; 72 older adults (control subjects) were recruited from the Montreal community. Other than age (50–90 years) and major brain lesions such as brain tumor or large stroke, there were no exclusion criteria to ensure a representative PD sample. Control subjects were excluded if they had a first-degree relative with PD or atypical parkinsonism, a diagnosis of a neurological disease, and if they had taken dopamine receptor blockers, metoclopramide, or reserpine in the last 6 months. The sample characteristics are summarized in Table 1. Patients completed the study assessments in their usual dopaminergic medicated state. The list of medications was retroactively extracted from the Québec Health Record. All participants completed the study in English or French, provided informed consent, and were paid $25. The study was approved by the McGill University Health Centre Research Ethics Board.

Participants completed mood questionnaires (Questionnaire for Impulsive-Compulsive Disorders in PD, Geriatric Depression Scale), the Montreal Cognitive Assessment, standard neuropsychological testing, additional neurocognitive testing, and MRI. Patients with PD

TABLE 1 *Sample characteristics*

	Control subjects (n = 72)	Patients with PD (n = 135)	*P* value
Age, y	63.3 (10.1)	64.3 (9.2)	0.48[a]
Male/female, n	25/47	95/40	<0.001[b]
Education, y	15.4 (3.3)	15.2 (3.1)	0.56[a]
MoCA score	27.1 (1.8)	25.8 (3.0)	0.03[c]
Disease duration		4.9 (4.1)	
UPDRS-III score		28.2 (13.6)	
Questionnaire for impulsive-compulsive disorders in PD	15.0 (10.7)	17.1 (10.6)	0.19[c]
Geriatric depression scale score	1.7 (3.0)	3.9 (4.1)	<0.001[c]
LED, mg[d]		848.3.0 (585.4)	
Also on DA agonist, n		18	
Also on MAO-B inhibitor, n		20	
Also on COMT inhibitor, n		17	
Not on PD medication, n		5	

Values represent mean and standard deviation.
[a]Group comparison evaluated using parametric independent samples *t* test.
[b]Group comparison evaluated using χ^2 test.
[c]Group comparison evaluated using nonparametric Mann–Whitney *U* test.
[d]Medication information was available for only 101/135 patients with PD.
Abbreviations: PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment; UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; DA, dopamine; MAO, monoamine oxidase; COMT, catechol-*O*-methyltransferase.

completed the Movement Disorder Society Unified Parkinson's Disease Rating Scale. Testing took place over one or two sessions within 90 days. Not all participants completed all assessments, so analyses were conducted on different but largely overlapping subsamples to maximize sample sizes and statistical power. The exact sample size for each analysis is indicated in the relevant results section, and participant characteristics for each subsample are in Supporting Information Table S1. Importantly, sample characteristics were similar across subsamples, and the key group differences were also maintained.

Cognitive Testing

Cognitive Measure of SN Degeneration

Reinforcement learning was measured using an adapted probabilistic learning task[29] with a focus on the learning phase of the task to computationally model learning rates. The task was administered using PsychoPy version 2020.2.10.[30] Three abstract visual stimulus pairs (AB, CD, EF) were presented, and participants learned to choose one stimulus of the pair based on the feedback provided after each trial. Feedback was probabilistic such that the probabilities for receiving positive feedback for choosing stimuli A, C, and E were 0.8, 0.7, and 0.6, respectively. See Supporting Information Methods and Supporting Information Fig. S1 for task details.

Cognitive Measures of LC Degeneration

Because of their previously demonstrated relationship to LC, the domains of interest were attention/working memory, executive function, and memory.[6,16,31-34] Attention/working memory were assessed using the Digit Span test (forward and backward) and the Trail Making Test Part A (TMT A). Executive function was assessed using the TMT A subtracted from TMT Part B (TMT B−A), the Delis-Kaplan Executive Function (D-KEFS) Color-Word Interference Test (CWIT) using response time on the interreference condition (condition 3: Inhibition), and the Brixton Spatial Anticipation Test (BSAT; number of errors). Memory was assessed using the Hopkins Verbal Learning Test (HVLT; total on trials 1, 2, and 3 and delayed recall) and the Rey Complex Figure Test (RCFT; immediate and delayed recalls). Scores for TMT, D-KEFS CWIT, and BSAT were multiplied by −1 to ensure that higher scores represent better performance.

