JMD
http://dx.doi.org/10.14802/jmd.14011 / J Mov Disord 2014;7(2):77-83
pISSN 2005-940X / eISSN 2093-4939

ORIGINAL ARTICLE

Dopamine Does Not Appear to Affect Mental Rotation in Parkinson's Disease

Gregory P. Crucian,[1] Sheyan Armaghani,[2] Avan Armaghani,[3] Paul S. Foster,[4] David W. Burks,[5,6] Barry Skoblar,[7] Valeria Drago,[8] Kenneth M. Heilman[5,6]

[1]Memphis, TN, USA
[2]Department of Orthopedics, Vanderbilt University Medical Center, Nashville, TN, USA
[3]Department of Internal Medicine, University of Florida, Gainesville, FL, USA
[4]Middle Tennessee State University, Murfreesboro, TN, USA
[5]Department of Neurology, University of Florida, Gainesville, FL, USA
[6]Malcom Randall VA Medical Center, Gainesville, FL, USA
[7]Private Practice, Wilmington, NC, USA
[8]Laboratorio LENITEM, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy

ABSTRACT

Objective Patients with Parkinson's disease (PD) often have deficits with mental rotation (MR). The neuropathological factors underlying these deficits, however, remain to be elucidated. One hypothesis suggests that dopamine depletion in nigro-striatal systems adversely influences MR. Another hypothesis suggests that deterioration of cortical (fronto-temporo-parietal basal ganglia) networks that mediate this function are responsible for this deficit. The goal of this study was to test the dopamine hypothesis by determining if dopamine abstinence negatively influences MR performance.

Methods Thirty three non-demented right-handed individuals with PD were assess for their ability to perform a pencil and paper MR test while "on" and "off" dopaminergic medications. Dopamine abstinence followed the typical overnight withdrawal procedures.

Results No differences in mental rotation abilities were found between "on" and "off" dopaminergic medications.

Conclusions These results suggest that other neuropathological factors, such as cortical-basal ganglia neurodegeneration, or dysfunction of other neurotransmitters systems, might account for these cognitive deficits and future research will have to test these alternative hypotheses.

Key Words Visual-spatial; Mental rotation; Parkinson's disease; Dopamine; Cognitive deficits.

Parkinson's disease (PD) is associated with deficits in a range of visual-spatial abilities.[1] For example, individuals with PD have exhibited difficulties performing three-dimensional mental rotations in free vision.[2,3] These research findings substantiate the detrimental impact that the parkinsonian pathology has on brain function. However, the association of PD with visual-spatial deficits has been inconsistent.[4]

Two major theories have been proposed to account for the visuospatial defects associated with PD. One theory suggests that cognitive deficits in PD are related to dopamine depletion in either nigro-striatal pathways or the mesocortical pathways that disrupt frontal-basal ganglia neural networks important in executive functions. This frontal-executive dysfunction has been thought to have secondary effects on other cognitive abilities in PD such as visual-spatial ability.[5] Partial support for the dopaminergic hypothesis comes from studies which have demonstrated that treatment with dopaminergic medication improves sustained concentration and complex problem solving

Received: February 23, 2014 **Revised:** August 1, 2014 **Accepted:** August 12, 2014
Corresponding author: Gregory P. Crucian, PhD, 1030 Jefferson Ave, Memphis, TN 38104, USA / **Tel:** +1-901-523-8990, x-4078 / **Fax:** +1-901-577-7371 / **E-mail:** gcrucian@gmail.com

in individuals with PD.[6-8] Dopamine dysfunction in PD has also been associated with some memory difficulties.[9] These results are consistent with findings of increased frontal cortical metabolism, reflecting decreased neural efficiency, in dopamine-abstinent PD subjects when performing a working memory task during functional imaging.[10] In order to normally perform a mental rotation task a person requires the use of working memory and must also be able to disengage from the initial stimulus. These functions are mediated by the frontal lobes and dopamine deficiency might impair these and other necessary functions. Other studies, however, have failed to find a relationship between levodopa treatment and complex problem solving (e.g., Wisconsin Card Sorting Test),[11] sustained concentration,[10,12] and memory.[12]

