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Cognition in Individuals at Risk for Parkinson's: Parkinson Associated Risk Syndrome (PARS) Study Findings

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Abstract

Objectives—The Parkinson Associated Risk Syndrome Study identified a cohort of healthy adults with hyposmia and dopamine transporter binding reduction to characterize individuals at risk for Parkinson's disease (PD). We describe the cognitive profile of this cohort.

Methods—Individuals older than 50 y without PD were recruited. Two hundred twenty-five completed cognitive testing and were included in the final analysis. A neuropsychological test battery was administered and normative scores created for global cognition, memory, executive function/working memory, processing speed/attention, visuospatial abilities, and language

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domains. Other non-motor symptoms (constipation, depression, anxiety, and rapid eye movement sleep behavior disorder) were assessed through questionnaires.

Results—Individuals with both hyposmia and reduced dopamine transporter binding ($n = 38$) had lower mean scores for global cognition, executive function/working memory, and memory compared with all other participants ($n = 187$). In separate multivariate logistic regression models, lower global cognition (odds ratio, 1.97, $P = 0.004$), and specifically executive function/working memory (odds ratio, 1.84, $P = 0.004$) scores were associated with membership in the hyposmia with dopamine transporter reduction group. Combining hyposmia with relative impairment on specific cognitive domains increased the odds of dopamine transporter binding reduction compared with hyposmia alone, with the greatest increase in odds for hyposmia plus executive function/working memory relative impairment (68% increase in odds from 4.14 to 6.96).

Conclusion—Changes in global cognitive abilities, and specifically executive function/working memory, are present in individuals at risk for PD. Combining non-motor features, including cognition, improves prediction of dopamine transporter binding reduction.

Keywords

Parkinson's; cognition; prodromal; dopaminergic deficit; hyposmia

Neurodegeneration in Parkinson's disease (PD) begins years before development of motor symptoms.¹ Increasingly we have recognized, largely based on multiple failed disease-modification trials,² that intervention must occur in the earliest stages of the disease to impact neurodegeneration. Characterization of the prodromal PD phase is essential to enable expeditious identification of individuals who may benefit from disease-modifying agents as they emerge. This provides the impetus for several ongoing studies, including the Parkinson Associated Risk Syndrome (PARS) study.^{3,4} The PARS cohort was established to test a two-stage screening strategy for PD consisting of olfactory testing followed by dopamine transporter (DAT) imaging.

The PARS includes a battery of assessments of non-motor symptoms selected based on evidence suggesting that they may be informative regarding prodromal PD. For example, the incidence of PD is nearly five times greater in individuals with constipation during midlife compared with those without,⁵ and the odds of developing PD in those with depression are more than three times greater than in those without.⁶ Increased anxiety is also associated with increased relative risk for PD,⁷ and more than 50% of individuals with rapid eye movement (REM) sleep behavior disorder (RBD) will go on to develop a neurodegenerative synucleinopathy.⁸ Although the prevalence of cognitive dysfunction in early PD is as high as 30%,^{9,10} and abnormalities in executive function, verbal memory, and attention have been shown in idiopathic RBD,¹¹ cognitive function in prodromal PD has not been well characterized. We herein examine the cognitive profile of individuals presumed to be at increased risk of PD based on hyposmia and DAT reduction.

Methods

The PARS protocol was approved by the Western Institutional Review Board, the Human Research Protection Office at the US Army Medical Research Material and Command, and

participating center local institutional review boards. Informed consent was obtained from each subject.

Methods for participant recruitment and assessments have been previously described.^{4,12} Briefly, regional mailings, email invitations, and posts to PD foundation websites were used to target individuals with or without a family history of PD living in specific geographic regions. Recruitment and study assessments occurred at 16 movement disorders specialty clinics in the United States. Inclusion criteria were (1) age older than 50 years (or within 10 years of age of onset of an affected PD relative) and (2) no known reason for abnormal olfaction (eg, nasal trauma, sinus infection/surgery). Exclusion criteria included (1) history of PD or other neurodegenerative disorder, (2) history of dementia or evidence for it on examination (including Mini-Mental State Examination score < 27), and (3) evidence of parkinsonism on examination thought to be consistent with PD (as determined by the investigator).