Other Cognitive Measures

To demonstrate the specificity of the relationships of the earlier cognitive tests to degeneration in the SN and LC, we also examined performance in the domains of

visuospatial function and language. Visuospatial function was assessed using the Clock Drawing Test (CDT) and the RCFT Copy trial. Language was assessed using the Letter Verbal Fluency (F, A, S; 1 minute per condition), Semantic Verbal Fluency (animals, actions; 1 minute per condition), and Boston Naming Test (errors without hints out of 60 items).

Neuroimaging

Participants underwent an MRI protocol that included 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (T1w) and 2D T1-weighted fast spin echo (neuromelanin-sensitive) sequences using a 3-T Siemens Prisma scanner with a 32-channel head coil. Imaging parameters are listed in Supporting Information Table S2. This study aimed to investigate the structural integrity of the SN and LC using neuromelanin-sensitive images.

Raw neuromelanin images underwent slice-by-slice normalization to remove inhomogeneities from the image using the MINC Toolkit[35] before being brought to stereotaxic space using transformations from each participant's respective T1w image. Both sequences were acquired in the same session, with the assumption that they are coregistered in raw space. The raw T1w images had undergone preprocessing via the NeuroImaging & Surgical Technologies Longitudinal Pipeline[36] and were nonlinearly registered to stereotaxic space using the PD126 template[37] as the registration target.

In standard space, the SN and LC regions were segmented using a single-atlas registration-based segmentation method. Specifically, the SN region of interest (ROI) was segmented manually by an expert radiologist on an in-house neuromelanin template. The LC ROI was derived from the probabilistic atlas from Brainstem Navigator[38] thresholded to cover the bright LC region on the in-house neuromelanin template and was also made symmetric. For each subject, the SN and LC were automatically segmented by mapping the template ROIs through the inverse of the nonlinear spatial subject-to-template transformation estimated with the NIST longitudinal processing pipeline.[39] All images were visually quality controlled for registration and segmentation accuracy, blinded to group status. Neuromelanin signal intensity from these regions was calculated as a contrast ratio, using the cerebral peduncles and pontine tegmentum as background intensity, respectively (Equation 1):

$$\text{Neuromelanin Signal Intensity} = \frac{\text{average ROI intensity}}{\text{average background intensity}} \quad (1)$$

This procedure has been validated by correlations with known clinical assessments[40] and known group differences.[39]

Analyses

Reinforcement Learning Drift Diffusion Model

Reinforcement learning was evaluated by applying a reinforcement learning drift diffusion model (RLDDM) on the probabilistic learning task data using the HDDM toolbox in Python.[41] The RLDDM uses the drift diffusion model as the choice policy within a reinforcement learning model, allowing us to also account for cognitive processes related to decision-making,[42] and uses hierarchical and Bayesian estimation to fit the model. We specified group (PD, control) as a condition for each parameter such that each group and individual had respective parameter distributions. The Bayesian approach estimates a posterior distribution of parameter values using the Markov Chain Monte Carlo method. We generated 15,000 samples and discarded the first 5000 samples. Convergence was assessed by removing participants with a Gelman-Rubin convergence diagnostic greater than 1.1. See Supplementary Methods for model details. Positive learning rate was our parameter of interest because it represents the speed of updating value from positive feedback.

Statistical Analyses

To evaluate group differences in demographic characteristics and standard cognitive tests, we conducted independent samples t tests (two-tailed), Mann–Whitney U tests, and χ^2 tests. To examine group differences in positive learning rates on the reinforcement learning task, we computed a Bayesian P value by calculating the proportion of the parameter's posterior distribution that overlapped between groups. To examine group differences in neuromelanin signal intensities, we conducted multiple linear regressions with group as an independent variable (effect coded, controls as reference).