The second theory suggests that the deficit in mental rotation associated with PD is related to the degradation of the cortical areas that are critical for the performance of this task. For example, Shelton and Pippitt[13] using functional magnetic resonance imaging (fMRI) reported that mental rotation is associated with activation of area MT or V5, a visual association area. Koshino et al.[14] using fMRI with a mental rotation task demonstrated that both the ventral ("what") and dorsal ("where") visual streams[15] as well as the prefrontal cortex were activated. Abe et al.[16] showed occipital and posterior parietal hypoperfusion in PD patients without dementia. Furthermore, it was also demonstrated that occipital hypoperfusion is likely to underlie impairment of visual cognition. Finally, Martin et al.[17] using (magnetic resonance imaging) voxel-based morphometry found that there was cortical atrophy and changes in the subcortical white matter in the visual and visual association cortex.

The goal of this study was to help determine which of these two hypotheses may best account for the deficit in mental rotation exhibited in non-demented patients with PD by assessing the influence of dopaminergic medication on mental rotation performance. It was predicted that, if dopamine depletion had adverse effects on higher cortical function such as visual-spatial ability, individuals with PD would perform better on a free visual field measure of mental rotations when receiving their prescribed dopaminergic medication than when in a dopaminergic abstinence state. The absence of improvement would provide evidence that degradation of the cortical networks mediating this function was most likely responsible for this mental rotation deficit.

MATERIALS & METHODS

Participants

Thirty-three right-handed participants (men = 20) who met the criteria for PD[18] were recruited. Exclusionary criteria for enrollment in this study included use of the left hand for writing, history of learning disabilities, history of other or concurrent neurological disorders, and history of major psychiatric disorder prior to PD onset. In addition to their dopaminergic medications, 23 of the participants were being treated with additional medications that could potentially affected cognition (e.g., lorazepam, verapamil, citalopram, oxybutynin, clonazepam, benazepril, paroxetine, tamazepam), whereas the remaining 10 PD participants were being treated only with dopaminergic agents. This research was conducted with full approval from the University of Florida Institutional Review Board. All participants provided signed informed consent prior to their enrollment in this study.

Presence of dementia was assessed with the Mini Mental State Exam (MMSE[19]) using a cut-off criterion of 27/30.[8] Participants were also administered the Geriatric Depression Scale (GDS[20]) to assess for depression. The motor portion of the United Parkinson's Disease Rating Scale (UPDRS[21]) was administered to characterize the PD volunteers' motor symptoms and level of dysfunction. Determination of symptom laterality (e.g., right, left, bilateral) and symptom type (rigid-akinetic, tremulous, undifferentiated) was operationally defined as exhibiting a preponderance of symptoms (i.e., > 2 point difference) on the respective items from the UPDRS. Current rather than onset symptoms were used in this classification because of the generally consistent patterns in symptom progression in PD,[22-24] and because current symptom severity provides an accurate reflection of the present extent of parkinsonian pathology.[25] A summary of participant demographic information is presented in Table 1.

Research participants also received standardized neuropsychological testing as part of a larger, ongoing research protocol. These neuropsychological tests were selected to assess for current level of gen-

eral intellectual abilities, language, and executive functions involving attention and concentration, mental processing speed, and set-shifting. These data are presented elsewhere.[26] As an indication of current general cognitive function, only results from the Wechsler Adult Intelligence Scale-Revised (WAIS-R[27]) Information subtest and Boston Naming Test (BNT[28]) along with the MMSE, are reported.

As the primary dependent variable, mental rotation ability was assessed with the Mental Rotations Test (MRT[29]). This psychometrically sound (internal consistency = 0.88; test-retest consistency = 0.83) paper and pencil test has 20 items with one target stimulus and four choices.[29] Two of the four choices are correct, but are presented in different two- and three-dimensional planes, as if "rotated" to a different perspective. This test requires the participant to select the two correct choices from the four possible options. Test stimuli were enlarged by approximately 20% to enhance viewing. Each example item was presented on a single page. Experimental test items were presented three per page, separated by blank space on the page. The participants responded on a separate answer sheet. Otherwise, test administration followed established procedures, including standardized instructions and a 10-minute time limit.[29] The dependent variable for this measure was the proportion of correct responses (number of correct items/total number of items attempted). Using a proportion correct score as the dependent variable was intended to correct for differences in psychomotor speed in test completion which may be a confound for these volunteers. An alternate version of this test was created by altering the order of presentation of the test items. Administration of alternate versions of this test was conducted in a random and counter-balanced fashion.

