Impact of the Dopamine System on Long-term Cognitive Impairment in Parkinson Disease

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

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BACKGROUND / RATIONALE

▶Prospective, longitudinal studies have found that dementia (PDD) may actually occur in up to 80% of Parkinson disease (PD) patients. In addition, approximately 25-30% of non-demented patients have mild cognitive impairment (PD-MCI).

▶Relatively little is known about how the dopamine system impacts global cognitive abilities and decline over time. It has long been hypothesized that early cognitive impairment in PD is driven mainly by dopaminergic deficits, and that later more severe impairment and dementia may depend on non-dopaminergic, specifically cholinergic, cortical dysfunction. However, this "dual syndrome hypothesis" has not been well tested.

▶Impairment in the dopamine system, assessed primarily with dopamine transporter (DAT) SPECT imaging, has been associated with decreased global(6) and specific(7, 8) cognitive abilities in preliminary studies, including longitudinal decline in early PD(9-11).

▶Regarding dopamine-related single-nucleotide polymorphisms (SNPs), the COMT val158met genotype has been associated with an increased cognitive decline or risk for developing MCI(13, 14), and the DRD2C957T genotype correlated with an overall increased risk of dementia(13). Another small, cross-sectional study reported associations with two DRD2 single nucleotide polymorphisms (SNPs) and dementia in PD(15).

▶In terms of PD medications, while research has demonstrated that levodopa may have acute or short-term beneficial effects on cognitive performance(16, 17), there is no evidence that choice of initial dopamine replacement therapy (i.e., levodopa, dopamine agonist or monoamine oxidase B inhibitor) makes a difference in terms of subsequent dementia rates(18, 19), and a trial of a monoamine oxidase B inhibitor (rasagiline) was negative for treatment of PD-MCI(20).

▶**To date, few studies have examined a large cohort of PD patients from disease onset annually for up to 7 years focused on the onset of cognitive impairment. Furthermore, the specific impact of three distinct aspects of the dopamine system on cognition over time has not been evaluated in a single study: (1) DAT integrity; (2) dopamine-related SNPs; and (3) total dopaminergic medication exposure. The results will help inform whether cognitive impairment in PD is a dopaminergic or non-dopaminergic feature, and whether disease-modifying therapies targeting the dopamine system might be expected to have beneficial effects on cognitive abilities.**

STUDY DESIGN

▶**Participants:** Up to 417 participants had baseline data available, and up to 238 participants had year 7 data available (for the latter, N=234 for MoCA, N=232 for detailed cognitive testing, N=238 for Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)(21) part I cognition score and N=235 for site investigator cognitive diagnosis).

▶**Clinical variables:** Clinical variables were examined as possible co-variates if associated with cognitive impairment in previous research. Fixed variables were age at enrollment, sex, education level and race. Time-varying variables for longitudinal analyses were REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)(22) score, total State-Trait Anxiety Inventory (STAI)(23) score, 15-item Geriatric Depression Scale (GDS-15)(24) score, MDS-UPDRS motor (UPDRS part 3) score ("off" score at baseline and "on" score at all subsequent visits), Anticholinergic Cognitive Burden (ACB) scale(25) score (an assessment of anticholinergic burden of prescribed medications), and cognitive-enhancing medication use (i.e., either acetylcholinesterase inhibitors or memantine).

▶**Definition of cognitive impairment:** The definitions of cognitive impairment were: (1) MoCA: score <26; (2) detailed cognitive testing: ≥2 tests impaired (>1.5 below standardized mean) from a cognitive battery of 5 tests, as previously defined(26); (3) MDS-UPDRS part I cognition score ≥2; and (4) site investigator diagnosis of cognitive impairment (either MCI(27) or dementia(28) guided by consensus criteria). The site investigator cognitive categorization is a partial dataset (data for 104/417 participants at baseline and 269/391 participants at year 1).

- ▶Cognitive impairment was determined at baseline and each annual visit. The longitudinal characterization of cognitive impairment was done two ways: (1) including all participants and considering cognitive impairment at each visit separately, including baseline ("any impairment"); and (2) including a subgroup of participants who developed consistent, incident cognitive impairment versus those participants who were never cognitively impaired ("incident impairment"). For the latter categorization, the impaired group could not be impaired at baseline, were required to have at least one visit after conversion, and once converted had to stay converted at all future visits. The unimpaired could never be impaired at any study visit and were required to have at least one post-baseline assessment. All other participants were excluded from the consistent, incident cognitive impairment analyses.

