Antisaccades and Executive Dysfunction in Early Drug-Naive Parkinson's Disease: The Discovery Study

Chrystalina A. Antoniades, PhD,[1]* Nele Demeyere, PhD,[2] Christopher Kennard, PhD,[1] Glyn W. Humphreys, PhD[2] and Michele T. Hu, PhD[1,3]

[1]*Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom* [2]*Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford, United Kingdom* [3]*Oxford Parkinson's Disease Centre, Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford, United Kingdom*

Abstract

Background: Cognitive impairment is well recognized in Parkinson's disease (PD), but when it begins to develop is unclear. The aim of this study was to identify early signs of cognitive impairment along with abnormalities in saccadic behavior in newly diagnosed unmedicated PD patients.

Methods: Nineteen drug-naive PD patients and 20 controls were examined using a battery of tests, including an antisaccade task, phonemic and semantic verbal fluencies, and a switching and rule finding task.

Results: With simple tasks, no differences were found between the two groups. However, cognitive performance of the two groups diverged with more complex tasks, occurring independently of PD-related motor impairment. Patients exhibited higher antisaccadic error rates and switch costs in the task switching test, and performed significantly worse in the rule finding task.

Conclusions: Certain cognitive domains and saccadic parameters are already significantly impoverished in newly diagnosed Parkinson's patients, even before the initiation of medication. © 2015 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease, eye movements, antisaccades, executive function, task switching

Although ample experimental evidence exists of cognitive impairment in Parkinson's disease (PD), the exact time these deficits first develop is unclear. Some have suggested that cognitive impairment could be present as early as the premotor phase,[1] but few studies have focused on patients with very early disease, and fewer still on entirely drug-naive patients.[2] The medication itself may contribute to some of these cognitive problems.[3]

Measurement of eye movements permits assessment of both behavior and motor function.[4,5] Execution of saccades involves multiple cortical and subcortical brain areas.[6] Prosaccades are natural and easy to perform, but antisaccades impose a higher demand on attentional and cognitive resources,[7] requiring suppression mechanisms to prevent the automatic execution of a visually driven saccade toward the stimulus. Imaging, animal models, and human lesion studies all suggest that the frontal eye field plays an important role in the suppression process.[8-10] Parkinson's patients have difficulty both in inhibiting the automatic response and in initiating a voluntary response in the opposite direction.[11,12] Antisaccades are also impaired by both levodopa and anticholinergic medication.[12]

We used a battery of tests, including the antisaccade task, verbal fluency tests, and task switching and rule finding tasks, to establish whether cognitive impairment is present in early PD before the introduction of any medication. Verbal fluency tests measure the capacity to generate words beginning with particular letters (phonemic fluency) or belonging to particular categories (semantic fluency). The former has been associated with frontal lobe function and the latter with temporoparietal function. Task switching and rule finding tasks have been used to look for deficits in behavioral flexibility that might be attributed, at least partially, to fronto-basal ganglia dysfunction.[13-15]

*Correspondence to: Dr. Chrystalina A. Antoniades, Nuffield Department of Clinical Neurosciences, Level 6, West Wing, John Radcliffe Hospital, University of Oxford, United Kingdom, E-mail: chrystalina.antoniades@ndcn.ox.ac.uk

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TABLE 1. Demographics, clinical characteristics and test scores in the de novo unmedicated PD group and control participants

	PD (n =19) Mean (range)	HC (n =20) Mean (range)
Age in years (SD)	68 (55-85)	67 (55-84)
M:F ratio	7:12	6:14
Disease duration from diagnosis (yrs)	0.67 (0.1-1.3)	N/A
UPDRS motor score (Part III)	22.7 (5-43)	1.6 (0-9)
MMSE mean (range)	28.4 (26-30)	28.6 (26-30)
Semantic fluency[a]	11.6 (5-17)	12.9 (8-19)
Phonemic fluency[a]	12.9 (6-19)	13.8 (7-19)
Prosaccadic latency (ms)	237.6 (176-342)	228.0 (175-327)
Antisaccadic error rates (%)	15. 0 (11-21)	8.7 (6-14)
Trails—switch cost	1.86 (0-6)	0
BRFST	2.58 (1-3)	2.90 (2-3)

[a]Age-related scaled semantic and phonemic fluencies.
PD, Parkinson's disease; HC, healthy controls; SD, standard deviation; M, male; F, female; UPDRS, Unified Parkinson's disease Rating Scale; MMSE, Mini-Mental state examination; BRFST, Birmingham rule finding and switching test.