Procedures

Participants were tested on two separate days, eight weeks apart, assessing the influence of dopaminergic medications on these cognitive functions. The WAIS-R Information subtest and BNT were administered only once during the first testing session because it was presumed that these tests of crystallized knowledge would show less sensitivity to medication-induced cognitive fluctuations. PD volunteers were tested both "on" and "off" dopaminergic medication, with test schedule (e.g., Day 1 = "off"; Day 2 = "on") assigned randomly. "Off" medication testing was conducted after an over-night abstinence period involving a minimum of approximately 12 hours, as per the usual clinical assessment.[30] Order of test administration ("on" vs. "off") during the individual sessions was pseudorandom. All testing followed standardized administration procedures.

RESULTS

Descriptive statistics for MRT accuracy from the current study are presented in Table 2. A summary of demographics and MRT results from our previous study using a different participant sample[2] is presented in Table 3. Visual comparison of the current data indicates that these men with PD are somewhat older and have slightly more education

Table 1. Participant demographics*

	Males	Females
Sample size	20	13
Age (years)	70.35 (8.45)	63.76 (8.75)
Education (years)	15.65 (3.34)	13.46 (2.44)
MMSE	28.80 (0.89)	28.92 (1.04)
WAIS-R Information	13.25 (2.63)	10.38 (2.53)
BNT	55.83 (5.92)	55.91 (2.98)
GDS (mean)	6.05 (4.30)	4.00 (3.51)
Duration (years)	4.84 (4.61)	5.47 (5.10)
UPDRS motor†	23.15 (8.86)	23.61 (13.07)
UPDRS laterality†		
Right	3	1
Left	3	1
Bilateral	14	11
UPDRS type†		
Rigid-akinetic	3	2
Tremor	2	1
Undifferentiated	15	10

*mean (standard deviation), †data was collected while the PD participant is "off" his or her dopaminergic medication. BNT: Boston Naming Test, GDS: Geriatric Depression Scale, MMSE: Mini Mental State Exam, PD: Parkinson's disease, UPDRS: United Parkinson's Disease Rating Scale, WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 2. Mental rotation test accuracy*

Medication status	Males	Females
"On" meds	61.97 (17.03)	59.49 (15.55)
99% confidence interval	51.08–72.87	46.27–72.63
"Off" meds	63.45 (17.22)	57.80 (9.74)
99% confidence interval	52.43–74.46	49.55–66.06

*mean (standard deviation).

Table 3. Comparative demographics and mental rotation test scores (from previous study)*

	Controls		PD	
	Males	Females	Males	Females
MRT proportion correct	71.45 (15.76)	55.97 (11.73)	58.16 (13.55)	53.23 (10.24)
Age (years)	66.44 (9.11)	63.22 (8.82)	62.72 (7.67)	62.23 (9.67)
Education (years)	14.32 (3.31)	13.86 (2.35)	14.75 (2.53)	13.39 (2.06)
MMSE	29.04 (0.99)	29.46 (0.81)	29.00 (0.98)	28.78 (0.80)
Duration (years)	-	-	11.68 (5.92)	10.15 (6.07)
UPDRS-motor	-	-	27.57 (11.03)	36.19 (15.12)

*mean (standard deviation); taken with permission from Crucian et al.[2] MMSE: Mini Mental State Exam, MRT: Mental Rotations Test, PD: Parkinson's disease, UPDRS: United Parkinson's Disease Rating Scale.

than the men with PD in the previous study. Duration of illness and symptom severity for this sample is somewhat less than in the previous sample. This visual comparison also indicates similar MRT accuracy performance between this group of participants with PD and that of the previous study.

One preliminary analysis was conducted on participants' data to assess for the influence of test day. This analysis revealed that average accuracy performance on test day one (61.91 ± 15.95) did not differ from that on day two (60.29 ± 15.10), indicating minimal practice effects associated with repeat testing [$t(32) = 0.74$, $p = 0.47$].