STUDY DESIGN (CONT'D)

▶**Dopamine system variables:** PPMI methodology for biological variable collection and analysis has previously been reported(29, 30), as has calculation of levodopa equivalent daily dose (LEDD), using published recommendations(31).

- ▶**DaTscan**: Two values for striatal dopamine integrity (DAT) based on DaTscan results were used: (1) mean striatal binding ratio (SBR) value (the average of right caudate, left caudate, right putamen and left putamen raw values), and (2) age- and sex-expected ratio for lowest putamen. DaTscan values for baseline and any values available for years 1 through 5 were used for longitudinal models. 413 participants had a DaTscan at baseline, 367 at year 1, 357 at year 2 or 3, and 299 at year 4 or 5.
- ▶**Genetics:** Genetic data was obtained from https://www.ppmi-info.org/. Single nucleotide polymorphisms (SNPs) previously associated or related to the dopamine system were included (Table 1). A SNP was removed if it was in high linkage disequilibrium (r2 > 0.8) with another SNP, resulting in the removal of DRD1 rs4532, DRD1 rs265981, SLC18A2 rs363224, and MAO-B rs6651806. SNPs were analyzed as dichotomous variable (presence of one or two copies of Allele 2).
- ▶**Levodopa equivalent daily dose:** Total LEDD was zero at baseline as all participants were untreated, and was calculated at every post-baseline visit, including all PD medications prescribed(31).

▶**Analyses:** Data was downloaded from Laboratory of Neuroimaging (LONI) on February 1, 2021. Statistical analyses were performed using programming language R 4.2.0. Data out to seven years was utilized. Longitudinal impairment association between SNPs and cognitive impairment was assessed using generalized estimating equations (GEEs) under a first-order autoregressive (AR-1) correlation structure in generalized linear models (GLM) with the logit link function. To assess the long-term impact of changes in DaTscan and LEDD on cognitive impairment a two-step procedure was implemented: (1) mixed effect analysis was conducted to assess the individual level of changes in DaTscan and LEDD, and (2) GEEs under the AR-1 were used to assess the associations between the changes in DaTscan and LEDD and cognitive impairment during the follow-up period. Clinical variables with p-value <0.3 on univariate analysis were included as covariates in all GLMs. For analyses of any cognitive impairment time-varying covariates were included, when applicable, and baseline cognitive impairment status was also included; for incident cognitive impairment baseline values for all covariates were utilized, and cognitive-enhancing medication use was not included as participants were taking a cognitive-enhancing medication at baseline. As all analyses reported herein are considered exploratory and hypothesis-generating, no correction for multiple comparisons were made, and level of significance 0.05 is considered a preliminary finding requiring replication.

RESULTS

Table 1. Participant characteristics longitudinally

Variable	Baseline (N=417)	Year 1 (N=391)	Year 2 (N=375)	Year 3 (N=363)	Year 4 (N=344)	Year 5 (N=314)	Year 6 (N=273)	Year 7 (N=239)
Cognitive Impairment								
MoCA, %	21.6	34.5	32.4	31.9	30.1	28.3	32.1	28.2
Cognitive test scores, %	15.4	18.5	16.0	18.6	17.5	18.4	17.3	19.8
MDS-UPDRS part I, %	3.1	4.1	8.5	9.4	11.4	12.4	12.6	16.4
Site investigator, %	7.7	14.5	16.3	21.9	21.7	19.7	21.8	28.5
Dopamine system								
Total striatum SBR, mean (SD)	1.40 (0.39)	1.24 (0.35)	1.16 (0.37)	0.96 (0.27)	1.02 (0.34)	0.91 (0.47)	NA	NA
Lowest putamen SBR, mean (SD)	0.33 (0.12)	0.29 (0.10)	0.27 (0.11)	0.21 (0.08)	0.24 (0.10)	0.22 (0.18)	NA	NA
LEDD, mean (SD)	N/A	180.95 (231.14)	333.19 (314.89)	444.68 (349.06)	529.68 (352.03)	613.85 (325.05)	709.20 (438.98)	763.63 (463.12)
Covariates								
RBDSQ, mean (SD)	4.2 (2.7)	4.2 (2.8)	4.6 (3.0)	4.7 (2.9)	5.0 (3.2)	5.0 (3.1)	5.2 (3.2)	5.7 (3.3)
STAI, mean (SD)	65.3 (18.1)	65.1 (18.7)	65.0 (18.6)	64.8 (18.8)	64.7 (18.8)	64.9 (19.4)	66.2 (19.0)	67.9 (18.9)
GDS, mean (SD)	2.3 (2.4)	2.6 (2.9)	2.6 (2.9)	2.6 (2.8)	2.6 (2.8)	2.8 (2.8)	2.8 (2.8)	3.2 (3.1)
UPDRS3, mean (SD)	20.9 (8.9)	23.1 (10.8)	22.9 (11.3)	23.9 (12.1)	24.0 (12.8)	24.5 (13.2)	24.1 (12.3)	24.4 (12.2)
ACB, mean (SD)	0.7 (1.3)	1.1 (1.6)	1.2 (1.8)	1.4 (1.9)	1.4 (1.9)	1.5 (1.9)	1.5 (1.9)	1.7 (2.0)
Cognitive-enhancing medication use, %	0	0.5	1.3	2.8	4.7	5.1	5.1	6.3