Self-Administered Non-motor Assessments

The following assessments were mailed to participants for self-administration:

1. Olfaction: assessed with the 40-item University of Pennsylvania Smell Identification Test.¹³ Subjects scoring in the 15th percentile or lower based on age and sex (based on study-specific norms, as described⁴) were classified as hyposmic; all others were considered normosmic.
2. Bowel movement frequency was assessed with an adapted version of a previously used questionnaire⁵; constipation was defined as less than 1 bowel movement per day.
3. Motor symptoms were assessed using the PD Symptom Rating Scale.¹⁴ Endorsement of two or more symptoms was considered positive.
4. RBD was assessed via a questionnaire administered to participants who had input from a bed partner (n = 143). The questionnaire was a three-item modified version of a validated RBD questionnaire.¹⁵ Subjects were considered to have RBD if any RBD symptom was reported to occur at least once per month.
5. Anxiety was assessed with the State-Trait Anxiety Inventory.¹⁶ A score greater than 39 on either the state or trait forms is considered significant anxiety.¹⁷
6. Depression was assessed with the Center for Epidemiological Studies Depression Scale. A score of 16 or higher indicates significant depression.¹⁸

Clinical Evaluation

All hyposmic subjects were invited to participate in the clinical and imaging assessments. Frequency matching was used to select a group of age- (within 5 years) and sex-matched normosmic controls in a 2:1 hyposmic:normosmic ratio. Participants underwent baseline clinical evaluations at the nearest participating movement disorder specialty clinic, including medical history and medication-use interview and administration of the Unified PD Rating

Scale (UPDRS) and a PD diagnostic questionnaire, which was completed by clinical investigators blinded to the results of olfactory testing and DAT imaging.

Imaging Evaluation

Dopamine transporter imaging using [^{123}I]-fluoro-propyl-beta-carbomethoxy-3beta-(4-iodophenyl) tropane ([^{123}I] β -CIT) single-photon emission computed tomography (SPECT) was performed at a single imaging center (Institute for Neurodegenerative Disorders, New Haven, CT, USA). Participants received an intravenous administration of 6 mCi [^{123}I] β -CIT. Single-photon emission computed tomography acquisition was performed as previously described.¹⁹ The striatal binding ratio (SBR) (mean binding in the bilateral putamen and caudate) was determined from SPECT images, using a standardized region of interest analysis. For the purpose of these analyses, baseline scans were categorized as DAT reduction (< 80% age-expected lowest putamen [^{123}I] β -CIT uptake) or no DAT reduction (>80% age-expected lowest putamen [^{123}I] β -CIT uptake)²¹. This cutoff was chosen to maximize detection of potentially at-risk individuals. Neuroimaging analyses were performed by experts blinded to all clinical information, neuropsychological test results, and olfactory testing.

Cognitive Assessments

Cognitive testing was introduced after study initiation, therefore a subset of participants did not undergo cognitive testing. Otherwise cognition was assessed (at the time of clinical or imaging evaluation) by using 23 variables from 17 tests that were specific to the following domains:

Memory—Memory was tested with the following tests: (1) Hopkins Verbal Learning Test—Revised (immediate and delayed recall and recognition),²² (2) Repeatable Battery for Assessment of Neuropsychological Status (RBANS Battery A, immediate and delayed recall of the “fire story” and figure recall),²³ and (3) Wechsler Memory Scale (WMS-III) logical memory story A, immediate and delayed recall.²⁴

Executive Function/Working Memory—Executive function/working memory was tested with the following tests: (1) Controlled Oral Word Association Test (phonemic fluency: total word generation for letters F, A, and S and semantic fluency: total word generation for male names, animal, fruit, and vegetable categories)²⁵; (2) Trail Making Test Part B (time to complete)²⁶; and (3) Wechsler Adult Intelligence Scale (WAIS)- III digit span backwards.²⁴