Another preliminary analysis was conducted on total UPDRS scores "on" and "off" medication to determine the effects of medication treatment on Parkinsonian motor signs. This analysis revealed a significant difference between "on" medication (mean = 19.30 ± 10.50) and "off" medication (23.33 ± 10.53), Wilcoxon $Z = 2.43$, $p = 0.015$, indicating that dopaminergic medication was successful in reducing severity of Parkinsonian symptoms.

For the main analysis, we assessed the effects of dopaminergic medication on mental rotation performance using a repeated measures analysis of covariance. The MRT accuracy score was the dependent variable (Table 2), with dopaminergic medication status as the within subjects variable, sex as the between subjects variable, and age, education and duration of illness as covariates. Sex was included as a factor because of previous findings of a sex difference on this task[31] whereas the covariates were included to account for variance associated with participant and disease characteristics. With respect to the covariates, this analysis revealed a significant influence of education [$F(1, 28) = 5.24$, mean square (MS) = 1877.362, $p = 0.03$], reflecting a positive correlation between education and mental rotation accuracy ($r = 0.43$, $p = 0.012$). The effect of dopaminergic medication status did not achieve significance [$F(1, 28) = 0.09$, MS = 7.333, $p = 0.77$]. Notably, the distributions in MRT accuracy between "on" medications [99% confidence interval (CI) = 53.23–68.73] and "off" medications (99% CI = 54.16–68.28) overlapped almost completely. Moreover, this analysis yielded an effect size of Partial Eta squared (ηp^2) = 0.003 associated with medication status. As an approximation of the proportion of total variance accounted for in MRT performance by medication status, this effect size is very small. No other effects or interactions achieved significance.

A series of supplemental analyses were conducted to assess the relationship between symptom characteristics of the participants with PD and their visual-spatial mental rotation performance. As noted above, parkinsonian symptoms were characterized using the UPDRS, with this assessment conducted while the individuals with PD were off their prescribed dopaminergic medications to reflect the greatest exacerbation of parkinsonian symptoms. Non-parametric analyses (e.g., chi-square) were used because of differences in the respective sample sizes. Examining the relationship between parkinsonian symptom presentation (e.g., rigid-akinetic, tremulous, undifferentiated) and average mental rotation performance revealed no differences [$X^2(2) = 1.23$, $p = 0.54$). Further, no differences were found when looking at the influence of parkinsonian symptom laterality (e.g., left, right, bilateral) on average MRT performance [$X^2(2) = 0.09$, $p = 0.96$). Assessing the relationship between average MRT performance and symptom severity (e.g., UPDRS Total score "off" medications) also revealed no significant correlation (rho = -0.285, $p = 0.11$). In examining the effects of other medications on mental rotation performance, an independent samples *t*-

test conducted on the average MRT score between those PD participants taking dopaminergic agents alone [mean = 58.33, standard deviation (SD) = 15.12, 99% CI = 42.80−73.87] and those taking additional medications that potentially impacted cognition (mean = 62.30, SD = 13.95, 99% CI = 54.10−70.50) revealed no difference in mental rotation performance [t(31) = 0.73, $p = 0.47$]. Examining the relationship between depression and mental rotation performance revealed no correlation between severity of depressive symptoms (e.g., average GDS total score) and average MRT performance (rho = 0.004, $p = 0.98$).

DISCUSSION

Whereas we cannot fully discard the possibility that dopaminergic medications influence cognitive ability in individuals with PD, results from this study indicate that dopaminergic treatment of non-demented individuals with PD has either a very small or no effect on mental rotation performance. As seen in Table 3, these current PD participants performed very similarly to our previous study[2] in which we demonstrated a main effect for Group along with a significant interaction between Group and Sex that was accounted for by a significant decline in mental rotation performance by the men with PD in our previous study. This result is in contrast to the finding of a positive benefit of these dopaminergic medications on the motor symptoms associated with PD. Based on the effect size reported in this study (approximately equivalent to a Cohen's d of 0.10), a very large sample of volunteers would be required to investigate this medication effect with adequate statistical power at conventional standards of significance.[32] These findings are consistent with, and provide further support to the existing literature on the limited cognitive effects of dopaminergic medications in PD.[10-12] Nevertheless, additional research needs to be conducted on the effects of dopaminergic medication on visual-spatial ability and other cognitive functions in PD to further corroborate these findings.