Materials and Methods

Participants

Nineteen drug-naive PD patients and 20 age-matched controls from the Oxford Discovery cohort (Table 1) were tested. Patients had clinically probable idiopathic PD (by UK PD brain bank criteria[16]) within 3 years from disease onset, with akinetic-rigid rather than tremor-dominant phenotype so that subjects with benign tremor disorders were excluded. Subjects with atypical parkinsonian features—screened for using the NINDS Parkinson's tool and a standardized examination[17]—were excluded. Controls were spouses or friends of the patients with no personal or family history of neurological or psychiatric disorders and taking no medication. A score of greater than 26 on the Mini-Mental State Examination[18] was an inclusion criterion, although this might not have completely excluded subjects with mild cognitive impairment.[19]

For phonemic and verbal fluency testing, the total number of words beginning with F, A, and S, and animals and boys' names generated over 60 seconds each were counted.[20]

Trails Test

The trails test has three components. In two baseline tasks (Fig. 1A), the participant is required to (i) connect the circles presented along with triangle distractors and (ii) connect triangles presented with circle distractors, going from the largest shape to the smallest in order. There is then an "executive load" condition in which the participant has to alternate between the circles and triangles, from the largest to the smallest. Performance on all tasks is timed. The contrast between the switching condition and the baselines provides a measure of how sensitive the individual is to the increased executive load under the switching condition, uncontaminated by slow motor speed per se. Before each task, the participant is given a practice trail.

Birmingham Rule Finding and Switching Test

Participants were shown a series of sheets containing a grid of gray and colored squares and a black dot (Fig. 1B) that moves on each successive sheet, according to some rule.[21] Participants were asked to show where they thought the dot would move next. However, the rule governing the pattern of movement could change, and when the participant's predictions no longer matched the movement of the dot, they would have to deduce the new rule.

Saccadic Eye Movement Recordings

Visually guided horizontal saccades were recorded using a head-mounted oculometer. We used an antisaccadic protocol[22] consisting of five blocks: 60 prosaccades, 40 antisaccades × 3, 60 prosaccades, with a break of 1 minute between blocks. In each experimental trial, a central fixation target was displayed for 1 to 2 seconds; then one of the peripheral targets chosen randomly either to the left or right was presented, and the central stimulus simultaneously removed. Records contaminated by excessive head movement or blinks were automatically removed by the software (LatencyMeter, Ober Consulting), which also determined the saccadic latency using a saccade-detection algorithm based on velocity and acceleration. Latencies below 80 ms or above 1,000 ms (<1% of saccades) were excluded.

Antisaccadic error rate (AER) was defined as the percentage of directional errors, or saccades triggered *toward* the lateral target. Neither prosaccadic latencies nor AERs were distributed normally; therefore, nonparametric statistics were used.

Results

Saccades

Median prosaccadic latencies did not differ between Parkinson's and control populations ($P = 0.43$, Fig. 1C), whereas AERs differed significantly (Fig. 1D) (mean of 15.1% for patients versus 8.7% for controls, $P < 10^{-6}$).

Prosaccadic latencies were not correlated with Unified Parkinson's Disease Rating Scale (UPDRS) part III (Spearman's rank correlation coefficient $r_s = 0.24$, $P = 0.31$), whereas AERs were significantly correlated with UPDRS III ($r_s = 0.55$, $P = 0.014$).

Executive Function

In the Oxford Cognitive Screen trail making test, both patients and controls achieved perfect or near-