RESULTS

Table 2. Dopamine transporter SBR and cognitive impairment

Cognitive outcome	Brain region			
	Baseline total striatum SBR estimate (p value)	Baseline lowest putamen SBR estimate (p value)	Change in total striatum SBR over time estimate (p value)	Change in lowest putamen SBR over time estimate (p value)
Any cognitive impairment				
MoCA	-0.038 (0.87)	-0.223 (0.76)	-3.224 (0.38)	-7.450 (0.59)
Cognitive test scores	-0.723 (0.005)	-1.109 (0.16)	3.007 (0.45)	21.124 (0.18)
MDS-UPDRS part I	-0.502 (0.10)	-1.037 (0.36)	-3.072 (0.53)	6.929 (0.71)
Site investigator	0.126 (0.61)	-0.195 (0.82)	-5.845 (0.13)	-9.804 (0.52)
Incident cognitive impairment				
MoCA	-0.547 (0.41)	0.418 (0.83)	7.333 (0.43)	0.128 (0.99)
Cognitive test scores	-3.201 (0.003)	-4.652 (0.11)	25.880 (0.12)	31.880 (0.41)
MDS-UPDRS part I	-1.627 (0.02)	-3.880 (0.08)	-4.679 (0.65)	22.109 (0.54)
Site investigator	-1.640 (0.07)	-6.361 (0.08)	1.106 (0.91)	14.906 (0.74)