Consistent with our previous results, we found no influence on mental rotation performance from PD symptom presentation (e.g., type, laterality, severity), severity of depression, or presence of other medications. It should also be noted that only two of these current participants were included in the previous study, indicating some consistency in the findings across samples. Nevertheless, given the relatively small sample sizes, these data should be interpreted cautiously. As before, we also found that PD was associated with a reduction in the usual male advantage that is typically found on this measure.[31]

Taken together, these findings do not support the hypothesis that dopaminergic deficiency in nigrostriatal pathways, which influence frontal-basal ganglia circuits, accounts for the visual-spatial deficits associated with PD. These finding do indirectly support the alternative postulate that this cognitive deficit is not being induced by dopamine deficiency but rather is related to other neuropathological changes associated with PD, most likely in the posterior cortical areas that have been demonstrated to be important in this function or in the prefrontal executive networks. With respect to frontal lobe function, cerebral atrophy[33] and Lewy bodies containing alpha-synuclein fibrils[34] have been found in frontal lobes of patients with PD. This neuropathology in PD has also been shown to affect other brain areas, including the medial temporal and parietal regions[35] and in the absence of an improvement with dopaminergic treatment these pathological changes might account for the impaired mental rotation performance seen in individuals with PD. However, it is also possible for other neurotransmitter defects to be responsible for these results. For example, there is some evidence that the mesocortical dopaminergic system, which also influences frontal lobe function and is also impaired in patients with PD, might not respond as well to levodopa treatment as does the nigro-striatal system.[9] Thus it might be a defect in this mesocortical system, rather than the nigrostriatal system that accounts for this impairment of mental rotation. In addition, other neurotransmitters, such as acetylcholine and serotonin, have been found to be altered in PD.[36]

Given the interconnections between the cortical structures such as the frontal and the posterior temporal and parietal lobes, as well as their connections with the basal ganglia,[37,38] and in light of the neuropathology associated with PD,[39] our results suggest these visual-spatial deficits in PD are likely due to dysfunction within a distributed neural network that is primarily within the right hemisphere.[40] Fu-

ture research, however, such as voxel-based morphometry will be needed to further elucidate the nature of this cognitive dysfunction in PD.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

This study was supported, in part, by the Department of Defense (DAM 17-98-1-8616), the Department of Veterans Affairs Research Service and the State of Florida Memory Disorder Clinics. We would like to thank Laura Grande, Jeannine Mielke, Brian Shenal, Robert Rhodes, and David B. FitzGerald for technical assistance in data collection, and Michael Okun, Hubert Fernandez, and Frank Skidmore for assistance in participant recruitment.