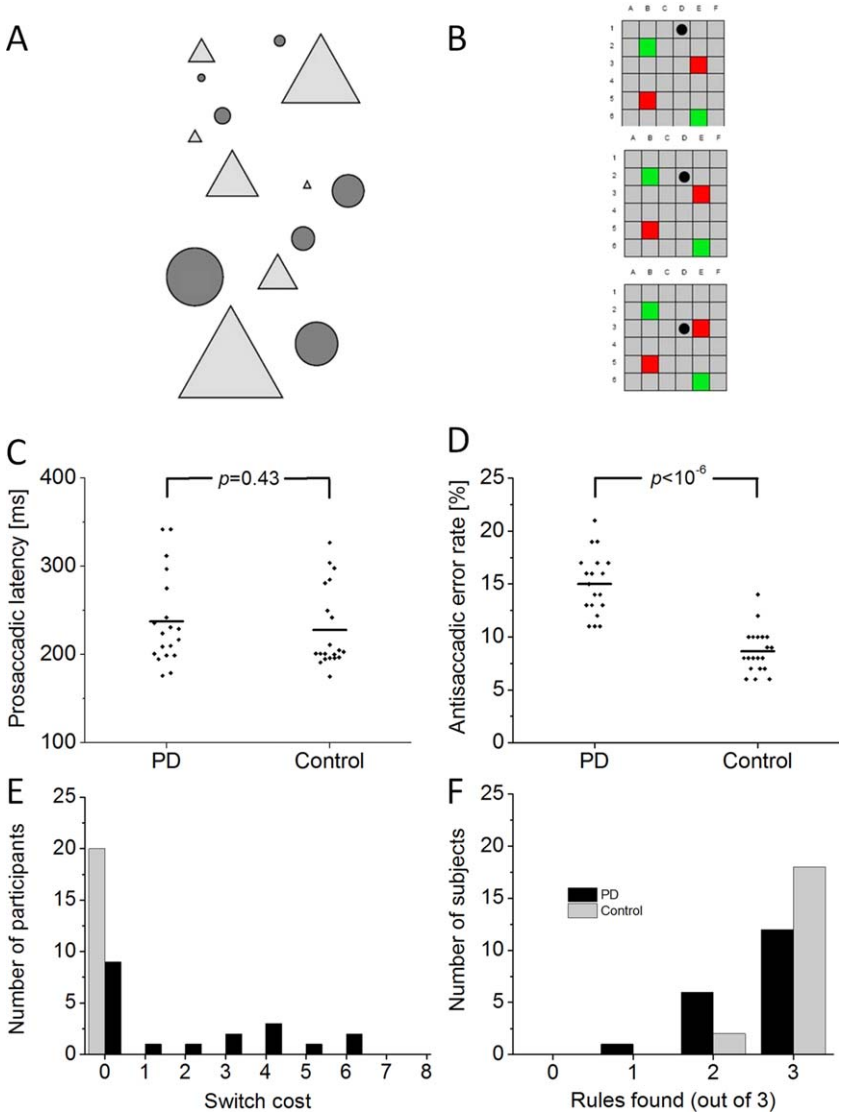

FIG. 1. (**A**) An example of the trail making task. The participant is instructed to first connect the circles starting from the largest to the smallest, the triangles being distractors; second connect the triangles, again starting from the largest shape to the smallest, with circle distractors; and last to alternate between the circles and triangles, from the largest to the smallest. (**B**) The Birmingham rule finding and switching test. Example of three grids from the test. In this example, the rule is that the dot moves down by one square each time. This sequence was shown to each participant as a practice example before the actual task. (**C** and **D**) The distribution of prosaccadic latencies and antisaccadic error rates for Parkinson's patients and healthy controls. (**E**) Results of the trail-making test. (**F**) Results of the rule-finding test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

perfect scores (5 or 6 correct responses out of 6) in the baseline conditions. In the more complex task (mixed shapes), the performance of the two groups diverged. Controls continued to make a maximum of one error (12 or 13 correct responses out of 13), but 9 of the 19 Parkinson's patients produced 10 or fewer correct responses. Subtracting the sum of the performance in the baseline tasks from the alternating trails performance gave a cost of switching measure. This was significantly higher for the PD group than for the controls (Mann-Whitney U test, $P = 0.0003$) (Fig. 1E).

In the rule-finding test, three rule changes were made as the sequence of grids was shown. Eighteen of 20 control subjects were able to identify all three changes, with the remaining two controls finding two of three changes (Fig. 1F). However, only 12 of 19 Parkinson's patients identified all three changes, with six finding two of three and one patient finding only a single change. The difference in performance on this test of the two groups was significant (Mann-Whitney U test, $P = 0.048$).

Switch cost was significantly correlated with AER in the patient group (Spearman's rank correlation coefficient $r_s = 0.67$, $P = 0.0018$). In the rule finding task, the number of rules found was significantly correlated with AER ($r_s = -0.78$, $P = 0.00008$). Neither switch

cost nor rule finding was correlated with UPDRS III ($r_s = 0.33$, $P = 0.17$ and $r_s = -0.40$, $P = 0.091$, respectively).

Verbal fluencies, both semantic and phonemic, did not differ significantly between the two groups. Mean phonemic fluencies were 12.9 for PD and 13.8 for controls (Mann-Whitney U test, $P = 0.40$). Mean semantic fluencies were 11.6 for PD and 12.9 for controls ($P = 0.34$).

Discussion

Our results confirm that although drug-naive early PD patients have preserved performance in simple tests such as prosaccadic latencies (similar to Terao et al.[23]), tasks designed to highlight more subtle deficits can separate them from controls. The patients have increased AERs and problems in task switching and rule finding.

A large body of literature exists on the neurophysiological processes underlying prosaccades and antisaccades.[23,24] Imaging in humans[25] and neurophysiological recordings in monkeys[26] show that the prefrontal cortex is involved in preparing saccade-related areas to perform a saccade. Data from switching tasks implicate the same area in the production of flexible cognitive behavior.[27] The current results are therefore consistent with the basal ganglia changes in the Parkinson's patients impacting on the operation of prefrontal cortices, even at the earliest stages of the disease. The lack of correlation of switching and rule finding performance with UPDRS III in this study suggests that cognitive impairment may affect AER independently of motor state.