Processing Speed/Attention—Processing speed and attention were measured by the following tests: (1) WAIS-III Digit Symbol Coding (raw score), (2) WAIS-III symbol search (raw score), (3) WAIS-III digit span forward,²⁴ and (4) Trail Making Test Part A (time to complete).²⁶

Visuospatial Function—Visuospatial function was tested by the (1) RBANS Battery A figure copying and line orientation,²³ (2) Clock Drawing Test, (3) WAIS III Block Design

(raw score),²⁴ (4) Test of Visual-Perceptual Skills (TVPS)-UL-R,²⁷ (5) Visual Object and Space Perception Battery (silhouettes animals and silhouettes objects).²⁸

Language—Language was tested with the Boston Naming Test (split half raw score).²⁹

Statistical Analyses

Baseline demographic and hyposmic/normosmic status for PARS subjects who did and did not complete the cognitive testing were compared using *t* tests and χ^2 tests.

Scores for each cognitive test were reversed, if needed, so that higher scores would indicate better performance. As previously described,³⁰ for each raw and unadjusted cognitive variable a *z* score for each subject was calculated by subtracting the mean and dividing by the standard deviation for the entire study population. A domain *z* score was then created by summing *z* scores for all tests pertaining to that domain, then subtracting the mean for that domain and dividing by the standard deviation for the resulting score. A global cognitive score based on the domain *z* scores was calculated in the same way; although the number of cognitive variables included in each domain varied, each cognitive domain was given equal weight when calculating the global cognitive score. For the purpose of these analyses, *z* scores were signed so that higher scores indicate better performance, and odds ratios are presented so that an odds ratio greater than 1 implies an increased risk of impairment. Because the sample was drawn from community-dwelling generally healthy and neurologically normal adults, we did not anticipate significant cognitive dysfunction in this group, and reference to impairment within this manuscript is relative. Most of the analyses used cognitive measures as continuous *z* scores, but, for defining groups with or without relative cognitive impairment, dichotomized variables were calculated based on a score greater than 1 standard deviation (SD) below the group standardized mean, within the range recommended to identify mild cognitive impairment in PD.³¹

Three groups were defined for comparison: (1) subjects with both hyposmia and a reduction in DAT binding (hyposmia/+DAT reduction group), (2) subjects with hyposmia without a reduction in DAT binding (hyposmia/-DAT reduction group), and (3) subjects with normosmia with no reduction in DAT binding (normosmia/-DAT reduction group). Among all of the groups, the hyposmia/+DAT reduction group is considered at greatest risk for PD, and the normosmia/-DAT reduction group is likely most representative of the general population because of the absence of the two primary risk factors being evaluated in the PARS study.

T tests and Kruskal-Wallis tests were used to compare cognitive function and SBR between groups, and the effect size was estimated using Cohen's *d*. Logistic regression models, with the domain *z* scores as predictors, were used to examine associations with group status and also with DAT reduction status. Relative cognitive impairment was evaluated in separate models by comparing subjects with both hyposmia and relatively worse cognitive performance with subjects with neither; non-motor symptoms were similarly evaluated. Models were adjusted for age, education, and sex, all factors that may influence cognitive performance. Influence plots were examined for possible outliers. All *P* values are two-tailed. Nominal *P* values are reported, and those *P* values from logistic regression models

that would remain significant after a Bonferroni correction are bolded. All analyses were performed using SAS software version 9.3 (SAS Institute).

Results

Sample

Of a total of 303 individuals (203 with hyposmia, and 100 with normosmia) who completed the baseline clinical and imaging evaluations for the PARS study, 225 also completed the detailed baseline cognitive testing and were included in the final analysis. Compared with those who completed the battery, those not tested ($n = 78$) were significantly younger (mean base-line age, 58.6 years [SD = 8.5] vs 66.0 [SD = 8.4], $P < 0.001$), and more likely to be female (58/78 [74%] vs 95/225 [42%], $P < 0.0001$), hyposmic (61/78 [78%] vs 142/225 [63%], $P = 0.01$), and to have a family member with PD (60/78 [77%] vs 86/225 [38%], $P < 0.001$).