To investigate brain-behavior relationships, we conducted multiple linear regressions on cognitive measures with SN and LC neuromelanin signal intensities as independent variables. Reinforcement learning was summarized by positive learning rates. Otherwise, cognitive performance was summarized by five composite scores representing attention/working memory, executive function, memory, visuospatial function, and language. Performance in each test was Z scored (separately for PD and control groups), then composite scores were computed by averaging across Z scores that fell within respective domains. Positive learning rates and composite scores were evaluated as dependent variables in separate analyses in patients with PD and in control subjects. We performed exploratory regressions investigating an interaction between SN and LC neuromelanin signal intensities when either structure significantly predicted cognitive performance.

All regressions controlled for age, sex (effect coded, males as reference), and years of education, and all continuous independent variables were Z scored. Significance was determined by an alpha level of less than 0.05.

Results

Reinforcement Learning Performance Is Impaired in PD

We compared reinforcement learning parameters between 117 participants with PD and 65 control subjects who completed the probabilistic learning task (Supporting Information Table S1). As expected, patients with PD had lower positive learning rates ($Mean_{PD} = 0.085$, $Mean_{Control} = 0.227$, $P = 0.01$) compared with control subjects (Fig. 1). See Supporting Information Table S3 for all results.

Cognitive Performance on Measures of LC Degeneration Is Impaired in PD

A subset of 61 patients with PD and 25 control subjects completed all 15 neuropsychological tests (Supporting Information Table S1). Overall, patients with PD had numerically worse performance on all cognitive measures relating to attention/working memory, executive function, and memory, but statistically significant differences were found on only executive function (TMT B-A, D-KEFS CWIT Inhibition) and memory (the HVLT total and delayed) scores (Table 2). Patients with PD also had numerically worse performance on average in the tests of visuospatial function and language, but group differences were not statistically different.

SN and LC Neuromelanin Signal Intensities Are Reduced in PD

A total of 81 patients with PD and 33 control subjects completed neuroimaging and the reinforcement learning task and/or all 15 neuropsychological measures (Supporting Information Table S1). We found that patients with PD had lower SN neuromelanin signal than control subjects ($\beta_{group} = -0.87$, $P < 0.001$; Fig. 2) and lower LC neuromelanin signal than control subjects ($\beta_{group} = -0.52$, $P = 0.01$). Full model results are listed in Supporting Information Table S4. Other clinical correlates of neuromelanin signal intensity can be found in Supporting Information Fig. S2.

Positive Reinforcement Learning Is Associated with SN Degeneration

A subset of 62 patients with PD and 25 control subjects completed the probabilistic learning task and neuroimaging (Supporting Information Table S1). In PD, lower SN neuromelanin signal intensity was associated with lower positive learning rates ($\beta_{SN} = 0.41$, $P = 0.02$; Fig. 3A), but there was no association between LC neuromelanin and positive learning rate ($\beta_{LC} = 0.02$, $P = 0.89$; Fig. 3A). Age, sex, and education were not significant predictors of positive learning rate ($Ps > 0.30$; Supporting Information Table S5). An exploratory analysis found no interaction between SN and LC signal intensity on positive learning rate ($\beta_{SN\times LC} = -0.02$, $P = 0.93$; Supporting Information Table S6).

We conducted an exploratory analysis in control subjects (n = 25). Surprisingly, higher SN neuromelanin signal intensity was associated with lower positive learning rates ($\beta_{SN} = -0.49$, $P = 0.02$), and as expected, there was no association between LC neuromelanin signal intensity and positive learning rate ($\beta_{LC} = -0.23$, $P = 0.26$; Supporting Information Table S5). However, the posterior distribution of positive learning rates in this smaller subsample of control subjects was not representative of the posterior distribution of positive learning rates in the overall sample of control subjects; thus, these results should be interpreted with caution (Supporting Information Fig. S3).