REFERENCES

1. Levin BE, Katzen HL. Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. Adv Neurol 2005;96:84-94.
2. Crucian GP, Barrett AM, Burks DW, Riestra AR, Roth HL, Schwartz RL, et al. Mental object rotation in Parkinson's disease. J Int Neuropsychol Soc 2003;9:1078-1087.
3. Amick MM, Schendan HE, Ganis G, Cronin-Golomb A. Frontostriatal circuits are necessary for visuomotor transformation: mental rotation in Parkinson's disease. Neuropsychologia 2006;44:339-349.
4. Waterfall ML, Crowe SF. Meta-analytic comparison of the components of visual cognition in Parkinson's disease. J Clin Exp Neuropsychol 1995;17:759-772.
5. Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. Trends Neurosci 1990; 13:21-29.
6. Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 1992;107:394-404.
7. Lange KW, Paul GM, Naumann M, Gsell W. Dopaminergic effects on cognitive performance in patients with Parkinson's disease. J Neural Transm Suppl 1995;46:423-432.
8. Malapani C, Pillon B, Dubois B, Agid Y. Impaired simultaneous cognitive task performance in Parkinson's disease: a dopamine-related dysfunction. Neurology 1994;44:319-326.
9. Mohr E, Fabbrini G, Ruggieri S, Fedio P, Chase TN. Cognitive concomitants of dopamine system stimulation in parkinsonian patients. J Neurol Neurosurg Psychiatry 1987;50: 1192-1196.
10. Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 2002;51:156-164.
11. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988;111(Pt 2):299-321.
12. Girotti F, Carella F, Grassi MP, Soliveri P, Marano R, Caraceni T. Motor and cognitive performances of parkinsonian patients in the on and off phases of the disease. J Neurol Neurosurg Psychiatry 1986;49:657-660.
13. Shelton AL, Pippitt HA. Motion in the mind's eye: comparing mental and visual rotation. Cogn Affect Behav Neurosci 2006;6:323-332.
14. Koshino H, Carpenter PA, Keller TA, Just MA. Interactions between the dorsal and the ventral pathways in mental rotation: an fMRI study. Cogn Affect Behav Neurosci 2005; 5:54-66.
15. Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Masfield RJW, editors. Analysis of Visual Behavior. Cambridge, MA: MIT Press, 1982;549-586.
16. Abe Y, Kachi T, Kato T, Arahata Y, Yamada T, Washimi Y, et al. Occipital hypoperfusion in Parkinson's disease without dementia: correlation to impaired cortical visual processing. J Neurol Neurosurg Psychiatry 2003;74:419-422.
17. Martin WR, Wieler M, Gee M, Camicioli R. Temporal lobe changes in early, untreated Parkinson's disease. Mov Disord 2009;24:1949-1954.
18. Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol 1992;32 Suppl:S125-S127.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
20. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983;17:37-49.
21. Fahn S, Elston RL. Unified parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent Developments in Parkinson's Disease. Vol 2. New York: MacMillan, 1987;153-163.
22. Dickson JM, Grünewald RA. Somatic symptom progression in idiopathic Parkinson's disease. Parkinsonism Relat Disord 2004;10:487-492.
23. Lee CS, Schulzer M, Mak E, Hammerstad JP, Calne S, Calne DB. Patterns of asymmetry do not change over the course of idiopathic parkinsonism: implications for pathogenesis. Neurology 1995;45(3 Pt 1):435-439.
24. Toth C, Rajput M, Rajput AH. Anomalies of asymmetry of clinical signs in parkinsonism. Mov Disord 2004;19:151-157.
25. Braak H, Rüb U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64:1404-1410.
26. Crucian GP, Armaghani S, Armaghani A, Foster PS, Burks DW, Skoblar B, et al. Visual-spatial disembedding in Parkinson's disease. J Clin Exp Neuropsychol 2010;32:190-200.
27. Wechsler D. Maunal of the Wechsler Adult Intelligence Scale-Revised. San Antonio, TX: Psychological Corporation, 1981.
28. Kaplan EF, Goodglass, H, Weintraub S. The Boston Naming Test. 2nd ed. Philadelphia: Lea & Febiger, 1983.
29. Vandenberg SG, Kuse AR. Mental rotations, a group test of three-dimensional spatial visualization. Percept Mot Skills 1978;47:599-604.
30. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006;30:1-23.
31. Linn MC, Petersen AC. Emergence and characterization of sex differences in spatial ability: a meta-analysis. Child Dev 1985;56:1479-1498.
32. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Revised ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1987.
33. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without

dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127(Pt 4):791-800.
34. Kingsbury AE, Daniel SE, Sangha H, Eisen S, Lees AJ, Foster OJ. Alteration in alpha-synuclein mRNA expression in Parkinson's disease. Mov Disord 2004;19:162-170.
35. Braak H, Del Tredici K. Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. Exp Neurol 2008;212:226-229.
36. Agid Y, Javoy-Agid F, Ruberg M. Biochemistry of neurotransmitters in Parkinson's disease. In: Marsden CD, Fahn S, editors. Movement Disorders 2. London: Butterworth, 1987;166-230.
37. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Brain Res Rev 2000; 31:236-250.
38. Clower DM, Dum RP, Strick PL. Substantia nigra pars reticulata provides input to area 7B of parietal cortex (abstract). Program No. 460.1. 2002 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2002. http://www.sfn.org/index.aspx?pagename=abstracts_ampublications.
39. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990;85:119-146.
40. Corballis MC. Mental rotation and the right hemisphere. Brain Lang 1997;57:100-121.