Among the 225 participants, 38 were in the hyposmia/+DAT reduction group, 104 participants were in the hyposmia/-DAT reduction group, and 76 were in the normosmia/-DAT reduction group (Fig. 1). Mean DAT SBR was 4.16 (SD = 0.82) in the hyposmia/+DAT reduction group compared with 5.96 (SD = 1.00) in the normosmia/-DAT reduction group ($P < 0.001$) (Fig. 2). No significant differences were found between the hyposmia/+DAT reduction group ($n = 38$) and all others ($n = 187$) in history of cardiovascular, neurological, or psychiatric disorders, or in use of antidepressant and antipsychotic medications, or medications for cognitive dysfunction or dementia.

Cognitive Performance in the Hyposmia/+DAT Reduction Group Versus All Other Subjects

Compared with the rest of the sample ($n=187$), the hyposmia/+DAT reduction group was more likely to be male and had lower DAT SBR and higher UPDRS scores, although UPDRS scores were low in both groups (Table 1) (despite the higher UPDRS motor scores, none of the participants included in this analysis, in any group, met criteria for a diagnosis of PD based on the investigator's opinion). The 38 individuals in this hyposmia/+DAT reduction group had significantly lower mean z scores of global cognition, executive function/working memory, and memory compared with all other participants combined on bivariate analyses, with small to medium effect sizes (Supplemental Data Table e-1).

In separate multivariate logistic regression models adjusted for age, sex, and years of education, worse global cognition (odds ratio [OR] = 1.97; 95% confidence interval [CI], 1.24-3.12), executive function/working memory (OR = 1.84; 95%CI, 1.21-2.81), memory (OR = 1.64; 95%CI, 1.09-2.48), and processing speed/attention (OR = 1.53; 95%CI, 1.00-2.34) were associated with the combination of hyposmia and DAT reduction (Table 2). Results were similar when three outliers were removed. When these results were adjusted for multiple comparisons using a Bonferroni correction for the six statistical test results shown in Table 2, the global cognition and executive function findings remained significant.

Cognitive Performance in the Hyposmia/+DAT Reduction Group Versus Normosmia/-DAT Reduction Group

When the hyposmia/+DAT reduction group (n=538) was compared with the normosmia/-DAT reduction group (n = 76) in separate multivariate logistic regression models, significant between-group differences were noted in global cognition (OR = 2.54; 95%CI, 1.42-4.54), executive function/working memory (OR = 2.03; 95%CI, 1.27-3.27), memory (OR = 1.71; 95%CI, 1.03-2.82), and processing speed/attention (OR = 1.91; 95%CI, 1.14-3.21) (Supplemental Data Table e-2). When these results were adjusted for multiple comparisons using a Bonferroni correction for the six statistical test results shown in Supplemental Data Table e-2, the global cognition and executive function findings remained significant.

Cognitive Performance in the Hyposmia/-DAT Reduction Group Versus Normosmia/-DAT Reduction Group

Comparisons of the hyposmia/-DAT reduction group (n = 104) with the normosmia/-DAT reduction group (n = 76) did not show significant differences in cognition between the two groups (Supplemental Data Table e-3).

