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. Heilman5,6

1Memphis, TN, USA
2Department of Orthopedics, Vanderbilt University Medical Center, Nashville, TN, USA
3Department of Internal Medicine, University of Florida, Gainesville, FL, USA
4Middle Tennessee State University, Murfreesboro, TN, USA
5Department of Neurology, University of Florida, Gainesville, FL, USA
6Malcom Randall VA Medical Center, Gainesville, FL, USA
7Private Practice, Wilmington, NC, USA
8Laboratorio 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. Dopamine abstinence followed the typical overnight withdrawal procedures.

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...
in individuals with PD.\textsuperscript{6-8} Dopamine dysfunction in PD has also been associated with some memory difficulties.\textsuperscript{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.\textsuperscript{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),\textsuperscript{11} sustained concentration,\textsuperscript{10,12} and memory.\textsuperscript{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\textsuperscript{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.\textsuperscript{14} using fMRI with a mental rotation task demonstrated that both the ventral (“what”) and dorsal (“where”) visual streams\textsuperscript{15} as well as the prefrontal cortex were activated. Abe et al.\textsuperscript{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.\textsuperscript{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\textsuperscript{10} 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 affect cognition (e.g., lorazepam, verapamil, citalopram, oxycodone, 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\textsuperscript{19}) using a cut-off criterion of 27/30.\textsuperscript{19} Participants were also administered the Geriatric Depression Scale (GDS\textsuperscript{20}) to assess for depression. The motor portion of the United Parkinson’s Disease Rating Scale (UPDRS\textsuperscript{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,\textsuperscript{22-24} and because current symptom severity provides an accurate reflection of the present extent of parkinsonian pathology.\textsuperscript{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). 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.26 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 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.
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 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 task13 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 (ηp²) = 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 [X²(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 [X²(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 (r = -0.285, p = 0.11). In examining the effects of other medications on mental rotation performance, an independent samples t-

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. MMSE: Mini Mental State Exam, MRT: Mental Rotations Test, PD: Parkinson’s disease, UPDRS: United Parkinson’s Disease Rating Scale.
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 study7 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.7 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 findings 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 atrophy35 and Lewy bodies containing alpha-synuclein fibrils36 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 regions35 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.3 Thus it might be a defect in this mesocortical system, rather than the nigro-striatal 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,17,36 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-
nature 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.

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