In summary, we found that greater SN degeneration was selectively associated with worse positive reinforcement learning in PD participants, and there is no significant association of age with reinforcement learning.

Attention/Working Memory and Executive Function Are Associated with LC Degeneration

A total of 61 patients with PD and 25 control subjects completed all 15 neuropsychological tests and neuroimaging (Supporting Information Table S1). In PD,

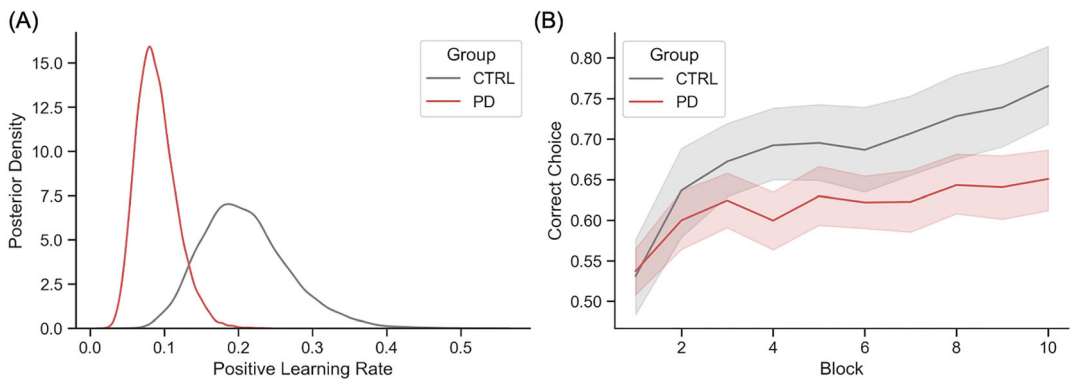

FIG. 1. Reward learning differences between groups. (**A**) Posterior distributions of the positive learning rates demonstrate that participants with Parkinson's disease (PD) are estimated to have lower positive learning rates compared with control subjects (CTRL). (**B**) The raw data are depicted as an average of correct or incorrect optimal choices (0 or 1) across 10 blocks of 15 trials each.

TABLE 2 *Group performance on neuropsychological assessments*

Measure	Control subjects (n = 25)	Patients with PD (n = 61)	*P* value
Attention/working memory			
Digit span forward	6.4 (1.4)	6.3 (1.1)	0.57[a]
Digit span backward	4.9 (1.3)	4.6 (1.4)	0.19[b]
TMT A, s	33.1 (11.0)	41.0 (23.5)	0.08[b]
Executive function			
TMT B−A, s	35.2 (21.2)	63.1 (67.3)	0.02[b]
D-KEFS CWIT inhibition, s	56.0 (14.8)	68.5 (24.7)	0.02[b]
BSAT	15.8 (6.1)	18.8 (8.4)	0.10[a]
Memory			
HVLT total (trials 1–3)	27.3 (4.2)	24.0 (5.8)	0.01[a]
HVLT delayed recall	9.7 (2.4)	8.3 (2.8)	0.04[b]
RCFT immediate recall	19.2 (7.2)	16.1 (7.4)	0.08[a]
RCFT delayed recall	19.1 (6.4)	15.9 (7.9)	0.08[a]
Visuospatial function			
CDT	8.8 (1.8)	8.5 (1.6)	0.16[b]
RCFT Copy	30.3 (4.6)	28.4 (5.4)	0.15[b]
Language			
Letter fluency	42.5 (10.4)	37.2 (12.8)	0.07[a]
Semantic fluency	40.7 (8.2)	36.0 (11.1)	0.06[a]
BNT	54.4 (4.2)	52.7 (4.8)	0.06[b]