Association of Cognitive Performance and DAT Reduction

As previously reported,¹² presence of hyposmia was strongly associated with DAT reduction in the PARS cohort. In the current analysis, hyposmic subjects with relative cognitive impairment (defined as >1 SD below the group mean score for the global or specific domain scores) were compared with normosmic subjects who were without cognitive impairment, for evidence of DAT reduction (using the cutoff of 80% of age-expected [¹²³I]β-CIT uptake to define DAT reduction). The odds ratio of hyposmia alone as a predictor of DAT reduction was 4.14 (95%CI, 1.68-10.16) in a logistic regression model adjusting for age, sex, and education. The odds ratios for DAT reduction increased over that for hyposmia alone when either relative global cognitive impairment or individual cognitive domain impairments were separately added to the model (Table 3). For example, presence of DAT reduction in subjects with hyposmia plus relative executive function/working memory impairment (n = 31; 35% with DAT binding 80%) was compared with nonimpaired normosmics (n = 74, 8% with DAT binding 80%), yielding an odds ratio of 6.96; 95% CI, 1.97-24.64, a 68% increase over that of hyposmia alone (4.14). When these results were adjusted for multiple comparisons using a Bonferroni correction for the six statistical test results shown in Table 3, the hyposmia + global cognitive impairment and hyposmia + executive function impairment findings remained significant.

Similarly, examining the combination of hyposmia in the presence of other non-motor symptoms in separate logistic regression models, adjusting for age at testing, sex, and education, the combination of hyposmia plus depression, compared with subjects with neither, increased the odds of having DAT reduction by 189%, from 4.14 (95% CI, 1.68-10.16) for hyposmia alone to 11.98 (95%CI, 2.93-48.95). (Additional adjustment for depression did not substantially change the results presented in the previous tables.) The combination of hyposmia and constipation (OR = 9.27; 95%CI, 2.46-35.02) also increased the odds of DAT reduction, whereas adding presence of either RBD symptoms or anxiety

did not meaningfully alter the odds compared with those for hyposmia alone (data not shown).

Associations with DAT reduction were also examined among the entire group of 142 patients with hyposmia (n = 38 with DAT reduction and n = 104 without) in a single logistic regression model including age, sex, education, global cognitive z score, and presence or absence of anxiety, depression, and constipation. Presence of depression (OR = 4.70; 95%CI, 0.77-28.78; $P = 0.09$) and worse global cognitive performance (OR = 1.58; 95%CI, 0.94-2.64; $P = 0.08$) were associated with DAT reduction.

Discussion

We found that cognitive performance was worse in a group of individuals enriched for risk of developing PD because of the presence of both hyposmia and DAT reduction. Cognitive differences in this cohort of individuals at risk for PD were most pronounced on the global cognitive measure, and more specifically for executive abilities (with some suggestion for memory and attention as well). This suggests that cognitive abnormalities may be part of the prodromal PD syndrome. This study extends the findings in early, untreated (incident) PD.⁹

Although a variety of non-motor symptoms may be part of prodromal PD, many, including hyposmia, constipation, and depression or anxiety, are relatively nonspecific, particularly in older adults. Findings from the PARS cohort presented here and elsewhere¹² suggest that combining various non-motor signs and symptoms along with hyposmia increases the association with DAT reduction. The results presented herein suggest the incorporation of cognitive performance into such models as well. Of course, predictive models will require optimization to minimize the tradeoff in negative predictive value that will occur for models with strong positive predictive value.

Very few studies have evaluated the cognitive profile of individuals at risk for PD. In the Honolulu-Asia Aging Study³¹ of 3,387 men without PD, 17% of those scoring in the lowest tertile on simple reaction time testing exhibited incidental Lewy bodies postmortem, compared with 6% in the other tertiles. In addition, those scoring in the lowest quartile on executive function scales had an incidence of PD of 26.1/10,000 person years, compared with 10.9 for those scoring in the highest quartile.

It is likely most individuals in the PARS cohort who have hyposmia without DAT deficit will not go on to develop PD. The cause of their hyposmia was not part of our analyses. Data suggest that the presence of hyposmia, irrespective of the underlying cause, is associated with cognitive dysfunction. Subjective cognitive complaints are common among individuals with isolated hyposmia,³² and among older adults without cognitive impairment, olfactory loss has been associated with increased risk of mild cognitive impairment and predicts conversion to Alzheimer's disease.³³ In our cohort, as well another hyposmic cohort examined for cognitive deficits,³⁴ subjects identified just on the basis of hyposmia (with no DAT reduction) did not show significant differences in cognition compared with those subjects without hyposmia. Ongoing longitudinal analyses of our cohort will investigate

whether presence of hyposmia itself, irrespective of the underlying cause, is associated with greater rates of decline in cognition over time.