No differences were found between patients and controls in verbal fluency tasks, even though evidence from brain imaging suggests that they recruit prefrontal brain regions.[28] This suggests that fluency tasks are relatively insensitive to small degrees of dysfunction and may fail to detect cognitive change in the early stages of PD.

Kitagawa and colleagues[12] demonstrated a pronounced difference in AERs between PD patients on and off anticholinergic medication. The AERs in our PD patients, and in those in Kitagawa's study who were not on anticholinergic medication, are similar, implying that PD itself has an impairing effect on AER but that anticholinergic medication makes this substantially worse. This is consistent with the fact that anticholinergic medication acts on the striatum, to which the dopaminergic nigral neurons project. Furthermore, although anticholinergic medications reduce tremor, they frequently worsen cognition, whereas cholinergic medication improves some aspects of PD dementia.

The non–tremor-dominant subjects chosen for our study may be more likely to experience early cognitive decline than tremor-dominant subjects,[29,30] to whom these results may not apply.

We are currently studying the participants longitudinally to ascertain whether saccadometry combined with executive function measures in the early drug-naïve state can predict the severity of future motor and non-motor features of PD. ■

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Impact of Parkinson's Disease Risk Loci on Age at Onset

Christina M. Lill, MD,[1]* Johnni Hansen, PhD,[2,3] Jørgen H. Olsen, MD,[2] Harald Binder, PhD,[4] Beate Ritz, MD, PhD[3] and Lars Bertram, MD[1,5]

[1]Platform for Genome Analytics, Institutes of Neurogenetics & Integrative and Experimental Genomics, University of Lübeck, Lübeck, Germany [2]Institute of Cancer Epidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark [3]Department of Epidemiology and Environmental Sciences, School of Public Health, University of California, Los Angeles, California, USA [4]Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Mainz, Germany [5]School of Public Health, Faculty of Medicine, The Imperial College of Science, Technology, and Medicine, London, UK

Abstract

Background: The aim of this study was to assess whether recently identified Parkinson's disease (PD) risk genes also influence age at onset in PD.

Methods: We genotyped 23 single-nucleotide polymorphisms in 1,526 Danish PD patients and performed linear regression analyses with age at onset. The combined impact of PD risk loci on age at onset was assessed by linear regression analyses using a weighted genetic risk score.

Results: The strongest effects were observed with rs12726330 in *GBA* (beta = –3.63, $P = 2.0 \times 10^{-5}$) and rs34311866 in *TMEM175/GAK* (beta = –1.19, $P = 4.0 \times 10^{-3}$), corresponding to a 3.6-y and 1.2-y decrease of age at onset per risk allele, respectively. The weighted genetic risk score yielded significant association with reduced onset age ($P = 3.98 \times 10^{-3}$), although the variance explained was small (0.6%), and the effect was mostly driven by polymorphisms in *GBA* and *TMEM175/GAK*.

Conclusions: Overall, our study indicates that *GBA* and *TMEM175/GAK* significantly alter age at onset in PD. © 2015 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease, PD, age at onset, genetic association, genome-wide association study, GWAS, genetic risk score, GAK, DGKQ, GBA, N370S

Genetic factors have a substantial impact on the phenotypic variance of Parkinson's disease (PD) disease status, with recent heritability estimates near approximately 60% (95% confidence interval, 40%-80%).[1] The largest genome-wide association study has identified 26 independent single-nucleotide polymorphisms (SNPs) that showed genome-wide significant association ($P < 5 \times 10^{-8}$) with PD risk and were validated in an independent sample.[2] Despite strong statistical support for association with PD risk, the overall impact of these SNPs on PD susceptibility is comparatively small.[2] This suggests that additional heritable, that is genetic or epigenetic, factors likely play a role in modifying susceptibility for PD. Furthermore, although the association between these 26 SNPs and PD risk can be considered as established, little is known about their potential impact on other PD-related traits. One such trait of interest is age at onset of PD, for which a recent estimate suggested very high heritability (ie, 98%; 95% confidence interval, 49%-100%).[1] The aim of this study was to investigate the individual (via single-SNP analyses) as well as combined (via the construction of a weighted genetic risk score) impact of PD susceptibility loci on age at onset

*Correspondence to: Dr. Christina Lill, Platform for Genome Analytics, Institutes of Neurogenetics & Integrative and Experimental Genomics, Maria-Goeppert-Str. 1, University of Lübeck, 23562 Lübeck, Germany, e-mail: christina.lill@uni-luebeck.de

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