Values represent mean performance raw scores (standard deviation).
[a]Group comparison evaluated using parametric independent samples *t* test.
[b]Group comparison evaluated using nonparametric Mann–Whitney *U* test.
Abbreviations: PD, Parkinson's disease; TMT A, Trail Making Test Part A; TMT B−A, Trail Making Test Part A subtracted from Trail Making Test Part B; D-KEFS CWIT, Delis-Kaplan Executive Function System Color-Word Interference Test; BSAT, Brixton Spatial Anticipation Test; HVLT, Hopkins Verbal Learning Test; RCFT, Rey Complex Figure Test; CDT, Clock Drawing Test; BNT, Boston Naming Test.

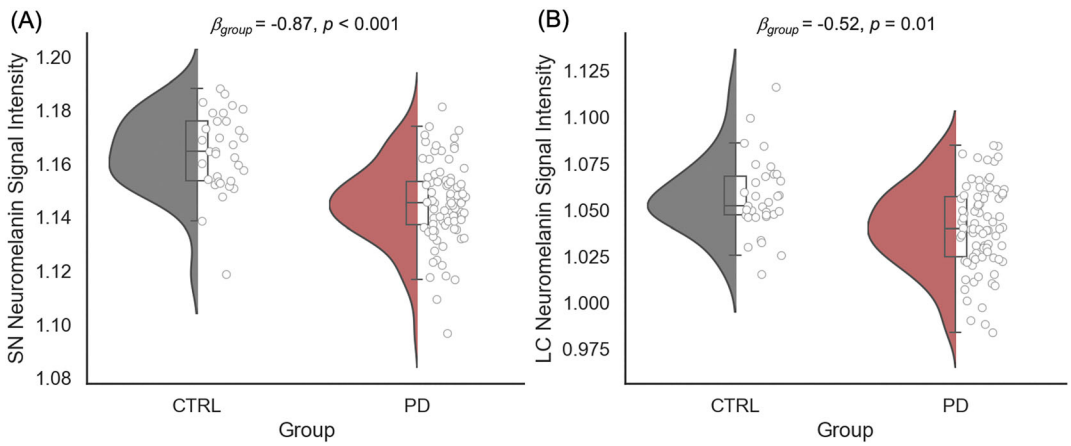

FIG. 2. Neuromelanin signal intensity differences between groups. Participants with Parkinson's disease (PD) have lower neuromelanin signal intensities compared with control subjects (CTRL) in (**A**) the substantia nigra (SN) and (**B**) the locus coeruleus (LC). Box and whisker plots represent the median, interquartile interval, minimum, and maximum. [Color figure can be viewed at wileyonlinelibrary.com]

lower LC neuromelanin signal intensity was associated with worse attention/working memory ($\beta_{LC} = 0.20$, $P = 0.01$; Fig. 3B) and executive function performance ($\beta_{LC} = 0.22$, $P = 0.01$; Fig. 3C), but not memory performance ($\beta_{LC} = 0.07$, $P = 0.69$; Fig. 3D). SN neuromelanin was not associated with performance in