Although our data do not allow any conclusions to be drawn regarding the cause of cognitive dysfunction in individuals potentially at risk of PD, several possibilities warrant consideration and future study. In the general population, an association between DAT binding and cognitive function was demonstrated in 12 individuals without PD,³⁵ and in a cohort of 491 PD patients, de novo at baseline, lower baseline striatal DAT binding was associated with global cognitive decline over a 22-month period.³⁶ Conversely, cognitive reductions in prodromal PD may be partially mediated by early extrastriatal disease pathology or nondopaminergic systems. This is supported by animal data; in a mouse model of PD, cognitive dysfunction (abnormalities in spatial learning and novel object recognition) was noted preceding motor abnormalities and before loss of dopaminergic neurons was expected.³⁷ In humans, abnormalities in noradrenergic³⁸ and cholinergic pathways³⁹ have been implicated in cognitive dysfunction in PD and are present even in early disease stages.⁴⁰ Involvement of these neurotransmitter systems occurs early in Braak's proposed pathologic staging,⁴¹ at a time when brainstem nuclei and the olfactory bulb are hypothesized to be involved by the pathologic process but before involvement of nigral or cortical neurons (ie, in the premotor PD phase), making them prime candidates for mediating cognitive dysfunction in prodromal PD. A stronger association of hyposmia with cholinergic, as compared with dopaminergic, denervation supports this hypothesis.⁴² Functional imaging of these other neurotransmitter systems in prodromal cohorts would offer a means for further investigation. Another consideration is that progression of neuropathology in PD does not conform to Braak's staging system in all cases.⁴³ Instead, possibly in at least a subset of patients with prodromal PD, cortical involvement with Lewy body pathology precedes nigral involvement, particularly in those more likely to ultimately be diagnosed with dementia with Lewy bodies.

A limitation of this study is that, because cognitive testing was implemented after study initiation, only 74% of the PARS sample completed it, so our sample may not be fully representative of the entire PARS cohort. Those who did not complete cognitive testing were younger than those who did, and our findings therefore also may not be generalized to younger PD at-risk groups. In addition, the PARS cohort was recruited from both family members of PD patients and the community, so this may not be entirely representative of a typical prodromal PD group. Although we administered a relatively large battery of neuropsychological tests, we acknowledge that some of the tests can be assigned to more than one cognitive domain. Furthermore, the approach we took of creating both domain scores and a global cognitive measure accounting for all the domains, although previously used³⁰, has not been explicitly validated. Future analyses could use principal components or factor analysis to assign the cognitive variables to domains in an unbiased fashion, and to validate the derivation of the global cognitive score from domain subscores. We emphasize that, because these analyses were exploratory, our results will need to be confirmed in a subsequent study. The RBD assessments were limited to only the subset of participants with a bed partner, and the questions administered may have lacked diagnostic accuracy. This may account for the lack of improvement in prediction of DAT reduction when adding RBD into the model along with hyposmia. Finally, because no cutoffs have been defined for what

is considered normal versus abnormal DAT binding in prodromal PD, we selected a liberal cutoff of 80% or less of age-expected putamen [^{123}I] β -CIT uptake to minimize risk of misclassification of at-risk individuals in the normal group. Future work examining cognition in larger cohorts with more conservative cutoffs is needed.

Our study demonstrates cognitive abnormalities in a PD at-risk cohort. Our data support the need to extensively characterize non-motor features of prodromal PD and suggest that combining a range of demographic and non-motor features may maximize the accuracy of predicting risk.³¹ The significance of these data, and their utility in clinical practice, will ultimately be determined through longitudinal follow-up currently underway to evaluate the rate of phenoconversion to PD among these at-risk subjects. This will allow us to validate our techniques for identifying prodromal individuals and our predictive models for determining their future risk of PD. Ongoing work to characterize prodromal PD will be essential in quantifying disease risk and ultimately identifying which individuals are candidates for disease-modifying interventions during the prodromal period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Frequency of hyposmia and dopamine transporter reduction in sample with cognitive testing.