Table 3. Dopamine-related SNPs and cognitive impairment

Cognitive outcome	Genetic SNP								
	DRD3 rs6280 estimate (p value)	DRD5 rs6283 Estimate (p value)	DRD5 rs1967550 estimate (p value)	SLC6A3 rs27072 Estimate (p value)	DRD1 rs686 Estimate (p value)	DDC rs1451375 estimate (p value)	SLC18A2 rs363387 estimate (p value)	SLC18A2 rs2015586 estimate (p value)	SLC18A2 rs363227 estimate (p value)
Any cognitive impairment									
MoCA	0.081 (0.65)	-0.005 (0.98)	0.082 (0.67)	-0.006 (0.98)	-0.052 (0.78)	-0.071 (0.70)	-0.391 (0.20)	0.143 (0.46)	-0.067 (0.76)
Test scores	0.248 (0.21)	0.027 (0.89)	0.097 (0.64)	-0.062 (0.77)	0.098 (0.62)	-0.181 (0.36)	-0.303 (0.39)	0.030 (0.89)	-0.357 (0.13)
MDS-UPDRS	0.243 (0.29)	0.333 (0.17)	0.222 (0.35)	0.030 (0.90)	0.439 (0.06)	0.017 (0.94)	-0.968 (0.01)	0.152 (0.55)	-0.139 (0.62)
Site investigator	0.095 (0.63)	0.043 (0.83)	0.124 (0.57)	-0.006 (0.98)	0.079 (0.70)	0.013 (0.95)	-0.260 (0.45)	0.307 (0.15)	0.212 (0.39)
Incident cognitive impairment									
MoCA	-1.246 (0.02)	-0.004 (0.99)	0.310 (0.56)	-0.091 (0.87)	-0.959 (0.06)	-0.218 (0.68)	0.095 (0.91)	0.538 (0.33)	0.623 (0.29)
Test scores	0.089 (0.88)	0.654 (0.27)	0.312 (0.62)	-0.372 (0.56)	-0.246 (0.67)	0.569 (0.41)	0.455 (0.59)	1.139 (0.15)	0.440 (0.47)
MDS-UPDRS	0.164 (0.73)	0.269 (0.58)	-0.642 (0.17)	0.706 (0.13)	0.829 (0.12)	0.135 (0.78)	0.032 (0.96)	0.847 (0.15)	0.064 (0.91)
Site investigator	0.691 (0.36)	1.346 (0.10)	0.004 (0.10)	-0.460 (0.56)	-0.746 (0.29)	-0.274 (0.68)	-0.381 (0.76)	-0.249 (0.73)	1.636 (0.05)
Cognitive outcome	Genetic SNP								
	SLC18A2 rs363276 estimate (p value)	DRD4 rs747302 estimate (p value)	DRD4 rs1800955 estimate (p value)	TH rs6356 estimate (p value)	DRD2 rs1800497 estimate (p value)	COMT rs4680 estimate (p value)	MAOB rs1799836 estimate (p value)	MAOB rs10521432 estimate (p value)	MAOB rs5905512 estimate (p value)
Any cognitive impairment									
MoCA	0.117 (0.57)	-0.291 (0.11)	-0.127 (0.51)	-0.030 (0.87)	0.250 (0.16)	0.164 (0.46)	-0.202 (0.27)	-0.202 (0.33)	0.399 (0.03)
Test scores	0.076 (0.73)	0.016 (0.94)	0.093 (0.67)	0.265 (0.18)	0.201 (0.31)	0.133 (0.57)	0.037 (0.85)	0.052 (0.81)	0.246 (0.22)
MDS-UPDRS	0.014 (0.96)	0.118 (0.62)	0.280 (0.29)	0.051 (0.82)	0.036 (0.87)	0.075 (0.77)	0.138 (0.55)	0.132 (0.59)	0.062 (0.77)
Site investigator	0.351 (0.12)	-0.201 (0.34)	-0.078 (0.71)	-0.114 (0.57)	0.034 (0.87)	0.155 (0.52)	-0.197 (0.31)	-0.317 (0.16)	0.367 (0.07)
Incident cognitive impairment									
MoCA	0.169 (0.77)	-0.617 (0.26)	0.499 (0.38)	0.003 (0.99)	0.519 (0.32)	0.238 (0.66)	-0.524 (0.29)	-0.493 (0.33)	0.532 (0.29)
Test scores	0.500 (0.39)	0.328 (0.59)	0.375 (0.56)	0.347 (0.56)	0.359 (0.54)	0.100 (0.88)	-0.582 (0.32)	-0.580 (0.40)	0.610 (0.30)
MDS-UPDRS	-0.006 (0.99)	0.334 (0.53)	1.287 (0.05)	-0.174 (0.71)	-0.094 (0.85)	0.754 (0.21)	-0.397 (0.42)	-0.770 (0.20)	0.178 (0.71)
Site investigator	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.658 (0.35)	-0.299 (0.66)

Table 4. Dopaminergic therapy and long-term cognitive impairment

Cognitive impairment outcome	Change in LEDD over time estimate (p value)
Any cognitive impairment	
MoCA	0.183 (0.20)
Test scores	0.408 (0.01)
MDS-UPDRS	0.629 (<0.001)
Site investigator	0.187 (0.22)
Incident cognitive impairment	
MoCA	0.901 (0.01)
Test scores	-0.062 (0.92)
MDS-UPDRS	1.183 (<0.001)
Site investigator	1.749 (0.005)

CONCLUSIONS

▶The findings provide preliminary evidence that the dopamine system is involved with cognitive decline in PD, including incident cognitive impairment.

▶ The predictive measures were **nigrostriatal dopaminergic integrity, multiple dopamine system-related genes**, and **chronic dopamine replacement therapy exposure**.

▶In addition, multiple other demographic and non-motor clinical variables predicted long-term cognitive decline (e.g., **increasing age, male sex, lower level of education, non-White race, and increasing severity of anxiety and depression**).

▶While the dopamine system, including dopaminergic medications, have been implicate in the etiology of certain psychiatric features in PD (e.g., depression, anxiety, impulse control disorder and psychosis), little is known about its impact on long-term cognitive course. The results reported herein, from a relatively large, longitudinal, biomarker-rich cohort study with a range of cognitive assessments, suggest that the dopamine system in PD is implicated not only in acute, early or domain-specific cognitive changes, but also in long-term cognitive impairment outcomes of great clinical significance to patients.

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PPMI data downloaded from PPMI website: http://www.ppmi-info.org/