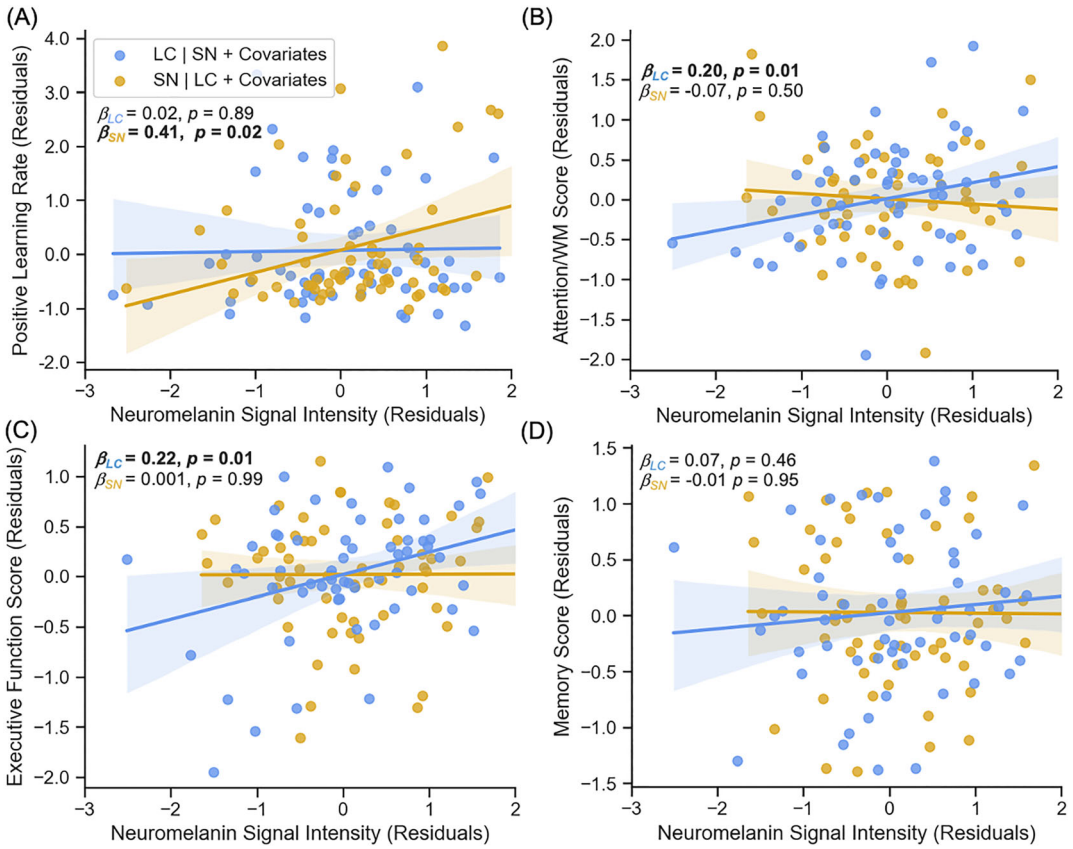

FIG. 3. Brain-behavior relationships in Parkinson's disease participants. (**A**) Substantia nigra (SN), but not locus coeruleus (LC), signal intensity was associated with positive learning rate. LC, but not SN, signal intensity was associated with (**B**) attention/working memory (WM) and (**C**) executive functioning. (**D**) Neither SN nor LC signal intensity was associated with memory. Figures demonstrate the standardized beta coefficients for SN signal intensity after accounting for LC signal intensity and covariates (age, sex, and years of education) in gold. Standardized beta coefficients for LC signal intensity after accounting for SN signal intensity and covariates are in blue.

any domain ($P > 0.50$; Supporting Information Table S7). To further confirm the selective effects of SN and LC degeneration on cognition, we examined their relationship to visuospatial function and language and found no associations in PD ($P > 0.10$; Supporting Information Table S7).

Across all five domains, we found that older age was a predictor of worse cognitive performance (attention/working memory: $\beta_{age} = -0.28$, $P = 0.004$; executive function: $\beta_{age} = -0.40$, $P < 0.001$; memory: $\beta_{age} = -0.47$, $P < 0.001$; visuospatial: $\beta_{age} = -0.38$, $P = 0.001$; language: $\beta_{age} = -0.31$, $P = 0.002$). The standardized beta estimate for the effect of age on cognitive performance was consistently larger than that of the effect of LC degeneration on cognitive performance. There were no effects of sex or education on any of the cognitive domains ($P > 0.16$; Supporting Information Table S7). We also did not find an interaction between LC and SN signal intensity on attention/working memory or executive function ($P > 0.40$; Table S6). We repeated analyses in control subjects and found neither SN nor LC neuromelanin signal intensity were significant predictors of any cognitive domain ($P > 0.14$; Supporting Information Table S7).