Fig. 2.
Representative dopamine transporter single-photon emission computed tomography images.
[Color figure can be viewed in the online issue, which is available at
wileyonlinelibrary.com.]

Table 1
Demographics and clinical features of hyposmia/+DAT reduction group versus all others

Variable	Hyposmia/+DAT Reduction Group ^a (n = 38)	All Others ^b (n = 187)	P Value for Differences ^c
Mean age at cognitive testing (SD; range)	65.7 (6.9; 49.4-79.1)	67.1 (8.4; 50.4-92.9)	0.50
Male sex (N, %)	28 (74%)	102 (55%)	0.03
Mean education in years (SD; range)	15.6 (2.7; 12.0-20.0)	16.0 (2.3; 9.0-20.0)	0.37
Family member with PD (n, %)	12 (32%)	74 (40%)	0.36
Smoking history, current or past (n, %)	20 (53%)	97 (52%)	0.99
Mean total UPDRS (SD; range)	4.6 (3.5; 0.0-11.0)	2.6 (3.5; 0.0-25.0)	<0.001
Mean striatal binding ratio (SD; range)	4.2 (0.8; 2.0-5.5)	5.8 (1.0; 2.5-9.3)	<0.001

^aDAT binding 80%.

^bNormosmia/-DAT reduction, hyposmia/-DAT reduction, or normosmics with DAT reduction.

^cKruskal-Wallis test or χ^2 test.

DAT, dopamine transporter; SD, standard deviation; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

Association of cognitive domains with membership in the hyposmia/DAT reduction group (n = 38) versus all others (n = 187)^a

Table 2

Variable	Regression Coefficient	Standard Error	Wald X ²	Odds Ratio	95% CI	P value
Global cognition	0.68	0.24	8.30	1.97	1.24-3.12	0.004^b
Executive function/working memory	0.61	0.21	8.18	1.84	1.21-2.81	0.004^b
Language	0.25	0.20	1.66	1.29	0.88-1.90	0.20
Memory	0.50	0.21	5.52	1.64	1.09-2.48	0.02
Processing speed/attention	0.43	0.22	3.92	1.53	1.00-2.34	0.048
Visuospatial	0.17	0.21	0.65	1.18	0.79-1.78	0.42

^aSeparate logistic regression models adjusted for age at testing, sex, and education.

^bGlobal cognition and executive function remained significant after adjusting for multiple comparisons using a Bonferroni corrected threshold for statistical significance of $P < 0.008$.
DAT, dopamine transporter.

Table 3
Association of hyposmia plus specific cognitive domain impairments^a with DAT reduction

Cognitive Domain	With Both Risk Factors	Without Either Risk Factor	Odds Ratio (95% CI) ^b	P Value
Hyposmia alone	142	83	4.14 (1.68-10.16)	0.002
Hyposmia + global cognitive impairment	36	76	6.86 (1.67-28.25)	0.008^c
Hyposmia + executive function/working memory impairment	31	74	6.96 (1.97-24.64)	0.003^c
Hyposmia + language impairment	23	70	3.57 (0.64-19.88)	0.15
Hyposmia + memory impairment	31	73	5.83 (1.48-23.04)	0.01
Hyposmia + processing speed/attention impairment	26	78	5.38 (1.14-25.30)	0.03
Hyposmia + visuospatial impairment	30	76	3.84 (0.98-15.11)	0.05

^a>1 SD below standardized mean score.

^bSeparate logistic regression models adjusted for age at testing, sex, and education.

^cHyposmia + global cognitive impairment and hyposmia + executive function impairment remained significant after adjusting for multiple comparisons using a Bonferroni corrected threshold for statistical significance of $P < 0.008$.