In summary, we found that LC degeneration was selectively associated with impaired attention/working memory and executive function, but not memory. In addition, age was a stronger predictor of worse cognitive performance than LC degeneration.

Sensitivity Analyses

All earlier brain-behavior analyses were repeated in the 42 patients with PD who completed all assessments (Supporting Information Table S1). The associations between SN neuromelanin and positive reinforcement learning ($\beta_{SN} = 0.28$, $P = 0.14$) and between LC neuromelanin and attention/working memory ($\beta_{LC} = 0.21$, $P = 0.07$) and executive function ($\beta_{LC} = 0.16$, $P = 0.08$) showed the same pattern as those conducted in the larger subsamples but did not reach significance (Supporting Information Table S8).

Discussion

The goal of this study was to identify aspects of the cognitive phenotype of PD that can be selectively attributed to SN and LC degeneration. In two overlapping

but partially independent samples, we found that (1) SN degeneration was associated with impaired learning from positive feedback; and (2) LC degeneration was associated with deficits in attention, working memory, and executive function, but these associations were not robust in the smaller completely overlapping subsample. Notably, positive reinforcement learning and SN degeneration were independent of age, whereas LC degeneration and all other cognitive deficits were age dependent. By focusing on the impact of severity of degeneration in the SN and LC, these findings extend previous pharmacological research and provide preliminary evidence that individual differences in degeneration in each of these systems are associated with differences in cognitive phenotypes in PD.

SN Degeneration Is Selectively Associated with Impaired Positive Reinforcement Learning

The finding that the severity of SN degeneration, measured by loss of neuromelanin signal, was associated with reduced learning from positive feedback in PD is consistent with literature demonstrating that reduced dopamine signaling is associated with impaired positive reinforcement learning and that there is a beneficial effect of dopamine replacement therapy on performance.[1,15,20,43] This finding extends our understanding of the role of dopamine depletion in cognitive impairment in a few ways. First, rather than studying the effects of a fixed dose of dopamine replacement, which cannot provide insight into the severity of the underlying dopamine deficit, we used neuromelanin MRI to establish the severity of degeneration.[4,5] Second, the relationship between SN neuromelanin signal and positive reinforcement learning was independent of age, and age was not a predictor of positive reinforcement learning rate. Our results, if replicated, therefore suggest that positive reinforcement learning could be used as an assessment to track, even in medicated patients, the specific PD-related, rather than age-related, effects of neurodegeneration, complementary to the way motor assessments of disease severity also correlate with neuromelanin signal.[16,18,19]

We did not find a relationship between SN neuromelanin and attention, working memory, and executive functioning after controlling for LC degeneration. Previous studies investigating the relationship between SN degeneration and cognitive performance have provided mixed results, with some suggestion that SN degeneration, or subregional SN degeneration, is associated with working memory and attention.[16-18] However, these studies did not control for LC degeneration, which we show is an important predictor of performance in these domains. Nonetheless, our results conflict with pharmacological studies in patients with PD showing an effect of dopamine replacement on performance on working memory and executive function tasks.[9,44,45] It is therefore possible that the assessment measures used in our standard neuropsychological battery were either not sensitive enough to the contributions of degeneration in the SN (e.g., due to too few trials, narrower range of performance) or not adequate for measuring the specific aspects of executive function thought to be most sensitive to dopamine state such as those related to executive control (e.g., task-set switching and working memory updating). Indeed, previous studies in PD that also used the digit span task as a measure of working memory did not find a relationship with SN degeneration or with dopamine medication status.[16,46] Furthermore, it has been shown that performance on reinforcement learning tasks also depends on working memory, raising the possibility that the relationship we found between SN neuromelanin and reinforcement learning rate may in fact reflect, to a degree, a reliance on working memory function.[47] It is also important to note that patients with PD were tested on their usual dopamine medications, which may have at least somewhat remediated dopamine-dependent deficits, thereby attenuating possible relationships to SN degeneration.

Positive reinforcement learning was impaired in patients with PD, even though they were on dopaminergic medication. Although some studies show improvement of learning deficits with medication,[9-15] our participants may have more advanced disease than those typically recruited for pharmacological studies. This also aligns with the clinical observation that dopamine replacement rarely fully restores motor symptoms, except for very mild disease. Given that reinforcement learning performance reflected individual differences in SN neurodegeneration even in medicated patients suggests its utility in clinical research.

LC Degeneration Is Selectively Associated with Attention, Working Memory, and Executive Function

We found that LC degeneration was associated with impaired attention and executive function in PD, but not with memory, visuospatial, language, or positive reinforcement learning. This is largely consistent with previous studies[6,16,33] and has been proposed to reflect the fact that frontal cortical regions like the prefrontal cortex (PFC), which are thought to play a critical role in top-down attention, working memory, and executive function, are also projection sites of LC neurons,[1,2] suggesting that the neural mechanism by which patients experience these impairments may be, at least in part, via the loss of innervation from the LC to the PFC.

We did not replicate previously reported relationships between LC degeneration and memory deficits,[16] although this has primarily been observed in older adults.[2,31,32,34] Although this could reflect insufficient selectivity in our memory measures (i.e., the RCFT is a measure of visual memory that also engages visuospatial function), it should be highlighted again that patients were in the dopamine *on* state, which could have enhanced dopamine *and*

noradrenaline levels because levodopa is a precursor of both catecholamines. This also raises the possibility that memory deficits in PD reflect involvement of other structures and neurotransmitter systems, such as the cholinergic basal forebrain projections to the hippocampus and amygdala.[48] The basal forebrain may also contribute more broadly to LC-related cognitive functions in that reduced cholinergic integrity and cortical innervation have been associated with cognitive deficits in PD that overlap with those found to relate to LC, namely, attention, working memory, and executive function.[48]

Limitations

An important limitation of our study was that we did not obtain all measurements in all participants, and therefore analyses were performed on subsamples of the dataset that did not entirely overlap. In particular, the subsample of controls with complete testing was small and demonstrated a posterior distribution of positive learning rates that did not reflect that of the overall control sample, suggesting poor generalizability of the results obtained in controls. This limited our ability to fully account for the effect of age. The effect of age is especially difficult to estimate in PD given its relationship to disease duration but is critical to consider because age-associated brain changes also occur in PD and appear to contribute to the cognitive phenotype in ways that overlap with the effects of neurodegeneration. Similarly, not all the associations obtained in the PD sample survived in the smaller subsample with all measures, highlighting the importance of replicating this work in an independent cohort. A second limitation is that patients were tested only in their medicated state, which could have affected cognitive performance as discussed earlier. We also did not have information about antidepressant medications, which may have also confounded some of the observed relationships. Future studies should investigate the relationships between degeneration and cognitive performance in the *off* state, as well as establish the contributions of other medications targeting ascending neurotransmitter systems. Finally, given that the literature examining dopaminergic medication effects on positive reinforcement learning has shown conflicting results that might depend on the task administered, it will be important to replicate the present results, ideally using several different types of reinforcement learning tasks, to establish the robustness of the result.

Summary

The goal of this study was to identify dissociable roles of SN and LC degeneration on different cognitive functions in early PD that reflect the disease above and beyond the effects of age. We found that SN, but not LC, degeneration is associated with positive reinforcement learning impairments, and that LC, but not SN, degeneration is associated with impairments in attention and executive function in overlapping samples, but this finding was not robust in the smaller subsample of participants who completed all measures and will need to be replicated. By providing a window into the PD-specific and age-independent effect of neurodegeneration on cognition, these preliminary results suggest that brain-behavior relationships can be leveraged to better understand the varying cognitive phenotypes in PD and highlight the potential value of developing performance-based measures of cognition that reflect PD-specific neurodegeneration.

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Data Availability Statement

Deidentified participant data are available upon request.

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